

AUGUST 21, 2018



Dale R. Folwell, CPA
STATE TREASURER OF NORTH CAROLINA
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PHARMACY AND THERAPEUTICS (P&T) COMMITTEE MEETING

NORTH CAROLINA STATE HEALTH PLAN
3200 ATLANTIC AVENUE, RALEIGH, NC 27604



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Pharmacy and Therapeutics (P&T) Committee Meeting

Tuesday, August 21st 2018, 6:30 p.m. to 8:00 p.m.

Agenda

Topic:

Presenter:

- | | | |
|----|---|--|
| 1. | Welcome <ul style="list-style-type: none"> • Call to Order • Roll Call | Carl Antolick III, Chair |
| 2. | Conflict of Interest Statement | Carl Antolick III, Chair |
| 3. | Old Business <ul style="list-style-type: none"> • Formulary Development and Management at CVS Caremark • Minutes from May 22, 2018 Meeting* • Recent Plan Formulary Decisions | Carl Antolick III, Chair |
| 4. | Formulary Updates* <ul style="list-style-type: none"> • Formulary Drug Exclusions • Tier Changes <ul style="list-style-type: none"> ○ Uptier ○ Downtier • Formulary Additions | Carl Antolick III, Chair
Heather Renee Jarnigan, CVS
Heather Renee Jarnigan, CVS |
| 5. | Utilization Management Policy Review* <ul style="list-style-type: none"> • New Policies Under Consideration <ul style="list-style-type: none"> ○ Nuedexta® Initial Prior Authorization ○ Topical NSAIDs Initial Prior Authorization with Quantity Limits ○ Topical Vitamin D Analogs Initial Prior Authorization ○ Chenodal® Initial Prior Authorization ○ Naprelan® Initial Prior Authorization ○ Thiola® Initial Prior Authorization | Carl Antolick III, Chair
Stephanie Morrison, CVS |
| 6. | Adjourn <ul style="list-style-type: none"> • Next Meeting: <i>Tuesday October 23, 2018 from 6:30 to 8:00 PM via webinar</i> | Carl Antolick III, Chair |

*Requires a recommendation from the P&T Committee



STATE HEALTH PLAN FOR TEACHERS AND STATE EMPLOYEES

ETHICS AWARENESS & CONFLICT OF INTEREST REMINDER

(to be read by the Chair of the P&T Committee or his or her designee at the beginning of each meeting)

In accordance with the NC State Health Plan for Teachers and State Employees' ethics policy, it is the duty of every member of the Pharmacy and Therapeutics ^{Committee}, whether serving in a vote casting or advisory capacity, to avoid both conflicts of interest and appearances of conflict.

Does any Committee member have any known conflict of interest or the appearance of any conflict with respect to any manufacturers of any medication to be discussed at today's meeting?

Or, if during the course of the evaluation process if you identify a conflict of interest or the appearance of a conflict.

If so, please identify the conflict or appearance of conflict and refrain from any undue participation¹ in the particular matter involved.

¹ "A public servant shall take appropriate steps, under the particular circumstances and considering the type of proceeding involved, to remove himself or herself to the extent necessary, to protect the public interest and comply with this Chapter, from any proceeding in which the public servant's impartiality might reasonably be questioned due to the public servant's familial, personal, or financial relationship with a participant in the proceeding." *See N.C.G.S. §138A-36 (c). If necessary, the Chairman or individual member involved should consult with his ethics liaison, legal counsel, or the State Ethics Commission to help determine the appropriate response in a given situation. Rev. 1-16-07*



Formulary Development and Management at CVS Caremark®

Development and management of drug formularies is an integral component in the pharmacy benefit management (PBM) services CVS Caremark provides to health plans and plan sponsors. Formularies have two primary functions: 1) to help the PBM provide pharmacy care that is clinically sound and affordable for plans and their plan members; and 2) to help manage drug spend through the appropriate selection and use of drug therapy.

Underlying principles of the CVS Caremark Formulary Development and Management Process include the following:

- CVS Caremark is committed to providing a clinically appropriate formulary.
- Decisions on formulary are made by a committee of independent, unaffiliated clinical pharmacists and physicians.
- The physician always makes the ultimate prescribing determination as to the most appropriate course of therapy.

The CVS Caremark formulary development process is based on nearly two decades of experience as well as extensive clinical pharmaceutical management resources. The formulary is developed and managed through the activities of the CVS Caremark National Pharmacy and Therapeutics (P&T) Committee (“P&T Committee”) and Formulary Review Committee (FRC).

CVS Caremark National Pharmacy and Therapeutics Committee

The P&T Committee is foundational in the process. The P&T Committee is an external advisory body of experts from across the United States, composed of 22 independent health care professionals including 18 physicians and four pharmacists, all of whom have broad clinical backgrounds and/or academic expertise regarding prescription drugs. A majority of the P&T Committee members are actively practicing pharmacists and physicians. Two physicians and two pharmacists are experts in the care of the elderly or disabled. One of the physicians is a medical ethicist. The role of the medical ethicist is to assist in the decision-making process by facilitating the discussion, as needed, and to provide unbiased feedback with respect to the logic and appropriateness of the conclusions drawn and the decisions reached. The composition of the P&T Committee exceeds the Centers for Medicare and Medicaid Services (CMS) P&T Committee requirements for Medicare Part D sponsors and also exceeds URAC standards.

CVS Caremark National Pharmacy and Therapeutics Committee Membership		
4 pharmacists, including	18 physicians, representing	
1 academic pharmacist	Allergy	Internal medicine
1 hospital pharmacist	Cardiology	Infectious disease
2 geriatric pharmacists	Clinical pharmacology	Pediatrics
	Endocrinology	Neurology
	Family practice	Medical ethics
	Gastroenterology	Pharmacoeconomics
	Gerontology	Pharmacology
	Hematology/oncology	Psychiatry-adult/ pediatric/adolescent
		Rheumatology

1. All drugs that are legally marketed under the Federal Food Drug and Cosmetic Act (e.g., “grandfathered” drugs).

The regular voting members on the P&T Committee are not employees of CVS Caremark. The P&T Committee is charged with reviewing all drugs, including generics that are represented on the CVS Caremark approved drug lists. The approvals made are non-biased, quality driven and evidence based. The clinical merit of the drug, not the cost, is the primary consideration of the P&T Committee.

New members are included on the current P&T Committee on the basis of active involvement in clinical practice (patient care), whether in the academic, hospital or community setting; national recognition in their specialty; contributions to medical and/or pharmacy literature; and previous experience with pharmacy and therapeutics committees. The P&T Committee members are compensated for their participation with an appropriate honorarium and any travel/hotel expenses incurred in the process of serving on the P&T Committee.

The P&T Committee meets face-to-face on a quarterly basis and, as needed, on an ad hoc basis. CVS Caremark has a stringent conflict of interest policy for P&T Committee members. CVS Caremark requires each P&T Committee member to complete a Conflict of Interest Disclosure Statement annually. Completed Conflict of Interest Statements are carefully scrutinized by the CVS Caremark Chief Health Officer and Vice President of Clinical Affairs responsible for formulary development and maintenance. An objective party in the CVS Caremark Compliance Department verifies that conflict of interest requirements have been met. Through this careful review, CVS Caremark helps ensure that the P&T Committee meets or exceeds all federal and state regulatory requirements for conflict of interest, including CMS, and all industry accreditation standards, including URAC and the National Committee for Quality Assurance (NCQA).

Clinical Formulary Department

The P&T Committee functions are supported by the CVS Caremark Clinical Formulary Department. Clinical pharmacists in the Formulary Department prepare individual Drug Monographs and Therapeutic Class Reviews following a comprehensive review of available clinical literature. Numerous references and information resources are used to assist in the evaluation and review of the medications under consideration for formulary addition. These peer-reviewed resources are selected based on being accurate, reliable, current, comprehensive and well-respected.

Formulary Development and Maintenance Process

The P&T Committee bases decisions on scientific evidence, standards of practice, peer-reviewed medical literature, accepted clinical practice guidelines and other appropriate information. The P&T Committee reviews medications from a purely clinical perspective; it does not have access to nor does it consider any information on rebates, negotiated discounts or net costs. In alignment with this clinical perspective, the P&T Committee also reviews new drug evaluations, new U.S. Food and Drug Administration (FDA)-approved indications, new clinical line extensions and publications on new clinical practice trends.

In evaluating new drugs for formulary inclusion, the P&T Committee reviews the individual drug monographs, pivotal clinical trials accompanying the drug monographs, and therapeutic class reviews prepared by the Clinical Formulary Department. P&T Committee members share insights based on their clinical practice and the quality of published literature. FDA-approved drug products¹ are reviewed and considered for inclusion on the Formulary and standard formularies/drug lists by the P&T Committee. The P&T Committee also reviews and approves all utilization management (UM) criteria (i.e., prior authorization, step therapy and quantity limits outside of FDA-approved labeling).

The P&T Committee reviews all standard formularies annually. The review is conducted by drug class to assure that the formulary recommendations previously established are maintained and to recommend additional changes for clinical appropriateness if advisable based on newly available pharmaceutical information. In addition, the P&T Committee reviews all UM criteria annually.

1. All drugs that are legally marketed under the Federal Food Drug and Cosmetic Act (e.g., "grandfathered" drugs).

Review of new drugs or new indications for drugs in six classes is expedited. These classes include the immunosuppressants, antidepressants, antipsychotics, anticonvulsants, antiretrovirals and antineoplastics. For drugs in these classes, the P&T Committee makes a National Formulary and Medicare Part D Drug List status decision within 90 days of launch/market availability. For drugs outside of these classes, the P&T Committee makes a National Formulary decision within 90 days of launch/market availability and a Medicare Part D Drug List status decision within 180 days of launch/market availability. In addition, the P&T Committee will make formulary status decisions for the Managed Medicaid Drug List and Health Exchanges Formularies within 90 days of launch/market availability of newly FDA-approved drugs, or will provide a clinical justification if this timeframe is not met.

Formulary Review Committee

The FRC is an internal CVS Caremark committee that evaluates additional factors that may affect the formulary. For example, when two or more drugs produce similar clinical results, the FRC may evaluate factors such as:

- Utilization trends
- Impact of generic drugs or drugs designated to become available over-the-counter
- Brand and generic pipeline
- Line of business
- Plan sponsor cost
- Applicable manufacturer agreement
- Potential impact on members

The FRC makes business recommendations based on such factors to the P&T Committee. It is important to note that any drug product must first be deemed safe and effective by the P&T Committee before it is considered eligible for inclusion on a CVS Caremark Formulary or Drug List, and that any recommendations made by the FRC must be approved by the P&T Committee before implementation.

Formulary Management

The formulary is a dynamic tool that may be responsive to changes in the marketplace. It is intended to offer savings to clients while ensuring clinically appropriate products are available for members to use. Clients may choose to utilize CVS Caremark formularies for their plans or use them as the foundation for custom formularies.

Most drug classes have multiple generic and low-cost brand-name options that cover the same indications as more costly brand-name options in the same class. The generic and low-cost brand-name options offer similar efficacy and safety. Since many brand-name drugs do not provide clear clinical and/or financial advantages when compared to available drug options within the therapeutic class, several strategies are available to promote cost-effective use of medications ranging from tiered copayments, excluding products from coverage or having a closed plan design.

- Tiered copayments encourage members to use preferred formulary drugs. A three-tier formulary—typically with generics in the first, lowest cost tier; preferred brand-name drugs at second tier; and non-preferred brand-name drugs at the highest-cost third tier—is the option chosen by the vast majority of plan sponsors working with CVS Caremark.
- Many of our standard formularies also exclude certain products from coverage. The excluded products have alternatives available that will deliver cost savings to plan sponsors.
- Closed formularies will cover a set number of products and the others are not covered unless the claim goes through an override process.

1. All drugs that are legally marketed under the Federal Food Drug and Cosmetic Act (e.g., “grandfathered” drugs).

Within these plan designs, clients may opt to implement a formulary exception process where members, after meeting certain criteria, could have an excluded product covered, or could receive a third-tier product at a second-tier copay.

All formularies include generic drugs, and generics are typically in the lowest tier of pricing for members. Brand-name products may be considered preferred or non-preferred in the common three-tier plan design. Preferred brand-name drugs are encouraged with a lower copay than non-preferred brand-name products.

Formulary Compliance

Plan design, as noted above, is primary in achieving formulary compliance. CVS Caremark also provides plan sponsors with a range of solutions that encourage the use of generics and preferred brand-name drugs. Many CVS Caremark clients choose a plan that requires that a cost-effective generic be used before a single-source brand in the same therapeutic class.

Promotion of generics. When an A-rated generic becomes available, it is considered preferred and proactively encouraged. At that point, significant efforts are made to transition utilization to the lower-cost generic product. Client plan design will direct the effort and can be very aggressive and only cover the generic, or be more moderate and require the member to pay the difference between the brand-name drug and the generic if the brand-name product is chosen. Some clients may no longer cover the brand-name drug if a generic is available.

Member-directed formulary education. Members are notified when a new brand-name or generic product replaces a product they are using on the formulary. They are also notified if a product they are using is removed from the drug list, which could occur due to withdrawal from the market for safety reasons. If a non-preferred product has been dispensed at a retail pharmacy due to a prescription marked "Dispense as Written," the member may also be alerted about alternative formulary product(s) that could be available at a lower copayment.

The website, Caremark.com, in addition to providing a simple way to order prescription refills, allows the member to access information about their specific drug list, pricing information and generic availability, as well as general drug and health information.

Improving Member Experience and Outcomes

CVS Caremark is focused on helping members achieve their health and wellness goals through proper understanding and utilization of their medications. There are a number of strategies used to support members in their desire for positive outcomes including:

- Helping them become knowledgeable about their plan, benefit structure and drug therapy management options
- Helping them understand and comply with their prescribed therapies by providing:
 - Adherence counseling with all new prescriptions (face-to-face at CVS Pharmacy® locations, by letter through mail service and retail network)
 - Refill reminders (letters, Interactive Voice Response [IVR], Internet) and non-adherent prompts (letters and phone calls)
 - Availability of automatic prescription renewals and refills
 - Information about ways to save on prescriptions by using lower-cost alternatives or lower-cost channels
- Coordinating with plan sponsors to promote enrollment in wellness and health management programs and offering appropriate and timely immunizations
- Making formularies readily available on Caremark.com

1. All drugs that are legally marketed under the Federal Food Drug and Cosmetic Act (e.g., "grandfathered" drugs).

PHARMACY AND THERAPEUTICS (P&T) COMMITTEE May 22, 2018

The meeting of the Pharmacy and Therapeutics (P&T) Committee of the North Carolina State Health Plan for Teachers and State Employees (The Plan) was called to order at 6:30 P.M. (EST) on Tuesday, May 22, 2018, via webinar, accessible to the public through the Plan's website. Quorum was present.

MEMBERS PRESENT:

Carl Antolick III, PharmD, Clinical Pharmacist, NCSHP (Chair)
John J. Engemann, MD, Infectious Disease Specialist, Raleigh Infectious Disease Associates, PA
Matthew K. Flynn, MD, Founder, Family Dermatology
Jennifer Burch, PharmD, Owner, Central Compounding Center
Michael D. Spiritos, MD, Chief Medical Officer, Duke Raleigh Hospital
Peter Robie, MD, General Internist, Wake Forest Baptist Community Physicians
Tony Gurley, RPh, JD, Owner/Pharmacy Manager, Glenwood South Pharmacy + Market
John Anderson, MD, MPH, Chief Medical Officer, Duke Primary Care
Heather Renee Jarnigan, RPh, Clinical Advisor, CVS Health (non-voting member)

MEMBERS ABSENT:

David Konanc, MD, Neurologist, Raleigh Neurology Associates
Joseph Shanahan, MD, Owner, Shanahan Rheumatology & Immunotherapy

STATE HEALTH PLAN STAFF:

Tracy Linton, Sr. Director, Plan Benefits
Dee Jones, Executive Administrator
Lucy Barreto, DDS, MHA, Healthcare Product Manager

Welcome:

The Chairperson welcomed the Committee members and guests to the webinar and performed roll call.

Conflict of Interest

In compliance with the requirements of Chapter 138A-15(e) of the State Government Ethics Act the Chairperson read the NCSHP's Ethics Awareness & Conflict of Interest Reminder to the P&T Committee members and requested that members who have either an actual or perceived conflict of interest identify the conflict and refrain from discussion and voting in those matters as appropriate. No conflicts of interest were noted.

Minutes from August P&T Meeting:

The Chairperson asked the P&T Committee members to review the February 2018 P&T meeting minutes, which were distributed prior to the meeting. There were no additions or corrections to the minutes so they were approved as is.

Old Business:

The Chairperson summarized some of the Plan's recent formulary decisions. This includes the MME-based Opioid utilization management that was implemented on March 1, 2018; approved formulary changes and additions that were approved at the last P&T Meeting went into effect 5/1/2018; the removal of several prior authorization criteria which included buprenorphine, buprenorphine/naloxone, Noxafil, Vfend, & PPI Step Therapy; the Plan's adoption of Acticlate & Zegerid prior authorizations.

Formulary Updates:

Heather Renee Jarnigan presented CVS Caremark's Quarterly Formulary Updates which will be effective August 1, 2018. This included drug removals and additions to the formulary as well as tier changes.

Dr. Jarnigan reviewed the following branded products that will be removed from the formulary: Synaderm, & Praluent. All products being removed have comparable preferred generic formulary options available as alternative therapies. There were no comments or opposition from the Committee members so the changes were approved as presented. Dr. Jarnigan also discussed the removal of all other 510(k) products as they are expensive, have a number of alternatives, and are being used by pharmacies to improve their profits. These included Neutrasal, Salivamax, & HPR Plus. Dr. Flynn asked if the Plan or CVS had a broader strategy to excluding drug manufacturers and all their products if they are hyperinflating their prices. Dr. Jarnigan commented that CVS did not, and Dr. Antolick commented that although the Plan was evaluating removing all products marketed by Valeant Pharmaceuticals but noted challenges in creating an unbiased policy to apply to all manufacturers as they all tend to inflate drug prices at some point or another. Dr. Flynn also noted that there's no emollient better than white petroleum and therefore did not have any issues with removing the rest of the 510(k) products presented. The changes were approved as presented.

Dr. Jarnigan identified all of the branded products that will be moving to a non-preferred status, or uptiered. They include: Sivextro, Namenda, Coartem, Alinia, Azilect, Beyaz, Lotronex, Voltaren, Fluoxetine, Furadantin and Parlodel. All of these products have formulary alternatives that are preferred. Dr. Robie had a question about the usefulness of Coartem in treating malaria as he was unfamiliar with the drug. Dr. Jarnigan confirmed that the medication was not used regularly as there are other preferred options. The changes were then approved as presented.

Dr. Jarnigan identified all of the branded products that will be moving to a preferred status, or duntiered. They include: Orfadin and Mydayis. The members of the P&T Committee were not asked to vote on this change as it was a positive benefit change for the Plan membership.

Dr. Jarnigan identified all of the medications that were being removed from CVS's New-to-Market block and would be available as covered products effective May 1, 2018. All of the products were new formulations or strengths of medications that were already on the formulary and include: Xhance, Esmolol, Zenpep, Makena, Imbruvica, Daliresp, Mydayis, Vancomycin/NaCl, Betamethasone, Mitomycin, Clenpiq, Palonosetron, Citranatal, Hyperrab and Vyvanse.

The Committee members also reviewed the following new molecular entities: Calquence, Fasenna, Imfinzi, Ozempic, Trogarzo, Xermelo, Odactra and Symdeko. The members of the P&T Committee were not asked to vote on this change as it was a positive benefit change for the Plan membership.

The Committee reviewed new utilization management criteria which included: Dupixent Enhanced Specialty Guideline Management, Odactra Prior Authorization policy, Eucrisa Step Therapy and Prior Authorization policy and the Topical Corticosteroids Prior Authorization and Quantity Limit policy. Dr. Flynn had concerns regarding the Dupixent criteria as not being appropriate for younger patients that have large affected body surface area. He also would like to see a requirement for a trial of systemic agents (such as UVB treatment) before Dupixent would be approved. Dr. Antolick noted that these concerns would be evaluated and that the Plan would not implement the Dupixent enhanced criteria at this time. Dr. Flynn noted that the Eucrisa Step Therapy would be less burdensome for providers so he would recommend that criteria over the other. In regards to the Topical Corticosteroids criteria Dr. Flynn noted that branded topical corticosteroids have no real use as there are numerous generic formulations that can be used even if a patient has a reaction to one of them. Dr. Flynn was against quantity limits on generic topical corticosteroids due to their relative low cost compared to other therapy options. The Plan decided to implement the Eucrisa Step Therapy policy, Odactra Prior Authorization policy, and the Brand Name Dermatological Topical Corticosteroids Prior Authorization policy based on the Committee's feedback. The Plan will implementation these policies for an August 1, 2018 start date. The Committee also reviewed current utilization management criteria which included: Praluent Specialty Guideline Management, Repatha Specialty Guideline Management, Omega-3 Step Therapy and Prior Authorization, Prolia Specialty Guideline Management and Xgeva Specialty Guideline Management. No other revisions were recommended by the Committee.

Adjourn

Dee Jones addressed the Committee by thanking them for their service and informing them of the deadline for completing their compensation forms. She informed the Committee that Dr. Antolick will collect the paperwork from them once they provide him with a date and time for collection. The meeting was adjourned at approximately 8:00 P.M. (EST), with the next meeting scheduled for August 21, 2018 at 6:30 PM EST via webinar.



Carl Antolick III, Chair

Recent Plan Formulary Decisions (Effective August 1, 2018)

1. Exclusions

- a. Hyperinflated products are removed from the formulary due to exorbitant price increases; multi-sourced branded medications; drugs in a class with multiple agents
- b. Other more cost effective alternatives on the formulary
- c. Drugs being removed from the formulary August 1, 2018:
 - i. SYNERDERM (hyper-inflation)
 - ii. PRALUENT (multiple drugs in PCSK9i class)

2. Uptiers

- a. Movement of a drug from preferred status to non-preferred status
- b. Mostly multi-sourced branded drugs with available generics or other preferred options
- c. Drugs moving to a higher tier:
 - i. SIVEXTRO, NAMENDA XR, COARTEM, ALINIA, AZILECT, BEYAZ, LOTRONEX, VOLTAREN, fluoxetine 60 mg, FURADANTIN suspension, PARLODEL

3. Downtiers

- a. Movement of a drug from non-preferred status to preferred status
- b. Mostly single-sourced branded drugs without available generics
- c. Drugs moving to a lower tier:
 - i. ORFADIN, MYDAYIS

4. Removal of CVS Caremark's New to Market Block

- a. Additions of new drugs or new formulations to the formulary
- b. Typically drugs that have been released to the market recently, but up to one year
- c. Drug being added to the formulary:
 - i. XHANCE, ESMOLOL, ZENPEP, MAKENA, IMBRUVICA, DALIRESP, MYDAYIS, VANCOMY/NACL, BETAMETH, MITOMYCIN, CLENPIQ, PALONOSETRON, CITRANATAL, HYPERRAB, VYVANSE, IMFINZI, OZEMPIC, TROGARZO, XERMELO, ODACTRA, SYMDEKO

5. New Utilization Management Policies

- a. Prior authorization criteria to help control pharmacy trend
- b. New policies approved and enacted:
 - i. Eucrisa Step Therapy policy
 - ii. Oductra Prior Authorization policy
 - iii. Brand Name Dermatological Topical Corticosteroids Prior Authorization policy

Effective formulary management is foundational to helping clients mitigate the impact of rising drug costs while ensuring appropriate access.

In the current era of high launch prices for prescription drugs and continued escalation in existing brand drug prices, CVS Health remains focused on ensuring patients get access to the medications they need at the lowest possible cost. Since 2012, we have utilized formulary inclusion and preferred placement to negotiate better pricing and greater discounts to lower costs for payors, when there are clinically equivalent alternatives available in the same therapy class.

Our formulary strategies have helped keep costs in check for payors despite year-over-year price increases, while also improving adherence.

Managed Formularies with Drug Removals Reduce Costs, Improve Adherence

2017 Gross Cost PMPM*



- Standard Formulary without drug removals
- Managed Formularies with drug removals

2017 Overall Trend

Standard Formulary without drug removals:

4.2%

Managed Formularies with drug removals:

1.7%

By keeping drugs affordable, we also helped **more members stay on therapy** in key categories**

- ↑ Hyperlipidemia 1.8
- ↑ Hypertension 1.2
- ↑ Diabetes 1.2

For 2019, we are removing 23 drugs from our Standard Control Formulary. Additionally for 2019, we will add back four drugs to the formulary. **The vast majority of plan members we serve – 98.76 percent –** will be able to stay on their current therapy. For members who will need to change to an alternative medication, we utilize advanced analytics and predictive modeling to conduct personalized outreach to help members make the change and ensure continuity of care.

Since 2012 when we introduced our innovative approach to formulary management, through 2019, **our formulary strategy is expected to deliver more than \$19 billion in cumulative savings** to PBM clients by providing preferred formulary placement to lower-cost brands, and encouraging the transition to generics when appropriate.

*Age-adjusted, post-rebate.

CVS Health Managed Formularies: Include Standard with Opt-In to Drug Removals, Advanced Control Formulary, and Template Value Formulary

**Percentage point increase in the number of optimally adherent members.

Adherence results may vary based upon a variety of factors such as plan design, demographics and programs adopted by the plan. Client-specific modeling available upon request.

We vigilantly monitor marketplace events and continue to develop and refine our cost-control strategies to help ensure clients can effectively address evolving dynamics. On July 1, 2018, we made changes to the PCSK9i class for Standard Control Formulary, Advanced Control Formulary and Advanced Control Specialty Formulary to help clients manage spend on these expensive medications by only including the lower-cost, therapeutically equivalent alternative. Similarly, we will now re-evaluate existing specialty therapy classes on a quarterly basis to determine appropriate formulary placement, including potentially removing, adjusting the tier placement of, or adding products.

A list of all drug changes to our 2019 Standard Control Formulary will be available around October 1, 2018.

QUARTERLY FORMULARY UPDATES

(Effective October 1, 2018)

1. Exclusions

- a. Hyperinflated products are removed from the Formulary due to exorbitant price increases, and specialty products are removed to reduce trend
- b. There are other more cost effective alternatives on the formulary
- c. Drugs Affected:
 - i. LAZANDA, LEVORPHANOL, ZOLPIMIST
 - ii. Fluocinonide 0.1% cream, hydrocortisone 1% in absorbase ointment (Solubiomix LLC), benzonatate 150 MG capsules (Solubiomix LLC).

2. Uptiers

- a. Movement of a drug from preferred status to non-preferred status
- b. Mostly multi-sourced branded drugs with available generics or other preferred options
- c. Drugs Affected:
 - i. BENZACLIN GEL 1-5%, MIRAPEX, MINASTRIN 24 FE chewable, APTENSIO XR, & QUILLIVANT XR suspension

3. Downtiers

- a. Movement of a drug from non-preferred status to preferred status
- b. Mostly single-sourced branded drugs without available generics
- c. Drugs Affected:
 - i. None

4. Removal of CVS Caremark's New to Market Block

- a. Additions of new drugs or new formulations to the formulary
- b. Typically drugs that have been released to the market recently, but up to one year
- c. Drug Affected:
 - i. CRYSVITA, IDHIFA, RADICAVA, STERITALC, PREVYMIS, KEVZARA, ANDEXXA, NORVIR, DAUNORUBICIN, ARNUITY ELLIPTA, MYLOTARG, BENZNIDAZOLE, MEPSEVII, JYNARQUE, BIKTARVY, DAPTOMYCIN, QVAR REDIHALER, TESTOSTERONE GEL 1%, & COAGADEX.

Hyperinflation Exclusions – Effective 10/1/2018

Brand Name	Generic Name	Therapeutic Category	CVS Status Change	Alternatives	Rationale	Specialty	Cost per fill	# Utilizers (YT)
LAZANDA all Strengths 100, 300, 400 MCG	fentanyl nasal spray	Analgesics/ Opioid Analgesics	3 → not covered	fentanyl transmucosal lozenge, Fentora (fentanyl citrate buccal), and Subsys (fentanyl sublingual spray).	Availability of additional generic options for managing breakthrough pain in cancer patients.	NO	\$1400	0
ZOLPIMIST 5 MG	zolpidem tartrate oral spray	Central Nervous System/ Hypnotics/ Nonbenzodiazepines	3 → not covered	eszopiclone, zolpidem, zolpidem ext-rel, zolpidem sublingual, Belsomra (suvorexant), and Silenor (doxepin).	Availability of additional generic options for short-term treatment of insomnia.	NO	\$100	6
LEVORPHANOL 2 MG (generic only)	levorphanol tablets	Analgesics/ Opioid Analgesics	1 → not covered	fentanyl transdermal, hydromorphone ext-rel, methadone, morphine ext-rel, Hysingla ER (hydrocodone ext-rel), Nucynta ER (tapentadol ext-rel), Oxycontin (oxycodone ext-rel).	Availability of additional options for managing severe pain.	NO	\$4500	23
FLUOCINONIDE 0.1% cream (generic only)	fluocinonide cream	Dermatologicals - Topical Corticosteroids	2 → not covered	betamethasone dipropionate augmented; clobetasol; fluocinonide cream 0.05%; fluocinonide gel 0.05%; halobetasol	Availability of additional generic topical corticosteroids	NO	\$2800	730

Hyperinflation Exclusions – Effective 10/1/2018

Brand Name	Generic Name	Therapeutic Category	CVS Status Change	Alternatives	Rationale	Specialty	Cost per fill	# Utilizers (YT)
HYDROCORTISONE 1% IN ABSORBASE ointment (Solubiomix LLC)	hydrocortisone 1% in absorbase ointment	Dermatologicals - Topical Corticosteroids	2 → not covered	hydrocortisone oint 1% (NDC 00168002031 or 00168002016)	Availability of additional lower cost NDC's	NO	\$1900	38
BENZONATATE 150MG (Solubiomix LLC)	benzonatate 150mg capsules	Antitussives- Nonnarcotic	2 → not covered	benzonatate cap 150mg (NDC 67877057401 or 67877012801); benzonatate cap 100mg; benzonatate cap 200mg	Availability of additional lower cost NDC's	NO	\$3300	20

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use LAZANDA safely and effectively. See full prescribing information for LAZANDA.

LAZANDA® (Fentanyl) Nasal Spray CII Initial U.S. Approval: 1968

WARNING: LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL EXPOSURE; CYTOCHROME P450 3A4 INTERACTION; RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS; RISK OF MEDICATION ERRORS; ADDICTION, ABUSE, AND MISUSE; REMS; and NEONATAL OPIOID WITHDRAWAL SYNDROME

See full prescribing information for complete boxed warning.

- Serious, life-threatening, and/or fatal respiratory depression has occurred. Monitor closely, especially upon initiation or following a dose increase. Due to the risk of fatal respiratory depression, LAZANDA is contraindicated in opioid non-tolerant patients and in management of acute or postoperative pain, including headache/migraines. (4, 5.1)
- Accidental exposure to LAZANDA, especially in children, can result in a fatal overdose of fentanyl. Keep out of reach of children. Ensure proper storage and disposal. (5.2)
- Concomitant use with CYP3A4 inhibitors (or discontinuation of CYP3A4 inducers) can result in a fatal overdose of fentanyl. (5.3, 7.)
- Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death. Reserve concomitant prescribing for use in patients for whom alternative treatment options are inadequate; limit dosages and durations to the minimum required and follow patients for signs and symptoms of respiratory depression and sedation (5.4, 7).
- When prescribing, do not convert patients on a mcg per mcg basis from any other oral transmucosal fentanyl product to LAZANDA. (2.1, 5.5)
- When dispensing, do not substitute with any other fentanyl products (5.5)
- LAZANDA exposes users to risks of addiction, abuse, and misuse, which can lead to overdose and death. Assess patient's risk before prescribing and monitor regularly for these behaviors and conditions. (5.6)
- LAZANDA is available only through a restricted program called the TIRF REMS Access program. Outpatients, healthcare professionals who prescribe to outpatients, pharmacies, and distributors are required to enroll in the program. (5.7)
- Prolonged use of LAZANDA during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated. If prolonged opioid use is required in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available. (5.8)

-----RECENT MAJOR CHANGES-----

Boxed Warning	12/2016
Dosage and Administration (2)	12/2016
Contraindications (4)	12/2016
Warnings and Precautions (5)	12/2016

-----INDICATIONS AND USAGE-----

LAZANDA is an opioid agonist indicated for the management of breakthrough pain in cancer patients 18 years of age and older who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain. (1)

Patients considered opioid tolerant are those who are taking, for one week or longer, around-the-clock medicine consisting of at least 60 mg of oral morphine per day, at least 25 mcg of transdermal fentanyl per hour, at least 30 mg of oral oxycodone per day, at least 8 mg of oral hydromorphone per day, at least 25 mg oral oxymorphone per day, at least 60 mg oral hydrocodone per day, or an equianalgesic dose of another opioid daily for a week or longer. Patients must remain on around-the-clock opioids while taking LAZANDA.

Limitations of Use

- Not for use in opioid non-tolerant patients.
- Not for use in the management of acute or postoperative pain, including headache/migraine, dental pain, or in the emergency room.

- As a part of the TIRF REMS Access program, LAZANDA may be dispensed only to outpatients enrolled in the program [see *Warnings and Precautions* (5.7)]. For inpatient administration of LAZANDA (e.g., hospitals, hospices, and long-term care facilities that prescribe for inpatient use), patient and prescriber enrollment is not required.

-----DOSAGE AND ADMINISTRATION-----

- Patients must require and use around-the-clock opioids when taking LAZANDA. (1)
- Use the lowest effective dose for the shortest duration consistent with individual patient treatment goals (2.1)
- Individualize dosing based on the severity of pain, patient response, prior analgesic experience, and risk factors for addiction, abuse, and misuse. (2.1)
- Initial dose of LAZANDA for all patients is 100 mcg (single spray into one nostril). (2.2)
- Individually titrate to an effective dose, from 100 mcg to 200 mcg to 300 mcg to 400 mcg to 600 mcg, and up to a maximum of 800 mcg, that provides adequate analgesia with tolerable side effects. (2.3)
- Dose is a single spray into one nostril, a single spray into each nostril (2 sprays), three single sprays (alternating nostrils), or two sprays into each nostril (4 sprays); no more than four doses per 24 hours. (2.2, 2.3)
- Wait at least 2 hours before treating another episode of breakthrough pain with LAZANDA. (2.2)
- During any episode, if adequate pain relief is not achieved within 30 minutes, the patient may use a rescue medication as directed by their healthcare provider. (2.3)
- When opioid therapy is no longer required, consider discontinuing LAZANDA along with a gradual downward dosing of other opioids to minimize possible withdrawal effects. (2.6)

-----DOSAGE FORMS AND STRENGTHS-----

- Nasal spray: each spray delivers 100 mcL of solution containing either 100 mcg, 300 mcg or 400 mcg fentanyl base. (3) Supplied in a 5 mL bottle containing 8 sprays.

-----CONTRAINDICATIONS-----

- Opioid non-tolerant patients (4)
- Management of acute or postoperative pain including headache/migraine and dental pain, or in emergency department. (4)
- Significant respiratory depression. (4)
- Acute or severe bronchial asthma in an unmonitored setting or in absence of resuscitative equipment. (4)
- Known or suspected gastrointestinal obstruction, including paralytic ileus. (4)
- Known hypersensitivity to fentanyl or components of LAZANDA. (4)

-----WARNINGS AND PRECAUTIONS-----

- Life-Threatening Respiratory Depression in Patients with Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients: Monitor closely, particularly during initiation and titration. (5.9)
- Serotonin Syndrome: Potentially life-threatening condition could result from concomitant serotonergic drug administration. Discontinue LAZANDA if serotonin syndrome is suspected. (5.10)
- Adrenal Insufficiency: If diagnosed, treat with physiologic replacement of corticosteroids, and wean patient off of the opioid. (5.11)
- Severe Hypotension: Monitor during dosage initiation and titration. Avoid use of LAZANDA in patients with circulatory shock. (5.12)
- Risks of Use in Patients with Increased Intracranial Pressure, Brain Tumors, Head Injury, or Impaired Consciousness: Monitor for sedation and respiratory depression. Avoid use of LAZANDA in patients with impaired consciousness or coma. (5.13)

-----ADVERSE REACTIONS-----

- Most common adverse reactions (incidence $\geq 5\%$) were vomiting, nausea, dizziness, pyrexia, and constipation. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact West Therapeutic Development, LLC at 1-844-4LAZANDA or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

-----DRUG INTERACTIONS-----

- Mixed Agonist/Antagonist and Partial Agonist Opioid Analgesics: Avoid use with LAZANDA because they may reduce analgesic effect of LAZANDA or precipitate withdrawal symptoms. (7)

-----USE IN SPECIFIC POPULATIONS-----

- Pregnancy: May cause fetal harm. (8.1)
- Lactation: Not Recommended. (8.2)
- Renal and Hepatic Impairment: Administer LAZANDA with caution. (8.6)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 05/2018

FULL PRESCRIBING INFORMATION: CONTENTS

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WARNING: LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL EXPOSURE; CYTOCHROME P450 3A4 INTERACTION; CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS; RISK OF MEDICATION ERRORS; ADDICTION, ABUSE, AND MISUSE; REMS; AND NEONATAL OPIOID WITHDRAWAL SYNDROME

Life-Threatening Respiratory Depression

Serious, life-threatening, and/or fatal respiratory depression has occurred in patients treated with LAZANDA, including following use in opioid non-tolerant patients and improper dosing. Monitor for respiratory depression, especially during initiation of LAZANDA or following a dose increase. The substitution of LAZANDA for any other fentanyl product may result in fatal overdose [see *Warnings and Precautions* (5.1)].

Due to the risk of respiratory depression, LAZANDA is contraindicated in the management of acute or postoperative pain including headache/migraine and in opioid non-tolerant patients [see *Contraindications* (4)].

Accidental Exposure

Accidental exposure of even one dose of LAZANDA, especially in children, can result in a fatal overdose of fentanyl [see *Warnings and Precautions* (5.1)]. Death has been reported in children who have accidentally ingested transmucosal immediate-release fentanyl products. LAZANDA must be kept out of reach of children [see *Warnings and Precautions* (5.2)].

Cytochrome P450 3A4 Interaction

The concomitant use of LAZANDA with all cytochrome P450 3A4 inhibitors may result in an increase in fentanyl plasma concentrations, which could increase or prolong adverse reactions and may cause potentially fatal respiratory depression. In addition, discontinuation of a concomitantly used cytochrome P450 3A4 inducer may result in an increase in fentanyl plasma concentration. Monitor patients receiving LAZANDA and any CYP3A4 inhibitor or inducer [see *Warnings and Precautions* (5.3), *Drug Interactions* (7), *Clinical Pharmacology* (12.2)].

Risks from Concomitant Use with Benzodiazepines or Other CNS Depressants

Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death [see *Warnings and Precautions* (5.4), *Drug Interactions* (7)].

- Reserve concomitant prescribing of LAZANDA and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate.
- Limit dosages and durations to the minimum required.
- Follow patients for signs and symptoms of respiratory depression and sedation.

Risk of Medication Errors

Substantial differences exist in the pharmacokinetic profile of LAZANDA compared to other fentanyl products that result in clinically important differences in the extent of absorption of fentanyl that could result in fatal overdose [see *Dosage and Administration* (2.1), *Warnings and Precautions* (5.5)].

- When prescribing, do not convert patients on a mcg per mcg basis from any other fentanyl products to LAZANDA.
- When dispensing, do not substitute a LAZANDA prescription for other fentanyl products.

Neonatal Opioid Withdrawal Syndrome

Prolonged use of LAZANDA during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available [see *Warnings and Precautions* (5.8)]

1 INDICATIONS AND USAGE

LAZANDA is indicated for the management of breakthrough pain in cancer patients 18 years of age and older who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain. Patients considered opioid tolerant are those who are taking, for one week or longer, around-the-clock medicine consisting of at least 60 mg of oral morphine per day, or at least 25 mcg of transdermal fentanyl per hour, or at least 30 mg oral oxycodone per day, or at least 8 mg oral hydromorphone per day, or at least 25 mg oral oxycodone per day, or at least 60 mg oral hydrocodone per day, or an equianalgesic dose of another opioid for a week or longer. Patients must remain on around-the-clock opioids when taking LAZANDA.

Limitations of Use:

- Not for use in opioid non-tolerant patients.
- Not for use in the management of acute or postoperative pain, including headache/migraine, dental pain, or in the emergency department [see *Contraindications* (3)].
- As a part of the TIRF REMS Access program, LAZANDA may be dispensed only to outpatients enrolled in the program. [see *Warnings and Precautions* (5.7)]. For inpatient administration of LAZANDA (e.g. hospitals, hospices, and long-term care facilities that prescribe for inpatient use), patient enrollment is not required.

2 DOSAGE AND ADMINISTRATION

2.1 Important Dosage and Administration Instructions

- Healthcare professionals who prescribe LAZANDA on an outpatient basis must enroll in the TIRF REMS Access program and comply with the requirements of the REMS to ensure safe use of LAZANDA [see *Warnings and Precautions* (5.7)].
- Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals.
- It is important to minimize the number of strengths available to patients at any time to prevent confusion and possible overdose.
- Initiate the dosing regimen for each patient individually, taking into account the patient's severity of pain, patient response, prior analgesic treatment experience, and risk factors for addiction, abuse, and misuse.
- Monitor patients closely for respiratory depression, especially within the first 24-72 hours of initiating therapy and following dosage increases with LAZANDA and adjust the dosage accordingly [see *Warnings and Precautions* (5.1)].
- Instruct patients and caregivers to take steps to store LAZANDA securely and to properly dispose of unused LAZANDA as soon as no longer needed [see *Warnings and Precautions* (5.2, 5.6), *Patient Counseling Information* (17)].
- LAZANDA is not bioequivalent with other fentanyl products. Do not convert patients on a mcg per mcg basis from other fentanyl products. There are no conversion directions available for patients on any other fentanyl products. (Note: This includes oral, transdermal, or parenteral formulations of fentanyl.) [see *Warnings and Precautions* (5.5)].
- LAZANDA is NOT a generic version of any other oral transmucosal fentanyl product [see *Warnings and Precautions* (5.5)].

2.2 Initial Dosage

Initiate treatment with LAZANDA for all patients (including those switching from another fentanyl product) using ONE 100 mcg spray of LAZANDA (1 spray in one nostril).

Repeat Dosing

- If adequate analgesia is obtained within 30 minutes of administration of the 100 mcg single spray, treat subsequent episodes of breakthrough pain with this dose.
- If adequate analgesia is not achieved with the first 100 mcg dose, dose escalate in a step-wise manner over consecutive episodes of breakthrough pain until adequate analgesia with tolerable side effects is achieved.
- Patients MUST wait at least 2 hours before treating another episode of breakthrough cancer pain with LAZANDA.

2.3 Titration and Maintenance of Therapy

Titration

The objective of dose titration is to identify an effective and tolerable maintenance dose for ongoing management of breakthrough cancer pain episodes. The effective and tolerable dose of LAZANDA will be determined by dose titration in individual patients.

Titration steps: If adequate analgesia is not achieved with the first 100 mcg dose, dose escalate in a step-wise manner over consecutive episodes of breakthrough pain until adequate analgesia with tolerable side effects is achieved.

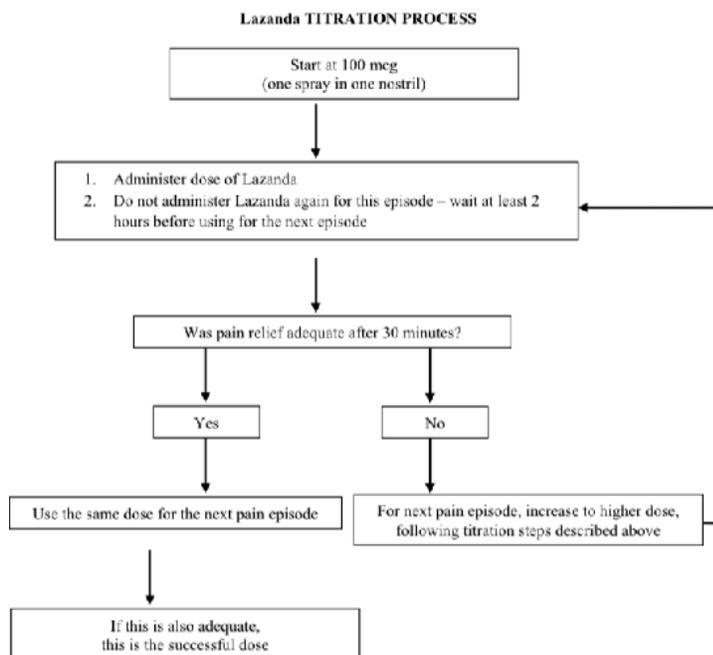
Patients MUST wait at least 2 hours before treating another episode of breakthrough cancer pain with LAZANDA.

The titration steps should be:

LAZANDA Dose	How to administer the dose
100 mcg	Using the 100 mcg dose; one spray in one nostril
200 mcg	Using the 100 mcg dose; a total of two sprays, as one spray in each nostril
300 mcg	Using the 100 mcg dose; a total of three sprays, alternating one spray in right nostril, second spray in left nostril, third spray in right nostril
400 mcg	Using the 100 mcg dose, a total of four sprays, alternating one spray in right nostril, second spray in left nostril, third spray in right nostril, and fourth spray in left nostril OR Using the 400 mcg dose; one spray in one nostril
600 mcg	Using the 300 mcg dose; total of two sprays, as one spray in each nostril
800 mcg	Using the 400 mcg dose; total of two sprays, as one spray in each nostril

Patients should confirm the dose of LAZANDA that works for them with a second episode of breakthrough pain and review their experience with their physicians to determine if that dose is appropriate, or whether a further adjustment is warranted.

The safety and efficacy of doses higher than 800 mcg have not been evaluated in clinical studies. Avoid the use of a combination of dose strengths to treat an episode as this may cause confusion and dosing errors.



In order to minimize the risk of LAZANDA-related adverse reactions and to identify the appropriate dose, it is imperative that patients be supervised closely by health professionals during the titration process.

Maintenance Therapy

Once an appropriate dose has been established, instruct patients to use that dose for each subsequent breakthrough cancer pain episode. Limit LAZANDA use to four or fewer doses per day.

Patients MUST wait at least 2 hours before treating another episode of breakthrough cancer pain with LAZANDA.

During any episode of breakthrough cancer pain, if there is inadequate pain relief after 30 minutes following LAZANDA dosing or if a separate episode of breakthrough cancer pain occurs before the next dose of LAZANDA is permitted (i.e. within 2 hours), the patients may use a rescue medication as directed by their healthcare provider.

2.4 Dose Re-Adjustment

If the response (analgesia or adverse reactions) to the titrated LAZANDA dose markedly changes, an adjustment of dose may be necessary to ensure that an appropriate dose is maintained.

If more than four episodes of breakthrough pain are experienced per day, re-evaluate the dose of the long-acting opioid used for persistent underlying

cancer pain. If the long-acting opioid or dose of long-acting opioid is changed, re-evaluate and re-titrate the LAZANDA dose as necessary to ensure the patient is on an appropriate dose.

Limit the use of LAZANDA to treat four or fewer episodes of breakthrough pain per day.

It is imperative that any dose re-titration is monitored carefully by a healthcare professional.

2.5 Administration of LAZANDA

Instruct patients on the proper use of LAZANDA.

1. Prime the device before use by spraying into the pouch (4 sprays in total). If the product has not been used for 5 days, re-prime by spraying once. For priming, follow the instructions provided [See *Medication Guide*].
2. Insert the nozzle of the LAZANDA bottle a short distance (about ½ inch or 1 cm) into the nose and point towards the bridge of the nose, tilting the bottle slightly.
3. Press down firmly on the finger grips until they hear a “click” and the number in the counting window advances by one.

Advise patients that the fine mist spray is not always felt on the nasal mucosal membrane and to rely on the audible click and the advancement of the dose counter to confirm a spray has been administered.

2.6 Discontinuation of Therapy

For patients no longer requiring opioid therapy, consider discontinuing LAZANDA along with a gradual downward titration of other opioids to minimize possible withdrawal effects. In patients who continue to take their chronic opioid therapy for persistent pain but no longer require treatment for breakthrough pain, LAZANDA therapy can usually be discontinued immediately [see *Drug Abuse and Dependence* (9.3)].

2.7 Disposal of LAZANDA

Instruct patients and caregivers to properly dispose of all unused, partially used and used LAZANDA bottles. The remaining liquid in all bottles must be sprayed into the pouch, provided in the pack, for safe disposal as soon as possible.

Instruct the patient how to do this correctly. If there are any unwanted therapeutic sprays remaining in the bottle, instruct the patient to spray these into the pouch until the number “8” appears in the counting window and there are no more full therapeutic sprays obtainable from the bottle. After the counter has advanced to “8”, the patient should continue to push down on the finger grips a total of four times in order to expel any residual medicine from the bottle. After the 8 therapeutic sprays have been emitted, the patient will not hear a click and the counter will not advance beyond “8”; further sprays emitted will not be full sprays and should always be trapped in the pouch, not used therapeutically.

Instruct the patient and caregiver to seal the pouch and place both it and the empty bottle into the child-resistant storage container. Patients must wash their hands with soap and water immediately after handling the pouch.

The patient must discard the child-resistant container containing the pouch and the bottle in the trash.

The patient or caregiver must continue to store the LAZANDA bottle in the specially provided child-resistant container and the pouch out of the reach of children until proper disposal, as described above, is possible.

Instruct the patient to dispose of the LAZANDA bottle and start a new one if it has been 60 days or more since they first used the bottle of LAZANDA.

In the event that caregivers or patients require additional assistance with the disposal of LAZANDA bottles, call the West Therapeutic Development, LLC toll-free number (1-866-458-6389).

3 DOSAGE FORMS AND STRENGTHS

Nasal Spray, LAZANDA is formulated to deliver a spray of 100 mcL of solution containing 100 mcg, 300 mcg or 400 mcg fentanyl base.

4 CONTRAINDICATIONS

LAZANDA is contraindicated in:

- Opioid non-tolerant patients: Life-threatening respiratory depression and death could occur at any dose in opioid non-tolerant patients [see *Indications and Usage* (1); *Warnings and Precautions* (5.1)].
- Acute or postoperative pain including headache/migraine and dental pain, or in the emergency department.
- Acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment [see *Warnings and Precautions* (5.9)].
- Known or suspected gastrointestinal obstruction, including paralytic ileus [see *Warnings and Precautions* (5.14)].

Known hypersensitivity to fentanyl or components of LAZANDA (e.g., anaphylaxis, hypersensitivity)[see *Adverse Reactions* (6.2)].

5 WARNINGS AND PRECAUTIONS

5.1 Life-Threatening Respiratory Depression

Serious, life-threatening, or fatal respiratory depression has been reported with the use of opioids, even when used as recommended. Respiratory depression, if not immediately recognized and treated, may lead to respiratory arrest and death. Management of respiratory depression may include close observation, supportive measures, and use of opioid antagonists, depending on the patient's clinical status [see *Overdosage* (10)].

Carbon dioxide (CO₂) retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids.

While serious, life-threatening, or fatal respiratory depression can occur at any time during the use of LAZANDA, the risk is greatest during the initiation of therapy or following a dosage increase. Monitor patients closely for respiratory depression, especially within the first 24-72 hours of initiating therapy with and following dosage increases of LAZANDA.

To reduce the risk of respiratory depression, proper dosing and titration of LAZANDA are essential [see *Dosage and Administration* (2.1)]. Overestimating the LAZANDA dosage can result in a fatal overdose with the first dose. The substitution of LAZANDA for any other fentanyl product may result in fatal overdose [see *Warnings and Precautions* (5.5)].

LAZANDA could be fatal to individuals for whom it is not prescribed and for those who are not opioid-tolerant.

Accidental ingestion of (or exposure to) even one dose of LAZANDA, especially by (in) children, can result in respiratory depression and death due to an overdose of fentanyl [see *Warnings and Precautions* (5.2)].

5.2 Increased Risk of Overdose in Children Due to Accidental Ingestion or Exposure

Death has been reported in children who have accidentally ingested transmucosal immediate-release fentanyl products.

Patients and their caregivers must be informed that LAZANDA contains a medicine in an amount which can be fatal to a child. Physicians and dispensing pharmacists must specifically question patients or caregivers about the presence of children in the home (on a full time or visiting basis) and counsel them regarding the dangers to children from inadvertent exposure.

Patients and their caregivers must be instructed to keep both used and unused dosage units out of the reach of children. While all units should be disposed of immediately after use, partially consumed units represent a special risk to children. In the event that a unit is not completely consumed it must be properly disposed as soon as possible [see *Patient Counseling Information* (17)].

Detailed instructions for the proper storage, administration, disposal, and important instructions for managing an overdose of LAZANDA are provided in the LAZANDA Medication Guide. Encourage patients to read this information in its entirety and give them an opportunity to have their questions answered.

5.3 Risks of Concomitant Use or Discontinuation of Cytochrome P450 3A4 Inhibitors and Inducers

Concomitant use of LAZANDA with a CYP3A4 inhibitor, such as macrolide antibiotics (e.g., erythromycin), azole-antifungal agents (e.g., ketoconazole), and protease inhibitors (e.g., ritonavir), may increase plasma concentrations of fentanyl and prolong opioid adverse reactions, which may cause potentially fatal respiratory depression [see *Warnings and Precautions* (5.2)], particularly when an inhibitor is added after a stable dose of LAZANDA is achieved. Similarly, discontinuation of a CYP3A4 inducer, such as rifampin, carbamazepine, and phenytoin, in LAZANDA treated patients may increase fentanyl plasma concentrations and prolong opioid adverse reactions. When using LAZANDA with CYP3A4 inhibitors or discontinuing CYP3A4 inducers in LAZANDA treated patients, monitor patients closely at frequent intervals and consider dosage reduction of LAZANDA until stable drug effects are achieved [see *Dosage and Administration* (2.3), *Drug Interactions* (7)].

Concomitant use of LAZANDA with CYP3A4 inducers or discontinuation of an CYP3A4 inhibitor could decrease fentanyl plasma concentrations, decrease opioid efficacy or, possibly, lead to a withdrawal syndrome in a patient who had developed physical dependence to fentanyl. When using LAZANDA with CYP3A4 inducers or discontinuing CYP3A4 inhibitors, monitor patients closely at frequent intervals and consider increasing the opioid dosage if needed to maintain adequate analgesia or if symptoms of opioid withdrawal occur [see *Dosage and Administration* (2.6), *Drug Interactions* (7)].

5.4 Risks from Concomitant Use with Benzodiazepines or Other CNS Depressants

Profound sedation, respiratory depression, coma, and death may result from the concomitant use of LAZANDA with benzodiazepines or other CNS depressants (e.g., non-benzodiazepine sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol). Because of these risks, reserve concomitant prescribing of these drugs for use in patients

for whom alternative treatment options are inadequate.

Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioid analgesics alone. Because of similar pharmacological properties, it is reasonable to expect similar risk with the concomitant use of other CNS depressant drugs with opioid analgesics [see *Drug Interactions* (7)].

If the decision is made to prescribe a benzodiazepine or other CNS depressant concomitantly with an opioid analgesic, prescribe the lowest effective dosages and minimum durations of concomitant use. In patients already receiving an opioid analgesic, prescribe a lower initial dose of the benzodiazepine or other CNS depressant than indicated in the absence of an opioid, and titrate based on clinical response. If an opioid analgesic is initiated in a patient already taking a benzodiazepine or other CNS depressant, prescribe a lower initial dose of the opioid analgesic, and titrate based on clinical response. Follow patients closely for signs and symptoms of respiratory depression and sedation.

Advise both patients and caregivers about the risks of respiratory depression and sedation when LAZANDA is used with benzodiazepines or other CNS depressants (including alcohol and illicit drugs). Advise patients not to drive or operate heavy machinery until the effects of concomitant use of the benzodiazepine or other CNS depressant have been determined. Screen patients for risk of substance use disorders, including opioid abuse and misuse, and warn them of the risk for overdose and death associated with the use of additional CNS depressants including alcohol and illicit drugs [see *Drug Interactions* (7), *Patient Counseling Information* (17)].

5.5 Risk of Medication Errors

When prescribing, DO NOT convert a patient to LAZANDA from any other fentanyl product on a mcg per mcg basis as LAZANDA and other fentanyl products are not equivalent on a microgram per microgram basis.

LAZANDA is NOT a generic version of other transmucosal immediate release fentanyl (TIRF) formulations. When dispensing, DO NOT substitute a LAZANDA prescription for any other TIRF formulation under any circumstances. Other TIRF formulations and LAZANDA are not equivalent. Substantial differences exist in the pharmacokinetic profile of LAZANDA compared to other fentanyl products including other TIRF formulations that result in clinically important differences in the rate and extent of absorption of fentanyl. As a result of these differences, the substitution of LAZANDA for any other fentanyl product may result in a fatal overdose.

There are no safe conversion directions available for patients on any other fentanyl products. (Note: This includes oral, transdermal, or parenteral formulations of fentanyl.) Therefore, for opioid tolerant patients, the initial dose of LAZANDA should always be ONE 100 mcg spray. Each patient should be individually titrated to provide adequate analgesia while minimizing side effects [see *Dosage and Administration* (2.3)].

5.6 Addiction, Abuse, and Misuse

LAZANDA contains fentanyl a Schedule II controlled substance. As an opioid, LAZANDA exposes users to the risks of addiction, abuse, and misuse [see *Drug Abuse and Dependence* (9)].

Although the risk of addiction in any individual is unknown, it can occur in patients appropriately prescribed LAZANDA. Addiction can occur at recommended dosages and if the drug is misused or abused.

Assess each patient's risk for opioid addiction, abuse, or misuse prior to prescribing LAZANDA, and monitor all patients receiving LAZANDA for the development of these behaviors and conditions. Risks are increased in patients with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depression). The potential for these risks should not, however, prevent the proper management of pain in any given patient. Patients at increased risk may be prescribed opioids such as LAZANDA, but use in such patients necessitates intensive counseling about the risks and proper use of LAZANDA along with intensive monitoring for signs of addiction, abuse, and misuse.

Opioids are sought by drug abusers and people with addiction disorders and are subject to criminal diversion. Consider these risks when prescribing or dispensing LAZANDA. Strategies to reduce these risks include prescribing the drug in the smallest appropriate quantity and advising the patient on the proper disposal of unused drug [see *Patient Counseling Information* (17)]. Contact local state professional licensing board or state controlled substances authority for information on how to prevent and detect abuse or diversion of this product.

5.7 Transmucosal Immediate Release Fentanyl (TIRF) Risk Evaluation and Mitigation Strategy (REMS) Access Program

Because of the risk of misuse, abuse, addiction, and overdose [see *Warnings and Precautions* (5.6)], LAZANDA is available only through a restricted program under a REMS called the TIRF REMS Access program. Under the TIRF REMS Access program, outpatients, healthcare professionals who prescribe to outpatients, pharmacies, and distributors must enroll in the program. For inpatient ad-

ministration (e.g. hospitals, hospices, and long-term care facilities that prescribe for inpatient use) of LAZANDA, patient and prescriber enrollment is not required.

Required components of the TIRF REMS Access program are:

- Healthcare professionals who prescribe LAZANDA must review the prescriber educational materials for the TIRF REMS Access program, enroll in the program, and comply with the REMS requirements.
- To receive LAZANDA, outpatients must understand the risks and benefits and sign a Patient-Prescriber Agreement.
- Pharmacies that dispense LAZANDA must enroll in the program and agree to comply with the REMS requirements.
- Wholesalers and distributors that distribute LAZANDA must enroll in the program and distribute only to authorized pharmacies.
- Further information, including a list of qualified pharmacies/distributors, is available at www.tirfremssaccess.com or by calling 1-866-822-1483.

5.8 Neonatal Opioid Withdrawal Syndrome

Prolonged use of LAZANDA during pregnancy can result in withdrawal in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. Observe newborns for signs of neonatal opioid withdrawal syndrome and manage accordingly. Advise pregnant women using opioids for a prolonged period of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available [see *Use in Specific Populations* (8.1), *Patient Counseling Information* (17)].

5.9 Life-Threatening Respiratory Depression in Patients with Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients

The use of LAZANDA in patients with acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment is contraindicated.

Patients with Chronic Pulmonary Disease: LAZANDA-treated patients with significant chronic obstructive pulmonary disease or cor pulmonale, and those with a substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression are at increased risk of decreased respiratory drive including apnea, even at recommended dosages of LAZANDA [see *Warnings and Precautions* (5.1)].

Elderly, Cachectic, or Debilitated Patients: Life-threatening respiratory depression is more likely to occur in elderly, cachectic, or debilitated patients because they may have altered pharmacokinetics or altered clearance compared to younger, healthier patients [see *Warnings and Precautions* (5.1)].

Monitor such patients closely, particularly when initiating and titrating LAZANDA and when LAZANDA is given concomitantly with other drugs that depress respiration [see *Warnings and Precautions* (5.1)].

Alternatively, consider the use of non-opioid analgesics in these patients.

5.10 Serotonin Syndrome with Concomitant Use of Serotonergic Drugs

Cases of serotonin syndrome, a potentially life-threatening condition, have been reported during concomitant use of fentanyl with serotonergic drugs. Serotonergic drugs include selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), triptans, 5-HT₃ receptor antagonists, drugs that affect the serotonergic neurotransmitter system (e.g., mirtazapine, trazodone, tramadol), and drugs that impair metabolism of serotonin (including MAO inhibitors, both those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue) [see *Drug Interactions* (7)]. This may occur within the recommended dosage range.

Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination, rigidity), and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). The onset of symptoms generally occurs within several hours to a few days of concomitant use, but may occur later than that. Discontinue LAZANDA if serotonin syndrome is suspected.

5.11 Adrenal Insufficiency

Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use. Presentation of adrenal insufficiency may include non-specific symptoms and signs including nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. If adrenal insufficiency is suspected, confirm the diagnosis with diagnostic testing as soon as possible. If adrenal insufficiency is diagnosed, treat with physiologic replacement doses of corticosteroids. Wean the patient off of the opioid to allow adrenal function to recover and continue corticosteroid treatment until adrenal function recovers. Other opioids may be tried as some cases reported use of a different opioid without recurrence of adrenal insufficiency. The information available does not identify any particular opioids as being more likely to be associated with adrenal insufficiency.

5.12 Severe Hypotension

LAZANDA may cause severe hypotension including orthostatic hypotension and syncope in ambulatory patients. There is increased risk in patients whose ability to maintain blood pressure has already been compromised by a reduced blood volume or concurrent administration of certain CNS depressant drugs (e.g. phenothiazines or general anesthetics) [see *Drug Interactions (7)*]. Monitor these patients for signs of hypotension after initiating or titrating the dosage of LAZANDA. In patients with circulatory shock, LAZANDA may cause vasodilation that can further reduce cardiac output and blood pressure. Avoid the use of LAZANDA in patients with circulatory shock.

5.13 Risks of Use in Patients with Increased Intracranial Pressure, Brain Tumors, Head Injury, or Impaired Consciousness

In patients who may be susceptible to the intracranial effects of CO₂ retention (e.g., those with evidence of increased intracranial pressure or brain tumors), LAZANDA may reduce respiratory drive, and the resultant CO₂ retention can further increase intracranial pressure. Monitor such patients for signs of sedation and respiratory depression, particularly when initiating therapy with LAZANDA.

Opioids may also obscure the clinical course in a patient with a head injury. Avoid the use of LAZANDA in patients with impaired consciousness or coma.

5.14 Risks of Use in Patients with Gastrointestinal Conditions

LAZANDA is contraindicated in patients with known or suspected gastrointestinal obstruction, including paralytic ileus.

The fentanyl in LAZANDA may cause spasm of the sphincter of Oddi. Opioids may cause increases in serum amylase. Monitor patients with biliary tract disease, including acute pancreatitis for worsening symptoms.

5.15 Increased Risk of Seizures in Patients with Seizure Disorders

The fentanyl in LAZANDA may increase the frequency of seizures in patients with seizure disorders, and may increase the risk of seizures occurring in other clinical settings associated with seizures. Monitor patients with a history of seizure disorders for worsened seizure control during LAZANDA therapy.

5.16 Risks of Driving and Operating Machinery

LAZANDA may impair the mental or physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery. Warn patients not to drive or operate dangerous machinery unless they are tolerant to the effects of LAZANDA and know how they will react to the medication.

5.17 Cardiac Disease

Intravenous fentanyl may produce bradycardia. Therefore, use LAZANDA with caution in patients with bradyarrhythmias.

6 ADVERSE REACTIONS

The following serious adverse reactions are described, or described in greater detail, in other sections:

- Life-Threatening Respiratory Depression [see *Warnings and Precautions (5.1)*]
- Interactions with benzodiazepines and other CNS Depressants [see *Warnings and Precautions (5.4)*]
- Addiction, Abuse, and Misuse [see *Warnings and Precautions (5.6)*]
- Neonatal Opioid Withdrawal Syndrome [see *Warnings and Precautions (5.8)*]
- Serotonin Syndrome [see *Warnings and Precautions (5.10)*]
- Adrenal Insufficiency [see *Warnings and Precautions (5.11)*]
- Severe Hypotension [see *Warnings and Precautions (5.12)*]
- Gastrointestinal Adverse Reactions [see *Warnings and Precautions (5.14)*]
- Seizures [see *Warnings and Precautions (5.15)*]

6.1 Clinical Studies Experience

Because clinical trials are conducted under widely varying conditions, adverse event rates observed in the clinical trials of a drug product cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of LAZANDA has been evaluated in a total of 523 opioid-tolerant patients with breakthrough cancer pain. The average duration of therapy in patients in the long-term study was 73 days, with 153 patients being treated for over 3 months. Patients continuing into the open-label extension period of the safety study have been treated for up to 26 months.

The clinical trials of LAZANDA were designed to evaluate safety and efficacy in treating breakthrough cancer pain; all patients were also taking concomitant opioids, such as sustained-release morphine, sustained-release oxycodone, or transdermal fentanyl, for their persistent cancer pain. The adverse reaction data presented in Table 1 reflect the actual percentage of patients experiencing each adverse effect among patients who received LAZANDA for breakthrough cancer pain along with a concomitant opioid for persistent cancer pain. There has been no attempt to correct for concomitant use of other opioids, duration of LAZANDA therapy, or cancer-related symptoms. Adverse events are included regardless of causality or severity. Table 1 lists adverse reactions with an overall frequency of 5% or greater within the total population that occurred during

titration by maximum dose received. The ability to assign LAZANDA a dose-response relationship to these adverse events is limited by the titration schemes used in these studies.

Table 1: Adverse Reactions That Occurred During Titration at a Frequency of >5%

System Organ Class MedDRA preferred term, n (%)	100 mcg (N=483)	200 mcg (N=380)	400 mcg (N=301)	800 mcg (N=161)	Total (N=516)
Gastrointestinal disorders					
Nausea	19 (4)	6 (2)	6 (2)	5 (3)	35 (7)
Vomiting	14 (3)	10 (3)	9 (3)	1 (1)	33 (6)
Nervous system disorders					
Dizziness	14 (3)	11 (3)	6 (2)	4 (2)	31 (6)

Table 2 lists, by dose, adverse reactions with an overall frequency of $\geq 5\%$ within the total population that occurred after a final titrated dose had been determined.

Table 2: Adverse Reactions That Occurred During Maintenance Treatment at a Frequency of $\geq 5\%$

System Organ Class MedDRA preferred term, n (%)	100 mcg (N=61)	200 mcg (N=68)	400 mcg (N=109)	800 mcg (N=108)	Total (N=346)
Gastrointestinal disorders					
Vomiting	18 (13)	5 (7)	9 (8)	12 (11)	34 (10)
Nausea	4 (7)	6 (9)	4 (4)	9 (8)	23 (7)
Constipation	6 (10)	1 (1)	8 (7)	5 (5)	20 (6)
General disorders and administration site conditions					
Pyrexia	3 (5)	5 (7)	8 (7)	6 (6)	22 (6)

The adverse reactions listed below represent those that occurred in $\geq 1\%$ of patients from clinical trials while receiving LAZANDA. Events are classified by system organ class.

Eye disorders: dry eye, swelling, ptosis, strabismus

Blood and Lymphatic System Disorders: anemia, neutropenia

Cardiac Disorders: cardiorespiratory arrest

Gastrointestinal Disorders: vomiting, nausea, constipation, diarrhea, abdominal pain, gastritis, ascites, dry mouth, dyspepsia, mouth ulcer, proctalgia

General Disorders and Administration Site Conditions: pyrexia, fatigue, edema

peripheral, asthenia, edema

Hepatobiliary Disorders: jaundice

Immune System Disorders: hypersensitivity

Infections and Infestations: urinary tract infection, pneumonia, nasopharyngitis,

infection, rhinitis, upper respiratory tract infection, bronchitis

Injury, Poisoning and Procedural Complications: fall

Investigations: weight decreased, blood alkaline phosphatase increased

Metabolism and Nutrition Disorders: dehydration, decreased appetite,

hyperglycemia, anorexia

Musculoskeletal and Connective Tissue Disorders: back pain, pain in extremity,

arthralgia

Nervous System Disorders: dizziness, somnolence, headache,

dysgeusia

Psychiatric Disorders: anxiety, insomnia, depression, confusional state,

disorientation, agitation

Respiratory, Thoracic and Mediastinal Disorders: dyspnea, epistaxis, cough,

pharyngolaryngeal pain, nasal discomfort, rhinorrhea, nasal congestion,

postnasal drip, pulmonary embolism

Skin and Subcutaneous Tissue Disorders: pruritus, hyperhidrosis, decubitus

ulcer, mouth ulceration

Vascular Disorders: hypertension, deep vein thrombosis

6.2 Postmarketing Experience

The following adverse reactions have been identified during post approval use of fentanyl. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Serotonin syndrome: Cases of serotonin syndrome, a potentially life-threatening condition, have been reported during concomitant use of opioids with serotonergic drugs.

Adrenal insufficiency: Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use.

Anaphylaxis: Anaphylaxis has been reported with ingredients contained in LAZANDA.

Androgen deficiency: Cases of androgen deficiency have occurred with chronic use of opioids [see *Clinical Pharmacology (12.2)*].

7 DRUG INTERACTIONS

Table 3 includes clinically significant drug interactions with LAZANDA.

Table 3: Clinically Significant Drug Interactions with LAZANDA

Inhibitors of CYP3A4	
<i>Clinical Impact:</i>	The concomitant use of LAZANDA and CYP3A4 inhibitors can increase the plasma concentration of fentanyl, resulting in increased or prolonged opioid effects, particularly when an inhibitor is added after a stable dose of LAZANDA is achieved [see <i>Warnings and Precautions (5.4)</i>]. After stopping a CYP3A4 inhibitor, as the effects of the inhibitor decline, the fentanyl plasma concentration will decrease [see <i>Clinical Pharmacology (12.3)</i>], resulting in decreased opioid efficacy or a withdrawal syndrome in patients who had developed physical dependence to fentanyl.
<i>Intervention:</i>	If concomitant use is necessary, consider dosage reduction of LAZANDA until stable drug effects are achieved. Monitor patients for respiratory depression and sedation at frequent intervals. If a CYP3A4 inhibitor is discontinued, consider increasing the LAZANDA dosage until stable drug effects are achieved. Monitor for signs of opioid withdrawal.
<i>Examples:</i>	Macrolide antibiotics (e.g., erythromycin), azole-antifungal agents (e.g. ketoconazole), protease inhibitors (e.g., ritonavir), grapefruit juice
CYP3A4 Inducers	
<i>Clinical Impact:</i>	The concomitant use of LAZANDA and CYP3A4 inducers can decrease the plasma concentration of fentanyl [see <i>Clinical Pharmacology (12.3)</i>], resulting in decreased efficacy or onset of a withdrawal syndrome in patients who have developed physical dependence to fentanyl [see <i>Warnings and Precautions (5.18)</i>]. After stopping a CYP3A4 inducer, as the effects of the inducer decline, the fentanyl plasma concentration will increase [see <i>Clinical Pharmacology (12.3)</i>], which could increase or prolong both the therapeutic effects and adverse reactions, and may cause serious respiratory depression.
<i>Intervention:</i>	If concomitant use is necessary, consider increasing the LAZANDA dosage until stable drug effects are achieved. Monitor for signs of opioid withdrawal. If a CYP3A4 inducer is discontinued, consider LAZANDA dosage reduction and monitor for signs of respiratory depression.
<i>Examples:</i>	Rifampin, carbamazepine, phenytoin
Benzodiazepines and Other Central Nervous System (CNS) Depressants	
<i>Clinical Impact:</i>	Due to additive pharmacologic effect, the concomitant use of benzodiazepines and other CNS depressants, including alcohol, can increase the risk of hypotension, respiratory depression, profound sedation, coma, and death.
<i>Intervention:</i>	Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate. Limit dosages and durations to the minimum required. Follow patients closely for signs of respiratory depression and sedation [see <i>Warnings and Precautions (5.4)</i>].
<i>Examples:</i>	Benzodiazepines and other sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol.

Serotonergic Drugs	
<i>Clinical Impact:</i>	The concomitant use of opioids with other drugs that affect the serotonergic neurotransmitter system has resulted in serotonin syndrome [see <i>Warnings and Precautions (5.10)</i>].
<i>Intervention:</i>	If concomitant use is warranted, carefully observe the patient, particularly during treatment initiation and dose adjustment. Discontinue LAZANDA if serotonin syndrome is suspected.
<i>Examples:</i>	Selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), triptans, 5-HT ₃ receptor antagonists, drugs that affect the serotonin neurotransmitter system (e.g., mirtazapine, trazodone, tramadol), monoamine oxidase (MAO) inhibitors (those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue).
Monoamine Oxidase Inhibitors (MAOIs)	
<i>Clinical Impact:</i>	MAOI interactions with opioids may manifest as serotonin syndrome [see <i>Warnings and Precautions (5.10)</i>] or opioid toxicity (e.g., respiratory depression, coma) [see <i>Warnings and Precautions (5.1)</i>].
<i>Intervention:</i>	The use of LAZANDA is not recommended for patients taking MAOIs or within 14 days of stopping such treatment.
<i>Examples:</i>	phenelzine, tranylcypromine, linezolid
Mixed Agonist/Antagonist and Partial Agonist Opioid Analgesics	
<i>Clinical Impact:</i>	May reduce the analgesic effect of LAZANDA and/or precipitate withdrawal symptoms.
<i>Intervention:</i>	Avoid concomitant use.
<i>Examples:</i>	butorphanol, nalbuphine, pentazocine, buprenorphine
Muscle Relaxants	
<i>Clinical Impact:</i>	fentanyl may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression.
<i>Intervention:</i>	Monitor patients for signs of respiratory depression that may be greater than otherwise expected and decrease the dosage of LAZANDA and/or the muscle relaxant as necessary.
Diuretics	
<i>Clinical Impact:</i>	Opioids can reduce the efficacy of diuretics by inducing the release of antidiuretic hormone.
<i>Intervention:</i>	Monitor patients for signs of diminished diuresis and/or effects on blood pressure and increase the dosage of the diuretic as needed.
Anticholinergic Drugs	
<i>Clinical Impact:</i>	The concomitant use of anticholinergic drugs may increase risk of urinary retention and/or severe constipation, which may lead to paralytic ileus.
<i>Intervention:</i>	Monitor patients for signs of urinary retention or reduced gastric motility when LAZANDA is used concomitantly with anticholinergic drugs.
Agents used to treat Allergic Rhinitis	
<i>Clinical Impact:</i>	The presence of allergic rhinitis is not expected to affect LAZANDA absorption. However, co-administration of a vasoconstrictive nasal decongestant such as oxymetazoline to treat allergic rhinitis leads to lower peak plasma concentrations and a delayed T _{max} of fentanyl that may cause LAZANDA to be less effective in patients with allergic rhinitis who use such decongestants, thus potentially impairing pain management. Additionally, in view of the possibility that the titration of a patient while they are experiencing an acute episode of rhinitis could lead to incorrect dose identification (particularly if they are using a vasoconstrictive decongestant), titration under these circumstances must be avoided [see <i>Clinical Pharmacology (12.3)</i>].
<i>Intervention:</i>	Avoid using LAZANDA in patients with allergic rhinitis and consider other products with a different route of administration.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Prolonged use of opioid analgesics during pregnancy may cause neonatal opioid withdrawal syndrome. Available data with LAZANDA in pregnant women are insufficient to inform a drug-associated risk for major birth defects and miscarriage.

In animal reproduction studies fentanyl administration to pregnant rats during organogenesis was embryocidal at doses within the range of the human recommended dosing for LAZANDA. No evidence of malformations were noted in animal studies completed to date [see *Data*].

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Prolonged use of opioid analgesics during pregnancy for medical or nonmedical purposes can result in physical dependence in the neonate and neonatal opioid withdrawal syndrome shortly after birth.

Neonatal opioid withdrawal syndrome presents as irritability, hyperactivity and abnormal sleep pattern, high pitched cry, tremor, vomiting, diarrhea and failure to gain weight. The onset, duration, and severity of neonatal opioid withdrawal syndrome vary based on the specific opioid used, duration of use, timing and amount of last maternal use, and rate of elimination of the drug by the newborn. Observe newborns for symptoms of neonatal opioid withdrawal syndrome and manage accordingly [see *Warnings and Precautions* (5.3)].

