MARCH 21, 2017

North Carolina State Health Plan
FOR TEACHERS AND STATE EMPLOYEES
A Division of the Department of State Treasurer

PHARMACY AND THERAPEUTICS (P&T) COMMITTEE MEETING

PRESENTED BY: IRA PROTAS & JAMILAH BRUNSON
NORTH CAROLINA STATE HEALTH PLAN
3200 ATLANTIC AVENUE, RALEIGH, NC 27604

BINDER DIVIDER

“Introduction”

North Carolina State Health Plan
FOR TEACHERS AND STATE EMPLOYEES
A Division of the Department of State Treasurer

Pharmacy and Therapeutics (P&T) Committee Meeting
March, 21st 2017

Agenda

	Topic	Presenter
I.	**Welcome**	Ira Protas
	• Call to Order	
II.	**Introductions**	Ira Protas
	• Ira Protas, RPh – Director of Pharmacy Benefits-Chair	
	• Carl Antolick III, PharmD – Clinical Pharmacist	
III.	**Conflict of Interest Statement**	Lotta Crabtree, JD
IV.	**Minutes from December, 28th 2016 Meeting**	Jamilah Brunson, PharmD
V.	**Old Business**	Jamilah Brunson, PharmD
	• SHP Formulary Customization Decision	
	• CVS Implementation	
	• Formulary Development and Management at CVS Caremark®	
VI.	**Light Meal**	
VII.	**2017 Q2 Formulary Updates**	Jamilah Brunson, PharmD
	• Removal of Hyperinflation Products	Carl Antolick III, PharmD
	• New to Market Blocked Removals (Formulary Additions)	
	• Products Changing Tiers	
VIII.	**Utilization Management Policy Review**	Jamilah Brunson, PharmD
	• Attention Deficit Hyperactivity Disorder (ADHD) Agents	
	• Insomnia Agents	
	• Narcolepsy Agents	
	• Long Acting Beta Agonists Policy	
	• Short Acting Beta Agonists Policy	
IX.	**Other Topics**	Jamilah Brunson, PharmD
	• Formulary Omissions	
	• Formulary Documents	
X.	**Next Meeting Date**	Ira Protas
	• May 23rd 2017	
	• Directions	

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 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 participation[1] 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*

Pharmacy and Therapeutics (P&T) Committee Meeting
December 13, 2016
6:00 PM – 8:00 PM
MINUTES

P&T Committee Members
Matthew Flynn, MD
Randy Grigg, MD
John Anderson, MD
Jennifer Burch, PharmD
Michael Spiritos, MD
John Engemann, MD
David Konanc, MD
Steven Bentsen, MD (Beacon HealthOptions)
Connie Rominger (BCBSNC)
Patti Forest, MD (State Health Plan)
Jamilah Brunson, PharmD (State Health Plan)
Lotta Crabtree, JD (State Health Plan) Interim Chair

State Health Plan (SHP) Staff
Natasha Davis
Neha Zadoo
Jennifer Gontarz
Lucy Barreto

SHP Contracted Vendors
H. Renee Jarnigan, RPh (CVS Health)
Robbie Wallace (CVS Health)

Guests
Mark Roshelli, Sanofi US

I. Welcome, Introductions and Conflict of Interest

Jamilah Brunson welcomed the committee members and guests.

II. Minutes from August 9, 2016 Meeting

The committee members reviewed and approved the August 9, 2016 minutes.

III. SHP Update

Jamilah shared information pertaining to the State Health Plan's ***Proposed 2017 Pharmacy Formulary and Benefit Design Changes*** relative to closed formulary drugs. The Board of Trustees approved the closed formulary in June, however, Lotta noted that statutes require the review and approval of formulary restrictions by the P & T committee.

Jamilah briefly referred to the formulary exception process that was distributed in the packet upon arrival. At the previous P&T meeting, this was completely addressed, therefore the State Health Plan provided mainly for reference.

Jamilah reviewed the physician FAX form in the packet that will be used for formulary exceptions. It was stated that an urgent review would be handled within 24 hours and non-urgent requests are handled within 72 hours by a coverage determination group at the PBM. Some physicians expressed concern if the coverage was denied, but the appeals process was offered.

Dr. Konanc and Dr. Grigg expressed concern with the administrative tasks associated with getting a drug approved, and weighing out the costs of personnel vs. savings to the SHP. Lotta Crabtree explained that choosing the closed formulary, with the given population, SHP stands to save $400-$500 million over three years, by CVS estimates. Jamilah added that the purpose of the P&T committee is to provide a forum to vet out any issues with drug coverage/exclusions.

Jamilah reviewed all drugs on the list by therapeutic class, engaging all members present for comments. The specific classes are listed below, to include the drugs under review.

Program Review of Non-Covered Drugs for 2017

Anti-infective class changes: Doryx, Nuvessa

Anti-viral class changes: Valcyte, Daklinza, Olysio, Zepatier, Viekira, Viekira XR, Technivie, Valtrex

Biologic class changes: Cuvitru, Pegasys, Extavia, Plegridy, Avonex, Kineret, Prolia, Otezla, Xeljanz, Zeljanz XR, Actemra, Orencia, Remicade, Cimzia, Simponi, Cosentyx

Cardiology class changes: EpiSnap Kit, Adrenaclick, Lescol XL, Liptruzet, Livalo, Matzim LA, Plavix, Teveten HCT, Lipitor, Norvasc, Praluent, QBRELIS, Pradaxa, Teveten, Edarbi, Byvalson, Atacand HCT, Edarbyclo, Exforge, Exforge HCT, Atacand, Diovan, Durlaza, Cardizem, Cardizem CD, Cardizem LA, Crestor, Tricor, Tyvaso, Ventavis, Adcirca, Revation, Remodulin, Advicor, Altoprev, Diovan HCT, Savaysa, Dutoprol, Opsumit, Prestalia

CNS class changes: Namzaric, Adzensys XR, Evekeo, Quillichew ER, Adderall XR, Fanatrex, Spritam, Khedezla, Oleptro, Cymbalta, venlafaxine ext-rel tabs (except 225 mg.), Rytary, Intuniv, Invega Trinz, Vraylar, Abilify, EXONDYS 51, Belsomra, Intermezzo, Lunesta, Rozerem, Onzetra Xsail, Amrix, Arthrotec, Fenortho, Naprelan, Tivorbex, Vivlodex, Lomaira, Qsymia, Lazanda, Zubsolv, Oxaydo, Xtampza,

Probuphine, Emend, Yosprala, Xenazine, Allzital, butalbital/APA/Caffeine capsules, Fioricet, Abstral, Embeda, Elavil 25mg tablets, Evzio