Labor or Delivery

Opioids cross the placenta and may produce respiratory depression and psycho-physiologic effects in neonates. An opioid antagonist, such as naloxone, must be available for reversal of opioid-induced respiratory depression in the neonate. LAZANDA is not recommended for use in pregnant women during or immediately prior to labor, when other analgesic techniques are more appropriate. Opioid analgesics, including LAZANDA, can prolong labor through actions which temporarily reduce the strength, duration, and frequency of uterine contractions. However, this effect is not consistent and may be offset by an increased rate of cervical dilation, which tends to shorten labor. Monitor neonates exposed to opioid analgesics during labor for signs of excess sedation and respiratory depression.

Data

Human Data

In women treated acutely with intravenous or epidural fentanyl during labor, symptoms of neonatal respiratory or neurological depression were no more frequent than would be expected in infants of untreated mothers.

Transient neonatal muscular rigidity has been observed in infants whose mothers were treated with intravenous fentanyl.

Animal Data

Fentanyl has been shown to be embryocidal in pregnant rats at doses of 30 mcg/kg intravenously (0.4 times the 800 mcg dose of LAZANDA on a mg/m² basis) and 160 mcg/kg subcutaneously (2 times the 800 mcg dose of LAZANDA based on a mg/m² basis). There was no evidence of teratogenicity reported.

No evidence of malformations or adverse effects on the fetus was reported in a published study in which pregnant rats were administered fentanyl continuously via subcutaneously implanted osmotic minipumps at doses of 10, 100, or 500 mcg/kg/day starting 2-weeks prior to breeding and throughout pregnancy. The high dose was approximately 6 times the human dose of 800 mcg LAZANDA per pain episode on a mg/m² basis and produced mean steady-state plasma levels that are 3 times higher than the mean C_{max} observed following administration of 800 mcg dose of LAZANDA in humans.

8.2 Lactation

Risk Summary

Fentanyl is present in breast milk. One published lactation study reports a relative infant dose of fentanyl of 0.024%. However, there is insufficient information to determine the effects of fentanyl on the breastfed infant and the effects of fentanyl on milk production.

Because of the potential for serious adverse reactions, including excess sedation and respiratory depression in a breastfed infant, advise patients that breastfeeding is not recommended during treatment with LAZANDA.

Clinical Considerations

Monitor infants exposed to LAZANDA through breast milk for excess sedation and respiratory depression. Withdrawal symptoms can occur in breastfed infants when maternal administration of an opioid analgesic is stopped, or when

breast-feeding is stopped.

8.3 Females and Males of Reproductive Potential

Infertility

Chronic use of opioids may cause reduced fertility in females and males of reproductive potential. It is not known whether these effects on fertility are reversible [see *Adverse Reactions* (6.2), *Clinical Pharmacology* (12.2), *Nonclinical Toxicology*(13.1)].

8.4 Pediatric Use

The safety and efficacy of LAZANDA have not been established in patients below the age of 18 years.

8.5 Geriatric Use

Of the 523 opioid tolerant cancer patients with breakthrough cancer pain in clinical studies of LAZANDA, 148 (28%) were aged 60 years and over. No clinically meaningful difference was noted in the safety profile of the group aged over 60 years versus that of younger patients in LAZANDA clinical trials.

Elderly patients have been shown to be more sensitive to the effects of fentanyl when administered intravenously compared with the younger population. Therefore, exercise caution when individually titrating LAZANDA in elderly patients to provide adequate efficacy while minimizing risk.

Respiratory depression is the chief risk for elderly patients treated with opioids, and has occurred after large initial doses were administered to patients who were not opioid-tolerant or when opioids were co-administered with other agents that depress respiration. Titrate the dosage of LAZANDA slowly in geriatric patients and monitor closely for signs of central nervous system and respiratory depression [see *Warnings and Precautions* (5.1)].

Fentanyl is known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

8.6 Patients with Renal or Hepatic Impairment

Insufficient information exists to make recommendations regarding the use of LAZANDA in patients with impaired renal or hepatic function. Fentanyl is metabolized primarily via the human CYP3A4 isoenzyme system and the inactive metabolite is mostly eliminated in urine. If the drug is used in these patients, it is to be used with caution because of the hepatic metabolism and renal excretion of fentanyl.

It is recommended that LAZANDA be titrated to clinical effect for all patients with special care taken in patients with severe renal or hepatic disease.

8.7 Sex

Both male and female opioid-tolerant cancer patients were studied for the treatment of breakthrough cancer pain. No clinically relevant sex differences were observed in adverse events.

8.8 Patients with Allergic (Seasonal) Rhinitis

The pharmacokinetic and safety profiles of LAZANDA in individuals with known allergic (seasonal) rhinitis showed no clinically meaningful differences in rate or extent of exposure to fentanyl, or in local tolerability of LAZANDA when compared to Asymptomatic (Unchallenged) state. However, when treated for their rhinitis with oxymetazoline, LAZANDA absorption was compromised [see *Pharmacokinetics* (12.3)].

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

LAZANDA contains fentanyl, a Schedule II controlled substance.

9.2 Abuse

LAZANDA contains fentanyl, a substance with a high potential for abuse similar to other opioids including hydrocodone, hydromorphone, methadone, morphine, oxycodone, oxymorphone, and tapentadol. LAZANDA can be abused and is subject to misuse, addiction, and criminal diversion [see *Warnings and Precautions* (5.6)].

All patients treated with opioids require careful monitoring for signs of abuse and addiction, since use of opioid analgesic products carries the risk of addiction even under appropriate medical use.

Prescription drug abuse is the intentional non-therapeutic use of a prescription drug, even once, for its rewarding psychological or physiological effects.

Drug addiction is a cluster of behavioral, cognitive, and physiological phenomena that develop after repeated substance use and includes: a strong desire to take the drug, difficulties in controlling its use, persisting in its use despite harmful consequences, a higher priority given to drug use than to other activities and obligations, increased tolerance, and sometimes a physical withdrawal.

"Drug-seeking" behavior is very common in persons with substance use disorders. Drug-seeking tactics include emergency calls or visits near the end

of office hours, refusal to undergo appropriate examination, testing, or referral, repeated "loss" of prescriptions, tampering with prescriptions, and reluctance to provide prior medical records or contact information for other treating health care provider(s). "Doctor shopping" (visiting multiple prescribers to obtain additional prescriptions) is common among drug abusers and people suffering from untreated addiction. Preoccupation with achieving adequate pain relief can be appropriate behavior in a patient with poor pain control. Abuse and addiction are separate and distinct from physical dependence and tolerance. Health care providers should be aware that addiction may not be accompanied by concurrent tolerance and symptoms of physical dependence in all addicts. In addition, abuse of opioids can occur in the absence of true addiction.

LAZANDA, like other opioids, can be diverted for non-medical use into illicit channels of distribution. Careful record-keeping of prescribing information, including quantity, frequency, and renewal requests, as required by state and federal law, is strongly advised.

Proper assessment of the patient, proper prescribing practices, periodic re-evaluation of therapy, and proper dispensing and storage are appropriate measures that help to limit abuse of opioid drugs.

Risks Specific to the Abuse of LAZANDA

LAZANDA is for intranasal transmucosal use only. Abuse of LAZANDA poses a risk of overdose and death. The risk is increased with concurrent abuse of LAZANDA with alcohol and other central nervous system depressants.

9.3 Dependence

Both tolerance and physical dependence can develop during chronic opioid therapy. Tolerance is the need for increasing doses of opioids to maintain a defined effect such as analgesia (in the absence of disease progression or other external factors). Tolerance may occur to both the desired and undesired effects of drugs, and may develop at different rates for different effects.

Physical dependence results in withdrawal symptoms after abrupt discontinuation or a significant dosage reduction of a drug. Withdrawal also may be precipitated through the administration of drugs with opioid antagonist activity (e.g., naloxone, nalmefene), mixed agonist/antagonist analgesics (e.g., pentazocine, butorphanol, nalbuphine), or partial agonists (e.g., buprenorphine). Physical dependence may not occur to a clinically significant degree until after several days to weeks of continued opioid usage.

Infants born to mothers physically dependent on opioids will also be physically dependent and may exhibit respiratory difficulties and withdrawal signs [see *Use in Specific Populations* (8.1)].

10 OVERDOSAGE

Clinical Presentation

Acute overdose with LAZANDA can be manifested by respiratory depression, somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, constricted pupils, and, in some cases, pulmonary edema, bradycardia, hypotension, partial or complete airway obstruction, atypical snoring, and death. Marked mydriasis rather than miosis may be seen with hypoxia in overdose situations [see *Clinical Pharmacology* (12.2)].

Treatment of Overdose

In case of overdose, priorities are: the reestablishment of a patent and protected airway and institution of assisted or controlled ventilation, if needed. Employ other supportive measures (including oxygen and vasopressors) in the management of circulatory shock and pulmonary edema as indicated. Cardiac arrest or arrhythmias will require advanced life-support techniques.

The opioid antagonists, naloxone or nalmefene, are specific antidotes to respiratory depression resulting from opioid overdose. For clinically significant respiratory or circulatory depression secondary to fentanyl overdose, administer an opioid antagonist. Opioid antagonists should not be administered in the absence of clinically significant respiratory or circulatory depression secondary to fentanyl overdose.

Because the duration of opioid reversal is expected to be less than the duration of action of fentanyl in LAZANDA, carefully monitor the patient until spontaneous respiration is reliably re-established. If the response to an opioid antagonist is suboptimal or only brief in nature, administer additional antagonist as directed by the product's prescribing information.

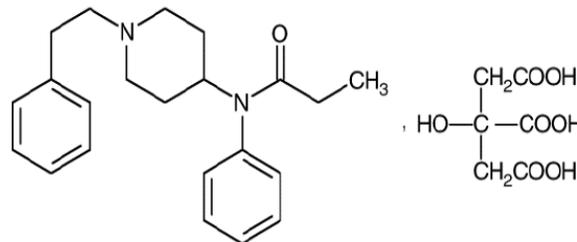
In an individual physically dependent on opioids, administration of the recommended usual dosage of the antagonist will precipitate an acute withdrawal syndrome. The severity of the withdrawal symptoms experienced will depend on the degree of physical dependence and the dose of the antagonist administered. If a decision is made to treat serious respiratory depression in the physically dependent patient, administration of the antagonist should be begun with care and by titration with smaller than usual doses of the antagonist.

11 DESCRIPTION

LAZANDA (fentanyl) nasal spray is a liquid formulation of fentanyl citrate, an

opioid agonist, intended for intranasal transmucosal administration. The product consists of a practically clear to clear, colorless, aqueous solution of fentanyl citrate in a glass multidose container to which is attached a metered-dose nasal spray pump with a visual and audible spray counter. Each actuation is designed to deliver a spray of 100 mL of solution containing 100 mcg, 300 mcg or 400 mcg fentanyl base, respectively. This enables doses of 100 mcg, 300 mcg or 400 mcg to be administered using a single spray into one nostril (1 spray) and 200 mcg, 600 mcg or 800 mcg to be administered using a single spray into both nostrils (2 sprays).

Active ingredient: Fentanyl citrate, USP is N-(1-phenethyl-4-piperidyl) propionilide citrate (1:1). Fentanyl is a highly lipophilic compound (octanol-water partition coefficient at pH 7.4 is 816:1). Fentanyl citrate is sparingly soluble in water (1:40). The molecular weight of the free base and citrate salt are 336.5 and 528.6, respectively. The pKa is 8.4. The compound has the following structural formula:



LAZANDA is available in 3 strengths of nasal spray: 100 mcg fentanyl (yellow label), 300 mcg fentanyl (blue label) and 400 mcg fentanyl (violet label). The strength is expressed as the amount of fentanyl free base per spray, e.g., the 100 mcg strength provides 100 mcg of fentanyl free base per 100 mL spray.

Inactive ingredients: mannitol, pectin, phenylethyl alcohol, propylparaben, sucrose, water. Sodium hydroxide and/or hydrochloric acid are added if required for pH adjustment.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Fentanyl is an opioid agonist whose principal therapeutic action is analgesia.

12.2 Pharmacodynamics

Effects on the Central Nervous System

Fentanyl produces respiratory depression by direct action on brain stem respiratory centers. The respiratory depression involves a reduction in the responsiveness of the brain stem respiratory centers to both increase in carbon dioxide tension and electrical stimulation.

Fentanyl causes miosis, even in total darkness. Pinpoint pupils are a sign of opioid overdose but are not pathognomonic (e.g., pontine lesions of hemorrhagic or ischemic origins may produce similar findings). Marked mydriasis rather than miosis may be seen due to hypoxia in overdose situations.

Effects on the Gastrointestinal Tract and Other Smooth Muscle

Fentanyl causes a reduction in motility associated with an increase in smooth muscle tone in the antrum of the stomach and duodenum. Digestion of food in the small intestine is delayed and propulsive contractions are decreased. Propulsive peristaltic waves in the colon are decreased, while tone may be increased to the point of spasm resulting in constipation. Other opioid-induced effects may include a reduction in biliary and pancreatic secretions, spasm of sphincter of Oddi, and transient elevations in serum amylase.

Effects on the Cardiovascular System

Fentanyl produces peripheral vasodilation which may result in orthostatic hypotension or syncope. Manifestations of histamine release and/or peripheral vasodilation may include pruritus, flushing, red eyes, sweating and/or orthostatic hypotension.

Effects on the Endocrine System

Opioids inhibit the secretion of adrenocorticotropic hormone (ACTH), cortisol, and luteinizing hormone (LH) in humans [see *Adverse Reactions* (6.2)]. They also stimulate prolactin, growth hormone (GH) secretion, and pancreatic secretion of insulin and glucagon.

Chronic use of opioids may influence the hypothalamic-pituitary-gonadal axis, leading to androgen deficiency that may manifest as low libido, impotence, erectile dysfunction, amenorrhea, or infertility. The causal role of opioids in the clinical syndrome of hypogonadism is unknown because the various medical, physical, lifestyle, and psychological stressors that may influence gonadal hormone levels have not been adequately controlled for in studies conducted to date [see *Adverse Reactions* (6.2)].

Effects on the Immune System

Opioids have been shown to have a variety of effects on components of the

immune system in in vitro and animal models. The clinical significance of these findings is unknown. Overall, the effects of opioids appear to be modestly immunosuppressive.

Concentration–Efficacy Relationships

The analgesic effects of fentanyl are related to the blood level of the drug, if proper allowance is made for the delay into and out of the CNS (a process with a 3- to 5-minute half-life).

In general, the effective concentration and the concentration at which toxicity occurs increase with increasing tolerance with any and all opioids. The rate of development of tolerance varies widely among individuals.

The minimum effective analgesic concentration of fentanyl for any individual patient may increase over time due to an increase in pain, the development of a new pain syndrome and/or the development of analgesic tolerance [see *Dosage and Administration* (2.1, 2.4)].

Concentration–Adverse Reaction Relationships

There is a relationship between increasing fentanyl plasma concentration and increasing frequency of dose- related opioid adverse reactions such as nausea, vomiting, CNS effects, and respiratory depression. In opioid- tolerant patients, the situation may be altered by the development of tolerance to opioid-related adverse reactions [see *Dosage and Administration* (2.1, 2.2, 2.3)].

Respiratory System

All opioid mu-receptor agonists, including fentanyl, produce dose-dependent respiratory depression. The risk of respiratory depression is less in patients receiving chronic opioid therapy who develop tolerance to respiratory depression and other opioid effects. Peak respiratory depressive effects may be seen as early as 15 to 30 minutes from the start of transmucosal fentanyl citrate product administration and may persist for several hours.

Serious or fatal respiratory depression can occur even at recommended doses. Although not observed with oral or nasal transmucosal fentanyl products in clinical trials, fentanyl given rapidly by intravenous injection in large doses may interfere with respiration by causing rigidity in the muscles of respiration. [see *Warnings and Precautions* (5.1), *Adverse Reactions* (6), *Overdosage* (10)].

12.3 Pharmacokinetics

Absorption

In a study that compared the relative bioavailability of LAZANDA and an oral transmucosal fentanyl citrate product, the bioavailability of fentanyl from LAZANDA was approximately 20% higher. Fentanyl is absorbed from the nasal mucosa following intranasal administration of LAZANDA, with median T_{max} values ranging from 15-21 min after administration of a single dose. C_{max} and AUC values for fentanyl following administration of LAZANDA increase linearly over the 100- to 800-mcg dose range.

Mean plasma concentration versus time profiles are presented in Figure 1. Mean pharmacokinetic parameters are presented in Table 4.

Figure 1.
Mean Plasma Fentanyl Concentration (pg/mL) in Normal Subjects Receiving 100, 200, 400 and 800 mcg Lazanda or 200 mcg OTFC

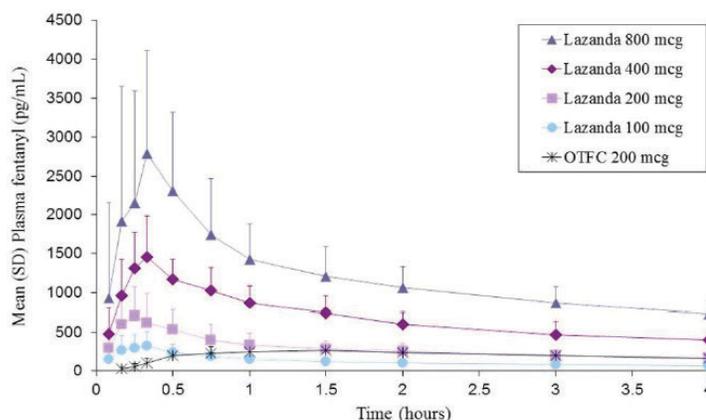


Table 4. Pharmacokinetic Parameters in Normal Subjects Receiving 100, 200, 400, and 800 mcg of LAZANDA or 200 mcg OTFC

PHARMACOKINETIC PARAMETERS	LAZANDA				OTFC
	100 mcg	200 mcg	400 mcg	800 mcg	200 mcg
T_{max} , hours median (range)	0.33 (0.08–1.50)	0.25 (0.17–1.60)	0.35 (0.25–0.75)	0.34 (0.17–3.00)	1.50 (0.50–8.00)
C_{max} , pg/mL Mean (%CV)	351.5 (51.3)	780.8 (48.4)	1552.1 (26.2)	2844.0 (56.0)	317.4 (29.9)
AUC _{inf} , pg.hour/mL Mean (%CV)	2460.5 (17.9)	4359.9 (29.8)	7513.4 (26.7)	17272 (48.9)	3735.0 (32.8)
$t_{1/2}$, hour Mean (%CV)	21.9 (13.6)	24.9 (51.3)	15.0 (24.7)	24.9 (92.5)	18.6 (31.4)

A pharmacokinetic study evaluated the cerebrospinal fluid (CSF) concentrations of fentanyl administered via the intranasal (LAZANDA) route. As presented in Table 5, the maximum concentration of fentanyl in the CSF as delivered by LAZANDA was reached at 1.0 hour. Values for the C_{max} and AUC_{0-6h} of fentanyl are also presented in Table 5.

Table 5 Cerebrospinal Pharmacokinetic Parameters in Normal Subjects Receiving 200 mcg of LAZANDA

PHARMACOKINETICS PARAMETERS	LAZANDA (fentanyl nasal spray) 200 mcg
T_{max} , hours Median (range)	1.01 (0.75–3.00)
C_{max} , pg /mL Mean (%CV)	84.54 (55.7)
AUC _{0-6h} , pg.hour/mL Mean (%CV)	300.25 (40.6)

In a pharmacokinetic study that evaluated multiple-dose pharmacokinetics of LAZANDA when two doses of LAZANDA are administered in the same nostril and are separated by a 1, 2 or 4 h time lapse, C_{max2} (C_{max} after second administration) was greater than C_{max1} (C_{max} after first administration), by 30% when LAZANDA was administered 1 h apart, by 25% when LAZANDA was administered 2 h apart and by 10% when LAZANDA was administered 4 h apart. Based on these results and based on T_{max} range of LAZANDA observed across pharmacokinetic studies, and frequency of breakthrough pain episodes in a cancer population, a waiting period of 2 h between two consecutive doses of LAZANDA is recommended [see *Dosage and Administration* (2.2, 2.3)].

In a pharmacokinetic study to evaluate differences in LAZANDA absorption in individuals with induced allergic (seasonal) rhinitis using Ragweed, no clinically meaningful differences were observed in rate or extent of exposure to fentanyl, when compared to the Asymptomatic (Unchallenged) state, indicating that presence of allergic rhinitis does not affect LAZANDA absorption. This study also assessed differences in LAZANDA absorption, if any, when co-administered with oxymetazoline, a nasal decongestant in subjects undergoing treatment for seasonal allergic rhinitis. The mean C_{max} and AUC_t values for Treated arm (Rhinitis treated with oxymetazoline) were about 32% and 10% lower, respectively compared to the Asymptomatic arm. In addition, mean T_{max} of LAZANDA in the Treated arm was 0.75 h (range 0.08-3 h) as compared to 0.25 h (0.17-1 h) for the Asymptomatic arm. These results indicate that co-administration with oxymetazoline in rhinitis leads to lower peak plasma concentrations and delayed T_{max} of LAZANDA [see *Drug Interactions* (7)].

Distribution

Fentanyl is highly lipophilic. The plasma protein binding of fentanyl is 80% to 85%. The main binding protein is alpha-1-acid glycoprotein, but both albumin and lipoproteins contribute to some extent. The mean volume of distribution at steady state (V_{ss}) was 4 L/kg.

Elimination

The total plasma clearance of fentanyl following intravenous administration is approximately 42 L/h.

Metabolism

The metabolic pathways following intranasal administration of LAZANDA have not been characterized in clinical studies. The progressive decline of fentanyl plasma concentrations results from the uptake of fentanyl in the tissues and biotransformation in the liver. Fentanyl is metabolized in the liver and in the intestinal mucosa to norfentanyl by cytochrome P450 3A4 isoform. In animal studies, norfentanyl was not found to be pharmacologically active.

Excretion

The disposition of fentanyl following intranasal administration of LAZANDA has not been characterized in a mass balance study. Fentanyl is primarily (more than 90%) eliminated by biotransformation to N-dealkylated and hydroxylated inac-

tive metabolites. Less than 7% of the administered dose is excreted unchanged in the urine, and only about 1% is excreted unchanged in the feces. The metabolites are mainly excreted in the urine, while fecal excretion is less important.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Long-term studies in animals to evaluate the carcinogenic potential of fentanyl have not been conducted.

Mutagenesis

Fentanyl citrate was not mutagenic in the in vitro Ames reverse mutation assay in *S. typhimurium* or *E. coli*, or the mouse lymphoma mutagenesis assay, and was not clastogenic in the in vivo mouse micronucleus assay.

Impairment of Fertility

Fentanyl has been shown to impair fertility in rats at doses of 30 mcg/kg subcutaneously. Conversion to human equivalent doses indicates this is within the range of the human recommended dosing for LAZANDA.

14 CLINICAL STUDIES

The efficacy of LAZANDA was evaluated in one clinical trial in opioid tolerant adult patients experiencing breakthrough cancer pain. Breakthrough cancer pain was defined as a transient flare of moderate-to-severe pain occurring in patients experiencing persistent cancer pain otherwise controlled with maintenance doses of opioid medications including at least 60 mg of oral morphine/day or an equianalgesic dose of another opioid (which could be fentanyl) for a week or longer. All patients were on stable doses of either long-acting oral opioids or transdermal fentanyl for their persistent cancer pain.

The clinical trial included an open-label titration phase where a dose was identified that provided adequate analgesia with tolerable side effects, within the range of 100 to 800 mcg. In the double-blind, placebo- controlled portion of the study, patients who were titrated to an adequate dose were randomized to a blinded sequence of 10 treatments with 7 being the identified dose of LAZANDA and 3 being placebo.

Of the patients who enrolled in the study, 73% achieved an adequate dose during the titration phase, 6% withdrew for lack of effective pain relief, and 5% withdrew due to adverse events.

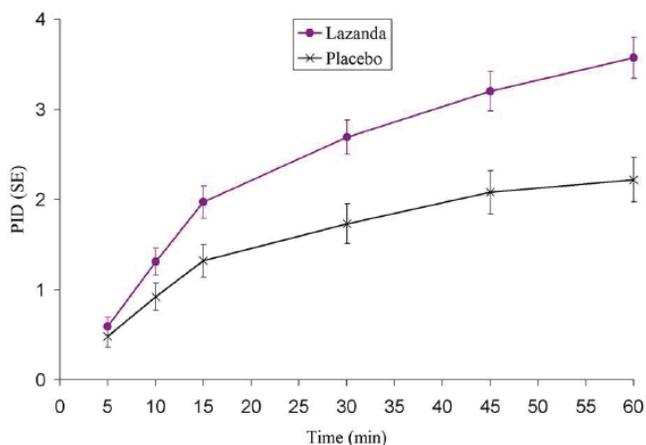
The distribution of final titrated doses is shown in Table 5. The final titrated dose of LAZANDA for breakthrough pain was not predicted from the daily maintenance dose of opioid used to manage the persistent cancer pain and, therefore, the dose was determined by titration starting at 100 mcg.

Table 6. Dose of LAZANDA Following Initial Titration (ITT population)

LAZANDA Dose	(N=83) n (%)
100 mcg	12 (14)
200 mcg	7 (8)
400 mcg	27 (33)
800 mcg	37 (45)

The primary outcome measure, the mean sum of the pain intensity difference at 30 minutes (SPID30), was statistically significantly higher for LAZANDA than for placebo (see Figure 2).

Figure 2. Pain Intensity Differences (PID) following LAZANDA or Placebo in Adult Patients with Breakthrough Cancer Pain



16 HOW SUPPLIED/STORAGE AND HANDLING

LAZANDA is available as a 5.3 mL capacity clear glass bottle with an attached metered-dose nasal spray pump incorporating a visual and audible spray counter, and a protective dust cover. Each glass bottle, contains 8 sprays of 100 mcL available in three different concentrations: 100 mcg/100 mcL, 300 mcg/100 mcL or 400 mcg/100 mcL concentration solution. Each bottle contains a net fill weight of 1.57 grams and, after priming, delivers 8 sprays.

The pump will remain primed for up to 5 days after priming or use. If the product has not been used for 5 days, re-prime by spraying once. The nasal spray delivers 8 full sprays. There are 3 product strengths and each 100 mcL spray contains either 100 mcg, 300 mcg or 400 mcg of fentanyl. Each bottle is supplied in a child-resistant container.

Bottles in their child-resistant containers are supplied in cartons containing 1 bottle with instructions for use. Each carton contains one carbon-lined pouch per bottle for disposal of priming sprays, unwanted doses and residual fentanyl solution.

LAZANDA Dosage Strength (fentanyl base)	Number of Bottles per Carton	NDC Number
100 mcg	1	13913-009-01
300 mcg	1	13913-013-01
400 mcg	1	13913-010-01

Store at up to 25°C. Do not freeze.

Return the bottle to the child-resistant container after each use. Put the bottle in its child-resistant container and the pouch in the cardboard carton and store securely out of the reach of children and protect from light.

Note: Carton and bottle label colors are a secondary aid in product identification. Confirm the printed dosage before dispensing.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Life-Threatening Respiratory Depression

Inform patients of the risk of life-threatening respiratory depression, including information that the risk is greatest when starting LAZANDA or when the dosage is increased, and that it can occur even at recommended dosages [see *Warnings and Precautions* (5.1)]. Advise patients how to recognize respiratory depression and to seek medical attention if breathing difficulties develop.

Increased Risk of Overdose and Death in Children Due to Accidental Exposure

- Healthcare providers and dispensing pharmacists must specifically question patients or caregivers about the presence of children in the home (on a full time or visiting basis) and counsel them regarding the dangers to children from inadvertent exposure [see *Warnings and Precautions* (5.2)].
- Inform patients and their caregivers that accidental exposure, especially in children, may result in respiratory depression or death [see *Warnings and Precautions* (5.2)].
- Instruct patients and their caregivers that in the event that a LAZANDA unit is not completely consumed, it must be properly disposed as soon as possible [see *Dosage and Administration* (2.7), *Patient Counseling Information; Disposal of Unused LAZANDA* (17)].
- Instruct patients and caregivers to keep both used and unused LAZANDA out of the reach of children [see *Warnings and Precautions* (5.2)].

Interactions with Benzodiazepines and Other CNS Depressants

Inform patients that potentially fatal additive effects may occur if LAZANDA is used with benzodiazepines or other CNS depressants, including alcohol, and not to use these concomitantly unless supervised by a health care provider [see *Warnings and Precautions* (5.4), *Drug Interactions* (7)].

Addiction, Abuse, and Misuse

Inform patients that the use of LAZANDA, even when taken as recommended, can result in addiction, abuse, and misuse, which can lead to overdose and death [see *Warnings and Precautions* (5.6)]. Instruct patients not to share LAZANDA with others and to take steps to protect LAZANDA from theft or misuse.

Transmucosal Immediate-Release Fentanyl (TIRF) REMS

Advise patients of the following information pertaining to the TIRF REMS

- Inform outpatients that they must be enrolled in the TIRF REMS Access program before they can receive LAZANDA.
- Allow patients the opportunity to ask questions and discuss any concerns regarding LAZANDA or the TIRF REMS Access program.
- As required by the TIRF REMS Access program, review the contents of the LAZANDA Medication Guide with every patient before initiating treatment with LAZANDA.

- Advise the patient that LAZANDA is available only from pharmacies that are enrolled in the TIRF REMS Access program, and provide them with the telephone number and website for information on how to obtain the drug.
- Advise the patient that only enrolled healthcare providers may prescribe LAZANDA.
- Inform the patient that they must sign the Patient-Prescriber Agreement to acknowledge that they understand the risks of LAZANDA.
- Advise patients that they may be requested to participate in a survey to evaluate the effectiveness of the TIRF REMS Access program [see *Warnings and Precautions* (5.7)].

Serotonin Syndrome

Inform patients that opioids could cause a rare but potentially life-threatening condition resulting from concomitant administration of serotonergic drugs. Warn patients of the symptoms of serotonin syndrome and to seek medical attention right away if symptoms develop. Instruct patients to inform their physicians if they are taking, or plan to take serotonergic medications. [see *Warnings and Precautions* (5.10), *Drug Interactions* (7)].

MAOI Interaction

Inform patients to avoid taking LAZANDA while using any drugs that inhibit monoamine oxidase. Patients should not start MAOIs while taking LAZANDA [see *Warnings and Precautions* (5.10); *Drug Interactions* (7)].

Adrenal Insufficiency

Inform patients that opioids could cause adrenal insufficiency, a potentially life-threatening condition. Adrenal insufficiency may present with non-specific symptoms and signs such as nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. Advise patients to seek medical attention if they experience a constellation of these symptoms [see *Warnings and Precautions* (5.11)].

Important Administration Instructions [see *Dosage and Administration* (2)]

- Instruct patients not to take LAZANDA for acute pain, postoperative pain, pain from injuries, headache, migraine, or any other short-term pain, even if they have taken other opioid analgesics for these conditions.
- Instruct patients on the meaning of opioid tolerance and LAZANDA is only to be used as a supplemental pain medication for patients with pain requiring regular opioids, who have developed tolerance to the opioid medication and who need additional opioid treatment of breakthrough pain episodes.
- Instruct patients that if they are not taking an opioid medication on a regular around-the-clock basis, they should not take LAZANDA.
- Advise patients that LAZANDA contains fentanyl, which is a pain medication similar to hydromorphone, methadone, morphine, oxycodone, oxycodone, hydrocodone, and tapentadol.
- Instruct patients that they MUST wait at least 2 hours before treating another episode of breakthrough pain with LAZANDA.
- Instruct patients to talk to their doctor if breakthrough pain is not alleviated or worsens after taking LAZANDA.
- Instruct patients to use LAZANDA exactly as prescribed by their doctor and not to take LAZANDA more often than prescribed.
- Instruct patients NOT to share LAZANDA and that sharing LAZANDA with anyone else could result in the other individual's death due to overdose.
- Instruct patients and their caregivers that the amount of fentanyl contained in a bottle can be fatal to a child. Patients and their caregivers must be instructed to keep LAZANDA in its child-resistant container at all times and to store it and the pouch securely and out of the reach of children.

Hypotension

Inform patients that LAZANDA may cause orthostatic hypotension and syncope. Instruct patients how to recognize symptoms of low blood pressure and how to reduce the risk of serious consequences should hypotension occur (e.g., sit or lie down, carefully rise from a sitting or lying position) [see *Warnings and Precautions* (5.12)].

Anaphylaxis

Inform patients that anaphylaxis have been reported with ingredients contained in LAZANDA. Advise patients how to recognize such a reaction and when to seek medical attention [see *Contraindications* (4), *Adverse Reactions* (6.2)].

Pregnancy

Neonatal Opioid Withdrawal Syndrome

Inform patients that prolonged use of LAZANDA during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated [see *Warnings and Precautions* (5.8), *Use in Specific Populations* (8.1)].

Embryo-Fetal Toxicity

Inform female patients of reproductive potential that LAZANDA can cause fetal harm and to inform their healthcare provider of a known or suspected pregnancy [see *Use in Specific Populations* (8.1)].

Lactation

Advise nursing mothers to monitor infants for increased sleepiness (more than

usual), breathing difficulties, or limpness. Instruct nursing mothers to seek immediate medical care if they notice these signs [see *Use in Specific Populations* (8.2)].

Infertility

Inform patients that chronic use of opioids may cause reduced fertility. It is not known whether these effects on fertility are reversible [see *Use in Specific Populations* (8.3)].

Driving or Operating Heavy Machinery

Inform patients that LAZANDA may impair the ability to perform potentially hazardous activities such as driving a car or operating heavy machinery. Advise patients not to perform such tasks until they know how they will react to the medication [see *Warnings and Precautions* (5.16)].

Constipation

Advise patients of the potential for severe constipation, including management instructions and when to seek medical attention [see *Adverse Reactions* (6.1)].

Disposal of Unused LAZANDA [see *Instructions for Use*]

- Advise patients to properly dispose of all unused, partially used and used LAZANDA bottles as soon as no longer needed.
- Instruct patients that, to dispose of LAZANDA properly, the remaining liquid in all bottles must be sprayed into the pouch provided in the pack for safe disposal as soon as possible. This includes any unwanted therapeutic sprays remaining in the bottle. After the counter has advanced to "8", the patient should continue to push down on the finger grips a total of four times in order to expel any residual medicine from the bottle. After the 8 therapeutic sprays have been emitted, the patient will not hear a click and the counter will not advance beyond "8"; further sprays emitted will not be full sprays and should always be trapped in the pouch, not used therapeutically.
- Instruct the patient and caregiver to seal the pouch and to place both the empty bottle and the sealed pouch into the child-resistant storage container and discard in the trash. LAZANDA must be stored in the specially provided child-resistant container out of the reach of children until proper disposal is possible.
- Instruct the patient and caregiver to wash their hands with soap and water immediately after handling the pouch.
- If the pouch is lost, instruct the patient and caregiver to use a pouch from another LAZANDA pack to prime and dispose of unused medicine from the current bottle as well as from the next bottle. If they do not have an empty pouch available, the patient or caregiver can order one by calling 1-844-4LAZANDA. They will receive the replacement pouch in the mail.

Rx Only

Distributed by West Therapeutic Development, LLC
Northbrook, IL 60062

For information about this product call: 1-844-4LAZANDA

U.S. Patent Numbers:

6, 432, 440
8, 216, 604
8, 889, 176
9, 078, 814
9, 814, 705
9, 731, 869

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OPS-BU.LAZ.1043

FDA Approved Labeling 12.19.08 3pm
 NovaDel Pharma Inc.
 Zolpimist (zolpidem tartrate) Oral Spray

New Drug Application
 NDA 022196, SN 0021
 December 2008

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Zolpimist safely and effectively. See full prescribing information for Zolpimist (zolpidem tartrate) Oral Spray 

Initial U.S. Approval: 1992

INDICATIONS AND USAGE

Zolpimist (zolpidem tartrate) Oral Spray is indicated for the short-term treatment of insomnia characterized by difficulties with sleep initiation. Zolpidem tartrate has been shown to decrease sleep latency for up to 35 days in controlled clinical studies. (1)

DOSAGE AND ADMINISTRATION

- Adult dose: 10 mg once daily immediately before bedtime. (2.1)
- Elderly/debilitated patients/hepatic impaired: 5 mg once daily immediately before bedtime. (2.2)
- Downward dosage adjustment may be necessary when used with CNS depressants. (2.3)
- Should not be taken with or immediately after a meal. (2.4)

DOSAGE FORMS AND STRENGTHS

Each metered actuation (one spray) of Zolpimist delivers 5 mg of zolpidem tartrate in 100 µL. After an initial priming of 5 actuations, there are 60 metered actuations in each child-resistant container. The total number of available doses is dependent on the number of actuations per dose (1 or 2 actuations) and the frequency of priming. (3)

CONTRAINDICATIONS

Known hypersensitivity to zolpidem tartrate.

WARNINGS AND PRECAUTIONS

- Need to evaluate for co-morbid diagnosis: Reevaluate if insomnia persists after 7 to 10 days of use. (5.1)
- Severe anaphylactic and anaphylactoid reactions: Angioedema and anaphylaxis have been reported. Do not rechallenge if such reactions occur. (5.2)
- Abnormal thinking, behavioral changes, and complex behaviors: May include "sleep-driving" and hallucinations. Immediately evaluate any new onset of behavioral changes. (5.3)
- Depression: Worsening of depression or suicidal thinking may occur. Prescribe the least amount feasible to avoid intentional overdose. (5.3, 5.6)
- Withdrawal effects: Symptoms may occur with rapid dose reduction or discontinuation. (5.4, 9.3)

- CNS-depressant effects: Use can impair alertness and motor coordination. If used in combination with other CNS depressants, dose reduction may be needed due to additive effects. Do not use with alcohol. (2.3, 5.5)
- Elderly/debilitated patients: Use lower dose due to impaired motor, cognitive performance, and increased sensitivity. (2.2, 5.6)
- Patients with hepatic impairment, mild to moderate COPD, impaired drug metabolism or hemodynamic responses, mild to moderate sleep apnea: Use with caution and monitor closely. (5.6)

ADVERSE REACTIONS

Most commonly observed adverse reactions were:

- Short-term (<10 nights): Drowsiness, dizziness, and diarrhea.
- Long-term (28-35 nights): Dizziness and drugged feelings. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact NovaDel Pharma Inc. at 1-800- and <http://www.novadel.com> or FDA at 1-800-FDA-1088 or <http://www.fda.gov/medwatch>.

DRUG INTERACTIONS

- CNS depressants: Enhanced CNS-depressant effects with combination use. Use with alcohol causes additive psychomotor impairment. (7.1)
- Imipramine: Decreased alertness observed with combination use. (7.1)
- Chlorpromazine: Impaired alertness and psychomotor performance observed with combination use. (7.1)
- Rifampin: Combination use decreases exposure to and effects of zolpidem. (7.2)
- Ketoconazole: Combination use increases exposure to and effect of zolpidem. (7.2)

USE IN SPECIFIC POPULATIONS

- Pregnancy: Based on animal data, zolpidem may cause fetal harm. (8.1)
- Nursing mothers: Infant exposure via breast milk. (8.3)
- Pediatric use: Safety and effectiveness have not been established. Hallucinations (incidence rate 7.4%) and other psychiatric and/or nervous system adverse reactions were observed frequently in a study of pediatric patients with Attention-Deficit/Hyperactivity Disorder. (5.6, 8.4)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Zolpimist (zolpidem tartrate) Oral Spray is indicated for the short-term treatment of insomnia characterized by difficulties with sleep initiation. Zolpidem tartrate has been shown to decrease sleep latency for up to 35 days in controlled clinical studies [*see Clinical Studies (14)*]. The clinical trials performed in support of efficacy were 4-5 weeks in duration with the final formal assessments of sleep latency performed at the end of treatment.

2 DOSAGE AND ADMINISTRATION

The dose of Zolpimist should be individualized.

2.1 Dosage in adults

The recommended dose for adults is 10 mg once daily immediately before bedtime. The total Zolpimist dose should not exceed 10 mg per day.

2.2 Special populations

Elderly or debilitated patients may be especially sensitive to the effects of zolpidem tartrate. Patients with hepatic insufficiency do not clear the drug as rapidly as normal subjects. The recommended dose of Zolpimist in both of these patient populations is 5 mg once daily immediately before bedtime [*see Warnings and Precautions (5.6)*].

2.3 Use with CNS depressants

Dosage adjustment may be necessary when Zolpimist is combined with other CNS-depressant drugs because of the potentially additive effects [*see Warnings and Precautions (5.5)*].

2.4 Administration

Zolpimist is packaged in a child-resistant container. For detailed instructions on how to use Zolpimist, refer to the Patient Instructions for Use (following the Medication Guide). Zolpimist must be primed before it is used for the first time. To prime, patients should be told to point the black spray opening away from their face and other people and spray 5 times. For administration, the child-resistant container should be held upright with the black spray opening pointed directly into the mouth. The patient should fully press down on the pump to make sure a full dose (5 mg) of Zolpimist is sprayed directly into the mouth over the tongue. If a 10 mg dose is prescribed, a second spray should be administered.

If the patient does not use Zolpimist for at least 14 days, it must be primed again with 1 spray. The patient should be referred to the Patient Instructions for Use included at the end of the Medication Guide.

The effect of Zolpimist may be slowed by ingestion with or immediately after a meal.

3 DOSAGE FORMS AND STRENGTHS

Zolpimist is available as a clear, colorless, and cherry flavored solution designed to be sprayed directly into the mouth over the tongue. Each metered actuation (one spray) of Zolpimist delivers 5 mg of zolpidem tartrate in 100 μ L. Two actuations deliver 10 mg of zolpidem tartrate.

After an initial priming of 5 actuations, there are 60 metered actuations in each child-resistant container. The total number of available doses is dependent on the number of actuations per dose (1 or 2 actuations) and the frequency of priming.

4 CONTRAINDICATIONS

Known hypersensitivity to zolpidem tartrate [*see Warnings and Precautions (5.2)*].

5 WARNINGS AND PRECAUTIONS

5.1 Need to evaluate for co-morbid diagnoses

Because sleep disturbances may be the presenting manifestation of a physical and/or psychiatric disorder, symptomatic treatment of insomnia should be initiated only after a careful evaluation of the patient. **The failure of insomnia to remit after 7 to 10 days of treatment may indicate the presence of a primary psychiatric and/or medical illness that should be evaluated.**

Worsening of insomnia or the emergence of new thinking or behavioral abnormalities may be the consequence of an unrecognized psychiatric or physical disorder. Such findings have emerged during the course of treatment with sedative-hypnotic drugs, including zolpidem.

5.2 Severe anaphylactic and anaphylactoid reactions

Rare cases of angioedema involving the tongue, glottis, or larynx have been reported in patients after taking the first or subsequent doses of sedative-hypnotics, including zolpidem. Some patients have had additional symptoms such as dyspnea, throat closing, or nausea and vomiting that suggest anaphylaxis. Some patients have required medical therapy in the emergency department. If angioedema involves the throat, glottis, or larynx, airway obstruction may occur and be fatal. Patients who develop angioedema after treatment with zolpidem should not be rechallenged with the drug.

5.3 Abnormal thinking and behavioral changes

A variety of abnormal thinking and behavioral changes have been reported to occur in association with the use of sedative-hypnotics. Some of these changes may be characterized by decreased inhibition (e.g., aggressiveness and extroversion that seemed out of character), similar to effects produced by alcohol and other CNS depressants. Visual and auditory hallucinations have been reported as well as behavioral changes such as bizarre behavior, agitation, and depersonalization. In controlled trials, <1% of adults with insomnia who received zolpidem reported hallucinations. In a clinical trial, 7.4% of pediatric patients with insomnia associated with attention-deficit/hyperactivity disorder (ADHD), who received zolpidem, reported hallucinations [*see Use in Specific Populations (8.4)*].

Complex behaviors such as “sleep-driving” (i.e., driving while not fully awake after ingestion of a sedative-hypnotic, with amnesia for the event) have been reported with sedative-hypnotics, including zolpidem. These events can occur in sedative-hypnotic-naïve as well as in sedative-hypnotic-experienced persons. Although behaviors such as “sleep-driving” may occur with Zolpimist alone at therapeutic doses, the use of alcohol and other CNS depressants with zolpidem tartrate appears to increase the risk of such behaviors, as does the use of zolpidem at doses exceeding the maximum recommended dose. Due to the risk to the patient and the community, discontinuation of Zolpimist should be strongly considered for patients who report a “sleep-driving” episode. Other complex behaviors (e.g., preparing and eating food, making

phone calls, or having sex) have been reported in patients who are not fully awake after taking a sedative-hypnotic. As with “sleep-driving”, patients usually do not remember these events. Amnesia, anxiety, and other neuropsychiatric symptoms may occur unpredictably.

In primarily depressed patients, worsening of depression, including suicidal thoughts and actions (including completed suicides), has been reported in association with the use of sedative-hypnotics.

It can rarely be determined with certainty whether a particular instance of the abnormal behaviors listed above is drug induced, spontaneous in origin, or a result of an underlying psychiatric or physical disorder. Nonetheless, the emergence of any new behavioral sign or symptom of concern requires careful and immediate evaluation.

5.4 Withdrawal effects

Following the rapid dose decrease or abrupt discontinuation of sedative-hypnotics, there have been reports of signs and symptoms similar to those associated with withdrawal from other CNS-depressant drugs [*see Drug Abuse and Dependence (9)*].

5.5 CNS-depressant effects

Zolpidem tartrate, like other sedative-hypnotic drugs, has CNS-depressant effects. Due to the rapid onset of action, Zolpimist should only be administered immediately prior to going to bed. Patients should be cautioned against engaging in hazardous occupations requiring complete mental alertness or motor coordination such as operating machinery or driving a motor vehicle after ingesting the drug, including potential impairment of the performance of such activities that may occur the day following administration of Zolpimist. Zolpidem tartrate showed additive effects when combined with alcohol and should not be taken with alcohol. Patients should also be cautioned about possible combined effects with other CNS-depressant drugs. Dosage adjustments may be necessary when Zolpimist is administered with such agents because of the potentially additive effects.

5.6 Special populations

Use in the elderly and/or debilitated patients: Impaired motor and/or cognitive performance after repeated exposure or unusual sensitivity to sedative-hypnotic drugs is a concern in the treatment of elderly and/or debilitated patients. Therefore, the recommended Zolpimist dosage is 5 mg in such patients to decrease the possibility of side effects [*see Dosage and Administration (2.2)*]. These patients should be closely monitored.

Use in patients with concomitant illness: Clinical experience with zolpidem tartrate in patients with concomitant systemic illness is limited. Caution is advisable in using Zolpimist in patients with diseases or conditions that could affect metabolism or hemodynamic responses.

Although studies did not reveal respiratory depressant effects at hypnotic doses of zolpidem in normal subjects or in patients with mild to moderate chronic obstructive pulmonary disease (COPD), a reduction in the Total Arousal Index together with a reduction in lowest oxygen saturation and increase in the times of oxygen desaturation below 80% and 90% was observed in patients with mild-to-moderate sleep apnea when treated with zolpidem tartrate (10 mg) when

compared to placebo. Since sedative-hypnotics have the capacity to depress respiratory drive, precautions should be taken if Zolpimist is prescribed to patients with compromised respiratory function. Post-marketing reports of respiratory insufficiency, most of which involved patients with pre-existing respiratory impairment, have been received. Zolpimist should be used with caution in patients with sleep apnea syndrome or myasthenia gravis.

Data in end-stage renal failure patients repeatedly treated with zolpidem tartrate did not demonstrate drug accumulation or alterations in pharmacokinetic parameters. No dosage adjustment in renally impaired patients is required; however, these patients should be closely monitored [see *Clinical Pharmacology (12.3)*].

A study in subjects with hepatic impairment did reveal prolonged elimination in this group; therefore, treatment should be initiated with 5 mg in patients with hepatic compromise, and they should be closely monitored [see *Dosage and Administration (2.2)* and *Clinical Pharmacology (12.3)*].

Use in patients with depression: As with other sedative-hypnotic drugs, Zolpimist should be administered with caution to patients exhibiting signs or symptoms of depression. Suicidal tendencies may be present in such patients and protective measures may be required. Intentional over-dosage is more common in this group of patients; therefore, the least amount of drug that is feasible should be prescribed for the patient at any one time.

Use in pediatric patients: Safety and effectiveness of zolpidem have not been established in pediatric patients. In an 8-week study in pediatric patients (6-17 years of age) with insomnia associated with ADHD, zolpidem did not decrease sleep latency compared to placebo. Hallucinations were reported in 7.4% of the pediatric patients who received zolpidem tartrate; none of the pediatric patients who received placebo reported hallucinations [see *Use in Specific Populations (8.4)*].

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed in greater detail in other sections of the labeling:

- Serious anaphylactic and anaphylactoid reactions [see *Warnings and Precautions (5.2)*].
- Abnormal thinking, behavior changes, and complex behaviors [see *Warnings and Precautions (5.3)*].
- Withdrawal effects [see *Warnings and Precautions (5.4)*].
- CNS-depressant effects [see *Warnings and Precautions (5.5)*].

6.1 Clinical trials experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating incidence rates.

Associated with discontinuation of treatment: Approximately 4% of 1,701 patients who received zolpidem tartrate at all doses (1.25 to 90 mg) in U.S. premarketing clinical trials discontinued treatment because of an adverse reaction. Reactions most commonly associated with discontinuation from U.S. trials were daytime drowsiness (0.5%), dizziness (0.4%), headache (0.5%), nausea (0.6%), and vomiting (0.5%).

Approximately 4% of 1,959 patients who received zolpidem at all doses (1 to 50 mg) in similar foreign trials discontinued treatment because of an adverse reaction. Reactions most commonly associated with discontinuation from these trials were daytime drowsiness (1.1%), dizziness/vertigo (0.8%), amnesia (0.5%), nausea (0.5%), headache (0.4%), and falls (0.4%).

Data from a clinical study in which selective serotonin reuptake inhibitor (SSRI)-treated patients were given zolpidem revealed that four of the seven discontinuations during double-blind treatment with zolpidem (n=95) were associated with impaired concentration, continuing or aggravated depression, and manic reaction; one patient treated with placebo (n=97) was discontinued after an attempted suicide.

Most commonly observed adverse reactions in controlled trials: During short-term treatment (up to 10 nights) with zolpidem tartrate at doses up to 10 mg, the most commonly observed adverse reactions associated with the use of zolpidem and seen at statistically significant differences from placebo-treated patients were drowsiness (reported by 2% of zolpidem patients), dizziness (1%), and diarrhea (1%). During longer-term treatment (28 to 35 nights) with zolpidem tartrate at doses up to 10 mg, the most commonly observed adverse reactions associated with the use of zolpidem and seen at statistically significant differences from placebo-treated patients were dizziness (5%) and drugged feelings (3%).

Adverse reactions observed at an incidence of $\geq 1\%$ in controlled trials: The following tables enumerate treatment-emergent adverse reactions frequencies that were observed at an incidence equal to 1% or greater among patients with insomnia who received zolpidem tartrate and at a greater incidence than placebo in U.S. placebo-controlled trials. Events reported by investigators were classified utilizing a modified World Health Organization (WHO) dictionary of preferred terms for the purpose of establishing event frequencies. The prescriber should be aware that these figures cannot be used to predict the incidence of side effects in the course of usual medical practice, in which patient characteristics and other factors differ from those that prevailed in these clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigators involving related drug products and uses, since each group of drug trials is conducted under a different set of conditions. However, the cited figures provide the physician with a basis for estimating the relative contribution of drug and nondrug factors to the incidence of side effects in the population studied.

The following table was derived from results of 11 placebo-controlled short-term U.S. efficacy trials involving zolpidem in doses ranging from 1.25 to 20 mg. The table is limited to data from doses up to and including 10 mg, the highest dose recommended for use.

**Incidence of Treatment-Emergent Adverse Reactions in
 Placebo-Controlled Clinical Trials Lasting up to 10 Nights
 (Percentage of patients reporting)**

Body System/ Adverse Reaction*	Zolpidem (≤10mg) (n=685)	Placebo (n=473)
Central and Peripheral Nervous System		
Headache	7	6
Drowsiness	2	-
Dizziness	1	-
Gastrointestinal System		
Diarrhea	1	-

*Reactions reported by at least 1% of patients treated with zolpidem tartrate and at a greater frequency than placebo.

The following table was derived from results of three placebo-controlled long-term efficacy trials involving zolpidem tartrate. These trials involved patients with chronic insomnia who were treated for 28 to 35 nights with zolpidem tartrate at doses of 5, 10, or 15 mg. The table is limited to data from doses up to and including 10 mg, the highest dose recommended for use. The table includes only adverse reactions occurring at an incidence of at least 1% for zolpidem tartrate patients.

**Incidence of Treatment-Emergent Adverse Reactions in
 Placebo-Controlled Clinical Trials Lasting up to 35 Nights
 (Percentage of patients reporting)**

Body System/ Adverse Reaction*	Zolpidem (≤10mg) (n=152)	Placebo (n=161)
Autonomic Nervous System		
Dry mouth	3	1
Body as a Whole		
Allergy	4	1
Back pain	3	2
Influenza-like symptoms	2	-
Chest pain	1	-
Cardiovascular System		
Palpitation	2	-
Central and Peripheral Nervous System		
Drowsiness	8	5
Dizziness	5	1
Lethargy	3	1
Drugged feeling	3	-
Lightheadedness	2	1
Depression	2	1
Abnormal dreams	1	-
Amnesia	1	-
Sleep disorder	1	-

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 Zolpimist (zolpidem tartrate) Oral Spray

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Gastrointestinal System		
Diarrhea	3	2
Abdominal pain	2	2
Constipation	2	1
Respiratory System		
Sinusitis	4	2
Pharyngitis	3	1
Skin and Appendages		
Rash	2	1

*Reactions reported by at least 1% of patients treated with zolpidem tartrate and at a greater frequency than placebo.

Dose relationship for adverse reactions: There is evidence from dose comparison trials suggesting a dose relationship for many of the adverse reactions associated with zolpidem tartrate use, particularly for certain CNS and gastrointestinal adverse reactions.

Oral tissue-related adverse reactions in Zolpimist pharmacokinetics studies: The effect of chronic daily administrations of Zolpimist on oral tissue has not been evaluated. In pharmacokinetic studies conducted with Zolpimist in healthy subjects, an oral soft tissue exam was performed and no signs of oral irritation were noted following administration of single doses of Zolpimist.

Adverse event incidence across the entire preapproval database: Zolpidem tartrate was administered to 3,660 subjects in clinical trials throughout the United States, Canada, and Europe. Treatment-emergent adverse event associated with clinical trial participation were recorded by clinical investigators using terminology of their own choosing. To provide a meaningful estimate of the proportion of individuals experiencing treatment-emergent adverse events, similar types of untoward events were grouped into a smaller number of standardized event categories and classified utilizing a modified WHO dictionary of preferred terms.

The frequencies presented, therefore, represent the proportions of the 3,660 individuals exposed to zolpidem tartrate, at all doses, who experienced an event of the type cited on at least one occasion while receiving zolpidem tartrate. All reported treatment-emergent adverse events are included, except those already listed in the table above of adverse events in placebo-controlled studies, those coding terms that are so general as to be uninformative, and those events where a drug cause was remote. It is important to emphasize that, although the events reported did occur during treatment with zolpidem tartrate, they were not necessarily caused by it.

Adverse events are further classified within body system categories and enumerated in order of decreasing frequency using the following definitions: frequent adverse events are defined as those occurring in greater than 1/100 subjects; infrequent adverse events are those occurring in 1/100 to 1/1,000 patients; rare events are those occurring in less than 1/1,000 patients.

Autonomic nervous system: Infrequent: increased sweating, pallor, postural hypotension, syncope. Rare: abnormal accommodation, altered saliva, flushing, glaucoma, hypotension, impotence, increased saliva, tenesmus.

Body as a whole: Frequent: asthenia. Infrequent: edema, falling, fatigue, fever, malaise, trauma. Rare: allergic reaction, allergy aggravated, anaphylactic shock, face edema, hot flashes, increased ESR, pain, restless legs, rigors, tolerance increased, weight decrease.

Cardiovascular system: Infrequent: cerebrovascular disorder, hypertension, tachycardia. Rare: angina pectoris, arrhythmia, arteritis, circulatory failure, extrasystoles, hypertension aggravated, myocardial infarction, phlebitis, pulmonary embolism, pulmonary edema, varicose veins, ventricular tachycardia.

Central and peripheral nervous system: Frequent: ataxia, confusion, euphoria, headache, insomnia, vertigo. Infrequent: agitation, anxiety, decreased cognition, detached, difficulty concentrating, dysarthria, emotional lability, hallucination, hypoesthesia, illusion, leg cramps, migraine, nervousness, paresthesia, sleeping (after daytime dosing), speech disorder, stupor, tremor. Rare: abnormal gait, abnormal thinking, aggressive reaction, apathy, appetite increased, decreased libido, delusion, dementia, depersonalization, dysphasia, feeling strange, hypokinesia, hypotonia, hysteria, intoxicated feeling, manic reaction, neuralgia, neuritis, neuropathy, neurosis, panic attacks, paresis, personality disorder, somnambulism, suicide attempts, tetany, yawning.

Gastrointestinal system: Frequent: dyspepsia, hiccup, nausea. Infrequent: anorexia, constipation, dysphagia, flatulence, gastroenteritis, vomiting. Rare: enteritis, eructation, esophagospasm, gastritis, hemorrhoids, intestinal obstruction, rectal hemorrhage, tooth caries.

Hematologic and lymphatic system: Rare: anemia, hyperhemoglobinemia, leukopenia, lymphadenopathy, macrocytic anemia, purpura, thrombosis.

Immunologic system: Infrequent: infection. Rare: abscess, herpes simplex, herpes zoster, otitis externa, otitis media.

Liver and biliary system: Infrequent: abnormal hepatic function, increased SGPT. Rare: bilirubinemia, increased SGOT.

Metabolic and nutritional: Infrequent: hyperglycemia, thirst. Rare: gout, hypercholesteremia, hyperlipidemia, increased alkaline phosphatase, increased BUN, periorbital edema.

Musculoskeletal system: Frequent: arthralgia, myalgia. Infrequent: arthritis. Rare: arthrosis, muscle weakness, sciatica, tendonitis.

Reproductive system: Infrequent: menstrual disorder, vaginitis. Rare: breast fibroadenosis, breast neoplasm, breast pain.

Respiratory system: Frequent: upper respiratory infection. Infrequent: bronchitis, coughing, dyspnea, rhinitis. Rare: bronchospasm, epistaxis, hypoxia, laryngitis, pneumonia.

Skin and appendages: Infrequent: pruritus. Rare: acne, bullous eruption, dermatitis, furunculosis, injection-site inflammation, photosensitivity reaction, urticaria.

Special senses: Frequent: diplopia, vision abnormal. Infrequent: eye irritation, eye pain, scleritis, taste perversion, tinnitus. Rare: conjunctivitis, corneal ulceration, lacrimation abnormal, parosmia, photopsia.

Urogenital system: Frequent: urinary tract infection. Infrequent: cystitis, urinary incontinence. Rare: acute renal failure, dysuria, micturition frequency, nocturia, polyuria, pyelonephritis, renal pain, urinary retention.

7 DRUG INTERACTIONS

7.1 CNS-active drugs

Since the systematic evaluations of zolpidem in combination with other CNS-active drugs have been limited, careful consideration should be given to the pharmacology of any CNS-active drug to be used with Zolpimist. Any drug with CNS-depressant effects could potentially enhance the CNS-depressant effects of zolpidem.

Zolpidem tartrate was evaluated in healthy subjects in single-dose interaction studies for several CNS drugs. Imipramine in combination with zolpidem produced no pharmacokinetic interaction other than a 20% decrease in peak levels of imipramine, but there was an additive effect of decreased alertness. Similarly, chlorpromazine in combination with zolpidem tartrate produced no pharmacokinetic interaction, but there was an additive effect of decreased alertness and psychomotor performance. A study involving haloperidol and zolpidem revealed no effect of haloperidol on the pharmacokinetics or pharmacodynamics of zolpidem. The lack of a drug interaction following single-dose administration does not predict a lack following chronic administration.

An additive effect on psychomotor performance between alcohol and zolpidem was demonstrated [*see Warnings and Precautions (5.5)*].

A single-dose interaction study with zolpidem 10 mg and fluoxetine 20 mg at steady-state levels in male volunteers did not demonstrate any clinically significant pharmacokinetic or pharmacodynamic interactions. When multiple doses of zolpidem and fluoxetine at steady-state concentrations were evaluated in healthy females, the only significant change was a 17% increase in the zolpidem half-life ($t_{1/2}$). There was no evidence of an additive effect in psychomotor performance.

Following five consecutive nightly doses of zolpidem 10 mg in the presence of sertraline 50 mg (17 consecutive daily doses at 7:00 am in healthy female volunteers), zolpidem maximum concentration (C_{max}) was significantly higher (43%) and time to maximum concentration (T_{max}) was significantly decreased (53%). Pharmacokinetics of sertraline and N-desmethylsertraline were unaffected by zolpidem.

7.2 Drugs that affect drug metabolism via cytochrome P450

Some compounds known to inhibit CYP3A may increase exposure to zolpidem. The effect of inhibitors of other P450 enzymes has not been carefully evaluated.

A randomized, double-blind, crossover interaction study in ten healthy volunteers between itraconazole (200 mg once daily for 4 days) and a single dose of zolpidem (10 mg) given 5 hours after the last dose of itraconazole resulted in a 34% increase in $AUC_{0-\infty}$ of zolpidem. There were no significant pharmacodynamic effects of zolpidem on subjective drowsiness, postural sway, or psychomotor performance.

A randomized, placebo-controlled, crossover interaction study in eight healthy female subjects between five consecutive daily doses of rifampin (600 mg) and a single dose of zolpidem (20 mg) given 17 hours after the last dose of rifampin showed significant reductions of the AUC (–73%), C_{max} (–58%), and $t_{1/2}$ (–36%) of zolpidem, together with significant reductions in the pharmacodynamic effects of zolpidem.

A randomized double-blind crossover interaction study in twelve healthy subjects showed that co-administration of single 5 mg dose of zolpidem tartrate with ketoconazole, a potent CYP3A4 inhibitor, given as 200 mg twice daily for 2 days increased C_{max} of zolpidem by a factor of 1.3 and increased the total AUC of zolpidem by a factor of 1.7 compared to zolpidem alone and prolonged the $t_{1/2}$ by approximately 30% along with an increase in the pharmacodynamic effects of zolpidem. Caution should be used when ketoconazole is given with zolpidem and consideration should be given to using a lower dose of zolpidem when ketoconazole and zolpidem are given together. Patients should be advised that use of Zolpimist with ketoconazole may enhance the sedative effects.

7.3 Other drugs with no interaction with zolpidem

A study involving cimetidine/zolpidem and ranitidine/zolpidem combinations revealed no effect of either drug on the pharmacokinetics or pharmacodynamics of zolpidem.

Zolpidem had no effect on digoxin pharmacokinetics and did not affect prothrombin time when given with warfarin in normal subjects.

7.4 Drug-laboratory test interactions

Zolpidem is not known to interfere with commonly employed clinical laboratory tests. In addition, clinical data indicate that zolpidem does not cross-react with benzodiazepines, opiates, barbiturates, cocaine, cannabinoids, or amphetamines in two standard urine drug screen.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

There are no adequate and well-controlled studies of Zolpimist in pregnant women. Zolpimist should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Studies to assess the effects on children whose mothers took zolpidem during pregnancy have not been conducted. There is a published case report documenting the presence of zolpidem in human umbilical cord blood. Children born to mothers taking sedative-hypnotic drugs may be at some risk for withdrawal symptoms from the drug during the postnatal period. In addition,

neonatal flaccidity has been reported in infants born of mothers who received sedative-hypnotic drugs during pregnancy.

Administration of zolpidem to pregnant rats and rabbits resulted in adverse effects on offspring development at doses greater than the maximum recommended human dose (MRHD) of 10 mg/day (8 mg/day zolpidem base); however, teratogenicity was not observed.

When zolpidem was administered at oral doses of 4, 20, and 100 mg base/kg (≈ 5 , 24, and 120 times the MRHD on a mg/m² basis) to pregnant rats during the period of organogenesis, dose-related decreases in fetal skull ossification were observed at all but the low dose, which is 5 times the MRHD on a mg/m² basis. In rabbits treated during organogenesis with zolpidem at oral doses of 1, 4, and 16 mg base/kg (≈ 2.5 , 10, and 40 times the MRHD on a mg/m² basis), increased embryo-fetal death and incomplete fetal skeletal ossification were seen at the highest dose tested. The no-effect dose for embryo-fetal toxicity in rabbits is ≈ 10 times the MRHD on a mg/m² basis. Administration of zolpidem to rats at oral doses of 4, 20, and 100 mg base/kg (≈ 5 , 24, and 120 times the MRHD on a mg/m² basis) during the latter part of pregnancy and throughout lactation produced decreased offspring growth and survival at all but the low dose, which is ≈ 5 times the MRHD on a mg/m² basis.

8.2 Labor and delivery

Zolpimist has no established use in labor and delivery [*see Pregnancy (8.1)*].

8.3 Nursing mothers

Zolpidem is excreted into human milk. Studies in lactating mothers indicate that the $t_{1/2}$ of zolpidem is similar to that in non-lactating women (2.6 ± 0.3 hours). Between 0.004% and 0.019% of the total administered dose is excreted into milk. The effect of zolpidem on the nursing infant is not known.

8.4 Pediatric use

Safety and effectiveness of zolpidem have not been established in pediatric patients.

In an 8-week controlled study, 201 pediatric patients (6-17 years of age) with insomnia associated with ADHD (90% of the patients were using psychoanaleptics) were treated with an oral solution of zolpidem (n=136) or placebo (n=65). Zolpidem did not significantly decrease latency to persistent sleep, compared to placebo, as measured by polysomnography after 4 weeks of treatment. Psychiatric and nervous system disorders comprised the most frequent ($> 5\%$) treatment emergent adverse reactions observed with zolpidem tartrate versus placebo and included dizziness (23.5% vs 1.5%), headache (12.5% vs 9.2%), and hallucinations (7.4% vs 0%) [*see Warnings and Precautions (5.6)*]. Ten patients on zolpidem (7.4%) discontinued treatment due to an adverse reaction.

8.5 Geriatric use

A total of 154 patients in U.S. controlled clinical trials and 897 patients in non-U.S. clinical trials who received zolpidem were ≥ 60 years of age. In a pool of U.S. patients receiving zolpidem at doses of ≤ 10 mg or placebo, there were three adverse reactions occurring at an incidence of at

least 3% for zolpidem tartrate and for which the zolpidem incidence was at least twice the placebo incidence (i.e., they could be considered drug related).

Adverse Reaction	Zolpidem	Placebo
Dizziness	3%	0%
Drowsiness	5%	2%
Diarrhea	3%	1%

A total of 30/1,959 (1.5%) non-U.S. patients receiving zolpidem reported falls, including 28/30 (93%) who were ≥ 70 years of age. Of these 28 patients, 23 (82%) were receiving zolpidem doses >10 mg. A total of 24/1,959 (1.2%) non-U.S. patients receiving zolpidem reported confusion, including 18/24 (75%) who were ≥ 70 years of age. Of these 18 patients, 14 (78%) were receiving zolpidem doses >10 mg.

The dose of Zolpimist in elderly patients is 5 mg to minimize the adverse effects related to impaired motor and/or cognitive performance and unusual sensitivity to sedative-hypnotic drugs [see *Warnings and Precautions (5.6)*].

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled substance

Zolpidem tartrate is classified as a Schedule IV controlled substance by federal regulation.

9.2 Abuse

Abuse and addiction are separate and distinct from physical dependence and tolerance. Abuse is characterized by misuse of the drug for non-medical purposes, often in combination with other psychoactive substances. Tolerance is a state of adaptation in which exposure to a drug induces changes that result in a diminution of one or more of the drug effects over time. Tolerance may occur to both desired and undesired effects of drugs and may develop at different rates for different effects.

Addiction is a primary, chronic, neurobiological disease with genetic, psychosocial, and environmental factors influencing its development and manifestations. It is characterized by behaviors that include one or more of the following: impaired control over drug use, compulsive use, continued use despite harm, and craving. Drug addiction is a treatable disease, using a multidisciplinary approach, but relapse is common.

Studies of abuse potential in former drug abusers found that the effects of single doses of zolpidem tartrate 40 mg were similar, but not identical, to diazepam 20 mg, while zolpidem tartrate 10 mg was difficult to distinguish from placebo.

Because persons with a history of addiction to, or abuse of, drugs or alcohol are at increased risk for misuse, abuse and addiction of zolpidem, they should be monitored carefully when receiving zolpidem or any other hypnotic.

9.3 Dependence

Physical dependence is a state of adaptation that is manifested by a specific withdrawal syndrome that can be produced by abrupt cessation, rapid dose reduction, decreasing blood level of the drug, and/or administration of an antagonist.

Sedative-hypnotics have produced withdrawal signs and symptoms following abrupt discontinuation. These reported symptoms range from mild dysphoria and insomnia to a withdrawal syndrome that may include abdominal and muscle cramps, vomiting, sweating, tremors, and convulsions. The following adverse reactions which are considered to meet the DSM-III-R criteria for uncomplicated sedative-hypnotic withdrawal were reported during U.S. clinical trials following placebo substitution occurring within 48 hours following last zolpidem treatment: fatigue, nausea, flushing, lightheadedness, uncontrolled crying, emesis, stomach cramps, panic attack, nervousness, and abdominal discomfort. These reported adverse reactions occurred at an incidence of 1% or less. However, available data cannot provide a reliable estimate of the incidence, if any, of dependence during treatment at recommended doses. Post-marketing reports of abuse, dependence, and withdrawal have been received.

10 OVERDOSAGE

10.1 Signs and symptoms

In postmarketing experience of overdose with zolpidem tartrate alone, or in combination with CNS-depressant agents, impairment of consciousness ranging from somnolence to coma, cardiovascular and/or respiratory compromise, and fatal outcomes have been reported.

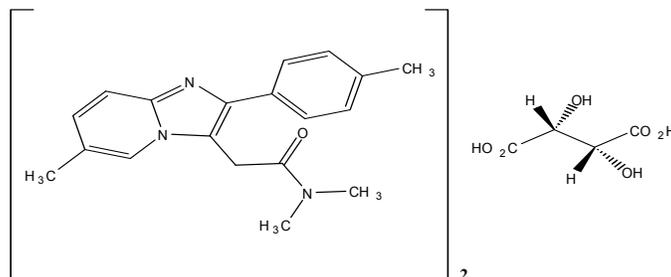
10.2 Recommended treatment

General symptomatic and supportive measures should be used along with immediate gastric lavage where appropriate. Intravenous fluids should be administered as needed. Zolpidem's sedative-hypnotic effect was shown to be reduced by flumazenil and therefore may be useful; however, flumazenil administration may contribute to the appearance of neurological symptoms (convulsions). As in all cases of drug overdose, respiration, pulse, blood pressure, and other appropriate signs should be monitored and general supportive measures employed. Hypotension and CNS depression should be monitored and treated by appropriate medical intervention. Sedating drugs should be withheld following zolpidem overdose, even if excitation occurs. The value of dialysis in the treatment of overdose has not been determined, although hemodialysis studies in patients with renal failure receiving therapeutic doses have demonstrated that zolpidem is not dialyzable.

As with the management of all overdose, the possibility of multiple drug ingestion should be considered. The physician may wish to consider contacting a poison control center for up-to-date information on the management of hypnotic drug product overdose.

11 DESCRIPTION

Zolpimist contains zolpidem tartrate, a non-benzodiazepine hypnotic of the imidazopyridine class. Chemically, zolpidem is *N,N*,6-trimethyl-2-*p*-tolylimidazo[1,2-*a*] pyridine-3-acetamide L-(+)-tartrate (2:1). It has the following structure:



Zolpidem tartrate is a white to off-white crystalline powder that is sparingly soluble in water, alcohol, and propylene glycol. It has a molecular weight of 764.89.

Zolpimist is available as an oral solution designed to be sprayed directly into the mouth over the tongue. Each metered actuation of Zolpimist delivers 5 mg of zolpidem tartrate in 100 μ L. Two actuations deliver 10 mg of zolpidem tartrate. Zolpimist includes the following inactive ingredients: artificial cherry flavor, benzoic acid, citric acid monohydrate, hydrochloric acid, neotame, propylene glycol, and purified water.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of action

Zolpidem, the active moiety of zolpidem tartrate, is a hypnotic agent with a chemical structure unrelated to benzodiazepines, barbiturates, or other drugs with known hypnotic properties. It interacts with a GABA-BZ receptor complex and shares some of the pharmacological properties of the benzodiazepines. In contrast to the benzodiazepines which non-selectively bind to and activate all BZ receptor subtypes, zolpidem *in vitro* binds the BZ₁ receptor preferentially with a high affinity ratio of the α_1/α_5 subunits. This selective binding of zolpidem on the BZ₁ receptor is not absolute, but it may explain the relative absence of myorelaxant and anticonvulsant effects in animal studies as well as the preservation of deep sleep (stages 3 and 4) in human studies of zolpidem at hypnotic doses.

12.3 Pharmacokinetics

Zolpimist (zolpidem tartrate) Oral Spray is bioequivalent to Ambien® tablets (Sanofi-Aventis). The pharmacokinetic profile of Zolpimist is characterized by rapid absorption from the oral mucosa and gastrointestinal tract, and a short $t_{1/2}$ in healthy subjects.

In a single-dose crossover study in 10 healthy young (18-40 years of age) male subjects administered 2.5, 5, and 10 mg Zolpimist, the results demonstrated a linear relationship to dose for mean C_{max} and $AUC_{0-\infty}$ over the range of doses administered in the study.

In a single-dose crossover study in 43 healthy young (18-45 years of age) subjects administered 5 and 10 mg Zolpimist, the means for C_{max} were 114 (range: 19 to 197) and 210 ng/mL (range: 77 to 401), respectively, occurring at a mean T_{max} of approximately 0.9 hours for both. The mean zolpidem $t_{1/2}$ was 2.7 (range: 1.7 to 5.0) and 3.0 hours (range: 1.7 to 8.4), for 5 and 10 mg Zolpimist, respectively. In the same study, the means for C_{max} were 123 (range: 53 to 221) and 219 ng/mL (range: 101 to 446) for 5 and 10 mg Ambien® tablets, respectively, occurring at a mean T_{max} of 0.9 and 1.0 hours, respectively. The mean zolpidem $t_{1/2}$ was 2.8 (range: 1.5 to 6.0) and 3.1 hours (range: 1.1 to 8.6) for the 5 and 10 mg Ambien® tablets, respectively.

Zolpidem is converted to inactive metabolites that are eliminated primarily by renal excretion. Total protein binding for zolpidem was found to be $92.5 \pm 0.1\%$ and remained constant, independent of concentration between 40 and 790 ng/mL. Zolpidem did not accumulate in young adults following nightly dosing with 20 mg zolpidem tartrate for 2 weeks.

A food-effect crossover study in 14 healthy young (18-45 years of age) male subjects compared the pharmacokinetics of Zolpimist 10 mg when administered while fasting at least 8 hours or 5 minutes after eating a standard high-fat meal. Results demonstrated that with food, mean $AUC_{0-\infty}$ and C_{max} were decreased by 27% and 58%, respectively, while mean T_{max} was prolonged by 225% (from 0.8 to 2.6 hours). These results suggest that, for faster sleep onset, as with all zolpidem products, Zolpimist should not be administered with or immediately after a meal.

Special Populations:

Elderly: In the elderly, the dose for zolpidem tartrate should be 5 mg [see *Warnings and Precautions (5) and Dosage and Administration (2)*]. This recommendation is based on several studies in which the mean C_{max} , $t_{1/2}$, and AUC were significantly increased when compared to results in young adults administered zolpidem tartrate. In a pharmacokinetic study of 24 elderly (≥ 65 years of age) subjects administered 5 mg Zolpimist, the means for C_{max} and AUC were 134 ng/mL and 493 ng*hr/mL respectively, following administration of a single 5 mg oral dose of Zolpimist. Zolpidem tartrate did not accumulate in elderly subjects following nightly oral dosing of 10 mg for 1 week.

Hepatic Impairment: The pharmacokinetics of zolpidem in eight patients with chronic hepatic insufficiency were compared to results in healthy subjects. Following a single 20 mg oral zolpidem tartrate dose, mean C_{max} and AUC were found to be two times (250 vs 499 ng/mL) and five times (788 vs 4,203 ng*hr/mL) higher, respectively, in hepatically compromised patients. T_{max} did not change. The mean $t_{1/2}$ in cirrhotic patients of 9.9 hours (range: 4.1 to 25.8 hours) was greater than that observed in normal subjects of 2.2 hours (range: 1.6 to 2.4 hours). Dosing should be modified accordingly in patients with hepatic insufficiency [see *Dosage and Administration (2.2) and Warnings and Precautions (5.6)*].

Renal Impairment: The pharmacokinetics of zolpidem were studied in 11 patients with end-stage renal failure (mean $Cl_{Cr} = 6.5 \pm 1.5$ mL/min) undergoing hemodialysis three times a week, who were dosed with zolpidem tartrate 10 mg orally each day for 14 or 21 days. No statistically significant differences were observed for C_{max} , T_{max} , $t_{1/2}$, and AUC between the first and last day of drug administration when baseline concentration adjustments were made. On Day 1, C_{max} was 172 ± 29 ng/mL (range: 46 to 344 ng/mL). After repeated dosing for 14 or 21 days, C_{max} was 203 ± 32 ng/mL (range: 28 to 316 ng/mL). On Day 1, T_{max} was 1.7 ± 0.3 hours (range: 0.5 to 3.0 hours); after repeated dosing T_{max} was 0.8 ± 0.2 hour (range: 0.5 to 2.0 hours). This variation is accounted for by noting that last-day serum sampling began 10 hours after the previous dose, rather than after 24 hours. This resulted in residual drug concentration and a shorter period to reach maximal serum concentration. On Day 1, $t_{1/2}$ was 2.4 ± 0.4 hours (range: 0.4 to 5.1 hours). After repeated dosing, $t_{1/2}$ was 2.5 ± 0.4 hours (range: 0.7 to 4.2 hours). AUC was 796 ± 159 ng*hr/mL after the first dose and 818 ± 170 ng*hr/mL after repeated dosing. Zolpidem was not hemodialyzable. No accumulation of unchanged drug appeared after 14 or 21 days. Zolpidem pharmacokinetics were not significantly different in renally impaired patients.

No dosage adjustment is necessary in patients with compromised renal function. However, as a general precaution, these patients should be closely monitored.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, mutagenesis, impairment of fertility

Carcinogenesis: Zolpidem was administered to mice and rats for 2 years at dietary dosages of 4, 18, and 80 mg base/kg. In mice, these doses are ≈ 2.5 , 10, and 50 times the maximum recommended human dose (MRHD) of 10 mg/day (8 mg zolpidem base) on mg/m^2 basis. In rats, these doses are ≈ 5 , 20, and 100 times the MRHD on a mg/m^2 basis. No evidence of carcinogenic potential was observed in mice. In rats, renal tumors (lipoma, liposarcoma) were seen at the mid- and high doses.

Mutagenesis: Zolpidem was negative in *in vitro* (bacterial reverse mutation, mouse lymphoma, and chromosomal aberration) and *in vivo* (mouse micronucleus) genetic toxicology assays.

Impairment of fertility: Oral administration of zolpidem (doses of 4, 20, and 100 mg base/kg or ≈ 5 , 24, and 120 times the MRHD on a mg/m^2 basis) to rats prior to and during mating, and continuing in females through postpartum day 25, resulted in irregular estrus cycles and prolonged precoital intervals. The no-effect dose for these findings is ≈ 24 times the MRHD on a mg/m^2 basis. There was no impairment of fertility at any dose tested.

CLINICAL STUDIES

14.1 Transient insomnia

Normal adults experiencing transient insomnia (n=462) during the first night in a sleep laboratory were evaluated in a double-blind, parallel group, single-night trial comparing two doses of zolpidem (7.5 and 10 mg) and placebo. Both zolpidem doses were superior to placebo on objective (polysomnographic) measures of sleep latency, sleep duration, and number of awakenings.

Normal elderly adults (mean age 68) experiencing transient insomnia (n=35) during the first two nights in a sleep laboratory were evaluated in a double-blind, crossover, 2-night trial comparing four doses of zolpidem (5, 10, 15, and 20 mg) and placebo. All zolpidem doses were superior to placebo on the two primary PSG parameters (sleep latency and efficiency) and all four subjective outcome measures (sleep duration, sleep latency, number of awakenings, and sleep quality).

14.2 Chronic insomnia

Zolpidem was evaluated in two controlled studies for the treatment of patients with chronic insomnia (most closely resembling primary insomnia, as defined in the APA Diagnostic and Statistical Manual of Mental Disorders, DSM-IVTM). Adult outpatients with chronic insomnia (n=75) were evaluated in a double-blind, parallel group, 5-week trial comparing two doses of zolpidem tartrate and placebo. On objective (polysomnographic) measures of sleep latency and sleep efficiency, zolpidem 10 mg was superior to placebo on sleep latency for the first 4 weeks and on sleep efficiency for weeks 2 and 4. Zolpidem was comparable to placebo on number of awakenings at both doses studied.

Adult outpatients (n=141) with chronic insomnia were also evaluated, in a double-blind, parallel group, 4-week trial comparing two doses of zolpidem and placebo. Zolpidem 10 mg was superior to placebo on a subjective measure of sleep latency for all 4 weeks, and on subjective measures of total sleep time, number of awakenings, and sleep quality for the first treatment week.

Increased wakefulness during the last third of the night as measured by polysomnography has not been observed in clinical trials with zolpidem.

14.3 Studies pertinent to safety concerns for sedative-hypnotic drugs

Next-day residual effects: Next-day residual effects of zolpidem tartrate were evaluated in seven studies involving normal subjects. In three studies in adults (including one study in a phase advance model of transient insomnia) and in one study in elderly subjects, a small but statistically significant decrease in performance was observed in the Digit Symbol Substitution Test (DSST) when compared to placebo. Studies of zolpidem tartrate in non-elderly patients with insomnia did not detect evidence of next-day residual effects using the DSST, the Multiple Sleep Latency Test (MSLT), and patient ratings of alertness.

Rebound effects: There was no objective (polysomnographic) evidence of rebound insomnia at recommended doses seen in studies evaluating sleep on the nights following discontinuation of zolpidem tartrate. There was subjective evidence of impaired sleep in the elderly on the first post-treatment night at doses above the recommended elderly dose of 5 mg.

Memory impairment: Controlled studies in adults utilizing objective measures of memory yielded no consistent evidence of next-day memory impairment following the administration of zolpidem tartrate. However, in one study involving zolpidem doses of 10 and 20 mg, there was a significant decrease in next-morning recall of information presented to subjects during peak drug effect (90 minutes post-dose) (i.e., these subjects experienced anterograde amnesia). There was also subjective evidence from adverse event data for anterograde amnesia occurring in association with the administration of zolpidem tartrate, predominantly at doses above 10 mg.

Effects on sleep stages: In studies that measured the percentage of sleep time spent in each sleep stage, zolpidem tartrate has generally been shown to preserve sleep stages. Sleep time spent in stages 3 and 4 (deep sleep) was found comparable to placebo with only inconsistent, minor changes in REM (paradoxical) sleep at the recommended dose.

16 HOW SUPPLIED/STORAGE AND HANDLING

Zolpimist is available in a child-resistant container. Each container includes a child-resistant cap and base with a metered-dose pump assembly and clear over cap. Each container contains 8.2 g of product formulation. One and two actuations of Zolpimist are equal to 5 and 10 mg of zolpidem tartrate, respectively. There are 60 metered actuations per container after 5 initial priming actuations. Zolpimist is supplied as:

NDC Number
 XXXXX-001-01

Size
 Carton includes a child-resistant container with 8.2 g of product formulation; 60 metered actuations per container

FDA Approved Labeling 12.19.08 3pm
NovaDel Pharma Inc.
Zolpimist (zolpidem tartrate) Oral Spray

New Drug Application
NDA 022196, SN 0021
December 2008

Store upright at 25 °C (77 °F) with excursions permitted to 15-30 °C (59-86 °F) (*USP* Controlled Room Temperature). Do not freeze. Avoid prolonged product exposure to temperatures above 30 °C (86 °F). The child-resistant container should be discarded when the labeled number of actuations (60 sprays) have been used.

KEEP OUT OF REACH OF CHILDREN.

17 PATIENT COUNSELING INFORMATION

Prescribers or other healthcare professionals should inform patients, their families, and their caregivers about the benefits and risks associated with treatment with sedative-hypnotics, should counsel them in its appropriate use, and should instruct them to read the accompanying Medication Guide and Patient Instructions for Use [*see Section 17.4 Medication Guide and Patient Instructions for Use*].

17.1 Severe anaphylactic and anaphylactoid reactions

Inform patients that severe anaphylactic and anaphylactoid reactions have occurred with zolpidem. Describe the signs/symptoms of these reactions and advise patients to seek medical attention immediately if any of them occur.

17.2 Sleep-driving and other complex behaviors

There have been reports of people getting out of bed after taking a sedative-hypnotic and driving their cars while not fully awake, often with no memory of the event. If a patient experiences such an episode, it should be reported to his or her doctor immediately, since “sleep-driving” can be dangerous. This behavior is more likely to occur when Zolpimist is taken with alcohol or other central nervous system depressants [*see Warnings and Precautions (5.3)*]. Other complex behaviors (e.g., preparing and eating food, making phone calls, or having sex) have been reported in patients who are not fully awake after taking a sedative-hypnotic. As with “sleep-driving”, patients usually do not remember these events.

In addition patients should be advised to report all concomitant medications to the prescriber. Patients should be instructed to report events such as “sleep-driving” and other complex behaviors immediately to the prescriber.

17.3 Administration instructions

See the Dosage and Administration section [*see Administration (2.4)*]. Zolpimist is packaged in a child-resistant container. Patients should be referred to the Patient Instructions for Use (following the Medication Guide) for detailed instructions on how to use Zolpimist. Patients should be counseled to take Zolpimist right before they get into bed and only when they are able to stay in bed a full night (7-8 hours) before being active again. Zolpimist should not be taken with or immediately after a meal. Advise patients NOT to take Zolpimist when drinking alcohol.

17.4 Medication Guide and Patient Instructions for Use

MEDICATION GUIDE
Zolpimist Oral Spray (C-IV)
(zolpidem tartrate)
 Spray, Metered for Oral Use

Read the Medication Guide that comes with Zolpimist before you start taking it and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking to your doctor about your medical condition or treatment.

What is the most important information I should know about Zolpimist?

After taking Zolpimist, you may get up out of bed while not being fully awake and do an activity that you do not know you are doing. The next morning, you may not remember that you did anything during the night. You have a higher chance for doing these activities if you drink alcohol or take other medicines that make you sleepy with Zolpimist. Reported activities include:

- driving a car (“sleep-driving”)
- making and eating food
- talking on the phone
- having sex
- sleep-walking

Call your doctor right away if you find out that you have done any of the above activities after taking Zolpimist.

Important:

1. Take Zolpimist exactly as prescribed

- Do not take more Zolpimist than prescribed.
- Take Zolpimist right before you get in bed, not sooner.

2. Do not take Zolpimist if you:

- drink alcohol
- take other medicines that can make you sleepy. Talk to your doctor about all of

your medicines. Your doctor will tell you if you can take Zolpimist with your other medicines.

- cannot get a full night sleep

What is Zolpimist?

Zolpimist is a sedative-hypnotic (sleep) medicine. Zolpimist is used in adults for the short-term treatment of a sleep problem called insomnia. Symptoms of insomnia include:

- trouble falling asleep

Zolpimist is not for children.

Zolpimist is a federally controlled substance (C-IV) because it can be abused and lead to dependence. Keep Zolpimist in a safe place to prevent misuse and abuse. Selling or giving away Zolpimist may harm others, and is against the law. Tell your doctor if you have ever abused or have been dependent on alcohol, prescription medicines, or street drugs.

Who should not take Zolpimist? Do not take Zolpimist if you have had an allergic reaction to zolpidem (Ambien, Ambien CR, Zolpimist). Some signs of allergic reaction may be swelling of the face, a feeling of the throat closing, or difficulty breathing shortly after taking Zolpidem.

See the end of this Medication Guide for a complete list of ingredients in Zolpimist.

Zolpimist may not be right for you. Before starting Zolpimist, tell your doctor about all of your health conditions, including if you:

- have a history of depression, mental illness, or suicidal thoughts
- have a history of drug or alcohol abuse or addiction
- have kidney or liver disease
- have a lung disease or breathing problems
- are pregnant, planning to become pregnant, or breastfeeding

Tell your doctor about all the medicines you take including prescription and nonprescription medicines, vitamins, and herbal supplements. Medicines can interact with each other, sometimes causing serious side effects. **Do not take Zolpimist with other medicines that can make you sleepy.**

Know the medicines you take. Keep a list of your medicines with you to show your doctor and pharmacist each time you get a new medicine.

How should I take Zolpimist?

- Take Zolpimist exactly as prescribed. Do not take more Zolpimist than prescribed for you.
- **Take Zolpimist right before you get into bed.**
- **Do not take Zolpimist unless you are able to stay in bed a full night (7-8 hours) before you must be active again.**
- For faster sleep onset, Zolpimist should NOT be taken with or immediately after a meal.
- Call your doctor if your insomnia worsens or is not better within 7 to 10 days. This may mean that there is

another condition causing your sleep problem.

- If you take too much Zolpimist or overdose, call your doctor or poison control center right away, or get emergency treatment.

What are the possible side effects of Zolpimist?

Serious side effects of Zolpimist include:

- **getting out of bed while not being fully awake and doing an activity that you do not know you are doing.** (See "What is the most important information I should know about Zolpimist?")
- **abnormal thoughts and behavior.** Symptoms include more outgoing or aggressive behavior than normal, confusion, agitation, hallucinations, worsening of depression, and suicidal thoughts or actions.
- **memory loss**
- **anxiety**
- **severe allergic reactions.** Symptoms include swelling of the tongue or throat, trouble breathing, and nausea and vomiting. Get emergency medical help if you get these symptoms after taking Zolpimist.

Call your doctor right away if you have any of the above side effects or any other side effects that worry you while using Zolpimist.

The most common side effects of Zolpimist are:

- drowsiness
- dizziness
- diarrhea
- "drugged feelings"
- You may still feel drowsy the next day after taking Zolpimist. **Do not drive or do other dangerous activities after**

taking Zolpimist until you feel fully awake.

After you stop taking a sleep medicine, you may have symptoms for 1 or 2 days such as: tiredness, trouble sleeping, nausea, flushing, lightheadedness, uncontrolled crying, vomiting, stomach cramps, panic attack, nervousness, and stomach area pain.

These are not all the side effects of Zolpimist. Ask your doctor or pharmacist for more information.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store Zolpimist?

- Store Zolpimist in an upright position at 59 °F to 86 °F (15 °C to 30 °C).
- Do not freeze.
- Avoid prolonged product exposure above 86 °F (30 °C).
- The child-resistant container should be thrown away when the 60 sprays have been used.

Keep Zolpimist and all medicines out of reach of children.

General Information about Zolpimist

- Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide.

- Do not use Zolpimist for a condition for which it was not prescribed.
- Do not share Zolpimist with other people, even if you think they may have the same symptoms that you have. It may harm them and it is against the law.

This Medication Guide summarizes the most important information about Zolpimist. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about Zolpimist that is written for healthcare professionals. For more information about Zolpimist, call 1-800-XXX-XXXX.

What are the ingredients in Zolpimist?

Active Ingredient: Zolpidem tartrate

Inactive Ingredients: artificial cherry flavor, benzoic acid, citric acid monohydrate, hydrochloric acid, neotame, propylene glycol, and purified water.

Rx Only

Revised December 2008

This Medication Guide has been approved by U.S. Food and Drug Administration.

NovaDel Pharma Inc.
Flemington, NJ 08822

Patient Instructions for Use Zolpimist (zolpidem tartrate) Spray, Metered for Oral Use

Be sure to carefully read, understand, and follow these instructions so that you use Zolpimist the right way. Ask your doctor or pharmacist if you have any questions about how to use Zolpimist.



Priming:

Before you use Zolpimist for the first time or if you have not used Zolpimist for 14 days, you will need to prime the pump (Steps 1-6). Otherwise go directly to Step 7.

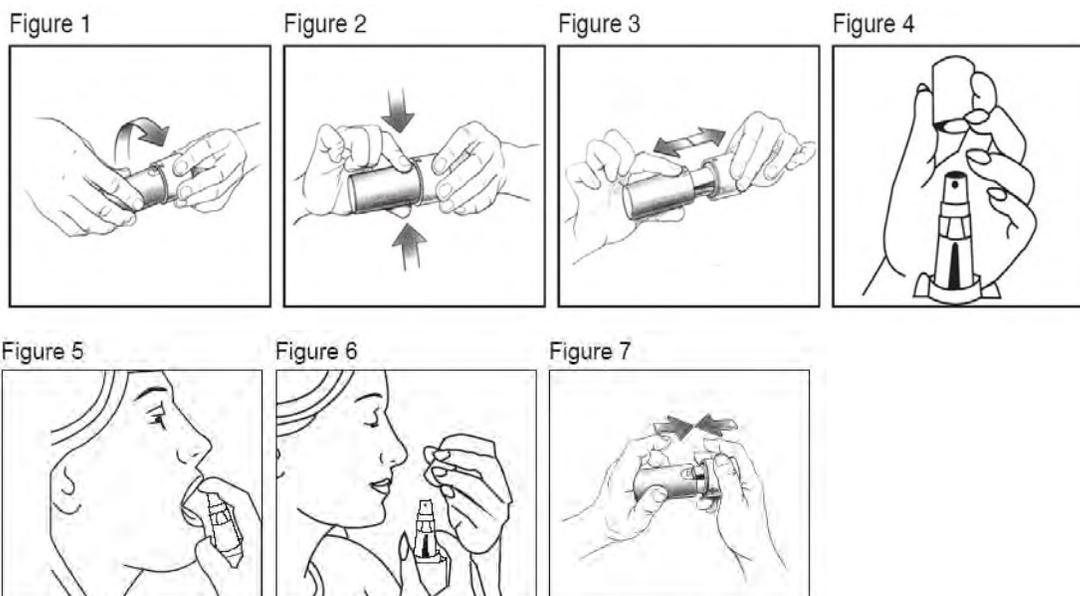
To prime the pump:

1. Line up the arrows on the child-resistant cap and base (see Figure 1).
2. Squeeze the cap at arrows (see Figure 2).
3. Pull the cap and base to separate (see Figure 3).
4. Remove the clear protective cap from the pump (see Figure 4).
5. Hold the container upright. Point the black spray opening in a safe direction away from your face and other people. Fully press down on the pump with your forefinger. Release the pump and let the pump return to the starting position.
6. Follow step 5 and press down on the pump 4 more times. You should see a fine spray. Zolpimist is now ready to use. Now go directly to Step 11.

Taking a dose of Zolpimist:

- **If you are using Zolpimist for the first time or you have not used Zolpimist for 14 days, you will need to prime the pump (Steps 1-6). Otherwise, there is no need to prime the pump.**
- **Take Zolpimist exactly as prescribed. Do not take more Zolpimist than prescribed for you.** Your doctor will tell you whether to take 1 or 2 sprays of Zolpimist.
- **Take Zolpimist right before you get into bed.**

- **Do not take Zolpimist unless you are able to stay in bed a full night (7-8 hours) before you must be active again.**
7. Line up the arrows on the child-resistant cap and base (see Figure 1).
 8. Squeeze the cap at arrows (see Figure 2).
 9. Pull the cap and base to separate (see Figure 3).
 10. Remove the clear protective cap from the pump (see Figure 4).
 11. Hold the container upright with the black spray opening pointed directly into your mouth. Fully press down on the pump to make sure that a full dose of Zolpimist is sprayed directly into your open mouth over your tongue (see Figure 5).
 12. Let the pump return to the starting position. If your doctor prescribed only one spray of Zolpimist (5 mg dose), go directly to Step 14.
 13. If your doctor prescribes a second spray of Zolpimist (10 mg dose), repeat Step 11.
 14. Put the clear protective cap back over the pump at the top of the child-resistant base after each use (see Figure 6).
 15. Snap the child-resistant cap back onto the base and rotate the child-resistant cap and the child-resistant base so that the arrows are not lined up (see Figure 7).
 16. The child-resistant container should be thrown away when the 60 sprays have been used.



There are no special requirements for cleaning and maintaining Zolpimist. Professional assistance regarding questions about product performance or use can be obtained by calling 1-800-XXX-XXXX.

See Medication Guide section “How should I store Zolpimist?” for instructions about how to store Zolpimist.

Manufactured for
NovaDel Pharma Inc.
Flemington, NJ 08822
by

NovaDel Pharma Inc.
Zolpimist (zolpidem tartrate) Oral Spray

New Drug Application
NDA 022196, SN 0021
December 2008

Rechon Life Sciences AB
SE-216 10 Limhamn, Sweden

Prepared December 2008

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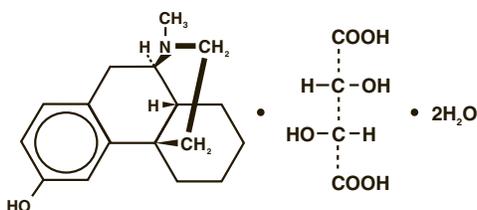
Roxane Laboratories, Inc.
Columbus, Ohio 43216

LEVORPHANOL 
TARTRATE
Tablets USP, 2 mg

R_x only

DESCRIPTION

Levorphanol tartrate is a potent opioid analgesic with a molecular formula of $C_{17}H_{23}NO \cdot C_4H_6O_6 \cdot 2H_2O$ and molecular weight 443.5. Each mg of levorphanol tartrate is equivalent to 0.58 mg levorphanol base. Chemically levorphanol is levo-3-hydroxy-N-methylmorphinan. The USP nomenclature is 17-methylmorphinan 3-ol tartrate (1:1)(Salt) dihydrate. The material has 3 asymmetric carbon atoms. The chemical structure is:



Levorphanol tartrate is a white crystalline powder, soluble in water and ether but insoluble in chloroform. Each tablet, for oral administration, contains 2 mg levorphanol tartrate. In addition, each tablet contains anhydrous lactose, corn starch, and magnesium stearate.

CLINICAL PHARMACOLOGY

Pharmacodynamics

Levorphanol is a potent synthetic opioid similar to morphine in its actions. Like other mu-agonist opioids it is believed to act at receptors in the periventricular and periaqueductal gray matter in both the brain and spinal cord to alter the transmission and perception of pain. Onset of analgesia and peak analgesic effect following administration of levorphanol are similar to morphine when administered at equianalgesic doses.

Levorphanol produces a degree of respiratory depression similar to that produced by morphine at equianalgesic doses, and like many mu-opioid drugs, levorphanol produces euphoria or has a positive effect on mood in many individuals.

As with other opioids, the blood levels required for analgesia are determined by the opioid tolerance of the patient and are likely to rise with chronic use. The rate of development of tolerance is highly variable and is determined by the dose, dosing interval, age, use of concomitant drugs and physical status of the patient. While blood levels of opioid drugs may be helpful in assessing individual cases, dosage is usually adjusted by careful clinical observation of the patient.

Pharmacokinetics

The pharmacokinetics of levorphanol have been studied in a limited number of cancer patients following intravenous (IV), intramuscular (IM) and oral (PO) administration. Following IV administration, plasma concentrations of levorphanol decline in a triexponential manner with a terminal half-life of 11 to 16 hours and a clearance of 0.78 to 1.1 L/kg/hr. Based on terminal half-life, steady-state plasma concentrations should be achieved by the third day of dosing. Levorphanol is rapidly distributed (<1 hr) and redistributed (1 to 2 hours) following IV administration and has a steady-state volume of distribution of 10 to 13 L/kg. *In vitro* studies of protein binding indicate that levorphanol is only 40% bound to plasma proteins.

No pharmacokinetic studies of the absorption of IM levorphanol are available, but clinical data suggests that absorption is rapid with onset of effects within 15 to 30 minutes of administration.

Levorphanol is well absorbed after PO administration with peak plasma concentrations occurring approximately 1 hour after dosing. The bioavailability of levorphanol tablets compared to IM or IV administration is not known.

Plasma concentrations of levorphanol following chronic administration in patients with cancer increased with the dose, but the analgesic effect was dependent on the degree of opioid tolerance of the patient. Expected steady-state plasma concentrations for a 6-hour dosing interval can reach 2 to 5 times those following a single dose, depending on the patient's individual clearance of the drug. Very high plasma concentrations of levorphanol can be reached in patients on chronic therapy due to the long half-life of the drug. One study in 11 patients using the drug for control of cancer pain reported plasma concentra-

tions from 5 to 10 ng/mL after a single 2 mg dose and up to 50 to 100 ng/mL after repeated oral doses of 20 to 50 mg/day.

Animal studies suggest that levorphanol is extensively metabolized in the liver and is eliminated as the glucuronide metabolite. This renally excreted inactive glucuronide metabolite accumulates with chronic dosing in plasma at concentrations that reach fivefold that of the parent compound.

The effects of age, gender, hepatic and renal disease on the pharmacokinetics of levorphanol are not known. As with all drugs of this class, patients at the extremes of age are expected to be more susceptible to adverse effects because of a greater pharmacodynamic sensitivity and probable increased variability in pharmacokinetics due to age or disease.

Clinical Trials

Clinical trials have been reported in the medical literature that investigated the use of levorphanol as a preoperative medication, as a postoperative analgesic and in the management of chronic pain due primarily to malignancy. In each of these clinical settings levorphanol has been shown to be an effective analgesic of the mu-opioid type and similar to morphine, meperidine or fentanyl.

Levorphanol has been studied in chronic cancer patients. Dosages were individualized to each patient's level of opioid tolerance. In one study, starting doses of 2 mg twice a day often had to be advanced by 50% or more within a few weeks of starting therapy. A study of levorphanol indicates that the relative potency is approximately 4 to 8 times that of morphine, depending on the specific circumstances of use. In postoperative patients, intramuscular levorphanol was determined to be about 8 times as potent as intramuscular morphine, whereas in cancer patients with chronic pain, it was found to be only about 4 times as potent.

INDIVIDUALIZATION OF DOSAGE

Accepted medical practice dictates that the dose of any opioid analgesic be appropriate to the degree of pain to be relieved, the clinical setting, the physical condition of the patient, and the kind and dose of concurrent medication.

Levorphanol has a long half-life similar to methadone or other slowly excreted opioids, rather than quickly excreted agents such as morphine or meperidine. Slowly excreted drugs may have some advantages in the management of chronic pain. Unfortunately, the duration of pain relief after a single dose of a slowly excreted opioid cannot always be predicted from pharmacokinetic principles, and the inter-dose interval may have to be adjusted to suit the patient's individual pharmacodynamic response.

Levorphanol is 4 to 8 times as potent as morphine and has a longer half-life. Because there is incomplete cross-tolerance among opioids, when converting a patient from morphine to levorphanol, the total *daily* dose of oral levorphanol should begin at approximately 1/15 to 1/12 of the total *daily* dose of oral morphine that such patients had previously required and then the dose should be adjusted to the patient's clinical response. If a patient is to be placed on fixed-schedule dosing (round-the-clock) with this drug, care should be taken to allow adequate time after each dose change (approximately 72 hours) for the patient to reach a new steady-state before a subsequent dose adjustment to avoid excessive sedation due to drug accumulation.

INDICATIONS AND USAGE

Levorphanol Tartrate Tablets USP are indicated for the management of moderate to severe pain where an opioid analgesic is appropriate.

CONTRAINDICATIONS

Levorphanol Tartrate Tablets USP are contraindicated in patients hypersensitive to levorphanol tartrate.

WARNINGS

Respiratory Depression

Levorphanol, like morphine, may be expected to produce serious or potentially fatal respiratory depression if given in an excessive dose, too frequently, or if given in full dosage to compromised or vulnerable patients. This is because the doses required to produce analgesia in the general clinical population may cause serious respiratory depression in vulnerable patients. Safe usage of this potent opioid requires that the dose and dosage interval be individualized to each patient based on the severity of the pain, weight, age, diagnosis and physical status of the patient, and the kind and dose of concurrently administered medication.

The initial dose of levorphanol should be reduced by 50% or more when the drug is given to patients with any condition affecting respiratory reserve or in conjunction with other drugs affecting the respiratory center. Subsequent doses should then be individually titrated according to the patient's response.

Respiratory depression produced by levorphanol tartrate can be reversed by naloxone, a specific antagonist (see **OVER-DOSAGE**).

Preexisting Pulmonary Disease

Because levorphanol causes respiratory depression, it should be administered with caution to patients with impaired respiratory reserve or respiratory depression from some other cause (e.g., from other medication, uremia, severe infection, obstructive respiratory conditions, restrictive respiratory diseases, intrapulmonary shunting or chronic bronchial asthma). As with other strong opioids, use of levorphanol in acute or severe bronchial asthma is not recommended (see **Respiratory Depression**).

Head Injury and Increased Intracranial Pressure

The respiratory depressant effects of levorphanol with carbon dioxide retention and secondary elevation of cerebral spinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions or pre-existing increase in intracranial pressure. Opioids, including levorphanol, produce effects that may obscure neurological signs of further increase in pressure in patients with head injuries. In addition, levorphanol may affect level of consciousness that may complicate neurological evaluation.

Cardiovascular Effects

The use of levorphanol in acute myocardial infarction or in cardiac patients with myocardial dysfunction or coronary insufficiency should be limited because the effects of levorphanol on the work of the heart are unknown.

Hypotensive Effect

The administration of levorphanol may result in severe hypotension in the postoperative patient or in any individual whose ability to maintain blood pressure has been compromised by a depleted blood volume or by administration of drugs, such as phenothiazines or general anesthetics. Opioids may produce orthostatic hypotension in ambulatory patients.

Use in Liver Disease

Levorphanol should be administered with caution to patients with extensive liver disease who may be vulnerable to excessive sedation due to increased pharmacodynamic sensitivity or impaired metabolism of the drug.

Biliary Surgery

Levorphanol has been shown to cause moderate to marked rises in pressure in the common bile duct when given in analgesic doses. It is not recommended for use in biliary surgery.

Use in Alcoholism or Drug Dependence

Levorphanol has an abuse potential as great as morphine, and the prescription of this drug must always balance the prospective benefits against the risk of abuse and dependence. The use of levorphanol in patients with a history of alcohol or other drug dependence, either active or in remission, has not been specifically studied (see **DRUG ABUSE AND DEPENDENCE**).

PRECAUTIONS

General

As with other opioids, the administration of levorphanol may obscure the diagnosis or clinical course in patients with acute abdominal conditions. Levorphanol should be administered with caution and the initial dose should be reduced in patients who are elderly or debilitated and in those patients with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, toxic psychosis, prostatic hypertrophy or urethral stricture, acute alcoholism, or delirium tremens.

Information for Patients

If levorphanol is administered to ambulatory patients, they should be cautioned against engaging in hazardous occupations requiring complete mental alertness such as operating machinery or driving a motor vehicle. They should also be warned that concurrent use of levorphanol with central nervous system depressants (e.g., alcohol, sedatives, hypnotics, other opioids, barbiturates, tricyclic antidepressants, phenothiazines, tranquilizers, skeletal muscle relaxants and antihistamines) may result in additive central nervous system depressant effects. Patients should be made aware of the risk of orthostatic hypotension, dizziness and syncope in ambulatory patients taking levorphanol.

Drug Interactions

Interactions with Other CNS Agents: Concurrent use of levorphanol with all central nervous system depressants (e.g., alcohol, sedatives, hypnotics, other opioids, general anesthetics, barbiturates, tricyclic antidepressants, phenothiazines, tranquilizers, skeletal muscle relaxants and antihistamines) may result in additive central nervous system depressant effects. Respiratory depression, hypotension, and profound sedation or coma may occur. When such combined therapy is contemplated, the dose of one or both agents should be reduced. Although no interaction between MAO inhibitors and levorphanol has been observed, it is not recommended for use with MAO inhibitors.

Most cases of serious or fatal adverse events involving levorphanol reported to the manufacturer or the FDA have involved either the administration of large initial doses of the drug or too frequent doses of the drug to non-opioid tolerant patients, or the simultaneous administration of levorphanol with other drugs affecting respiration (see **INDIVIDUALIZATION OF DOSE** and **WARNINGS**). The initial dose of levorphanol should be reduced by approximately 50% or more when it is given to patients along with another drug affecting respiration.

Interactions with Mixed Agonist/Antagonist Opioid Analgesics: Agonist/antagonist analgesics (e.g., pentazocine, nalbuphine, butorphanol, dezocine and buprenorphine) should NOT be administered to a patient who has received or is receiving a course of therapy with a pure agonist opioid analgesic such as levorphanol. In opioid-dependent patients, mixed agonist/

antagonist analgesics may precipitate withdrawal symptoms.

Use in Ambulatory Patients

Levorphanol has been used in both inpatient and outpatient settings, but both physicians and patients must be aware of the risk of orthostatic hypotension, dizziness and syncope in ambulatory patients.

As with other opioids the use of levorphanol may impair mental and/or physical abilities required for the performance of potentially hazardous tasks or for the exercise of normal good judgment and patients and staff should be advised accordingly.

Concurrent use of levorphanol with central nervous system depressants (e.g., alcohol, sedatives, hypnotics, other opioids, barbiturates, tricyclic antidepressants, phenothiazines, tranquilizers, skeletal muscle relaxants and antihistamines) may result in additive central nervous system depressant effects.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No information about the effects of levorphanol on carcinogenesis, mutagenesis, or fertility is available.

Pregnancy

Teratogenic Effects: Pregnancy Category C: Levorphanol has been shown to be teratogenic in mice when given a single oral dose of 25 mg/kg. The tested dose caused a near 50% mortality of the mouse embryos. There are no adequate and well-controlled studies in pregnant women. Levorphanol should be used in pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects: Babies born to mothers who have been taking opioids regularly prior to delivery may be physically dependent.

A study in rabbits has demonstrated that at doses of 1.5 to 20 mg/kg, levorphanol administered intravenously crosses the placental barrier and depresses fetal respiration.

Labor and Delivery

The use of levorphanol in labor and delivery in humans has not been studied. However, as with other opioids, administration of levorphanol to the mother during labor and delivery may result in respiratory depression in the newborn. Therefore, its use during labor and delivery is not recommended.

Nursing Mothers

Studies of levorphanol concentrations in breastmilk have not been performed. However, morphine, which is structurally similar to levorphanol, is excreted in human milk. Because of the potential for serious adverse reactions from levorphanol in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Levorphanol is not recommended in children under the age of 18 years as the safety and efficacy of the drug in this population has not been established.

Geriatric Use

The initial dose of the drug should be reduced by 50% or more in the infirm elderly patient, even though there have been no reports of unexpected adverse events in older populations. All drugs of this class may be associated with a profound or prolonged effect in elderly patients for both pharmacokinetic and pharmacodynamic reasons and caution is indicated.

ADVERSE REACTIONS

In approximately 1400 patients treated with levorphanol in controlled clinical trials, the type and incidence of side effects were those expected of an opioid analgesic, and no unforeseen or unusual toxicity was reported.

Drugs of this type are expected to produce a cluster of typical opioid effects in addition to analgesia, consisting of nausea, vomiting, altered mood and mentation, pruritus, flushing, difficulties in urination, constipation, and biliary spasm. The frequency and intensity of these effects appears to be dose related. Although listed as adverse events these are expected pharmacologic actions of these drugs and should be interpreted as such by the clinician.

The following adverse events have been reported with the use of levorphanol:

Body as a Whole: abdominal pain, dry mouth, sweating

Cardiovascular System: cardiac arrest, shock, hypotension, arrhythmias including bradycardia and tachycardia, palpitations, extra-systoles

Digestive System: nausea, vomiting, dyspepsia, biliary tract spasm

Nervous System: coma, suicide attempt, convulsions, depression, dizziness, confusion, lethargy, abnormal dreams, abnormal thinking, nervousness, drug withdrawal, hypokinesia, dyskinesia, hyperkinesia, CNS stimulation, personality disorder, amnesia, insomnia

Respiratory System: apnea, cyanosis, hypoventilation

Skin & Appendages: pruritus, urticaria, rash, injection site reaction

Special Senses: abnormal vision, pupillary disorder, diplopia

Urogenital System: kidney failure, urinary retention, difficulty urinating

DRUG ABUSE AND DEPENDENCE

WARNING: May Be Habit Forming.

Levorphanol is a schedule II Controlled Substance. All drugs of this class (mu-opioids of the morphine type) are habit forming and should be stored, prescribed, used and disposed of accordingly. Psychological/physical dependence and tolerance may develop upon repeated administration of levorphanol.

Discontinuation of levorphanol after chronic use has been reported to result in withdrawal syndromes, and some reports of overuse and self-reported addiction have been received. Neither withdrawal nor withdrawal symptoms are usually expected in postoperative patients who used the drug for less than a week or in patients who are gradually tapered off the drug after longer use.

OVERDOSAGE

Most reports of overdosage known to the manufacturer and to the FDA involve three clinical situations. These are: 1) the use of larger than recommended doses or too frequent doses, 2) administration of the drug to children or small adults without any reduction in dosage, and 3) the use of the drug in ordinary dosage in patients compromised by concurrent illness.

As with all opioids, overdose can occur due to accidental or intentional misuse of this product, especially in infants and children who may gain access to the drug in the home. Based on its pharmacology, levorphanol overdosage would be expected to produce signs of respiratory depression, cardiovascular failure (especially in predisposed patients), and/or central nervous system depression. Serious overdosage with levorphanol is characterized by respiratory depression (a decrease in respiratory rate and/or tidal volume, periodic breathing, cyanosis), extreme somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, constricted pupils, and sometimes bradycardia and hypotension. In severe overdosage, apnea, circulatory collapse, cardiac arrest and death may occur.

Treatment

The specific treatment of suspected levorphanol tartrate overdosage is immediate establishment of an adequate airway and ventilation, followed (if necessary) by intravenous naloxone. The respiratory and cardiac status of the patient should be continuously monitored and appropriate supportive measures instituted, such as oxygen, intravenous fluids, and/or vasopressors if required. Physicians are reminded that the duration of levorphanol action far

exceeds the duration of action of naloxone, and repeated dosing with naloxone may be required. Naloxone should be administered cautiously to persons known or suspected to be physically dependent on levorphanol. In such cases an abrupt and complete reversal of opioid effects may precipitate an acute abstinence syndrome. If necessary to administer naloxone to the physically dependent patient, the antagonist should be administered with extreme care and by titration with smaller than usual doses of the antagonist.

DOSAGE AND ADMINISTRATION

Oral

The usual recommended starting dose for oral administration is 2 mg. This may be repeated in 6 to 8 hours as needed, provided the patient is assessed for signs of hypoventilation and excessive sedation. If necessary, the dose may be increased to up to 3 mg every 6 to 8 hours, after adequate evaluation of the patient's response. Higher doses may be appropriate in opioid tolerant patients. Dosage should be adjusted according to the severity of the pain; age, weight and physical status of the patient; the patient's underlying diseases; use of concomitant medications; and other factors (see **INDIVIDUALIZATION OF DOSAGE, WARNINGS** and **PRECAUTIONS**). Total oral daily doses of more than 6 to 12 mg in 24 hours are generally not recommended as starting doses in nonopioid tolerant patients; lower total *daily* doses may be appropriate.

Use in Chronic Pain

The dosage of levorphanol in patients with cancer or with other conditions for which chronic opioid therapy is indicated must be individualized (see **INDIVIDUALIZATION OF DOSAGE**). Levorphanol is 4 to 8 times as potent as morphine and has a longer half-life. Because there is incomplete, cross-tolerance among opioids, when converting a patient from morphine to levorphanol, the total *daily* dose of oral levorphanol should begin at approximately 1/15 to 1/12 of the total *daily* dose of oral morphine that such patients had previously required and then the dose should be adjusted to the patient's clinical response. If a patient is to be placed on fixed-schedule dosing (round-the-clock) with this drug, care should be taken to allow adequate time after each dose change (approximately 72 hours) for the patient to reach a new steady-state before a subsequent dose adjustment to avoid excessive sedation due to drug accumulation.

Note: As with all controlled substances, abuse by health care personnel is possible and the drug should be handled accordingly.

HOW SUPPLIED

Levorphanol Tartrate Tablets USP, 2 mg
White, scored tablets (Identified 54 410).
NDC 0054-0438-25: Bottles of 100 tablets.

Store at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature]. Dispense in a tight container as defined in the USP/NF.

DEA Order Form Required**10003340/04****Revised July 2011**

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Boehringer Ingelheim

Roxane Laboratories

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use VANOS Cream safely and effectively. See full prescribing information for VANOS Cream.

VANOS® (fluocinonide) cream, 0.1%

For topical use

Initial U.S. Approval: 1971

INDICATIONS AND USAGE

VANOS Cream is a corticosteroid indicated for the relief of the inflammatory and pruritic manifestations of corticosteroid responsive dermatoses in patients 12 years of age or older. (1)

Limitation of Use:

- Treatment beyond 2 consecutive weeks is not recommended and the total dosage should not exceed 60 g per week because of the potential for the drug to suppress the hypothalamic-pituitary-adrenal (HPA) axis. (1)
- Avoid use on the face, groin, or axillae. (1.2)
- Avoid use in perioral dermatitis or rosacea.

DOSAGE AND ADMINISTRATION

For topical use only. VANOS Cream is not for ophthalmic, oral, or intravaginal use. (2)

Psoriasis: apply a thin layer once or twice daily to the affected skin areas. (2)

Atopic Dermatitis: apply a thin layer once daily to the affected skin areas. (2)

Corticosteroid Responsive Dermatoses, other than psoriasis or atopic dermatitis: apply a thin layer once or twice daily to the affected areas. (2)

DOSAGE FORMS AND STRENGTHS

Cream, 0.1% (3)

CONTRAINDICATIONS

None (4)

WARNINGS AND PRECAUTIONS

- VANOS Cream has been shown to suppress the HPA axis. Systemic absorption of VANOS Cream may produce reversible hypothalamic-pituitary-adrenal (HPA) axis suppression, Cushing's syndrome, hyperglycemia and unmask latent diabetes (5.1)
- Systemic absorption may require evaluation for HPA axis suppression (5.1)
- Modify use should HPA axis suppression develop (5.1)
- Potent corticosteroids, use on large areas, prolonged use or occlusive use may increase systemic absorption (5.3)
- Local adverse reactions with topical steroids may include atrophy, striae, irritation, acneiform eruptions, hypopigmentation and allergic contact dermatitis and may be more likely to occur with occlusive use or more potent corticosteroids (5.3)
- Children may be more susceptible to systemic toxicity when treated with topical corticosteroids (5.1, 8.4)

ADVERSE REACTIONS

The most commonly reported adverse reactions ($\geq 1\%$) were headache, application site burning, nasopharyngitis, and nasal congestion. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Medicis, The Dermatology Company at 1-800-900-6389 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling

Revised: 03/2012

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- 1.2 Limitation of Use

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Indication

VANOS (fluocinonide) Cream, 0.1%, is indicated for the relief of the inflammatory and pruritic manifestations of corticosteroid responsive dermatoses in patients 12 years of age or older [see *Use in Specific Populations* (8.4)].

1.2 Limitation of Use

Treatment beyond 2 consecutive weeks is not recommended and the total dosage should not exceed 60 g per week because the safety of VANOS Cream for longer than 2 weeks has not been established and because of the potential for the drug to suppress the hypothalamic-pituitary-adrenal (HPA) axis. Therapy should be discontinued when control of the disease is achieved. If no improvement is seen within 2 weeks, reassessment of the diagnosis may be necessary. Do not use more than half of the 120 g tube per week.

VANOS Cream should not be used in the treatment of rosacea or perioral dermatitis, and should not be used on the face, groin, or axillae.

2 DOSAGE AND ADMINISTRATION

For topical use only. VANOS Cream is not for ophthalmic, oral, or intravaginal use.

For psoriasis, apply a thin layer of VANOS Cream once or twice daily to the affected skin areas as directed by a physician. Twice daily application for the treatment of psoriasis has been shown to be more effective in achieving treatment success during 2 weeks of treatment.

For atopic dermatitis, apply a thin layer of VANOS Cream once daily to the affected skin areas as directed by a physician. Once daily application for the treatment of atopic dermatitis has been shown to be as effective as twice daily treatment in achieving treatment success during 2 weeks of treatment [see *Clinical Studies* (14)].

For corticosteroid responsive dermatoses, other than psoriasis or atopic dermatitis, apply a thin layer of VANOS Cream once or twice daily to the affected areas as directed by a physician.

3 DOSAGE FORMS AND STRENGTHS

Cream, 0.1%.

Each gram of VANOS Cream contains 1 mg of fluocinonide in a white to off-white cream base.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Effect on Endocrine System

Systemic absorption of topical corticosteroids, including Vanos Cream, can produce reversible hypothalamic-pituitary-adrenal (HPA) axis suppression with the potential for clinical glucocorticosteroid insufficiency. This may occur during treatment or upon withdrawal of the topical corticosteroid. In addition, the use of VANOS Cream for longer than 2 weeks may suppress the immune system [see *Nonclinical Toxicology* (13.1)].

HPA axis suppression has been observed with VANOS Cream, 0.1% applied once or twice daily in 2 out of 18 adult patients with plaque-type psoriasis, 1 out of 31 adult patients with atopic dermatitis and 4 out of 123 pediatric patients with atopic dermatitis [see *Use in Specific Population* (8.4) and *Clinical Pharmacology* (12.2)].

Because of the potential for systemic absorption, use of topical corticosteroids, including Vanos Cream, may require that patients be periodically evaluated for HPA axis suppression. Factors that predispose a patient using a topical corticosteroid to HPA axis suppression include the use of more potent steroids, use over large surface areas, use over prolonged periods, use under occlusion, use on an altered skin barrier, and use in patients with liver failure.

An ACTH stimulation test may be helpful in evaluating patients for HPA axis suppression. If HPA axis suppression is documented, an attempt should be made to gradually withdraw the drug, to reduce the frequency of application, or to substitute a less potent steroid. Manifestations of adrenal

insufficiency may require supplemental systemic corticosteroids. Recovery of HPA axis function is generally prompt and complete upon discontinuation of topical corticosteroids.

Cushing's syndrome, hyperglycemia, and unmasking of latent diabetes mellitus can also result from systemic absorption of topical corticosteroids.

Use of more than one corticosteroid-containing product at the same time may increase the total systemic absorption of topical corticosteroids.

Studies conducted in pediatric patients demonstrated reversible HPA axis suppression after use of VANOS Cream. Pediatric patients may be more susceptible than adults to systemic toxicity from equivalent doses of VANOS Cream due to their larger skin surface-to-body-mass ratios [See *Use in Specific Populations* (8.4)].

5.2 Local Adverse Reactions with Topical Corticosteroids

Local adverse reactions may be more likely to occur with occlusive use, prolonged use or use of higher potency corticosteroids. Reactions may include atrophy, striae, telangiectasis, burning, itching, irritation, dryness, folliculitis, acneiform eruptions, hypopigmentation, perioral dermatitis, allergic contact dermatitis, secondary infection, and miliaria. Some local adverse reactions may be irreversible.

5.3 Concomitant Skin Infections

If concomitant skin infections are present or develop, an appropriate antifungal or antibacterial agent should be used. If a favorable response does not occur promptly, use of VANOS Cream should be discontinued until the infection has been adequately controlled.

5.4 Allergic Contact Dermatitis

If irritation develops, VANOS Cream should be discontinued and appropriate therapy instituted. Allergic contact dermatitis with corticosteroids is usually diagnosed by observing failure to heal rather than noting a clinical exacerbation as with most topical products not containing corticosteroids. Such an observation should be corroborated with appropriate diagnostic patch testing.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

In clinical trials, a total of 443 adult subjects with atopic dermatitis or plaque-type psoriasis were treated once daily or twice daily with VANOS Cream for 2 weeks. The most commonly observed adverse reactions in these clinical trials were as follows:

Table 1: Most Commonly Observed Adverse Reactions (≥1%) in Adult Clinical Trials

Adverse Reaction	VANOS Cream, once daily (n=216)	VANOS Cream, twice daily (n=227)	Vehicle Cream, once or twice daily (n=211)
Headache	8 (3.7%)	9 (4.0%)	6 (2.8%)
Application Site Burning	5 (2.3%)	4 (1.8%)	14 (6.6%)
Nasopharyngitis	2 (0.9%)	3 (1.3%)	3 (1.4%)
Nasal Congestion	3 (1.4%)	1 (0.4%)	0

Safety in patients 12 to 17 years of age was similar to that observed in adults.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post approval use of VANOS Cream:

Administration Site Conditions: discoloration, erythema, irritation, pruritus, swelling, pain and condition aggravated.

Immune System Disorders: hypersensitivity.

Nervous System Disorders: headache and dizziness.

Skin and Subcutaneous Tissue Disorders: acne, dry skin, rash, skin exfoliation and skin tightness.

Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects: Pregnancy Category C

There are no adequate and well-controlled studies in pregnant women. Therefore, VANOS Cream should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Corticosteroids have been shown to be teratogenic in laboratory animals when administered systemically at relatively low dosage levels. Some corticosteroids have been shown to be teratogenic after dermal application in laboratory animals.

8.3 Nursing Mothers

Systemically administered corticosteroids appear in human milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. It is not known whether topical administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in breast milk. Nevertheless, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

Safety and efficacy of VANOS Cream in pediatric patients younger than 12 years of age have not been established; therefore use in pediatric patients younger than 12 years of age is not recommended.

HPA axis suppression was studied in 4 sequential cohorts of pediatric patients with atopic dermatitis covering at least 20% of the body surface area, treated once daily or twice daily with VANOS Cream. The first cohort of 31 patients (mean 36.3% BSA) 12 to < 18 years old; the second cohort included 31 patients (mean 39.0% BSA) 6 to < 12 years old; the third cohort included 30 patients (mean 34.6% BSA) 2 to < 6 years old; the fourth cohort included 31 patients (mean 40.0% BSA) 3 months to < 2 years old. VANOS Cream caused HPA-axis suppression in 1 patient in the twice daily group in Cohort 1, 2 patients in the twice daily group in Cohort 2, and 1 patient in the twice daily group in Cohort 3. Follow-up testing 14 days after treatment discontinuation, available for all 4 suppressed patients, demonstrated a normally responsive HPA axis. Signs of skin atrophy were present at baseline and severity was not determined making it difficult to assess local skin safety. Therefore, the safety of VANOS Cream in patients younger than 12 years of age has not been demonstrated [see *Warnings and Precautions (5.2)*].

HPA axis suppression has not been evaluated in patients with psoriasis who are less than 18 years of age.

Because of a higher ratio of skin surface area to body mass, pediatric patients are at a greater risk than adults of HPA-axis suppression and Cushing's syndrome when they are treated with topical corticosteroids. They are therefore also at greater risk of adrenal insufficiency during or after withdrawal of treatment. Adverse effects including striae have been reported with inappropriate use of topical corticosteroids in infants and children.

HPA-axis suppression, Cushing's syndrome, linear growth retardation, delayed weight gain, and intracranial hypertension have been reported in children receiving topical corticosteroids. Manifestations of adrenal suppression in children include low plasma cortisol levels and absence of response to cosyntropin (ACTH₁₋₂₄) stimulation. Manifestations of intracranial hypertension include bulging fontanelles, headaches, and bilateral papilledema.

8.5 Geriatric Use

Clinical studies of VANOS Cream did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

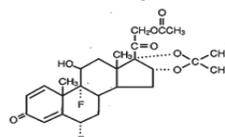
10 OVERDOSAGE

Topically applied VANOS Cream can be absorbed in sufficient amounts to produce systemic effects [see *Warnings and Precautions (5.1)*].

11 DESCRIPTION

VANOS (fluocinonide) Cream, 0.1% contains fluocinonide, a synthetic corticosteroid for topical dermatologic use. The corticosteroids constitute a class of primarily synthetic steroids used topically as anti-inflammatory and antipruritic agents. Fluocinonide has the chemical name 6 alpha, 9 alpha-difluoro-11 beta, 21-dihydroxy-16 alpha, 17 alpha-isopropylidenedioxypregna-1, 4-diene-3,20-dione 21-acetate. Its chemical formula is C₂₆H₃₂F₂O₇ and it has a molecular weight of 494.58.

It has the following chemical structure:



Fluocinonide is an almost odorless white to creamy white crystalline powder. It is practically insoluble in water and slightly soluble in ethanol.

Each gram of VANOS Cream contains 1 mg micronized fluocinonide in a cream base of propylene glycol USP, dimethyl isosorbide, glyceryl stearate (and) PEG-100 stearate, glyceryl monostearate NF, purified water USP, carbopol 980 NF, diisopropanolamine, and anhydrous citric acid USP.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Corticosteroids play a role in cellular signaling, immune function, inflammation, and protein regulation; however, the precise mechanism of action of VANOS Cream in corticosteroid responsive dermatoses is unknown.

12.2 Pharmacodynamics

Vasoconstrictor studies performed with VANOS Cream in healthy subjects indicate that it is in the super-high range of potency as compared with other topical corticosteroids; however, similar blanching scores do not necessarily imply therapeutic equivalence.

Application of VANOS Cream twice daily for 14 days in 18 adult subjects with plaque-type psoriasis (10–50% BSA, mean 19.6% BSA) and 31 adult subjects (17 treated once daily; 14 treated twice daily) with atopic dermatitis (2–10% BSA, mean 5% BSA) showed demonstrable HPA-axis suppression in 2 subjects with psoriasis (with 12% and 25% BSA) and 1 subject with atopic dermatitis (treated once daily, 4% BSA) where the criterion for HPA-axis suppression is a serum cortisol level of less than or equal to 18 micrograms per deciliter 30 minutes after stimulation with cosyntropin (ACTH₁₋₂₄) [see *Warnings and Precautions (5.1)*].

HPA-axis suppression following application of VANOS Cream, 0.1% (once or twice daily) was also evaluated in 123 pediatric patients from 3 months to < 18 years of age with atopic dermatitis (mean BSA range 34.6% - 40.0%). HPA-axis suppression was observed in 4 patients in the twice daily groups. Follow-up testing 14 days after treatment discontinuation demonstrated a normally responsive HPA axis in all 4 suppressed patients [see *Warnings and Precautions (5.1) and Use in Specific populations (8.4)*].

12.3 Pharmacokinetics

The extent of percutaneous absorption of topical corticosteroids is determined by many factors including the vehicle and the integrity of the epidermal barrier. Topical corticosteroids can be absorbed from normal intact skin. Inflammation and/or other disease processes in the skin may increase percutaneous absorption.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal studies have not been performed to evaluate the carcinogenic potential of VANOS Cream because of severe immunosuppression induced in a 13-week dermal rat study. The effects of fluocinonide on fertility have not been evaluated.

Fluocinonide revealed no evidence of mutagenic or clastogenic potential based on the results of two *in vitro* genotoxicity tests (Ames test and chromosomal aberration assay using human lymphocytes). However, fluocinonide was positive for clastogenic potential when tested in the *in vivo* mouse micronucleus assay.

Topical (dermal) application of 0.0003%-0.03% fluocinonide cream to rats once daily for 13 weeks resulted in a toxicity profile generally associated with long term exposure to corticosteroids including decreased skin thickness, adrenal atrophy, and severe immunosuppression. A NOAEL could not be determined in this study. In addition, topical (dermal) application of 0.1% fluocinonide cream plus UVR exposure to hairless mice for 13 weeks and 150-900 mg/kg/day of 0.1% fluocinonide cream to minipigs (a model which more closely approximates human skin) for 13 weeks produced glucocorticoid-related suppression of the HPA axis, with some signs of immunosuppression noted in the dermal minipig study. Although the clinical relevance of the findings in animals to humans is not clear, sustained glucocorticoid-related immune suppression may increase the risk of infection and possibly the risk for carcinogenesis.

Topical doses of 0% (fluocinonide cream vehicle), 0.0001%, 0.005% and 0.001% fluocinonide cream were evaluated in a 52 week dermal photocarcinogenicity study (40 weeks of treatment followed by 12 weeks of observation) conducted in hairless albino mice with concurrent exposure to low level ultraviolet radiation. Topical treatment with increasing concentrations of fluocinonide cream did not have an adverse effect in this study. The results of this study suggest that topical treatment with VANOS Cream would not enhance photo-carcinogenesis.

14 CLINICAL STUDIES

Two adequate and well-controlled efficacy and safety studies of VANOS Cream have been completed, one in adult subjects with plaque-type psoriasis (Table 2), and one in adult subjects with atopic dermatitis (Table 3). In each of these studies, subjects with between 2% and 10% body surface area involvement at baseline treated all affected areas either once daily or twice daily with VANOS Cream for 14 consecutive days. The primary measure of efficacy was the proportion of subjects whose condition was cleared or almost cleared at the end of treatment. The results of these studies are presented in the tables below as percent and number of patients achieving treatment success at Week 2.

Table 2: Plaque-type Psoriasis in Adults

	VANOS Cream, once daily (n=107)	Vehicle, once daily (n=54)	VANOS Cream, twice daily (n=107)	Vehicle, twice daily (n=55)
Subjects cleared	0 (0)	0 (0)	6 (6%)	0 (0)
Subjects achieving treatment success*	19 (18%)	4 (7%)	33 (31%)	3 (5%)

*Cleared or almost cleared

Table 3: Atopic Dermatitis in Adults

	VANOS Cream, once daily (n=109)	Vehicle, once daily (n=50)	VANOS Cream, twice daily (n=102)	Vehicle, twice daily (n=52)
Subjects cleared	11 (10%)	0 (0)	17 (17%)	0 (0)
Subjects achieving treatment success*	64 (59%)	6 (12%)	58 (57%)	10 (19%)

*Cleared or almost cleared

No efficacy studies have been conducted to compare VANOS (fluocinonide) Cream, 0.1% with any other topical corticosteroid product, including fluocinonide cream 0.05%.

16 HOW SUPPLIED/STORAGE AND HANDLING

VANOS Cream is white to off-white in color and is supplied in tubes as follows:

30 g (NDC 99207-525-30)
60 g (NDC 99207-525-60)
120 g (NDC 99207-525-10)

Store at controlled room temperature: 15° to 30°C (59° to 86°F).

Keep the tube tightly closed.

17 PATIENT COUNSELING INFORMATION

[See FDA-approved patient labeling (Patient Information)]

Patients using VANOS Cream should receive the following information and instructions. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or unintended effects:

- VANOS Cream is to be used as directed by the physician. It is for external use only. Avoid contact with the eyes. It should not be used on the face, groin, and underarms.
- VANOS Cream should not be used for any disorder other than that for which it was prescribed.
- The treated skin area should not be bandaged or otherwise covered or wrapped, so as to be occlusive unless directed by the physician.
- Patients should report to their physician any signs of local adverse reactions.
- Other corticosteroid-containing products should not be used with VANOS Cream without first talking to the physician.
- As with other corticosteroids, therapy should be discontinued when control is achieved. If no improvement is seen in 2 weeks, the patient should be instructed to contact a physician. The safety of the use of VANOS Cream for longer than 2 weeks has not been established.
- Patients should be informed to not use more than 60 g per week of VANOS Cream. Do not use more than half of the 120 g tube per week.
- Patients should inform their physicians that they are using VANOS Cream if surgery is contemplated.
- Patients should wash their hands after applying medication.

PATIENT INFORMATION

VANOS® (VAN-ōs) (fluocinonide)

Cream 0.1%

Important: For skin use only. Do not get VANOS Cream in your eyes, mouth, or vagina. Not for use on the face, groin, or underarms.

Read the Patient Information that comes with VANOS Cream before you start using it and each time you get a refill. There may be new information. This leaflet does not take the place of talking to your doctor about your condition or treatment.

What is VANOS Cream?

VANOS Cream is a prescription corticosteroid medicine used on the skin (topical) to treat adults and children 12 years and older with certain skin conditions that cause red, flaky, and itchy skin.

- You should not use VANOS Cream for longer than 2 weeks in a row.
- You should not use more than 60 grams of VANOS Cream or more than half of the 120 gram tube in 1 week.
- Vanos Cream should not be used:
 - if you have skin swelling or redness on the nose of face (rosacea)
 - for a scaly or bumpy rash around your mouth (perioral dermatitis)
 - on your face, underarms, or groin area

It is not known if VANOS Cream is safe and effective in children under 12 years of age.

What should I tell my doctor before using VANOS Cream?

Before using VANOS Cream, tell your doctor if you:

- have had irritation or other skin reaction to a steroid medicine in the past
- adrenal gland problems
- plan to have surgery
- are pregnant or plan to become pregnant. It is not known if VANOS Cream will harm your unborn baby. Talk to your doctor if you are pregnant or plan to become pregnant.
- are breast-feeding or plan to breastfeed. It is not known if VANOS Cream passes into your breast milk. Talk to your doctor about the best way to feed your baby if you use Vanos Cream.

Tell your doctor about all the medicine you take including prescriptions and non-prescriptions medicines, vitamins, and herbal supplements.

Especially tell your doctor if you take a corticosteroid medicine by mouth or use other products on your skin that contain corticosteroids. Ask your doctor or pharmacist if you are not sure.

Know the medicines you take. Keep a list of your medicines with you to show your doctor and pharmacist when you get a new medicine.

How should I use VANOS Cream?

- **See “What is VANOS Cream?”**
- Use VANOS Cream exactly as your doctor tells you.
- This medicine is for use on the skin only. Do not use VANOS Cream in your eyes, mouth or vagina.
- Wash your hands after you use VANOS Cream.
- Do not use VANOS Cream for longer than 2 weeks in a row.
- Talk to your doctor if your skin does not get better after 2 weeks of treatment with VANOS Cream.
- Do not bandage or cover the skin treated with VANOS Cream unless your doctor tells you to.

What are the possible side effects with VANOS Cream?

VANOS Cream may cause side effects, including:

- **Symptoms of a disorder where the adrenal gland does not make enough of certain hormones (adrenal insufficiency) during treatment or after stopping treatment.** Your doctor may do blood tests to check you for adrenal insufficiency while you are using VANOS Cream. Tell your doctor if you have any of these symptoms of adrenal insufficiency:
 - tiredness that worsens and does not go away
 - nausea or vomiting
 - dizziness or fainting
 - muscle weakness
 - irritability and depression
 - loss of appetite
 - weight loss
- **Cushing’s syndrome, when the body is exposed to too much of the hormone cortisol.** Your doctor may do tests to check for this. Symptoms can include:
 - weight gain, especially around your upper back and midsection
 - slow healing of cuts, insect bites and infections
 - tiredness and muscle weakness
 - depression, anxiety and irritability
 - roundness of your face (moon face)
 - new or worsening high blood pressure

The most common side effect of VANOS Cream is burning of your skin treated with VANOS Cream.

Talk to your doctor about any side effect that bothers you or that does not go away.

These are not all the side effects with VANOS Cream. Ask your doctor or pharmacist for more information.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

You may also report side effects to Medicis at 1-800-900-6389.

How should I store VANOS Cream?

- Store VANOS Cream at room temperature, between 59°F to 86°F (15°C to 30°C).
- Keep the tube tightly closed.

Keep VANOS Cream and all medicines out of the reach of children.

General information about VANOS Cream

Medicines are sometimes prescribed for purposes other than those listed in the Patient Information leaflet. Do not use VANOS Cream for a condition for which it was not prescribed. Do not give VANOS Cream to other people, even if they have the same symptoms you have. It may harm them.

This Patient Information leaflet summarizes the most important information about VANOS Cream. If you would like more information, talk with your doctor. You can also ask your pharmacist or doctor for information about VANOS Cream that is written for healthcare professionals.

What are the ingredients in VANOS Cream?

Active ingredient: fluocinonide 0.1%

Inactive ingredients: propylene glycol, dimethyl isosorbide, glyceryl stearate (and) PEG-100 stearate, glyceryl monostearate, purified water, carbopol 980, diisopropanolamine, and anhydrous citric acid.

This Patient Information has been approved by the U.S. Food and Drug Administration.

Manufactured for:
Medicis, The Dermatology Company
Scottsdale, AZ 85256

Manufactured by:
Contract Pharmaceuticals Ltd.
Mississauga, Ontario
Canada L5N 6L6

Product of Italy

U.S. Patents 6,765,001; 7,217,422; 7,220,424; 7,771,733; 7,794,738 and
Patents Pending

VANOS is a registered trademark of Medicis Pharmaceutical Corporation.

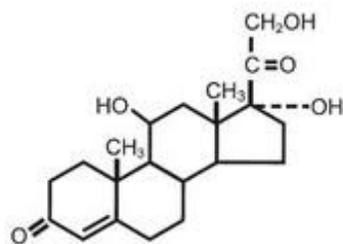
Approved xx/2012
05100253

HYDROCORTISONE 1% IN ABSORBASE- hydrocortisone 1% in absorbase ointment Solubiomix

Hydrocortisone 1% in Absorbase

DESCRIPTION

Hydrocortisone 1% in Absorbase® contains 10 mg/g of micronized hydrocortisone USP in a special absorption ointment base. Absorbase® is a water-in-oil emulsion composed of cholesterolized petrolatum and purified water USP. The product will absorb water into the internal emulsion phase, yet form a hydrophobic film on the skin. Hydrocortisone USP is C₂₁H₃₀O₅; Pregn-4-ene-3, 20-dione, 11, 17, 21-trihydroxy-, (11 beta)-, Cortisol, and has the structural formula:



Action

Topical corticosteroids are primarily effective as anti-inflammatory, anti-pruritic and vasoconstrictive agents.

CLINICAL PHARMACOLOGY:

Topical corticosteroids share anti-inflammatory, anti-pruritic and vasoconstrictive actions.

The mechanism of anti-inflammatory activity of the topical corticosteroids is unclear. Various laboratory methods, including vasoconstrictor assays, are used to compare and predict potencies and/or clinical efficacies of the topical corticosteroids. There is some evidence to suggest that a recognizable correlation exists between vasoconstrictor potency and therapeutic efficacy in man.

Pharmacokinetics

The extent of percutaneous absorption of topical corticosteroids is determined by many factors including the vehicle, the integrity of the epidermal barrier, and the use of occlusive dressings.

Topical corticosteroids can be absorbed from normal intact skin. Inflammation and/or other disease processes in the skin increase percutaneous absorption. Occlusive dressings substantially increase the percutaneous absorption of topical corticosteroids. Thus, occlusive dressings may be a valuable therapeutic adjunct for the treatment of resistant dermatoses.

Once absorbed through the skin, topical corticosteroids are handled through pharmacokinetic pathways similar to systemically administered corticosteroids. Corticosteroids are bound to plasma proteins in varying degrees. Corticosteroids are metabolized primarily in the liver and are then excreted by the kidneys. Some of the topical corticosteroids and their metabolites are also excreted into the bile.

undefined

Topical corticosteroids are indicated for the relief of the inflammatory and pruritic manifestations of corticosteroid responsive dermatoses.

PRECAUTIONS

General

Systemic absorption of topical corticosteroids has produced reversible hypothalamic-pituitary-adrenal (HPA) axis suppression, manifestations of Cushing's syndrome, hyperglycemia, and glucosuria in some patients.

Conditions which augment systemic absorption include the application of the more potent steroids, use over large surface areas, prolonged use, and the addition of occlusive dressings.

Therefore, patients receiving a large dose of a potent topical steroid applied to a large surface area or under an occlusive dressing should be evaluated periodically for evidence of HPA axis suppression by using the urinary free cortisol and ACTH stimulation tests. If HPA axis suppression is noted, an attempt should be made to withdraw the drug, to reduce the frequency of application, or to substitute a less potent steroid.

Recovery of HPA axis function is generally prompt and complete upon discontinuation of the drug. Infrequently, signs and symptoms of steroid withdrawal may occur, requiring supplemental systemic corticosteroids.

Children may absorb proportionally larger amounts of topical corticosteroids and thus be more susceptible to systemic toxicity.

If irritation develops, topical corticosteroids should be discontinued and appropriate therapy instituted.

In the presence of dermatological infections, the use of an appropriate antifungal or antibacterial agent should be instituted. If a favorable response does not occur promptly, the corticosteroid should be discontinued until the infection has been adequately controlled.

Information for the Patient

Patients using topical corticosteroids should receive the following information and instructions:

This medication is to be used as directed by the physician. It is for external use only. Avoid contact with the eyes.

Patients should be advised not to use this medication for any disorder other than that for which it was prescribed.

The treated skin area should not be bandaged or otherwise covered or wrapped so as to be occlusive unless directed by the physician.

Patients should report any signs of local adverse reactions, especially under occlusive dressing.

Parents of pediatric patients should be advised not to use tight-fitting diapers or plastic pants on a child being treated in the diaper area, as these garments may constitute occlusive dressings.

Laboratory Tests

The following tests may be helpful in evaluating the HPA axis suppression:

Urinary free cortisol test

ACTH stimulation test

Carcinogenesis, Mutagenesis, and Impairment of Fertility

Long-term animal studies have not been performed to evaluate the carcinogenic potential or the effect on fertility of topical corticosteroids.

Studies to determine mutagenicity with prednisolone and hydrocortisone have revealed negative results.

Pregnancy Category C

Corticosteroids are generally teratogenic in laboratory animals when administered systemically at relatively low dosage levels. The more potent corticosteroids have been shown to be teratogenic after dermal application in laboratory animals. There are no adequate and well-controlled studies in pregnant

women on teratogenic effects from topically applied corticosteroids. Therefore, topical corticosteroids should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Drugs of this class should not be used extensively on pregnant patients, in large amounts, or for prolonged periods of time.

Nursing Mothers

It is not known whether topical administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in breast milk. Systemically administered corticosteroids are secreted into breast milk in quantities not likely to have a deleterious effect on the infant. Nevertheless, caution should be exercised when topical corticosteroids are administered to a nursing woman.

Pediatric Use

Pediatric patients may demonstrate greater susceptibility to topical corticosteroid-induced HPA axis suppression and Cushing's syndrome than mature patients because of a larger skin surface area to body weight ratio.

Hypothalamic-pituitary-adrenal (HPA) axis suppression, Cushing's syndrome and intracranial hypertension have been reported in children receiving topical corticosteroids. Manifestations of adrenal suppression in children include linear growth retardation, delayed weight gain, low plasma cortisol levels, and absence of response to ACTH stimulation. Manifestations of intracranial hypertension include bulging fontanelles, headaches, and bilateral papilledema.

Administration of topical corticosteroids to children should be limited to the least amount compatible with an effective therapeutic regimen. Chronic corticosteroid therapy may interfere with the growth and development of children.

ADVERSE REACTIONS:

The following local adverse reactions are reported infrequently with topical corticosteroids, but may occur more frequently with the use of occlusive dressings. These reactions are listed in approximate decreasing order of occurrence:

- Burning
- Itching
- Irritation
- Dryness
- Folliculitis
- Hypertrichosis
- Acneiform eruptions
- Hypopigmentation
- Perioral dermatitis
- Allergic contact dermatitis
- Maceration of the skin
- Secondary infection
- Skin atrophy
- Striae
- Miliaria

OVERDOSAGE:

Topically applied corticosteroids can be absorbed in sufficient amounts to produce systemic effects.

DOSAGE & ADMINISTRATION:

Topical corticosteroids are generally applied to the affected area as a thin film from two to four times daily depending on the severity of the condition.

Occlusive dressings may be used for the management of psoriasis or recalcitrant conditions.

If an infection develops, the use of occlusive dressing should be discontinued and appropriate antimicrobial therapy instituted.

HOW SUPPLIED:

Each gram of Hydrocortisone 1% in Absorbase[®] contains 10 mg of micronized Hydrocortisone USP. Supplied in a 4 oz. jar (110 g) (NDC 69499-322-10).

Caution

Federal law prohibits dispensing without prescription. For external use only.

Pharmacist

Water may bleed from this product due to the nature of the water-in-oil emulsion. This separation does not affect the stability of hydrocortisone. The Absorbase[®] base should be remixed if necessary before dispensing. Store at controlled room temperature 15°-30° C (59°-86° F). Dispense in well-closed containers.

STORE AT CONTROLLED ROOM TEMPERATURE 15°-30° C (59°-86° F).

Solubiomix

Madisonville, LA 70447

PACKAGE LABEL:

69499-322-10

10 g

HYDROCORTISONE 1% IN ABSORBASE[®]
Hydrocortisone Ointment, USP 1%

Each gram contains 10 mg of micronized Hydrocortisone USP in an aqueous cholesterolized petrolatum emulsion base.

For External Use Only. Not for Ophthalmic Use.

USUAL DOSAGE: See insert labeling.

Dispense in a well-closed container.

BATCH:

EXP:

Each gram contains 10 mg of micronized Hydrocortisone USP in an aqueous cholesterolized petrolatum emulsion base.

For External Use Only. Not for Ophthalmic Use.

Store at 20°-25°C (68°-77°F); excursions permitted to 15°-30°C (59°-86°F). [See USP controlled room temperature].

USUAL DOSAGE: See insert labeling.

Dispense in a well-closed container.

Absorbase® is a registered trademark of CMP Pharma

Rev. 02/2018

NDC 69499-322-10

**Hydrocortisone 1%
in Absorbase®**

**Hydrocortisone
Ointment, USP 1%**

Rx Only



SOLUBIOMIX
INNOVATING HEALTH SOLUTIONS

Net Wt 110 g

3
N
69499-322-10
0



HYDROCORTISONE 1% IN ABSORBASE

hydrocortisone 1% in absorbase ointment

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:69499-322
Route of Administration	TOPICAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
HYDROCORTISONE (UNII: WI4X0X7BPJ) (HYDROCORTISONE - UNII:WI4X0X7BPJ)	HYDROCORTISONE	10 mg in 1 g

Inactive Ingredients

Ingredient Name	Strength
PETROLATUM (UNII: 4T6H12BN9U)	
water (UNII: 059QF0KO0R)	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:69499-322-10	110 g in 1 JAR; Type 0: Not a Combination Product	11/02/2016	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA088138	11/02/2016	

Labeler - Solubiomix (079640556)

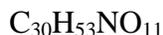
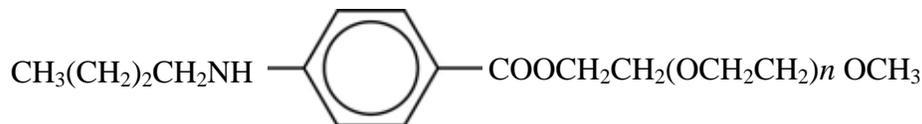
Revised: 2/2018

Solubiomix

TESSALON®
100 mg Perles
200 mg Capsules
 (benzonatate, USP)

DESCRIPTION

TESSALON, a non-narcotic oral antitussive agent, is 2, 5, 8, 11, 14, 17, 20, 23, 26-nonaoxaocacosan-28-yl p-(butylamino) benzoate; with a molecular weight of 603.7.



Each TESSALON Perle contains:
 Benzonatate, USP 100 mg

Each TESSALON Capsule contains:
 Benzonatate, USP 200 mg

TESSALON Capsules also contain: D&C Yellow 10, gelatin, glycerin, methylparaben and propylparaben.

CLINICAL PHARMACOLOGY

TESSALON acts peripherally by anesthetizing the stretch receptors located in the respiratory passages, lungs, and pleura by dampening their activity and thereby reducing the cough reflex at its source. It begins to act within 15 to 20 minutes and its effect lasts for 3 to 8 hours. TESSALON has no inhibitory effect on the respiratory center in recommended dosage.

INDICATIONS AND USAGE

TESSALON is indicated for the symptomatic relief of cough.

CONTRAINDICATIONS

Hypersensitivity to benzonatate or related compounds.

WARNINGS

Hypersensitivity

Severe hypersensitivity reactions (including bronchospasm, laryngospasm and cardiovascular collapse) have been reported which are possibly related to local anesthesia from sucking or chewing the capsule instead of swallowing it. Severe reactions have required intervention with vasopressor agents and supportive measures.

Psychiatric Effects

Isolated instances of bizarre behavior, including mental confusion and visual hallucinations, have also been reported in patients taking TESSALON in combination with other prescribed drugs.

Accidental Ingestion and Death in Children

Keep TESSALON out of reach of children. Accidental ingestion of TESSALON resulting in death has been reported in children below age 10. Signs and symptoms of overdose have been reported within 15-20 minutes and death has been reported within one hour of ingestion. If accidental ingestion occurs, seek medical attention immediately (see OVERDOSAGE).

PRECAUTIONS

Benzonatate is chemically related to anesthetic agents of the para-amino-benzoic acid class (e.g. procaine; tetracaine) and has been associated with adverse CNS effects possibly related to a prior sensitivity to related agents or interaction with concomitant medication.

Information for patients:

Swallow TESSALON Capsules and Perles whole. Do not break, chew, dissolve, cut, or crush TESSALON Capsules and Perles. Release of TESSALON from the capsule in the mouth can produce a temporary local anesthesia of the

oral mucosa and choking could occur. If numbness or tingling of the tongue, mouth, throat, or face occurs, refrain from oral ingestion of food or liquids until the numbness has resolved. If the symptoms worsen or persist, seek medical attention.

Keep TESSALON out of reach of children. Accidental ingestion resulting in death has been reported in children. Signs and symptoms of overdose have been reported within 15-20 minutes and death has been reported within one hour of ingestion. Signs and symptoms may include restlessness, tremors, convulsions, coma and cardiac arrest. If accidental ingestion occurs, seek medical attention immediately.

Overdosage resulting in death may occur in adults.

Do not exceed a single dose of 200 mg and a total daily dosage of 600 mg. If you miss a dose of TESSALON, skip that dose and take the next dose at the next scheduled time. Do not take 2 doses of TESSALON at one time.

Usage in Pregnancy: Pregnancy Category C. Animal reproduction studies have not been conducted with TESSALON. It is also not known whether TESSALON can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. TESSALON should be given to a pregnant woman only if clearly needed.