Dermatology class changes: Alcortin A, Aloquin, Pennsaid, Noritate, Carac, flurouracil cream 0.5%, Tolak, Apexicon E, clobetasol propionate 0.05% spray, Clobex, Olux-E, Sernivo, Ultravate, Denavir, Novacort, Urevaz, Aczone 7.5% gel, Avar AER 9.5-5%, Avar LS AER 10-2%, ASTERO

Diabetes class changes: Invokana, Invokamet, Kazano, Kombiglyze XR, Nesina, Onglyza, Oseni, Riomet, Lantus, Fortamet, Glumetza, Invokamet XR, Glyxambi, non-BD needles and syringes, Non-One Touch Ultra/Verio Test strips, Actos, Bydureon, Byetta, Humalog, Humalog 50/50, Humalog 75/25, Humulin 70/30, Humulin N, Humulin R, Apidra, Afrezza, Synjardy, Toujeo

Endocrine class changes: Cetylev, Androgel, Fortesta, Testim, testosterone gel 1%, Vogelxo, Bravelle, Gonal-F, Repronex, Millipred, Rayos, Zurampic, Genotropin, Norditropin, Nutropin AQ, Omnitrope, SAizen, Zomactan, RElistor, Makena, DexPak, Natesto

Gastrointestinal class changes: Asacol HD, Delzicol, Gialax Kit, Zegerid, Prevacid, Protonix, Nexium capsule, Nexium granules, omeprazole-sod bicarb capsules

Genitourinary class changes: Jalyn, Oxytrol, Detrol LA, Enablex, Toviaz, Gelnique

Hematologic class changes: Procrit, Idelvion, Adynovate, Afstyla, Vonvendi, Amicar, Ferriprox, Neupogen, Helixate FS

Immunosuppressive class changes: Envarsus XR

Nephrology class changes: Fosrenol, Keveyis

Nutrition class changes: Carnitor, Elfolate, Enbrace HR

Oncology class changes: Farydak, Evomela, Tasigna, Odomzo, Cotellic, Xtandi, Cabometyx, Alecensa, Gleevec, Nilandron

Ophthalmic class changes: Lastacraft, Lumigan

Osteoarthritis class changes: Euflexxa, Gelsyn-3, Genvisc, Hymovis, Monovisc, Orthovisc, Synvisc, Synvisc-One

Otic class changes: Floxin, Otiprio, Otovel

Respiratory class changes: Obredon, Beconase AQ, Nasonex, Omnaris, Qnasl, Rhinocort Aqua, Ticanase, Ticaspray Pak, Veramyst, Zetonna, Incruse Ellipta, Proventil HFA, Aerospan, Alvesco, Ventolin HFA, Xoponex HFA, Seebri, Tudorza Pressair, Utibron Neohaler, Stiolto Respimat, Symbicort, Cinqair, Tobi, Tobi Podhaler

Various committee members had expressed concerns over the following drugs to be removed from coverage:

Belsomra (suvorexant): Dr. Konanc expressed concern about the non-formulary status citing the unique mechanism of action in comparison to the formulary alternatives. He request member (utilization) impact be considered.

Oleptro (trazadone ext rel tab): Dr. Grigg expressed concern citing issues with somnolence for patients requiring high doses for the depression indication; immediate release formulation is sufficient for those utilizing the agent for sleep, not depression.

Farydak (panobinostat): Dr. Spiritos concerned there is no formulary alternative or "me too" drug on the market for this drug.

Tasigna: P&T raised concern that this is a first-line agent with data in the literature that supports its superiority in this class. CVS must provide rationale; SHP to provide utilization.

Alecensa (alectinib): This drug is preferred for patients with NSCLC with brain metastasis and the guideline recommends for patients with ALK positive mutation that has failed Xalkori (crizotinib).

Cabometyx (cabozantinib): P&T does not recommend exclusion – wants rationale and member utilization.

All voted in favor of the exclusions with the exception of further review of the above six drugs in the coming months. The committee agreed that the final decision for exclusion or inclusion in the formulary would be made by the Plan's Executive Administrator. In the meantime, providers can use the exception process for these drugs when appropriate.

Following the meeting, the Plan reached out to Dr. Shanahan for comments on the following drug exclusions and is waiting for response: Kineret, Otezla, Xeljanz and Xeljanz XR, Actemra, Orencia, Remicade, Cimzia, Simponi and Cosentyx.

I. Other Topics

Dr. Flynn asked for a mobile app version of the formulary and drugs requiring prior authorization. Dr. Konanc added that the ability to interface with EMR at the point of care would be helpful as well. Robby Wallace from CVS agreed to look into this topic to see how CVS could support provider tools through the Surescripts network. Electronic prior authorization is available through CoverMyMeds. More information can be shared at the next P&T meeting.

The next P&T Committee meeting will be held on Tuesday, February 21, 2017.

North Carolina State Health Plan
FOR TEACHERS AND STATE EMPLOYEES
A Division of the Department of State Treasurer
3200 Atlantic Avenue • Raleigh, NC 27604 • Phone: 919-814-4400 • Fax: 919-855-5818 • www.shpnc.org

To:
Mona M. Moon, Executive Administrator, State Health Plan

From:
State Health Plan Clinical Team
Jamilah Brunson, Clinical Pharmacist Manager, State Health Plan
Carl Antolick, Clinical Pharmacist, State Health Plan
Dr. Patti Forest, Medical Director, State Health Plan

Date:
January 31, 2017

Re:
Formulary Customizations Analysis related to Pharmacy & Therapeutics (P&T) Committee 2017 Formulary Evaluation

The Plan's P&T Committee met on December 13, 2016, to review the proposed Custom Formulary. Of primary interest was the proposed list of excluded medications. After extensive discussions, the Committee requested that the Plan consider including the following five medications on the formulary: Cabometyx, Farydak, Alecensa, Belsomra and Tasigna.

After the meeting, CVS Caremark, the Pharmacy Benefit Manager (PBM), notified the Plan that Cabometyx was slated to move back onto the formulary, therefore this one was added to the Custom Formulary. The clinical team has completed the analysis on the remaining medications:

- Farydak has one preferred and four non-preferred formulary alternatives. The P&T specialist expressed concern due to the unique mechanism of action and use in patients that have failed the first choice options. There is a formulary exception process in place for these patients. It is also one of the medications that the Plan chose to "grandfather" for existing patients; therefore, members who were on the medication prior to the transition will continue to have access to it without an exception. Utilization was limited to one unique member in 2016.
- Alecensa has two non-preferred formulary alternatives. The P&T specialist expressed concern due to data that the drug is preferred in patients with brain metastasis. There is a formulary exception process in place for those patients. Alecensa is also "grandfathered" for existing patients. Utilization was limited to five unique members in 2016.
- Belsomra is an insomnia agent for which there are numerous preferred formulary alternatives. Belsomra is "grandfathered" for existing patients with the new PBM implementation and the P&T specialist mainly wanted the rationale behind the non-formulary status. This exclusion rationale has been provided.

- Tasigna has three preferred formulary alternatives. The P&T specialist expressed concern due to the unique mechanism of action and use as first choice for some specific indications. The formulary exception process is in place for those patients. Utilization was limited to 28 unique member in 2016.

Due to the limited utilization, grandfathered status, formulary alternatives and clinical rationale for the exclusion, it is the recommendation of the clinical team to maintain the non-formulary, (excluded) status of Farydak, Alecensa, Belsomra and Tasigna. The exception process is available to members who meet the medical necessity criteria.

Patti Forest, MD Medical Director

Jamilah Brunson, Clinical Pharmacist

Carl Antolick, Clinical Pharmacist

Recommendation accepted: 1/31/2017

Mona M. Moon, Executive Administrator

CVS Health

At CVS Health, we are acting vigilantly to help our clients contain their costs while supporting their members with affordable prescription drugs benefits. A key to containing cost is effective formulary management. This is essential at a time when escalating drug prices as well as the introduction of new costly therapies are creating significant challenges to the affordability of health care. Our solutions include rapid responses to the quickly evolving market.

Our 2017 formulary management strategy continues to address emerging cost drivers with new, market-leading enhancements:

- **Embracing the Future with Biosimilars and Follow-on Biologics**
  Biosimilar and follow-on biologics will be included as a key component of our 2017 standard formulary strategy, replacing higher cost drugs within the categories. This will include the biosimilar Zarxio®, replacing Neupogen®, to decrease the risk of infection in patients receiving treatment for certain forms of cancer, and the follow-on product Basaglar® – approved in Europe as a biosimilar – replacing the insulin Lantus®, for treatment of diabetes. We anticipate significant savings for many clients and members, as the removal of higher cost products will enable near-term value, with additional future opportunities for savings resulting from market competition as more new products are launched.
- **Creating Additional Client Value with Indication-Based Formulary**
  Indication-based formulary is a more precise management strategy related to a drug's treatment indication or diagnosis and the value that therapy delivers to each individual patient. Given the growing number of supplemental indications for many drugs, utilizing an indication-based formulary helps expand our negotiating strength to improve formulary positioning and rebates for products, creating opportunities for more value in the form of client and member savings.

CVS Health has been the market leader in formulary innovation.

Beginning in 2012 we were the first to remove drugs from our formulary and in 2015 the first to pioneer new-to-market drug evaluations to lessen future member disruption and generate lower costs for our clients when new products and line extensions are launched.

106-39009M1 080116

Starting January 1, 2017 we will apply an indication-based strategy to further contain hepatitis C treatment costs. Also starting January 1, clients can benefit from an indication-based formulary within the autoimmune category, specifically psoriasis, which is among the biggest cost growth drivers for many plans, by adopting Advanced Control or Advanced Control Specialty formularies or a Preferred Drug Plan Design (PDPD). Additional indication-based opportunities and categories will be evaluated as they emerge throughout the year.

- **Tackling Hyperinflationary Drugs to Reduce Their Cost Impact**
  CVS Health is taking a stand against egregious drug price increases that unnecessarily add costs for clients and their members. On a quarterly basis, products with egregious cost inflation that have readily-available, clinically-appropriate and more cost-effective alternatives may be evaluated and potentially removed from the formulary. For example, among the hyperinflationary drugs that will be removed in 2017 is Alcortin® A External Gel by Novum Pharmaceuticals which saw a price inflation of 2856.8 percent in the last three years[2].

Our rigorous approach to formulary management **will help generate a total savings of more than $9 billion for clients from 2012 through 2017**[1].

We are also taking steps to address "limited source generics" which are products with limited generic manufacturers resulting in significant cost in the market. These products will be evaluated and if appropriate, be excluded during the year.

CVS Health offers a range of formulary management options that maintain clinical integrity and help reduce pharmacy costs for clients and members. We minimize transition issues by communicating with members and prescribers in advance to help members move to clinically appropriate medications prior to implementation of the formulary changes.

Effective January 1, 2017 we expect to remove 35 products from our standard formulary, including 10 hyperinflationary drugs. These formulary modifications will help reduce costs for clients and plan members.

[1] CVS Health Trade Finance, 2012 – 2017E
[2] Medispan data, 2013 to Q1 2016

106-39009M1 080116

2017 Standard Formulary List of Removals and Updates

CLASS	PRODUCTS
Analgesics	Butalbital/APAP/Caffeine Capsules (All Brands and Generics, not tablets)
Antiandrogens	Xtandi, Nilandron oral tablets HYP
Antidepressants- SNRI's	Venlafaxine ER Tablets, except 225mg (All Brands and Generics)
Antilipemics	Crestor (MSB)
Beta Blocker Combinations	Dutoprol oral tablets HYP
Carnitine Deficiency Agents	Carnitor/ Carnitor SF oral solution (MSB) HYP
CML - Oncology	Gleevec (MSB), Tasigna
CNS - Huntington's Disease	Xenazine (MSB)
Colony Stimulating Factors	Neupogen
Corticosteroids	DexPak oral tablets HYP, Millipred/ Millipred DP oral tablets, dose pack and oral solution HYP
Cystic Fibrosis	Tobi Podhaler/ Tobi (MSB)
Dermatology	Alcortin A gel HYP, Aloquin gel HYP, Novacort gel HYP
Hemophilia	Helixate FS
Hepatitis C	Daklinza, Olysio, Technivie, Zepatier
IBS Constipation	Amitiza P
Insulin	Lantus, Toujeo
Nasal Steroid Combinations	Dymista P
NSAID's	Duexis NP, Vimovo NP
Opioid Analgesics	Abstral
Opioid Antagonists	Evzio
Oral Anticoagulants	Pradaxa
Overactive Bladder	Enablex (MSB), Gelnique, Toviaz P
PAH Endothelin-Receptor Antagonists	Opsumit
Pen Needles/Syringes	All non-Becton Dickinson pen needles and syringes*
Potassium Supplements	Klor-Con oral pack for solution HYP
Proton Pump Inhibitors	Nexium (MSB), Zegerid oral suspension and capsules (MSB) HYP
Short Acting Beta Agonists	Proventil, Ventolin

HYP = Hyperinflation drug NP = Non Preferred drug being added back P = Preferred drug being added back

CVSHealth

*Diabetic supplies including pens/needles not included in count

This document contains references to brand-name prescription drugs that are trademarks or registered trademarks of pharmaceutical manufacturers not affiliated with CVS Caremark.