Nursing mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk caution should be exercised when TESSALON is administered to a nursing woman.

Carcinogenesis, mutagenesis, impairment of fertility: Carcinogenicity, mutagenicity, and reproduction studies have not been conducted with TESSALON.

Pediatric Use: Safety and effectiveness in children below the age of 10 have not been established. Accidental ingestion resulting in death has been reported in children below age 10. Keep out of reach of children.

ADVERSE REACTIONS

Potential Adverse Reactions to TESSALON may include:

Hypersensitivity reactions including bronchospasm, laryngospasm, cardiovascular collapse possibly related to local anesthesia from chewing or sucking the capsule.

CNS: sedation; headache; dizziness; mental confusion; visual hallucinations.

GI: constipation; nausea; GI upset.

Dermatologic: pruritus; skin eruptions.

Other: nasal congestion; sensation of burning in the eyes; vague "chilly" sensation; numbness of the chest; hypersensitivity.

Deliberate or accidental overdose has resulted in death, particularly in children.

OVERDOSAGE

Intentional and unintentional overdose may result in death, particularly in children.

The drug is chemically related to tetracaine and other topical anesthetics and shares various aspects of their pharmacology and toxicology. Drugs of this type are generally well absorbed after ingestion.

Signs and Symptoms:

The signs and symptoms of overdose of benzonatate have been reported within 15-20 minutes. If capsules are chewed or dissolved in the mouth, oropharyngeal anesthesia will develop rapidly, which may cause choking and airway compromise.

CNS stimulation may cause restlessness and tremors which may proceed to clonic convulsions followed by profound CNS depression. Convulsions, coma, cerebral edema and cardiac arrest leading to death have been reported within 1 hour of ingestion.

Treatment:

In case of overdose, seek medical attention immediately. Evacuate gastric contents and administer copious amounts of activated charcoal slurry. Even in the conscious patient, cough and gag reflexes may be so depressed as to necessitate special attention to protection against aspiration of gastric contents and orally administered materials. Convulsions should be treated with a short-acting barbiturate given intravenously and carefully titrated for the smallest effective dosage. Intensive support of respiration and cardiovascular-renal function is an essential feature of the treatment of severe intoxication from overdosage.

Do not use CNS stimulants.

DOSAGE AND ADMINISTRATION

Adults and Children over 10 years of age: Usual dose is one 100 mg or 200 mg capsule three times a day as needed for cough. If necessary to control cough, up to 600 mg daily in three divided doses may be given. **TESSALON should be swallowed whole.** TESSALON Capsules and Perles are not to be broken, chewed, dissolved, cut or crushed.

HOW SUPPLIED

Perles, 100 mg (yellow);
bottles of 100
NDC 0069-0122-01
Imprint: T.

Perles, 100 mg (yellow);
bottles of 500
NDC 0069-0122-02
Imprint: T

Capsules, 200 mg (yellow);
bottles of 100
NDC 0069-0124-01
Imprint: 0698.

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].

Rev. 12/15

Mfd by
Catalent Pharma Solutions
St. Petersburg, Florida 33716

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Madison, New Jersey 07940

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Uptiers – Effective 10/1/2018

Brand Name	Generic Name	Therapeutic Category	Alternatives	Rationale	Tier Change	Specialty	Utilizers (YT)
BENZACLIN gel 1-5% (MSB)	clindamycin and benzoyl peroxide	Topical/ Dermatology/ Acne	Preferred options include adapalene, benzoyl peroxide, clindamycin solution, clindamycin-benzoyl peroxide, erythromycin solution, erythromycin-benzoyl peroxide, tretinoin, Acanya (clindamycin-benzoyl peroxide), Atralin (tretinoin), Differin (adapalene), Epiduo (adapalene-benzoyl peroxide), Retin-A Micro (tretinoin gel microsphere), and Tazorac (tazarotene).	Availability of additional options for the topical treatment of acne.	2 → 3	NO	10
MIRAPEX ER tablets 0.75, 1.5, 2.25, 3, 4.5 MG (MSB)	pramipexole extended release	Central Nervous System/ Antiparkinsonian Agents	Preferred options include pramipexole, pramipexole ext-rel, ropinirole, ropinirole ext-rel.	Availability of generic options for the treatment of Parkinson's disease.	2 → 3	NO	5
MINASTRIN 24 CHEW FE Tablets 1/0.02 MG (MSB)	Norethindrone Acetate and Ethinyl Estradiol	Endocrine and Metabolic/ Contraceptives/ Monophasic	Preferred options include ethinyl estradiol-drospirenone, ethinyl estradiol-drospirenone-levomefolate, ethinyl estradiol-norethindrone acetate, ethinyl estradiol-norethindrone acetate-iron, and Safyral	Availability of additional contraceptive options.	2 → 3	NO	99

SSB = single source brand (no generic available)

MSB = multi-sourced brand (generics available)

Uptiers – Effective 10/1/2018

Brand Name	Generic Name	Therapeutic Category	Alternatives	Rationale	Tier Change	Specialty	Utilizers (YT)
APTENSIO XR capsules 10, 15, 20, 30, 40, 50, 60 MG (SSB)	methylphenidate HCl extended-release	Central Nervous System/ Attention Deficit Hyperactivity Disorder	Preferred options include amphetamine-dextroamphetamine mixed salts ext-rel, methylphenidate ext-rel, Mydayis (amphetamine-dextroamphetamine mixed salts ext-rel), and Vyvanse (lisdexamfetamine).	Availability of additional options for the treatment of Attention Deficit Hyperactivity Disorder (ADHD).	2 → 3	NO	198
QUILLIVANT XR Suspension 25 MG/5 ML (SSB)	methylphenidate HCl extended-release	Central Nervous System/ Attention Deficit Hyperactivity Disorder	Preferred options include amphetamine-dextroamphetamine mixed salts ext-rel, methylphenidate ext-rel, Mydayis (amphetamine-dextroamphetamine mixed salts ext-rel), and Vyvanse (lisdexamfetamine).	Availability of additional options for the treatment of Attention Deficit Hyperactivity Disorder (ADHD).	2 → 3	NO	184

SSB = single source brand (no generic available)

MSB = multi-sourced brand (generics available)

Addition of New Medications – Effective 10/1/2018

Brand Name	Generic Name	Indication	Therapeutic Category	Specialty	Proposed NC Status/Tier	Comments
CRYSVITA Injection 10, 20, 30 MG/ML	burosumab-twza	Fibroblast growth factor 23 blocking antibody for (XLH)	Endocrine and Metabolic/ Miscellaneous	YES	6	Burosumab-twza indicated X-linked hypophosphatemia; product has orphan drug and breakthrough status; Can restore phosphorus
IDHIFA Tablets 50, 100 MG	enasidenib	Relapsed or refractory acute myeloid leukemia	Antineoplastic Agents/ Isocitrate Dehydrogenase-2 (IDH2) Inhibitors	YES	6	Enasidenib is indicated for relapsed or refractory AML with the IDH-2 mutation; orphan drug indication; first & only oral targeted inhibitor of IDH2
RADICAVA Injection 30 MG	endaravone	First ALS drug in 20 years. Slow decline in the loss of physical function	Central Nervous Center/Neuromuscular Agents	YES	6	Endaravone is indicated for the treatment of ALS; orphan drug indication.
STERITALC Powder 2, 3, 4 GM	talcum pleurodesis	non-soluble talcum which induces permanent pleurodesis	Respiratory/ Miscellaneous	NO	3	Sterile talc - sclerosing agent for PTX/pleural effusion; no UM available. Sterile Talc product already on formulary at tier 3.
PREVMIS Injection & tablets 240, 480 MG 240/12, 480/24 MG/ML	letermovir	prevent cytomegalovirus after stem cell transplant	Antivirals/CMV Agents	NO	3	Tx CMV; FDA approved 11/17
NORVIR Powder 100 MG	ritonavir	Powder is for pediatric patients with HIV-1	Anti-Infectives/ Antiretroviral Agents/ Protease Inhibitors	YES	2	New strength of existing product formulation

Addition of New Medications – Effective 10/1/2018

Brand Name	Generic Name	Indication	Therapeutic Category	Specialty	Proposed NC Status/Tier	Comments
KEVZARA Injection 150/1.14, 200/1.14 MG/ML	sarilumab	rheumatoid arthritis; inhibits IL-6 receptor signaling.	Immunologic Agents/ Autoimmune Agents/ Rheumatoid Arthritis	YES	5	Product has both SGM and Specialty QL. Sarilumab indicated for tx of mod-sev RA in patients with inadeq response or intolerance to one or more DMARDs.
ANDEXXA Injection 100 MG	coagulation factor Xa (recombinant) inactivated-zhzo	reversal of anticoagulation due to life-threatening or uncontrolled bleeding	Endocrine and Metabolic/ Detoxification Agents	NO	3	Factor Xa for the reversal of apixaban or rivaroxaban anticoagulation.
DAUNORUBICIN Injection 50 MG, 20 MG/4 ML	daunorubicin	Chemotherapy for AML, ALL, CML, and Kaposi's sarcoma	Antineoplastic Agents/ Miscellaneous	NO	3	SSB formulation of daunorubicin (generic already on formulary at tier 1).
ARNUITY ELLIPTA Inhalation 50 MCG	Fluticasone furoate	maintenance treatment of asthma	Respiratory/ Steroid Inhalants	NO	3	New strength of existing product formulation. Arnuity Ellipta 100 mcg already on formulary at tier 3.
MYLOTARG Injection 4.5 MG	Gemtuzumab ozogamicin	CD33-positive acute myeloid leukemia	Antineoplastic Agents/ Miscellaneous	YES	6	Gemtuzumab ozgamicin indicated for tx of newly-diagnosed cluster of differentiation (CD)-33 positive AML; orphan drug designation.

Addition of New Medications – Effective 10/1/2018

Brand Name	Generic Name	Indication	Therapeutic Category	Specialty	Proposed NC Status/Tier	Comments
BENZNIDAZOLE Tablets 12.5, 100 MG	benznidazole	Antiparasitic for Chagas disease	Anti-Infectives/ Anthelmintics	NO	3	Tx of Chagas Dz (American trypanosomiasis) in pediatrics (age 2-12); orphan drug designation
MEPSEVII Injection 10 MG/5 ML	vestronidase alfa-vjvk	First and only enzyme replacement therapy for Sly syndrome	Endocrine and Metabolic/ Metabolic Modifiers	YES	6	Tx for mucopolysaccharidosis VII (MPS VII) also known as Sly Syndrome
JYNARQUE Tablets 15, 30, 45, 60, 90 MG	tolvaptan	selective vasopressin V2-receptor antagonist; treatment of ADPKD	Endocrine and Metabolic/ Vasopressin Antagonist	YES	6	Tx for hyper- & euvolemic hyponatremia; Tolvaptan is not a new drug entity (same active ingredient as Samsca)
BIKTARVY Tablets	bictegravir, emtricitabine, and tenofovir alafenamide	Complete, 1-pill, once a day HIV-1 treatment for adults	Anti-Infectives/ Antiretroviral Agents/ Antiretroviral Combinations	YES	2	HIV at Tier 2 for NCSHP; Copay \$74
DAPTOMYCIN Injection 350 MG	daptomycin	Lipopeptide antibiotic bactericidal against Gram-positives	Anti-Infectives/ Miscellaneous	NO	3	New strength - not a new formulation
QVAR REDIHALER Inhalation 40, 80 MCG	beclomethasone dipropionate HFA	Corticosteroid for maintenance treatment of asthma	Respiratory/ Steroid Inhalants	NO	2	Qvar Inhaler on formulary (tier 2) - Addition of Redihaler (new breath actuated inhaler device)

Addition of New Medications – Effective 10/1/2018

Brand Name	Generic Name	Indication	Therapeutic Category	Specialty	Proposed NC Status/Tier	Comments
TESTOSTERONE Gel 1% (50 MG)	testosterone	replacement therapy for hypogonadism	Endocrine and Metabolic/ Androgens	NO	1	Addition of generic testosterone gel 1% (generic alternative to Androderm, Testim, Vogelxo)
COAGADEX Injection 250, 500 units	coagulation factor X (Human)	first and only treatment specifically for hereditary factor X deficiency	Hematologic/ Antihemophilic Products	YES	6	Coagulation Factor X indicated for factor X deficiency a rare bleeding disorder

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ANDEXXA safely and effectively. See [Full Prescribing Information for ANDEXXA](#).

ANDEXXA® (coagulation factor Xa (recombinant), inactivated-zhzo) Lyophilized Powder for Solution For Intravenous Injection
Initial U.S. Approval: 2018

WARNING: THROMBOEMBOLIC RISKS, ISCHEMIC RISKS, CARDIAC ARREST, AND SUDDEN DEATHS

See full prescribing information for complete boxed warning

Treatment with ANDEXXA has been associated with serious and life-threatening adverse events, including: (5.1)

- Arterial and venous thromboembolic events
- Ischemic events, including myocardial infarction and ischemic stroke
- Cardiac arrest
- Sudden deaths

Monitor for thromboembolic events and initiate anticoagulation when medically appropriate. Monitor for symptoms and signs that precede cardiac arrest and provide treatment as needed.

INDICATIONS AND USAGE

ANDEXXA, coagulation factor Xa (recombinant), inactivated-zhzo is a recombinant modified human Factor Xa (FXa) protein indicated for patients treated with rivaroxaban and apixaban, when reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding. (1)

This indication is approved under accelerated approval based on the change from baseline in anti-FXa activity in healthy volunteers. An improvement in hemostasis has not been established. Continued approval for this indication may be contingent upon the results of studies to demonstrate an improvement in hemostasis in patients. (1,14)

Limitation of Use

ANDEXXA has not been shown to be effective for, and is not indicated for, the treatment of bleeding related to any FXa inhibitors other than apixaban and rivaroxaban. (1)

DOSAGE AND ADMINISTRATION

For intravenous use only.

- Dose ANDEXXA based on the specific FXa inhibitor, dose of FXa inhibitor, and time since the patient's last dose of FXa inhibitor. (2)
- Administer as an intravenous (IV) bolus, with a target rate of 30 mg/min, followed by continuous infusion for up to 120 minutes.
- There are two dosing regimens:

Dose*	Initial IV Bolus	Follow-On IV Infusion
Low Dose	400 mg at a target rate of 30 mg/min	4 mg/min for up to 120 minutes
High Dose	800 mg at a target rate of 30 mg/min	8 mg/min for up to 120 minutes

*The safety and effectiveness of more than one dose have not been evaluated.

DOSAGE FORMS AND STRENGTHS

ANDEXXA is available as a lyophilized powder in single-use vials of 100 mg of coagulation factor Xa (recombinant), inactivated-zhzo. (3)

CONTRAINDICATIONS

None. (4)

WARNINGS AND PRECAUTIONS

- Arterial and venous thromboembolic events, ischemic events, and cardiac events, including sudden death, have occurred during treatment with ANDEXXA. Resume anticoagulant therapy as soon as medically appropriate following treatment with ANDEXXA. (5.1)
- Re-elevation or incomplete reversal of anticoagulant activity can occur. (5.2)

ADVERSE REACTIONS

The most common adverse reactions ($\geq 5\%$) in patients receiving ANDEXXA were urinary tract infections and pneumonia. (6.1)

The most common adverse reactions ($\geq 3\%$) in healthy volunteers treated with ANDEXXA were infusion-related reactions.

To report SUSPECTED ADVERSE REACTIONS, contact Portola Pharmaceuticals, Inc. at 1-866-777-5947 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See [17](#) for PATIENT COUNSELING INFORMATION

FULL PRESCRIBING INFORMATION: CONTENTS***WARNING: THROMBOEMBOLIC RISKS, ISCHEMIC RISKS, CARDIAC ARREST, AND SUDDEN DEATH****1 INDICATIONS AND USAGE****2 DOSAGE AND ADMINISTRATION**

- 2.1 Dose
- 2.2 Reconstitution
- 2.3 Administration
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FULL PRESCRIBING INFORMATION

WARNING: THROMBOEMBOLIC RISKS, ISCHEMIC RISKS, CARDIAC ARREST, AND SUDDEN DEATHS

Treatment with ANDEXXA has been associated with serious and life-threatening adverse events, including: (5.1)

- **Arterial and venous thromboembolic events**
- **Ischemic events, including myocardial infarction and ischemic stroke**
- **Cardiac arrest**
- **Sudden deaths**

Monitor for thromboembolic events and initiate anticoagulation when medically appropriate. Monitor for symptoms and signs that precede cardiac arrest and provide treatment as needed.

1 INDICATIONS AND USAGE

ANDEXXA is indicated for patients treated with rivaroxaban and apixaban, when reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding.

This indication is approved under accelerated approval based on the change from baseline in anti-FXa activity in healthy volunteers [see *Clinical Studies (14)*]. An improvement in hemostasis has not been established. Continued approval for this indication may be contingent upon the results of studies to demonstrate an improvement in hemostasis in patients.

Limitation of Use

ANDEXXA has not been shown to be effective for, and is not indicated for, the treatment of bleeding related to any FXa inhibitors other than apixaban and rivaroxaban.

2 DOSAGE AND ADMINISTRATION

For intravenous use only.

2.1 Dose

There are two dosing regimens (see [Table 1](#)). The safety and efficacy of an additional dose has not been established.

Table 1: ANDEXXA Dosing Regimens

Dose*	Initial IV Bolus	Follow-On IV Infusion
Low Dose	400 mg at a target rate of 30 mg/min	4 mg/min for up to 120 minutes
High Dose	800 mg at a target rate of 30 mg/min	8 mg/min for up to 120 minutes

*The safety and effectiveness of more than one dose have not been evaluated.

The recommended dosing of ANDEXXA is based on the specific FXa inhibitor, dose of FXa inhibitor, and time since the patient's last dose of FXa inhibitor (see [Table 2](#)).

Table 2: ANDEXXA Dose Based on Rivaroxaban or Apixaban Dose (Timing of FXa Inhibitor Last Dose Before ANDEXXA Initiation)

FXa Inhibitor	FXa Inhibitor Last Dose	< 8 Hours or Unknown	≥ 8 Hours
Rivaroxaban	≤ 10 mg	Low Dose	Low Dose
Rivaroxaban	> 10 mg / Unknown	High Dose	
Apixaban	≤ 5 mg	Low Dose	
Apixaban	> 5 mg / Unknown	High Dose	

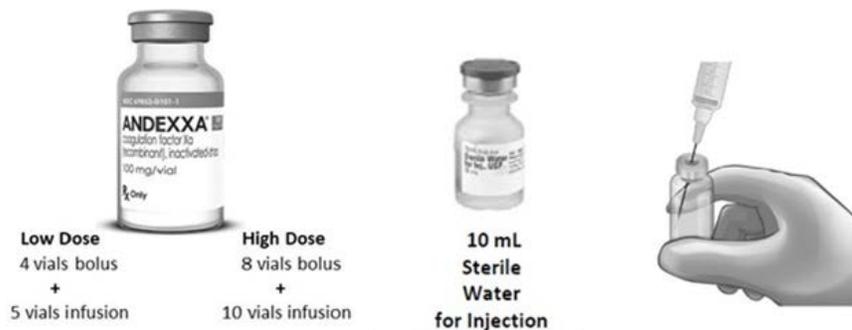
2.2 Reconstitution

Upon reconstitution, the parenteral drug product should be inspected visually for particulate matter and discoloration prior to administration.

- The reconstituted solution contains coagulation factor Xa (recombinant), inactivated-zhzo at a concentration of 10 mg/mL.
- Reconstituted ANDEXXA in vials is stable at room temperature for up to 8 hours, or may be stored for up to 24 hours at 2°C to 8°C.
- Reconstituted ANDEXXA in IV bags is stable at room temperature for up to 8 hours, or may be stored for up to 16 hours at 2°C to 8°C.

IV Bolus Preparation

- Reconstitute each 100 mg vial of ANDEXXA ([Figure A](#)) using a 10-mL syringe and 20-gauge (or higher) needle. Slowly inject 10 mL Sterile Water for Injection (SWFI), USP, directing the solution onto the inside wall of the vial to minimize foaming ([Figure A](#)).



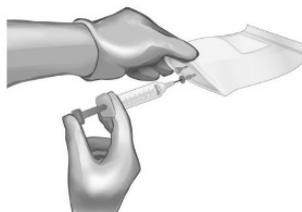
(Figure A)

- To reduce the total reconstitution time needed during preparation, reconstitute all required vials in succession.
- To ensure dissolution of the cake or powder, gently swirl each vial until complete dissolution of powder occurs. Do not shake; shaking could lead to foaming (Figure B). Typical dissolution time for each vial is approximately 3 to 5 minutes. If dissolution is incomplete, discard the vial and do not use the product.



(Figure B)

- Use 60-mL or larger syringe with a 20-gauge (or higher) needle to withdraw the reconstituted ANDEXXA solution from each of the vials until the required dosing volume is achieved. Note the total volume withdrawn into the syringe.
- Transfer the ANDEXXA solution from the syringe into an empty polyolefin or polyvinyl chloride IV bag with a volume of 250 mL or less (Figure C).



(Figure C)

- Discard the syringe and needle.
- Discard the vials, including any unused portion.

Continuous IV Infusion Preparation

- Follow the same procedure outlined above for IV bolus preparation. Reconstitute the number of vials needed based on the dose requirements. More than one 40 to 60-mL syringe, or an equivalent 100-mL syringe, may be used for transfer of reconstituted solution to the IV bag.
- Infusion will require a 0.2 or 0.22 micron in-line polyethersulfone or equivalent low protein-binding filter.

2.3 Administration

- Administer ANDEXXA intravenously, using a 0.2 or 0.22 micron in-line polyethersulfone or equivalent low protein-binding filter.
- Start the bolus at a target rate of approximately 30 mg/minute.
- Within 2 minutes following the bolus dose, administer the continuous IV infusion for up to 120 minutes.

2.4 Restarting Antithrombotic Therapy

Patients treated with FXa inhibitor therapy have underlying disease states that predispose them to thromboembolic events. Reversing FXa inhibitor therapy exposes patients to the thrombotic risk of their underlying disease. To reduce the risk of thrombosis, resume anticoagulant therapy as soon as medically appropriate following treatment with ANDEXXA.

3 DOSAGE FORMS AND STRENGTHS

ANDEXXA is available as a lyophilized powder in single-use vials of 100 mg of coagulation factor Xa (recombinant), inactivated-zhzo.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Thromboembolic and Ischemic Risks

Arterial and venous thromboembolic events, ischemic events, and cardiac events, including sudden death, were observed within 30 days post-ANDEXXA administration in 33 of the 185 patients (18%) evaluable for safety in the ongoing ANNEXA-4 study. The median time to first event was 6 days. Of the 86 patients who were re-anticoagulated prior to a thrombotic event, 11 (12.7%) patients experienced a thromboembolic, ischemic event, cardiac event or death.

Monitor patients treated with ANDEXXA for signs and symptoms of arterial and venous thromboembolic events, ischemic events, and cardiac arrest. To reduce thromboembolic risk, resume anticoagulant therapy as soon as medically appropriate following treatment with ANDEXXA [*see Dosage and Administration (2.4)*].

The safety of ANDEXXA has not been evaluated in patients who experienced thromboembolic events or disseminated intravascular coagulation within two weeks prior to the life-threatening bleeding event requiring treatment with ANDEXXA. Safety of ANDEXXA also has not been evaluated in patients who received prothrombin complex concentrates, recombinant factor VIIa, or whole blood products within seven days prior to the bleeding event.

5.2 Re-elevation or Incomplete Reversal of Anti-FXa Activity

The time course of anti-FXa activity following ANDEXXA administration was consistent among the healthy volunteer studies and the ANNEXA-4 study in bleeding patients [see *Clinical Studies (14)*]. Compared to baseline, there was a rapid and substantial decrease in anti-FXa activity corresponding to the ANDEXXA bolus. This decrease was sustained through the end of the ANDEXXA continuous infusion. Following the infusion, there was an increase in anti-FXa activity, which peaked 4 hours after infusion in ANNEXA-4 subjects. After this peak, the anti-FXa activity decreased at a rate similar to the clearance of the FXa inhibitors.

Thirty-eight patients who were anticoagulated with apixaban had baseline levels of anti-FXa activity >150 ng/mL. Nineteen of these 38 (50%) patients experienced a > 93% decrease from baseline anti-FXa activity after administration of ANDEXXA. Eleven patients who were anticoagulated with rivaroxaban had baseline anti-FXa activity levels > 300 ng/mL. Five of the 11 patients experienced a > 90% decrease from baseline anti-FXa activity after administration of ANDEXXA.

6 ADVERSE REACTIONS

The most common adverse reactions ($\geq 5\%$) in patients receiving ANDEXXA were urinary tract infections and pneumonia.

The most common adverse reactions ($\geq 3\%$) in healthy volunteers treated with ANDEXXA were infusion-related reactions.

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

In the pooled safety analysis of clinical trials of ANDEXXA, 223 healthy volunteers received FXa inhibitors followed by treatment with ANDEXXA. The frequency of adverse reactions was similar in the ANDEXXA-treated group (120/223, 54%) and the placebo-treated group (54/94, 57%). Infusion-related adverse reactions occurred in 18% (39/223) of the ANDEXXA-treated group, and was the only adverse reaction that occurred more frequently than in the placebo group. No serious or severe adverse reactions were reported.

The ANNEXA-4 study is an ongoing multinational, prospective, open-label study using ANDEXXA in patients presenting with acute major bleeding who have recently received a FXa

inhibitor. To date, safety data are available for 185 patients. Approximately half of the patients are male with median age of 78 years. Patients had received either apixaban (98/185, 53%) or rivaroxaban (72/185, 40%), as anticoagulation treatment for atrial fibrillation (143/185, 77%) or venous thromboembolism (48/185, 26%). In the majority of patients, ANDEXXA was used to reverse anticoagulant therapy following either an intracranial hemorrhage (106; 57%) or a gastrointestinal bleed (58; 31%), with the remaining 21 patients (11%) experiencing bleeding at other sites. Patients were assessed at a 30-day follow-up visit following infusion of ANDEXXA.

Deaths

In the ongoing ANNEXA-4 study, there were 25 deaths (14%) prior to the Day 30 follow-up visit. Eight patients died within 10 days after the ANDEXXA infusion. The percentage of patients, by bleeding type, who died prior to the Day 30 follow-up visit was: 14% for intracranial bleeding, 10% for gastrointestinal bleeding, and 19% for other bleeding types.

Thromboembolic Events

In the ongoing ANNEXA-4 study, 33/185 (17.8%) patients experienced one or more of the following events: deep venous thrombosis (11/33; 33%), ischemic stroke (9/33; 24%), acute myocardial infarction (5/33; 15%), pulmonary embolism (5/33; 15%), cardiogenic shock (3/33; 9%), sudden death (2/33; 6%), congestive heart failure (2/33; 6%), acute respiratory failure (2/33; 6%), cardiac arrest (1/33; 3%), cardiac thrombus (1/33; 3%), embolic stroke (1/33; 3%), iliac artery thrombosis (1/33; 3%), and non-sustained ventricular tachycardia (1/33; 3%). The median time to the first event in these 33 subjects was 6 days. Eleven of 33 (33%) patients were on antithrombotic therapy at the time of the event. [see [Warnings and Precautions \(5.1\)](#)].

No thromboembolic events were observed in 223 healthy volunteers who received FXa inhibitors and were treated with ANDEXXA.

Infusion-related Reactions

Infusion-related reactions occurred in 18% (39/223) of ANDEXXA-treated healthy volunteers vs. 6% (6/94) of placebo-treated subjects. These reactions were characterized by a range of symptoms including flushing, feeling hot, cough, dysgeusia, and dyspnea. Symptoms were mild to moderate in severity, and 90% (35/39) did not require treatment. One subject with a history of hives prematurely discontinued ANDEXXA after developing mild hives.

6.2 Immunogenicity

As with all therapeutic proteins, there is the potential for immunogenicity. Using an electrochemiluminescence (ECL)-based assay, 145 ANDEXXA-treated healthy subjects were tested for antibodies to ANDEXXA as well as antibodies cross-reacting with Factor X (FX) and FXa. Low titers of anti-ANDEXXA antibodies were observed in 26/145 healthy subjects (17%); 6% (9/145) were first observed at Day 30 with 20 subjects (14%) still having titers at the last time point (Days 44 to 48). To date, the pattern of antibody response in patients in the

ANNEXA-4 study has been similar to that observed in healthy volunteers with 6% (6/98) of the patients having antibodies against ANDEXXA. None of these anti-ANDEXXA antibodies were neutralizing. No antibodies cross-reacting with FX or FXa were detected in healthy subjects (0/145) or in bleeding patients (0/98) to date.

Detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to ANDEXXA with the incidence of antibodies to other products may be misleading.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no adequate and well-controlled studies of ANDEXXA in pregnant women to inform patients of associated risks. Animal reproductive and development studies have not been conducted with ANDEXXA.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Clinical Considerations

Labor or Delivery

The safety and effectiveness of ANDEXXA during labor and delivery have not been evaluated.

8.2 Lactation

Risk Summary

There is no information regarding the presence of ANDEXXA in human milk, the effects on the breastfed child, or the effects on milk production.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ANDEXXA and any potential adverse effects on the breastfed child from ANDEXXA or from the underlying maternal condition.

8.4 Pediatric Use

The safety and efficacy of ANDEXXA in the pediatric population have not been studied.

8.5 Geriatric Use

Of the 185 subjects in the ANNEXA-4 study of ANDEXXA, 161 were 65 years of age or older and 113 were 75 years of age or older. No overall differences in safety or efficacy were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

The pharmacokinetics of ANDEXXA in older (≥ 65 years, $n=10$) patients were not different compared to younger (18-45 years, $n=10$) patients.

11 DESCRIPTION

ANDEXXA (coagulation factor Xa (recombinant), inactivated-zhzo) is a sterile, white to off-white lyophilized powder available in single-use vials, containing 100 mg of coagulation factor Xa formulated with the inactive ingredients tromethamine (Tris), L-arginine hydrochloride, sucrose (2% w/v), mannitol (5% w/v), and polysorbate 80 (0.01% w/v) at pH 7.8. After reconstitution of the lyophilized powder with sterile Water for Injection for intravenous (IV) administration, the product is a clear, colorless to slightly yellow solution. ANDEXXA contains no preservatives.

The active ingredient in ANDEXXA is a genetically modified variant of human Factor Xa. The active site serine was substituted with alanine, rendering the molecule unable to cleave and activate prothrombin. The gamma-carboxyglutamic acid (Gla) domain was removed to eliminate the protein's ability to assemble into the prothrombinase complex, thus removing the potential anti-coagulant effects.

No additives of human or animal origin are used in the manufacture of ANDEXXA. The recombinant protein is produced in a genetically engineered Chinese Hamster Ovary (CHO) cell expression system and has a molecular weight of approximately 41 kDa. The manufacturing process incorporates two validated virus clearance steps.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Coagulation factor Xa (recombinant), inactivated-zhzo exerts its procoagulant effect by binding and sequestering the FXa inhibitors, rivaroxaban and apixaban. Another observed procoagulant effect of the ANDEXXA protein is its ability to bind and inhibit the activity of Tissue Factor Pathway Inhibitor (TFPI). Inhibition of TFPI activity can increase tissue factor-initiated thrombin generation.

12.2 Pharmacodynamics

The effects of ANDEXXA can be measured using assays for its anti-FXa activity, free fraction of FXa inhibitor and thrombin generation. In addition to its ability to sequester the FXa

inhibitors, rivaroxaban and apixaban, ANDEXXA has been shown to inhibit the Tissue Factor Pathway Inhibitor (TFPI) activity.

The dose and dosing regimen of ANDEXXA that are required to reverse anti-FXa activity and to restore thrombin generation were determined in dose-ranging studies on healthy volunteers. Dosing of ANDEXXA, as a bolus followed by a 2-hour continuous infusion, resulted in a rapid decrease in anti-FXa activity (within two minutes after the completion of the bolus administration) followed by reduced anti-FXa activity that was maintained throughout the duration of the continuous infusion [see *Clinical Studies (14)*]. The anti-FXa activity returned to the placebo levels approximately 2 hours after completion of a bolus or continuous infusion. Whereas, TFPI activity in plasma was sustained for at least 22 hours following ANDEXXA administration.

Elevation of Tissue Factor (TF)-initiated thrombin generation above the baseline range (prior to anticoagulation) occurred within two minutes following a bolus administration of ANDEXXA and was maintained throughout the duration of the continuous infusion. The TF-initiated thrombin generation was elevated above placebo for up to 22 hours. The sustained elevation of thrombin generation over the baseline range, and sustained elevation over placebo were not observed in a contact-activated thrombin generation assay (an assay that is not affected by TF-TFPI interaction).

12.3 Pharmacokinetics

Distribution

The volume of distribution (V_d) for ANDEXXA is approximately equivalent to the blood volume of 5 L.

Elimination

Clearance for ANDEXXA is approximately 4.3 L/hr. The elimination half-life ranges from 5 to 7 hours.

Drug-Drug Interaction

The pharmacokinetics of ANDEXXA was not affected by apixaban (5 mg orally BID for 6 days) or rivaroxaban (20 mg orally once daily for 6 days).

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No animal studies were performed to evaluate the effects of ANDEXXA on carcinogenesis, mutagenesis, or impairment of fertility.

14 CLINICAL STUDIES

The safety and efficacy of ANDEXXA were evaluated in two prospective, randomized, placebo-controlled studies, conducted in healthy volunteers. Both studies examined the percent change in anti-FXa activity, from baseline to nadir, for the low-dose and high-dose regimens of bolus followed by continuous infusion. Nadir is defined as the smallest value measured within 5 minutes after the end of the continuous infusion.

Study 1 (NCT02207725) – apixaban reversal

In Study 1, healthy subjects (median age: 57 years; range: 50 to 73 years) received apixaban 5 mg twice daily for 3.5 days to achieve steady-state. At 3 hours after the last apixaban dose ($\sim C_{\max}$), ANDEXXA or placebo was administered. Eight subjects received placebo and 24 received ANDEXXA, administered as a 400 mg intravenous (IV) bolus followed by a 4 mg per minute continuous infusion for 120 minutes (total 480 mg).

Study 2 (NCT02220725) – rivaroxaban reversal

In Study 2, healthy subjects (median age: 57 years, range: 50 to 68 years) received rivaroxaban 20 mg once per day for 4 days to achieve steady-state. At 4 hours after the last rivaroxaban dose ($\sim C_{\max}$), ANDEXXA or placebo was administered. Thirteen subjects received placebo and 26 received ANDEXXA, administered as an 800 mg IV bolus followed by an 8 mg per minute continuous infusion for 120 minutes (total 960 mg).

Reduction in Anti-FXa Activity

The percent change from baseline in anti-FXa activity at its nadir was statistically significant ($p < 0.0001$) in favor of the ANDEXXA groups compared to placebo in both Studies 1 and 2. The results of Study 1 and Study 2 are provided in [Table 3](#) (see below).

The time courses of anti-FXa activity before and after ANDEXXA administration are shown in [Figure 1](#).

Table 3 - A : Change in Anti-FXa Activity/Study 1 (apixaban)

Anti-FXa Activity	ANDEXXA n=23	Placebo n=8
Mean baseline ng/mL (\pm SD)	173.0 (50.5)	191.7 (34.4)
Mean ng/mL (\pm SD) change from baseline at the nadir ^a	-160.6 (49.3)	-63.2 (18.1)
Mean % (\pm SD) change from baseline at the nadir ^a	-92.3 (2.8)	-32.7 (5.6)
95% Confidence interval (CI) ^b	-59.5 (-64.1, -55.2)	
p-value	< 0.0001 ^c	

Table 3 - B : Change in Anti-FXa Activity/Study 2 (rivaroxaban)

Anti-FXa Activity	ANDEXXA n=26	Placebo n=13
Mean baseline ng/mL (\pm SD)	335.3 (91.0)	317.2 (91.0)
Mean ng/mL (\pm SD) change from baseline at the nadir ^a	-324.5 (89.2)	-14.4 (58.8)
Mean % (\pm SD) change from baseline at the nadir ^a	-96.7 (1.8)	-44.6 (11.8)
95% Confidence interval (CI) ^b	-51.9 (-58.0, -47.0)	
p-value	< 0.0001 ^c	

SD = Standard deviation

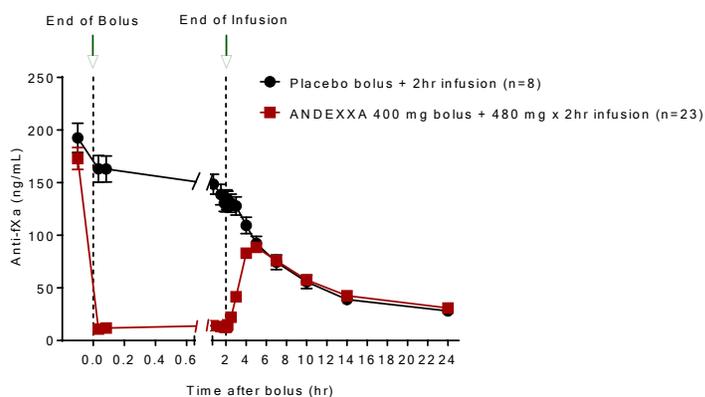
Note: Baseline is the last assessment obtained prior to the first dose of ANDEXXA or placebo.

^a Nadir is the smallest value for anti-FXa activity at the 110 minute (10 minutes prior to the end of the infusion) time point, 2-minute time point before completion of the infusion, or the 5 minute time point after the completion of the infusion for each subject.

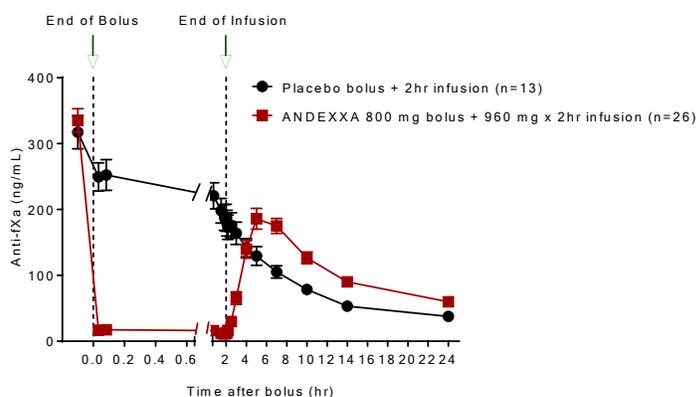
^b The CI is for the Hodges-Lehman estimate of shift.

^c p-value obtained from a 2-sided exact Wilcoxon rank-sum test.

Figure 1: Change in Anti-FXa Activity (ng/mL) in Subjects Anticoagulated with Apixaban (A – Study 1) and Rivaroxaban (B – Study 2)



(A)



(B)

Anti-FXa activity was measured prior to and after ANDEXXA or placebo administration.

Dashed lines indicate the end of the bolus or infusion. A break in the x-axis is added to better visualize the immediate, short-term dynamics of anti-FXa activity following ANDEXXA treatment. The points on the graph represent the mean anti-FXa activity level; error bars illustrate standard error. There was a statistically significant difference ($p < 0.05$) in the percent change of anti-FXa activity normalized to pre-bolus between ANDEXXA and placebo until 2 hours after administration of infusion.

A. Apixaban – with ANDEXXA 400 mg IV bolus plus 4 mg/min infusion for 120 minutes.

B. Rivaroxaban – with ANDEXXA 800 mg IV bolus plus 8 mg/min infusion for 120 minutes.

ANNEXA-4 (NCT02329327)

In an ongoing multinational, prospective, single-arm, open-label study, ANDEXXA was administered to patients taking FXa inhibitors who presented with acute major bleeding.

Interim results of the study include data for 185 patients. Of the 185 patients, 129 were considered efficacy-evaluable, defined as patients who: 1) were dosed with ANDEXXA; 2) had a baseline anti-FXa activity above 75 ng/mL; and 3) were adjudicated as meeting eligibility criteria for acute major bleeding. [also see [Adverse Reactions \(6\)](#)].

For anti-FXa activity, the median decrease from baseline to nadir was -93% for apixaban and -90% for rivaroxaban. ANDEXXA has not been shown to be effective for bleeding related to any FXa inhibitors other than apixaban and rivaroxaban.

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

ANDEXXA is supplied in cartons of 4 single-use vials each containing 100 mg of ANDEXXA as a white to off-white lyophilized cake or powder.

NDC 69853-0101-1

Storage and Handling

Unopened vials should be stored refrigerated at 2°C to 8°C (36°F to 46°F). DO NOT FREEZE.

17 PATIENT COUNSELING INFORMATION

Inform patients that reversing FXa inhibitor therapy increases the risk of thromboembolic events. Arterial and venous thromboembolic events, ischemic events, cardiac events, and sudden death were observed within 30 days following ANDEXXA administration. [see [Warnings and Precautions \(5.1\)](#)].

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HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use CRYSVITA safely and effectively. See full prescribing information for CRYSVITA.

CRYSVITA® (burosumab-twza) injection, for subcutaneous use
Initial U.S. Approval: 2018

INDICATIONS AND USAGE

CRYSVITA is a fibroblast growth factor 23 (FGF23) blocking antibody indicated for the treatment of X-linked hypophosphatemia (XLH) in adult and pediatric patients 1 year of age and older. (1)

DOSAGE AND ADMINISTRATION

For subcutaneous use only (2)

- **Pediatric XLH:** Starting dose regimen is 0.8 mg/kg of body weight rounded to the nearest 10 mg, administered every two weeks. The minimum starting dose is 10 mg up to a maximum dose of 90 mg. (2.1)
Dose may be increased up to approximately 2 mg/kg (maximum 90 mg), administered every two weeks to achieve normal serum phosphorus. (2.1)
- **Adult XLH:** Dose regimen is 1 mg/kg body weight rounded to the nearest 10 mg up to a maximum dose of 90 mg administered every four weeks. (2.2)

DOSAGE FORMS AND STRENGTHS

Injection: 10 mg/mL, 20 mg/mL, or 30 mg/mL in a single-dose vial (3)

CONTRAINDICATIONS

- Do not use CRYSVITA with oral phosphate and active vitamin D analogs. (4)
- Do not initiate CRYSVITA if serum phosphorus is within or above the normal range for age. (4)
- CRYSVITA is contraindicated in patients with severe renal impairment or end stage renal disease. (4)

WARNINGS AND PRECAUTIONS

- **Hypersensitivity:** Discontinue CRYSVITA if serious hypersensitivity reactions occur and initiate appropriate medical treatment. (5.1)
- **Hyperphosphatemia and Risk of Nephrocalcinosis:** For patients already taking CRYSVITA, dose interruption and/or dose reduction may be required based on a patient's serum phosphorus levels. (5.2)
- **Injection Site Reactions:** Administration of CRYSVITA may result in local injection site reactions. Discontinue CRYSVITA if severe injection site reactions occur and administer appropriate medical treatment. (5.3, 6.1)

ADVERSE REACTIONS

Most common adverse reactions (≥25%) in pediatric XLH patients are: headache, injection site reaction, vomiting, pyrexia, pain in extremity, vitamin D decreased. (6.1)

Most common adverse reactions (≥5% and in at least 2 patients more than placebo) in adult XLH patients are: back pain, headache, tooth infection, restless leg syndrome, vitamin D decreased, dizziness, constipation, blood phosphorus increased. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact **Ultragenyx at 1-888-756-8657 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.**

See 17 for PATIENT COUNSELING INFORMATION

Revised: 04/2018

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- 2.2 Adult Patients with X-linked Hypophosphatemia (18 years of age and older)
- 2.3 Missed Dose
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* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

CRYSVITA is indicated for the treatment of X-linked hypophosphatemia (XLH) in adult and pediatric patients 1 year of age and older.

2 DOSAGE AND ADMINISTRATION

CRYSVITA is administered by subcutaneous injection and should be administered by a healthcare provider.

Discontinue oral phosphate and active vitamin D analogs 1 week prior to initiation of treatment. Fasting serum phosphorus concentration should be below the reference range for age prior to initiation of treatment.

2.1 Pediatric Patients with X-linked Hypophosphatemia (1 to less than 18 years of age)

The recommended starting dose regimen is 0.8 mg/kg of body weight, rounded to the nearest 10 mg, administered every two weeks. The minimum starting dose is 10 mg up to a maximum dose of 90 mg.

After initiation of treatment with CRYSVITA, measure fasting serum phosphorus every 4 weeks for the first 3 months of treatment, and thereafter as appropriate. If serum phosphorus is above the lower limit of the reference range for age and below 5 mg/dL, continue treatment with the same dose. Follow dose adjustment schedule below to maintain serum phosphorus within the reference range for age.

Dose Adjustment

Reassess fasting serum phosphorus level 4 weeks after dose adjustment.

Do not adjust CRYSVITA more frequently than every 4 weeks.

Dose Increase: If serum phosphorus is below the reference range for age, the dose may be increased stepwise up to approximately 2 mg/kg, administered every two weeks (maximum dose of 90 mg) according to the dosing schedule shown in [Table 1](#).

Table 1: Pediatric Dose Schedule for Stepwise Dose Increase

Body Weight (kg)	Starting Dose (mg)	First Dose Increase to (mg)	Second Dose Increase to (mg)
10 - 14	10	15	20
15 - 18	10	20	30
19 - 31	20	30	40
32 - 43	30	40	60
44 - 56	40	60	80
57 - 68	50	70	90
69 - 80	60	90	90
81 - 93	70	90	90
94 - 105	80	90	90
106 and greater	90	90	90

Dose Decrease: If serum phosphorus is above 5 mg/dL, withhold the next dose and reassess the serum phosphorus level in 4 weeks. The patient must have serum phosphorus below the reference range for age to reinitiate CRYSVITA. Once serum phosphorus is below the reference range for age, treatment may be restarted according to the dose schedule shown in [Table 2](#). Reassess serum phosphorus level 4 weeks after dose adjustment. If the level remains below the reference range for age after the re-initiation dose, the dose can be adjusted according to [Table 1](#).

Table 2: Pediatric Dose Schedule for Re-Initiation of Therapy

Previous Dose (mg)	Re-Initiation Dose (mg)
10	5
15	10
20	10
30	10
40	20
50	20
60	30
70	30
80	40
90	40

2.2 Adult Patients with X-linked Hypophosphatemia (18 years of age and older)

The recommended dose regimen in adults is 1 mg/kg body weight, rounded to the nearest 10 mg up to a maximum dose of 90 mg, administered every four weeks.

After initiation of treatment with CRYSVITA, assess fasting serum phosphorus on a monthly basis, measured 2 weeks post-dose, for the first 3 months of treatment, and thereafter as appropriate. If serum phosphorus is within the normal range, continue with the same dose.

Dose Decrease

Reassess fasting serum phosphorus level 2 weeks after dose adjustment.

Do not adjust CRYSVITA more frequently than every 4 weeks.

If serum phosphorus is above the normal range, withhold the next dose and reassess the serum phosphorus level after 4 weeks. The patient must have serum phosphorus below the normal range to be able to reinitiate CRYSVITA. Once serum phosphorus is below the normal range, treatment may be restarted at approximately half the initial starting dose up to a maximum dose of 40 mg every 4 weeks according to the dose schedule shown in [Table 3](#). Reassess serum phosphorus 2 weeks after any change in dose.

Table 3: Adult Dose Schedule for Re-Initiation of Therapy

Previous Dose (mg)	Re-Initiation Dose (mg)
40	20
50	20
60	30
70	30
80 and greater	40

2.3 Missed Dose

If a patient misses a dose, resume CRYSVITA as soon as possible at the prescribed dose.

2.4 General Considerations for Subcutaneous Administration

Injection sites should be rotated with each injection administered at a different anatomic location (upper arms, upper thighs, buttocks, or any quadrant of abdomen) than the previous injection. Do not inject into moles, scars, or areas where the skin is tender, bruised, red, hard, or not intact.

The maximum volume of CRYSVITA per injection site is 1.5 mL. If more than 1.5 mL is required on a given dosing day, the total volume of CRYSVITA should be split and administered at two different injection sites. Monitor for signs of reactions.

Visually inspect CRYSVITA for particulate matter and discoloration prior to administration. CRYSVITA is a sterile, preservative-free, clear to slightly opalescent and colorless to pale brown-yellow solution for subcutaneous injection. Do not use if the solution is discolored or cloudy or if the solution contains any particles or foreign particulate matter.

3 DOSAGE FORMS AND STRENGTHS

Injection: 10 mg/mL, 20 mg/mL, or 30 mg/mL clear to slightly opalescent and colorless to pale brown-yellow solution in a single-dose vial.

4 CONTRAINDICATIONS

Do not use CRYSVITA with oral phosphate and active vitamin D analogs.

Do not initiate CRYSVITA treatment if serum phosphorus is within or above the normal range for age.

CRYSVITA is contraindicated in patients with severe renal impairment or end stage renal disease because these conditions are associated with abnormal mineral metabolism.

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity

Hypersensitivity reactions (e.g. rash, urticaria) have been reported in patients with CRYSVITA. Discontinue CRYSVITA if serious hypersensitivity reactions occur and initiate appropriate medical treatment [see *Adverse Reactions (6.1)*].

5.2 Hyperphosphatemia and Risk of Nephrocalcinosis

Increases in serum phosphorus to above the upper limit of normal may be associated with an increased risk of nephrocalcinosis. For patients already taking CRYSVITA, dose interruption and/or dose reduction may be required based on a patient's serum phosphorus levels [see *Dosage and Administration (2)*].

5.3 Injection Site Reactions

Administration of CRYSVITA may result in local injection site reactions. Discontinue CRYSVITA if severe injection site reactions occur and administer appropriate medical treatment [see *Adverse Reactions (6.1)*].

6 ADVERSE REACTIONS

The following adverse reactions are described below and elsewhere in the labeling:

- Hypersensitivity [see *Warnings and Precautions (5.1)*]
- Hyperphosphatemia and Risk of Nephrocalcinosis [see *Warnings and Precautions (5.2)*]
- Injection Site Reactions [see *Warnings and Precautions (5.3)*]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Adverse Reactions in Pediatric Patients with XLH

The safety data described below reflect exposure to CRYSVITA in 65 pediatric XLH patients that included 52 exposed for at least 64 weeks (Study 1) and 13 exposed for at least 40 weeks (Study 2). Overall, pediatric XLH patients have been exposed to CRYSVITA for a mean duration of 108 weeks (min 40.9, max 150.0). CRYSVITA was studied in two pediatric open-label phase 2 studies (Study 1, ages 5 to 12 years, n = 52; Study 2, ages ≥ 1 to < 5 years, n = 13). Overall, the patient population was 1-12 years (mean age 7.4 years), 51% male, and 89% white/Caucasian and diagnosed with XLH. In Study 1, 26 of the patients received CRYSVITA at a mean dose of 1.05 mg/kg (range 0.4 – 2.0 mg/kg) every 2 weeks at Week 64; the other 26 patients received CRYSVITA every 4 weeks. In Study 2, patients received CRYSVITA at a mean dose of 0.89 mg/kg (range 0.8 – 1.2 mg/kg) every 2 weeks at Week 40. Adverse reactions reported in more than 10% of CRYSVITA-treated patients from Studies 1 and 2 are shown in [Table 4](#).

Table 4: Adverse Reactions Reported in More Than 10% of Pediatric Patients Receiving CRYSVITA in Studies 1 and 2

Adverse Reaction	Study 1 (N=52) n (%)	Study 2 (N=13) n (%)	Overall (N=65) n (%)
Headache	38 (73)	1 (8)	39 (60)
Injection site reaction ¹	35 (67)	3 (23)	38 (59)
Vomiting	25 (48)	6 (46)	31 (48)
Pyrexia	23 (44)	8 (62)	31 (48)
Pain in extremity	24 (46)	3 (23)	27 (42)
Vitamin D decreased ²	19 (37)	2 (15)	21 (32)
Rash ³	14 (27)	1 (8)	15 (23)
Toothache	12 (23)	2 (15)	14 (22)
Myalgia	9 (17)	1 (8)	10 (15)
Tooth abscess	8 (15)	3 (23)	11 (17)
Dizziness ⁴	8 (15)	0 (0)	8 (12)

n = number of patients with an event; N = total number of patients who received at least one dose of CRYSVITA

¹ Injection site reaction includes: injection site reaction, injection site erythema, injection site pruritus, injection site swelling, injection site pain, injection site rash, injection site bruising, injection site discoloration, injection site discomfort, injection site hematoma, injection site hemorrhage, injection site induration, injection site macule, and injection site urticaria

² Vitamin D decreased includes: vitamin D deficiency, blood 25-hydroxycholecalciferol decreased, and vitamin D decreased

³ Rash includes: rash, rash pruritic, rash maculopapular, and rash pustular

⁴ Dizziness includes: dizziness, and dizziness exertional

Hypersensitivity Reactions

In pediatric patients, the most frequent potential hypersensitivity events were rash (22%), injection site rash (6%), and urticaria (5%).

Hyperphosphatemia

In pediatric studies, there were no events of hyperphosphatemia reported.

Injection Site Reactions (ISR)

In pediatric studies, approximately 58% of the patients had a local reaction (e.g. injection site urticaria, erythema, rash, swelling, bruising, pain, pruritus, and hematoma) at the site of CRYSVITA injection. Injection site reactions were generally mild in severity, occurred within 1 day of injection, lasted approximately 1 to 3 days, required no treatment, and resolved in almost all instances.

Adverse Reactions in Adult Patients with XLH

The safety data described below reflect exposure to CRYSVITA in 68 adult XLH patients, age 20-63 years (mean age 41 years), of whom most were white/Caucasian (81%) and female (65%). These patients were enrolled in a randomized, double-blind, placebo-controlled Phase 3 study in adults with XLH (Study 3: CRYSVITA = 68, Placebo = 66), in which patients received CRYSVITA at a mean dose of 0.95 mg/kg (range 0.3 – 1.2 mg/kg) subcutaneously every 4 weeks at Week 24. Adverse reactions reported in more than 5% of CRYSVITA-treated patients and 2 patients or more than with placebo from the 24-week placebo-controlled portion of Study 3 are shown in [Table 5](#).

Table 5: Adverse Reactions Occurring in More Than 5% of CRYSVITA-Treated Adult Patients and in at Least 2 Patients More Than with Placebo in Study 3

Adverse Reaction	CRYSVITA (N=68) n (%)	Placebo (N=66) n (%)
Back pain	10 (15)	6 (9)
Headache ¹	9 (13)	6 (9)
Tooth infection ²	9 (13)	6 (9)
Restless legs syndrome	8 (12)	5 (8)
Vitamin D decreased ³	8 (12)	3 (5)
Dizziness	7 (10)	4 (6)
Constipation	6 (9)	0 (0)
Blood phosphorus increased ⁴	4 (6)	0 (0)

n = number of patients with an event; N = total number of patients who received at least one dose of CRYSVITA or placebo

¹ Headache includes: headache, and head discomfort

² Tooth infection includes: tooth abscess, and tooth infection

³ Vitamin D decreased includes: vitamin D deficiency, blood 25-hydroxycholecalciferol decreased, and vitamin D decreased

⁴ Blood phosphorus increased includes: blood phosphorus increased, and hyperphosphatemia

Hypersensitivity Reactions

In the double-blind period of Study 3, approximately 6% of patients in both the CRYSVITA and placebo treatment groups experienced a hypersensitivity event. The events were mild or moderate and did not require discontinuation.

Hyperphosphatemia

In the double-blind period of Study 3, 7% of patients in the CRYSVITA treatment group experienced hyperphosphatemia meeting the protocol-specified criteria for dose reduction (either a single serum phosphorus greater than 5.0 mg/dL or serum phosphorus greater than 4.5 mg/dL [the upper limit of normal] on two occasions). The hyperphosphatemia was managed with dose reduction. The dose for all patients meeting the protocol-specified criteria was reduced 50 percent. A single patient required a second dose reduction for continued hyperphosphatemia.

Injection Site Reactions (ISR)

In the double-blind period of Study 3, approximately 12% of patients in both the CRYSVITA and placebo treatment groups had a local reaction (e.g. injection site reaction, erythema, rash, bruising, pain, pruritus, and hematoma) at the site of the injection. Injection site reactions were generally mild in severity, occurred within 1 day of injection, lasted approximately 1 to 3 days, required no treatment, and resolved in almost all instances.

Restless Leg Syndrome (RLS)

In the double-blind period of Study 3, approximately 12% of the CRYSVITA treatment group had worsening of baseline restless leg syndrome (RLS) or new onset RLS of mild to moderate severity; these events did not lead to dose discontinuation. Nonserious RLS has also been reported in other repeat dose adult XLH studies; in one case, worsening baseline RLS led to drug discontinuation and subsequent resolution of the event.

Spinal Stenosis

Spinal stenosis is prevalent in adults with XLH and spinal cord compression has been reported. In the CRYSVITA phase 2 and phase 3 studies of adults with XLH (total N=176), a total of 6 patients underwent spinal surgery. Most of these cases appeared to involve progression of a pre-existing spinal stenosis. It is unknown if CRYSVITA therapy exacerbates spinal stenosis or spinal cord compression.

6.2 Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to burosumab-twza in the studies described below with the incidence of antibodies in other studies or to other products may be misleading.

Pre-existing anti-drug antibodies (ADA) have been detected in up to 10% of patients in clinical studies. ADA was not detected in patients who were antibody negative at the start of treatment. However, the assay used to measure ADA is subject to interference by serum burosumab-twza, possibly resulting in an underestimation of the incidence of antibody formation. Due to the limitation of the assay conditions, the potential clinical impact of antibodies to burosumab-twza is not known.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available data on CRYSVITA use in pregnant women to inform a drug-associated risk of adverse developmental outcomes. In utero, burosumab-twza exposure in cynomolgus monkeys did not result in teratogenic effects. Adverse effects such as late fetal loss and preterm birth were observed in pregnant cynomolgus monkeys, however, these effects are unlikely to indicate clinical risk because they occurred at a drug exposure that was 64-fold higher, by AUC, than the human exposure at 1 mg/kg every 4 weeks and were accompanied in the non-XLH monkeys by maternal hyperphosphatemia and placental mineralization (see *Data*). Serum phosphorus levels should be monitored throughout pregnancy [see *Dosage and Administration (2.2)*]. Report pregnancies to the Ultragenyx Adverse Event reporting line at 1-888-756-8657.

The background risk of major birth defects and miscarriage for the indicated population is unknown; however, the estimated background risk in the U.S. general population of major birth defects is 2% to 4% and of miscarriage is 15% to 20% of clinically recognized pregnancies.

Data

Animal Data

In a reproductive toxicity study in pregnant cynomolgus monkeys without XLH, burosumab-twza was administered intravenously once every two weeks from Day 20 of pregnancy to parturition or cesarean section on Day 133, which includes the period of organogenesis, at doses of 1-, 7- and 64-fold human exposure at the adult human dose of 1 mg/kg every 4 weeks. The treatment did not result in teratogenic effects in fetuses or offspring. An increase in late fetal loss, a shortened gestation period, and an increased incidence of preterm births were observed at 64-fold the human exposure at the adult human dose of 1 mg/kg every 4 weeks, concomitant with maternal hyperphosphatemia and placental mineralization. Burosumab-twza was detected in serum from fetuses indicating transport across the placenta. Hyperphosphatemia but no ectopic mineralization was present in fetuses and offspring of dams exposed to 64-fold human exposure at the 1 mg/kg dose every 4 weeks. Burosumab-twza did not affect pre- and postnatal growth including survivability of the offspring.

8.2 Lactation

Risk Summary

There is no information regarding the presence of burosumab-twza in human milk, or the effects of burosumab-twza on milk production or the breastfed infant. Maternal IgG is present in breast milk. However, the effects of local gastrointestinal exposure and limited systemic exposure to burosumab-twza in the breastfed infant are unknown. The lack of clinical data during lactation precludes a clear determination of the risk of CRYSVITA to an infant during lactation. Therefore, the developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for CRYSVITA and any potential adverse effects on the breastfed infant from CRYSVITA or from the underlying maternal condition.

8.4 Pediatric Use

Safety and efficacy of CRYSVITA have been established in pediatric patients 1 year and older. Efficacy in pediatric patients 1 year and older with XLH is based on open label studies of 52 pediatric

patients 5 to 12 years of age with XLH (Study 1), and in 13 pediatric patients 1 to 4 years of age with XLH (Study 2) evaluating serum phosphorus and radiographic findings. Efficacy in adolescents is supported by studies in pediatric patients less than 13 years of age. Dosing in this age group was derived using modeling and simulation of adult and pediatric PK and PD data.

Safety and efficacy for CRYSVITA in pediatric patients with XLH below the age of 1 have not been established [see *Adverse Reactions (6.1)* and *Clinical Studies (14)*].

8.5 Geriatric Use

Clinical studies of CRYSVITA did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

10 OVERDOSAGE

There have been no reports of overdose with CRYSVITA. CRYSVITA has been administered in pediatric clinical trials without dose limiting toxicity using doses up to 2 mg/kg body weight with a maximal dose of 90 mg, administered every two weeks. In adult clinical trials, no dose limiting toxicity has been observed using doses up to 1 mg/kg or a maximal total dose of 128 mg every 4 weeks. In non-XLH rabbits and cynomolgus monkeys, ectopic mineralization in multiple tissues and organs was observed at doses of burosumab-twza that resulted in supra-physiologic serum phosphate levels. Adverse effects on bone including reductions in bone mineral density, bone mineralization and bone strength were also observed at exposure greater than human exposure [see *Nonclinical Toxicology (13.2)*].

In case of overdose, it is recommended that serum phosphorus levels, serum calcium levels and renal function be measured immediately and monitored periodically until resolution to normal/baseline levels. In case of hyperphosphatemia, withhold CRYSVITA and initiate appropriate medical treatment.

11 DESCRIPTION

Burosumab-twza is a human immunoglobulin G subclass 1 (IgG1), anti-human fibroblast growth factor 23 (FGF23) antibody produced by recombinant DNA technology using Chinese hamster ovary cells. Burosumab-twza is composed of two heavy chain (γ 1-chain) molecules and two light chain (κ -chain) molecules. Each heavy chain has an N-linked carbohydrate moiety at asparagine 297 (Asn297). The molecular weight of burosumab-twza determined by mass spectrometry is approximately 147,000.

CRYSVITA (burosumab-twza) injection for subcutaneous administration is supplied as a sterile, preservative-free, clear to slightly opalescent and colorless to pale brown-yellow solution in a single-dose vial.

Each 1 mL of solution contains 10 mg, 20 mg or 30 mg of burosumab-twza, L-histidine (1.55 mg), L-methionine (1.49 mg), polysorbate 80 (0.5 mg), D-sorbitol (45.91 mg) in Water for Injection, USP. Hydrochloric acid may be used to adjust to a pH of 6.25.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

X-linked hypophosphatemia is caused by excess fibroblast growth factor 23 (FGF23) which suppresses renal tubular phosphate reabsorption and the renal production of 1,25 dihydroxy vitamin D. Burosumab-twza binds to and inhibits the biological activity of FGF23 restoring renal phosphate reabsorption and increasing the serum concentration of 1,25 dihydroxy vitamin D.

12.2 Pharmacodynamics

Following SC administration in XLH patients, higher burosumab-twza concentrations were associated with greater increase of serum phosphorus levels. The increase in serum phosphorus was reversible and returned to baseline with elimination of systemic burosumab-twza.

Ratio of renal tubular maximum reabsorption rate of phosphate to glomerular filtration rate (T_mP/GFR) showed dose-dependent increases from baseline [see *Clinical Studies (14)*].

Elevation in serum total FGF23 was observed after initiation of burosumab-twza treatment, however, the clinical implication is unknown.

12.3 Pharmacokinetics

The following pharmacokinetic parameters were observed in patients with XLH administered the approved recommended starting dosage based on a 70 kg patient, unless otherwise specified.

Burosumab-twza exhibited linear pharmacokinetics following SC injections within the dose range of 0.1 to 1 mg/kg (0.08 to 0.8 times the maximum approved recommended dosage based on a 70 kg patient).

The steady-state trough mean (\pm SD) concentration of burosumab-twza was 5.8 (\pm 3.4) mcg/mL in adult patients.

Absorption

The burosumab-twza mean T_{max} values ranged from 8 to 11 days.

Distribution

The apparent volume of distribution of burosumab-twza is 8 L.

Elimination

The apparent clearance is 0.290 L/day. The half-life of burosumab-twza is approximately 19 days.

Metabolism

The exact pathway for burosumab-twza metabolism has not been characterized. Burosumab-twza is expected to be degraded into small peptides and amino acids via catabolic pathways.

Specific Populations

No clinical significant difference in burosumab-twza pharmacokinetics was observed based on age.

The effect of renal or hepatic impairment on the pharmacokinetics of burosumab-twza is unknown.

Pediatric Patients

The steady-state trough concentration was 15.8 (\pm 9.4) mcg/mL in patients aged 5-12 years, and 11.2 (\pm 4.6) mcg/mL in patients aged 1-4 years.

Body Weight

Clearance and volume of distribution of burosumab-twza increases with body weight.

Drug Interaction Studies

No drug interaction studies have been conducted with CRYSVITA.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

The carcinogenic potential of burosumab-twza has not been evaluated in long term animal studies.

Studies have not been performed to evaluate the mutagenic potential of burosumab-twza.

No specific fertility studies have been performed in animals to evaluate the effects of burosumab-twza.

Toxicology studies with burosumab-twza of up to 40 weeks duration in non-XLH cynomolgus monkeys did not show significant adverse effects on female reproductive organs at doses up to 65-fold human exposure at the dose of 1 mg/kg every 4 weeks. In male monkeys, minimal mineralization of the rete testis or seminiferous tubules associated with hyperphosphatemia was observed at 11- to 37-fold human exposure, but semen analysis did not show any adverse effects.

13.2 Animal Toxicology and/or Pharmacology

In rabbits and cynomolgus monkeys, inhibition of FGF23 signaling by burosumab-twza increased serum phosphate and 1,25 dihydroxy vitamin D. Ectopic mineralization in multiple tissues and organs was observed at doses of burosumab-twza that resulted in supra-physiologic serum phosphate levels in the non-XLH animals. In a study in wild type (WT) and hypophosphatemic Hyp mice, a murine model of XLH, ectopic mineralization was markedly less in Hyp mice.

In adult cynomolgus monkeys, burosumab-twza increased bone turnover, mineral content and/or mineral density and cortical thickness at 37- to 65-fold human exposure at the dose of 1 mg/kg every 4 weeks. Adverse effects on bone including reductions in bone mineral density, bone mineralization and bone strength were observed in adult male monkeys at 37- to 47-fold human exposure at the dose of 1 mg/kg every 4 weeks.

In juvenile cynomolgus monkeys, burosumab-twza increased bone turnover, mineral content and/or mineral density and/or cortical thickness at 0.5- to 5-fold clinical pediatric exposure. Bone mineralization was decreased in a male monkey at 5-fold pediatric exposure but there was no effect on bone strength. Burosumab-twza did not affect bone development in juvenile monkeys at doses up to 5-fold pediatric exposure.

14 CLINICAL STUDIES

14.1 Pediatric X-linked Hypophosphatemia

CRYSVITA has been evaluated in 65 pediatric patients with XLH.

Study 1 (NCT 02163577) is a randomized, open-label study in 52 prepubescent XLH patients, 5 to 12 years old, which compared treatment with CRYSVITA administered every 2 weeks versus every 4 weeks. Following an initial 16-week dose titration phase, patients completed 48-weeks of treatment with CRYSVITA every 2 weeks. All 52 patients completed at least 64 weeks on study; no patient discontinued. Burosumab-twza dose was adjusted to target a fasting serum phosphorus concentration of 3.5 to 5.0 mg/dL based on the fasting phosphorus level the day of dosing. Twenty-six of 52 patients received CRYSVITA every two weeks up to a maximum dose of 2 mg/kg. The average dose was 0.73 mg/kg (range: 0.3, 1.5) at week 16, 0.98 mg/kg (range: 0.4, 2.0) at week 40 and 1.04 mg/kg (range: 0.4, 2.0) at week 60. The remaining 26 patients received CRYSVITA every four weeks. At study entry, the mean age of patients was 8.5 years and 46% were male. Ninety-six percent had received oral phosphate and active vitamin D analogs for a mean (SD) duration of 7 (2.4) years. Oral phosphate and active vitamin D analogs were discontinued prior to study enrollment. Ninety-four percent of patients had radiographic evidence of rickets at baseline.

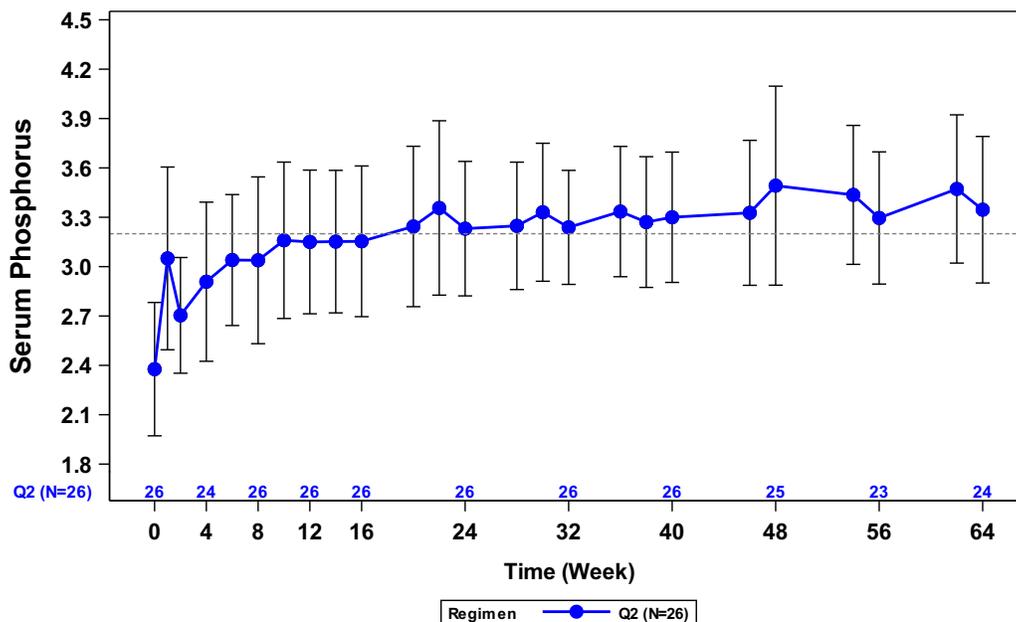
Study 2 (NCT 02750618) is a 64-week open-label study in 13 pediatric XLH patients, 1 to 4 years old. Patients received CRYSVITA at a dose of 0.8 mg/kg every two weeks with titration up to 1.2 mg/kg based on serum phosphorus measurements. All patients completed at least 40 weeks on study; no patients discontinued. At study entry, the mean age of patients was 2.9 years and 69% were male. All patients had radiographic evidence of rickets at baseline and had received oral phosphate and active vitamin D analogs for a mean (SD) duration of 16.9 (13.9) months. Oral phosphate and active vitamin D analogs were discontinued prior to study enrollment.

Serum Phosphorus

In Study 1, CRYSVITA increased mean (SD) serum phosphorus levels from 2.4 (0.40) at baseline to 3.3 (0.40) and 3.4 (0.45) mg/dL at week 40 and week 64 in the patients who received CRYSVITA every 2 weeks ([Figure 1](#)). The ratio of renal tubular maximum reabsorption rate of phosphate to glomerular filtration rate (TmP/GFR) increased in these patients from mean (SD) of 2.2 (0.49) at baseline to 3.3 (0.60) and 3.4 (0.53) mg/dL at week 40 and week 64.

In Study 2, CRYSVITA increased mean (SD) serum phosphorus levels from 2.5 (0.28) mg/dL at baseline to 3.5 (0.49) mg/dL at week 40.

Figure 1: Serum Phosphorus Levels (mg/dL) Over Time in Children 5-12 Years Receiving CRYSVITA Every 2 Weeks in Study 1^a



- a) Serum Phosphorus Level (mg/dL) (Mean \pm SD) - Q2W. The dotted line represents the lower limit of normal (3.2 mg/dL) for patients in Study 1.

Radiographic Evaluation of Rickets

Radiographs from 52 CRYSVITA-treated XLH patients in Study 1 and 13 patients in Study 2 were examined to assess XLH-related rickets using the 10-point Thatcher Rickets Severity Score (RSS) and the 7-point Radiographic Global Impression of Change (RGI-C). The RSS score is assigned based on images of the wrist and knee from a single timepoint, with higher scores indicating greater rickets severity. The RGI-C score is assigned based on side-by-side comparisons of wrist and knee radiographs from two timepoints, with higher scores indicating greater improvement in radiographic evidence of rickets. A RGI-C score of $\geq +2.0$ was defined as radiographic evidence of substantial healing.

In Study 1, baseline mean (SD) RSS total score was 1.9 (1.17) in patients receiving CRYSVITA every two weeks. After 40 weeks of treatment with CRYSVITA, mean total RSS decreased from 1.9 to 0.8 (see Table 6). After 40 weeks of treatment with CRYSVITA, the mean RGI-C Global score was $+1.7$ in patients receiving CRYSVITA every two weeks. Eighteen out of 26 patients achieved an RGI-C score of $\geq +2.0$. These findings were maintained at week 64 as shown in Table 6.

In Study 2, baseline mean (SD) total RSS was 2.9 (1.37) in 13 patients. After 40 weeks of treatment with CRYSVITA, mean total RSS decreased from 2.9 to 1.2 and the mean (SE) RGI-C Global score was $+2.3$ (0.08). All 13 patients achieved a RGI-C global score $\geq +2.0$. The mean (SE) lower limb deformity as assessed by RGI-C, using standing long leg radiographs, was $+1.3$ (0.14) (see Table 6).

Table 6: Rickets Response in Children 1-12 Years Receiving CRYSVITA Every 2 Weeks in Study 1 and Study 2

Endpoint Timepoint	CRYSVITA Every 2 Weeks	
	Study 1 (N=26)	Study 2 (N=13)
RSS Total Score		
Baseline Mean (SD)	1.9 (1.17)	2.9 (1.37)
LS Mean change from baseline in total score ^a (reduction indicates improvement) with 95% CI		
Week 40	-1.1 (-1.28, -0.85)	-1.7 (-2.03, -1.44)
Week 64	-1.0 (-1.2, -0.79)	
RGI-C Global Score		
LS Mean score ^a (positive indicates healing) with 95% CI		
Week 40	+1.7 (+1.48, +1.84)	+2.3 (+2.16, +2.51)
Week 64	+1.6 (+1.34, +1.78)	

a) The estimates of LS means and 95% CI (confidence interval) are from the generalized estimation equation model accounting for baseline RSS, visits and regimen and its interaction for Study 1 and from ANCOVA model accounting for age and baseline RSS for Study 2.

Serum Alkaline Phosphatase Activity

For Study 1, mean (SD) serum total alkaline phosphatase activity was 462 (110) U/L at baseline and decreased to 354 (73) U/L at Week 64 (-23%, $p < 0.0001$) in the patients who received CRYSVITA every 2 weeks.

For Study 2, mean (SD) serum total alkaline phosphatase activity was 549 (194) U/L at baseline and decreased to 335 (88) U/L at Week 40 (mean change: -36%).

Growth

In Study 1, CRYSVITA treatment for 64 weeks increased standing mean (SD) height Z score from -1.72 (1.03) at baseline to -1.54 (1.13) in the patients who received CRYSVITA every two weeks (LS mean change of +0.19 (95% CI: 0.09 to 0.29)).

14.2 Adult X-linked Hypophosphatemia

Study 3 (NCT 02526160) is a randomized, double-blind, placebo-controlled study in 134 adult XLH patients. The study comprises a 24-week placebo-controlled treatment phase. CRYSVITA was administered at a dose of 1 mg/kg every 4 weeks. At study entry, the mean age of patients was 40 years (range 19 to 66 years) and 35% were male. All patients had skeletal pain associated with XLH/osteomalacia at baseline. The baseline mean (SD) serum phosphorus concentration was below the lower limit of normal at 1.98 (0.31) mg/dL. Oral phosphate and active vitamin D analogs were not allowed during the study. One patient in the CRYSVITA group discontinued treatment.

Study 4 (NCT 02537431) is a 48-week, open-label, single-arm study in 14 adult XLH patients to assess the effects of CRYSVITA on improvement of osteomalacia as determined by histologic and histomorphometric evaluation of iliac crest bone biopsies. Patients received 1 mg/kg CRYSVITA every four weeks. At study entry, the mean age of patients was 40 years (range 25 to 52 years) and 43% were male. Oral phosphate and active vitamin D analogs were not allowed during the study.

Serum Phosphorus

In Study 3 at baseline, mean (SD) serum phosphorus was 1.9 (0.32) and 2.0 (0.30) mg/dL in the placebo and CRYSVITA groups respectively. During the initial 24 weeks of treatment, mean (SD) serum phosphorus across the midpoints of dose intervals (2 weeks post dose) was 2.1 (0.30) and 3.2 (0.53) mg/dL in the placebo and CRYSVITA groups, and mean (SD) serum phosphorus across the ends of dose intervals was 2.0 (0.30) and 2.7 (0.45) mg/dL in the placebo and CRYSVITA groups.