106-39009M1 080116

BINDER DIVIDER

"Formulary Updates"

Removal of Hyperinflation Products

- As discussed during the implementation phase, CVS Caremark has a number formulary management strategies to help manage drug spend through appropriate selection and use of drug therapy. One of the new strategies for 2017 is hyperinflation management. This strategy targets drugs with year-over-year price inflation that have readily available clinically appropriate and more cost effective alternatives.
- This strategy was encompassed in the formulary changes that were effective 1/1/17 announced last August. Some of those exclusions were Alcortin A, Aloquin, Novacort and Dutoprol. All have generic alternatives and CVS Caremark has not found any significant member disruption or challenges as part of this strategy.
- At that time, based on past experience, CVS Caremark did not anticipate any exclusions during quarterly updates; however, with the negative impact potential these products can have on trend, including these in the quarterly changes is certainly appropriate and the most effective way to address this challenge.

DRUG NAME	Tier Status Change	Rationale	Alternatives	# Utilizers (YTD)
E.E.S.® suspension ***(erythromycin ethylsuccinate)***	**3--> Not Covered**	**Availability of a generic option.**	***erythromycin ethylsuccinate***	**0**
ERYPED® suspension ***(erythromycin ethylsuccinate)***	**3--> Not Covered**	**Hyperinflation Exclusion - Availability of a generic option.**	***erythromycin ethylsuccinate***	**0**
MACRODANTIN® capsules ***(nitrofurantoin)***	**2--> Not Covered**	**Hyperinflation Exclusion - Availability of a generic option.**	***nitrofurantoin***	**0**
BETAPACE® tablets ***(sotalol)***	**2--> Not Covered**	**Hyperinflation Exclusion - Availability of a generic option for the treatment of life-threatening, documented ventricular arrhythmias.**	***sotalol***	**0**
BETAPACE AF® tablets ***(sotalol)***	**2--> Not Covered**	**Hyperinflation Exclusion - Availability of a generic option for the treatment of life-threatening, documented ventricular arrhythmias.**	***sotalol***	**0**

DRUG NAME	Tier Status Change	Rationale	Alternatives	# Utilizers (YTD)
LANOXIN® tablets *(digoxin)*	2--> Not Covered	Hyperinflation Exclusion - Availability of a generic option.	*digoxin*	0
DYRENIUM® capsules *(triamterene)*	3--> Not Covered	Hyperinflation Exclusion - Availability of another potassium-sparing diuretic for heart failure or edema.	*amiloride*	4
ZONEGRAN® capsules *(zonisamide)*	3--> Not Covered	Hyperinflation Exclusion - Availability of a generic option.	*zonisamide*	4
CAFERGOT® tablets *(caffeine/ergotamine)*	3--> Not Covered	Hyperinflation Exclusion - Availability of other options as therapy to abort or prevent vascular headaches.	naratriptan, rizatriptan, sumatriptan, zolmitriptan, RELPAX®, and ZOMIG® nasal spray	0
MIACALCIN® injection *(calcitonin-salmon)*	2--> Not Covered	Hyperinflation Exclusion - Availability of a generic option.	alendronate, calcitonin-salmon, ibandronate, risedronate, ATELVIA®, and FORTEO®.	0
MIACALCIN® spray *(calcitonin-salmon)*	3--> Not Covered	Hyperinflation Exclusion - Availability of a generic option.	*calcitonin-salmon*	0
UROXATRAL® tablet 10MG *(alfuzosin)*	3--> Not Covered	Hyperinflation Exclusion - Availability of options for the treatment of signs and symptoms of benign prostatic hyperplasia.	*alfuzosin er, tamsulosin*	1
RIMSO-50® solution *(dimethyl sulfoxide)*	3--> Not Covered	Hyperinflation Exclusion - Availability of an option for symptomatic relief of patients with interstitial cystitis.	ELMIRON® *(pentosane polysulfate)*	0
VANOXIDE-HC® lotion *(benzoyl peroxide/hydrocortisone)*	3--> Not Covered	Hyperinflation Exclusion - Availability of options for the treatment of acne vulgaris and oily skin.	*benzoyl peroxide*	2

	2014 Drug Utilization					2015 Drug Utilization					2016 Drug Utilization				
Drug Name	Total Member Cost	Total Plan Cost	Net Rxs	Unique Rx Count	Average AWP/Rx	Total Member Cost	Total Plan Cost	Net Rxs	Unique Rx Count	Average AWP/Rx	Total Member Cost	Total Plan Cost	Net Rxs	Unique Rx Count	Average AWP/Rx
CAFERGOT	$ 200.00	$ 929.48	3	3	$ 480.00	$ 1,000.00	$ 5,989.51	25	15	$ 325.00	$ 1,326.00	$ 11,462.30	26	13	$ 582.00
DYRENIUM	$ 6,742.52	$ 9,522.33	92	18	$ 210.00	$ 8,696.52	$ 31,100.28	105	21	$ 482.00	$ 8,924.00	$ 38,924.98	102	19	$ 587.00
E.E.S. 200	$ 4,800.00	$ 36,782.15	76	29	$ 640.00	$ 4,096.00	$ 59,496.19	68	25	$ 1,091.00	$ 3,064.00	$ 53,374.05	44	15	$ 1,506.00
ERYPED 200	$ 5,184.00	$ 26,045.61	81	34	$ 445.00	$ 6,321.33	$ 49,040.31	95	29	$ 678.00	$ 5,032.00	$ 64,512.18	69	22	$ 1,207.00
ERYPED 400	$ 1,024.00	$ 10,595.86	16	9	$ 840.00	$ 768.00	$ 13,595.25	12	8	$ 1,392.00	$ 784.00	$ 22,878.94	12	6	$ 2,316.00
LANOXIN	$ 19,614.73	$ 14,954.97	449	75	$ 98.00	$ 13,604.44	$ 25,906.02	304	49	$ 174.00	$ 11,110.57	$ 36,240.89	208	41	$ 387.00
MACRODANTIN	$ 1,996.00	$ 9,662.94	36	13	$ 388.00	$ 1,517.00	$ 8,815.76	30	8	$ 403.00	$ 681.55	$ 4,020.60	14	5	$ 402.00
MIACALCIN	$ 300.00	$ 163.83	3	2	$ 178.00	$ 300.00	$ 1,538.65	6	1	$ 361.00	$ 264.00	$ 2,713.20	3	2	$ 1,154.00
RIMSO-50	$ 448.00	$ 381.78	7	2	$ 136.00	$ 64.00	$ 796.65	1	1	$ 1,023.00	$ 1,160.00	$ 8,846.24	17	4	$ 682.00
UROXATRAL	$ 6,019.85	$ 17,928.70	71	16	$ 707.00	$ 5,791.72	$ 23,700.69	48	11	$ 1,021.00	$ 4,600.00	$ 22,030.23	26	6	$ 1,220.00
VANOXIDE-HC	$ 512.00	$ 39.87	8	5	$ 72.00	$ 512.00	$ 5.99	8	4	$ 70.00	$ 704.00	$ 2,347.15	10	5	$ 360.00
ZONEGRAN	$ 6,364.83	$ 52,698.38	93	11	$ 851.00	$ 5,724.00	$ 66,750.40	75	10	$ 1,432.00	$ 7,969.92	$ 115,188.76	83	8	$ 1,861.00
Grand Total	**$ 53,205.93**	**$ 179,705.90**	**935**	**217**	**$ 5,045.00**	**$ 48,395.01**	**$ 286,735.70**	**777**	**182**	**$ 8,452.00**	**$ 45,620.04**	**$ 382,539.52**	**614**	**146**	**$ 12,264.00**

	2015 Price Change					2016 Price Change					Total 3-Year Price Change				
Drug Name	Total Member Cost	Total Plan Cost	Net Rxs	Unique Rx Count	Average AWP/Rx	Total Member Cost	Total Plan Cost	Net Rxs	Unique Rx Count	Average AWP/Rx	Total Member Cost	Total Plan Cost	Net Rxs	Unique Rx Count	Average AWP/Rx
CAFERGOT	400%	544%	733%	400%	-32%	33%	91%	4%	-13%	79%	563%	1133%	767%	333%	21%
DYRENIUM	29%	227%	14%	17%	130%	3%	25%	-3%	-10%	22%	32%	309%	11%	6%	180%
E.E.S. 200	-15%	62%	-11%	-14%	70%	-25%	-10%	-35%	-40%	38%	-36%	45%	-42%	-48%	135%
ERYPED 200	22%	88%	17%	-15%	52%	-20%	32%	-27%	-24%	78%	-3%	148%	-15%	-35%	171%
ERYPED 400	-25%	28%	-25%	-11%	66%	2%	68%	0%	-25%	66%	-23%	116%	-25%	-33%	176%
LANOXIN	-31%	73%	-32%	-35%	78%	-18%	40%	-32%	-16%	122%	-43%	142%	-54%	-45%	295%
MACRODANTIN	-24%	-9%	-17%	-38%	4%	-55%	-54%	-53%	-38%	0%	-66%	-58%	-61%	-62%	4%
MIACALCIN	0%	839%	100%	-50%	103%	-12%	76%	-50%	100%	220%	-12%	1556%	0%	0%	548%
RIMSO-50	-86%	109%	-86%	-50%	652%	1713%	1010%	1600%	300%	-33%	159%	2217%	143%	100%	401%
UROXATRAL	-4%	32%	-32%	-31%	44%	-21%	-7%	-46%	-45%	19%	-24%	23%	-63%	-63%	73%
VANOXIDE-HC	0%	-85%	0%	-20%	-3%	38%	39084%	25%	25%	414%	38%	5787%	25%	0%	400%
ZONEGRAN	-10%	27%	-19%	-9%	68%	39%	73%	11%	-20%	30%	25%	119%	-11%	-27%	119%
Grand Total	**-9%**	**60%**	**-17%**	**-16%**	**68%**	**-6%**	**33%**	**-21%**	**-20%**	**45%**	**-14%**	**113%**	**-34%**	**-33%**	**143%**

New to Market Blocked Products

- COSENTYX® *(secukinumab)* and VIEKIRA XR® *(dasabuvir, ombitasvir, paritaprevir, and ritonavir)* will be removed from the new-to-market block and will be excluded. This change is neutral for the State Health Plan since the Plan already recognizes these products as exclusions. This step formalizes the removal from NTM block.
- A host of medications have been removed from the new-to-market block and will be added to the formulary.

DRUG	THERAPEUTIC CLASS	NC SHP Formulary Tier
BENDEKA VIA 100/4ML	Antineoplastic Agents/ Alkylating Agents	6
CABOMETYX TAB 20MG	Antineoplastic Agents/ Antineoplastic Emzyme Inhibitors	6
CABOMETYX TAB 40MG	Antineoplastic Agents/ Antineoplastic Emzyme Inhibitors	6
CABOMETYX TAB 60MG	Antineoplastic Agents/ Antineoplastic Emzyme Inhibitors	6
NUWIQ INJ 500UNIT	Hematologic/ Hemophilia Agents	5
PORTRAZZA INJ 800/50ML	Antineoplastic Agents/ Antineoplastic Antibodies	6
COTELLIC TAB 20MG	Antineoplastic Agents/ Enzyme Inhibitors	6
LINZESS CAP 72MCG	Gastrointestinal/ Irritable Bowel Syndrome	2
VEMLIDY TAB 25MG	Anti-infectives/ Antivirals/ Hepatitis B Agents	6
LARTRUVO INJ 190/19ML	Antineoplastic Agents/ Antineoplastic Antibodies	6
ADZENYS XR ODT 3.1MG	Central Nervous System/ Attention Deficit Hyperactivity Disorder	3
ADZENYS XR ODT 6.3MG	Central Nervous System/ Attention Deficit Hyperactivity Disorder	3
ADZENYS XR ODT 9.4MG	Central Nervous System/ Attention Deficit Hyperactivity Disorder	3
ADZENYS XR ODT 12.5MG	Central Nervous System/ Attention Deficit Hyperactivity Disorder	3
ADZENYS XR ODT 15.7 MG	Central Nervous System/ Attention Deficit Hyperactivity Disorder	3
ADZENYS XR ODT 18.8MG	Central Nervous System/ Attention Deficit Hyperactivity Disorder	3
QUILLICHEW CHW 20MG ER	Central Nervous System/ Attention Deficit Hyperactivity Disorder	3
QUILLICHEW CHW 30MG ER	Central Nervous System/ Attention Deficit Hyperactivity Disorder	3
QUILLICHEW CHW 40MG ER	Central Nervous System/ Attention Deficit Hyperactivity Disorder	3
ONZETRA EXHA PWD 11MG	Central Nervous System/ Migraine/ Selective Serotonin Agonists	3
ZEMBRACE SYM 3/0.5ML	Central Nervous System/ Migraine/ Selective Serotonin Agonists	3
RAYALDEE CAP 30MCG	Nutritional/ Supplements/ Vitamins/ Vitamin D	3
OBREDON SOL	Antitussive/ Expectorant	3
OCALIVA TAB 10MG	Farnesoid X Receptor Agonist	6
OCALIVA TAB 5MG	Farnesoid X Receptor Agonist	6
KEVEYIS TAB 50MG	Carbonic Anhydrase Inhibitor	3
KYPROLIS SOL 30MG	Antineoplastic Agents/ Proteasome Inhibitor	6
EMEND SUS 125MG	Antiemetic/ Substance P/Neurokinin 1 Receptor Antagonist	3
IMPAVIDO CAP 50MG	Antiparasitic Agent	3

CVSHealth

Drug Summary

Cabometyx™ (cabozantinib) Tablets
Exelixis, Inc.