A total of 94% of patients treated with CRYSVITA achieved a serum phosphorus level above the lower limit of normal (LLN) compared to 8% in the placebo group through week 24 ([Table 7](#)).

Table 7: Proportion of Adult Patients Achieving Mean Serum Phosphorus Levels Above the LLN at the Midpoint of the Dose Interval in Study 3

	Placebo (N = 66)	CRYSVITA (N = 68)
Achieved Mean Serum Phosphorus > LLN Across Midpoints of Dose Intervals Through Week 24 - n (%)	5 (8%)	64 (94%)
95% CI	(3.3, 16.5)	(85.8, 97.7)
p-value ^a		< 0.0001

The 95% CIs are calculated using the Wilson score method.

^a P-value is from Cochran-Mantel-Haenszel (CMH) testing for association between achieving the primary endpoint and treatment group, adjusting for randomization stratifications.

At baseline, the mean (SD) ratio of renal tubular maximum reabsorption rate of phosphate to glomerular filtration rate (TmP/GFR) was 1.60 (0.37) and 1.68 (0.40) mg/dL in the placebo and CRYSVITA groups respectively. At week 22 (midpoint of a dose interval), mean (SD) TmP/GFR was 1.69 (0.37) and 2.73 (0.75) mg/dL in the placebo and CRYSVITA groups. At week 24 (end of a dose interval), mean (SD) TmP/GFR was 1.73 (0.42) and 2.21 (0.48) mg/dL in the placebo and CRYSVITA groups.

Radiographic Evaluation of Osteomalacia

In Study 3, a skeletal survey was conducted at baseline to identify osteomalacia-related fractures and pseudofractures. Osteomalacia-related fractures are defined as atraumatic lucencies extending across both bone cortices and pseudofractures are defined as atraumatic lucencies extending across one cortex. There were 52% of patients who had either active (unhealed) fractures (12%) or active pseudofractures (47%) at baseline. The active fractures and pseudofractures were predominantly located in the femurs, tibia/fibula, and metatarsals of the feet. Assessment of these active fracture/pseudofracture sites at week 24 demonstrated a higher rate of complete healing in the CRYSVITA group compared to placebo as shown in [Table 8](#). During treatment through week 24, a total of 6 new fractures or pseudofractures appeared in 68 patients receiving CRYSVITA, compared to 8 new abnormalities in 66 patients receiving placebo.

Table 8: Comparison of Fracture Healing with CRYSVITA vs Placebo in Study 3

	Active Fractures		Active Pseudofractures		Total Fractures	
	Placebo n (%)	CRYSVITA n (%)	Placebo n (%)	CRYSVITA n (%)	Placebo n (%)	CRYSVITA n (%)
No. of fractures at baseline	13	14	78	51	91	65
Healed at week 24	0 (0%)	7 (50%)	7 (9%)	21 (41%)	7 (8%)	28 (43%)

Bone Histomorphometry

In Study 4, after 48 weeks of treatment, healing of osteomalacia was observed in ten patients as demonstrated by decreases in Osteoid volume/Bone volume (OV/BV) from a mean (SD) score of 26% (12.4) at baseline to 11% (6.5), a change of -57%. Osteoid thickness (O.Th) declined in eleven patients from a mean (SD) of 17 (4.1) micrometers to 12 (3.1) micrometers, a change of -33%. Mineralization lag time (MLt) declined in 6 patients from a mean (SD) of 594 (675) days to 156 (77) days, a change of -74%.

16 HOW SUPPLIED/STORAGE AND HANDLING

CRYSVITA (burosumab-twza) injection for subcutaneous administration is supplied as a sterile, preservative-free, clear to slightly opalescent and colorless to pale brown-yellow solution. The product is available as one single-dose vial per carton in the following strengths:

10 mg/mL (NDC# 69794-102-01)

20 mg/mL (NDC# 69794-203-01)

30 mg/mL (NDC# 69794-304-01)

CRYSVITA vials must be stored in the original carton until the time of use under refrigerated conditions at 36°F to 46°F (2°C to 8°C). Keep CRYSVITA vial in the original carton to protect from light until time of use.

Do not freeze or shake CRYSVITA.

Do not use CRYSVITA beyond the expiration date stamped on the carton.

CRYSVITA vials are single-dose only. Discard any unused product.

17 PATIENT COUNSELING INFORMATION

Hypersensitivity Reactions

Advise patients that CRYSVITA may cause hypersensitivity events such as rash, injection site rash and urticaria. Instruct the patients to contact their physician if such reactions occur [see *Adverse Reactions (6.1)*].

Injection Site Reactions

Inform patients that injection site reactions (e.g. erythema, rash, swelling, bruising, pain, pruritus, urticaria, and hematoma) have occurred at the site of CRYSVITA injection. Instruct the patients to contact their physician if such reactions occur [see *Adverse Reactions (6.1)*].

Restless Leg Syndrome

Advise patients that CRYSVITA can induce RLS or worsen the symptoms of existing RLS. Instruct the patients to contact their physician if such a reaction occurs [see *Adverse Reactions (6.1)*].

Pregnancy

Report pregnancies to the Ultragenyx Adverse Event reporting line at 1-888-756-8657 [see *Use in Specific Populations (8.1)*].

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HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use MEPSEVII safely and effectively. See full prescribing information for MEPSEVII.

MEPSEVII™ (vestronidase alfa-vjvk) injection, for intravenous use
Initial U.S. Approval: 2017

WARNING: ANAPHYLAXIS

See full prescribing information for complete boxed warning.

- Anaphylaxis has occurred with MEPSEVII administration, as early as the first dose (5.1), therefore appropriate medical support should be readily available when MEPSEVII is administered.
- Closely observe patients during and for 60 minutes after MEPSEVII infusion (2.2, 5.1).
- Immediately discontinue the MEPSEVII infusion if the patient experiences anaphylaxis (2.2, 5.1).

INDICATIONS AND USAGE

MEPSEVII is a recombinant human lysosomal beta glucuronidase indicated in pediatric and adult patients for the treatment of Mucopolysaccharidosis VII (MPS VII, Sly syndrome).

Limitations of Use

The effect of MEPSEVII on the central nervous system manifestations of MPS VII has not been determined. (1)

DOSAGE AND ADMINISTRATION

- The recommended dosage is 4 mg/kg administered every two weeks as an intravenous infusion. (2.1)

- Premedication with a non-sedating antihistamine with or without an anti-pyretic is recommended 30 to 60 minutes prior to the start of the infusion. (2.2, 5.1)
- Administer the infusion over approximately 4 hours. In the first hour of infusion, infuse 2.5% of the total volume. After the first hour, the rate can be increased to infuse the remainder of the volume over 3 hours as tolerated. See Table 1 in the full prescribing information for the rate of infusion by dose and body weight. (2.4)
- For additional information on preparation, administration, and storage see the full prescribing information. (2.3, 2.4)

DOSAGE FORMS AND STRENGTHS

Injection: 10 mg/5 mL (2 mg/mL) in a single-dose vial (3)

CONTRAINDICATIONS

None (4)

ADVERSE REACTIONS

Most common adverse reactions (≥1 patient) are: infusion site extravasation, diarrhea, rash, anaphylaxis, infusion site swelling, peripheral swelling and pruritus. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Ultragenyx at 1-888-756-8657 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 11/2017

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- 2.2 Premedication
- 2.3 Preparation Instructions
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* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: ANAPHYLAXIS

- Anaphylaxis has occurred with MEPSEVII administration, as early as the first dose [see *Warnings and Precautions (5.1)*], therefore appropriate medical support should be readily available when MEPSEVII is administered.
- Closely observe patients during and for 60 minutes after MEPSEVII infusion [see *Dosage and Administration (2.2)*, *Warnings and Precautions (5.1)*].
- Immediately discontinue the MEPSEVII infusion if the patient experiences anaphylaxis [see *Dosage and Administration (2.2)*, *Warnings and Precautions (5.1)*].

1 INDICATIONS AND USAGE

MEPSEVII is indicated in pediatric and adult patients for the treatment of Mucopolysaccharidosis VII (MPS VII, Sly syndrome).

Limitations of Use

The effect of MEPSEVII on the central nervous system manifestations of MPS VII has not been determined.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

MEPSEVII should be administered under the supervision of a healthcare professional with the capability to manage anaphylaxis. Premedication is recommended 30 to 60 minutes prior to the start of the infusion [see *Dosage and Administration (2.2)*].

The recommended dosage of MEPSEVII is 4 mg/kg administered by intravenous infusion every two weeks.

Administer the infusion over approximately 4 hours. Infuse the first 2.5% of the total volume over the first hour. After the first hour, increase the infusion rate as tolerated in order to complete infusion over the following 3 hours according to the recommended rate guidelines in Table 1 [see *Dosage and Administration (2.4)*].

2.2 Premedication

- Administration of a non-sedating antihistamine with or without an anti-pyretic medication is recommended 30 to 60 minutes prior to the start of the infusion for patient comfort.

- Follow the instructions in Table 1 for the rate of MEPSEVII infusion [see *Dosage and Administration (2.4)*].
- Observe patients closely during the infusion and following the infusion for a minimum of 60 minutes for the development of anaphylaxis [see *Warnings and Precautions (5.1)*].
- Discontinue the infusion immediately if the patient experiences a severe systemic reaction, including anaphylaxis [see *Warnings and Precautions (5.1)*].

2.3 Preparation Instructions

Prepare MEPSEVII according to the following steps using aseptic technique:

1. Determine the number of vials to be diluted based on the patient's actual weight and the recommended dose of 4 mg/kg, using the following calculations (a-b):
 - a. Total dose (mg) = Patient's weight (kg) x 4 mg/kg (recommended dose)
 - b. Total number of vials = Total dose (mg) divided by 10 mg/vial
2. Round to the next whole vial and remove the required number of vials from the refrigerator to allow them to reach room temperature. Do not heat, microwave or shake vials.
 - a. Volume (mL) of calculated dose = Total dose (mg) divided by the 2 mg/mL concentration
3. The final solution will be a 1:1 dilution of MEPSEVII with 0.9% Sodium Chloride Injection, USP. More than 1:1 dilution may be used if the patient can tolerate additional infusion volume, taking into consideration cardiac function and fluid status.
4. For a 1:1 dilution, prepare the solution at room temperature, as follows:
 - a. Select an empty infusion bag, sized upon the total volume of the final solution.
 - b. Prior to withdrawing MEPSEVII from the vial, visually inspect the solution for particulate matter and discoloration. Because this is a protein solution, slight flocculation (thin translucent fibers) may occur. The MEPSEVII solution should be colorless to slightly yellow. Discard if the solution is discolored or if there is particulate matter in the solution.
 - c. Slowly withdraw the volume of the calculated MEPSEVII dose from the appropriate number of vials (step 2a) using caution to avoid excessive agitation and any air or frothing. Use a sufficiently large needle (18 gauge) to minimize bubbles in the solution.
 - d. Slowly add MEPSEVII to the infusion bag using care to avoid agitation, ensuring liquid to liquid contact without generating bubbles or turbulence.
 - e. Add 0.9% Sodium Chloride Injection, USP equal to the volume of MEPSEVII to the infusion bag.
 - f. Gently rock the infusion bag to ensure proper distribution of MEPSEVII. **Do not shake the solution.**

2.4 Administration Instructions

Administer MEPSEVII as follows:

1. The rate of infusion: In the first hour infuse 2.5% of the total volume, and infuse the remaining volume over the subsequent three hours (see Table 1). Account for any dead space in the lines to ensure 2.5% of the total infusion volume is delivered into the patient's bloodstream during the first hour of infusion.
2. Use an infusion set equipped with an in-line, low-protein binding 0.2 micron filter to administer the diluted MEPSEVII solution.
3. Do not flush the line containing MEPSEVII to avoid a rapid bolus of infused enzyme. Due to the low infusion rate, additional saline may be added through a separate line (piggyback or Y tube) to maintain sufficient intravenous flow to prevent clotting or line blockage.
4. Do not infuse with other products in the infusion tubing. Compatibility with other products has not been evaluated.
5. Use MEPSEVII immediately after dilution and complete the infusion within 42 hours from the time of dilution. Discard any unused product.

Stability

If immediate use is not possible, the diluted solution may be stored up to 36 hours under refrigeration at 2°C to 8°C (36°F to 46°F) followed by up to 6 hours at room temperature up to a maximum of 25°C (77°F).

Table 1. Recommended Infusion Rate Schedule by Patient Weight for Administration of MEPSEVII at Recommended Dose of 4 mg/kg

Patient Weight Range (kg)	Total MEPSEVII Dose Range (mg)	Total MEPSEVII Volume (rounded) (mL)	Total Infusion Volume of Drug and diluent (infused over 4 hours) (mL)	Infusion Rate for 1 st Hour (2.5%) (mL/h)	Infusion Rate per Hour for Subsequent 3 Hours (97.5%/3) (mL/h)
3.5-5.9	14-23.6	10	20	0.5	6.5
6-8.4	24-33.6	15	30	0.8	9.8
8.5-10.9	34-43.6	20	40	1	13
11-13.4	44-53.6	25	50	1.3	16.3
13.5-15.9	54-63.6	30	60	1.5	19.5
16-18.4	64-73.6	35	70	1.8	22.8
18.5-20.9	74-83.6	40	80	2	26
21-23.4	84-93.6	45	90	2.3	29.3
23.5-25.9	94-103.6	50	100	2.5	32.5
26-28.4	104-113.6	55	110	2.8	35.8
28.5-30.9	114-123.6	60	120	3	39
31-33.4	124-133.6	65	130	3.3	42.3
33.5-35.9	134-143.6	70	140	3.5	45.5
36-38.4	144-153.6	75	150	3.8	48.8
38.5-40.9	154-163.6	80	160	4	52
41-43.4	164-173.6	85	170	4.3	55.3
43.5-45.9	174-183.6	90	180	4.5	58.5
46-48.4	184-193.6	95	190	4.8	61.8
48.5-50.9	194-203.6	100	200	5	65
51-53.4	204-213.6	105	210	5.3	68.3
53.5-55.9	214-223.6	110	220	5.5	71.5
56-58.4	224-233.6	115	230	5.8	74.8
58.5-60.9	234-243.6	120	240	6	78
61-63.4	244-253.6	125	250	6.3	81.3
63.5-65.9	254-263.6	130	260	6.5	84.5
66-68.4	264-273.6	135	270	6.8	87.8
68.5-70.9	274-283.6	140	280	7	91

3 DOSAGE FORMS AND STRENGTHS

Injection: 10 mg/5 mL (2 mg/mL) as a colorless to slightly yellow liquid in a single-dose vial.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Anaphylaxis

Anaphylaxis to MEPSEVII was reported in 2 of 20 patients in the clinical program [see *Adverse Reactions (6.1)*]. These reactions occurred during MEPSEVII infusion and were observed as early as the first dose of MEPSEVII for one patient. Manifestations included respiratory distress, cyanosis, decreased oxygen saturation, and hypotension. The two patients with anaphylaxis to MEPSEVII during the clinical trials had one occurrence each and tolerated subsequent infusions of MEPSEVII, without recurrence.

Anaphylaxis can be life-threatening. MEPSEVII should be administered under the supervision of a healthcare professional with the capability to manage anaphylaxis. Patients should be observed for 60 minutes after MEPSEVII administration. If severe systemic reactions occur, including anaphylaxis, immediately discontinue the MEPSEVII infusion and provide appropriate medical treatment. Prior to discharge, inform patients of the signs and symptoms of anaphylaxis and instruct them to seek immediate medical care if symptoms occur. Consider the risks and benefits of re-administering MEPSEVII following anaphylaxis.

6 ADVERSE REACTIONS

The following serious adverse reactions are described below and elsewhere in the labeling:

- Anaphylaxis [see *Warnings and Precautions (5.1)*]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The MEPSEVII clinical program included 23 patients aged 5 months to 25 years who received treatment with MEPSEVII at doses up to 4 mg/kg once every two weeks for up to 164 weeks. Nineteen patients were younger than 18 years of age. Of these 23 patients, 20 patients were evaluable for adverse reactions and 23 patients were evaluable for immunogenicity.

Adverse Reactions from the Randomized Start Trial

Table 2 summarizes the adverse reactions that occurred in Study 301, a randomized start trial in 12 patients with MPS VII between the ages of 8 and 25 years [see *Clinical Studies (14)*].

Adverse reactions in Table 2 occurred in one or more patients treated with MEPSEVII at a dosage of 4 mg/kg at a higher patient frequency than placebo. Adverse reaction incidence rates are presented in the table below to account for the different duration of exposure to active treatment vs. placebo.

Table 2. Adverse Reactions in Patients with MPS VII in Study 301

Adverse Reaction	MEPSEVII N =12 n (Incidence Rate*)	Placebo N=9 n (Incidence Rate*)
Infusion site extravasation	4 (0.5)	1 (0.4)
Diarrhea	3 (0.4)	0 (0.0)
Rash	3 (0.4)	2 (0.7)
Anaphylaxis	2 (0.2)	0 (0.0)
Infusion site swelling	1 (0.1)	0 (0.0)
Peripheral swelling	1 (0.1)	0 (0.0)
Pruritus	1 (0.1)	0 (0.0)

n = number of reactions

*Adverse reaction incidence rates calculated per 8.3 patient years for exposure to MEPSEVII, and 2.7 years of exposure for placebo

Febrile Convulsion

One patient receiving a dose of 4 mg/kg experienced a febrile convulsion during MEPSEVII treatment at week 66. The infusion was stopped, the patient received anticonvulsants, antipyretics and antibiotics, and the adverse reaction resolved. The patient subsequently was re-challenged without recurrence and continued on treatment.

6.2 Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to vestronidase alfa-vjbk with the incidence of antibodies to other products may be misleading.

Immunogenicity data were available from 23 patients. Eighteen out of 23 patients (78%) developed anti-vestronidase alfa-vjbk antibodies (ADA). Ten of the 18 (55.6%) ADA-positive patients developed neutralizing antibodies (NAb) on at least one occasion. There is no correlation between ADA titer and NAb development.

Six treatment naïve patients had pre-existing ADA titers at baseline. ADAs were detected in five of these six patients post-treatment. The post-treatment ADA titers were the same as or below the baseline ADA titer values in two patients, but one of these two patients was positive for NAb. ADA titer values after treatment increased 64-fold in two patients and 364-fold in the third patient.

The presence of ADA titer does not appear to affect reduction in the pharmacodynamic marker, urinary glycosaminoglycans (uGAGs), as assessed in clinical trials.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available data on MEPSEVII use in pregnant women to determine a drug-associated risk of adverse developmental outcomes. In animal reproduction studies, vestronidase alfa-vjbc administered intravenously to pregnant rats and rabbits during the period of organogenesis showed no maternal toxicity or adverse developmental outcomes at doses causing maternal serum exposures (AUC) up to 1.6 and 10 times, respectively for rats and rabbits, the exposure at the recommended human dose (*see Data*).

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Data

Animal Data

In animal reproduction studies, vestronidase alfa-vjbc administered intravenously to pregnant rats (once a week) and rabbits (once every 3 days) during the period of organogenesis showed no adverse developmental outcomes at doses up to 20 mg/kg. The 20 mg/kg dose in rats and rabbits provides approximately 1.6 and 10 times the human exposure (AUC) of 57.9 hr*mcg/mL at the 4 mg/kg dose administered once every other week, respectively.

8.2 Lactation

Risk Summary

There are no data on the presence of vestronidase alfa-vjbc in either human or animal milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for MEPSEVII and any potential adverse effects on the breastfed infant from vestronidase alfa-vjbc or from the underlying maternal condition.

8.4 Pediatric Use

The safety and effectiveness of MEPSEVII have been established in pediatric patients less than 18 years of age [*see Adverse Reactions (6), Clinical Studies (14)*].

8.5 Geriatric Use

Clinical trials of MEPSEVII did not include any patients aged 65 and over. It is not known whether elderly patients respond differently from younger patients.

11 DESCRIPTION

Vestronidase alfa-vjbc is a recombinant human lysosomal beta glucuronidase which is a purified human enzyme produced by recombinant DNA technology in a Chinese hamster ovary cell line.

Purified vestronidase alfa-vjbc exists as a homotetramer, with each monomer consisting of 629 amino acids. The calculated isotope average molecular mass of each non-glycosylated peptide chain is 72,562 Da.

The amino acid sequence for vestronidase alfa-vjbc is the same as the amino acid sequence for human beta-glucuronidase (GUS).

MEPSEVII (vestronidase alfa-vjbc) injection for intravenous infusion is a sterile, preservative-free, non-pyrogenic, colorless to slightly yellow liquid supplied in a single-dose vial. Each mL of solution contains vestronidase alfa-vjbc (2 mg), L-histidine (3.1 mg), polysorbate 20 (0.1 mg), sodium chloride (7.88 mg) and sodium phosphate monobasic dihydrate (3.12 mg). The pH of the solution is 6.0.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Mucopolysaccharidosis VII (MPS VII or Sly syndrome) is a lysosomal disorder characterized by the deficiency of GUS that results in GAG accumulation in cells throughout the body leading to multisystem tissue and organ damage.

Vestronidase alfa-vjbc is a recombinant form of human GUS and is intended to provide exogenous GUS enzyme for uptake into cellular lysosomes. Mannose-6-phosphate (M6P) residues on the oligosaccharide chains allow binding of the enzyme to cell surface receptors, leading to cellular uptake of the enzyme, targeting to lysosomes and subsequent catabolism of accumulated GAGs in affected tissues.

12.2 Pharmacodynamics

In all patients evaluated, MEPSEVII treatment resulted in reduction of urinary excretion of GAGs including chondroitin sulfate and dermatan sulfate, which was sustained with continued treatment.

12.3 Pharmacokinetics

The pharmacokinetics of vestronidase alfa-vjbc were evaluated in a total of 19 MPS VII patients including 15 pediatric patients and 4 adults. Serum exposures of vestronidase alfa-vjbc appeared to increase approximately proportionally from 1 mg/kg (0.25 times the approved recommended dosage) to 2 mg/kg (0.5 times the approved recommended dosage), and 4 mg/kg (the recommended dosage). After repeated dosing of 4 mg/kg every other week, the mean \pm standard deviation of maximal concentration (C_{max}) was 20.0 ± 8.1 mcg/mL (range: 6.6 to 34.9 mcg/mL); and the mean \pm standard deviation of area under the concentration-time curve from time zero to the last measurable concentration (AUC_{0-t}) was 3440 ± 1430 mcg*min/mL (range: 1130 to 5820 mcg*min/mL). Vestronidase alfa-vjbc concentrations in pediatric patients less than 5 years of age were similar to the concentrations in older children and adults.

Distribution

After repeated dosing of 4 mg/kg every other week in MPS VII patients, the mean \pm standard deviation of the total volume of distribution (V_{ss}) was 260 ± 130 mL/kg (range: 97 to 598 mL/kg).

Elimination

After repeated dosing of 4 mg/kg every other week in MPS VII patients, the mean \pm standard deviation of the total clearance (CL) was 1.3 ± 0.7 mL/min/kg (range: 0.6 to 3.3 mL/min/kg); the mean \pm standard deviation of the elimination half-life ($t_{1/2}$) was 155 ± 37 minutes (range: 51 to 213 minutes). The inter- and intra-subject variability (coefficient of variation) in total clearance (CL) was 59% and 13%, respectively.

Metabolism

Vestronidase alfa-vjbk is a recombinant human enzyme and is therefore eliminated by proteolytic degradation into small peptides and amino acids.

Excretion

No excretion studies have been conducted in humans. Vestronidase alfa-vjbk is not expected to be eliminated through renal or fecal excretion.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies in animals to evaluate carcinogenic potential or studies to evaluate the mutagenic potential have not been performed with vestronidase alfa-vjbk.

Vestronidase alfa-vjbk at intravenous doses up to 20 mg/kg administered weekly to rats prior to mating and after mating on gestation days 6, 9, 12, 15 and 18 (females), [approximately up to 4.5 times (male rats) and 1.6 times (female rats) the human AUC_{0-t} of 3440 mcg*min/mL at the 4 mg/kg dose administered once every other week] was found to have no adverse effect on fertility and reproductive performance of male and female rats.

14 CLINICAL STUDIES

The clinical program for MEPSEVII included 23 patients with MPS VII, 17 of whom were evaluable for efficacy, 20 for safety, and 23 for immunogenicity. Patients were enrolled in clinical trials and expanded access protocols receiving treatment at doses up to 4 mg/kg once every two weeks for up to 164 weeks. The patients ranged in age from 5 months to 25 years. Sixteen patients were younger than 18 years of age.

Studies 301 and 202

Study UX003-CL301 (referred to as Study 301, NCT02230566) was a randomized start trial of MEPSEVII 4 mg/kg every two weeks in patients with MPS VII. Twelve patients were randomized to one of four placebo durations before crossing over to active treatment. Three patients received MEPSEVII immediately for a duration of 48 weeks, 3 patients received placebo for 8 weeks then MEPSEVII for 40 weeks, 3 patients received placebo for 16 weeks then MEPSEVII for 32 weeks, and 3 patients received placebo for 24 weeks then MEPSEVII for 24 weeks. Of the 12 patients enrolled in the trial, 4 were male and 8 were female and ranged in age from 8 to 25 years (median 14 years). Nine patients were younger than 18 years of age. The majority of the patients were white (75%), with 50% of Hispanic or Latino ethnicity. Patients who were enrolled in Study 301 were eligible to roll over to Study UX003-CL202 (referred to as Study 202, NCT02432144), an open-label extension trial in

which patients received additional doses of MEPSEVII at 4 mg/kg intravenously every other week for up to 124 weeks.

In Study 301, motor function, forced vital capacity, and visual acuity were assessed after 24 weeks of MEPSEVII treatment and measured against pre-specified minimal important differences. The extremely small population of patients with MPS VII globally necessitated the enrollment of all patients able to participate resulting in a highly heterogeneous group. Clinical endpoints were not assessable in some patients due to their extent of disease, age or level of cognition. Repeated assessments of the six minute walk test (6MWT) were feasible in ten of 12 patients and are described further below. Of the three patients who improved on their 6MWT (Figure 1, left panel), two also were noted to have improvement in balance and gross motor proficiency as assessed by the Bruininks-Oseretsky Test of Motor Proficiency (BOT-2).

In this trial, the mean difference in 6MWT distance between MEPSEVII and placebo treatment periods in patients able to perform the test at baseline and subsequent visits through Week 24 is shown in Table 3. The mean difference in 6MWT distance increases with increased treatment duration, however, due to the small size of the trial, standard errors are large.

Table 3. Mean Difference in 6MWT Distance (meters) Between MEPSEVII and Placebo Treatment (Study 301) in Patients with MPS VII

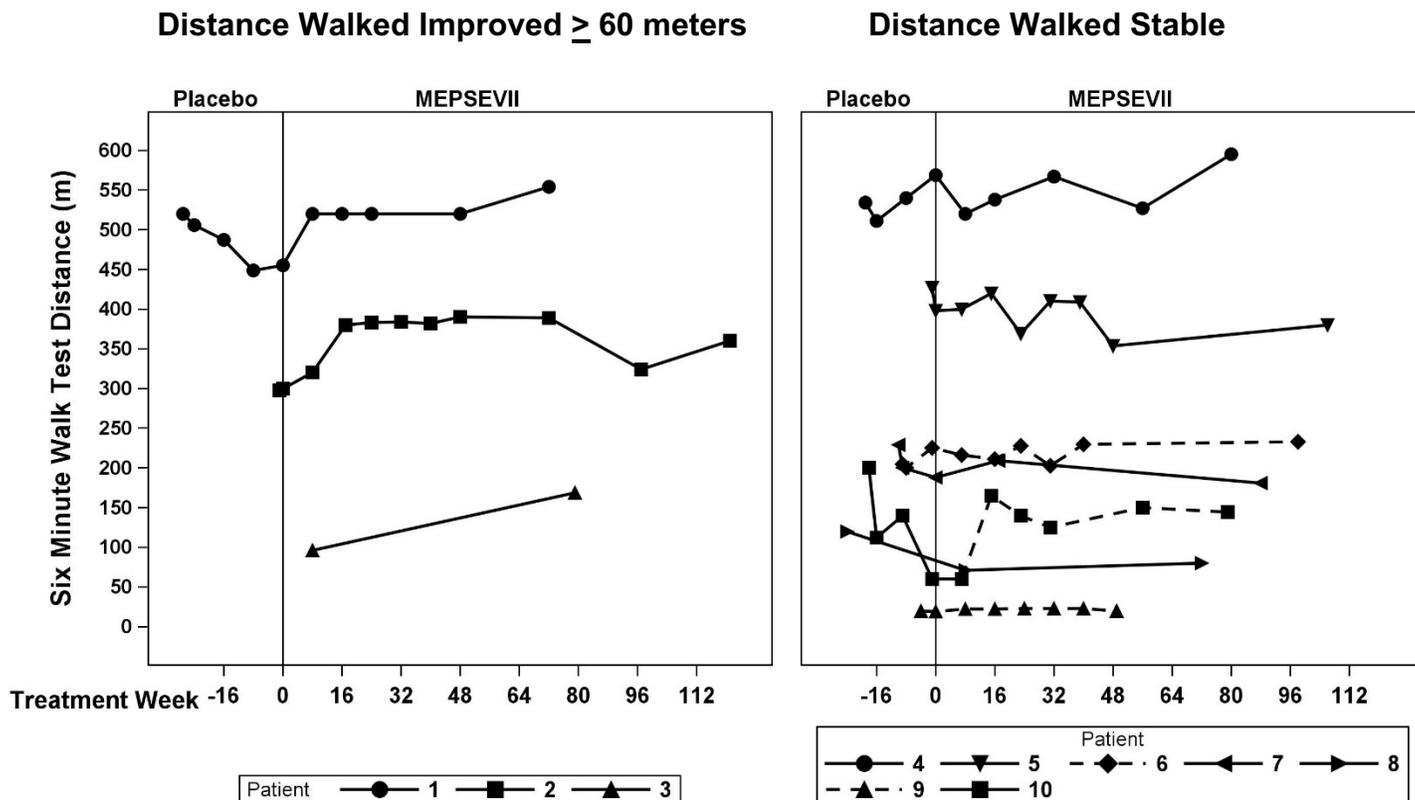
Duration of MEPSEVII Treatment	LS mean 6MWT (meters) (\pm Standard Error)*	Number and Treatment Assignment of Patients Included in Analysis**
8 weeks	-11 (\pm 24)	5 placebo period; 8 MEPSEVII period
16 weeks	13 (\pm 32)	5 placebo period; 8 MEPSEVII period
24 weeks	18 (\pm 33)	5 placebo period; 8 MEPSEVII period

*ANCOVA analysis of change from baseline in least squares (LS) mean between placebo and MEPSEVII for different periods, after adjusting for study cohort, age, and baseline 6MWT distance. Patients who used assistive devices were imputed as zeros in the analysis.

**Number and treatment assignment of patients included in the analysis was based upon a randomized start trial design and patient ability to complete testing. Due to no placebo period for the three patients who received 48 weeks of MEPSEVII in the first cohort of the randomized start design, more data were available for analyses during the treatment period (n=8) than during the placebo period (n=5). While data from 8 participants were available at each time point, due to missing observations, the 8 participants were not the same across all time points.

The observed individual 6MWT distances for the 10 patients who could perform the test in Study 301 and Study 202 through Week 120 are presented in Figure 1. The course of three patients with improvement in distance walked of at least 60 meters compared to the start of MEPSEVII treatment (Week 0) is shown in the left panel; the relatively stable course in the remaining seven patients, including those who used assistive devices, is shown in the right panel.

Figure 1. 6MWT Distance for MPS VII Patients in Studies 301 and 202



Patient 10 did not use an assistive device at baseline but started using an assistive device post-baseline from Treatment Week 8. Patients 6 and 9 consistently used an assistive device at all visits. A solid line indicates the unassisted assessments and a dotted line indicates the assisted assessments.

Liver and Spleen Volume

In Study 301, imaging by MRI or ultrasound to assess liver and spleen volume was performed in seven of the 12 patients. Most liver volumes were normal or below normal size at baseline (mean 1,591 mL, range 742 to 2,207 mL), and on average were unchanged after treatment (mean 1,459 mL, range 876 to 1,851 mL).

Spleen volumes generally were normal or below normal size at baseline (mean 325 mL, range 131 to 491 mL) and on average were unchanged after treatment (mean 360 mL, range 200 to 582 mL).

Other Investigations

Study UX003-CL201 (referred to as Study 201, NCT01856218) was a single arm, open-label, dose exploration trial completed outside the United States that enrolled three MPS VII patients, ranging in age from 5 years to 25 years. Two patients were male; two patients were white and one was Asian. After 120 weeks of exposure to MEPSEVII, one patient demonstrated a 21% improvement over baseline in forced vital capacity (FVC% predicted) on pulmonary function testing in addition to a 105 meter improvement in the 6MWT. Two other patients with baseline hepatosplenomegaly had reduction in liver volume (24% and 53%) and spleen volume (28% and 47%) after 36 weeks of MEPSEVII treatment.

Expanded access to MEPSEVII treatment was provided to a pediatric patient with MPS VII who required continuous ventilatory support at the start of treatment and was subsequently able to tolerate 9 hours daily off ventilator support after 164 weeks of MEPSEVII treatment.

16 HOW SUPPLIED/STORAGE AND HANDLING

MEPSEVII (vestronidase alfa-vjvk) injection is a colorless to slightly yellow liquid supplied as a carton containing one 10 mg/5 mL (2 mg/mL) single-dose vial (NDC 69794-001-01).

Store under refrigeration at 2°C to 8°C (36°F to 46°F). Do not freeze or shake. Protect from light.

17 PATIENT COUNSELING INFORMATION

Anaphylaxis

Advise patients and caregivers that anaphylaxis has occurred with MEPSEVII administration. Inform patients of the signs and symptoms of anaphylaxis, and have them seek immediate medical care should signs and symptoms occur [see *Warnings and Precautions (5.1)*].

Manufactured by:
Ultragenyx Pharmaceutical Inc.
Novato, CA 94949
U.S. License No. 2040

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use IDHIFA safely and effectively. See full prescribing information for IDHIFA.

IDHIFA® (enasidenib) tablets, for oral use
Initial U.S. Approval: 2017

WARNING: DIFFERENTIATION SYNDROME

See full prescribing information for complete boxed warning.

Patients treated with IDHIFA have experienced symptoms of differentiation syndrome, which can be fatal if not treated. If differentiation syndrome is suspected, initiate corticosteroid therapy and hemodynamic monitoring until symptom resolution (5.1, 6.1).

INDICATIONS AND USAGE

IDHIFA is an isocitrate dehydrogenase-2 inhibitor indicated for the treatment of adult patients with relapsed or refractory acute myeloid leukemia (AML) with an isocitrate dehydrogenase-2 (IDH2) mutation as detected by an FDA-approved test (1.1).

DOSAGE AND ADMINISTRATION

100 mg orally once daily until disease progression or unacceptable toxicity (2.2).

DOSAGE FORMS AND STRENGTHS

Tablets: 50 mg or 100 mg (3).

CONTRAINDICATIONS

None (4).

WARNINGS AND PRECAUTIONS

Embryo-Fetal Toxicity: IDHIFA can cause fetal harm when administered to a pregnant woman. Advise of the potential risk to a fetus (5.2, 8.1, 8.3).

ADVERSE REACTIONS

The most common adverse reactions (≥20%) included nausea, vomiting, diarrhea, elevated bilirubin, and decreased appetite (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Celgene Corporation at 1-888-423-5436 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

USE IN SPECIFIC POPULATIONS

Lactation: Advise women not to breastfeed (8.2).

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 08/2017

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*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: DIFFERENTIATION SYNDROME

Patients treated with IDHIFA have experienced symptoms of differentiation syndrome, which can be fatal if not treated. Symptoms may include fever, dyspnea, acute respiratory distress, pulmonary infiltrates, pleural or pericardial effusions, rapid weight gain or peripheral edema, lymphadenopathy, bone pain, and hepatic, renal, or multi-organ dysfunction. If differentiation syndrome is suspected, initiate corticosteroid therapy and hemodynamic monitoring until symptom resolution [see *Warnings and Precautions (5.1) and Adverse Reactions (6.1)*].

1 INDICATIONS AND USAGE

1.1 Acute Myeloid Leukemia

IDHIFA is indicated for the treatment of adult patients with relapsed or refractory acute myeloid leukemia (AML) with an isocitrate dehydrogenase-2 (IDH2) mutation as detected by an FDA-approved test.

2 DOSAGE AND ADMINISTRATION

2.1 Patient Selection

Select patients for the treatment of AML with IDHIFA based on the presence of IDH2 mutations in the blood or bone marrow [see *Indications and Usage (1.1) and Clinical Studies (14.1)*]. Information on FDA-approved tests for the detection of IDH2 mutations in AML is available at <http://www.fda.gov/CompanionDiagnostics>.

2.2 Recommended Dosage

The recommended starting dose of IDHIFA is 100 mg taken orally once daily with or without food until disease progression or unacceptable toxicity. For patients without disease progression or unacceptable toxicity, treat for a minimum of 6 months to allow time for clinical response.

Do not split or crush IDHIFA tablets. Administer IDHIFA tablets orally about the same time each day. If a dose of IDHIFA is vomited, missed, or not taken at the usual time, administer the dose as soon as possible on the same day, and return to the normal schedule the following day.

2.3 Monitoring and Dosage Modifications for Toxicities

Assess blood counts and blood chemistries for leukocytosis and tumor lysis syndrome prior to the initiation of IDHIFA and monitor at a minimum of every 2 weeks for at least the first 3 months during treatment. Manage any abnormalities promptly [see *Adverse Reactions (6.1)*].

Interrupt dosing or reduce dose for toxicities. See Table 1 for dosage modification guidelines.

Table 1: Dosage Modifications for IDHIFA-Related Toxicities

Adverse Reaction	Recommended Action
<ul style="list-style-type: none"> Differentiation syndrome 	<ul style="list-style-type: none"> If differentiation syndrome is suspected, administer systemic corticosteroids and initiate hemodynamic monitoring [see <i>Warnings and Precautions (5.1)</i>]. Interrupt IDHIFA if severe pulmonary symptoms requiring intubation or ventilator support, and/or renal dysfunction persist for more than 48 hours after initiation of corticosteroids [see <i>Warnings and Precautions (5.1)</i>]. Resume IDHIFA when signs and symptoms improve to Grade 2* or lower.
<ul style="list-style-type: none"> Noninfectious leukocytosis (white blood cell [WBC] count greater than $30 \times 10^9/L$) 	<ul style="list-style-type: none"> Initiate treatment with hydroxyurea, as per standard institutional practices. Interrupt IDHIFA if leukocytosis is not improved with hydroxyurea, and then resume IDHIFA at 100 mg daily when WBC is less than $30 \times 10^9/L$.
<ul style="list-style-type: none"> Elevation of bilirubin greater than 3 times the upper limit of normal (ULN) sustained for ≥ 2 weeks without elevated transaminases or other hepatic disorders 	<ul style="list-style-type: none"> Reduce IDHIFA dose to 50 mg daily. Resume IDHIFA at 100 mg daily if bilirubin elevation resolves to less than 2 x ULN.
<ul style="list-style-type: none"> Other Grade 3* or higher toxicity considered related to treatment including tumor lysis syndrome 	<ul style="list-style-type: none"> Interrupt IDHIFA until toxicity resolves to Grade 2* or lower. Resume IDHIFA at 50 mg daily; may increase to 100 mg daily if toxicities resolve to Grade 1* or lower. If Grade 3* or higher toxicity recurs, discontinue IDHIFA.

*Grade 1 is mild, Grade 2 is moderate, Grade 3 is serious, Grade 4 is life-threatening.

3 DOSAGE FORMS AND STRENGTHS

IDHIFA is available in the following tablet strengths:

- 50-mg tablet: Pale yellow to yellow oval-shaped film-coated tablet debossed “ENA” on one side and “50” on the other side.
- 100-mg tablet: Pale yellow to yellow capsule-shaped film-coated tablet debossed “ENA” on one side and “100” on the other side.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Differentiation Syndrome

In the clinical trial, 14% of patients treated with IDHIFA experienced differentiation syndrome, which may be life-threatening or fatal if not treated. Differentiation syndrome is associated with rapid proliferation and differentiation of myeloid cells. While there is no diagnostic test for differentiation syndrome, symptoms in patients treated with IDHIFA included acute respiratory distress represented by dyspnea and/or hypoxia (68%) and need for supplemental oxygen (76%); pulmonary infiltrates (73%) and pleural effusion (45%); renal impairment (70%); fever (36%); lymphadenopathy (33%); bone pain (27%); peripheral edema with rapid weight gain (21%); and pericardial effusion (18%). Hepatic, renal, and multi-organ dysfunction have also been observed. Differentiation syndrome has been observed with and without concomitant hyperleukocytosis, and as early as 10 days and at up to 5 months after IDHIFA initiation.

If differentiation syndrome is suspected, initiate oral or intravenous corticosteroids (e.g., dexamethasone 10 mg every 12 hours) and hemodynamic monitoring until improvement. Taper corticosteroids only after resolution of symptoms. Symptoms of differentiation syndrome may recur with premature discontinuation of corticosteroid treatment. If severe pulmonary symptoms requiring intubation or ventilator support, and/or renal dysfunction persist for more than 48 hours after initiation of corticosteroids, interrupt IDHIFA until signs and symptoms are no longer severe [see *Dosage and Administration* (2.3)]. Hospitalization for close observation and monitoring of patients with pulmonary and/or renal manifestation is recommended.

5.2 Embryo-Fetal Toxicity

Based on animal embryo-fetal toxicity studies, IDHIFA can cause embryo-fetal harm when administered to a pregnant woman. In animal embryo-fetal toxicity studies, enasidenib caused embryo-fetal toxicities starting at 0.1 times the steady state clinical exposure based on the area under the concentration-time curve (AUC) at the recommended human dose. Advise females of reproductive potential to use effective contraception during treatment with IDHIFA and for at least 1 month after the last dose of IDHIFA. Advise males with female partners of reproductive potential to use effective contraception during treatment with IDHIFA and for at least 1 month after the last dose of IDHIFA. Pregnant women, patients becoming pregnant while receiving IDHIFA, or male patients with pregnant female partners should be apprised of the potential risk to the fetus [see *Use in Specific Populations* (8.1, 8.3)].

6 ADVERSE REACTIONS

The following serious adverse reactions are described elsewhere in the labeling:

- Differentiation Syndrome [see *Warnings and Precautions* (5.1)]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety evaluation of single-agent IDH1FA is based on 214 patients with relapsed or refractory AML who were assigned to receive 100 mg daily [see *Clinical Studies (14.1)*]. The median duration of exposure to IDH1FA was 4.3 months (range 0.3 to 23.6). The 30-day and 60-day mortality rates observed with IDH1FA were 4.2% (9/214) and 11.7% (25/214), respectively.

The most common adverse reactions ($\geq 20\%$) of any grade were nausea, vomiting, diarrhea, elevated bilirubin and decreased appetite.

Serious adverse reactions were reported in 77.1% of patients. The most frequent serious adverse reactions ($\geq 2\%$) were leukocytosis (10%), diarrhea (6%), nausea (5%), vomiting (3%), decreased appetite (3%), tumor lysis syndrome (5%), and differentiation syndrome (8%). Differentiation syndrome events characterized as serious included pyrexia, renal failure acute, hypoxia, respiratory failure, and multi-organ failure.

Overall, 92 of 214 patients (43%) required a dose interruption due to an adverse reaction; the most common adverse reactions leading to dose interruption were differentiation syndrome (4%) and leukocytosis (3%). Ten of 214 patients (5%) required a dose reduction due to an adverse reaction; no adverse reaction required dose reduction in more than 2 patients. Thirty-six of 214 patients (17%) permanently discontinued IDH1FA due to an adverse reaction; the most common adverse reaction leading to permanent discontinuation was leukocytosis (1%).

Adverse reactions reported in the trial are shown in Table 2.

Table 2: Adverse Reactions Reported in $\geq 10\%$ (Any Grade) or $\geq 3\%$ (Grade 3-5) of Patients with Relapsed or Refractory AML

Body System Adverse Reaction	IDH1FA (100 mg daily) N=214	
	All Grades N=214 n (%)	\geq Grade 3 N=214 n (%)
Gastrointestinal Disorders^a		
Nausea	107 (50)	11 (5)
Diarrhea	91 (43)	17 (8)
Vomiting	73 (34)	4 (2)
Metabolism and Nutrition Disorders		
Decreased appetite	73 (34)	9 (4)
Tumor lysis syndrome ^b	13 (6)	12 (6)
Blood and Lymphatic System Disorders		
Differentiation syndrome ^c	29 (14)	15 (7)
Noninfectious leukocytosis	26 (12)	12 (6)

Nervous System Disorders		
Dysgeusia	25 (12)	0 (0)

^a Gastrointestinal disorders observed with IDHIFA treatment can be associated with other commonly reported events such as abdominal pain, and weight decreased.

^b Tumor lysis syndrome observed with IDHIFA treatment can be associated with commonly reported uric acid increased.

^c Differentiation syndrome can be associated with other commonly reported events such as respiratory failure, dyspnea, hypoxia, pyrexia, peripheral edema, rash, or renal insufficiency.

Other clinically significant adverse reactions occurring in $\leq 10\%$ of patients included:

Respiratory, Thoracic, and Mediastinal Disorders: Pulmonary edema, acute respiratory distress syndrome

Changes in selected post-baseline laboratory values that were observed in patients with relapsed or refractory AML are shown in Table 3.

Table 3: Most Common ($\geq 20\%$) New or Worsening Laboratory Abnormalities Reported in Patients with Relapsed or Refractory AML

Parameter ^a	IDHIFA (100 mg daily) N=214	
	All Grades (%)	Grade ≥ 3 (%)
Total bilirubin increased	81	15
Calcium decreased	74	8
Potassium decreased	41	15
Phosphorus decreased	27	8

^a Includes abnormalities occurring up to 28 days after last IDHIFA dose, if new or worsened by at least one grade from baseline, or if baseline was unknown. The denominator varies based on data collected for each parameter (N=213 except phosphorous N=209).

Elevated Bilirubin

IDHIFA may interfere with bilirubin metabolism through inhibition of UGT1A1 [see *Clinical Pharmacology (12.3)*]. Thirty-seven percent of patients (80/214) experienced total bilirubin elevations ≥ 2 x ULN at least one time. Of those patients who experienced total bilirubin elevations ≥ 2 x ULN, 35% had elevations within the first month of treatment, and 89% had no concomitant elevation of transaminases or other severe adverse events related to liver disorders. No patients required a dose reduction for hyperbilirubinemia; treatment was interrupted in 3.7% of patients, for a median of 6 days. Three patients (1.4%) discontinued IDHIFA permanently due to hyperbilirubinemia.

Noninfectious Leukocytosis

IDHIFA can induce myeloid proliferation resulting in a rapid increase in white blood cell count.

Tumor Lysis Syndrome

IDHIFA can induce myeloid proliferation resulting in a rapid reduction in tumor cells which may pose a risk for tumor lysis syndrome.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on animal embryo-fetal toxicity studies, IDHIFA can cause fetal harm when administered to a pregnant woman. There are no available data on IDHIFA use in pregnant women to inform a drug-associated risk of major birth defects and miscarriage. In animal embryo-fetal toxicity studies, oral administration of enasidenib to pregnant rats and rabbits during organogenesis was associated with embryo-fetal mortality and alterations to growth starting at 0.1 times the steady state clinical exposure based on the AUC at the recommended human dose (*see Data*). If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, advise the patient of the potential risk to a fetus.

Adverse outcomes in pregnancy occur regardless of the health of the mother or the use of medications. The background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2%-4% and 15%-20%, respectively.

Data

Animal Data

Enasidenib administered to pregnant rats at a dose of 30 mg/kg twice daily during organogenesis (gestation days 6-17) was associated with maternal toxicity and adverse embryo-fetal effects including post-implantation loss, resorptions, decreased viable fetuses, lower fetal birth weights, and skeletal variations. These effects occurred in rats at approximately 1.6 times the clinical exposure at the recommended human daily dose of 100 mg/day.

In pregnant rabbits treated during organogenesis (gestation days 7-19), enasidenib was maternally toxic at doses equal to 5 mg/kg/day or higher (exposure approximately 0.1 to 0.6 times the steady state clinical exposure at the recommended daily dose) and caused spontaneous abortions at 5 mg/kg/day (exposure approximately 0.1 times the steady state clinical exposure at the recommended daily dose).

8.2 Lactation

Risk Summary

There are no data on the presence of enasidenib or its metabolites in human milk, the effects on the breastfed infant, or the effects on milk production. Because many drugs are excreted in human milk and because of the potential for adverse reactions in breastfed infants, advise women not to breastfeed during treatment with IDHIFA and for at least 1 month after the last dose.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

Based on animal embryo-fetal toxicity studies, IDHIFA can cause fetal harm when administered to a pregnant woman [*see Use in Specific Populations (8.1)*].

Obtain a pregnancy test on females of reproductive potential prior to starting treatment with IDHIFA.

Contraception

Females

Advise females of reproductive potential to avoid becoming pregnant while receiving IDHIFA. Advise females of reproductive potential to use effective contraception during treatment with IDHIFA and for at least 1 month after the last dose. Coadministration of IDHIFA may increase or decrease the concentrations of combined hormonal contraceptives. The clinical significance of this potential drug interaction is unknown at this time.

Males

Advise males with female partners of reproductive potential to use effective contraception during treatment with IDHIFA and for at least 1 month after the last dose of IDHIFA.

Infertility

Based on findings in animals, IDHIFA may impair fertility in females and males of reproductive potential. It is not known whether these effects on fertility are reversible [see *Nonclinical Toxicology (13.1)*].

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

No dosage adjustment is required for IDHIFA based on age. In the clinical study, 61% of 214 patients were aged 65 years or older, while 24% were older than 75 years. No overall differences in effectiveness or safety were observed between patients aged 65 years or older and younger patients.

11 DESCRIPTION

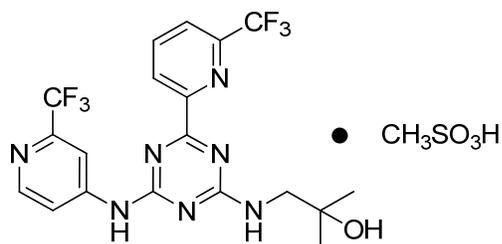
IDHIFA (enasidenib) is an inhibitor of isocitrate dehydrogenase-2 (IDH2) enzyme. Enasidenib is available as the mesylate salt with the chemical name:

2-methyl-1-[[4-[6-(trifluoromethyl)pyridin-2-yl]-6-[[2-(trifluoromethyl)pyridin-4-yl]amino]-1,3,5-triazin-2-yl]amino]propan-2-ol methanesulfonate.

Or

2-Propanol, 2-methyl-1-[[4-[6-(trifluoromethyl)-2-pyridinyl]-6-[[2-(trifluoromethyl)-4-pyridinyl]amino]-1,3,5-triazin-2-yl]amino]-, methanesulfonate (1:1).

The chemical structure is:



The empirical formula is $C_{19}H_{17}F_6N_7O \cdot CH_3SO_3H$ ($C_{20}H_{21}F_6N_7O_4S$), and the molecular weight is 569.48 g/mol. Enasidenib is practically insoluble (solubility ≤ 74 mcg/mL) in aqueous solutions across physiological pH range (pH 1.2 and 7.4).

IDHIFA (enasidenib) is available as a 50-mg tablet (equivalent to 60 mg enasidenib mesylate) and a 100-mg tablet (equivalent to 120 mg enasidenib mesylate) for oral administration. Each tablet contains inactive ingredients of colloidal silicon dioxide, hydroxypropyl cellulose, hypromellose acetate succinate, iron oxide yellow, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polyvinyl alcohol, sodium lauryl sulfate, sodium starch glycolate, talc, and titanium dioxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Enasidenib is a small molecule inhibitor of the isocitrate dehydrogenase 2 (IDH2) enzyme. Enasidenib targets the mutant IDH2 variants R140Q, R172S, and R172K at approximately 40-fold lower concentrations than the wild-type enzyme in vitro. Inhibition of the mutant IDH2 enzyme by enasidenib led to decreased 2-hydroxyglutarate (2-HG) levels and induced myeloid differentiation in vitro and in vivo in mouse xenograft models of IDH2 mutated AML. In blood samples from patients with AML with mutated IDH2, enasidenib decreased 2-HG levels, reduced blast counts and increased percentages of mature myeloid cells.

12.2 Pharmacodynamics

Cardiac Electrophysiology

The potential for QTc prolongation with enasidenib was evaluated in an open-label study in patients with advanced hematologic malignancies with an IDH2 mutation. Based on the QTc data for a single dose of 30 mg to 650 mg and multiple doses of 100 mg daily in the fasted state, no large mean changes in the QTc interval (>20 ms) were observed following treatment with enasidenib.

12.3 Pharmacokinetics

The peak plasma concentration (C_{max}) is 1.3 mcg/mL [% coefficient of variation (CV%) 56.4] after a single dose of 100 mg, and 13 mcg/mL (CV% 46.3) at steady state for 100 mg daily. The area under concentration time curve (AUC) of enasidenib increases in an approximately dose proportional manner from 50 mg (0.5 times approved recommended dosage) to 450 mg (4.5 times approved recommended dosage) daily dose. Steady-state plasma levels are reached within 29 days of once-daily dosing. Accumulation is approximately 10-fold when administered once daily.

Absorption

The absolute bioavailability after 100 mg oral dose of enasidenib is approximately 57%. After a single oral dose, the median time to C_{max} (T_{max}) is 4 hours.

Distribution

The mean volume of distribution (Vd) of enasidenib is 55.8 L (CV% 29). Human plasma protein binding of enasidenib is 98.5% and of its metabolite AGI-16903 is 96.6% in vitro.

Enasidenib is not a substrate for P-glycoprotein or BCRP, while AGI-16903 is a substrate of both P-glycoprotein and BCRP. Enasidenib and AGI-16903 are not substrates of MRP2, OAT1, OAT3, OATP1B1, OATP1B3, and OCT2.

Elimination

Enasidenib has a terminal half-life of 137 hours (CV% 41) and a mean total body clearance (CL/F) of 0.74 L/hour (CV% 71).

Metabolism

Enasidenib accounted for 89% of the radioactivity in circulation and AGI-16903, the N-dealkylated metabolite, represented 10% of the circulating radioactivity.

In vitro studies suggest that metabolism of enasidenib is mediated by multiple CYP enzymes (e.g., CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4), and by multiple UGTs (e.g., UGT1A1, UGT1A3, UGT1A4, UGT1A9, UGT2B7, and UGT2B15). Further metabolism of the metabolite AGI-16903 is also mediated by multiple enzymes (e.g., CYP1A2, CYP2C19, CYP3A4, UGT1A1, UGT1A3, and UGT1A9).

Excretion

Eighty-nine percent (89%) of enasidenib is eliminated in feces and 11% in the urine. Excretion of unchanged enasidenib accounts for 34% of the radiolabeled drug in the feces and 0.4% in the urine.

Specific Populations

No clinically meaningful effect on the pharmacokinetics of enasidenib was observed for the following covariates: age (19 years to 100 years), race (White, Black, or Asian), mild hepatic impairment [defined as total bilirubin \leq upper limit of normal (ULN) and aspartate transaminase (AST) $>$ ULN or total bilirubin 1 to 1.5 times ULN and any AST], renal impairment (defined as creatinine clearance \geq 30 mL/min by Cockcroft-Gault formula), sex, body weight (39 kg to 136 kg), and body surface area.

Drug Interaction Studies

In vitro studies suggest that enasidenib inhibits the activity of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A4, and UGT1A1. Enasidenib inhibits P-gp, BCRP, OAT1, OATP1B1, OATP1B3, and OCT2, but not MRP2 or OAT3. Enasidenib induces CYP2B6 and CYP3A4.

In vitro studies suggest that the metabolite AGI-16903 inhibits the activity of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP2D6. AGI-16903 inhibits BCRP, OAT1, OAT3, OATP1B1, and OCT2, but not P-gp, MRP2, or OATP1B3.

Coadministration of IDHIFA may increase or decrease the concentrations of combined hormonal contraceptives. The clinical significance of this potential drug interaction is unknown at this time.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been performed with enasidenib.

Enasidenib was not mutagenic in an in vitro bacterial reverse mutation (Ames) assay. Enasidenib was not clastogenic in an in vitro human lymphocyte chromosomal aberration assay, or in an in vivo rat bone marrow micronucleus assay.

Fertility studies in animals have not been conducted with enasidenib. In repeat-dose toxicity studies with twice daily oral administration of enasidenib in rats up to 90-days in duration, changes were reported in male and female reproductive organs including seminiferous tubular degeneration, hypospermia, atrophy of the seminal vesicle and prostate, decreased corpora lutea and increased atretic follicles in the ovaries, and atrophy in the uterus.

14 CLINICAL STUDIES

14.1 Acute Myeloid Leukemia

The efficacy of IDHIFA was evaluated in an open-label, single-arm, multicenter, two-cohort clinical trial (Study AG221-C-001, NCT01915498) of 199 adult patients with relapsed or refractory AML and an IDH2 mutation, who were assigned to receive 100 mg daily dose. Cohort 1 included 101 patients and Cohort 2 included 98 patients. IDH2 mutations were identified by a local diagnostic test and retrospectively confirmed by the Abbott RealTime™ IDH2 assay, or prospectively identified by the Abbott RealTime™ IDH2 assay, which is the FDA-approved test for selection of patients with AML for treatment with IDHIFA. IDHIFA was given orally at starting dose of 100 mg daily until disease progression or unacceptable toxicity. Dose reductions were allowed to manage adverse events.

The baseline demographic and disease characteristics are shown in Table 4. The baseline demographics and disease characteristics were similar in both study cohorts.

Table 4: Baseline Demographic and Disease Characteristics in Patients with Relapsed or Refractory AML

Demographic and Disease Characteristics	IDHIFA (100 mg daily) N=199
Demographics	
Age (Years) Median (Min, Max)	68 (19, 100)
Age Categories, n (%)	
<65 years	76 (38)
≥65 years to <75 years	74 (37)
≥75 years	49 (25)
Sex, n (%)	
Male	103 (52)
Female	96 (48)
Race, n (%)	
White	153 (77)

Black	10 (5)
Asian	1 (1)
Native Hawaiian/Other Pacific Islander	1 (1)
Other / Not Provided	34 (17)
Disease Characteristics, n (%)	
ECOG PS^a, n (%)	
0	46 (23)
1	124 (62)
2	28 (14)
Relapsed AML, n (%)	95 (48)
Refractory AML, n (%)	104 (52)
IDH2 Mutation^b, n (%)	
R140	155 (78)
R172	44 (22)
Time from Initial AML Diagnosis (months)	
Median (min, max) (172 patients)	11.3 (1.2, 129.1)
Cytogenetic Risk Status, n (%)	
Intermediate	98 (49)
Poor	54 (27)
Missing /Failure	47 (24)
Prior Stem Cell Transplantation for AML, n (%)	
	25 (13)
Transfusion Dependent at Baseline^c, n (%)	
	157 (79)
Number of Prior Anticancer Regimens, n (%)^d	
1	89 (45)
2	64 (32)
≥3	46 (23)
Median number of prior therapies (min, max)	2 (1, 6)

ECOG PS: Eastern Cooperative Oncology Group Performance Status.

^a 1 patient had missing baseline ECOG PS.

^b For 3 patients with different mutations detected in bone marrow compared to blood, the result of blood is reported.

^c Patients were defined as transfusion dependent at baseline if they received any red blood cell or platelet transfusions within the 8-week baseline period.

^d Includes intensive and/or nonintensive therapies.

Efficacy was established on the basis of the rate of complete response (CR)/complete response with partial hematologic recovery (CRh), the duration of CR/CRh, and the rate of conversion from transfusion dependence to transfusion independence. The efficacy results are shown in Table 5 and were similar in both cohorts. The median follow-up was 6.6 months (range, 0.4 to 27.7 months). Similar CR/CRh rates were observed in patients with either R140 or R172 mutation.

Table 5: Efficacy Results in Patients with Relapsed or Refractory AML

Endpoint	IDHIFA (100 mg daily) N=199
CR^a n (%)	37 (19)
95% CI	(13, 25)
Median DOR^b (months)	8.2
95% CI	(4.7, 19.4)
CRh^c n (%)	9 (4)
95% CI	(2, 8)
Median DOR (months)	9.6
95% CI	(0.7, NA)
CR/CRh n (%)	46 (23)
95% CI	(18, 30)
Median DOR (months)	8.2
95% CI	(4.3, 19.4)

CI: confidence interval, NA: not available.

^a CR (complete remission) was defined as <5% of blasts in the bone marrow, no evidence of disease, and full recovery of peripheral blood counts (platelets >100,000/microliter and absolute neutrophil counts [ANC] >1,000/microliter).

^b DOR (duration of response) was defined as time since first response of CR or CRh to relapse or death, whichever is earlier.

^c CRh (complete remission with partial hematological recovery) was defined as <5% of blasts in the bone marrow, no evidence of disease, and partial recovery of peripheral blood counts (platelets >50,000/microliter and ANC >500/microliter).

For patients who achieved a CR/CRh, the median time to first response was 1.9 months (range, 0.5 to 7.5 months) and the median time to best response of CR/CRh was 3.7 months (range, 0.6 to 11.2 months). Of the 46 patients who achieved a best response of CR/CRh, 39 (85%) did so within 6 months of initiating IDHIFA.

Among the 157 patients who were dependent on red blood cell (RBC) and/or platelet transfusions at baseline, 53 (34%) became independent of RBC and platelet transfusions during any 56-day post baseline period. Of the 42 patients who were independent of both RBC and platelet transfusions at baseline, 32 (76%) remained transfusion independent during any 56-day post baseline period.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

50-mg tablet: Pale yellow to yellow oval-shaped film-coated tablet debossed “ENA” on one side and “50” on the other side.

- 30-count bottles of 50-mg tablets with a desiccant canister (NDC 59572-705-30)

100-mg tablet: Pale yellow to yellow capsule-shaped film-coated tablet debossed “ENA” on one side and “100” on the other side.

- 30-count bottles of 100-mg tablets with a desiccant canister (NDC 59572-710-30)

16.2 Storage

Store at 20°C-25°C (68°F-77°F); excursions permitted between 15°C-30°C (59°F-86°F) [see USP Controlled Room Temperature]. Keep the bottle tightly closed. Store in the original bottle (with a desiccant canister) to protect from moisture.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Differentiation Syndrome

Advise patients on the risks of developing differentiation syndrome as early as 10 days and during the first 5 months on treatment. Ask patients to immediately report any symptoms suggestive of differentiation syndrome, such as fever, cough or difficulty breathing, bone pain, rapid weight gain or swelling of their arms or legs, to their healthcare provider for further evaluation [see *Boxed Warning and Warnings and Precautions (5.1)*].

Tumor Lysis Syndrome

Advise patients on the risks of developing tumor lysis syndrome. Advise patients on the importance of maintaining high fluid intake, and the need for frequent monitoring of blood chemistry values [see *Dosage and Administration (2.3) and Adverse Reactions (6.1)*].

Gastrointestinal Adverse Reactions

Advise patients on risk of experiencing gastrointestinal reactions such as diarrhea, nausea, vomiting, decreased appetite, and changes in their sense of taste. Ask patients to report these events to their healthcare provider, and advise patients how to manage them [see *Adverse Reactions (6.1)*].

Elevated Blood Bilirubin

Inform patients that taking IDHIFA may cause elevated blood bilirubin, which is due to its mechanism of action, and not due to liver damage. Advise patients to report any changes to the color of their skin or the whites of their eyes to their healthcare provider for further evaluation [see *Adverse Reactions (6.1)*].

Embryo-Fetal Toxicity and Use of Contraceptives

Advise female patients with reproductive potential to use effective contraceptive methods while receiving IDHIFA and to avoid pregnancy while on treatment and for 1 month after completion of treatment. Advise patients to notify their healthcare provider immediately in the event of a pregnancy or if pregnancy is suspected during IDHIFA treatment. Advise males with female partners of reproductive potential to use effective contraception during treatment with IDHIFA and for at least 1 month after the last dose of IDHIFA. Coadministration of IDHIFA may increase or decrease the concentrations of combined hormonal contraceptives. The clinical significance of this potential drug interaction is unknown at this time [see *Warnings and Precautions (5.2) and Use in Specific Populations (8.3)*].

Lactation

Advise women not to breastfeed during treatment with IDHIFA and for at least 1 month after the final dose [see *Use in Specific Populations* (8.2)].

Dosing and Storage Instructions

- Advise patients not to chew or split the tablets but swallow whole with a cup of water.
- Instruct patients that if they miss a dose or vomit after a dose of IDHIFA, to take it as soon as possible on the same day and return to normal schedule the following day. Warn patients not to take 2 doses to make up for the missed dose [see *Dosage and Administration* (2.2)].
- Keep IDHIFA in the original container. Keep the container tightly closed with desiccant canister inside to protect the tablets from moisture [see *How Supplied/Storage and Handling* (16.2)].

Manufactured for and marketed by:
Celgene Corporation
Summit, NJ 07901

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Agiros Pharmaceuticals
Cambridge, MA 02139

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Pat. www.celgene.com/therapies

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IDHPI.002/MG.002 08/17

MEDICATION GUIDE

IDHIFA® (eyed-HEE-fuh)
(enasidenib) tablets

What is the most important information I should know about IDHIFA?**IDHIFA may cause serious side effects, including:**

- **Differentiation Syndrome.** Differentiation syndrome is a condition that affects your blood cells which may be life-threatening or lead to death if not treated. Differentiation syndrome has happened within 10 days and up to 5 months after starting IDHIFA. Call your healthcare provider or go to the nearest hospital emergency room right away if you develop any of the following symptoms of differentiation syndrome while taking IDHIFA:
 - fever
 - cough
 - shortness of breath
 - swelling of arms and legs
 - swelling around neck, groin, or underarm area
 - fast weight gain (greater than 10 pounds within a week)
 - bone pain

If you develop any of these symptoms of differentiation syndrome, your healthcare provider may start you on a medicine taken by mouth or given through a vein (intravenous) called corticosteroids and may monitor you in the hospital.

What is IDHIFA?

IDHIFA is a prescription medicine used to treat people with acute myeloid leukemia (AML) with an isocitrate dehydrogenase-2 (IDH2) mutation whose disease has come back or has not improved after previous treatment(s). It is not known if IDHIFA is safe and effective in children.

Before taking IDHIFA, tell your healthcare provider about all of your medical conditions, including if you:

- Are pregnant or plan to become pregnant. IDHIFA can cause harm to your unborn baby if taken during pregnancy.
 - If you are able to become pregnant, your healthcare provider will do a pregnancy test before you start taking IDHIFA.
 - **Females** who are able to become pregnant and who take IDHIFA should use effective birth control (contraception) during treatment with IDHIFA and for at least 1 month after your last dose of IDHIFA.
 - **Males** who have female partners that are able to become pregnant should use effective birth control during treatment with IDHIFA and for at least 1 month after your last dose of IDHIFA.
 - IDHIFA may affect how hormonal contraceptives work and may cause them to not work as well.
 - Talk to your healthcare provider about birth control methods that may be right for you while taking IDHIFA.
 - IDHIFA may cause fertility problems in females and males, which may affect your ability to have children. Talk to your healthcare provider if you have concerns about fertility.
- Are breastfeeding or plan to breastfeed. It is not known if IDHIFA passes into your breast milk. You should not breastfeed during your treatment with IDHIFA and for at least 1 month after your last dose of IDHIFA.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

How should I take IDHIFA?

- Take IDHIFA exactly as your healthcare provider tells you to.
- Take IDHIFA 1 time a day at the same time each day.
- Swallow IDHIFA tablets whole. Do not chew or split the tablet.
- Swallow IDHIFA with 8 ounces (one cup) of water.
- IDHIFA can be taken with or without food.
- If you miss a dose of IDHIFA or vomit after taking a dose of IDHIFA, take the dose of IDHIFA as soon as possible on the same day. Then take your next dose the next day at your regularly scheduled time. **Do not** take 2 doses at the same time to make up for the missed dose.
- Your healthcare provider should do blood tests to check your blood counts before you start IDHIFA treatment and at a minimum of every 2 weeks for at least the first 3 months during treatment to check for side effects.

What are the possible side effects of IDHIFA?**IDHIFA may cause serious side effects, including:**

See “What is the most important information I should know about IDHIFA?”

The most common side effects of IDHIFA include:

- nausea
- vomiting
- diarrhea
- jaundice
- decreased appetite

Tell your healthcare provider if you have any changes to the color of your skin or the whites of your eyes.

Your healthcare provider will monitor you for side effects during treatment and may tell you to stop taking IDHIFA if you develop certain side effects.

These are not all the possible side effects of IDHIFA.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store IDHIFA?

- Store IDHIFA at room temperature from 68°F to 77°F (20°C to 25°C).
- Keep IDHIFA in the original container.
- Keep the container tightly closed with desiccant canister inside to protect the tablets from moisture.

Keep IDHIFA and all medicines out of the reach of children.**General information about the safe and effective use of IDHIFA**

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not take IDHIFA for conditions for which it was not prescribed. Do not give IDHIFA to other people, even if they have the same symptoms you have. It may harm them. You can ask your pharmacist or healthcare provider for information about IDHIFA that is written for health professionals.

What are the ingredients in IDHIFA?

Active ingredient: enasidenib

Inactive ingredients: colloidal silicon dioxide, hydroxypropyl cellulose, hypromellose acetate succinate, iron oxide yellow, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polyvinyl alcohol, sodium lauryl sulfate, sodium starch glycolate, talc, and titanium dioxide

Manufactured for and marketed by: Celgene Corporation, Summit, NJ 07901

Licensed from: Agios Pharmaceuticals, Cambridge, MA 02139

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Pat. <http://www.celgene.com/therapies>

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For more information go to www.IDHIFA.com or call 1-888-423-5436.

This Medication Guide has been approved by the U.S. Food and Drug Administration

Issued: AUG 2017

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use JYNARQUE safely and effectively. See full prescribing information for JYNARQUE.

JYNARQUE™ (tolvaptan) tablets for oral use
Initial U.S. Approval: 2009

WARNING: RISK OF SERIOUS LIVER INJURY

See full prescribing information for complete boxed warning.

- JYNARQUE (tolvaptan) can cause serious and potentially fatal liver injury. Acute liver failure requiring liver transplantation has been reported (5.1)
- Measure transaminases and bilirubin before initiating treatment, at 2 weeks and 4 weeks after initiation, then continuing monthly for the first 18 months and every 3 months thereafter (5.1)
- JYNARQUE is available only through a restricted distribution program called the JYNARQUE REMS Program (5.2)

INDICATIONS AND USAGE

JYNARQUE is a selective vasopressin V₂-receptor antagonist indicated to slow kidney function decline in adults at risk of rapidly progressing autosomal dominant polycystic kidney disease (ADPKD) (1)

DOSAGE AND ADMINISTRATION

- Recommended dosage (2.1)

Initial Dosage		Titration Step		Target Dosage	
1st Dose	45 mg	1st Dose	60 mg	1st Dose	90 mg
2nd Dose (8 hours later)	15 mg	2nd Dose (8 hours later)	30 mg	2nd Dose (8 hours later)	30 mg
Total Daily Dose	60 mg	Total Daily Dose	90 mg	Total Daily Dose	120 mg

- Dose adjustment is recommended for patients taking moderate CYP 3A inhibitors (2.4, 5.4, 7.1)

DOSAGE FORMS AND STRENGTHS

- Tablets: 15 mg, 30 mg, 45 mg, 60 mg and 90 mg (3)

CONTRAINDICATIONS

- History of signs or symptoms of significant liver impairment or injury, does not include uncomplicated polycystic liver disease (4)
- Concomitant use of strong CYP 3A inhibitors is contraindicated (4)
- Uncorrected abnormal blood sodium concentrations (4, 5.3)
- Unable to sense or respond to thirst (4)
- Hypovolemia (4)
- Hypersensitivity to tolvaptan or any of its components (4)
- Uncorrected urinary outflow obstruction (4)
- Anuria (4)

WARNINGS AND PRECAUTIONS

- Hyponatremia, dehydration and hypovolemia: May require intervention (5.3)

ADVERSE REACTIONS

Most common observed adverse reactions with JYNARQUE (incidence >10% and at least twice that for placebo) were thirst, polyuria, nocturia, pollakiuria and polydipsia (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Otsuka America Pharmaceutical, Inc. at 1-800-438-9927 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

Avoid concomitant use with:

- Strong CYP 3A Inducers (7.1)
- OATP1B1/3 and OAT3 Transporter Substrates (7.2)
- BCRP Transporter Substrates (7.3)
- V₂-Receptor Agonists (7.4)

USE IN SPECIFIC POPULATIONS

- Pregnancy: May cause fetal harm (8.1)
- Lactation: Breastfeeding not recommended (8.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 04/2018

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JYNARQUE™ (tolvaptan)

FULL PRESCRIBING INFORMATION

WARNING: RISK OF SERIOUS LIVER INJURY

JYNARQUE (tolvaptan) can cause serious and potentially fatal liver injury. Acute liver failure requiring liver transplantation has been reported [see *Warnings and Precautions (5.1)*].

Measure ALT, AST and bilirubin before initiating treatment, at 2 weeks and 4 weeks after initiation, then monthly for the first 18 months and every 3 months thereafter [see *Warnings and Precautions (5.1)*]. Prompt action in response to laboratory abnormalities, signs, or symptoms indicative of hepatic injury can mitigate, but not eliminate, the risk of serious hepatotoxicity.

Because of the risks of serious liver injury, JYNARQUE is available only through a restricted distribution program under a Risk Evaluation and Mitigation Strategy (REMS) called the JYNARQUE REMS Program [see *Warnings and Precautions (5.2)*].

1 INDICATIONS AND USAGE

JYNARQUE is indicated to slow kidney function decline in adults at risk of rapidly progressing autosomal dominant polycystic kidney disease (ADPKD).

2 DOSAGE AND ADMINISTRATION**2.1 Recommended Dosage**

The initial dosage for JYNARQUE is 60 mg orally per day as 45 mg taken on waking and 15 mg taken 8 hours later. Titrate to 60 mg plus 30 mg then to 90 mg plus 30 mg per day if tolerated with at least weekly intervals between titrations. Patients may down-titrate based on tolerability. Encourage patients to drink enough water to avoid thirst or dehydration.

2.2 Monitoring

To mitigate the risk of significant or irreversible liver injury, perform blood testing for ALT, AST and bilirubin prior to initiation of JYNARQUE, at 2 and 4 weeks after initiation, monthly for 18 months and every 3 months thereafter. Monitor for concurrent symptoms that may indicate liver injury [see *Warnings and Precautions (5.1)*].

2.3 Missed Doses

If a dose of JYNARQUE is not taken at the scheduled time, take the next dose at its scheduled time.

2.4 Co-Administration with CYP 3A InhibitorsCYP 3A Inhibitors

Concomitant use of strong CYP 3A inhibitors is contraindicated [see *Contraindications (4)* and *Warnings and Precautions (5.4)*].

In patients taking concomitant moderate CYP 3A inhibitors, reduce the dose of JYNARQUE per Table 1. Consider further reductions if patients cannot tolerate the reduced dose [see *Warnings and Precautions (5.4)* and *Drug Interactions (7.1)*]. Interrupt JYNARQUE temporarily for short term therapy with moderate CYP 3A inhibitors if the recommended reduced doses are not available.

Table 1: Dose adjustment for patients taking moderate CYP 3A inhibitors

Standard Morning and Afternoon Dose (mg)	Dose (mg) with Moderate CYP 3A Inhibitors
90 mg and 30 mg	45 mg and 15 mg
60 mg and 30 mg	30 mg and 15 mg
45 mg and 15 mg	15 mg and 15 mg

3 DOSAGE FORMS AND STRENGTHS

JYNARQUE (tolvaptan) is supplied as non-scored, blue, shallow-convex, immediate release tablets, debossed with "OTSUKA" and the tablet strength (mg) on one side.

JYNARQUE 15 mg tablets are triangular, 30 mg tablets are round, 45 mg tablets are square, 60 mg tablets are rectangular, and 90 mg tablets are pentagonal.

4 CONTRAINDICATIONS

JYNARQUE is contraindicated in patients:

- With a history, signs or symptoms of significant liver impairment or injury. This contraindication does not apply to uncomplicated polycystic liver disease [see *Warnings and Precautions (5.1)*]
- Taking strong CYP 3A inhibitors
- With uncorrected abnormal blood sodium concentrations [see *Warnings and Precautions (5.3)*]
- Unable to sense or respond to thirst [see *Warnings and Precautions (5.3)*]
- Hypovolemia [see *Warnings and Precautions (5.3)*]

JYNARQUE™ (tolvaptan)

- Hypersensitivity (e.g., anaphylaxis, rash) to tolvaptan or any component of the product [see *Adverse Reactions (6)*]
- Uncorrected urinary outflow obstruction
- Anuria

5 WARNINGS AND PRECAUTIONS**5.1 Serious Liver Injury**

JYNARQUE can cause serious and potentially fatal liver injury. Acute liver failure requiring liver transplantation has been reported in the post-marketing ADPKD experience. Discontinuation in response to laboratory abnormalities or signs or symptoms of liver injury (such as fatigue, anorexia, nausea, right upper abdominal discomfort, vomiting, fever, rash, pruritus, icterus, dark urine or jaundice) can reduce the risk of severe hepatotoxicity.