INDICATION

Cabometyx (cabozantinib) is indicated for the treatment of advanced renal cell carcinoma (RCC) in patients who have received prior antiangiogenic therapy.

KEY POINTS

Cabometyx (cabozantinib) is a new oral kinase inhibitor that provides an additional subsequent treatment option in patients with advanced RCC that has progressed on prior antiangiogenic therapy. Cabometyx (cabozantinib) is recommended before the administration of Afinitor (everolimus) as subsequent therapy for the treatment of relapsed or Stage IV and medically or surgically unresectable kidney cancer in the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (NCCN Guidelines®).

CLINICIAL EFFICACY

The clinical efficacy of Cabometyx (cabozantinib) was evaluated in the phase 3, randomized, open-label trial, METEOR. Cabometyx (cabozantinib) 60 mg daily significantly prolonged progression-free survival (PFS) and overall survival (OS) and significantly improved objective response rate in patients with advanced or metastatic renal cell carcinoma who experienced disease progression after receiving one or more vascular endothelial growth factor receptor (VEGFR)-targeted therapies compared with Afinitor (everolimus).

SAFETY

Warnings and precautions associated with Cabometyx (cabozantinib) include an increased risk of hemorrhage, gastrointestinal (GI) perforation and fistulas, thrombotic events, hypertension and hypertensive crisis, diarrhea, palmar-plantar erythrodysesthesia syndrome (PPES), reversible posterior leukoencephalopathy syndrome, and embryo-fetal toxicity. Diarrhea, fatigue, nausea, decreased appetite and weight, PPES, hypertension, and constipation are the most common adverse events associated with the administration of Cabometyx (cabozantinib).

DOSAGE AND ADMINISTRATION

The recommended dose of Cabometyx (cabozantinib) is 60 mg once daily without food until patients no longer experience clinical benefit or experience unacceptable toxicity. Cabometyx (cabozantinib) should be swallowed whole and should not be crushed. Additionally, a missed dose should not be taken within 12 hours of the next dose, and food (e.g., grapefruit or grapefruit juice) or nutritional supplements that are known to inhibit cytochrome P450 (CYP) should not be ingested while receiving treatment with Cabometyx (cabozantinib).

Cabometyx (cabozantinib) should be withheld at least 28 days prior to surgery, including dental surgery. Dose interruption and adjustment recommendations are provided for various adverse events, including Grade 3 or 4 adverse events, intolerable Grade 2 adverse events, development of unmanageable fistula or GI perforation, severe hemorrhage, arterial thromboembolic events, and nephrotic syndrome. In addition, dosage adjustments are provided for concomitant administration with CYP3A4 inducers and inhibitors and in patients with hepatic impairment in the Cabometyx (cabozantinib) prescribing information.

PLACE IN THERAPY

- Cabometyx (cabozantinib) offers an additional subsequent treatment option in patients with advanced RCC that has progressed on prior antiangiogenic therapy and is recommended before the administration of Afinitor (everolimus) in the NCCN® Treatment Guidelines.
- Cabometyx (cabozantinib) demonstrated superior efficacy in the treatment of advanced RCC in patients who had progressed after VEGFR-targeted therapy compared with Afinitor (everolimus).
- Cabometyx (cabozantinib) is in phase 3 trials for the treatment of advanced hepatocellular carcinoma and in phase 2 trials for the treatment of metastatic non-small cell lung cancer in combination with Tarceva (erlotinib), metastatic hormone receptor-positive breast cancer, second-lime treatment of grade IV astrocytic tumors, and second- and third-line treatment of metastatic castration-resistant prostate cancer.

DRUG SUMMARY PREPARED BY:

Lisa Raff, Pharm.D. ,BCPS
June 21, 2016

This document includes the clinical opinions of CVS Caremark based on the information available at the time this document was written. The document contains summarized information is not a substitute for reading the original literature. Economic and other considerations may influence an individual client's formulary decision. The document contains prescription brand name drugs that are registered or trademarks of pharmaceutical manufacturers that are not affiliated with CVS Caremark.

CVS/caremark

SPECIALTY GUIDELINE MANAGEMENT

CABOMETYX (cabozantinib)

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
Cabometyx is approved for treatment of patients with advanced renal cell carcinoma who have received prior anti-angiogenic therapy.

All other indications are considered experimental/investigational and are not a covered benefit.

II. CRITERIA FOR APPROVAL

A. Renal Cell Carcinoma
Authorization of 12 months may be granted to members prescribed Cabometyx for renal cell carcinoma who meet all of the following:
1. The member's disease is advanced or metastatic
2. The member's disease expresses clear cell histology
3. The member has received and progressed on or after prior treatment with a vascular endothelial growth factor receptor (VEGFR) targeting tyrosine kinase inhibitor

III. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must meet ALL initial authorization criteria.

IV. DOSAGE AND ADMINISTRATION

Approvals may be subject to dosing limits in accordance with FDA-approved labeling, accepted compendia, and/or evidence-based practice guidelines.

V. REFERENCES

1. Cabometyx [package insert]. South San Francisco, CA: Exelixis; April 2016.

CVS/caremark™

CVS Caremark Pharmacy & Therapeutics
Drug Monograph

Cotellic (cobimetinib) tablets
Genentech USA, Inc.

INTRODUCTION

Cotellic (cobimetinib) is a mitogen-activated extracellular signal-regulated kinase (MEK) inhibitor that has demonstrated significantly improved progression-free survival (PFS) when administered in combination with Zelboraf (vemurafenib), a BRAF kinase inhibitor, vs. Zelboraf (vemurafenib) alone in unresectable or metastatic melanoma with a BRAF V600E or V600K mutation (ADIS, 2015; Cotellic prescribing information, 2015).

U.S. Food and Drug Administration (FDA)-Review Designation

Cotellic (cobimetinib) was approved by the FDA on November 10, 2015 with a review designation of 1P (FDA, 2015). Cotellic (cobimetinib) is a new molecular entity that underwent priority review, was granted fast track status in combination with Zelboraf (vemurafenib), and orphan drug designation (ADIS, 2015; FDA, 2015).

INDICATIONS

Cotellic (cobimetinib) is indicated in combination with Zelboraf (vemurafenib), for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600E or V600K mutation (Cotellic prescribing information, 2015). Cotellic (cobimetinib) is not indicated for the treatment of patients with wild-type BRAF melanoma.

CLINICAL PHARMACOLOGY

Mechanism of Action

Cobimetinib is reversible inhibitor of mitogen-activated protein kinase (MAPK)/MEK1 and MEK2 (Cotellic prescribing information, 2015). MEK proteins are upstream regulators of the extracellular signal-related kinase (ERK) pathway, which promotes cellular proliferation. BRAF V600E and K mutations result in constitutive activation of the BRAF pathway which includes MEK1 and MEK2. In mice implanted with tumor cell lines expressing BRAF V600E, cobimetinib inhibited tumor cell growth. Cobimetinib and vemurafenib target two different kinases in the retrovirus associated sequence RAS/RAF/MEK/ERK pathway. Compared to either drug alone, coadministration of Cotellic (cobimetinib) and Zelboraf (vemurafenib) resulted in increased apoptosis in vitro and reduced tumor growth in mouse implantation models of tumor cell lines harboring BRAF V600E mutations. Cobimetinib also prevented vemurafenib-mediated growth enhancement of a wild-type BRAF tumor cell line in an in vivo mouse implantation model.

Pharmacokinetics

Table 1: Selected Pharmacokinetics of Cobimetinib

Oral Bioavailability	T_{max}	Protein Binding	Metabolism	$T_{1/2}$ (hours)
46%	2.4 hours (1 hour to 24 hours)	95%	Extensively via CYP3A and UGT2B7	44

CYP = cytochrome P450 isoenzyme
UGT =UDP-Glucuronosyltransferase
$T_{1/2}$ = half life
T_{max} = time to maximum plasma concentration

(Cotellic prescribing information, 2015)

Pharmacogenomics

There are no pharmacogenomic data available for Cotellic (cobimetinib) at this time.

CLINICAL EFFICACY

Updated PFS and correlative biomarker analysis data from January 2015 from the pivotal trial coBRIM, **Co**m**b**ined Vemu**r**afenib and Cob**i**metinib in *BRAF*-mutated **M**elanoma, were presented as an oral abstract at the 2015 American Society of Clinical Oncology (ASCO) meeting (Larkin, 2015). Updated median PFS and objective response rate (ORR) data are depicted in Table 2, and Table 3 outlines the design and initial data from the coBRIM study. It was confirmed with longer follow-up that co-existence of the BRAF V600 and baseline activating RAS/RAF/receptor tyrosine kinases (RTK) mutations do not seem to affect disease progression or the rate of response to Cotellic (cobimetinib) plus Zelboraf (vemurafenib) or Zelboraf (vemurafenib) only. An additional interim analysis of OS will be conducted after 256 deaths have occurred.

Table 2: Updated Efficacy of Cotellic (cobimetinib) for the Treatment of BRAF-Mutated Unresectable or Metastatic Melanoma

Endpoint January 16, 2015	Cotellic (cobimetinib) + Zelboraf (vemurafenib) (n = 247)	Zelboraf (n = 248)	Hazard-Ratio (95% CI)	p-value
Median PFS (months) (95% CI)	12.3 (9.5 to 13.4)	7.2 (5.6 to 7.5)	0.58 (0.46 to 0.72)	Not provided
ORR† (%)	70	50	Not available	
Complete response (%)	16	11		
Partial response (%)	54	40		

† Defined as complete or partial response according to RECIST
CI = confidence interval
PFS = progression free survival
ORR = objective response rate
RECIST = Response Evaluation Criteria in Solid Tumors (version 1.1)

(Larkin, 2015)

Table 3: Efficacy of Cotellic (cobimetinib) for the Treatment of BRAF-Mutated Unresectable or Metastatic Melanoma

Study, Treatments, and Groups	Study Design and Endpoints	Study Criteria	Results
Larkin, 2014 Evidence Level Ib **Cotellic (cobimetinib)** 60 mg orally daily for the first 21 days of each 28-day cycle* ***plus*** **Zelboraf (vemurafenib)** 960 mg orally twice daily days 1 through 28* (n = 247) *vs.* **Zelboraf** 960 mg orally twice daily days 1 through 28* (n = 248)	(N = 495) **Study Design:** International, multicenter, randomized, double-blinded, placebo controlled phase 3 study **Objective:** To assess the efficacy and safety of Cotellic plus Zelboraf vs. Zelbroaf alone in the treatment of *BRAF*-mutated melanoma **Primary Endpoints:** Investigator-assessed PFS according to RECIST **Secondary Endpoints:** OS; confirmed ORR†; DOR; PFS assessed by independent review facility; safety	**Inclusion Criteria:** Patient ≥ 18 years if age (median age 56 years; 59% male), histologically confirmed, unresectable, locally advanced stage IIIC or stage IV melanoma with a BRAF V600 mutation; measurable disease according to RECIST, ECOG performance status 0 or 1‡; adequate hematologic, hepatic, renal, and cardiac function; no or stable (≥ 3 week) brain metastases **Exclusion Criteria:** Negative test result for *BRAF* V600 mutation	**Efficacy** **Endpoint** / **Cotellic + Zelboraf (n = 247)** / **Zelboraf (n = 248)** / **Hazard-Ratio (95% CI)** / **p-value** Median PFS[a] (months) (95% CI): 9.9 (9.0 to NR) / 6.2 (5.6 to 7.4) / 0.51 (0.39 to 0.68) / < 0.001 Median PFS[b] (months) (95% CI): 11.3 (8.5 to NR) / 6.0 (5.6 to 7.5) / 0.60 (0.45 to 0.79) / < 0.001 ORR† (%) (95% CI): 68 (61 to 73) (n = 167) / 45 (38 to 51) (n = 111) / Not available / < 0.001 Complete response (%): 10 / 4 / Not available / Not provided Partial response (%): 57 / 40 Stable disease (%): 20 / 42 Progressive disease (%): 8 / 10 Median DOR (months) (95% CI): NR (9.3 to NR) / 7.3 (5.8 to NR) OS at 9 months (%) (95% CI): 81 (75 to 87) / 73 (65 to 80) / 0.65 (0.42 to 1.00) / 0.046 Median OS[cd] (months): NR / NR a Investigator assessment b Independent facility review assessment c Data for OS from the first interim analysis are immature, and did not cross the prespecified hazard-ratio for significance d Patients were stratified according to geographic region and metastasis classification • At time of data collection, 85 patients had died primarily as a result of disease progression (96% of deaths in the Zelboraf arm and 85% of deaths in the Cotellic plus Zelboraf arm) **Safety** • Combination of Cotellic plus Zelboraf were associated with higher grade 1 or 2 adverse events (> 50%) including serous retinopathy, diarrhea, nausea, vomiting, photosensitivity, elevated aminotransferase levels, and an increased creatine kinase level. Equivalent rates of grade 3 adverse events were observed between the 2 study groups, and 9% of patients in Zelboraf arm and 13% in the Cotellic plus Zelboraf arm experienced grade 4 adverse events. • 3 deaths were attributed to adverse events in the Zelboraf arm, and 6 deaths in the Cotellic plus Zelboraf arm. • Toxic events leading to withdrawal from treatment occurred in 12% of patients in the Zelboraf arm and 13% in the Cotellic plus Zelboraf arm. **Comments/Study Limitations:** Study funded by manufacturer of Cotellic; study was designed with 2 interim analyses, the first performed at time of final analysis of PFS, triggered by 206 progression events (data above), and the second analysis of OS, triggered after 256 deaths (data pending). Assessment of OS performed at the first interim analysis had not crossed the prespecified hazard-ratio for significance, and complete data are needed before conclusions can be made in regards to OS. **Conclusion:** Cotellic plus Zelboraf improved PFS and ORR vs. Zelboraf alone in BRAF-mutated melanoma, with early evidence of improved OS, and with an acceptable safety profile.