In a 3-year placebo-controlled trial and its open-label extension (in which patients' liver tests were monitored every 4 months), evidence of serious hepatocellular injury (elevations of hepatic transaminases of at least 3 times ULN combined with elevated bilirubin at least 2 times the ULN) occurred in 0.2% (3/1487) of tolvaptan treated patients compared to none of the placebo treated patients.

To reduce the risk of significant or irreversible liver injury, assess ALT, AST and bilirubin prior to initiation of JYNARQUE, at 2 weeks and 4 weeks after initiation, then monthly for 18 months and every 3 months thereafter.

At the onset of signs or symptoms consistent with hepatic injury or if ALT, AST, or bilirubin increase to >2 times ULN, immediately discontinue JYNARQUE, obtain repeat tests as soon as possible (within 48-72 hours), and continue testing as appropriate. If laboratory abnormalities stabilize or resolve, JYNARQUE may be reinitiated with increased frequency of monitoring as long as ALT and AST remain below 3 times ULN.

Do not restart JYNARQUE in patients who experience signs or symptoms consistent with hepatic injury or whose ALT or AST ever exceeds 3 times ULN during treatment with tolvaptan, unless there is another explanation for liver injury and the injury has resolved.

In patients with a stable, low baseline AST or ALT, an increase above 2 times baseline, even if less than 2 times upper limit of normal, may indicate early liver injury. Such elevations may warrant treatment suspension and prompt (48-72 hours) re-evaluation of liver test trends prior to reinitiating therapy with more frequent monitoring.

5.2 JYNARQUE REMS Program

JYNARQUE is available only through a restricted distribution program under a Risk Evaluation and Mitigation Strategy (REMS) called the JYNARQUE REMS Program, because of the risks of liver injury [see *Warnings and Precautions (5.1)*].

Notable requirements of the JYNARQUE REMS Program include the following:

- Prescribers must be certified by enrolling in the REMS program.
- Prescribers must inform patients receiving JYNARQUE about the risk of hepatotoxicity associated with its use and how to recognize the signs and symptoms of hepatotoxicity and the appropriate actions to take if it occurs.
- Patients must enroll in the REMS program and comply with ongoing monitoring requirements [see *Warnings and Precautions (5.1)*].
- Pharmacies must be certified by enrolling in the REMS program and must only dispense to patients who are authorized to receive JYNARQUE.

Further information, including a list of qualified pharmacies/distributors, is available at www.JYNARQUEREMS.com or by telephone at 1-877-726-7220.

5.3 Hyponatremia, Dehydration and Hypovolemia

JYNARQUE increases free water clearance and, as a result, may cause dehydration, hypovolemia and hyponatremia. Therefore, ensure abnormalities in sodium concentrations are corrected prior to initiation of therapy.

Instruct patients to drink water when thirsty, and throughout the day and night if awake. Monitor for weight loss, tachycardia and hypotension because they may signal dehydration.

In the two double-blind, placebo-controlled trials of patients with ADPKD, hyponatremia (defined as any serum sodium concentration >150 mEq/L) was observed in 4.0% versus 0.6% and 1.4% versus 0% of tolvaptan-treated versus placebo-treated patients, respectively. The rate of dehydration and hypovolemia in the two studies was 2.1% versus 0.7% and 2.3% versus 0.4% for tolvaptan-treated versus placebo-treated patients, respectively.

During JYNARQUE therapy, if serum sodium increases above normal range or the patient becomes hypovolemic or dehydrated and fluid intake cannot be increased, then suspend JYNARQUE until serum sodium, hydration status and volume status is within the normal range.

5.4 Co-Administration with Inhibitors of CYP 3A

Concomitant use of JYNARQUE with drugs that are moderate or strong CYP 3A inhibitors (e.g., ketoconazole, itraconazole, lopinavir/ritonavir, indinavir/ritonavir, ritonavir, and conivaptan) increases tolvaptan exposure [see *Drug Interactions*].

JYNARQUE™ (tolvaptan)

(7.1) and *Clinical Pharmacology* (12.3)]. Use with strong CYP 3A inhibitors is contraindicated; dose reduction of JYNARQUE is recommended for patients while taking moderate CYP 3A inhibitors [see *Dosage and Administration* (2.4) and *Contraindications* (4)].

6 ADVERSE REACTIONS

The following adverse reactions are discussed in more detail in other sections of the labeling:

- Serious Liver Injury [see *Boxed Warning and Warnings and Precautions* (5.1)]
- Hyponatremia, Dehydration and Hypovolemia [see *Warnings and Precautions* (5.3)]
- Drug Interactions with Inhibitors of CYP 3A [see *Warnings and Precautions* (5.4)]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. JYNARQUE has been studied in over 3000 patients with ADPKD. Long-term, placebo-controlled safety information of JYNARQUE in ADPKD is principally derived from two trials where 1,413 subjects received tolvaptan and 1,098 received placebo for at least 12 months across both studies.

TEMPO 3:4-NCT00428948: A Phase 3, Double-Blind, Placebo-Controlled, Randomized Trial in Early, Rapidly-Progressing ADPKD

The TEMPO3:4 trial employed a two-arm, 2:1 randomization to tolvaptan or placebo, titrated to a maximally-tolerated total daily dose of 60-120 mg. A total of 961 subjects with rapidly progressing ADPKD were randomized to JYNARQUE. Of these, 742 (77%) subjects who were treated with JYNARQUE remained on treatment for at least 3 years. The average daily dose in these subjects was 96 mg daily.

Adverse events that led to discontinuation were reported for 15.4% (148/961) of subjects in the JYNARQUE group and 5.0% (24/483) of subjects in the placebo group. Aquaretic effects were the most common reasons for discontinuation of JYNARQUE. These included pollakiuria, polyuria, or nocturia in 63 (6.6%) subjects treated with JYNARQUE compared to 1 subject (0.2%) treated with placebo.

Table 2 lists the adverse reactions that occurred in at least 3% of ADPKD subjects treated with JYNARQUE and at least 1.5% more than on placebo.

Adverse Reaction	Tolvaptan (N=961)			Placebo (N=483)		
	Number of Subjects	Proportion (%) [*]	Annualized Rate [†]	Number of Subjects	Proportion (%) [*]	Annualized Rate [†]
Increased urination [§]	668	69.5	28.6	135	28.0	10.3
Thirst [‡]	612	63.7	26.2	113	23.4	8.7
Dry mouth	154	16.0	6.6	60	12.4	4.6
Fatigue	131	13.6	5.6	47	9.7	3.6
Diarrhea	128	13.3	5.5	53	11.0	4.1
Dizziness	109	11.3	4.7	42	8.7	3.2
Dyspepsia	76	7.9	3.3	16	3.3	1.2
Decreased appetite	69	7.2	3.0	5	1.0	0.4
Abdominal distension	47	4.9	2.0	16	3.3	1.2
Dry skin	47	4.9	2.0	8	1.7	0.6
Rash	40	4.2	1.7	9	1.9	0.7
Hyperuricemia	37	3.9	1.6	9	1.9	0.7
Palpitations	34	3.5	1.5	6	1.2	0.5

^{*}100x (Number of subjects with an adverse event/N)

[†]100x (Number of subjects with an adverse event/Total subject years of drug exposure)

[‡]Thirst includes polydipsia and thirst

[§]Increased urination includes micturition urgency, nocturia, pollakiuria, polyuria

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REPRISE-NCT02160145: A Phase 3, Randomized-Withdrawal, Placebo-Controlled, Double-Blind, Trial in Late Stage 2 to Early Stage 4 ADPKD

The REPRISE trial employed a 5-week single-blind titration and run-in period for JYNARQUE prior to the randomized double-blind period. During the JYNARQUE titration and run-in period, 126 (8.4%) of the 1496 subjects discontinued the study, 52 (3.5%) were due to aquaretic effects and 10 (0.7%) were due to liver test findings. Because of this run-in design, the adverse reaction rates observed during the randomized period are not described.

Liver Injury:

In the two double-blind, placebo-controlled trials, ALT elevations >3 times ULN were observed at an increased frequency with JYNARQUE compared with placebo (4.9% [80/1637] versus 1.1% [13/1166], respectively) within the first 18 months after initiating treatment and increases usually resolved within 1 to 4 months after discontinuing the drug.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of tolvaptan. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to estimate their frequency reliably or establish a causal relationship to drug exposure.

Hepatobiliary Disorders: Liver failure requiring transplant

Immune System Disorders: Anaphylaxis

7 DRUG INTERACTIONS**7.1 CYP 3A Inhibitors and Inducers****CYP 3A Inhibitors**

Tolvaptan's AUC was 5.4 times as large and C_{max} was 3.5 times as large after co-administration of tolvaptan and 200 mg ketoconazole [see *Warnings and Precautions* (5.4) and *Clinical Pharmacology* (12.3)]. Larger doses of the strong CYP 3A inhibitor would be expected to produce larger increases in tolvaptan exposure. Concomitant use of tolvaptan with strong CYP 3A inhibitors is contraindicated [see *Contraindications* (4)].

Dose reduction of JYNARQUE is recommended for patients while taking moderate CYP 3A inhibitors [see *Dosage and Administration* (2.4)]. Patients should avoid grapefruit juice beverages while taking JYNARQUE.

Strong CYP 3A Inducers

Co-administration of JYNARQUE with strong CYP 3A inducers reduces exposure to JYNARQUE [see *Clinical Pharmacology* (12.3)]. Avoid concomitant use of JYNARQUE with strong CYP 3A inducers [see *Dosage and Administration* (2.4)].

7.2 OATP1B1/3 and OAT3 Transporter Substrates

The oxobutyric acid metabolite of tolvaptan is an inhibitor of OATP1B1/B3 and OAT3 in vitro. Patients who take JYNARQUE should avoid concomitant use with OATP1B1/B3 and OAT3 substrates (e.g., statins, bosentan, glyburide, nateglinide, repaglinide, methotrexate, furosemide), as the plasma concentrations of these substrates may be increased [see *Clinical Pharmacology* (12.3)].

7.3 BCRP Transporter Substrates

Tolvaptan is an inhibitor of BCRP. Patients who take JYNARQUE should avoid concomitant use with BCRP substrates (e.g., rosuvastatin) [see *Clinical Pharmacology* (12.3)].

7.4 V₂-Receptor Agonist

As a V₂-receptor antagonist, tolvaptan will interfere with the V₂-agonist activity of desmopressin (dDAVP). Avoid concomitant use of JYNARQUE with a V₂-agonist.

8 USE IN SPECIFIC POPULATIONS**8.1 Pregnancy****Risk Summary**

Available data with JYNARQUE use in pregnant women are insufficient to determine if there is a drug associated risk of adverse developmental outcomes. In embryo-fetal development studies, pregnant rats and rabbits received oral tolvaptan during organogenesis. At maternally non-toxic doses, tolvaptan did not cause any developmental toxicity in rats or in rabbits at exposures approximately 4- and 1-times, respectively, the human exposure at the maximum recommended human dose (MRHD) of 90/30 mg. However, effects on embryo-fetal development occurred in both species at maternally toxic doses. In rats, reduced fetal weights and delayed fetal ossification occurred at 17-times the human exposure. In rabbits, increased abortions, embryo-fetal death, fetal microphthalmia, open eyelids, cleft palate, brachymelia and skeletal malformations occurred at approximately 3-times the human exposure (see *Data*). Advise pregnant women of the potential risk to the fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. The estimated background risk of major birth defects and miscarriage in the U.S. general population is 2-4% and 15-20% of clinically recognized pregnancies, respectively.

JYNARQUE™ (tolvaptan)

Data

Animal Data

Oral administration of tolvaptan during the period of organogenesis in Sprague-Dawley rats produced no evidence of teratogenesis at doses up to 100 mg/kg/day. Lower body weights and delayed ossification were seen at 1000 mg/kg, which is approximately 17-times the exposure in humans at the 90/30 mg dose (AUC_{24h} 6570 ng h/mL). The fetal effects are likely secondary to maternal toxicity (decreased food intake and low body weights). In a prenatal and postnatal study in rats, tolvaptan had no effect on physical development, reflex function, learning ability or reproductive performance at doses up to 1000 mg/kg/day.

In New Zealand White rabbits, placental transfer was demonstrated with C_{max} values in the yolk sac fluid approximating 22.7% of the value in maternal rabbit serum. In embryo-fetal studies, teratogenicity (microphthalmia, embryo-fetal mortality, cleft palate, brachymelia and fused phalanx) was evident in rabbits at 1000 mg/kg (approximately 3 times the exposure at the 90/30 mg dose). Body weights and food consumption were lower in dams at all doses, equivalent to 0.6 to 3- times the human exposure at the 90/30 mg dose.

8.2 Lactation

Risk Summary

There are no data on the presence of tolvaptan in human milk, the effects on the breastfed infant, or the effects on milk production. Tolvaptan is present in rat milk. When a drug is present in animal milk, it is possible that the drug will be present in human milk, but relative levels may vary (see Data). Because of the potential for serious adverse reactions, including liver toxicity, electrolyte abnormalities (e.g., hyponatremia), hypotension, and volume depletion in breastfed infants, advise women not to breastfeed during treatment with JYNARQUE.

Data

In lactating rats administration of radiolabeled tolvaptan, lacteal radioactivity concentrations reached the highest level at 8 hours after administration and then decreased gradually with time with a half-life of 27.3 hours. The level of activity in milk ranged from 1.5- to 15.8-fold those in blood over the period of 72 hours post-dose. In a prenatal and postnatal study in rats, maternal toxicity was noted at 100 mg/kg/day or higher (≥ 4.4 times the human exposure at the 90/30 mg dose). Increased perinatal death and decreased body weight of the offspring were observed during the lactation period and after weaning at approximately 17.3 times the human exposure at the 90/30 mg dose.

8.4 Pediatric Use

Safety and effectiveness of JYNARQUE in pediatric patients have not been established.

8.5 Geriatric Use

Clinical studies of tolvaptan did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

8.6 Use in Patients with Hepatic Impairment

Because of the risk of serious liver injury, use is contraindicated in patients with a history, signs or symptoms of significant liver impairment or injury. This contraindication does not apply to uncomplicated polycystic liver disease which was present in 60% and 66% of patients in TEMPO 3:4 and REPRISÉ, respectively. No specific exclusion for hepatic impairment was implemented in TEMPO 3:4. However, REPRISÉ excluded patients with ADPKD who had hepatic impairment or liver function abnormalities other than that expected for ADPKD with typical cystic liver disease [see Contraindications (4)].

8.7 Use in Patients with Renal Impairment

Efficacy studies included patients with normal and reduced renal function [see Clinical Studies (14)]. TEMPO 3:4 required patients to have an estimated creatinine clearance ≥ 60 mL/min, while REPRISÉ included patients with $eGFR_{CKD-EPI}$ 25 to 65 mL/min/1.73m².

10 OVERDOSAGE

Single oral doses up to 480 mg (4 times the maximum recommended daily dose) and multiple doses up to 300 mg once daily for 5 days have been well tolerated in trials in healthy subjects. There is no specific antidote for tolvaptan intoxication. The signs and symptoms of an acute overdose can be anticipated to be those of excessive pharmacologic effect: a rise in serum sodium concentration, polyuria, thirst, and dehydration/hypovolemia.

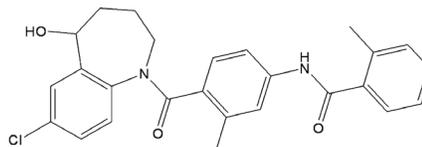
No mortality was observed in rats or dogs following single oral doses of 2000 mg/kg (maximum feasible dose). A single oral dose of 2000 mg/kg was lethal in mice, and symptoms of toxicity in affected mice included decreased locomotor activity, staggering gait, tremor and hypothermia.

JYNARQUE™ (tolvaptan)

In patients with suspected JYNARQUE overdose, assessment of vital signs, electrolyte concentrations, ECG and fluid status is recommended. Continue replacement of water and electrolytes until aquaresis abates. Dialysis may not be effective in removing JYNARQUE because of its high binding affinity for human plasma protein (>98%).

11 DESCRIPTION

JYNARQUE contains tolvaptan, a selective vasopressin V₂-receptor antagonist in immediate release tablets for oral administration available in 15 mg, 30 mg, 45 mg, 60 mg and 90 mg strengths. Tolvaptan is (\pm)-4'-[(7-chloro-2,3,4,5-tetrahydro-5-hydroxy-1H-1-benzazepin-1-yl) carbonyl]- α -tolu-*m*-toluidide. The empirical formula is C₂₆H₂₅ClN₂O₃. Molecular weight is 448.94. The chemical structure is:



Inactive ingredients include corn starch, hydroxypropyl cellulose, lactose monohydrate, low-substituted hydroxypropyl cellulose, magnesium stearate and microcrystalline cellulose and FD&C Blue No. 2 Aluminum Lake as colorant.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Tolvaptan is a selective vasopressin V₂-receptor antagonist with an affinity for the V₂-receptor that is 1.8 times that of native arginine vasopressin (AVP). Tolvaptan affinity for the V₂-receptor is 29 times that for the V_{1a}-receptor. Decreased binding of vasopressin to the V₂-receptor in the kidney lowers adenylate cyclase activity resulting in a decrease in intracellular adenosine 3', 5'-cyclic monophosphate (cAMP) concentrations. Decreased cAMP concentrations prevent aquaporin 2 containing vesicles from fusing with the plasma membrane, which in turn causes an increase in urine water excretion, an increase in free water clearance (aquaresis) and a decrease in urine osmolality. In human ADPKD cyst epithelial cells, tolvaptan inhibited AVP-stimulated *in vitro* cyst growth and chloride-dependent fluid secretion into cysts. In animal models, decreased cAMP concentrations were associated with decreases in the rate of growth of total kidney volume and the rate of formation and enlargement of kidney cysts. Tolvaptan metabolites have no or weak antagonist activity for human V₂-receptors compared with tolvaptan.

12.2 Pharmacodynamics

In healthy subjects or patients with $eGFR$ s as low as 10 mL/min/1.73m² receiving a single dose of tolvaptan, the onset of the aquaretic effects occurs within 1 to 2 hours post-dose. In healthy subjects, single doses of 60 mg and 90 mg produce a peak effect of about a 9 mL/min increase in urine excretion rate is observed between 4 and 8 hours post-dose. Higher doses of tolvaptan do not increase the peak effect in urine excretion rate but sustain the effect for a longer period of time.

Urine excretion rate returns to baseline within 24 hours following the maximum recommended 90 mg dose of tolvaptan.

Changes in free water clearance mirror the changes in urine excretion rate. Increased free water clearance causes an increase in serum sodium concentration unless fluid intake is increased to match urine output.

Increases in urine excretion rate and free water clearance are positively correlated with baseline glomerular filtration rate with increases in both values observed in patients with creatinine clearance as low as 15 mL/min.

With the recommended split-dose regimens, tolvaptan inhibits vasopressin from binding to the V₂-receptor in the kidney for the entire day, as indicated by increased urine output and decreased urine osmolality. Following a 90/30 mg split-dose regimen in patients with $eGFR > 60$ mL/min/1.73 m², the change in mean daily urine volume was about 4 L for a mean total daily volume of about 7 L. In patients with $eGFR < 30$ mL/min/1.73 m², the mean change in daily urine volume was about 2 L for a total daily urine volume of about 5 L.

Plasma concentrations of native AVP may increase (avg. 2-9 pg/mL) with tolvaptan treatment and return to baseline levels when treatment is stopped.

During tolvaptan treatment, small changes in renal function are expected and the changes are independent of baseline renal function. Glomerular filtration rate is decreased about 6%-10% and uric acid clearance is decreased about 20%-25%. Percent changes in renal plasma flow are highly correlated to percent changes in GFR. These changes are reversed upon discontinuation of tolvaptan.

Cardiac Electrophysiology

No prolongation of the QT interval was observed with tolvaptan following multiple doses of 300 mg/day for 5 days.

JYNARQUE™ (tolvaptan)**12.3 Pharmacokinetics**

In healthy subjects, the pharmacokinetics of tolvaptan after single doses of up to 480 mg and multiple doses up to 300 mg once daily have been studied. In ADPKD patients, single doses up to 120 mg and multiple split-doses up to 90/30 mg have been studied.

Absorption:

In healthy subjects, peak concentrations of tolvaptan are observed between 2 and 4 hours post-dose. Peak concentrations increase less than dose proportionally with doses greater than 240 mg.

The absolute bioavailability of tolvaptan decreases with increasing doses. The absolute bioavailability of tolvaptan following an oral dose of 30 mg is 56% (range 42-80%).

Co-administration of 90 mg JYNARQUE with a high-fat meal (~1000 calories, of which 50% are from fat) doubles peak concentrations but has no effect on the AUC of tolvaptan; tolvaptan may be administered with or without food.

Distribution:

Tolvaptan binds to both albumin and α 1-acid glycoprotein and the overall protein binding is >98%; binding is not affected by disease state. The volume of distribution of tolvaptan is about 3 L/kg. The pharmacokinetic properties of tolvaptan are stereospecific, with a steady-state ratio of the S-(-) to the R-(+) enantiomer of about 3. When administered as multiple once-daily 300 mg doses to healthy subjects or as split-dose regimens to patients with ADPKD, tolvaptan's accumulation factor is <1.2. There is marked inter-subject variation in peak and average exposure to tolvaptan with a percent coefficient of variation ranging between 30 and 60%.

Metabolism and Elimination:

Tolvaptan is metabolized almost exclusively by CYP 3A. Fourteen metabolites have been identified in plasma, urine and feces; all but one were also metabolized by CYP 3A and none are pharmacodynamically active. After oral administration of radiolabeled tolvaptan, tolvaptan was a minor component in plasma representing 3% of total plasma radioactivity; the oxobutyric acid metabolite was present at 52.5% of total plasma radioactivity with all other metabolites present at lower concentrations than tolvaptan. The oxobutyric acid metabolite shows a plasma half-life of ~180 h. About 40% of radioactivity was recovered in urine (<1% as unchanged tolvaptan) and 59% in feces (19% as unchanged tolvaptan). Following intravenous infusion, tolvaptan half-life is approximately 3 hours. Following single oral doses to healthy subjects, the estimated half-life of tolvaptan increases from 3 hours for a 15 mg dose to approximately 12 hours for 120 mg and higher doses due to more prolonged absorption of tolvaptan at higher doses; apparent clearance is approximately 4 mL/min/kg and does not appear to change with increasing dose.

Specific Populations**Age, Gender and Race**

Age, gender and race have no effect on tolvaptan pharmacokinetics.

Hepatic Impairment

In studies involving patients with hepatic impairment (Child-Pugh class A-C), but without ADPKD; moderate (class A, B) or severe (class C) hepatic impairment decreases the clearance and increases the volume of distribution of tolvaptan.

Renal Impairment

In subjects with creatinine clearances ranging from 10-124 mL/min administered a single dose of 60 mg tolvaptan, the AUC and C_{max} of plasma tolvaptan was increased 90% and 10%, respectively, for subjects with clearances of <30 mL/min compared to subjects with clearances >60 mL/min [see Use in Special Populations (8.7)].

In ADPKD patients with estimated creatinine clearance >60 mL/min, pharmacokinetics were similar to healthy subjects.

Drug Interactions:**Impact of Other Drugs on Tolvaptan****Strong CYP 3A Inhibitors**

Tolvaptan's C_{max} and AUC were, respectively, 3.5 times and 5.4 times as high following ketoconazole 200 mg given one day prior to and concomitantly with 30 mg tolvaptan.

Moderate CYP 3A4 Inhibitors

Fluconazole: Fluconazole 400 mg given one day prior and 200 mg given concomitantly produced an 80% and 200% increase in tolvaptan C_{max} and AUC, respectively.

Grapefruit Juice: When 60 mg tolvaptan was taken with 240 mL regular strength grapefruit juice, tolvaptan C_{max} and AUC increased 90% and 60%, respectively.

CYP 3A Inducers

Rifampin: Rifampin 600 mg once daily for 7 days followed by a single 240 mg dose of tolvaptan decreased both tolvaptan C_{max} and AUC about 85%.

JYNARQUE™ (tolvaptan)**Other Drugs**

Co-administration of lovastatin, digoxin, furosemide, and hydrochlorothiazide with tolvaptan has no clinically relevant impact on the exposure to tolvaptan.

Impact of Tolvaptan on Other Drugs**CYP 3A Substrates**

Co-administration of lovastatin and tolvaptan increases the AUC of lovastatin and its active metabolite lovastatin- β hydroxy acid by 40% and 30%, respectively. These are non-clinically significant increases in exposure.

P-gp Substrates

Digoxin: Digoxin 0.25 mg was administered once daily for 12 days. Tolvaptan 60 mg, was co-administered once daily on Days 8 to 12. Digoxin C_{max} and AUC were increased 30% and 20%, respectively.

Transporter Substrates

Tolvaptan is a substrate of P-gp and an inhibitor of P-gp and BCRP. The oxobutyric acid metabolite of tolvaptan is an inhibitor of OATP1B1/B3 and OAT3; *in vitro* studies indicate that tolvaptan or the oxobutyric acid metabolite of tolvaptan may have the potential to increase exposure of drugs that are substrates of these transporters [see Drug Interactions (7.2), (7.3)].

Other Drugs

Co-administration of tolvaptan did not meaningfully alter the pharmacokinetics of warfarin, furosemide, hydrochlorothiazide, or amiodarone (or its active metabolite, desethylamiodarone).

13 NONCLINICAL TOXICOLOGY**13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility****Carcinogenesis**

The carcinogenic potential of JYNARQUE was assessed in 2-year carcinogenicity studies in mice and rats. Tolvaptan was not tumorigenic in male or female rats at doses up to 1000 mg/kg/day (1.9-5.1 times the human exposure at the 90/30 mg dose), in male mice at doses up to 60 mg/kg/day (0.4 times the human exposure at the 90/30 mg dose) and to female mice at doses up to 100 mg/kg/day (0.7 times the human exposure at the 90/30 mg dose).

Mutagenesis

Tolvaptan was not clastogenic in the *in vitro* chromosomal aberration test in Chinese hamster lung fibroblast cells or the *in vivo* rat micronucleus assay and was not mutagenic in the *in vitro* bacterial reverse mutation assay.

Impairment of fertility

In a fertility study in which male and female rats were administered tolvaptan orally at 100, 300 or 1000 mg/kg/day, altered estrous cycles due to prolongation of diestrus were observed in dams given 300 and 1000 mg/kg/day (9.7- and 17.3 times the human exposure at the 90/30 mg dose). Tolvaptan had no effect on copulation or fertility indices. There were also no effects on the incidences of early or late resorption, dead fetuses, pre- or post-implantation loss, external anomalies, or fetal body weights.

14 CLINICAL STUDIES

JYNARQUE was shown to slow the rate of decline in renal function in patients at risk of rapidly progressing ADPKD in two trials; TEMPO 3:4 in patients at earlier stages of disease and REPRISE in patients at later stages. The findings from these trials, when taken together, suggest that JYNARQUE slows the loss of renal function progressively through the course of the disease.

TEMPO 3:4-NCT00428948: A Phase 3, Double-Blind, Placebo-Controlled, Randomized Trial in Early, Rapidly-Progressing ADPKD

In TEMPO 3:4, 1445 adult patients (age >18 years) with early (estimated creatinine clearance [eCrCl] \geq 60 mL/min), rapidly-progressing (total kidney volume [TKV] \geq 750 mL and age <51 years) ADPKD (diagnosed by modified Ravine criteria) were randomized 2:1 to treatment with tolvaptan or placebo. Patients were treated for up to 3 years; patients who discontinued medication prematurely were only required to attend clinic visits to assess renal function for up to 42 days after treatment withdrawal and to attend telephone visits at all scheduled visits for up to 36 months. Patients who completed treatment at the 3-year visit had treatment interrupted for 2-6 weeks to assess renal function post treatment. Patients received treatment twice a day (first dose on waking, second dose approximately 9 hours later). Patients were initiated on 45 mg/15 mg, and up-titrated weekly to 60 mg/30 mg and then to 90 mg/30 mg as tolerated. Patients were to maintain the highest tolerated dose for 3 years, but could interrupt, decrease and/or increase as clinical circumstances warranted within the range of titrated doses. All patients were encouraged to drink adequate water to avoid thirst or dehydration and before bedtime.

JYNARQUE™ (tolvaptan)

The primary endpoint was the intergroup difference for rate of change of TKV normalized as a percentage. The key secondary composite endpoint (ADPKD progression) was time to multiple clinical progression events of: 1) worsening kidney function (defined as a persistent 25% reduction in reciprocal serum creatinine during treatment from end of titration to last on-drug visit); 2) medically significant kidney pain (defined as requiring prescribed leave, last-resort analgesics, narcotic and anti-nociceptive, radiologic or surgical interventions); 3) worsening hypertension (defined as a persistent increase in blood pressure category or an increased anti-hypertensive prescription); 4) worsening albuminuria (defined as a persistent increase in albumin/creatinine ratio category).

At baseline, average estimated glomerular filtration rate (eGFR) was 82 mL/min/1.73 m² (CKD-Epidemiology formula) and mean TKV was 1692 mL (height adjusted 972 mL/m). Approximately 35% had an eGFR of 90 mL/min/1.73 m² or greater, 48% had an eGFR between 60-89 mL/min/1.73 m², 14% had an eGFR of 45-60 mL/min/1.73 m², and 3% had an eGFR of <45 mL/min/1.73 m². The subjects' mean age was 39 years, 48% were female, 84% were Caucasian, 13% were Asian, and 1.7% were Black or African-American. Approximately 80% had hypertension and approximately 71% were taking an agent that acts on the renin-angiotensin system. Of the 770 subjects who submitted to genetic analysis in TEMPO 3:4's open-label extension, 749 (97%) had an identifiable mutation in the PKD1 (656 or 88%), or PKD2 (93 or 12%) gene.

The trial met its prespecified primary endpoint of 3-year change in TKV (p<0.0001). The difference in TKV between treatment groups mostly developed within the first year, the earliest assessment, with little further difference in years two and three. In years 4 and 5 during the TEMPO 3:4 extension trial, both groups received JYNARQUE and the difference between the groups in TKV was not maintained. Tolvaptan has little effect on kidney size beyond what accrues during the first year of treatment.

The relative rate of ADPKD-related events was decreased by 13.5% in tolvaptan-treated patients, (44 vs. 50 events per 100 person-years; hazard ratio, 0.87; 95% CI, 0.78 to 0.97; p=0.0095). As shown in the table below, the result of the key secondary composite endpoint was driven by effects on worsening kidney function and kidney pain events. In contrast, there was no effect of tolvaptan on either progression of hypertension or albuminuria. Few subjects in either arm required a radiologic or surgical intervention for kidney pain. Most kidney pain events reflected use of a medication to treat pain such as use of paracetamol, tricyclic antidepressants, narcotics and other non-narcotic agents.

Event	Tolvaptan		Placebo		Hazard Ratio, 95% CI
	Total Number of Events (Events per 100 person-years)	Number of Subjects with an Event (percentage)	Total Number of Events (Events per 100 person-years)	Number of Subjects with an Event (percentage)	
Composite	1049 (43.9)	572 (59.5)	665 (50.0)	341 (70.6)	0.87 (0.78,0.97)
Worsening Kidney Function	44 (1.9)	42 (4.6)	64 (4.8)	61 (12.8)	0.39 (0.26,0.57)
Kidney Pain	113 (4.7)	95 (9.9)	97 (7.3)	78 (16.2)	0.64 (0.47,0.89)
Onset or progression of hypertension	734 (30.7)	426 (44.3)	426 (32.1)	244 (50.5)	0.94 (0.81,1.09)
Worsening Albuminuria	195 (8.2)	195 (20.3)	103 (7.8)	101 (20.9)	1.04 (0.84,1.28)

The third endpoint (kidney function slope) was assessed as slope of eGFR during treatment (from end of titration to last on-drug visit). The estimated difference in the annual rate of change in those who contributed to the analysis was 1.0 mL/min/1.73m²/year with a 95% confidence interval of (0.6, 1.4). Of the subjects enrolled in the trial, 5 % of subjects in the tolvaptan arm and 2% in the placebo arm either had missing baseline data or discontinued from treatment prior to the end of the titration visit and hence were excluded from the analysis. In the extension trial, eGFR differences produced by the third year of the TEMPO 3:4 trial were maintained over the next 2 years of JYNARQUE treatment.

The efficacy profile was generally consistent across subgroups of interest for this indication; few Black or African-American patients were enrolled in the trial.

JYNARQUE™ (tolvaptan)**REPRISE-NCT02160145: A Phase 3, Double-Blind, Placebo-Controlled, Randomized Withdrawal Trial in Later-Stage ADPKD**

REPRISE was a double-blind, placebo-controlled randomized withdrawal trial in adult patients (age 18-65) with chronic kidney disease (CKD) with an eGFR between 25 and 65 mL/min/1.73m² if younger than age 56; or eGFR between 25 and 44 mL/min/1.73m², plus eGFR decline >2.0 mL/min/1.73m²/year if between age 56-65. Subjects were to be treated for 12 months; after completion of treatment, patients entered a 3-week follow-up period to assess renal function. The primary endpoint was the treatment difference in the change of eGFR from pre-treatment baseline to post-treatment follow-up, annualized by dividing by each subject's treatment duration.

Prior to randomization, patients were required to complete sequential single-blind run-in periods during which they received placebo for 1 week, followed by tolvaptan titration for 2 weeks, and then treatment with tolvaptan at the highest tolerated dose achieved during titration for 3 weeks. During the titration period, tolvaptan was up-titrated every 3-4 days from a daily oral dose of 30 mg/15 mg to 45 mg/15 mg, 60 mg/30 mg and up to a maximum dose of 90 mg/30 mg. Only patients who could tolerate the two highest doses of tolvaptan (60 mg/30 mg or 90 mg/30 mg) for the subsequent 3 weeks were randomized 1:1 to treatment with tolvaptan or placebo.

Patients were maintained on their highest tolerated dose for a period of 12 months but could interrupt, decrease and/or increase as clinical circumstances warranted within the range of titrated doses. All patients were encouraged to start drinking an adequate amount of water at screening and continuing through the end of the trial to avoid thirst or dehydration.

A total of 1519 subjects were enrolled in the study. Of these, 1370 subjects successfully completed the pre-randomization period and were randomized and treated during the 12-month double-blind period. Because 57 subjects did not complete the off-treatment follow-up period, 1313 subjects were included in the primary efficacy analysis.

For subjects randomized, the baseline, average estimated glomerular filtration rate (eGFR) was 41 mL/min/1.73 m² (CKD-Epidemiology formula) and historical TKV, available in 318 (23%) of subjects, averaged 2026 mL. Approximately 5%, 75% and 20% had an eGFR 60 mL/min/1.73 m² or greater, between 30-59 mL/min/1.73 m², and between 25 and 29 mL/min/1.73 m², respectively. The subjects' mean age was 47 years, 50% were female, 92% were Caucasian, 4% Black or African-American and 3% were Asian, 93% had hypertension, and 87% of subjects were taking antihypertensive agents affecting the angiotensin converting enzyme or receptor. Of the 115 (8%) of subjects who had prior genetic tests, only 54 (47%) knew their results with 48 (89%) of these having PKD1 and 6 (11%) having PKD2 mutations.

In the randomized period, the change of eGFR from pretreatment baseline to post-treatment follow-up was -2.3 mL/min/1.73 m²/year with tolvaptan as compared with -3.6 mL/min/1.73 m²/year with placebo, corresponding to a treatment effect of 1.3 mL/min/1.73 m²/year assessed using a linear mixed effect model of annualized eGFR (CKD-EPI) showed a difference between treatment groups of 1.0 mL/min/ m²/year that was also statistically significant (p < 0.0001).

The efficacy profile was generally consistent across subgroups of interest for this indication; few Black or African-American patients were enrolled in the trial.

16 HOW SUPPLIED/STORAGE AND HANDLING**16.1 How Supplied**

JYNARQUE (tolvaptan) is supplied as non-scored, blue, shallow-convex, immediate release tablets, debossed with "OTSUKA" and the tablet strength (mg) on one side.

JYNARQUE (tolvaptan) 15 mg tablets are triangular, 30 mg tablets are round, 45 mg tablets are square, 60 mg tablets are rectangular, and 90 mg tablets are pentagonal.

JYNARQUE (tolvaptan) tablets are supplied as:

Morning and Afternoon Doses	NDC	
	7-Day Blister Card (Containing 14 Tablets)	28-Day Carton (4 Blister Cards Containing a Total of 56 Tablets)
45 mg and 15 mg	59148-087-07	59148-087-28
60 mg and 30 mg	59148-088-07	59148-088-28
90 mg and 30 mg	59148-089-07	59148-089-28

JYNARQUE™ (tolvaptan)**16.2 Storage and Handling**

Store at 20°C to 25°C (68°F to 77°F), excursions permitted between 15°C and 30°C (59°F to 86°F) [see USP controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

As part of patient counseling, healthcare providers must review the JYNARQUE Medication Guide with every patient [see *Medication Guide*].

Serious Liver Injury

Advise patients that blood testing is required before starting JYNARQUE, at 2 weeks and 4 weeks after initiation, then monthly during the first 18 months of therapy and every 3 months thereafter as a requirement to reduce the risk of serious liver injury [see *Boxed Warning and Warning and Precautions (5.1)*].

Advise patients to immediately stop taking JYNARQUE and notify their healthcare provider if they have symptoms or signs (e.g., abnormal transaminase elevations) of hepatic injury (such as fatigue, anorexia, nausea, right upper abdominal discomfort or tenderness, vomiting, fever, rash, pruritus, icterus, dark urine or jaundice) [see *Warning and Precautions (5.1)*].

JYNARQUE REMS Program

Advise patients that JYNARQUE is only available through a restricted program called the JYNARQUE REMS Program [see *Warning and Precautions (5.2)*]. Inform the patient of the following notable requirement:

- Patients must enroll in the program and comply with ongoing monitoring requirements [see *Warning and Precautions (5.1)*]

Advise patients that JYNARQUE is only available only through restricted distribution from certified specialty pharmacies participating in the JYNARQUE REMS program. Therefore, provide patients with the telephone number and web site for information on how to obtain the product [see *Warning and Precautions (5.2)*].

JYNARQUE™ (tolvaptan)**Hypertremia, Dehydration and Hypovolemia**

Advise patients to drink water to avoid thirst, throughout the day and night. Patients should stop taking JYNARQUE and notify their healthcare provider if they have symptoms or signs of sodium imbalance or dehydration (e.g., dizziness, fainting, weight loss, palpitations, confusion, weakness, gait instability) [see *Warning and Precautions (5.3)*]. Advise the patient that if they cannot drink enough water for any reason (no access to water, cannot sense thirst, unable to maintain hydration due to vomiting, diarrhea) they should stop taking JYNARQUE and inform their health care provider right away [see *Warning and Precautions (5.3)*].

Pregnancy

Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to inform their prescriber of a known or suspected pregnancy [see *Use in Specific Populations (8.1)*].

Lactation

Advise women not to breastfeed during treatment with JYNARQUE [see *Use in Specific Populations (8.2)*].

Manufactured by Otsuka Pharmaceutical Co., Ltd., Tokyo, 101-8535 Japan

Distributed and marketed by Otsuka America Pharmaceutical, Inc., Rockville, MD 20850 USA

JYNARQUE is a trademark of Otsuka Pharmaceutical Co., Ltd., Tokyo, 101-8535 Japan

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MEDICATION GUIDE
JYNARQUE™ (jin-AR-kew)
(tolvaptan)
Tablets

What is the most important information I should know about JYNARQUE?

JYNARQUE can cause serious side effects, including:

- **Serious liver problems.** JYNARQUE can cause serious liver problems that can lead to the need for a liver transplant or can lead to death. Stop taking JYNARQUE and call your healthcare provider right away if you get any of the following symptoms:
 - feeling tired
 - loss of appetite
 - nausea
 - right upper stomach (abdomen) pain or tenderness
 - vomiting
 - fever
 - rash
 - itching
 - yellowing of the skin and white part of the eye (jaundice)
 - dark urine

To help reduce your risk of liver problems, your healthcare provider will do a blood test to check your liver:

- **before you start taking JYNARQUE**
- **at 2 weeks and 4 weeks after you start treatment with JYNARQUE**
- **then monthly for 18 months during treatment with JYNARQUE**
- **and every 3 months from then on**

It is important to stay under the care of your healthcare provider during treatment with JYNARQUE.

Because of the risk of serious liver problems JYNARQUE is only available through a restricted distribution program called the JYNARQUE Risk Evaluation and Mitigation Strategy (REMS) Program.

- Before you start treatment with JYNARQUE, you must enroll in the JYNARQUE REMS Program. Talk to your healthcare provider about how to enroll in the program.
- JYNARQUE can only be dispensed by a certified pharmacy that participates in the JYNARQUE REMS Program. Your healthcare provider can give you information on how to find a certified pharmacy.

What is JYNARQUE?

JYNARQUE is a prescription medicine used to slow kidney function decline in adults who are at risk of rapidly progressing autosomal dominant polycystic kidney disease (ADPKD).

It is not known if JYNARQUE is safe and effective in children.

Do not take JYNARQUE if you:

- have a history of liver problems or have signs or symptoms of liver problems, excluding polycystic liver disease.
- cannot feel if you are thirsty or cannot replace fluids by drinking.
- have been told that the amount of sodium (salt) in your blood is too high or too low.
- are dehydrated.
- are allergic to tolvaptan or any of the ingredients in JYNARQUE. See the end of this Medication Guide for a complete list of ingredients in JYNARQUE.
- are unable to urinate.

JYNARQUE™ (tolvaptan)**Before taking JYNARQUE, tell your healthcare provider about all your medical conditions, including if you:**

- have a history of sodium levels that are too low.
- are pregnant or plan to become pregnant. It is not known if tolvaptan will harm your unborn baby. Tell your healthcare provider if you become pregnant or think that you may be pregnant.
- are breast-feeding or plan to breastfeed. It is not known if tolvaptan passes into your breast milk. Do not breastfeed during treatment with JYNARQUE. Talk to your healthcare provider about the best way to feed your baby during this time.

Tell your healthcare provider about all the medicines you take including prescription medicines, over-the-counter medicines, vitamins and herbal supplements.

- Taking JYNARQUE with certain medicines could cause you to have too much tolvaptan in your blood. JYNARQUE should not be taken with certain medications. Your healthcare provider can tell you if it is safe to take JYNARQUE with other medicines.
- Do not start taking a new medicine without talking to your healthcare provider.
- Keep a list of your medicines to show your healthcare provider and pharmacist.

How should I take JYNARQUE?

- Take JYNARQUE exactly as your healthcare provider tells you to.
- Take JYNARQUE orally two times each day. Take the first dose of JYNARQUE when you wake up and take the second dose 8 hours later.
- Be sure to drink enough water so that you will not get thirsty or become dehydrated.
- If you miss a dose of JYNARQUE, take the next dose at your regular time.
- If you take too much JYNARQUE, call your healthcare provider or go to the nearest hospital emergency room right away.

What should I avoid while taking JYNARQUE?

- Do not drink grapefruit juice during treatment with JYNARQUE. This could cause you to have too much tolvaptan in your blood.

What are the possible side effects of JYNARQUE?

JYNARQUE may cause serious side effects, including:

See “What is the most important information I should know about JYNARQUE?”

- **Too much sodium in your blood (hyponatremia) and loss of too much body fluid (dehydration).** In some cases, dehydration can lead to extreme loss of body fluid called hypovolemia. You should drink water when you are thirsty and throughout the day and night. Stop taking JYNARQUE and call your healthcare provider if you cannot drink enough water for any reason, such as not having access to water, or vomiting or diarrhea. Tell your healthcare provider if you get any of the following symptoms:
 - dizziness
 - fainting
 - weight loss
 - a change in the way your heart beats
 - feel confused or weak

The **most common side effects** of JYNARQUE include:

- thirst and drinking more fluid than normal
- making large amounts of urine, urinating often and urinating at night

These are not all the possible side effects of JYNARQUE. **Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.**

How should I store JYNARQUE?

JYNARQUE comes in a child-resistant package. Store JYNARQUE between 68°F to 77°F (20°C to 25°C).

Keep JYNARQUE and all medicines out of the reach of children.

JYNARQUE™ (tolvaptan)**General information about the safe and effective use of JYNARQUE.**

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use JYNARQUE for a condition for which it was not prescribed. Do not give JYNARQUE to other people, even if they have the same symptoms you have. It may harm them.

What are the ingredients in JYNARQUE?

Active ingredient: tolvaptan

Inactive ingredients: corn starch, hydroxypropyl cellulose, lactose monohydrate, low-substituted hydroxypropyl cellulose, magnesium stearate and microcrystalline cellulose, and FD&C Blue no. 2 Aluminum Lake as colorant.

Manufactured by Otsuka Pharmaceutical Co., Ltd., Tokyo, 101-8535 Japan

Distributed and marketed by Otsuka America Pharmaceutical, Inc., Rockville, MD 20850 USA

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For more information about JYNARQUE, go to www.JYNARQUEREMS.com or call 1-877-726-7220.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

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Issued: 04/2018

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use KEVZARA® safely and effectively. See full prescribing information for KEVZARA.

KEVZARA® (sarilumab) injection, for subcutaneous use

Initial U.S. Approval: 2017

WARNING: RISK OF SERIOUS INFECTIONS

See full prescribing information for complete boxed warning.

- Serious infections leading to hospitalization or death including bacterial, viral, invasive fungal, and other opportunistic infections have occurred in patients receiving KEVZARA. (5.1)
- If a serious infection develops, interrupt KEVZARA until the infection is controlled. (5.1)
- Cases of tuberculosis (TB) have been reported. Prior to starting KEVZARA, test for latent TB; if positive, start treatment for TB. (5.1)
- Closely monitor patients for signs and symptoms of infection during treatment with KEVZARA. (5.1)

INDICATIONS AND USAGE

KEVZARA® is an interleukin-6 (IL-6) receptor antagonist indicated for treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response or intolerance to one or more disease-modifying antirheumatic drugs (DMARDs). (1)

DOSAGE AND ADMINISTRATION

- KEVZARA may be used as monotherapy or in combination with methotrexate (MTX) or other conventional DMARDs. (2.1)
- The recommended dosage of KEVZARA is 200 mg once every two weeks, administered as a subcutaneous injection. (2.1)

General Considerations for Administration

- KEVZARA initiation is not recommended in patients with ANC less than 2000/mm³, platelets less than 150,000/mm³ or liver transaminases above 1.5 times ULN. (2.2)

Dosage Modifications

- Modify dosage to manage neutropenia, thrombocytopenia, and/or elevated liver transaminases. (2.1, 2.4)

DOSAGE FORMS AND STRENGTHS

Injection: 150 mg/1.14 mL or 200 mg/1.14 mL solution in a single-dose pre-filled syringe (3)
Injection: 150 mg/1.14 mL or 200 mg/1.14 mL solution in a single-dose pre-filled pen (3)

CONTRAINDICATIONS

KEVZARA is contraindicated in patients with known hypersensitivity to sarilumab or any of the inactive ingredients. (4)

WARNINGS AND PRECAUTIONS

- Serious Infections: Avoid KEVZARA use during an active infection. (5.1)
- Neutropenia, Thrombocytopenia, Elevated Liver Enzymes, Lipid Abnormalities: Monitor laboratory parameters. (5.2)
- Gastrointestinal (GI) Perforation: Risk may be increased with concurrent diverticulitis or concomitant use of NSAIDs or corticosteroids. Promptly evaluate acute abdominal signs or symptoms. (5.3)
- Hypersensitivity reactions. (5.5)
- Live vaccines: Avoid use with KEVZARA due to the risk of infection. Follow vaccination guidelines. (5.7, 7.3)

ADVERSE REACTIONS

Most common adverse reactions (incidence at least 3%) are neutropenia, increased ALT, injection site erythema, upper respiratory infections and urinary tract infections. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact sanofi-aventis at 1-800-633-1610 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

USE IN SPECIFIC POPULATIONS

- Lactation: Discontinue drug or nursing taking into consideration importance of drug to mother. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

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FULL PRESCRIBING INFORMATION

WARNING: RISK OF SERIOUS INFECTIONS

Patients treated with KEVZARA are at increased risk for developing serious infections that may lead to hospitalization or death [see *Warnings and Precautions* (5.1), *Adverse Reactions* (6.1)]. Opportunistic infections have also been reported in patients receiving KEVZARA. Most patients who developed infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids.

Avoid use of KEVZARA in patients with an active infection.

Reported infections include:

- Active tuberculosis, which may present with pulmonary or extrapulmonary disease. Patients should be tested for latent tuberculosis before KEVZARA use and during therapy. Treatment for latent infection should be initiated prior to KEVZARA use.
- Invasive fungal infections, such as candidiasis, and pneumocystis. Patients with invasive fungal infections may present with disseminated, rather than localized, disease.
- Bacterial, viral and other infections due to opportunistic pathogens.

Closely monitor patients for signs and symptoms of infection during treatment with KEVZARA. If a serious infection develops, interrupt KEVZARA until the infection is controlled.

Consider the risks and benefits of treatment with KEVZARA prior to initiating therapy in patients with chronic or recurrent infection.

1 INDICATIONS AND USAGE

KEVZARA[®] is indicated for treatment of adult patients with moderately to severely active rheumatoid arthritis (RA) who have had an inadequate response or intolerance to one or more disease-modifying antirheumatic drugs (DMARDs).

2 DOSAGE AND ADMINISTRATION**2.1 Recommended Dosage**

KEVZARA may be used as monotherapy or in combination with methotrexate (MTX) or other conventional DMARDs.

The recommended dosage of KEVZARA is 200 mg once every two weeks given as a subcutaneous injection.

Reduce dose to 150 mg once every two weeks for management of neutropenia, thrombocytopenia and elevated liver enzymes [see *Dosage and Administration* (2.4), *Warnings and Precautions* (5.2) and *Adverse Reactions* (6.1)].

2.2 General Considerations for Administration

- KEVZARA initiation is not recommended in patients with an absolute neutrophil count (ANC) less than 2000 per mm³, platelet count less than 150,000 per mm³, or who have ALT or AST above 1.5 times the upper limit of normal (ULN) [see *Dosage and Administration* (2.4) and *Warnings and Precautions* (5.2)].
- Prior to initiating KEVZARA, test patients for latent tuberculosis (TB). If positive, consider treating for TB prior to KEVZARA use [see *Warnings and Precautions* (5.1)].
- Avoid using KEVZARA with biological DMARDs because of the possibility of increased immunosuppression and increased risk of infection. The concurrent use of KEVZARA with biological DMARDs such as TNF antagonists, IL-1R antagonists, anti-CD20 monoclonal antibodies and selective co-stimulation modulators has not been studied.
- Avoid KEVZARA use in patients with active infections [see *Warnings and Precautions* (5.1)].

2.3 Important Administration Instructions

- KEVZARA is intended for use under the guidance of a healthcare professional. A patient may self-inject KEVZARA or the patient's caregiver may administer KEVZARA. Provide proper training to patients and/or caregivers on the preparation and administration of KEVZARA prior to use according to the Instructions for Use (IFU).
- Allow the pre-filled syringe to sit at room temperature for 30 minutes prior to subcutaneous injection. Do not warm KEVZARA in any other way.
- If using a pre-filled pen, allow the pre-filled pen to sit at room temperature for 60 minutes prior to subcutaneous injection. Do not warm KEVZARA in any other way.
- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. KEVZARA solution should be clear and colorless to pale yellow. Do not use if the solution is cloudy, discolored or contains particles, or if any part of the pre-filled syringe or pre-filled pen appears to be damaged.
- Instruct patients to inject the full amount in the syringe or pen (1.14 mL), which provides 200 mg or 150 mg of KEVZARA, according to the directions provided in the IFU.
- Rotate injection sites with each injection. Do not inject into skin that is tender, damaged, or has bruises or scars.

2.4 Dosage Modifications for Laboratory Abnormalities or Serious Infection

If a patient develops a serious infection, hold treatment with KEVZARA until the infection is controlled. Modify dosage in case of neutropenia, thrombocytopenia or liver enzyme elevations (see Table 1). For treatment initiation criteria, see *Dosage and Administration* (2.2).

Table 1: KEVZARA Dosage Modification for Neutropenia, Thrombocytopenia, or Elevated Liver Enzymes

Low Absolute Neutrophil Count (ANC) [see <i>Warnings and Precautions</i> (5.2) and <i>Clinical Pharmacology</i> (12.2)]	
Lab Value (cells/mm ³)	Recommendation
ANC greater than 1000	Maintain current dosage of KEVZARA.
ANC 500–1000	Hold treatment with KEVZARA until ANC greater than 1000. KEVZARA can then be resumed at 150 mg every two weeks and increased to 200 mg every two weeks as clinically appropriate.

Table 1: KEVZARA Dosage Modification for Neutropenia, Thrombocytopenia, or Elevated Liver Enzymes (continued)

ANC less than 500	Discontinue KEVZARA.
Low Platelet Count [see <i>Warnings and Precautions</i> (5.2)]	
Lab Value (cells/mm ³)	Recommendation
50,000–100,000	Hold treatment with KEVZARA until platelets greater than 100,000. KEVZARA can then be resumed at 150 mg every two weeks and increased to 200 mg every two weeks as clinically appropriate.
Less than 50,000	If confirmed by repeat testing, discontinue KEVZARA.
Liver Enzyme Abnormalities [see <i>Warnings and Precautions</i> (5.2)]	
Lab Value	Recommendation
ALT greater than ULN to 3 times ULN or less	Consider dosage modification of concomitant DMARDs as clinically appropriate.
ALT greater than 3 times ULN to 5 times ULN or less	Hold treatment with KEVZARA until ALT less than 3 times ULN. KEVZARA can then be resumed at 150 mg every two weeks and increased to 200 mg every two weeks as clinically appropriate.
ALT greater than 5 times ULN	Discontinue KEVZARA.

3 DOSAGE FORMS AND STRENGTHS

Injection: 150 mg/1.14 mL or 200 mg/1.14 mL colorless to pale-yellow solution in a single-dose pre-filled syringe.

Injection: 150 mg/1.14 mL or 200 mg/1.14 mL colorless to pale-yellow solution in a single-dose pre-filled pen.

4 CONTRAINDICATIONS

KEVZARA is contraindicated in patients with known hypersensitivity to sarilumab or any of the inactive ingredients [see *Warnings and Precautions* (5.5) and *Adverse Reactions* (6.1)].

5 WARNINGS AND PRECAUTIONS**5.1 Serious Infections**

Serious and sometimes fatal infections due to bacterial, mycobacterial, invasive fungal, viral, or other opportunistic pathogens have been reported in patients receiving immunosuppressive agents including KEVZARA for rheumatoid arthritis (RA). The most frequently observed serious infections with KEVZARA included pneumonia and cellulitis [see *Adverse Reactions* (6.1)]. Among opportunistic infections, tuberculosis, candidiasis, and pneumocystis were reported with KEVZARA. Some patients presented with disseminated rather than localized disease and were often taking concomitant immunosuppressants such as methotrexate or corticosteroids, which in addition to RA may predispose them to infections. While not reported in KEVZARA clinical studies, other serious infections (e.g., histoplasmosis, cryptococcus, aspergillosis) have been reported in patients receiving other immunosuppressive agents for the treatment of RA.

Avoid use of KEVZARA in patients with an active infection, including localized infections. Consider the risks and benefits of treatment prior to initiating KEVZARA in patients who have:

- chronic or recurrent infection;
- a history of serious or opportunistic infections;
- underlying conditions, in addition to RA, that may predispose them to infection;
- been exposed to tuberculosis; or
- lived in or traveled to areas of endemic tuberculosis or endemic mycoses.

Closely monitor patients for the development of signs and symptoms of infection during treatment with KEVZARA, as signs and symptoms of acute inflammation may be lessened due to suppression of the acute phase reactants [see *Dosage and Administration* (2.4), *Adverse Reactions* (6.1)].

Hold treatment with KEVZARA if a patient develops a serious infection or an opportunistic infection. Perform prompt and complete diagnostic testing appropriate for an immunocompromised patient who develops a new infection during treatment with KEVZARA; initiate appropriate antimicrobial therapy, and closely monitor the patient.

Tuberculosis

Evaluate patients for tuberculosis (TB) risk factors and test for latent infection prior to initiating treatment with KEVZARA. Treat patients with latent TB with standard antimycobacterial therapy before initiating KEVZARA. Consider anti-TB therapy prior to initiation of KEVZARA in patients with a past history of latent or active TB in whom an adequate course of treatment cannot be confirmed, and for patients with a negative test for latent TB but having risk factors for TB infection. When considering anti-TB therapy, consultation with a physician with expertise in TB may be appropriate.

Closely monitor patients for the development of signs and symptoms of TB including patients who tested negative for latent TB infection prior to initiating therapy.

Viral Reactivation

Viral reactivation has been reported with immunosuppressive biologic therapies. Cases of herpes zoster were observed in clinical studies with KEVZARA [see *Adverse Reactions* (6.1)]. The risk of Hepatitis B reactivation with KEVZARA is unknown since patients who were at risk for reactivation were excluded.

5.2 Laboratory Abnormalities**Neutropenia**

Treatment with KEVZARA was associated with a higher incidence of decrease in absolute neutrophil count (ANC), including neutropenia [see *Adverse Reactions* (6.1)].

- Assess neutrophil count prior to initiation of KEVZARA and monitor neutrophil count 4 to 8 weeks after start of therapy and every 3 months thereafter [see *Clinical Pharmacology* (12.2)]. For recommendations regarding initiating KEVZARA therapy and dosage modifications based on ANC results see *Dosage and Administration* (2.2 and 2.4).
- Based on the pharmacodynamics of the changes in ANC [see *Clinical Pharmacology* (12.2)], use results obtained at the end of the dosing interval when considering dose modification.

Thrombocytopenia

Treatment with KEVZARA was associated with a reduction in platelet counts in clinical studies [see *Adverse Reactions (6.1)*].

- Assess platelet count prior to initiation of KEVZARA and monitor platelets 4 to 8 weeks after start of therapy and every 3 months thereafter. For recommendations regarding initiating KEVZARA therapy and dosage modifications based on platelet counts see *Dosage and Administration (2.2 and 2.4)*.

Elevated Liver Enzymes

Treatment with KEVZARA was associated with a higher incidence of transaminase elevations. These elevations were transient and did not result in any clinically evident hepatic injury in clinical studies [see *Adverse Reactions (6.1)*]. Increased frequency and magnitude of these elevations were observed when potentially hepatotoxic drugs (e.g., MTX) were used in combination with KEVZARA.

- Assess ALT/AST levels prior to initiation of KEVZARA and monitor ALT and AST levels 4 to 8 weeks after start of therapy and every 3 months thereafter. When clinically indicated, consider other liver function tests such as bilirubin. For recommendations regarding initiating KEVZARA therapy and dosage modifications based on transaminase elevations see *Dosage and Administration (2.2 and 2.4)*.

Lipid Abnormalities

Treatment with KEVZARA was associated with increases in lipid parameters such as LDL cholesterol, HDL cholesterol and/or triglycerides [see *Adverse Reactions (6.1)*].

- Assess lipid parameters approximately 4 to 8 weeks following initiation of treatment with KEVZARA, then at approximately 6 month intervals.
- Manage patients according to clinical guidelines for the management of hyperlipidemia.

5.3 Gastrointestinal Perforation

Gastrointestinal perforations have been reported in clinical studies, primarily as complications of diverticulitis. GI perforation risk may be increased with concurrent diverticulitis or concomitant use of NSAIDs or corticosteroids. Promptly evaluate patients presenting with new onset abdominal symptoms [see *Adverse Reactions (6.1)*].

5.4 Immunosuppression

Treatment with immunosuppressants may result in an increased risk of malignancies. The impact of treatment with KEVZARA on the development of malignancies is not known but malignancies were reported in clinical studies [see *Adverse Reactions (6.1)*].

5.5 Hypersensitivity Reactions

Hypersensitivity reactions have been reported in association with KEVZARA [see *Adverse Reactions (6.1)*]. Hypersensitivity reactions that required treatment discontinuation were reported in 0.3% of patients in controlled RA trials. Injection site rash, rash, and urticaria were the most frequent hypersensitivity reactions. Advise patients to seek immediate medical attention if they experience any symptoms of a hypersensitivity reaction. If anaphylaxis or other hypersensitivity reaction occurs, stop administration of KEVZARA immediately. Do not administer KEVZARA to patients with known hypersensitivity to sarilumab [see *Contraindications (4)* and *Adverse Reactions (6.1)*].

5.6 Active Hepatic Disease and Hepatic Impairment

Treatment with KEVZARA is not recommended in patients with active hepatic disease or hepatic impairment, as treatment with KEVZARA was associated with transaminase elevations [see *Adverse Reactions (6.1)*, *Use in Specific Populations (8.6)*].

5.7 Live Vaccines

Avoid concurrent use of live vaccines during treatment with KEVZARA due to potentially increased risk of infections; clinical safety of live vaccines during KEVZARA treatment has not been established. No data are available on the secondary transmission of infection from persons receiving live vaccines to patients receiving KEVZARA. The interval between live vaccinations and initiation of KEVZARA therapy should be in accordance with current vaccination guidelines regarding immunosuppressive agents [see *Drug Interactions (7.3)*].

6 ADVERSE REACTIONS

The following serious adverse reactions are described elsewhere in labeling:

- Serious infections [see *Warnings and Precautions (5.1)*]
- Neutropenia, thrombocytopenia, elevated liver enzymes, lipid abnormalities [see *Warnings and Precautions (5.2)*]
- Gastrointestinal perforation [see *Warnings and Precautions (5.3)*]
- Immunosuppression [see *Warnings and Precautions (5.4)*]
- Hypersensitivity reactions [see *Warnings and Precautions (5.5)*]

6.1 Clinical Trials Experience

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

All patients in the safety data described below had moderately to severely active rheumatoid arthritis. The safety of KEVZARA in combination with conventional DMARDs was evaluated based on data from seven studies, of which two were placebo-controlled, consisting of 2887 patients (long-term safety population). Of these, 2170 patients received KEVZARA for at least 24 weeks, 1546 for at least 48 weeks, 1020 for at least 96 weeks, and 624 for at least 144 weeks.

The pre-rescue placebo-controlled population includes patients from the two Phase 3 efficacy studies (Studies 1 and 2) from weeks 0 to 16 for Study 1 and weeks 0 to 12 for Study 2, and was used to assess common adverse reactions and laboratory abnormalities prior to patients being permitted to switch from placebo to KEVZARA. In this population, 582 patients, 579 patients, and 579 patients received KEVZARA 200 mg, KEVZARA 150 mg, or placebo once every two weeks, respectively, in combination with conventional DMARDs.

The 52-week placebo-controlled population includes patients from one Phase 2 study of 12 week duration and two Phase 3 efficacy studies (one of 24 week duration and the other of 52 week duration). This placebo-controlled population includes all subjects from the double-blind, placebo-controlled periods from each study and was analyzed under their original randomization assignment. In this population, 661 patients, 660 patients, and 661 patients received KEVZARA 200 mg, KEVZARA 150 mg, or placebo once every two weeks, respectively, in combination with conventional DMARDs. Most safety data are described for the pre-rescue population. For rarer events, the 52-week placebo-controlled population is used.

The most common serious adverse reactions were infections [see *Warnings and Precautions (5.1)*]. The most frequent adverse reactions (occurring in at least 3% of patients treated with KEVZARA in combination with DMARDs) observed with KEVZARA in the clinical studies were neutropenia, increased ALT, injection site erythema, upper respiratory infections, and urinary tract infections.

In the pre-rescue placebo-controlled population, premature discontinuation due to adverse reactions occurred in 8%, 6% and 3% of patients treated with KEVZARA 200 mg, KEVZARA 150 mg, and placebo, respectively.

The most common adverse reaction (greater than 1%) that resulted in discontinuation of therapy with KEVZARA was neutropenia.

The use of KEVZARA as monotherapy was assessed in 132 patients, of which 67 received KEVZARA 200 mg and 65 patients received KEVZARA 150 mg without concomitant DMARDs. The safety profile was generally consistent with that in the population receiving concomitant DMARDs.

Overall Infections

In the pre-rescue placebo-controlled population, the rate of infections in the 200 mg and 150 mg KEVZARA + DMARD group was 110 and 105 events per 100 patient-years, respectively, compared to 81 events per 100 patient-years in the placebo + DMARD group. The most commonly reported infections (2% to 4% of patients) were upper respiratory tract infections, urinary tract infections, and nasopharyngitis.

In the 52-week placebo-controlled population, 0.8% of patients (5 patients) treated with KEVZARA 200 mg + DMARD, 0.6% (4 patients) treated with KEVZARA 150 mg + DMARD and 0.5% (3 patients) treated with placebo + DMARD had an event of herpes zoster [see *Warnings and Precautions (5.1)*]. The overall rate of infections with KEVZARA + DMARD in the long-term safety population was consistent with rates in the controlled periods of the studies.

Serious Infections

In the pre-rescue population, the rate of serious infections in the 200 mg and 150 mg KEVZARA + DMARD group was 3.8 and 4.4 events per 100 patient-years, respectively, compared to 2.5 events per 100 patient-years in the placebo + DMARD group. In the 52-week placebo-controlled population, the rate of serious infections in the 200 mg and 150 mg KEVZARA + DMARD group was 4.3 and 3.0 events per 100 patient-years, respectively, compared to 3.1 events per 100 patient-years in the placebo + DMARD group.

In the long-term safety population, the overall rate of serious infections was consistent with rates in the controlled periods of the studies. The most frequently observed serious infections included pneumonia and cellulitis. Cases of opportunistic infection have been reported [see *Warnings and Precautions (5.1)*].

Gastrointestinal Perforation

In the 52-week placebo-controlled population, one patient on KEVZARA therapy experienced a gastrointestinal (GI) perforation (0.11 events per 100 patient-years).

In the long-term safety population, the overall rate of GI perforation was consistent with rates in the controlled periods of the studies. Reports of GI perforation were primarily reported as complications of diverticulitis including lower GI perforation and abscess. Most patients who developed GI perforations were taking concomitant nonsteroidal anti-inflammatory medications (NSAIDs) or corticosteroids. The contribution of these concomitant medications relative to KEVZARA in the development of GI perforations is not known [see *Warnings and Precautions (5.3)*].

Hypersensitivity Reactions

In the pre-rescue placebo-controlled population, the proportion of patients who discontinued treatment due to hypersensitivity reactions was higher among those treated with KEVZARA (0.3% in 200 mg, 0.2% in 150 mg) than placebo (0%). The rate of discontinuations due to hypersensitivity in the long-term safety population was consistent with the placebo-controlled period.

Injection Site Reactions

In the pre-rescue placebo-controlled population, injection site reactions were reported in 7% of patients receiving KEVZARA 200 mg, 6% receiving KEVZARA 150 mg, and 1% receiving placebo. These injection site reactions (including erythema and pruritus) were mild in severity for the majority of patients and necessitated drug discontinuation in 2 (0.2%) patients receiving KEVZARA.

Laboratory Abnormalities

Decreased neutrophil count

In the pre-rescue placebo-controlled population, decreases in neutrophil counts less than 1000 per mm³ occurred in 6% and 4% of patients in the 200 mg KEVZARA + DMARD and 150 mg KEVZARA + DMARD group, respectively, compared to no patients in the placebo + DMARD groups. Decreases in neutrophil counts less than 500 per mm³ occurred in 0.7% of patients in both the 200 mg KEVZARA + DMARD and 150 mg KEVZARA + DMARD groups. Decrease in ANC was not associated with the occurrence of infections, including serious infections.

In the long-term safety population, the observations on neutrophil counts were consistent with what was seen in the placebo-controlled clinical studies [see *Warnings and Precautions (5.2)*].

Decreased platelet count

In the pre-rescue placebo-controlled population, decreases in platelet counts less than 100,000 per mm³ occurred in 1% and 0.7% of patients on 200 mg and 150 mg KEVZARA + DMARD, respectively, compared to no patients on placebo + DMARD, without associated bleeding events.

In the long-term safety population, the observations on platelet counts were consistent with what was seen in the placebo-controlled clinical studies [see *Warnings and Precautions (5.2)*].

Elevated liver enzymes

Liver enzyme elevations in the pre-rescue placebo-controlled population (KEVZARA + DMARD or placebo + DMARD) are summarized in Table 2. In patients experiencing liver enzyme elevation, modification of treatment regimen, such as interruption of KEVZARA or reduction in dose, resulted in decrease or normalization of liver enzymes [see *Dosage and Administration (2.4)*]. These elevations were not associated with clinically relevant increases in direct bilirubin, nor were they associated with clinical evidence of hepatitis or hepatic impairment [see *Warnings and Precautions (5.2)*].

Table 2: Incidence of Liver Enzyme Elevations in Adults with Moderately to Severely Active Rheumatoid Arthritis^a

	Placebo + DMARD N=579	KEVZARA 150 mg + DMARD N=579	KEVZARA 200 mg + DMARD N=582
AST			
Greater than ULN to 3 times ULN or less	15%	27%	30%
Greater than 3 times ULN to 5 times ULN	0%	1%	1%
Greater than 5 times ULN	0%	0.7%	0.2%

Table 2: Incidence of Liver Enzyme Elevations in Adults with Moderately to Severely Active Rheumatoid Arthritis[†] (continued)

	Placebo + DMARD N=579	KEVZARA 150 mg + DMARD N=579	KEVZARA 200 mg + DMARD N=582
ALT			
Greater than ULN to 3 times ULN or less	25%	38%	43%
Greater than 3 times ULN to 5 times ULN	1%	4%	3%
Greater than 5 times ULN	0%	1%	0.7%

ULN = Upper Limit of Normal

[†]Phase 3 placebo-controlled safety population through the pre-rescue period

Lipid Abnormalities

Lipid parameters (LDL, HDL, and triglycerides) were first assessed at 4 weeks following initiation of KEVZARA + DMARDs in the placebo-controlled population. Increases were observed at this time point with no additional increases observed thereafter. Changes in lipid parameters from baseline to Week 4 are summarized below:

- Mean LDL increased by 12 mg/dL in the KEVZARA 150 mg every two weeks + DMARD group and 16 mg/dL in the KEVZARA 200 mg every two weeks + DMARD group.
- Mean triglycerides increased by 20 mg/dL in the KEVZARA 150 mg every two weeks + DMARD group and 27 mg/dL in the KEVZARA 200 mg every two weeks + DMARD group.
- Mean HDL increased by 3 mg/dL in both the KEVZARA 150 mg every two weeks + DMARD and KEVZARA 200 mg every two weeks + DMARD groups.

In the long-term safety population, the observations in lipid parameters were consistent with what was observed in the placebo-controlled clinical studies.

Malignancies

In the 52-week placebo-controlled population, 9 malignancies (exposure-adjusted event rate of 1.0 event per 100 patient-years) were diagnosed in patients receiving KEVZARA + DMARD compared to 4 malignancies in patients in the control group (exposure-adjusted event rate of 1.0 event per 100 patient-years).

In the long-term safety population, the rate of malignancies was consistent with the rate observed in the placebo-controlled period [see *Warnings and Precautions* (5.4)].

Other Adverse Reactions

Adverse reactions occurring in 2% or more of patients on KEVZARA + DMARD and greater than those observed in patients on placebo + DMARD are summarized in Table 3.

Table 3: Common Adverse Reactions[†] in Adults with Moderately to Severely Active Rheumatoid Arthritis[†]

Preferred Term	Placebo + DMARD (N=579)	KEVZARA 150 mg + DMARD (N=579)	KEVZARA 200 mg + DMARD (N=582)
Neutropenia	0.2%	7%	10%
Alanine aminotransferase increased	2%	5%	5%
Injection site erythema	0.9%	5%	4%
Injection site pruritus	0.2%	2%	2%
Upper respiratory tract infection	2%	4%	3%
Urinary tract infection	2%	3%	3%
Hypertriglyceridemia	0.5%	3%	1%
Leukopenia	0%	0.9%	2%

[†]Adverse reactions occurring in 2% or more in the 150 mg KEVZARA + DMARD or 200 mg KEVZARA + DMARD groups and greater than observed in Placebo + DMARD

[†]Pre-rescue, placebo-controlled population

Medically relevant adverse reactions occurring at an incidence less than 2% in patients with rheumatoid arthritis treated with KEVZARA in controlled studies was oral herpes.

6.2 Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to sarilumab in the studies described below with the incidence of antibodies in other studies or to other products may be misleading.

In the pre-rescue population, 4.0% of patients treated with KEVZARA 200 mg + DMARD, 5.7% of patients treated with KEVZARA 150 mg + DMARD and 1.9% of patients treated with placebo + DMARD, exhibited an anti-drug antibody (ADA) response. Neutralizing antibodies (NAb) were detected in 1.0% of patients on KEVZARA 200 mg + DMARD, 1.6% of patients on KEVZARA 150 mg + DMARD, and 0.2% of patients on placebo + DMARD.

In patients treated with KEVZARA monotherapy, 9.2% of patients exhibited an ADA response with 6.9% of patients also exhibiting NABs. Prior to administration of KEVZARA, 2.3% of patients exhibited an ADA response.

No correlation was observed between ADA development and either loss of efficacy or adverse reactions.

7 DRUG INTERACTIONS

7.1 Use with Other Drugs for Treatment of Rheumatoid Arthritis

Population pharmacokinetic analyses did not detect any effect of methotrexate (MTX) on sarilumab clearance. KEVZARA has not been investigated in combination with JAK inhibitors or biological DMARDs such as TNF antagonists [see *Dosage and Administration* (2.2)].

7.2 Interactions with CYP450 Substrates

Various *in vitro* and limited *in vivo* human studies have shown that cytokines and cytokine modulators can influence the expression and activity of specific cytochrome P450 (CYP) enzymes and therefore have the potential to alter the pharmacokinetics of concomitantly administered drugs that are substrates of these enzymes. Elevated interleukin-6 (IL-6) concentration may down-regulate CYP activity such as in patients with RA and hence increase drug levels compared to subjects without RA. Blockade of IL-6 signaling by IL-6R α antagonists such as KEVZARA might reverse the inhibitory effect of IL-6 and restore CYP activity, leading to altered drug concentrations.

The modulation of IL-6 effect on CYP enzymes by KEVZARA may be clinically relevant for CYP substrates with a narrow therapeutic index, where the dose is individually adjusted. Upon initiation or discontinuation of KEVZARA, in patients being treated with CYP substrate medicinal products, perform therapeutic monitoring of effect (e.g., warfarin) or drug concentration (e.g., theophylline) and adjust the individual dose of the medicinal product as needed.

Exercise caution when coadministering KEVZARA with CYP3A4 substrate drugs where decrease in effectiveness is undesirable, e.g., oral contraceptives, lovastatin, atorvastatin, etc. The effect of KEVZARA on CYP450 enzyme activity may persist for several weeks after stopping therapy [see *Clinical Pharmacology* (12.3)].

7.3 Live Vaccines

Avoid concurrent use of live vaccines during treatment with KEVZARA [see *Warnings and Precautions* (5.7)].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to KEVZARA during pregnancy. Physicians are encouraged to register patients and pregnant women are encouraged to register themselves by calling 1-877-311-8972.

Risk Summary

The limited human data with KEVZARA in pregnant women are not sufficient to inform drug-associated risk for major birth defects and miscarriage. Monoclonal antibodies, such as sarilumab, are actively transported across the placenta during the third trimester of pregnancy and may affect immune response in the in utero exposed infant [see *Clinical Considerations*]. From animal data, and consistent with the mechanism of action, levels of IgG, in response to antigen challenge, may be reduced in the fetus/infant of treated mothers [see *Clinical Considerations and Data*]. In an animal reproduction study, consisting of a combined embryo-fetal and pre- and postnatal development study with monkeys that received intravenous administration of sarilumab, there was no evidence of embryotoxicity or fetal malformations with exposures up to approximately 84 times the maximum recommended human dose (MRHD) [see *Data*]. The literature suggests that inhibition of IL-6 signaling may interfere with cervical ripening and dilatation and myometrial contractile activity leading to potential delays of parturition [see *Data*].

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriages in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively. KEVZARA should be used in pregnancy only if the potential benefit justifies the potential risk to the fetus.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Monoclonal antibodies are increasingly transported across the placenta as pregnancy progresses, with the largest amount transferred during the third trimester. Risks and benefits should be considered prior to administering live or live-attenuated vaccines to infants exposed to KEVZARA in utero [see *Warnings and Precautions* (5.7)]. From the animal data, and consistent with the mechanism of action, levels of IgG, in response to antigen challenge, may be reduced in the fetus/infant of treated mothers [see *Data*].

Data

Animal Data

In a combined embryo-fetal and pre- and postnatal development study, pregnant cynomolgus monkeys received sarilumab at intravenous doses of 0, 5, 15, or 50 mg/kg/week from confirmation of pregnancy at gestation day (GD) 20, throughout the period of organogenesis (up to approximately GD 50), and continuing to natural birth of infants at around GD 165. Maintenance of pregnancy was not affected at any doses. Sarilumab was not embryotoxic or teratogenic with exposures up to approximately 84 times the MRHD (based on AUC with maternal intravenous doses up to 50 mg/kg/week). Sarilumab had no effect on neonatal growth and development evaluated up to one month after birth. Sarilumab was detected in the serum of neonates up to one month after birth, suggesting that the antibody had crossed the placenta.

Following antigen challenge, decreased IgG titers attributed to the immunosuppressive action of sarilumab were evident in studies with older monkeys, with exposures up to approximately 80 times the MRHD (based on AUC with intravenous doses up to 50 mg/kg/week) and juvenile mice treated with an analogous antibody, which binds to murine IL-6R α to inhibit IL-6 mediated signaling, at subcutaneous doses up to 200 mg/kg/week. These findings suggest the potential for decreased IgG titers, following antigen challenge, in infants of mothers treated with KEVZARA.

Parturition is associated with significant increases of IL-6 in the cervix and myometrium. The literature suggests that inhibition of IL-6 signaling may interfere with cervical ripening and dilatation and myometrial contractile activity leading to potential delays of parturition. For mice deficient in IL-6 (IL6^{-/-} null mice), parturition was delayed relative to wild-type (IL6^{+/+}) mice. Administration of recombinant IL-6 to IL6^{-/-} null mice restored the normal timing of delivery.

8.2 Lactation

Risk Summary

No information is available on the presence of sarilumab in human milk, the effects of the drug on the breastfed infant, or the effects of the drug on milk production. Maternal IgG is present in human milk. If sarilumab is transferred into human milk, the effects of local exposure in the gastrointestinal tract and potential limited systemic exposure in the infant to sarilumab are unknown. The lack of clinical data during lactation precludes clear determination of the risk of KEVZARA to an infant during lactation; therefore, the developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for KEVZARA and the potential adverse effects on the breastfed child from KEVZARA or from the underlying maternal condition.

8.4 Pediatric Use

Safety and efficacy of KEVZARA in pediatric patients have not been established.

8.5 Geriatric Use

Of the total number of patients in clinical studies of KEVZARA [see *Clinical Studies (14)*], 15% were 65 years of age and over, while 1.6% were 75 years and over. In clinical studies, no overall differences in safety and efficacy were observed between older and younger patients. The frequency of serious infection among KEVZARA and placebo-treated patients 65 years of age and older was higher than those under the age of 65. As there is a higher incidence of infections in the elderly population in general, caution should be used when treating the elderly.

8.6 Hepatic Impairment

The safety and efficacy of KEVZARA have not been studied in patients with hepatic impairment, including patients with positive HBV or HCV serology [see *Warnings and Precautions (5.6)*].

8.7 Renal Impairment

No dose adjustment is required in patients with mild to moderate renal impairment. KEVZARA has not been studied in patients with severe renal impairment [see *Clinical Pharmacology (12.3)*].

11 DESCRIPTION

Sarilumab is a human recombinant monoclonal antibody of the IgG1 subclass that binds to the IL-6 receptor and has an approximate molecular weight of 150 kDa. Sarilumab is produced by recombinant DNA technology in Chinese Hamster Ovary cell suspension culture.

KEVZARA (sarilumab) injection for subcutaneous administration is supplied as a sterile, colorless to pale yellow, preservative-free solution of approximately pH 6.0. KEVZARA is supplied in a single-dose pre-filled syringe or pre-filled pen. Each syringe or pen delivers 1.14 mL of solution containing 150 mg or 200 mg of sarilumab, arginine (8.94 mg), histidine (3.71 mg), polysorbate 20 (2.28 mg), sucrose (57 mg) and Water for Injection, USP.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Sarilumab binds to both soluble and membrane-bound IL-6 receptors (sIL-6R and mIL-6R), and has been shown to inhibit IL-6-mediated signaling through these receptors. IL-6 is a pleiotropic pro-inflammatory cytokine produced by a variety of cell types including T- and B-cells, lymphocytes, monocytes, and fibroblasts. IL-6 has been shown to be involved in diverse physiological processes such as T-cell activation, induction of immunoglobulin secretion, initiation of hepatic acute phase protein synthesis, and stimulation of hematopoietic precursor cell proliferation and differentiation. IL-6 is also produced by synovial and endothelial cells leading to local production of IL-6 in joints affected by inflammatory processes such as rheumatoid arthritis.

12.2 Pharmacodynamics

Following single-dose subcutaneous administration of sarilumab 200-mg and 150-mg in patients with RA, rapid reduction of CRP levels was observed. Levels were reduced to normal within 2 weeks after treatment initiation. Following single-dose sarilumab administration, in patients with RA, absolute neutrophil counts decreased to the nadir between 3 to 4 days and thereafter recovered towards baseline [see *Warnings and Precautions (5.2)*]. Treatment with sarilumab resulted in decreases in fibrinogen and serum amyloid A, and increases in hemoglobin and serum albumin.

12.3 Pharmacokinetics

Absorption

The pharmacokinetics of sarilumab were characterized in 1770 patients with rheumatoid arthritis (RA) treated with sarilumab which included 631 patients treated with 150 mg and 682 patients treated with 200 mg doses by subcutaneous injection every two weeks for up to 52 weeks. The median t_{max} was observed in 2 to 4 days.

At steady state, exposure over the dosing interval measured by area under curve (AUC) increased 2-fold with an increase in dose from 150 to 200 mg every two weeks. Steady state was reached in 14 to 16 weeks with a 2- to 3-fold accumulation compared to single dose exposure.

For the 150 mg every two weeks dose regimen, the estimated mean (\pm SD) steady-state AUC, C_{min} and C_{max} of sarilumab were 202 ± 120 mg.day/L, 6.35 ± 7.54 mg/L, and 20.0 ± 9.20 mg/L, respectively. For the 200 mg every two weeks dose regimen, the estimated mean (\pm SD) steady-state AUC, C_{min} and C_{max} of sarilumab were 395 ± 207 mg.day/L, 16.5 ± 14.1 mg/L, and 35.6 ± 15.2 mg/L, respectively.

Distribution

In patients with RA, the apparent volume of distribution at steady state was 7.3 L.

Elimination

Sarilumab is eliminated by parallel linear and non-linear pathways. At higher concentrations, the elimination is predominantly through the linear, non-saturable proteolytic pathway, while at lower concentrations, non-linear saturable target-mediated elimination predominates. The half-life of sarilumab is concentration-dependent. At 200 mg every 2 weeks, the concentration-dependent half-life is up to 10 days in patients with RA at steady state. At 150 mg every 2 weeks, the concentration-dependent half-life is up to 8 days in patients with RA at steady state.

After the last steady state dose of 150 mg and 200 mg sarilumab, the median times to non-detectable concentration are 28 and 43 days, respectively.

Population pharmacokinetic analyses in patients with RA revealed that there was a trend toward higher apparent clearance of sarilumab in the presence of anti-sarilumab antibodies.

Metabolism

The metabolic pathway of sarilumab has not been characterized. As a monoclonal antibody sarilumab is expected to be degraded into small peptides and amino acids via catabolic pathways in the same manner as endogenous IgG.

Excretion

Monoclonal antibodies, including sarilumab, are not eliminated via renal or hepatic pathways.

Specific Populations

Population pharmacokinetic analyses in adult patients with rheumatoid arthritis showed that age, gender and race did not meaningfully influence the pharmacokinetics of sarilumab. Although body weight influenced the pharmacokinetics of sarilumab, no dose adjustments are recommended for any of these demographics.

Hepatic impairment

No formal study of the effect of hepatic impairment on the pharmacokinetics of sarilumab was conducted.

Renal impairment

No formal study of the effect of renal impairment on the pharmacokinetics of sarilumab was conducted. Based on population pharmacokinetic analysis of data from 1770 patients with RA, including patients with mild (creatinine clearance (CL_{cr}): 60 to 90 mL/min; N=471 at baseline) or moderate (CL_{cr} : 30 to 60 mL/min; N=74 at baseline) renal impairment, CL_{cr} was correlated with sarilumab exposure. However, the effect of CL_{cr} on exposure is not sufficient to warrant a dose adjustment [see *Use in Specific Populations (8.7)*]. Patients with severe renal impairment were not studied.

Drug-Drug Interactions

CYP450 substrates

Simvastatin is a CYP3A4 and OATP1B1 substrate. In 17 patients with RA, one week following a single 200-mg subcutaneous administration of sarilumab, exposure of simvastatin and simvastatin acid decreased by 45% and 36%, respectively [see *Drug Interactions (7.2)*].

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No long-term animal studies have been performed to establish the carcinogenicity potential of sarilumab. Literature indicates that the IL-6 pathway can mediate anti-tumor responses by promoting increased immune cell surveillance of the tumor microenvironment. However, available published evidence also supports that IL-6 signaling through the IL-6 receptor may be involved in pathways that lead to tumorigenesis. The malignancy risk in humans from an antibody that disrupts signaling through the IL-6 receptor, such as sarilumab, is presently unknown.

Fertility and reproductive performance were unaffected in male and female mice treated with an analogous antibody, which binds to murine IL-6R α to inhibit IL-6 mediated signaling, at subcutaneous doses of 10, 25, and 100 mg/kg twice per week.

14 CLINICAL STUDIES

Design of Clinical Studies in Adults with Moderately to Severely Active RA

The efficacy and safety of KEVZARA were assessed in two randomized, double-blind, placebo-controlled multicenter studies (Study 1 and Study 2) in patients older than 18 years with moderately to severely active rheumatoid arthritis (RA) diagnosed according to American College of Rheumatology (ACR) criteria. Patients had at least 8 tender and 6 swollen joints at baseline.

Study 1 evaluated 1197 patients with moderately to severely active rheumatoid arthritis who had inadequate clinical response to methotrexate (MTX). Patients received subcutaneous KEVZARA 200 mg, KEVZARA 150 mg, or placebo every two weeks with concomitant MTX. After Week 16 in Study 1, patients with an inadequate response could have been rescued with KEVZARA 200 mg every two weeks.

Study 2 evaluated 546 patients with moderately to severely active rheumatoid arthritis who had an inadequate clinical response or were intolerant to one or more TNF- α antagonists. Patients received subcutaneous KEVZARA 200 mg, KEVZARA 150 mg, or placebo every two weeks with concomitant conventional DMARDs (MTX, sulfasalazine, leflunomide, and/or hydroxychloroquine). After Week 12 in Study 2, patients with an inadequate response could have been rescued with KEVZARA 200 mg every two weeks.

In Studies 1 and 2, the primary endpoint was the proportion of patients who achieved an ACR20 response at Week 24. Other key endpoints evaluated included change from baseline in HAQ-DI at Week 16 in Study 1 and at Week 12 in Study 2, and change from baseline in van der Heijde-modified Total Sharp Score (mTSS) at Week 52 in Study 1.

Clinical Response

The percentages of KEVZARA every two weeks + MTX/DMARD-treated patients achieving ACR20, ACR50 and ACR70 responses in Studies 1 and 2 are shown Table 4. In both studies, patients treated with either 200 mg or 150 mg of KEVZARA every two weeks + MTX/DMARD had higher ACR20, ACR50, and ACR70 response rates versus placebo + MTX/DMARD-treated patients at Week 24.

In Studies 1 and 2, a greater proportion of patients treated with KEVZARA 200 mg or 150 mg every two weeks plus MTX/DMARD achieved a low level of disease activity as measured by a Disease Activity Score 28-C-Reactive Protein (DAS28-CRP) <2.6 compared with placebo + MTX/DMARD at the end of the studies (Table 4). In Study 1, the proportion of patients achieving DAS28-CRP <2.6 who had at least 3 or more active joints at the end of Week 24 was 33.1%, 37.8% and 20%, in the KEVZARA 200 mg + MTX/DMARD arm, KEVZARA 150 mg + MTX/DMARD arm, and placebo arm respectively.

Table 4: Clinical Response in Placebo-Controlled Studies 1 and 2 in Adults with Moderately to Severely Active RA[†]

	Percentage of Patients					
	Study 1			Study 2		
	Placebo + MTX N=398	KEVZARA 150 mg + MTX N=400	KEVZARA 200 mg + MTX N=399	Placebo + DMARD (s) [†] N=181	KEVZARA 150 mg + DMARD (s) [†] N=181	KEVZARA 200 mg + DMARD (s) [†] N=184
ACR20						
Week 12	34.7%	54.0%	64.9%	37.6%	54.1%	62.5%
Difference from placebo, (95% CI) [‡]		19.4% (12.6%, 26.1%)	30.2% (23.6%, 36.8%)		16.6% (6.7%, 26.5%)	25.3% (15.7%, 34.8%)
Week 24[§]	33.4%	58.0%	66.4%	33.7%	55.8%	60.9%
Difference from placebo, (95% CI) [‡]		24.6% (18.0%, 31.3%)	33.0% (26.5%, 39.5%)		22.1% (12.6%, 31.6%)	27.4% (17.7%, 37.0%)
Week 52	31.7%	53.5%	58.6%			
Difference from placebo, (95% CI) [‡]		21.9% (15.2%, 28.5%)	27.0% (20.5%, 33.6%)	NA [¶]	NA [¶]	NA [¶]
ACR50						
Week 12	12.3%	26.5%	36.3%	13.3%	30.4%	33.2%
Difference from placebo, (95% CI) [‡]		14.2% (8.9%, 19.6%)	24.1% (18.4%, 29.8%)		17.1% (9.2%, 25.1%)	20.1% (12.0%, 28.3%)

Table 4: Clinical Response in Placebo-Controlled Studies 1 and 2 in Adults with Moderately to Severely Active RA (continued)

	Percentage of Patients					
	Study 1			Study 2		
	Placebo + MTX N=398	KEVZARA 150 mg + MTX N=400	KEVZARA 200 mg + MTX N=399	Placebo + DMARD (s) [†] N=181	KEVZARA 150 mg + DMARD (s) [†] N=181	KEVZARA 200 mg + DMARD (s) [†] N=184
Week 24	16.6%	37.0%	45.6%	18.2%	37.0%	40.8%
Difference from placebo, (95% CI) [‡]		20.4% (14.5%, 26.3%)	29.1% (23.0%, 35.1%)		18.8% (10.2%, 27.4%)	22.8% (14.0%, 31.6%)
Week 52	18.1%	40.0%	42.9%	NA [¶]	NA [¶]	NA [¶]
Difference from placebo, (95% CI) [‡]		21.9% (15.8%, 28.0%)	24.8% (18.7%, 30.9%)			
ACR70						
Week 12	4.0%	11.0%	17.5%	2.2%	13.8%	14.7%
Difference from placebo, (95% CI) [‡]		7.0% (3.4%, 10.6%)	13.5% (9.4%, 17.7%)		11.6% (6.2%, 17.0%)	12.5% (7.1%, 17.9%)
Week 24	7.3%	19.8%	24.8%	7.2%	19.9%	16.3%
Difference from placebo, (95% CI) [‡]		12.5% (7.8%, 17.1%)	17.5% (12.6%, 22.5%)		12.7% (6.1%, 19.3%)	9.2% (2.8%, 15.7%)
Week 52	9.0%	24.8%	26.8%	NA [¶]	NA [¶]	NA [¶]
Difference from placebo, (95% CI) [‡]		15.7% (10.6%, 20.8%)	17.8% (12.6%, 23.0%)			
Major clinical response[#]						
Responders	3.0%	12.8%	14.8%	NA [¶]	NA [¶]	NA [¶]
Difference from placebo, (95% CI) [‡]		9.7% (6.1%, 13.4%)	11.8% (7.9%, 15.6%)			
DAS28-CRP < 2.6[‡]						
Week 12						
Percentage of patients	4.8%	18.0%	23.1%	3.9%	17.1%	17.9%
Difference from placebo (95% CI) [‡]		13.3% (9.0%, 17.5%)	18.3% (13.7%, 23.0%)		13.3% (7.3%, 19.3%)	14.1% (8.0%, 20.3%)
Week 24						
Percentage of patients	10.1%	27.8%	34.1%	7.2%	24.9%	28.8%
Difference from placebo (95% CI) [‡]		17.7% (12.5%, 23.0%)	24.0% (18.5%, 29.5%)		17.7% (10.5%, 24.9%)	21.7% (14.3%, 29.1%)

*Patients who were rescued or discontinued were considered non-responders for the analyses included in this table. In Study 1, at week 52, 196, 270, and 270 patients remained on placebo, KEVZARA 150 mg, and KEVZARA 200 mg respectively.

†DMARDs in Study 2 included MTX, sulfasalazine, leflunomide, and/or hydroxychloroquine

‡Weighted estimate of the rate difference; CI=confidence interval

§Primary end point

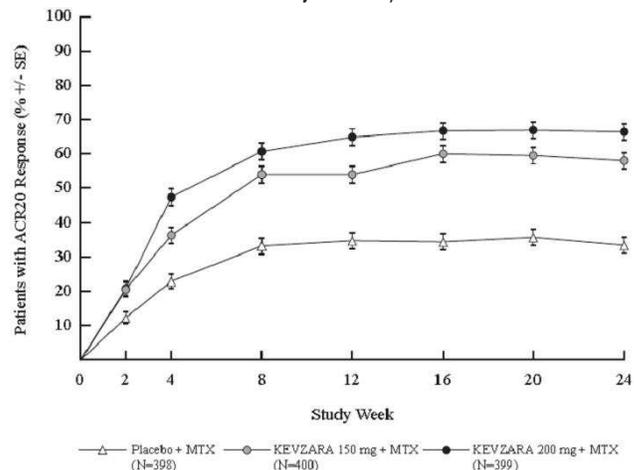
¶NA=Not Applicable as Study 2 was a 24-week study

#Major clinical response = ACR70 for at least 24 consecutive weeks during the 52-week period.

‡Patients with DAS28-CRP <2.6 may have active joints

The percent ACR20 response by visit in Study 1 is shown in Figure 1. A similar response curve was observed in Study 2.

Figure 1: Percent of ACR20 Response by Visit for Study 1 (Adults with Moderately to Severely Active RA)



The results of the components of the ACR response criteria at Week 12 for Studies 1 and 2 are shown in Table 5.

Table 5: Mean Change from Baseline in Components of ACR Score at Week 12 (Prior to Rescue) in Adults with Moderately to Severely Active RA

Component means (range/units)	Study 1			Study 2		
	Placebo + MTX (N=398)	KEVZARA 150 mg + MTX (N=400)	KEVZARA 200 mg + MTX (N=399)	Placebo + DMARD(s) (N=181)	KEVZARA 150 mg + DMARD(s) (N=181)	KEVZARA 200 mg + DMARD(s) (N=184)
Tender Joints (0-68)						
Baseline	26.80	27.21	26.50	29.42	27.66	29.55
Week 12	16.25	12.88	11.78	19.18	13.38	13.10
Change from baseline	-10.51	-14.42	-14.94	-9.79	-14.11	-15.92
Swollen Joints (0-66)						
Baseline	16.68	16.60	16.77	20.21	19.60	19.97
Week 12	9.66	7.50	6.79	12.50	8.82	8.28
Change from baseline	-7.02	-9.03	-10.12	-7.25	-10.77	-10.89
Pain VAS* (0-100 mm)						
Baseline	63.71	65.48	66.71	71.57	71.02	74.86
Week 12	49.25	41.47	36.93	54.77	43.45	41.66
Change from baseline	-14.45	-23.73	-29.77	-16.12	-27.95	-32.77
Physician global VAS* (0-100 mm)						
Baseline	62.86	63.43	63.59	68.39	68.10	67.76
Week 12	39.25	31.32	28.47	43.73	33.65	30.18
Change from baseline	-23.63	-31.85	-34.84	-24.60	-34.92	-36.92
Patient global VAS* (0-100 mm)						
Baseline	63.70	64.43	66.49	68.77	67.71	70.89
Week 12	49.37	41.52	38.05	53.67	41.99	41.74
Change from baseline	-13.92	-22.88	-28.39	-15.05	-26.05	-28.83
HAQ-DI (0-3)						
Baseline	1.61	1.63	1.69	1.80	1.72	1.82
Week 12	1.34	1.15	1.13	1.49	1.23	1.33

Table 5: Mean Change from Baseline in Components of ACR Score at Week 12 (Prior to Rescue) in Adults with Moderately to Severely Active RA (continued)

Component means (range/units)	Study 1			Study 2		
	Placebo + MTX (N=398)	KEVZARA 150 mg + MTX (N=400)	KEVZARA 200 mg + MTX (N=399)	Placebo + DMARD(s) (N=181)	KEVZARA 150 mg + DMARD(s) (N=181)	KEVZARA 200 mg + DMARD(s) (N=184)
Change from baseline	-0.27	-0.47	-0.57	-0.29	-0.50	-0.49
CRP (mg/L)						
Baseline	20.46	22.57	22.23	26.02	23.60	30.77
Week 12	19.61	9.24	3.30	21.72	9.21	4.58
Change from baseline	-0.58	-13.59	-18.31	-3.39	-14.24	-25.91

*VAS=visual analog scale

Radiographic Response

In Study 1, structural joint damage was assessed radiographically and expressed as the van der Heijde-modified Total Sharp Score (mTSS) and its components, the erosion score and joint space narrowing score. Radiographs of hands and feet were obtained at baseline, 24 weeks, and 52 weeks and scored independently by at least two well-trained readers who were blinded to treatment group and visit number.

Both doses of KEVZARA + MTX were superior to placebo + MTX in the change from baseline in mTSS over 52 weeks (see Table 6). Less progression of both erosion and joint space narrowing scores over 52 weeks was reported in the KEVZARA + MTX treatment groups compared to the placebo + MTX group.

Treatment with KEVZARA + MTX was associated with significantly less radiographic progression of structural damage as compared with placebo + MTX. At Week 52, 55.6% of patients receiving KEVZARA 200 mg + MTX and 47.8% of patients receiving KEVZARA 150 mg + MTX had no progression of structural damage (as defined by a change in the Total Sharp Score of zero or less) compared with 38.7% of patients receiving placebo.

Table 6: Mean Radiographic Change from Baseline at Week 52 in Study 1 in Adults with Moderately to Severely Active RA

	Study 1		
	Placebo + MTX (N=398)	KEVZARA 150 mg + MTX (N=400)	KEVZARA 200 mg + MTX (N=399)
Modified Total Sharp Score (mTSS)			
Mean change	2.78	0.90	0.25
LS [†] mean difference (95% CI [‡])		-1.88 (-2.74, -1.01)	-2.52 (-3.38, -1.66)
Erosion score			
Mean change	1.46	0.42	0.05
LS [†] mean difference (95% CI [‡])		-1.03 (-1.53, -0.53)	-1.40 (-1.90, -0.90)
Joint space narrowing score			
Mean change	1.32	0.47	0.20
LS [†] mean difference (95% CI [‡])		-0.85 (-1.34, -0.35)	-1.12 (-1.61, -0.63)

*Week 52 analysis employs linear extrapolation method to impute missing or post-rescue data

†LS=least squares

‡CI=confidence interval

Physical Function Response

In Studies 1 and 2, physical function and disability were assessed by the Health Assessment Questionnaire Disability Index (HAQ-DI). Patients receiving KEVZARA 200 mg every two weeks + MTX/DMARD and KEVZARA 150 mg every two weeks + MTX/DMARD demonstrated greater improvement from baseline in physical function compared to placebo + MTX/DMARD at Week 16 and Week 12 in Studies 1 and 2, respectively (Table 7).

Table 7: Physical function in Studies 1 and 2 in Adults with Moderately to Severely Active RA

	Study 1			Study 2		
	Week 16			Week 12		
	Placebo + MTX (N=398)	KEVZARA 150 mg + MTX (N=400)	KEVZARA 200 mg + MTX (N=399)	Placebo + DMARD(s) (N=181)	KEVZARA 150 mg + DMARD(s) (N=181)	KEVZARA 200 mg + DMARD(s) (N=184)
HAQ-DI						
Change from baseline	-0.30	-0.54	-0.58	-0.29	-0.50	-0.49
Difference from placebo (95% CI) [†]		-0.24 (-0.31, -0.16)	-0.26 (-0.34, -0.18)		-0.20 (-0.32, -0.09)	-0.21 (-0.33, -0.10)
% of patients with clinically meaningful improvement [†]	42.5%	53.8%	57.4%	35.9%	47%	51.1%

*Difference in adjusted mean change from baseline compared with placebo + DMARD at Week 16 (Study 1) or Week 12 (Study 2) and 95% confidence interval for that difference.

†Change from baseline greater than 0.3 units

Other Health Related Outcomes

General health status was assessed by the Short Form health survey (SF-36) in Studies 1 and 2. Patients receiving KEVZARA 200 mg every two weeks + MTX/DMARD demonstrated greater improvement from baseline compared to placebo + MTX/DMARD in the physical component summary (PCS) at Week 24, but there was no evidence of a difference between the treatment groups in the mental component summary (MCS) at Week 24. Patients receiving KEVZARA 200 mg + MTX/DMARD reported greater improvement relative to placebo in the domains of *Physical Functioning, Role Physical, Bodily Pain, General Health Perception, Vitality, Social Functioning and Mental Health, but not in the Role Emotional domain.*

16 HOW SUPPLIED/STORAGE AND HANDLING

KEVZARA (sarilumab) injection is supplied as a colorless to pale yellow solution in a single-dose pre-filled syringes and single-dose pre-filled pens.

Strength	Package Size	NDC Number
150 mg/1.14 mL	2 syringes per pack	0024-5908-01
200 mg/1.14 mL	2 syringes per pack	0024-5910-01

Strength	Package Size	NDC Number
150 mg/1.14 mL	2 pre-filled pens per pack	0024-5920-01
200 mg/1.14 mL	2 pre-filled pens per pack	0024-5922-01

Storage and Stability

Refrigerate at 36°F to 46°F (2°C to 8°C) in original carton to protect from light. Do not freeze. Do not shake.

If needed, patients/caregivers may store KEVZARA at room temperature up to 77°F (25°C) up to 14 days in the outer carton. Do not store above 77°F (25°C). After removal from the refrigerator, use KEVZARA within 14 days or discard.

17 PATIENT COUNSELING INFORMATION

Advise the patients to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

Infections

Inform patients that KEVZARA may lower their resistance to infections. Instruct patients to contact their physician immediately when symptoms suggesting infection appear, to ensure rapid evaluation and appropriate treatment [see *Warning and Precautions* (5.1)].

Gastrointestinal Perforation

Inform patients that some patients, particularly those also taking NSAIDs, and/or steroids, have had tears (perforations) of the stomach or intestines. Inform patients that gastrointestinal perforations have been reported in KEVZARA-treated patients in clinical studies, primarily as a complication of diverticulitis. Instruct patients to contact their physician immediately when symptoms of severe, persistent abdominal pain appear to ensure rapid evaluation and appropriate treatment.

Hypersensitivity and Serious Allergic Reaction

Assess patient suitability for home use for SC injection. Inform patients that some patients who have been treated with KEVZARA have developed serious allergic reactions. Advise patients to seek immediate medical attention if they experience any symptom of serious allergic reactions.

Pregnancy Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to KEVZARA during pregnancy. Encourage participation in the registry [see *Use in Specific Populations* (8.1)].

Instruction on Injection Technique

Instruct patients and caregivers to read the Instructions for Use before the patient starts using KEVZARA, and each time the patient gets a refill as there may be new information they need to know. Provide guidance to patients and caregivers on proper subcutaneous injection technique, including aseptic technique, and how to use the pre-filled syringe or pre-filled pen correctly [see *Instructions for Use*].

The pre-filled syringe or pre-filled pen should be left at room temperature for 30 minutes or 60 minutes respectively (see the Instructions for Use) prior to use. The syringe or pen should be used within 14 days after being taken out of the refrigerator. A puncture-resistant container should be used to dispose the used pre-filled syringes or pre-filled pens and should be kept out of the reach of children. Instruct patients or caregivers in the technique as well as proper pre-filled syringe or pre-filled pen disposal, and caution against reuse of these items.

**REGENERON
SANOFI GENZYME**

Manufactured by:
sanofi-aventis U.S. LLC
Bridgewater, NJ 08807
A SANOFI COMPANY
U.S. License # 1752

Marketed by:

sanofi-aventis U.S. LLC (Bridgewater, NJ 08807) and

Regeneron Pharmaceuticals, Inc. (Tarrytown, NY 10591)

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Issue Date: April 2018

**MEDICATION GUIDE
KEVZARA® (KEV-za-ra)
(sarilumab)
injection, for subcutaneous use**

What is the most important information I should know about KEVZARA?

KEVZARA can cause serious side effects including:

- 1. Serious Infections.** KEVZARA is a prescription medicine that affects your immune system. KEVZARA can lower the ability of your immune system to fight infections. Some people have serious infections while using KEVZARA, including tuberculosis (TB), and infections caused by bacteria, fungi, or viruses that can spread throughout the body. Some people have died from these infections.

Your healthcare provider should test you for TB before starting KEVZARA.

- Your healthcare provider should monitor you closely for signs and symptoms of TB during treatment with KEVZARA.

You should not start using KEVZARA if you have any kind of infection unless your healthcare provider says it is okay.

Before starting KEVZARA, tell your healthcare provider if you:

- think you have an infection or have symptoms of an infection, with or without a fever:
 - sweats or chills
 - muscle aches
 - cough
 - shortness of breath
 - blood in your phlegm
 - weight loss
 - warm, red or painful skin or sores on your body
 - diarrhea or stomach pain
 - burning when you urinate or urinating more often than normal
 - feeling very tired

- are being treated for an infection.
- get a lot of infections or have infections that keep coming back.
- have diabetes, HIV, or a weak immune system. People with these conditions have a higher chance of getting infections.
- have TB, or have been in close contact with someone with TB.
- live or have lived, or have traveled to certain parts of the country (such as the Ohio and Mississippi River valleys and the Southwest) where there is an increased chance of getting certain fungal infections (histoplasmosis, coccidioidomycosis, or blastomycosis). These infections may happen more often or become more severe if you use KEVZARA. Ask your healthcare provider if you do not know if you have lived in an area where these infections are common.
- have or have had hepatitis.

After starting KEVZARA, call your healthcare provider right away if you have any symptoms of an infection.

2. Changes in certain laboratory test results.

Your healthcare provider should do blood tests before you start KEVZARA, 4 to 8 weeks after starting KEVZARA, and then every 3 months during treatment to check for:

- low neutrophil count.** Neutrophils are white blood cells that help the body fight off bacterial infections. A low neutrophil count is common with KEVZARA, and can be severe.
- low platelet count.** Platelets are blood cells that help with blood clotting and stop bleeding.
- increase in certain liver function tests.** An increase in certain liver function tests is common with KEVZARA, and can be severe.

Your healthcare provider may not prescribe KEVZARA if your neutrophil or platelet counts are too low, or your liver function tests are too high. Your healthcare provider may stop your KEVZARA treatment for a period of time or change your dose if needed because of changes in these blood test results.

Your healthcare provider should do blood tests 4 to 8 weeks after starting KEVZARA and then every 6 months during treatment to check for an:

- increase in blood cholesterol levels.**

- 3. Tears (perforation) of the stomach or intestines.** Tell your healthcare provider if you have had a condition known as diverticulitis (inflammation in parts of the large intestine) or ulcers in your stomach or intestines. Some people using KEVZARA get tears in their stomach or intestine. This happens most often in people who also take nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, or methotrexate. Call your healthcare provider right away if you have fever and stomach (abdominal) pain that does not go away.

- 4. Cancer.** KEVZARA may increase your risk of certain cancers by changing the way your immune system works. Tell your healthcare provider if you have ever had any type of cancer.

See "What are the possible side effects with KEVZARA?" for more information about side effects.

What is KEVZARA?

KEVZARA is an injectable prescription medicine called an Interleukin-6 (IL-6) receptor blocker. KEVZARA is used to treat adults with moderately to severely active rheumatoid arthritis (RA) after at least one other medicine called a disease modifying antirheumatic drug (DMARD) has been used and did not work well or could not be tolerated.

It is not known if KEVZARA is safe and effective in children.

Who should not use KEVZARA?

Do not use KEVZARA if you are allergic to sarilumab or any of the ingredients in KEVZARA. See the end of this Medication Guide for a complete list of ingredients in KEVZARA.

Before using KEVZARA, talk to your healthcare provider about all of your medical conditions, including if you:

- have an infection. See **"What is the most important information I should know about KEVZARA?"**
- have liver problems.
- have had stomach (abdominal) pain or been diagnosed with diverticulitis or ulcers in your stomach or intestines.
- have recently received or are scheduled to receive a vaccine. People who take KEVZARA should not receive live vaccines.
- plan to have surgery or a medical procedure.
- are pregnant or plan to become pregnant. It is not known if KEVZARA will harm your unborn baby.

Pregnancy Registry: Sanofi has a registry for pregnant women who use KEVZARA. The purpose of this registry is to gather information about the health of the pregnant mother and her baby. If you are pregnant or become pregnant while using KEVZARA, talk to your healthcare provider about how you can join this pregnancy registry or call 1-877-311-8972 to enroll.

- are breastfeeding or plan to breastfeed. It is not known if KEVZARA passes into your breast milk. Talk to your healthcare provider about the best way to feed your baby if you use KEVZARA.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

Especially tell your healthcare provider if you use:

- any other medicines to treat your RA. You should not take rituximab (Rituxan[®]), etanercept (Enbrel[®]), infliximab (Remicade[®]), anakinra (Kineret[®]), adalimumab (Humira[®]), abatacept (Orencia[®]), certolizumab (Cimzia[®]), golimumab (Simponi[®]), tocilizumab (Actemra[®]), or tofacitinib (Xeljanz[®]) while you are using KEVZARA. Using KEVZARA with these medicines may increase your risk of infection.
- medicines that affect the way certain liver enzymes work. Ask your healthcare provider if you are not sure if your medicine is one of these.

Know the medicines you take. Keep a list of them to show to your healthcare provider and pharmacist when you get a new medicine.

How should I use KEVZARA?

- **See the detailed Instructions for Use that come with this Medication Guide for instructions about the right way to prepare and give your KEVZARA injections at home.**
- KEVZARA is given as an injection under the skin (subcutaneous injection).
- KEVZARA is available as a single-use pre-filled syringe or single-use pre-filled pen. Your healthcare provider will prescribe the dose and type of KEVZARA that is best for you.
- If your healthcare provider decides that you or a caregiver can give the injections of KEVZARA at home, you or your caregiver should receive training on the right way to prepare and inject KEVZARA. Do not try to inject KEVZARA until you have been shown the right way to give the injections by your healthcare provider.
- Inject 1 dose of KEVZARA every 2 weeks.

What are the possible side effects of KEVZARA?

KEVZARA can cause serious side effects, including:

- **See "What is the most important information I should know about KEVZARA?"**
- **Serious allergic reactions.** Serious allergic reactions can happen with KEVZARA. Get medical attention right away if you have any of the following signs of a serious allergic reaction:
 - shortness of breath or trouble breathing
 - swelling of the lips, tongue, or face
 - chest pain
 - feeling dizzy or faint
 - moderate or severe stomach (abdominal) pain or vomiting

Common side effects of KEVZARA include:

- injection site redness
- upper respiratory tract infection
- urinary tract infection
- nasal congestion, sore throat, and runny nose

These are not all of the possible side effects of KEVZARA.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

You may also report side effects to sanofi-aventis at 1-800-633-1610.

How should I store KEVZARA?

- Store KEVZARA in the refrigerator at 36°F to 46°F (2°C to 8°C). Store KEVZARA in the original carton until use to protect it from light.
- **Do not** freeze KEVZARA.
- **Do not** shake KEVZARA.
- KEVZARA may be stored at room temperature up to 77°F (25°C) for up to **14** days in the original outer carton.
- Throw away KEVZARA if it has been kept at room temperature and not been used within **14** days.

Keep KEVZARA and all medicines out of the reach of children.

General Information about the safe and effective use of KEVZARA.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use KEVZARA for a condition for which it was not prescribed. Do not give KEVZARA to other people, even if they have the same symptoms you have. It may harm them.

You can ask your healthcare provider or pharmacist for information about KEVZARA that was written for health professionals.

What are the ingredients in KEVZARA?

Active Ingredient: sarilumab

Inactive Ingredients: arginine, histidine, polysorbate 20, sucrose, and Water for Injection, USP.

REGENERON

SANOFI GENZYME

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For more information, go to www.KEVZARA.com or call 1-844-KEVZARA (1-844-538-9272).

This Medication Guide has been approved by the U.S. Food and Drug Administration
Revised: April 2018

SAI-FPLR-SL-APR18a

Rx Only

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use RADICAVA safely and effectively. See full prescribing information for RADICAVA.

RADICAVA (edaravone injection), for intravenous use
Initial U.S. Approval: 2017

----- **INDICATIONS AND USAGE** -----

RADICAVA is indicated for the treatment of amyotrophic lateral sclerosis (ALS) (1)

----- **DOSAGE AND ADMINISTRATION** -----

The recommended dosage is 60 mg administered as an intravenous infusion over 60 minutes as follows:

- Initial treatment cycle: daily dosing for 14 days followed by a 14-day drug-free period
- Subsequent treatment cycles: daily dosing for 10 days out of 14-day periods, followed by 14-day drug-free periods. (2)

----- **DOSAGE FORMS AND STRENGTHS** -----

Injection: 30 mg/100 mL in a single-dose polypropylene bag (3)

----- **CONTRAINDICATIONS** -----

Patients with a history of hypersensitivity to edaravone or any of the inactive ingredients in RADICAVA (4)

----- **WARNINGS AND PRECAUTIONS** -----

- Hypersensitivity Reactions: Advise patients to seek immediate medical care (5.1)
- Sulfite Allergic Reactions: RADICAVA contains sodium bisulfite, which may cause allergic type reactions (5.2)

----- **ADVERSE REACTIONS** -----

Most common adverse reactions (at least 10% and greater than placebo) are contusion, gait disturbance, and headache (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact MT Pharma America, Inc. at 1-888-292-0058 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----- **USE IN SPECIFIC POPULATIONS** -----

- Pregnancy: Based on animal data, may cause fetal harm. (8.1)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 5/2017

FULL PRESCRIBING INFORMATION: CONTENTS*

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

RADICAVA is indicated for the treatment of amyotrophic lateral sclerosis (ALS).

2 DOSAGE AND ADMINISTRATION

2.1 Dosage Information

The recommended dosage of RADICAVA is an intravenous infusion of 60 mg administered over a 60-minute period according to the following schedule:

- An initial treatment cycle with daily dosing for 14 days, followed by a 14-day drug-free period
- Subsequent treatment cycles with daily dosing for 10 days out of 14-day periods, followed by 14-day drug-free periods.

2.2 Preparation and Administration Information

RADICAVA is for intravenous infusion only.

Preparation

Do not use if the oxygen indicator has turned blue or purple before opening the package [*see How Supplied/Storage and Handling (16.1, 16.2)*]. Once the overwrap package is opened, use within 24 hours [*see Storage and Handling (16.2)*].

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Administration

Administer each 60 mg dose of RADICAVA injection as two consecutive 30 mg intravenous infusion bags over a total of 60 minutes (infusion rate approximately 1 mg per minute [3.33 mL per minute]).

Promptly discontinue the infusion upon the first observation of any signs or symptoms consistent with a hypersensitivity reaction [*see Warnings and Precautions (5.1, 5.2)*].

Other medications should not be injected into the infusion bag or mixed with RADICAVA.

3 DOSAGE FORMS AND STRENGTHS

RADICAVA is supplied for intravenous infusion in a single-dose polypropylene bag containing 30 mg of edaravone in 100 mL of clear, colorless aqueous solution.

4 CONTRAINDICATIONS

RADICAVA is contraindicated in patients with a history of hypersensitivity to edaravone or any of the inactive ingredients of this product. Hypersensitivity reactions and anaphylactic reactions have occurred [*see Warnings and Precautions (5.1, 5.2)*].

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity Reactions

Hypersensitivity reactions (redness, wheals, and erythema multiforme) and cases of anaphylaxis (urticaria, decreased blood pressure, and dyspnea) have been reported in spontaneous postmarketing reports with RADICAVA.

Patients should be monitored carefully for hypersensitivity reactions. If hypersensitivity reactions occur, discontinue RADICAVA, treat per standard of care, and monitor until the condition resolves [*see Contraindications (4)*].

5.2 Sulfite Allergic Reactions

RADICAVA contains sodium bisulfite, a sulfite that may cause allergic type reactions, including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in susceptible people. The overall prevalence

of sulfite sensitivity in the general population is unknown. Sulfite sensitivity occurs more frequently in asthmatic people.

6 ADVERSE REACTIONS

The following serious adverse reactions are described elsewhere in the labeling:

- Hypersensitivity Reactions [see [Warnings and Precautions \(5.1\)](#)]
- Sulfite Allergic Reactions [see [Warnings and Precautions \(5.2\)](#)]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In randomized, placebo-controlled trials, 184 ALS patients were administered RADICAVA 60 mg in treatment cycles for 6 months. The population consisted of Japanese patients who had a median age of 60 years (range 29-75) and were 59% male. Most (93%) of these patients were living independently at the time of screening.

Most Common Adverse Reactions Observed During Clinical Studies

Table 1 lists the adverse reactions that occurred in $\geq 2\%$ of patients in the RADICAVA-treated group and that occurred at least 2% more frequently than in the placebo-treated group in randomized placebo-controlled ALS trials. The most common adverse reactions that occurred in $\geq 10\%$ of RADICAVA-treated patients were contusion, gait disturbance, and headache.

Table 1: Adverse Reactions from Pooled Placebo-Controlled Trials^a that Occurred in $\geq 2\%$ of RADICAVA-Treated Patients and $\geq 2\%$ More Frequently than in Placebo Patients

Adverse Reaction	RADICAVA ^b (N=184) %	Placebo (N=184) %
Contusion	15	9
Gait disturbance	13	9
Headache	10	6
Dermatitis	8	5
Eczema	7	4
Respiratory failure, respiratory disorder, hypoxia	6	4
Glycosuria	4	2
Tinea infection	4	2

^a Pooled placebo-controlled studies include two additional studies with 231 additional patients, all using the same treatment regimen [see *Clinical Studies (14)*].

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of RADICAVA outside of the United States. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Skin and subcutaneous tissue disorders: Hypersensitivity reactions and anaphylaxis.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no adequate data on the developmental risk associated with the use of RADICAVA in pregnant women. In animal studies, administration of edaravone to pregnant rats and rabbits resulted in adverse developmental effects (increased mortality, decreased growth, delayed sexual development, and altered behavior) at clinically relevant doses. Most of these effects occurred at doses that were also associated with maternal toxicity (*see Animal Data*).

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively. The background risk for major birth defects and miscarriage in patients with ALS is unknown.

Data

Animal Data

In rats, intravenous administration of edaravone (0, 3, 30, or 300 mg/kg/day) throughout the period of organogenesis resulted in reduced fetal weight at all doses. In dams allowed to deliver naturally, offspring weight was reduced at the highest dose tested. Maternal toxicity was also observed at the highest dose tested. There were no adverse effects on reproductive function in the offspring. A no-effect dose for embryofetal developmental toxicity was not identified; the low dose is less than the recommended human dose of 60 mg, on a body surface area (mg/m²) basis.

In rabbits, intravenous administration of edaravone (0, 3, 20, or 100 mg/kg/day) throughout the period of organogenesis resulted in embryofetal death at the highest dose tested, which was associated with maternal toxicity. The higher no-effect dose for embryofetal developmental toxicity is approximately 6 times the recommended human dose (RHD) on a body surface area (mg/m²) basis.

The effects on offspring of edaravone (0, 3, 20, or 200 mg/kg/day), administered by intravenous injection to rats from GD 17 throughout lactation, were assessed in two studies. In the first study, offspring mortality was observed at the high dose and increased activity was observed at the mid and high doses. In the second study, there was an increase in stillbirths, offspring mortality, and delayed physical development (vaginal opening) at the highest dose tested. Reproduction function in offspring was not affected in either study. Maternal toxicity was evident in both studies at all but the lowest dose tested. The no-effect dose for developmental toxicity (3 mg/kg/day) is less than the RHD on a mg/m² basis.

8.2 Lactation

Risk Summary

There are no data on the presence of edaravone in human milk, the effects on the breastfed infant, or the effects of the drug on milk production. Edaravone and its metabolites are excreted in the milk of lactating rats. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for RADICAVA and any potential adverse effects on the breastfed infant from RADICAVA or from the underlying maternal condition.

8.4 Pediatric Use

Safety and effectiveness of RADICAVA in pediatric patients have not been established.

8.5 Geriatric Use

Of the 184 patients with ALS who received RADICAVA in 3 placebo-controlled clinical trials, a total of 53 patients were 65 years of age and older, including 2 patients 75 years of age and older. No overall differences in safety or effectiveness were observed between these patients and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

8.6 Renal Impairment

The effect of renal impairment on the pharmacokinetics of RADICAVA has not been studied. However, renal impairment is not expected to significantly affect the exposure to edaravone. No dose adjustment is needed in these patients.

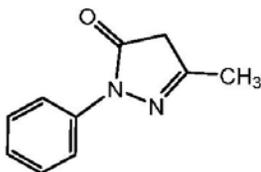
8.7 Hepatic Impairment

The effect of hepatic impairment on the pharmacokinetics of RADICAVA has not been studied. No dose adjustment is needed for patients with mild or moderate hepatic impairment. No specific dosing recommendation can be provided for patients with severe hepatic impairment.

11 DESCRIPTION

The active ingredient in RADICAVA is edaravone, which is a member of the substituted 2-pyrazolin-5-one class. The chemical name of edaravone is [3-methyl-1-phenyl-2-pyrazolin-5-one]. The molecular formula is $C_{10}H_{10}N_2O$ and the molecular weight is 174.20.

The chemical structure is:



Edaravone is a white crystalline powder with a melting point of 129.7°C. It is freely soluble in acetic acid, methanol, or ethanol and slightly soluble in water or diethyl ether.

RADICAVA injection is a clear, colorless liquid provided as a sterile solution.

RADICAVA injection is supplied for intravenous infusion in a polypropylene bag containing 30 mg edaravone in 100 mL isotonic, sterile, aqueous solution, which is further overwrapped with polyvinyl alcohol (PVA) secondary packaging. The overwrapped package also contains an oxygen absorber and oxygen indicator to minimize oxidation. Each bag contains the following inactive ingredients: L-cysteine hydrochloride hydrate (10 mg), sodium bisulfite (20 mg). Sodium chloride is added for isotonicity and phosphoric acid and sodium hydroxide are added to adjust to pH 4.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The mechanism by which RADICAVA exerts its therapeutic effect in patients with ALS is unknown.

12.3 Pharmacokinetics

RADICAVA is administered by IV infusion. The maximum plasma concentration (C_{max}) of edaravone was reached by the end of infusion. There was a trend of more than dose-proportional increase in area under the concentration-time curve (AUC) and C_{max} of edaravone. With multiple-dose administration, edaravone does not accumulate in plasma.

Distribution

Edaravone is bound to human serum proteins (92%), mainly to albumin, with no concentration dependence in the range of 0.1 to 50 micromol/L.

Elimination

The mean terminal elimination half-life of edaravone is 4.5 to 6 hours. The half-lives of its metabolites are 2 to 2.8 hours.

Metabolism

Edaravone is metabolized to a sulfate conjugate and a glucuronide conjugate, which are not pharmacologically active. The glucuronide conjugation of edaravone involves multiple uridine diphosphate glucuronosyltransferase (UGT) isoforms (UGT1A6, UGT1A9, UGT2B7, and UGT2B17) in the liver and kidney. In human plasma, edaravone is mainly detected as the sulfate conjugate, which is presumed to be formed by sulfotransferases.

Excretion

In Japanese and Caucasian healthy volunteer studies, edaravone was excreted mainly in the urine as its glucuronide conjugate form (70-90% of the dose). Approximately 5-10% of the dose was recovered in the urine as sulfate conjugate, and only 1% of the dose or less was recovered in the urine as unchanged form. *In vitro* studies suggest that sulfate conjugate of edaravone is hydrolyzed back to edaravone, which is then converted to the glucuronide conjugate in the human kidney before excretion into the urine.

Specific Populations

Geriatric Patients

No age effect on edaravone pharmacokinetics has been found [*see Use in Specific Populations (8.5)*].

Patients with Renal and Hepatic Impairment

No pharmacokinetic data are available in patients with renal impairment or hepatic impairment [see *Use in Specific Populations* (8.6, 8.7)].

Male and Female Patients

No gender effect on edaravone pharmacokinetics has been found.

Racial or Ethnic Groups

There were no significant racial differences in C_{max} and AUC of edaravone between Japanese and Caucasian subjects.

Drug Interaction Studies

The pharmacokinetics of edaravone is not expected to be significantly affected by inhibitors of CYP enzymes, UGTs, or major transporters.

In vitro studies demonstrated that, at clinical dose, edaravone and its metabolites are not expected to significantly inhibit cytochrome P450 enzymes (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A4), UGT1A1, UGT2B7, or transporters (P-gp, BCRP, OATP1B1, OATP1B3, OAT1, OAT3, and OCT2) in humans. Edaravone and its metabolites are not expected to induce CYP1A2, CYP2B6, or CYP3A4 at the clinical dose level of RADICAVA.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

The carcinogenic potential of edaravone has not been adequately assessed.

Mutagenesis

Edaravone was negative in *in vitro* (bacterial reverse mutation and Chinese hamster lung chromosomal aberration) and *in vivo* (mouse micronucleus) assays.

Impairment of Fertility

Intravenous administration of edaravone (0, 3, 20, or 200 mg/kg) prior to and throughout mating in males and females and continuing in females to gestation day 7 had no effect on fertility; however, disruption of the estrus cycle and mating behavior was observed at the highest dose tested. No effects on reproductive function were observed at the lower doses, which are up to 3 times the RHD of 60 mg, on a body surface area (mg/m²) basis.

14 CLINICAL STUDIES

The efficacy of RADICAVA for the treatment of ALS was established in a 6-month, randomized, placebo-controlled, double-blind study conducted in Japanese patients with ALS who were living independently and met the following criteria at screening:

1. Functionality retained most activities of daily living (defined as scores of 2 points or better on each individual item of the ALS Functional Rating Scale – Revised [ALSFERS-R; described below])
2. Normal respiratory function (defined as percent-predicted forced vital capacity values of [%FVC] \geq 80%)
3. Definite or Probable ALS based on El Escorial revised criteria
4. Disease duration of 2 years or less

The study enrolled 69 patients in the RADICAVA arm and 68 in the placebo arm. Baseline characteristics were similar between these groups, with over 90% of patients in each group being treated with riluzole.

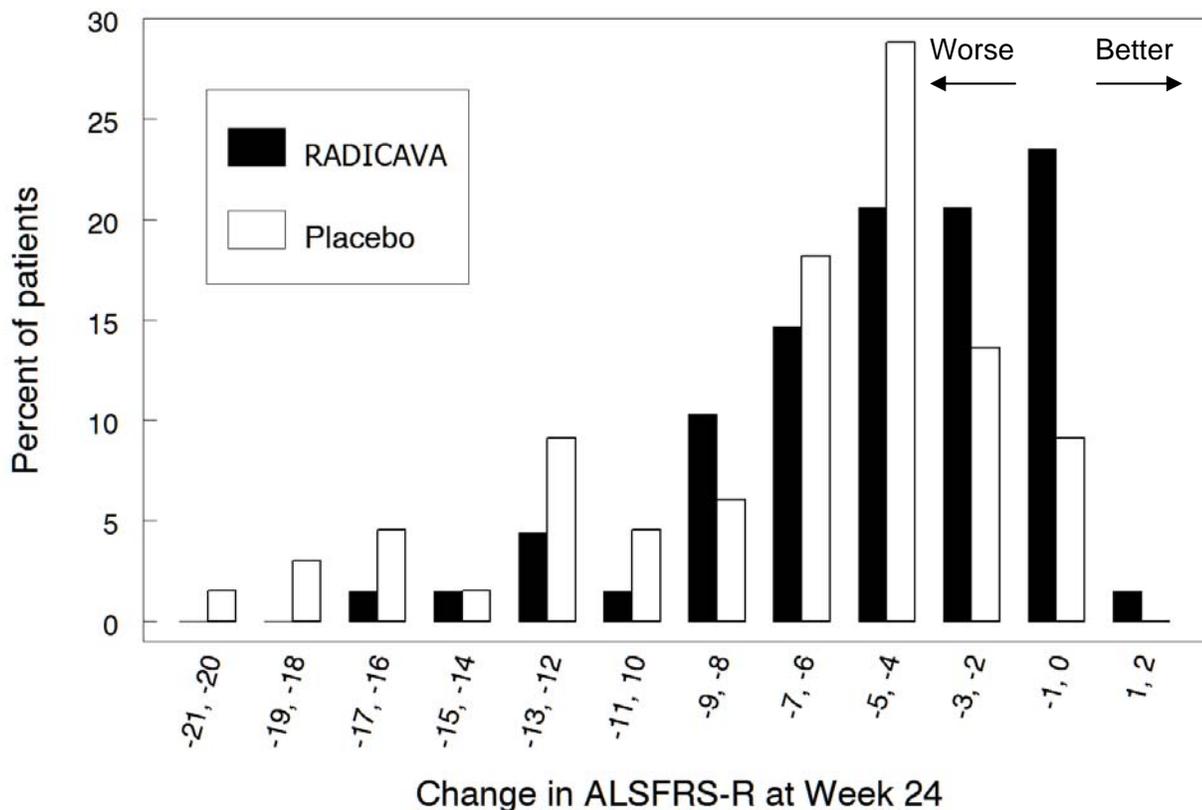
RADICAVA was administered as an intravenous infusion of 60 mg given over a 60 minute period according to the following schedule:

- An initial treatment cycle with daily dosing for 14 days, followed by a 14-day drug-free period (Cycle 1)
- Subsequent treatment cycles with daily dosing for 10 days out of 14-day periods, followed by 14-day drug-free periods (Cycles 2-6).

The primary efficacy endpoint was a comparison of the change between treatment arms in the ALSFRS-R total scores from baseline to Week 24. The ALSFRS-R scale consists of 12 questions that evaluate the fine motor, gross motor, bulbar, and respiratory function of patients with ALS (speech, salivation, swallowing, handwriting, cutting food, dressing/hygiene, turning in bed, walking, climbing stairs, dyspnea, orthopnea, and respiratory insufficiency). Each item is scored from 0-4, with higher scores representing greater functional ability. The decline in ALSFRS-R scores from baseline was significantly less in the RADICAVA-treated patients as compared to placebo (see Table 3). The distribution of change in ALSFRS-R scores from baseline to Week 24 by percent of patients is shown in Figure 1.

Table 3: Analysis of Change from Baseline to Week 24 in ALSFRS-R Scores

Treatment		Change from Baseline LS Mean \pm SE (95% CI)	Treatment Difference (RADICAVA – placebo [95% CI])	<i>p</i> - value
RADICAVA 60mg		-5.01 \pm 0.64	2.49 (0.99, 3.98)	0.0013
Placebo		-7.50 \pm 0.66		

Figure 1: Distribution of Change from Baseline to Week 24 in ALSFRS-R Scores

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

RADICAVA injection is supplied as a 30 mg/100 mL (0.3 mg/mL) clear, colorless, sterile solution for intravenous infusion in single-dose polypropylene bags, each overwrapped with polyvinyl alcohol (PVA) secondary packaging containing an oxygen absorber and oxygen indicator, which should be pink to reflect appropriate oxygen levels [see *Dosage and Administration* (2.2) and *How Supplied/Storage and Handling* (16.2)]. These are supplied in cartons as listed below.

NDC 70510-2171-1 30 mg/100 mL (0.3 mg/mL) single-dose bag

NDC 70510-2171-2 2 bags per carton

16.2 Storage and Handling

Store at up to 25°C (77°F). Excursions permitted from 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Protect from light. Store in overwrapped package to protect from oxygen degradation until time of use. The oxygen indicator will turn blue or purple if the oxygen has exceeded acceptable levels. Once the overwrap package is opened, use within 24 hours.

17 PATIENT COUNSELING INFORMATION

Advise the patients to read the FDA-approved patient labeling (Patient Information).

Hypersensitivity Reactions

Advise patients to seek immediate medical care if they experience signs or symptoms of a hypersensitivity reaction [*see Warnings and Precautions (5.1)*].

Sulfite Allergic Reactions

Advise patients about potential for sulfite sensitivity. Inform patients that RADICAVA contains sodium bisulfite, which may cause allergic type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes, and to seek immediate medical care if they experience these signs or symptoms [*see Warnings and Precautions (5.2)*].

Pregnancy and Breastfeeding

Advise patients to notify their healthcare provider if they become pregnant or intend to become pregnant during RADICAVA therapy [*see [Use in Specific Populations \(8.1\)](#)*].

Advise patients to notify their healthcare provider if they intend breastfeed or are breastfeeding an infant [*see [Use in Specific Populations \(8.2\)](#)*].

Marketed and distributed by:

MT Pharma America, Inc., a US subsidiary of Mitsubishi Tanabe Pharma Corporation
525 Washington Blvd., Suite 400,
Jersey City, NJ 07310

RADICAVA is a trademark of Mitsubishi Tanabe Pharma Corporation

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XXXXXXX [XX/X(month/year)]

Iss. 05/17

PATIENT INFORMATION
RADICAVA (phonetic spelling)
(edaravone injection)
for intravenous infusion

What is RADICAVA?

RADICAVA is a prescription medicine used to treat people with Amyotrophic Lateral Sclerosis (ALS). It is not known if RADICAVA is safe and effective in children.

Do not receive RADICAVA if you are allergic to edaravone or any of the ingredients in RADICAVA. See the end of this leaflet for a complete list of ingredients in RADICAVA.

Before you receive RADICAVA, tell your healthcare provider about all of your medical conditions, including if you:

- have asthma.
- are allergic to other medicines.
- are pregnant or plan to become pregnant. It is not known if RADICAVA will harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if RADICAVA passes into your breastmilk. You and your healthcare provider should decide if you will receive RADICAVA or breastfeed.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

How will I receive RADICAVA?

- You will be prescribed RADICAVA by a healthcare provider. RADICAVA will be given by intravenous (IV) infusion into your vein.
- It takes about 1 hour to receive the full dose of RADICAVA.
- Your healthcare provider will tell you how often you will receive RADICAVA.
- Your healthcare provider will monitor you closely during your treatment with RADICAVA.

What are the possible side effects of RADICAVA?

RADICAVA may cause serious side effects including:

1. Hypersensitivity (allergic) reactions. Hypersensitivity reactions have happened in people receiving RADICAVA and can happen after your infusion is finished. Tell you healthcare provider right away or go to the nearest emergency room if you have any of the following symptoms:

- | | | |
|----------------------|--------------------------------------|------------|
| • hives | • swelling of the lips, tongue, face | • fainting |
| • breathing problems | • dizziness | |
| • itching | • wheezing | |

2. Sulfite allergic reactions. RADICAVA contains sodium bisulfite, a sulfite that may cause a type of allergic reaction that can be serious and life-threatening. Sodium bisulfite can also cause less severe allergic reactions, for example, asthma episodes, in certain people. Sulfite sensitivity can happen more often in people who have asthma than in people who do not have asthma. Tell you healthcare provider right away or go to the nearest emergency room if you have any of the following symptoms:

- | | | |
|-----------------------------------|---|------------|
| • hives | • swelling of the lips, tongue, face | • wheezing |
| • trouble breathing or swallowing | • dizziness | • fainting |
| • itching | • asthma attack (in people with asthma) | |

Your healthcare provider will monitor you during treatment to watch for signs and symptoms of all the serious side effects.

The most common side effects of RADICAVA include bruising (contusion), problems walking (gait disturbance), and headache.

These are not all the possible side effects of RADICAVA. Call your healthcare provider for medical advice about side effects.

You may report side effects to MT Pharma America, Inc. at 1-888-292-0058 or FDA at 1-800-FDA-1088 or

www.fda.gov/medwatch.

What are the ingredients in RADICAVA?

Active ingredient: edaravone

Inactive ingredients: L-cysteine hydrochloride hydrate, sodium bisulfite, sodium chloride, phosphoric acid and sodium hydroxide.

Marketed and distributed by: MT Pharma America, Inc., a US subsidiary of Mitsubishi Tanabe Pharma Corporation, 525 Washington Blvd., Suite 400, Jersey City, NJ 07310

For more information, go to www.Radicava.com or call 1-888-292-0058.

This Patient Information or Medication Guide has been approved by the U.S. Food and Drug Administration

Revised or Issued: 05/2017

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use MYLOTARG safely and effectively. See full prescribing information for MYLOTARG.

MYLOTARG™ (gemtuzumab ozogamicin) for injection, for intravenous use

Initial U.S. Approval: 2000

WARNING: HEPATOTOXICITY

See full prescribing information for complete boxed warning.

Hepatotoxicity, including severe or fatal hepatic veno-occlusive disease (VOD), also known as sinusoidal obstruction syndrome (SOS), has been reported in association with the use of MYLOTARG. (5.1, 6.1)

RECENT MAJOR CHANGES

Dosage and Administration, Recommended Dosage (2.2)	4/2018
Dosage and Administration, Instructions for Reconstitution, Dilution, and Administration (2.4)	4/2018

INDICATIONS AND USAGE

MYLOTARG is a CD33-directed antibody-drug conjugate indicated for:

- treatment of newly-diagnosed CD33-positive acute myeloid leukemia (AML) in adults (1.1).
- treatment of relapsed or refractory CD33-positive AML in adults and in pediatric patients 2 years and older (1.2).

DOSAGE AND ADMINISTRATION

- Newly-diagnosed, de novo AML (combination regimen):
 - *Induction*: 3 mg/m² (up to one 4.5 mg vial) on Days 1, 4, and 7 in combination with daunorubicin and cytarabine (2.2).
 - *Consolidation*: 3 mg/m² on Day 1 (up to one 4.5 mg vial) in combination with daunorubicin and cytarabine. (2.2).
- Newly-diagnosed AML (single-agent regimen):
 - *Induction*: 6 mg/m² (not limited to one 4.5 mg vial) on Day 1 and 3 mg/m² (not limited to one 4.5 mg vial) on Day 8 (2.2).
 - *Continuation*: For patients without evidence of disease progression following induction, up to 8 continuation courses of MYLOTARG 2 mg/m² (not limited to one 4.5 mg vial) on Day 1 every 4 weeks (2.2).
- Relapsed or refractory AML (single-agent regimen):
 - 3 mg/m² (up to one 4.5 mg vial) on Days 1, 4, and 7 (2.2).

FULL PRESCRIBING INFORMATION: CONTENTS***WARNING: HEPATOTOXICITY****1 INDICATIONS AND USAGE**

- 1.1 CD33-positive Acute Myeloid Leukemia (AML)
- 1.2 Relapsed or Refractory CD33-positive AML

2 DOSAGE AND ADMINISTRATION

- 2.1 Premedication and Special Considerations
- 2.2 Recommended Dosage
- 2.3 Dose Modifications for Toxicities
- 2.4 Instructions for Reconstitution, Dilution, and Administration

3 DOSAGE FORMS AND STRENGTHS**4 CONTRAINDICATIONS****5 WARNINGS AND PRECAUTIONS**

- 5.1 Hepatotoxicity, Including Veno-occlusive Liver Disease (VOD)
- 5.2 Infusion Related Reactions (Including Anaphylaxis)
- 5.3 Hemorrhage
- 5.4 QT Interval Prolongation
- 5.5 Use in AML with Adverse-Risk Cytogenetics
- 5.6 Embryo-Fetal Toxicity

6 ADVERSE REACTIONS

- 6.1 Clinical Trials Experience
- 6.2 Postmarketing Experience
- 6.3 Immunogenicity

- Premedicate with a corticosteroid, antihistamine, and acetaminophen 1 hour prior to MYLOTARG (2.1).

DOSAGE FORMS AND STRENGTHS

For Injection: 4.5 mg as a lyophilized cake or powder in a single-dose vial for reconstitution and dilution (3).

CONTRAINDICATIONS

Hypersensitivity to MYLOTARG or any of its components (4).

WARNINGS AND PRECAUTIONS

- Infusion related reactions (including anaphylaxis): Premedicate with a corticosteroid, acetaminophen, and diphenhydramine. Monitor patients during and for at least 1 hour after the end of the infusion. Interrupt the infusion, administer steroids or antihistamines, or permanently discontinue treatment as necessary (2.1, 5.2, and 6).
- Hemorrhage: Severe, including fatal, hemorrhage may occur when MYLOTARG is used at recommended doses. Monitor platelet counts frequently (5.3 and 6.1).
- Embryo-fetal toxicity: Can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and use of effective contraception (5.6, 8.1, and 8.3).

ADVERSE REACTIONS

The most common adverse reactions (greater than 15%) were hemorrhage, infection, fever, nausea, vomiting, constipation, headache, increased AST, increased ALT, rash, and mucositis (6).

To report SUSPECTED ADVERSE REACTIONS, contact Pfizer Inc at 1-800-438-1985 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

USE IN SPECIFIC POPULATIONS

Lactation: Advise not to breastfeed (8.2).

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 4/2018

8 USE IN SPECIFIC POPULATIONS

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- 8.2 Lactation
- 8.3 Females and Males of Reproductive Potential
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- 12.1 Mechanism of Action
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13 NONCLINICAL TOXICOLOGY

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14 CLINICAL STUDIES

- 14.1 Newly-Diagnosed CD33-positive AML
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15 REFERENCES**16 HOW SUPPLIED/STORAGE AND HANDLING**

- 16.1 Storage and Handling

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*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: HEPATOTOXICITY

Hepatotoxicity, including severe or fatal hepatic veno-occlusive disease (VOD), also known as sinusoidal obstruction syndrome (SOS), has been reported in association with the use of MYLOTARG as a single agent, and as part of a combination chemotherapy regimen. Monitor frequently for signs and symptoms of VOD after treatment with MYLOTARG. (5.1 and 6.1)

1 INDICATIONS AND USAGE

1.1 Newly-Diagnosed CD33-positive Acute Myeloid Leukemia (AML)

MYLOTARG is indicated for the treatment of newly-diagnosed CD33-positive acute myeloid leukemia in adults.

1.2 Relapsed or Refractory CD33-positive AML

MYLOTARG is indicated for the treatment of relapsed or refractory CD33-positive acute myeloid leukemia in adults and in pediatric patients 2 years and older.

2 DOSAGE AND ADMINISTRATION

2.1 Premedication and Special Considerations

- Premedicate adults with acetaminophen 650 mg orally and diphenhydramine 50 mg orally or intravenously 1 hour prior to MYLOTARG dosing and 1 mg/kg methylprednisolone or an equivalent dose of an alternative corticosteroid within 30 minutes prior to infusion of MYLOTARG. Premedicate children with acetaminophen 15 mg/kg (maximum of 650 mg), diphenhydramine 1 mg/kg (maximum of 50 mg), and 1 mg/kg methylprednisolone orally or intravenously; additional doses of acetaminophen and diphenhydramine may be administered every 4 hours after the initial pretreatment dose. Repeat with the same dose of methylprednisolone or an equivalent corticosteroid for any sign of an infusion reaction, such as fever, chills, hypotension, or dyspnea during the infusion or within 4 hours afterwards [*see Warnings and Precautions (5.2)*].
- Use appropriate measures to prevent tumor lysis syndrome.
- For patients with hyperleukocytosis (leukocyte count greater than or equal to 30 Gi/L), cytoreduction is recommended prior to administration of MYLOTARG.

2.2 Recommended Dosage

Newly-Diagnosed De Novo CD33-positive AML (combination regimen)

A treatment course including MYLOTARG in combination therapy for adults with newly-diagnosed de novo CD33-positive AML consists of 1 induction cycle and 2 consolidation cycles [*see Clinical Studies (14.1)*].

For the induction cycle, the recommended dose of MYLOTARG is 3 mg/m² (up to one 4.5 mg vial) on Days 1, 4, and 7 in combination with daunorubicin and cytarabine. For patients requiring a second induction cycle, do NOT administer MYLOTARG during the second induction cycle.

For the consolidation cycles, the recommended dose of MYLOTARG is 3 mg/m² on Day 1 (up to one 4.5 mg vial) in combination with daunorubicin and cytarabine.

Newly-Diagnosed CD33-positive AML (single-agent regimen)

A treatment course of MYLOTARG as a single agent for adults with newly-diagnosed CD33-positive AML consists of 1 cycle of induction and up to 8 cycles of continuation therapy [see *Clinical Studies (14.1)*].

For the induction cycle, the recommended dose of MYLOTARG is 6 mg/m² (not limited to one 4.5 mg vial) as a single agent on Day 1, and 3 mg/m² (not limited to one 4.5 mg vial) on Day 8.

For continuation, the recommended dose of MYLOTARG is 2 mg/m² (not limited to one 4.5 mg vial) as a single agent on Day 1 every 4 weeks.

Relapsed or Refractory CD33-positive AML (single-agent regimen)

The recommended dose of MYLOTARG as a single agent for treatment of relapsed or refractory CD33-positive AML is 3 mg/m² (up to one 4.5 mg vial) on Days 1, 4, and 7. Treatment in the relapsed or refractory setting consists of a single course of MYLOTARG [see *Clinical Studies (14.1)*].

2.3 Dosage Modifications for Toxicities

Monitor blood counts frequently through resolution of cytopenias. Monitor blood counts and chemistries at least three times per week through recovery from treatment-related toxicities. Management of some adverse reactions [see *Warnings and Precautions (5)* and *Adverse Reactions (6)*] may require dose interruptions or permanent discontinuation of MYLOTARG Table 1 shows the dose modification guidelines for hematologic and nonhematologic toxicities.

Table 1. Dosage Modifications for Hematologic and Nonhematologic Toxicities

Hematologic and Nonhematologic Toxicities	Recommended Action
For patients receiving MYLOTARG in combination therapy	
Persistent thrombocytopenia	<ul style="list-style-type: none"> If platelet count does not recover to greater than or equal to 100 Gi/L within 14 days following the planned start date of the consolidation cycle (14 days after hematologic recovery following previous cycle), discontinue MYLOTARG (do not administer MYLOTARG in the consolidation cycles).
Persistent neutropenia	<ul style="list-style-type: none"> If neutrophil count does not recover to greater than 0.5 Gi/L within 14 days following the planned start date of the consolidation cycle (14 days after hematologic recovery following previous cycle), discontinue MYLOTARG (do not administer MYLOTARG in the consolidation cycles).
For all patients receiving MYLOTARG (Monotherapy or in Combination)	
VOD	<ul style="list-style-type: none"> Discontinue MYLOTARG [see <i>Warnings and Precautions (5.1)</i>].
Total bilirubin greater than 2 × ULN, or AST and/or ALT greater than 2.5 × ULN	<ul style="list-style-type: none"> Delay treatment with MYLOTARG until recovery of total bilirubin to less than or equal to 2 × ULN and AST and ALT to less than or equal to 2.5 × ULN prior to each dose.

Table 1. Dosage Modifications for Hematologic and Nonhematologic Toxicities

Hematologic and Nonhematologic Toxicities	Recommended Action
	<ul style="list-style-type: none"> • Omit scheduled dose if delayed more than 2 days between sequential infusions.
Infusion-related reactions	<ul style="list-style-type: none"> • Interrupt the infusion and institute appropriate medical management. • Administer acetaminophen, diphenhydramine and/or methylprednisolone, if needed (see Section 2.1) • Provide supportive care measures as needed. • For mild, moderate or severe infusion related reactions, once symptoms resolve, consider resuming the infusion at no more than half the rate at which the reaction occurred. Repeat the procedure above in the event of recurrence of symptoms. • Permanently discontinue MYLOTARG upon occurrence of a severe infusion reaction or for any life-threatening infusion reaction [see <i>Warnings and Precautions (5.2)</i>].
Other severe or life-threatening non-hematologic toxicities	<ul style="list-style-type: none"> • Delay treatment with MYLOTARG until recovery to a severity of no more than mild. • Omit scheduled dose if delayed more than 2 days between sequential infusions.

Abbreviations: ALT=alanine aminotransferase; AST=aspartate aminotransferase; VOD=veno-occlusive disease; ULN=upper limit of normal.

2.4 Instructions for Reconstitution, Dilution, and Administration

Use appropriate aseptic technique for the reconstitution and dilution procedures. Protect the reconstituted and diluted MYLOTARG solution from light.

Reconstitution

- MYLOTARG is a cytotoxic drug. Follow applicable special handling and disposal procedures.¹
- Calculate the dose (mg) and number of vials of MYLOTARG required.
- Prior to reconstitution, allow drug product vials to reach ambient temperature for approximately 5 minutes.
- Reconstitute each vial with 5 mL of Sterile Water for Injection, USP to obtain a concentration of 1 mg/mL of MYLOTARG that delivers 4.5 mL (4.5 mg).
- Gently swirl the vial to aid dissolution. **DO NOT SHAKE.**
- Inspect the reconstituted solution for particulates and discoloration. The reconstituted solution may contain small white to off-white, opaque to translucent, and amorphous to fiber-like particles.
- MYLOTARG contains no bacteriostatic preservatives.
- Use reconstituted solution immediately or after being refrigerated at 2-8°C (36-46°F) for up to 1 hour. **PROTECT FROM LIGHT. DO NOT FREEZE.**

Dilution

- Calculate the required volume of the reconstituted solution needed to obtain the appropriate dose according to patient body surface area. Withdraw this amount from the vial(s) using a syringe. **PROTECT FROM LIGHT.** Discard any unused reconstituted solution left in the vial.

Doses must be mixed to a concentration between 0.075 mg/mL to 0.234 mg/mL according to the following instructions:

- Doses less than 3.9 mg must be prepared for administration by syringe. Add the reconstituted MYLOTARG solution to a syringe with 0.9% Sodium Chloride Injection to a final concentration between 0.075 mg/mL to 0.234 mg/mL. PROTECT FROM LIGHT.
- Doses greater than or equal to 3.9 mg are to be diluted in a syringe or an IV bag in an appropriate volume of 0.9% Sodium Chloride Injection to ensure a final concentration between 0.075 mg/mL to 0.234 mg/mL. PROTECT FROM LIGHT.
- Gently invert the infusion container to mix the diluted solution. DO NOT SHAKE.
- Following dilution with 0.9% Sodium Chloride Injection, MYLOTARG solution should be infused immediately. If not used immediately, store at room temperature (15-25°C; 59-77°F) for up to 6 hours, which includes the 2-hour infusion time and 1-hour, if needed, to allow the refrigerated diluted solution to equilibrate to room temperature. The diluted solution can be refrigerated at 2-8°C (36-46°F) for up to 12 hours which includes up to 1-hour in the vial post-reconstitution. PROTECT FROM LIGHT and DO NOT FREEZE.

Administration

- **Use an in-line 0.2 micron polyethersulfone (PES) filter for infusion of MYLOTARG.**
- Protect the intravenous bag from light using a light-blocking cover during infusion. The infusion line does not need to be protected from light.
- Infuse the diluted solution over 2 hours.
- Do not mix MYLOTARG with, or administer as an infusion with, other medicinal products.

3. DOSAGE FORMS AND STRENGTHS

For injection: 4.5 mg as a white to off-white lyophilized cake or powder in a single-dose vial for reconstitution and further dilution.

4. CONTRAINDICATIONS

MYLOTARG is contraindicated in patients with a history of hypersensitivity to the active substance in MYLOTARG or any of its components or to any of the excipients. Reactions have included anaphylaxis [*see Warnings and Precautions (5.2) and Adverse Reactions (6)*].

5 WARNINGS AND PRECAUTIONS

5.1 Hepatotoxicity, Including Veno-occlusive Liver Disease (VOD)

Hepatotoxicity, including life-threatening and sometimes fatal hepatic VOD events, have been reported in patients receiving MYLOTARG as a single agent or as part of a combination chemotherapy regimen [*see Adverse Reactions (6)*].

In ALFA-0701, VOD events were reported in 6/131 (5%) patients during or following treatment with MYLOTARG, or following later hematopoietic stem cell transplantation (HSCT). The median time from the MYLOTARG dose to onset of VOD was 9 days (range: 2-298 days), with 5 events occurring within 28 days of any dose of MYLOTARG and 1 event occurring greater than 28 days after the last dose of MYLOTARG. Three of the 6 VOD events were fatal. VOD was also reported in 2 patients in the control arm of ALFA-0701 after receiving MYLOTARG as a therapy for relapsed AML.

In MyloFrance-1 (MYLOTARG 3 mg/m² on Days 1, 4 and 7), VOD events were reported in none of the 57 patients during or following treatment, or following HSCT after completion of MYLOTARG treatment.

Based on an analysis across trials, the risk of VOD was higher in adult patients who received higher doses of MYLOTARG as monotherapy, in patients with moderate or severe hepatic impairment prior to receiving MYLOTARG, in patients treated with MYLOTARG after HSCT, and in patients who underwent HSCT after treatment with MYLOTARG. Patients who had moderate/severe hepatic impairment prior to treatment with MYLOTARG were 8.7 times more likely to develop VOD compared to patients without moderate/severe hepatic impairment at baseline. Patients treated with MYLOTARG for relapse after HSCT were 2.6 times more likely to develop VOD compared to patients without prior HSCT. Patients who underwent HSCT following MYLOTARG treatment were 2.9 times more likely to develop VOD after HSCT compared to patients without HSCT following MYLOTARG treatment. Although no relationship was found between VOD and time of HSCT relative to higher MYLOTARG monotherapy doses, the ALFA-0701 study recommended an interval of 2 months between the last dose of MYLOTARG and HSCT. In MyloFrance-1, no patients underwent HSCT within 3.5 months of MYLOTARG therapy.

Assess ALT, AST, total bilirubin, and alkaline phosphatase prior to each dose of MYLOTARG. After treatment with MYLOTARG, monitor frequently for signs and symptoms of VOD; these may include elevations in ALT, AST, total bilirubin, hepatomegaly (which may be painful), rapid weight gain, and ascites. Monitoring only total bilirubin may not identify all patients at risk of VOD. For patients who develop abnormal liver tests, more frequent monitoring of liver tests and clinical signs and symptoms of hepatotoxicity is recommended. For patients who proceed to HSCT, monitor liver tests frequently during the post-HSCT period, as appropriate.

Manage signs or symptoms of hepatic toxicity by dose interruption or discontinuation of MYLOTARG [*see Dosage and Administration (2.3)*]. In patients who experience VOD, discontinue MYLOTARG and treat according to standard medical practice.

5.2 Infusion-Related Reactions (Including Anaphylaxis)

Life-threatening or fatal infusion related-reactions can occur during or within 24 hours following infusion of MYLOTARG [*see Adverse Reactions (6)*]. Signs and symptoms of infusion-related reactions may include fever, chills, hypotension, tachycardia, hypoxia and respiratory failure.

Premedicate prior to MYLOTARG infusion [*see Dosage and Administration (2.1)*]. Monitor vital signs frequently during infusion. Interrupt infusion immediately for patients who develop evidence of infusion reaction, especially dyspnea, bronchospasm, or hypotension. Monitor patients during and for at least 1 hour after the end of the infusion or until signs and symptoms completely resolve. Discontinue use of MYLOTARG in patients who develop signs or symptoms of anaphylaxis, including severe respiratory symptoms or clinically significant hypotension [*see Dosage and Administration (2.2)*].

5.3 Hemorrhage

MYLOTARG is myelosuppressive and can cause fatal or life-threatening hemorrhage due to prolonged thrombocytopenia. In ALFA-0701, (MYLOTARG in combination with chemotherapy), all grades and Grade 3-4 bleeding events were reported in 118/131 (90%) and 27/131 (21%) patients, respectively. Fatal bleeding events (including cerebral hematoma, intracranial hematoma, and subdural hematoma) occurred in 4/131 (3%) patients. Thrombocytopenia with platelet counts less than 50 Gi/L persisting more than 42 days occurred in 19 (19%) patients in the induction phase [*see Adverse Reactions (6)*]. The proportion of patients with persistent thrombocytopenia increased with progressive treatment phases and was higher in patients treated with MYLOTARG plus chemotherapy than with chemotherapy alone [*see Adverse Reactions (6)*].

In AML-19 (MYLOTARG monotherapy at 6 mg/m² Day 1 and 3 mg/m² Day 8), all grades and Grade 3 or higher bleeding were reported in 28/111 (25%) and 14/111 (13%) patients, respectively. Fatal bleeding occurred in 1/111 (1%). In MyloFrance-1 (MYLOTARG 3 mg/m² as monotherapy), Grade 3 bleeding was reported in 4/57 (7%) patients, but no patient experienced Grade 4 hemorrhage.

Assess blood counts prior to each dose of MYLOTARG and monitor blood counts frequently after treatment with MYLOTARG until resolution of cytopenias. Monitor patients for signs and symptoms of bleeding during treatment with MYLOTARG. Manage severe bleeding, hemorrhage or persistent thrombocytopenia using dose delay or permanent discontinuation of MYLOTARG [see *Dosage and Administration (2.2)*], and provide supportive care per standard practice.

5.4 QT Interval Prolongation

QT interval prolongation has been observed in patients treated with other drugs containing calicheamicin. When administering MYLOTARG to patients who have a history of or predisposition for QTc prolongation, who are taking medicinal products that are known to prolong QT interval, and in patients with electrolyte disturbances, obtain electrocardiograms (ECGs) and electrolytes prior to the start of treatment and as needed during administration.

5.5 Use in AML with Adverse-Risk Cytogenetics

In subgroup analyses in ALFA-0701, the addition of MYLOTARG to standard combination chemotherapy did not improve event-free survival in the subgroup of patients having adverse-risk cytogenetics (HR 1.11; 95% CI: 0.63, 1.95). For patients being treated with MYLOTARG in combination with daunorubicin and cytarabine for newly-diagnosed de novo AML, when cytogenetics testing results become available consider whether the potential benefit of continuing treatment with MYLOTARG outweighs the risks for the individual patient.

5.6 Embryo-Fetal Toxicity

Based on its mechanism of action and findings from animal studies, MYLOTARG can cause embryo-fetal harm when administered to a pregnant woman. In animal studies, gentuzumab ozogamicin caused embryo-fetal toxicity, starting at a dose that was approximately 0.4 times the exposure in patients at the maximum recommended dose, based on the area under the concentration-time curve (AUC). Advise females of reproductive potential to use effective contraception during treatment with MYLOTARG and for at least 6 months after the final dose of MYLOTARG. Advise males with female partners of reproductive potential to use effective contraception during treatment with MYLOTARG and for at least 3 months after the last dose of MYLOTARG. Apprise pregnant women of the potential risk to the fetus. Advise women to contact their healthcare provider if they become pregnant or if pregnancy is suspected during treatment with MYLOTARG [see *Use in Specific Populations (8.1, 8.3)*, *Clinical Pharmacology (12.1)*, and *Nonclinical Toxicology (13.1)*].

6 ADVERSE REACTIONS

The following serious adverse reactions associated with MYLOTARG are discussed in detail in other sections of the prescribing information:

- Hepatotoxicity, including VOD [see *Warnings and Precautions (5.1)*]
- Infusion related reactions [see *Warnings and Precautions (5.2)*]
- Hemorrhage [see *Warnings and Precautions (5.3)*]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Combination Therapy in Newly-Diagnosed De Novo CD33-positive AML

The safety evaluation of MYLOTARG (3 mg/m² Day 1, 4 and 7 in combination with daunorubicin and cytarabine [DA]) in adults is based on data from ALFA-0701 for 131 patients treated with MYLOTARG plus DA and in 137 patients treated with DA alone [see *Clinical Studies (14.1)*]. In this study, 123 patients received all 3 fractionated doses of MYLOTARG and 7 patients missed at least 1 dose, with a mean total dose administered during induction of 14.51 mg (range: 4.6-18.0). MYLOTARG was received by 91 (70%) patients in the MYLOTARG arm during Consolidation 1 and 64 (49%) patients in the MYLOTARG arm during Consolidation 2.

Safety data consisting of selected TEAEs considered most important for understanding the safety profile of MYLOTARG as well as all adverse events (AEs) that led to the permanent discontinuation of treatment were retrospectively collected. The selected TEAEs consisted of all grades hemorrhages, all grades VOD, and severe infections.

Discontinuation due to any adverse reaction occurred in 31% of patients in the MYLOTARG arm versus 7% in the DA arm. The most frequent (greater than or equal to 1%) adverse reactions for patients treated with MYLOTARG that led to permanent discontinuation were thrombocytopenia (15%), VOD (3%), and septic shock (2%).

Fatal adverse reactions occurred in 8 patients (6%) in the MYLOTARG arm versus 3 patients (2%) in the DA arm. In the MYLOTARG arm, 3 patients died of VOD, 4 patients died of hemorrhage-related events (CNS hemorrhage, hemorrhagic shock), and 1 patient died of suspected cardiac cause. In the DA arm, 3 patients died of sepsis.

Table 2. Selected Grade 3 and Higher Adverse Reactions in Patients with Newly-Diagnosed De Novo AML in ALFA-0701

	MYLOTARG + Daunorubicin + Cytarabine (n, %)	Daunorubicin + Cytarabine (n, %)
<u>Induction</u>	N = 131	N = 137
Infection ^a	61 (47%)	53 (39%)
Hemorrhage ^b	24 (18%)	12 (9%)
Veno-occlusive liver disease ^c	3 (2%)	0
<u>Consolidation 1</u>	N = 91	N = 103
Infection ^a	50 (55%)	43 (42%)
Hemorrhage ^b	5 (5%)	0
Veno-occlusive liver disease ^c	0	0
<u>Consolidation 2</u>	N = 64	N = 107
Infection ^a	32 (50%)	54 (50%)
Hemorrhage ^b	4 (6%)	0
Veno-occlusive liver disease ^c	0	0

Abbreviations: AML=acute myeloid leukemia; N=number of patients; PT=preferred term.

^a Infection is a grouped term consisting of multiple preferred terms.

^b Hemorrhage is a grouped term consisting of multiple preferred terms.

^c Veno-occlusive liver disease includes the following reported PTs: Veno-occlusive liver disease, veno-occlusive disease.

All patients in ALFA-0701 developed severe neutropenia, thrombocytopenia and anemia. The incidence of Grade 3-4 thrombocytopenia that was prolonged in the absence of active leukemia was higher in patients treated with MYLOTARG (Table 3).

Table 3: Prolonged Cytopenias^a in ALFA-0701

	MYLOTARG + Daunorubicin + Cytarabine (n/N, %)	Daunorubicin + Cytarabine (n/N, %)
<u>Induction</u>		
Prolonged thrombocytopenia	19/101 (19%)	7/97 (7%)
Prolonged neutropenia	3/106 (3%)	0/101 (0%)
<u>Consolidation 1</u>		
Prolonged thrombocytopenia	21/87 (24%)	6/91 (7%)
Prolonged neutropenia	3/88 (3%)	1/97 (1%)
<u>Consolidation 2</u>		
Prolonged thrombocytopenia	22/62 (35%)	25/103 (24%)
Prolonged neutropenia	1/62 (2%)	2/105 (2%)

^a Platelets less than 50 Gi/L or neutrophils less than 0.5 Gi/L lasting past cycle Day 42 in the absence of active leukemia.

Table 4 summarizes shifts in selected chemistry abnormalities by treatment arm for patients treated in ALFA-0701.

Table 4. ALFA-0701 – Chemistry Laboratory Values: Shifts in Subjects with Baseline Grade 2 or Lower Values

Laboratory Abnormality	<u>MYLOTARG + Daunorubicin + Cytarabine</u>		<u>Daunorubicin + Cytarabine</u>	
	Subjects (n) with baseline Grade less than or equal to 2	Progressed to Grade greater than or equal to 3 (n, %)	Subjects (n) with baseline Grade less than or equal to 2	Progressed to Grade greater than or equal to 3 (n, %)
Hypophosphatemia	117	75 (64%)	127	52 (41%)
Hypokalemia	127	73 (57%)	133	41 (31%)
Hyponatremia	129	57 (44%)	134	36 (27%)
Alkaline phosphatase increased	120	16 (13%)	128	7 (5%)
Aspartate aminotransferase increased	126	18 (14%)	132	11 (8%)
Alanine aminotransferase increased	124	13 (10%)	132	20 (15%)
Blood bilirubin increased	119	9 (8%)	126	5 (4%)

Monotherapy for Newly-Diagnosed CD33-positive AML

The safety evaluation of MYLOTARG (6 mg/m² then 3 mg/m², with 7 days between the doses) as monotherapy is based on a randomized, open-label, Phase 3 trial of MYLOTARG (N=118) versus best supportive care (BSC) (N=119) in patients with previously untreated AML who were considered ineligible for intensive chemotherapy in Study AML-19 [see *Clinical Studies (14.1)*].

The overall incidence of any Grade adverse reactions reported in AML-19 was 87% in the MYLOTARG arm and 90% in the BSC arm. The incidence of Grade greater than or equal to 3 adverse reactions was 61% in the MYLOTARG arm and 68% in the BSC arm. Death due to any Adverse Event was reported in the MYLOTARG arm of 19 (17%) compared to the BSC arm of 23 (20%).

Table 5. Selected Adverse Reactions in AML-19

	MYLOTARG n=111		Best Supportive Care n=114	
	Any Grade	Grade \geq 3	Any Grade	Grade \geq 3
Liver	57 (51%)	8 (7%)	52 (46%)	7 (6%)
Fatigue	51 (46%)	13 (12%)	69 (61%)	24 (21%)
Infection	49 (44%)	39 (35%)	48 (42%)	39 (34%)
Cardiac	31 (28%)	7 (6%)	37 (33%)	16 (14%)
Bleeding	28 (25%)	14 (13%)	34 (30%)	14 (12%)
Febrile neutropenia	20 (18%)	20 (18%)	27 (24%)	27 (24%)
Metabolic	18 (16%)	4 (4%)	17 (15%)	7 (6%)
Renal	7 (6%)	4 (4%)	9 (8%)	5 (4%)

Monotherapy for Relapsed or Refractory CD33-positive AML

The adverse reactions described in this section reflect exposure to MYLOTARG 3 mg/m² on Days 1, 4 and 7 as monotherapy in 57 patients with relapsed AML treated on MyloFrance-1 [see *Clinical Studies (14.1)*]. All 57 (100%) patients received the 3 planned doses of MYLOTARG.

During the treatment period, Grade 3 treatment-emergent adverse events (TEAEs) that occurred in greater than 1% patients included sepsis (32%), fever (16%), rash (11%), pneumonia (7%), bleeding (7%), mucositis (4%), pain (4%), diarrhea (2%), headaches (2%), tachycardia (2%), and lung edema (2%). No Grade 4 toxicity was observed. All grade TEAEs that occurred in greater than 15% of patients included fever (79%), infection (42%), increased AST (40%), bleeding (23%), nausea and vomiting (21%), constipation (21%), mucositis (21%), headache (19%), increased ALT (16%), and rash (16%). No infectious deaths occurred. Grade 1 or 2 hyperbilirubinemia developed in 4 (7%) patients. No episodes of VOD occurred. Seven patients received HSCT after MYLOTARG treatment. Three patients received an allogeneic BMT and 4 patients were treated with autologous BMT. No patients developed VOD following HSCT.

6.2 Postmarketing Experience

The following adverse drug reactions have been identified during post-approval use of MYLOTARG. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Gastrointestinal Disorders: Neutropenic colitis*

Infections and Infestations: fungal lung infections including Pulmonary mycosis and Pneumocystis jirovecii pneumonia* ; and bacterial infections including Stenotrophomonas infection

Renal and Urinary Disorders: Hemorrhagic cystitis¹

Respiratory, Thoracic and Mediastinal Disorders: Interstitial pneumonia¹

* including fatal events

6.3 Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. Immunogenicity of MYLOTARG was not studied in clinical trials using the recommended dose regimens.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on its mechanism of action and findings from animal studies [*see Clinical Pharmacology (12.1) and Nonclinical Toxicology (13.1)*], MYLOTARG can cause embryo-fetal harm when administered to a pregnant woman. There are no available data on MYLOTARG use in pregnant women to inform a drug-associated risk of major birth defects and miscarriage. In rat embryo-fetal development studies, gemtuzumab ozogamicin caused embryo-fetal toxicity at maternal systemic exposures that were greater than or equal to 0.4 times the exposure in patients at the maximum recommended dose, based on AUC (*see Data*). If MYLOTARG is used during pregnancy, or if the patient becomes pregnant while taking MYLOTARG, advise the patient of the potential risk to a fetus.

Adverse outcomes in pregnancy occur regardless of the health of the mother or the use of medications. The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data

In an embryo-fetal development study in rats, pregnant animals received daily intravenous doses up to 1.2 mg/m²/day gemtuzumab ozogamicin during the period of organogenesis. Embryo-fetal toxicities including fetal growth retardation as evidenced by decreased live fetal weights, incidence of fetal wavy ribs and delayed skeletal ossification were observed at greater than or equal to 0.15 mg/m²/day. Increased embryo-fetal lethality and fetal morphological anomalies (digital malformations, absence of the aortic arch, anomalies in the long bones in the forelimbs, misshapen scapula, absence of a vertebral centrum, and fused sternbrae) were observed at greater than or equal to 0.36 mg/m²/day. All doses with embryo-fetal effects were observed in the presence of maternal toxicity that included decreases in gestational body weight gain, food consumption, and gravid

uterine weight. The lowest dose at which embryo-fetal effects were observed in rats (0.15 mg/m²/day) was 0.4 times the exposure in patients at the maximum recommended human dose, based on AUC.

8.2 Lactation

Risk Summary

There are no data on the presence of gemtuzumab ozogamicin or its metabolites in human milk, the effects on the breastfed infant, or the effects on milk production. Because of the potential for adverse reactions in breastfed infants, women should not breastfeed during treatment with MYLOTARG and for at least 1 month after the final dose.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

Based on animal studies, MYLOTARG can cause fetal harm when administered to a pregnant woman [*see Use in Specific Populations (8.1) and Nonclinical Toxicology (13.1)*]. Verify the pregnancy status of females of reproductive potential prior to initiating MYLOTARG.

Contraception

Females

Advise females of reproductive potential to avoid becoming pregnant while receiving MYLOTARG. Advise females of reproductive potential to use effective contraception during treatment with MYLOTARG and for at least 6 months after the last dose [*see Nonclinical Toxicology (13.1)*].

Males

Advise males with female partners of reproductive potential to use effective contraception during treatment with MYLOTARG and for at least 3 months after the last dose [*see Nonclinical Toxicology (13.1)*].

Infertility

Females

Based on findings in animals, MYLOTARG may impair fertility in females of reproductive potential [*see Nonclinical Toxicology (13.1)*].

Males

Based on findings in animals, MYLOTARG may impair fertility in males of reproductive potential [*see Nonclinical Toxicology (13.1)*].

8.4 Pediatric Use

The safety and efficacy of MYLOTARG in combination with daunorubicin and cytarabine have not been established in the pediatric patients with newly-diagnosed de novo AML.

The safety and efficacy of MYLOTARG as a single agent in the pediatric patients with relapsed or refractory AML is supported by a single-arm trial in 29 patients in the following age groups: 1 patient 1 month to less than 2 years old, 13 patients 2 years to less than 12 years old, and 15 patients 12 years to 18 years old. A literature review included an additional 96 patients with ages ranging from 0.2 to 21 years. No differences in efficacy and safety were observed by age.

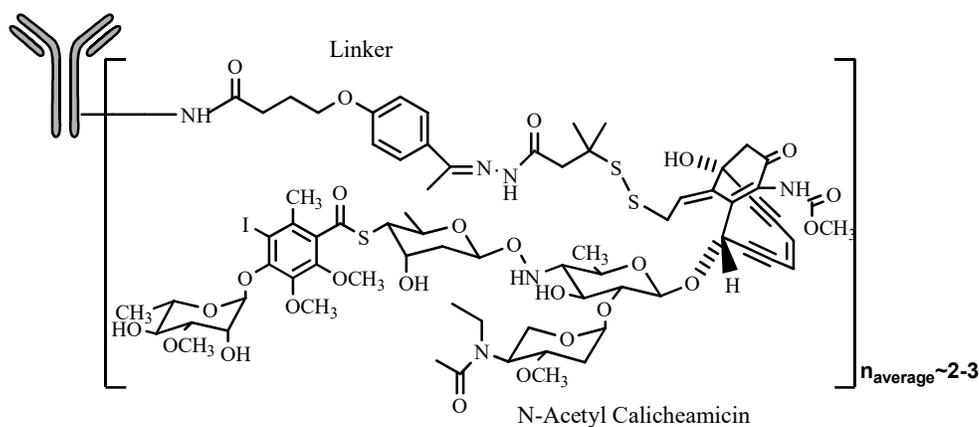
8.5 Geriatric Use

Use of MYLOTARG in combination with daunorubicin and cytarabine in newly-diagnosed adult patients with de novo AML is supported by a randomized, controlled trial that included 50 patients greater than or equal to 65 years old. No overall differences in safety or effectiveness were observed between these subjects and younger subjects. Use of MYLOTARG monotherapy in newly-diagnosed adult patients with AML is supported by a randomized controlled trial with 118 patients treated with MYLOTARG. All patients were over the age of 60 years and 65% of patients were above 75 years. No overall differences in effectiveness were observed by age.

Use of MYLOTARG as single-agent treatment of relapsed or refractory AML is supported by a single-arm trial that included 27 patients 65 years or older. No overall differences in effectiveness were observed between these patients and younger patients. Elderly patients experienced a higher rate of fever and severe or greater infections.

11. DESCRIPTION

Gemtuzumab



Gemtuzumab ozogamicin is an antibody-drug conjugate (ADC) composed of the CD33-directed monoclonal antibody (hP67.6; recombinant humanized immunoglobulin [Ig] G4, kappa antibody produced by mammalian cell culture in NS0 cells) that is covalently linked to the cytotoxic agent N-acetyl gamma calicheamicin. Gemtuzumab ozogamicin consists of conjugated and unconjugated gemtuzumab. The conjugated molecules differ in the number of activated calicheamicin derivative moieties attached to gemtuzumab. The number of conjugated calicheamicin derivatives per gemtuzumab molecule ranges from predominantly zero to 6, with an average of 2 to 3 moles of calicheamicin derivative per mole of gemtuzumab.

MYLOTARG (gemtuzumab ozogamicin) for Injection is supplied as a sterile, white to off-white, preservative-free lyophilized cake or powder for intravenous administration. Each single-dose vial delivers 4.5 mg gemtuzumab ozogamicin. Inactive ingredients are dextran 40 (41.0 mg), sodium chloride (26.1 mg), sodium phosphate dibasic anhydrous (2.7 mg), sodium phosphate monobasic monohydrate (0.45 mg), and

sucrose (69.8 mg). After reconstitution with 5 mL of Sterile Water for Injection USP, the concentration is 1 mg/mL of gemtuzumab ozogamicin with a deliverable volume of 4.5 mL (4.5 mg).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Gemtuzumab ozogamicin is a CD33-directed antibody-drug conjugate (ADC). The antibody portion (hP67.6) recognizes human CD33 antigen. The small molecule, N-acetyl gamma calicheamicin, is a cytotoxic agent that is covalently attached to the antibody via a linker. Nonclinical data suggest that the anticancer activity of gemtuzumab ozogamicin is due to the binding of the ADC to CD33-expressing tumor cells, followed by internalization of the ADC-CD33 complex, and the intracellular release of N-acetyl gamma calicheamicin dimethyl hydrazide via hydrolytic cleavage of the linker. Activation of N-acetyl gamma calicheamicin dimethyl hydrazide induces double-strand DNA breaks, subsequently inducing cell cycle arrest and apoptotic cell death.

12.2 Pharmacodynamics

Saturation of a high percentage of CD33 antigenic sites is presumed to be required for maximum delivery of calicheamicin to leukemic blast cells. Near maximal peripheral CD33 saturation was observed across studies after gemtuzumab ozogamicin dosing at dose levels of 2 mg/m² and above.

At 9 mg/m² gemtuzumab ozogamicin (2 doses, 14 days apart), the risk for VOD increases as the C_{max} of the first dose of gemtuzumab ozogamicin increases. The increase in VOD is more prominent in patients with prior stem cell transplantation.

12.3 Pharmacokinetics

There are no clinical PK data for the fractionated regimen. When gemtuzumab ozogamicin is administered at 9 mg/m² (2 doses, 14 days apart), the C_{max} following the first dose for patients who received 9 mg/m² gemtuzumab ozogamicin was 3.0 mg/mL and increased to 3.6 mg/mL after the second dose.

Distribution

N-acetyl gamma calicheamicin dimethyl hydrazide is approximately 97% bound to human plasma proteins in vitro. Population PK analyses found the total volume of distribution of hP67.6 antibody (sum of V1 [6.31 L] and V2 [15.1 L]) to be approximately 21.4 L in patients.

Elimination

The clearance (CL) value of hP67.6 from plasma was 0.35 L/h after the first dose and 0.15 L/h after the second dose, a decrease of roughly 60%. The terminal plasma half-life (t_{1/2}) for hP67.6 was 62 hours after the first dose and 90 hours after the second dose.

Metabolism

In vitro studies demonstrated that N-acetyl gamma calicheamicin dimethyl hydrazide is extensively metabolized, primarily via nonenzymatic reduction of the disulfide moiety.

Specific Populations

Age, race, sex, mild or moderate renal impairment (creatinine clearance [CL_{cr}] 30-89 mL/min calculated by the Cockcroft-Gault equation) or mild hepatic impairment had no clinically significant effect on the pharmacokinetics of gemtuzumab ozogamicin. The pharmacokinetics of gemtuzumab ozogamicin in patients with severe renal impairment (CL_{cr} 15-29 mL/min) or moderate (total bilirubin greater than 1.5x to 3.0x ULN) and severe hepatic impairment (total bilirubin greater than 3x ULN) is unknown.

Drug Interaction Studies

No clinical drug interaction studies have been performed.

In vitro studies

At clinically relevant concentrations, gemtuzumab ozogamicin had a low potential to:

- *Inhibit CYP450 Enzymes:* CYP1A2, CYP2A6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4/5.

At clinically relevant concentrations, N-acetyl gamma calicheamicin dimethyl hydrazide had a low potential to:

- *Inhibit CYP450 Enzymes:* CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4/5.
- *Induce CYP450 Enzymes:* CYP1A2, CYP2B6, and CYP3A4.
- *Inhibit UGT Enzymes:* UGT1A1, UGT1A4, UGT1A6, UGT1A9, and UGT2B7.
- *Inhibit Drug Transporters:* P-gp (P-glycoprotein), breast cancer resistance protein (BCRP), organic anion transporter (OAT)1 and OAT3, organic cation transporter (OCT)2, and organic anion transporting polypeptide (OATP)1B1 and OATP1B3.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Formal carcinogenicity studies have not been conducted with gemtuzumab ozogamicin. In toxicity studies, rats were dosed weekly for 6 weeks with gemtuzumab ozogamicin at doses up to 7.2 mg/m²/week. After 6 weeks of dosing, rats developed oval cell hyperplasia in the liver, which is considered a potentially preneoplastic finding, at 7.2 mg/m²/week (approximately 16 times the exposure in patients at the maximum recommended dose, based on AUC). Other preneoplastic or neoplastic changes observed with other antibody-calicheamicin conjugates in rats included basophilic and/or eosinophilic altered cell foci and hepatocellular adenomas. The relevance of these animal findings to humans is uncertain.

Gemtuzumab ozogamicin was clastogenic in vivo in the bone marrow of mice that received single doses greater than or equal to 22.1 mg/m². This is consistent with the known induction of DNA breaks by calicheamicin. N-acetyl gamma calicheamicin dimethyl hydrazide (the released cytotoxic agent) was mutagenic in the bacterial reverse mutation assay and clastogenic in the in vitro micronucleus assay in human TK6 cells.

In a female fertility study, female rats were administered daily intravenous doses of gemtuzumab ozogamicin up to 1.08 mg/m² for 14 days before mating with untreated male rats. Significant decreases in the numbers of corpora lutea and implants were observed at 1.08 mg/m², and dose-related decreases and increases in the number of live and dead embryos were observed at doses tested (approximately 0.4 times the exposure in patients at the maximum recommended dose, based on AUC). Increased embryofetal lethality at ≥0.36 mg/m² was observed in the presence of maternal toxicity that included decreases in gestational body weight and food

consumption. Additional findings in female reproductive organs (ovarian atrophy and decreased numbers of follicles associated with atrophy of the uterus, vagina and mammary glands) occurred in rats and monkeys after dosing with other antibody-calicheamicin conjugates.

Fertility was assessed in male rats administered daily intravenous doses of gemtuzumab ozogamicin from 0.12 to 1.08 mg/m² for 28 days, followed by mating with untreated females, either at the end of the dosing period or after a 9-week drug-free period. Male fertility index was decreased at doses ≥0.12 mg/m² (approximately 1.2 times the exposure in patients at the maximum recommended dose, based on AUC). Effects on testes and epididymides occurred at ≥0.12 mg/m², including smaller size and lower weights in addition to adverse effects on sperm. Partial recovery was noted for some effects. Additional effects in male reproductive organs occurred in repeat-dose toxicology studies and included effects on mammary gland, testes, and epididymides in rats at ≥2.4 mg/m²/week and effects on testes and epididymides in monkeys at 21.6 mg/m²/week. Testicular effects in male monkeys with other antibody-calicheamicin conjugates included degeneration of seminiferous tubules and decreased epididymidal sperm, which did not reverse following a 6-week drug-free period.

14 CLINICAL STUDIES

14.1 Newly-Diagnosed CD33-positive AML

Study ALFA-0701

MYLOTARG in combination with chemotherapy was investigated in ALFA-0701 (NCT00927498), a multicenter, randomized, open-label Phase 3 study of 271 patients with newly-diagnosed de novo AML age 50 to 70 years. Patients were randomized (1:1) to receive induction therapy consisting of daunorubicin (60 mg/m² on Days 1 to 3) and cytarabine (200 mg/m² on Days 1 to 7) (DA) with (n=135) or without (n=136) MYLOTARG 3 mg/m² (up to maximum of one vial) on Days 1, 4, and 7. Patients who did not achieve a response after first induction could receive a second induction with daunorubicin and cytarabine alone. Patients with response received consolidation therapy with 2 courses of treatment including daunorubicin (60 mg/m² on Day 1 of consolidation course 1; 60 mg/m² on Days 1 and 2 of consolidation course 2) and cytarabine (1 g/m² every 12 hours on Days 1 to 4) with or without MYLOTARG 3 mg/m² (up to a maximum of one vial) on Day 1 according to their initial randomization. Patients who experienced remission were also eligible for allogeneic transplantation. An interval of at least 2 months between the last dose of MYLOTARG and transplantation was recommended.

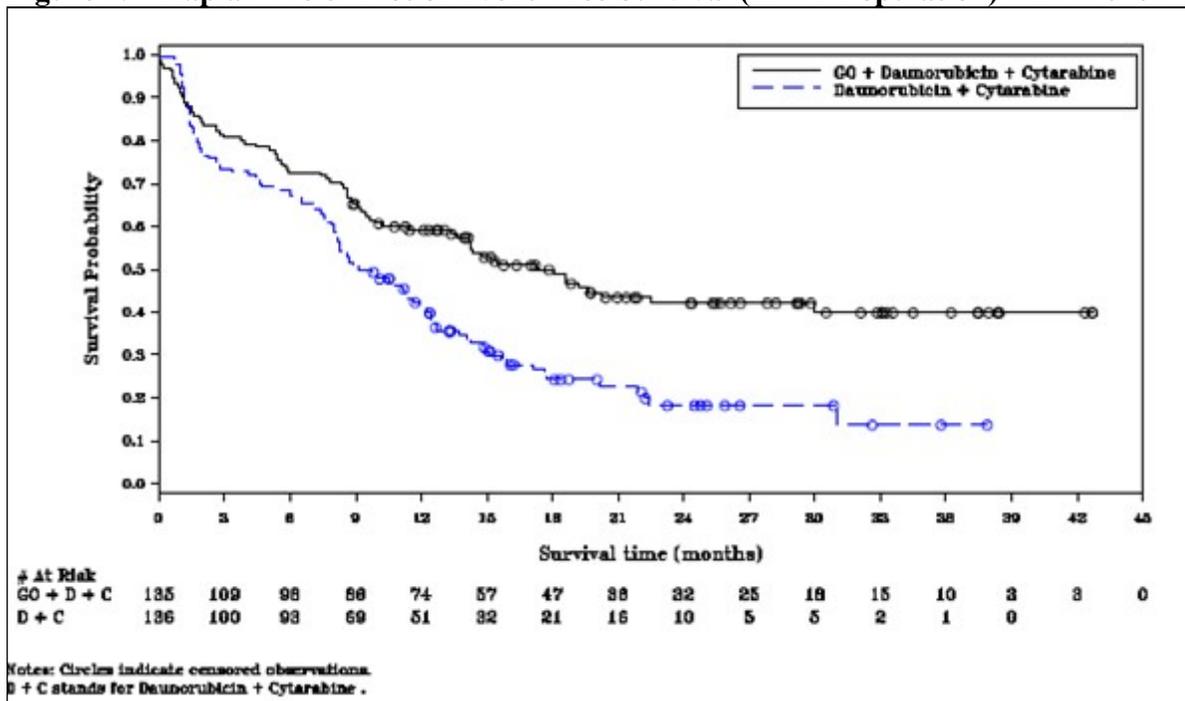
The median age of the patients was 62 years (range, 50-70), 137 female and 134 male, and 88% had an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 to 1 at baseline. Baseline characteristics were balanced between treatment arms with the exception of gender as a higher percentage of males were enrolled in the MYLOTARG arm (55%) than in the DA alone arm (44%). Overall, 59%, 65%, and 70% of patients had documented favorable/intermediate risk and 33%, 27%, and 21% had poor/adverse disease by the National Comprehensive Cancer Network (NCCN), European LeukemiaNet (ELN), and cytogenetic risk classifications, respectively. CD33 expression on AML blasts by flow cytometry harmonized from local laboratory results was determined in 194/271 (72%) patients overall. Few patients (14%) had low CD33 expression (less than 30% of blasts), and none had no expression of CD33.

Efficacy was established on the basis of event-free survival (EFS), measured from the date of randomization until induction failure, relapse, or death by any cause. Per protocol, induction failure was defined as failure to achieve CR or CRp in induction, and date of induction failure was defined as date of marrow evaluation after the last course of induction. Median EFS was 17.3 months in the MYLOTARG arm versus 9.5 months in the control arm; hazard ratio (HR) 0.56 (95% CI: 0.42-0.76); 2-sided p less than 0.001 by log-rank test.

In an exploratory analysis of EFS defined as failure to achieve CR in induction, relapse, or death from any cause and using the date of randomization as the date of induction failure, median EFS was 13.6 months for MYLOTARG + DA and 8.8 months for DA with HR 0.68 (95% CI: 0.51-0.91).

The Kaplan-Meier plot for per-protocol EFS is shown in Figure 1. There was no statistically significant difference between treatment arms in overall survival.

Figure 1. Kaplan-Meier Plot of Event-Free Survival (mITT Population) ALFA-0701 Trial



Abbreviations: C=cytarabine; D=daunorubicin; GO=gemtuzumab ozogamicin; mITT=modified intent-to-treat.

Study AML-19

MYLOTARG single-agent therapy was evaluated in Study AML-19 (NCT00091234), a multicenter, randomized, open-label Phase 3 study comparing MYLOTARG to best supportive care (BSC) for patients with newly-diagnosed AML who were a) greater than 75 years of age or b) 61 to 75 years of age with a World Health Organization performance status (WHO PS) greater than 2 or were unwilling to receive intensive chemotherapy. Patients were randomized 1:1 and stratified by age (61-75 vs 76-80 years vs ≥ 81 years), CD33 positivity of bone marrow blasts (less than 20% vs 20-80% vs greater than 80% vs unknown), initial white blood cell count (less than 30 vs greater than or equal to $30 \times 10^9/L$), WHO PS (0-1 vs 2 vs 3-4), and institution.

During induction, MYLOTARG 6 mg/m^2 was given on Day 1 and MYLOTARG 3 mg/m^2 was given on Day 8. Patients with no evidence of disease progression or significant toxicities after MYLOTARG induction received continuation therapy as outpatients with up to 8 courses of treatment including MYLOTARG 2 mg/m^2 on Day 1 every 4 weeks. Patients continued therapy if they did not experience significant toxicities, relapse, or disease progression. BSC included standard supportive care measures and hydroxyurea or other anti-metabolites for palliative purposes.

In total, 118 patients were randomized to treatment with MYLOTARG and 119 patients to BSC. Overall, the median age of patients was 77 years (range, 62-88 years), and most patients (65%) had a WHO PS of 0 to 1 at baseline. Baseline characteristics were balanced between treatment arms with the exception of gender and

cytogenetics. Compared to the BSC arm, the MYLOTARG arm had a higher percentage of females (52% vs 39%) and patients with favorable/intermediate risk cytogenetics (50% vs 38%). The proportion with adverse cytogenetics was similar between arms (28% vs 27%). Fewer patients on the MYLOTARG arm had missing cytogenetics data (22% vs 35%). CD33 expression on AML blasts by flow cytometry at a centralized location was determined in 235/237 (99%) patients; 10% had CD33 expression less than 20%.

The efficacy of MYLOTARG was established on the basis of improvement in overall survival (OS). The hazard ratio (HR) for OS was 0.69 (95% CI: 0.53-0.90) (2-sided p=0.005 by log-rank test). Median OS was 4.9 months in the MYLOTARG arm versus 3.6 months in the control arm.

14.2 Relapsed or refractory CD33-positive AML

Study MyloFrance-1

The efficacy of MYLOTARG as a single agent was evaluated in MyloFrance-1 a phase 2, single-arm, open-label study in adults with CD33-positive AML in first relapse. Patients with secondary leukemia or a prior autologous or allogeneic stem cell transplantation were excluded. Study treatment included a single course of MYLOTARG 3 mg/m² on Days 1, 4, and 7. Consolidation therapy consisted of cytarabine intravenously every 12 hours for 3 days. The cytarabine dose was 3 g/m² for patients less than 55 years old and 1 g/m² for patients 55 years or older and/or patients with a creatinine clearance below 50 mL/minute. Hematopoietic stem cell transplantation (HSCT) was allowed after treatment with MYLOTARG, but it was recommended to delay HSCT by at least 90 days following MYLOTARG.

There were 57 patients treated with MYLOTARG. Overall, the median age of patients was 64 years (range 22-80 years). The median duration of first remission was 10 months. Forty-four (78%) patients had intermediate-risk and 12 (22%) poor-risk cytogenetics.

The efficacy of MYLOTARG was established on the basis of complete remission (CR) rate and duration of remission. Fifteen (26%; 95% CI 16% - 40%) patients achieved CR following a single course of MYLOTARG. Median relapse-free survival, measured from the first documentation of CR to the date of relapse or death, was 11.6 months.

15 REFERENCES

1. OSHA Hazardous Drugs. OSHA. [Accessed on June 9, 2017, from <http://www.osha.gov/SLTC/hazardousdrugs/index.html>]

16 HOW SUPPLIED/STORAGE AND HANDLING

MYLOTARG (gemtuzumab ozogamicin) for Injection is a white to off-white lyophilized cake or powder supplied in a carton (NDC 0008-4510-01) containing one 4.5 mg single-dose vial [*see Dosage and Administration (2)*].

16.1 Storage and Handling

Refrigerate (2-8°C; 36-46°F) MYLOTARG vials and store in the original carton to protect from light. DO NOT FREEZE.

MYLOTARG is a cytotoxic drug. Follow applicable special handling and disposal procedures.¹

17. PATIENT COUNSELING INFORMATION

Hepatotoxicity, Including Veno-occlusive Liver Disease (VOD)

Inform patients that liver problems, including severe, life-threatening, or fatal VOD may develop during MYLOTARG treatment. Prior to receiving MYLOTARG, inform patients who previously received, or will receive an HSCT that they may be at increased risk for developing VOD. Inform patients that the risk of developing VOD after an allogeneic HSCT is increased after receiving treatment with MYLOTARG. Inform patients that signs or symptoms of liver toxicity, including rapid weight gain, right upper quadrant pain and tenderness, hepatomegaly, and ascites should be monitored regularly during treatment, but these symptoms may not identify all patients at risk or prevent the complications of liver toxicity. Inform patients that liver problems may require dosing interruption or permanent discontinuation of MYLOTARG [see *Warnings and Precautions (5.1)*].

Hemorrhage

Inform patients that decreased platelet counts, which may be life-threatening, may develop during MYLOTARG treatment and that complications associated with decreased platelet counts may include bleeding/hemorrhage events, which may be life-threatening or fatal. Inform patients to report signs and symptoms of bleeding/hemorrhage during treatment with MYLOTARG. Inform patients that severe bleeding/hemorrhage may require dosing interruption or permanent discontinuation of MYLOTARG [see *Warnings and Precautions (5.3)*].

Infusion Related Reactions

Advise patients to contact their health care provider if they experience signs and symptoms of infusion related reactions, including symptoms such as fever, chills, rash, or breathing problems [see *Warnings and Precautions (5.2)*].

Pregnancy and Breastfeeding

Advise men and women of reproductive potential to use effective contraception during MYLOTARG treatment and for at least 3 and 6 months, respectively, after the last dose [see *Use in Specific Populations (8.3)*]. Advise women of childbearing potential to avoid becoming pregnant while receiving MYLOTARG. Advise women to contact their healthcare provider if they become pregnant, or if pregnancy is suspected, during treatment with MYLOTARG. Inform the patient of the potential hazard to the fetus [see *Warnings and Precautions (5.6)* and *Use in Specific Populations (8.1)*]. Advise women against breastfeeding while receiving MYLOTARG and for 1 month after the last dose [see *Use in Specific Populations (8.2)*].

This product's label may have been updated. For full prescribing information, please visit www.mylotarg.com.

Manufactured by



Wyeth Pharmaceuticals Inc

A subsidiary of Pfizer Inc, Philadelphia, PA 19101

US License No. 003

LAB-0868-2.0

Utilization Management for Formulary Adds

<i>Policy Name</i>	<i>Policy Type</i>
<i>Coagadex® SGM</i>	Specialty guideline management
<i>Corticosteroid Oral Inhalation Limit Policy</i>	Quantity Limit
<i>Crysvita® SGM</i>	Specialty guideline management
<i>Idhifa® SGM</i>	Specialty guideline management
<i>Jynarque® SGM</i>	Specialty guideline management
<i>Kevzara® SGM</i>	Specialty guideline management
<i>Specialty Quantity Limit Kevzara</i>	Quantity Limit
<i>Mepsevii® SGM</i>	Specialty guideline management
<i>Mylotarg® SGM</i>	Specialty guideline management
<i>Radicava® SGM</i>	Specialty guideline management

*Listed policies will be enacted October 1, 2018

Reference number(s)

1942-A

SPECIALTY GUIDELINE MANAGEMENT

COAGADEX (coagulation Factor X [human])

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indication

Coagadex is indicated in adults and children (aged 12 years and above) with hereditary Factor X deficiency for:

- A. On-demand treatment and control of bleeding episodes
- B. Perioperative management of bleeding in patients with mild hereditary Factor X deficiency.

Limitation of Use:

Perioperative management of bleeding in major surgery in patients with moderate and severe hereditary Factor X deficiency has not been studied.

All other indications are considered experimental/investigational and are not a covered benefit.

II. CRITERIA FOR INITIAL APPROVAL

Hereditary Factor X Deficiency

- A. Indefinite authorization may be granted for on-demand treatment and control of bleeding episodes.
- B. Authorization of 1 month may be granted for perioperative management of bleeding in members with mild disease (i.e., baseline Factor X assay level $\geq 5\%$).

III. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must meet ALL initial authorization criteria.

IV. REFERENCES

1. Coagadex [package insert]. Durham, NC: Bio Products Laboratory USA, Inc.; October 2015.
2. National Hemophilia Foundation. MASAC recommendations concerning products licensed for the treatment of hemophilia and other bleeding disorders. Revised August 2017. MASAC Document # 250. Accessed December 8, 2017.
3. Mumford AD, Ackroyd S, Alikhan R, et al. Guideline for the diagnosis and management of the rare coagulation disorders: a United Kingdom Haemophilia Centre Doctors' Organization guideline on behalf of the British Committee for Standards in Haematology. *Br J Haematol.* 2014;167(3):304-26.

Reference number(s)
1942-A

4. Brown DL, Kouides PA. Diagnosis and treatment of inherited factor X deficiency. *Haemophilia*. 2008;14(6):1176-82.

QUANTITY LIMIT CRITERIA

DRUG CLASS CORTICOSTEROID ORAL INHALATION

BRAND NAME
(generic)

AEROSPAN
(flunisolide)

ALVESCO
(ciclesonide)

ARMONAIR RESPICLICK
(fluticasone propionate)

ARNUITY ELLIPTA
(fluticasone furoate)

ASMANEX HFA
(mometasone furoate)

ASMANEX TWISTHALER
(mometasone furoate)

FLOVENT DISKUS
(fluticasone propionate)

FLOVENT HFA
(fluticasone propionate)

PULMICORT FLEXHALER
(budesonide)

PULMICORT RESPULES
(budesonide)

QVAR
(beclomethasone)

QVAR REDHALER
(beclomethasone)

Status: CVS Caremark Criteria

Type: Quantity Limit

POLICY

FDA-APPROVED INDICATIONS

Aerospan

Aerospan inhalation aerosol is indicated for the maintenance treatment of asthma as prophylactic therapy in adult and pediatric patients 6 years of age and older.

Aerospan Inhalation Aerosol is NOT indicated in children less than 6 years of age.

Alvesco

Alvesco is indicated for the maintenance treatment of asthma as prophylactic therapy in adult and adolescent patients 12 years of age and older.

Alvesco is NOT indicated for children under 12 years of age.

ArmonAir Respiclick

Armonair Respiclick is indicated for the maintenance treatment of asthma as prophylactic therapy in patients 12 years of age and older.

Arnuity Ellipta

Arnuity Ellipta is indicated for the once-daily maintenance treatment of asthma as prophylactic therapy in patients aged 5 years and older.

Asmanex HFA

Asmanex HFA is indicated for the maintenance treatment of asthma as prophylactic therapy in patients 12 years of age and older.

Asmanex Twisthaler

Asmanex Twisthaler is indicated for the maintenance treatment of asthma as prophylactic therapy in patients 4 years of age and older.

Asmanex Twisthaler is NOT indicated in children less than 4 years of age.

Flovent Diskus

Flovent Diskus is indicated for the maintenance treatment of asthma as prophylactic therapy in patients aged 4 years and older.

Flovent HFA

Flovent HFA Inhalation Aerosol is indicated for the maintenance treatment of asthma as prophylactic therapy in patients aged 4 years and older.

Pulmicort Flexhaler

Pulmicort Flexhaler is indicated for the maintenance treatment of asthma as prophylactic therapy in patients six years of age or older.

Pulmicort Respules

Pulmicort Respules is indicated for the maintenance treatment of asthma and as prophylactic therapy in children 12 months to 8 years of age.

QVAR

QVAR is indicated in the maintenance treatment of asthma as prophylactic therapy in patients 5 years of age and older.

QVAR RediHaler

QVAR RediHaler is indicated in the maintenance treatment of asthma as prophylactic therapy in patients 4 years of age and older.

Important Limitations of Use

Oral inhaled corticosteroids are NOT indicated for the relief of acute bronchospasm.

REFERENCES

1. Aerospan [package insert]. Somerset, NJ: Meda Pharmaceuticals, Inc.; June 2017.
2. Alvesco [package insert]. Marlborough, MA: Sunovion Pharmaceuticals, Inc.; January 2013.
3. ArmonAir Respiclick [package insert]. Frazer, PA: Teva Respiratory, LLC; October 2017.
4. Arnuity Ellipta [package insert]. Research Triangle Park, NC: GlaxoSmithKline; May 2018.
5. Asmanex HFA [package insert]. White Station, NJ: Merck Sharp & Dohme Corp.; July 2016.
6. Asmanex Twisthaler [package insert]. White Station, NJ: Merck Sharp & Dohme Corp.; September 2014.
7. Flovent Diskus [package insert]. Research Triangle Park, NC: GlaxoSmithKline; July 2017.
8. Flovent HFA [package insert]. Research Triangle Park, NC: GlaxoSmithKline; July 2017.
9. Pulmicort Flexhaler [package insert]. Wilmington, DE: AstraZeneca LP; October 2016.
10. Pulmicort Respules [package insert]. Wilmington, DE: AstraZeneca LP; November 2016.
11. QVAR [package insert]. Horsham, PA: Teva Respiratory, LLC; October 2017.
12. QVAR RediHaler [package insert]. Horsham, PA: Teva Respiratory, LLC; August 2017.

LIMIT CRITERIA				
Medication**	Starting Dose	Maximum** Daily Dose	Package Size	1 Month Limit* 3 Months Limit*
Aerospan 80mcg	1-4 inhalations twice daily	8 inhalations (640mcg)	120 inhalations per 8.9gm canister	2 packages (8.9gm each) / 25 days 6 packages (8.9gm each) / 75 days
Alvesco 80mcg**	1-3 inhalations twice daily	6 inhalations**	60 inhalations per 6.1gm canister	3 packages (6.1gm each) / 25 days 9 packages (6.1gm each) / 75 days
Alvesco 160 mcg	1-2 inhalations twice daily	4 inhalations (640mcg)	60 inhalations per 6.1gm canister	2 packages (6.1gm each) / 25 days 6 packages (6.1gm each) / 75 days
Armonair Respiclick 55mcg**	1 inhalation twice daily	2 inhalations**	60 inhalations per inhaler	1 package / 25 days 3 packages / 75 days
Armonair Respiclick 113mcg**	1 inhalation twice daily	2 inhalations**	60 inhalations per inhaler	1 package / 25 days 3 packages / 75 days
Armonair Respiclick 232mcg	1 inhalation twice daily	2 inhalations (464mcg)	60 inhalations per inhaler	1 package / 25 days 3 packages / 75 days
Arnuity Ellipta 50	1 inhalation once daily	1 inhalation	30 blisters per inhaler	1 package (30 blisters) / 25 days 3 packages (30 blisters each) / 75 days
Arnuity Ellipta 100**	1 inhalation once daily	1 inhalation**	30 blisters per inhaler	1 package (30 blisters) / 25 days 3 packages (30 blisters each) / 75 days
Arnuity Ellipta 200	1 inhalation once daily	1 inhalation (200mcg)	30 blisters per inhaler	1 package (30 blisters) / 25 days 3 packages (30 blisters each) / 75 days
Asmanex HFA 100mcg**	2 inhalations twice daily	4 inhalations**	120 inhalations per 13gm canister	1 package / 25 days 3 packages / 75 days
Asmanex HFA 200mcg	2 inhalations twice daily	4 inhalations (800mcg)	120 inhalations per 13gm canister	1 package / 25 days 3 packages / 75 days
Asmanex Twisthaler 110mcg**	1 inhalation once daily	2 inhalations**	30 inhalation units per package	2 packages / 25 days 6 packages / 75 days
Asmanex Twisthaler 220mcg	1-2 inhalations once-twice daily	4 inhalations (880mcg)	30 inhalation units per package 60 inhalation units per package 120 inhalation units per package	4 packages / 25 days 12 packages / 75 days 2 packages / 25 days 6 packages / 75 days 1 package / 25 days 3 packages / 75 days
Flovent Diskus 50mcg**	1-3 inhalations twice daily	6 inhalations**	60 blisters per device	3 packages (60 blisters each) / 25 days 9 packages (60 blisters each) / 75 days
Flovent Diskus 100mcg**	1-4 inhalations twice daily	8 inhalations**	60 blisters per device	4 packages (60 blisters each) / 25 days 12 packages (60 blisters each) / 75 days
Flovent Diskus 250mcg	1-4 inhalations twice daily	8 inhalations (2000mcg)	60 blisters per device	4 packages (60 blisters each) / 25 days 12 packages (60 blisters each) / 75 days
Flovent HFA 44mcg**	2-4 inhalations twice daily	8 inhalations**	120 inhalations per 10.6gm canister	2 packages (10.6gm each) / 25 days 6 packages (10.6gm each) / 75 days
Flovent HFA 110mcg**	1-3 inhalations twice daily	6 inhalations**	120 inhalations per 12gm canister	2 packages (12gm each) / 25 days 6 packages (12gm each) / 75 days
Flovent HFA 220mcg	1-4 inhalations twice daily	8 inhalations (1760mcg)	120 inhalations per 12gm canister	2 packages (12gm each) / 25 days 6 packages (12gm each) / 75 days
Pulmicort Flexhaler 90mcg**	2-3 inhalations twice daily	6 inhalations**	60 inhalations per device	3 packages / 25 days 9 packages / 75 days
Pulmicort Flexhaler 180mcg	1-4 inhalations twice daily	8 inhalations (1440mcg)	120 inhalations per device	2 packages / 25 days 6 packages / 75 days
Pulmicort Respules 0.25mg**	nebulization of 1-2 respules (2-4mL) daily	3 respules**	30 respules (2mL each) per carton	3 packages (90 respules x 2mL) / 25 days 9 packages (270 respules x 2mL) / 75 days

Pulmicort Respules 0.5mg	nebulization of 1-2 respules (2-4mL) daily	2 respules (1mg)	30 respules (2mL each) per carton	2 packages (60 respules x 2mL) / 25 days 6 packages (180 respules x 2mL) / 75 days
Pulmicort Respules 1mg	nebulization of 1 respule (2mL) daily	1 respule (1mg)	30 respules (2mL each) per carton	1 package (30 respules x 2mL) / 25 days 3 packages (90 respules x 2mL) / 75 days
QVAR 40mcg**	1-3 inhalations twice daily	6 inhalations**	120 inhalations per 8.7gm canister	2 packages (8.7gm each) / 25 days 6 packages (8.7gm each) / 75 days
QVAR 80mcg	1-4 inhalations twice daily	8 inhalations (640mcg)	120 inhalations per 8.7gm canister	2 packages (8.7gm each) / 25 days 6 packages (8.7gm each) / 75 days
QVAR RediHaler 40mcg**	1-3 inhalations twice daily	6 inhalations**	120 inhalations per 10.6gm canister	2 packages (10.6gm each) / 25 days 6 packages (10.6gm each) / 75 days
QVAR RediHaler 80mcg	1-4 inhalations twice daily	8 inhalations (640mcg)	120 inhalations per 10.6gm canister	2 packages (10.6gm each) / 25 days 6 packages (10.6gm each) / 75 days

*The duration of 25 days is used for a 30-day fill period and 75 days is used for a 90-day fill period to allow time for refill processing.

*The limit criteria apply to both brand and generic, if available.

**Utilize higher strength available.

Reference number(s)

2562-A

SPECIALTY GUIDELINE MANAGEMENT

CRYSVITA (burosumab-twza)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indications

Crysvita is indicated for the treatment of X-linked hypophosphatemia in adult and pediatric patients 1 year or older.

All other indications are considered experimental/investigational and are not a covered benefit.

II. CRITERIA FOR INITIAL APPROVAL

X-linked hypophosphatemia

Indefinite authorization may be granted for treatment of X-linked hypophosphatemia when either of the following criteria are met:

- A. Genetic testing was conducted to confirm a PHEX (phosphate regulating gene with homology to endopeptidases located on the X chromosome) mutation in the patient or a directly related family member with appropriate X-linked inheritance.
- B. Serum fibroblast growth factor 23 (FGF23) level is greater than 30 pg/ml.

III. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must meet all initial authorization criteria.

IV. REFERENCES

1. Crysvita [package insert]. Novato, CA: Ultragenyx Pharmaceutical; April 2018.

Reference number(s)

2238-A

SPECIALTY GUIDELINE MANAGEMENT

IDHIFA (enasidenib)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indication

Idhifa is indicated for the treatment of adult patients with relapsed or refractory acute myeloid leukemia (AML) with an isocitrate dehydrogenase-2 (IDH2) mutation as detected by an FDA-approved test.

All other indications are considered experimental/investigational and are not a covered benefit.

II. CRITERIA FOR INITIAL APPROVAL

Authorization of 12 months may be granted for the treatment of relapsed or refractory acute myeloid leukemia with an isocitrate dehydrogenase-2 (IDH2) mutation as detected by an FDA-approved test.

III. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must meet all initial authorization criteria.

IV. REFERENCES

1. Idhifa [package insert]. Summit, NJ: Celgene Corporation; August 2017.

Reference number

2572-A

SPECIALTY GUIDELINE MANAGEMENT

JYNARQUE (tolvaptan)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indication¹

Jynarque is indicated to slow kidney function decline in adults at risk of rapidly progressing autosomal dominant polycystic kidney disease (ADPKD).

All other indications are considered experimental/investigational and are not a covered benefit.

II. CRITERIA FOR INITIAL APPROVAL

Authorization of 12 months may be granted for patients who are initiating Jynarque therapy for the treatment of rapidly progressing autosomal dominant polycystic kidney disease (ADPKD).

III. CONTINUATION OF THERAPY

Authorization of 12 months may be granted to patients who have demonstrated a beneficial response to Jynarque therapy (e.g., slowed kidney function decline).

IV. REFERENCE

1. Jynarque [package insert]. Rockville, MD: Otsuka America Pharmaceutical, Inc.; April 2018.

Reference number

1957-A

SPECIALTY GUIDELINE MANAGEMENT

KEVZARA (sarilumab)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indication

Kevzara is indicated for treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response or intolerance to one or more disease-modifying antirheumatic drugs (DMARDs)

All other indications are considered experimental/investigational and are not a covered benefit.

II. CRITERIA FOR INITIAL APPROVAL

Moderately to severely active rheumatoid arthritis (RA)

- A. Authorization of 24 months may be granted for members who have previously received Kevzara or any other biologic DMARD or targeted synthetic DMARD (e.g., Xeljanz) indicated for moderately to severely active rheumatoid arthritis.
- B. Authorization of 24 months may be granted for treatment of moderately to severely active RA when any of the following criteria is met:
 1. Member has experienced an inadequate response to at least a 3-month trial of methotrexate despite adequate dosing (i.e., titrated to 20 mg/week).
 2. Member has an intolerance or contraindication to methotrexate (see Appendix).

III. CONTINUATION OF THERAPY

Authorization of 24 months may be granted for all members (including new members) who meet all initial authorization criteria and achieve or maintain positive clinical response after at least 3 months of therapy with Kevzara as evidenced by low disease activity or improvement in signs and symptoms of RA.

IV. OTHER

Member has a pretreatment tuberculosis (TB) screening with a TB skin test or an interferon gamma release assay (e.g., QFT-GIT, T-SPOT.TB).

Note: Members who have received Kevzara or any other biologic DMARD or targeted synthetic DMARD (e.g., Xeljanz) are exempt from requirements related to TB screening in this Policy.

Reference number
1957-A

V. APPENDIX: Examples of Contraindications to Methotrexate

1. Alcoholism, alcoholic liver disease or other chronic liver disease
2. Breastfeeding
3. Blood dyscrasias (e.g., thrombocytopenia, leukopenia, significant anemia)
4. Elevated liver transaminases
5. History of intolerance or adverse event
6. Hypersensitivity
7. Interstitial pneumonitis or clinically significant pulmonary fibrosis
8. Myelodysplasia
9. Pregnancy or planning pregnancy (male or female)
10. Renal impairment
11. Significant drug interaction

VI. REFERENCES

1. Kevzara [package insert]. Bridgewater, NJ: Sanofi-aventis, U.S. LLC /Regeneron Pharmaceuticals, Inc.; May 2017.
2. Genovese MC, Fleischmann R, Kivitz AJ, et al. Sarilumab plus methotrexate in patients with active rheumatoid arthritis and inadequate response to methotrexate: results of a phase III study. *Arthritis Rheumatol.* June 2015;67(6):1424-37.
3. Strand V, Reaney M, Chen C, et al. Sarilumab improves patient-reported outcomes in rheumatoid arthritis patients with inadequate response/intolerance to tumour necrosis factor inhibitors. *RMD Open.* 2017; 3:e000416. doi: 10.1136/rmdopen-2016-000416.

Reference number

1953-H

SPECIALTY QUANTITY LIMIT PROGRAM

KEVZARA (sarilumab)

I. PROGRAM DESCRIPTION

The standard limit is designed to allow a quantity sufficient for the most common uses of the medication. The recommended dosing parameters for all FDA-approved indications fall within the standard limits. Coverage of an additional quantity may be reviewed on a case-by-case basis upon request.

II. COVERED QUANTITIES

Medication	Standard Limit	FDA-recommended dosing
Kevzara (sarilumab) 150 mg/1.14 mL single-dose pre-filled syringe	1 pack (2 x 150 mg syringe) per 4 weeks	Rheumatoid arthritis (adult): <ul style="list-style-type: none"> • 200 mg once every two weeks • Reduce dose to 150 mg once every two weeks for management of neutropenia, thrombocytopenia and elevated liver enzymes
Kevzara (sarilumab) 150 mg/1.14 mL single-dose pre-filled pen	1 pack (2 x 150 mg pen) per 4 weeks	
Kevzara (sarilumab) 200 mg/1.14 mL single-dose pre-filled syringe	1 pack (2 x 200 mg syringe) per 4 weeks	
Kevzara (sarilumab) 200 mg/1.14 mL single-dose pre-filled pen	1 pack (2 x 200 mg pen) per 4 weeks	

III. REFERENCE

1. Kevzara [package insert]. Bridgewater, NJ: Sanofi-aventis, U.S. LLC /Regeneron Pharmaceuticals, Inc.; April 2018.

Reference number(s)

2415-A

SPECIALTY GUIDELINE MANAGEMENT

MEPSEVII (vestronidase alfa-vjbk)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indications

Mepsevii is indicated in pediatric and adult patients for the treatment of Mucopolysaccharidosis VII (MPS VII, Sly syndrome).

All other indications are considered experimental/investigational and are not a covered benefit.

II. CRITERIA FOR INITIAL APPROVAL

Mucopolysaccharidosis VII (MPS VII, Sly syndrome)

Indefinite authorization may be granted for treatment of MPS VII (Sly syndrome) when the diagnosis of MPS VII was confirmed by enzyme assay demonstrating a deficiency of beta-glucuronidase enzyme activity or by genetic testing.

III. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must meet all initial authorization criteria.

IV. REFERENCES

1. Mepsevii [package insert]. Novato, CA: Ultragenyx; November 2017.

Reference number(s)

2299-A

SPECIALTY GUIDELINE MANAGEMENT

Mylotarg (gemtuzumab ozogamicin)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indications

1. Newly diagnosed CD33-positive acute myeloid leukemia in adults
2. Relapsed or refractory CD33-positive AML in adults and pediatric patients 2 years and older

Compendial Use

Mylotarg is indicated in high risk patients with acute promyelocytic leukemia (APL).

All other indications are considered experimental/investigational and are not a covered benefit.

II. CRITERIA FOR INITIAL APPROVAL

Acute Myeloid Leukemia (AML)/ Acute Promyelocytic Leukemia (APL)

Authorization of 12 months may be granted for the treatment of AML/APL if the tumor is CD33-positive as confirmed by testing or analysis to identify the CD33 antigen.

III. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must meet all initial authorization criteria.

IV. REFERENCES

1. Mylotarg [package insert]. Philadelphia, PA: Pfizer; Sept 2017.
2. Clinical Consult. CVS Caremark Clinical Programs Review. Focus on Hem-Onc UM programs. September 12, 2017.

Reference number

1961-A

SPECIALTY GUIDELINE MANAGEMENT

RADICAVA (edaravone)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indications

Radicava is indicated for the treatment of amyotrophic lateral sclerosis (ALS).

All other indications are considered experimental/investigational and are not a covered benefit.

II. PRESCRIBER SPECIALTIES

This medication must be prescribed by or in consultation with a neuromuscular specialist.

III. CRITERIA FOR INITIAL APPROVAL

Authorization of 6 months may be granted for treatment of ALS when all of the following criteria are met:

- A. Diagnosis of definite or probable ALS
- B. Duration of ALS is 2 years or less
- C. Functional ability is retained for most activities of daily living (ADLs)
- D. Ventilatory support, noninvasive or invasive, is not required

IV. CONTINUATION OF THERAPY

Authorization of 6 months may be granted for members continuing with Radicava therapy when the following criteria are met:

- A. Diagnosis of definite or probable ALS
- B. There is a clinical benefit from Radicava therapy such as stabilization of functional ability and maintenance of ADLs
- C. Invasive ventilation is not required

V. REFERENCES

1. Radicava [package insert]. Jersey City, NJ: MT Pharma America, Inc.; May 2017.
2. EFNS Task Force on Diagnosis and Management of Amyotrophic Lateral Sclerosis; Andersen PM, et al. EFNS guidelines on the Clinical Management of Amyotrophic Lateral Sclerosis (MALS) – revised report of an EFNS task force. *Eur J Neurol.* 2012;19(3):360-75.

Utilization Management, New Policies

<i>Policy Name</i>	<i>Policy Type</i>
<i>Nuedexta</i> [®]	Initial Prior Authorization
<i>Topical NSAIDs</i>	Initial Prior Authorization with Quantity Limits
<i>Topical Vitamin D Analogs</i>	Initial Prior Authorization
<i>Chenodal</i> [®]	Initial Prior Authorization; NCSHP Custom Criteria
<i>Naprelan</i> [®]	Initial Prior Authorization; NCSHP Custom Criteria
<i>Thiola</i> [®]	Initial Prior Authorization; NCSHP Custom Criteria

*Any policies approved by the P&T Committee will go into effect October 1, 2018.

PRIOR AUTHORIZATION CRITERIA

BRAND NAME
(generic)

NUEDEXTA
(dextromethorphan hydrobromide/quinidine sulfate)

Status: CVS Caremark Criteria

Type: Initial Prior Authorization

POLICY

FDA-APPROVED INDICATIONS

Nuedexta is indicated for the treatment of pseudobulbar affect (PBA). PBA occurs secondary to a variety of otherwise unrelated neurologic conditions, and is characterized by involuntary, sudden, and frequent episodes of laughing and/or crying. PBA episodes typically occur out of proportion or incongruent to the underlying emotional state. PBA is a specific condition, distinct from other types of emotional lability that may occur in patients with neurological disease or injury.

COVERAGE CRITERIA

The requested drug will be covered with prior authorization when the following criteria are met:

- The patient has a diagnosis of pseudobulbar affect (PBA)

REFERENCES

1. Nuedexta [package insert]. Aliso Viejo, CA: Avanir Pharmaceuticals, Inc.; January 2016.
2. AHFS DI (Adult and Pediatric) [database online]. Hudson, OH: Lexi-Comp, Inc.; http://online.lexi.com/lco/action/index/dataset/complete_ashp [available with subscription]. Accessed July 2017.
3. Micromedex Solutions [database online]. Greenwood Village, CO: Truven Health Analytics Inc. Updated periodically. www.micromedexsolutions.com [available with subscription]. Accessed July 2017.
4. Piro E, Brooks B, Cummings J, et al. Dextromethorphan Plus Ultra Low-Dose Quinidine Reduces Pseudobulbar Affect. *Ann Neurol* 2010;68:693-702.
5. Miller R, Jackson C, Kasarskis E, et al. Practice Parameter update: The care of the patient with amyotrophic lateral sclerosis: Multidisciplinary care, symptom management, and cognitive/behavioral impairment (an evidence-based review): Report of the Subcommittee of the American Academy of Neurology Quality Standards. *Neurology* 2009;73:1227–1233.
6. Rosen H. Dextromethorphan/Quinidine sulfate (Zenvia) for Pseudobulbar Affect. *Drugs Today (Barc)* 2008;44(9):661–668.
7. Shaibani AI. Efficacy and safety of dextromethorphan/quinidine at two dosage levels for diabetic neuropathic pain: a double-blind, placebo-controlled, multicenter study. *Pain Med* 2012 Feb; 13(2): 243-54.

PRIOR AUTHORIZATION CRITERIA

BRAND NAME

(generic) (diclofenac sodium topical solution 1.5%)

KLOFENSAID II

(diclofenac sodium topical solution 1.5%)

PENNSAID

(diclofenac sodium topical solution 2%)

Status: CVS Caremark Criteria

Type: Initial Prior Authorization with Quantity Limit

POLICY

FDA-APPROVED INDICATIONS

Diclofenac sodium topical solution is indicated for the treatment of the pain of osteoarthritis of the knee(s).

COVERAGE CRITERIA

The requested drug will be covered with prior authorization when the following criteria are met:

- The patient has osteoarthritis pain of the knee(s)

AND

- Treatment with diclofenac topical solution is necessary due to intolerance or a contraindication to oral nonsteroidal anti-inflammatory drugs (NSAIDs)

Quantity Limits apply.

REFERENCES

- Pennsaid [package insert]. Deerfield, IL: Horizon Pharma USA, Inc.; May 2016.
- Diclofenac topical liquid 1.5% [package insert]. Weston, FL: Apotex Corp.; October 2016.
- AHFS DI (Adult and Pediatric) [database online]. Hudson, OH: Lexi-Comp, Inc.; http://online.lexi.com/lco/action/index/dataset/complete_ashp [available with subscription]. September 2017.
- Micromedex Solutions [database online]. Greenwood Village, CO: Truven Health Analytics Inc. Updated periodically. www.micromedexsolutions.com [available with subscription]. September 2017.

*QUANTITY LIMIT

This quantity limit should accumulate across all drugs and strengths up to highest quantity listed depending on the order the claims are processed. Accumulation does not apply if limit is coded for daily dose.

Medication	4 Weeks Limit*	12 Weeks Limit*
Pennsaid (diclofenac sodium top soln 2%)	2 bottles (112gm each) 224gm / 21 days	6 bottles (112gm each) 672gm / 63 days
diclofenac sodium top soln 1.5%	3 bottles (150mL each) 450mL / 21 days	9 bottles (150mL each) 1350mL / 63 days
Klofenaid II (diclofenac sodium top soln 1.5%)	3 bottles (150mL each) 450mL / 21 days	9 bottles (150mL each) 1350mL / 63 days

* The duration of 21 days is used for a 28-day fill period and 63 days is used for an 84-day fill period to allow time for refill processing.

PRIOR AUTHORIZATION CRITERIA

DRUG CLASS	VITAMIN D ANALOGS TOPICAL
BRAND NAME (generic)	(calcipotriene topical scalp solution)
	CALCITRENE (calcipotriene ointment)
	DOVONEX (calcipotriene cream)
	ENSTILAR (calcipotriene/betamethasone dipropionate foam)
	SORILUX (calcipotriene foam)
	TACLONEX (calcipotriene/betamethasone dipropionate ointment, suspension)
	VECTICAL (calcitriol ointment)

Status: CVS Caremark Criteria
Type: Initial Prior Authorization

POLICY

FDA-APPROVED INDICATIONS

Calcipotriene Topical Scalp Solution

Calcipotriene Topical Scalp Solution 0.005% is indicated for the topical treatment of chronic, moderately severe psoriasis of the scalp. The safety and effectiveness of topical calcipotriene in dermatoses other than psoriasis have not been established.

Calcitrene

Calcitrene Topical Ointment (calcipotriene 0.005%) is indicated for the treatment of plaque psoriasis in adults. The safety and effectiveness of topical calcipotriene in dermatoses other than psoriasis have not been established.

Dovonex

Dovonex Cream (calcipotriene 0.005%) is indicated for the treatment of plaque psoriasis. The safety and effectiveness of topical calcipotriene in dermatoses other than psoriasis have not been established.

Enstilar

Enstilar Foam (calcipotriene 0.005%/betamethasone/dipropionate 0.064%) is indicated for the topical treatment of plaque psoriasis in patients 18 years of age and older.

Sorilux

Sorilux foam (calcipotriene 0.005%) is indicated for the topical treatment of plaque psoriasis of the scalp and body in patients 18 years and older.

Taclonex

Taclonex Ointment (calcipotriene 0.005%/betamethasone 0.064%) is indicated for the topical treatment of plaque psoriasis in patients 12 years of age and older.

Taclonex

Taclonex Topical Suspension (calcipotriene 0.005%/betamethasone 0.064%) is a vitamin D analog and a corticosteroid combination product indicated for the topical treatment of:

- Plaque psoriasis of the scalp and body in patients 18 years and older
- Plaque psoriasis of the scalp in patients age 12 to 17 years

Vectical

Vectical Ointment (calcitriol 3 mcg/g) is indicated for the topical treatment of mild to moderate plaque psoriasis in adults 18 years and older.

Limitations of Use

Vectical Ointment should not be applied to the eyes, lips, or facial skin.

COVERAGE CRITERIA

The requested drug will be covered with prior authorization when the following criteria are met:

- The requested drug is being prescribed for the treatment of psoriasis.
- AND**
- The patient experienced an inadequate treatment response, intolerance, or contraindication to a generic topical steroid (e.g., betamethasone dipropionate, clobetasol propionate, desoximetasone, or fluocinonide).

REFERENCES

1. Calcipotriene Topical Scalp Solution [package insert]. South Plainfield, NJ: G&W Laboratories, Inc.; November 2016.
2. Calcitriene Ointment [package insert]. Hawthorne, NY: Taro Pharma, a division of Taro Pharmaceuticals U.S.A., Inc.; April 2012.
3. Dovonex Cream [package insert]. Parsippany, NJ: LEO Pharma Inc.; April 2014.
4. Sorilux [package insert]. Greenville, NC: Mayne Pharma.; April 2017.
5. Enstilar Foam [package insert]. Madison, NJ: LEO Pharma, Inc.; November 2016.
6. Taclonex Ointment [package insert]. Madison, NJ: LEO Pharma, Inc.; January 2017.
7. Taclonex Topical Suspension [package insert]. Parsippany, NJ: LEO Pharma, Inc.; January 2017.
8. Vectical Ointment [package insert]. Fort Worth, Texas: Galderma Laboratories, L.P.; September 2016.
9. AHFS DI (Adult and Pediatric) [database online]. Hudson, OH: Lexi-Comp, Inc.; http://online.lexi.com/lco/action/index/dataset/complete_ashp [available with subscription]. Accessed May 2017.
10. Micromedex Solutions [database online]. Greenwood Village, CO: Truven Health Analytics Inc. Updated periodically. www.micromedexsolutions.com [available with subscription]. Accessed May 2017.
11. Menter A, Korman N, Elmets C, et al. American Academy of Dermatology Work Group. Guidelines of care for the management of psoriasis and psoriatic arthritis: Section 6. Guidelines of care for the treatment of psoriasis and psoriatic arthritis: case-based presentations and evidence-based conclusions. *J Am Acad Dermatol.* 2011; 65(1):137-74.
12. National Psoriasis Foundation. Topical Treatments for Psoriasis. <http://www.psoriasis.org>. Accessed May 2017.

Chenodal Custom PA Sample Criteria:**CRITERIA FOR APPROVAL**

- 1 Is the patient pregnant?
- 2 Does the patient have the diagnosis of cerebrotendinous xanthomatosis (CTX)?
[If yes, then no further questions.]

[Note: Documentation of clinical, laboratory data to support diagnosis is required]
- 3 Does the patient have the diagnosis of radiolucent stones in well-opacifying gallbladders?
- 4 Is the patient at increased surgical risk due to systemic disease or age?
- 5 Does the patient have hepatocyte dysfunction or bile ductal abnormalities such as intra hepatic cholestasis, primary biliary cirrhosis or sclerosing cholangitis?
- 6 Has the gallbladder been confirmed as nonvisualizing after two consecutive single doses of dye?
- 7 Are the stones radiopaque or radiolucent bile pigment stones?
- 8 Does the patient have gallstone complications or compelling reasons for gallbladder surgery including unremitting acute cholecystitis, cholangitis, biliary obstruction, gallstone pancreatitis or biliary gastrointestinal fistula?
- 9 Will liver enzymes be monitored while the patient is receiving Chenodal?
- 10 Has the patient been using Chenodal for 24 months?
- 11 Does the patient have a documented contraindication, intolerance or allergy to ursodiol?
[If yes, then no further questions.]
- 12 Does the patient have a documented failure to an adequate trial of one month of ursodiol?

	Yes	No
1.	Deny	Go to 2
2.	Approve, 12 months	Go to 3

3.	Go to 4	Deny
4.	Go to 5	Deny
5.	Deny	Go to 6
6.	Deny	Go to 7
7.	Deny	Go to 8
8.	Deny	Go to 9
9.	Go to 10	Deny
10.	Deny	Go to 11
11.	Approve, 12 months	Go to 12
12.	Approve, 12 months	Deny

PRIOR AUTHORIZATION CRITERIA

BRAND NAME
(generic)

NAPRELAN
(naproxen sodium extended release)

Status: Client Requested Criteria

Type: Initial Prior Authorization

Ref # *****

CRITERIA FOR APPROVAL

1	Is the patient 18 years of age or older? [If no, then no further questions.]	Yes	No
2	Is the requested drug being prescribed for the relief of the signs and symptoms of any of the following: A) Rheumatoid Arthritis, B) Osteoarthritis, C) Ankylosing Spondylitis, D) Gouty Arthritis, E) Mild to Moderate Pain? [If no, then no further questions.]	Yes	No
3	Has the patient had an inadequate treatment response to BOTH immediate-release and delayed-release naproxen?	Yes	No

Mapping Instructions

	Yes	No
1.	Go to 2	Deny
2.	Go to 3	Deny
3.	Approve, 12 months	Deny

PRIOR AUTHORIZATION CRITERIA

CLASS	GENITOURINARY AGENTS		
PRODUCT NAME (brand/generic)	THIOLA (tiopronin tablets)		
Status: Client Requested Criteria			
Type: Initial Prior Authorization			Ref # C13867-A

<u>CRITERIA FOR APPROVAL</u>			
1	Is the requested drug being used for the prevention of cystine (kidney) stone formation who has severe homozygous cystinuria with urinary cystine greater than 500 milligrams per day?	Yes	No
2	Is patient resistant to treatment with the conservative measures of high fluid intake, alkali and diet modification?	Yes	No
3	Has the patient had an adverse reactions to d-penicillamine?	Yes	No

Mapping Instructions		
	Yes	No
1.	Go to 2	Deny
2.	Go to 3	Deny
3.	Approve, 12 months	Deny

REFERENCES

- NCSHP Medical Exception Policy.

Written by: UM Development (JG)
 Date Written: 08/2018
 Revised:
 Reviewed: Medical Affairs (TP) 08/2018
 MDCcommittee XX/2018

The Participating Group signed below hereby accepts and adopts as its own the criteria for use with Prior Authorization, as administered by CVS Caremark.

Signature	Date
Client Name	