* Dose reductions and interruptions were permitted based on adverse events per the protocol
† Defined as complete or partial response according to RECIST
‡ Performance status scale used to assess disease progression and effects on daily living; 0 = asymptomatic, 1 = restricted in strenuous activity but ambulatory and able to do light work

Evidence Level Ib = evidence from a randomized, controlled trial
CI = confidence interval
DOR = duration of response
ECOG = Eastern Cooperative Oncology Group
NR = not reached
ORR = objective response rate
OS = overall survival
PFS = progression-free survival
RECIST = Response Evaluation Criteria in Solid Tumors version 1.1

(Larkin, 2014)

Efficacy Data in the Elderly

Clinical studies of Cotellic (cobimetinib) did not include sufficient numbers of patients aged 65 years and older to determine whether they respond differently from younger patients (Cotellic prescribing information, 2015).

SAFETY

Contraindications

There are no known contraindications to Cotellic (cobimetinib) (Cotellic prescribing information, 2015).

Warnings and Precautions

New Primary Malignancies

In the pivotal trial, the following cutaneous malignancies or premalignant conditions occurred in the Cotellic (cobimetinib) with Zelboraf (vemurafenib) arm and the Zelboraf (vemurafenib) arm: cutaneous squamous cell carcinoma (cuSCC) or keratoacanthoma (KA) (6% and 20%), basal cell carcinoma (4.5% and 2.4%), and second primary melanoma (0.8% and 2.4%). Patients receiving Cotellic (cobimetinib) with Zelboraf (vemurafenib) had a median time to detection of first cuSCC/KA of four months (range: two months to 11 months), and the median time to detection of basal cell carcinoma of four months (range: 27 days to 13 months). The time to onset in the two patients with second primary melanoma was nine months and 12 months (Cotellic prescribing information, 2015).

Dermatologic evaluations should be performed prior to initiation of therapy and every two months while receiving therapy (Cotellic prescribing information, 2015). Suspicious skin lesions should be managed with excision and dermato pathologic evaluation. No dose modifications are recommended for Cotellic (cobimetinib). Dermatologic monitoring should be conducted for six months following discontinuation of Cotellic (cobimetinib) when administered with Zelboraf (vemurafenib).

Hemorrhage

Hemorrhage, including major hemorrhages defined as symptomatic bleeding in a critical area or organ, can occur with Cotellic (cobimetinib) (Cotellic prescribing information, 2015). In the pivotal trial, the incidence of Grade 3 to 4 hemorrhages was 1.2% in patients receiving Cotellic (cobimetinib) with Zelboraf (vemurafenib), and 0.8% in patients receiving Zelboraf (vemurafenib). Hemorrhage of all grades was 13% in patients receiving Cotellic (cobimetinib) with Zelboraf (vemurafenib), and 7% in patients receiving Zelboraf (vemurafenib). Cerebral hemorrhage occurred in 0.8% of patients receiving Cotellic (cobimetinib) with Zelboraf (vemurafenib), and in none of the patients receiving Zelboraf (vemurafenib). Gastrointestinal tract hemorrhage (3.6% vs. 1.2%), reproductive system hemorrhage (2.0% vs. 0.4%), and hematuria (2.4% vs. 0.8%) also occurred at a higher incidence in patients receiving Cotellic (cobimetinib) with Zelboraf (vemurafenib) compared with patients receiving Zelboraf (vemurafenib).

Cotellic (cobimetinib) should be withheld for Grade 3 hemorrhagic events (Cotellic prescribing information, 2015). If improved to Grade 0 or 1 within four weeks, Cotellic (cobimetinib) should be resumed at a lower dose level. Cotellic (cobimetinib) should be discontinued for Grade 4 hemorrhagic events and any Grade 3 hemorrhagic events that do not improve.

Cardiomyopathy

Cardiomyopathy, defined as symptomatic and asymptomatic decline in left ventricular ejection fraction (LVEF), can occur with Cotellic (cobimetinib) (Cotellic prescribing information, 2015). The safety of Cotellic (cobimetinib) has not been established in patients with a baseline LVEF that is either below the institutional lower limit of normal (LLN) or below 50%.

Patients were assessed for decreases in LVEF with echocardiograms or Multi Gated Acquisition (MUGA) scan at baseline, weeks 5, 17, 29, 43, and then every four to six months thereafter while receiving treatment in the pivotal trial (Cotellic prescribing information, 2015). Grade 2 or 3 decreases in LVEF occurred in 26% of patients receiving Cotellic (cobimetinib) and in 19% of patients receiving Zelboraf (vemurafenib). The median time to first onset of LVEF decrease was four months (range: 23 days to 13 months). Dose interruption and/or reduction occurred in 22% of patients with decreased LVEF, and 14% required permanent discontinuation. Decreased LVEF resolved to above the LLN or within 10% of baseline in 62% of patients receiving Cotellic (cobimetinib), with a median time to resolution of three months (range: four days to 12 months).

LVEF should be evaluated prior to initiation, one month after initiation, and every three months thereafter until discontinuation of Cotellic (cobimetinib) (Cotellic prescribing information, 2015). Events of left ventricular dysfunction should be managed through treatment interruption, reduction, or discontinuation. In patients restarting Cotellic (cobimetinib) after a dose reduction or interruption, LVEF should be evaluated at approximately two weeks, four weeks, 10 weeks, and 16 weeks, and then as clinically indicated.

Severe Dermatologic Reactions

Severe rash and other skin reactions can occur with Cotellic (cobimetinib) (Cotellic prescribing information, 2015). In the pivotal trial, Grade 3 to 4 rashes occurred in 16% of patients receiving Cotellic (cobimetinib) with Zelboraf (vemurafenib) and in 17% of patients receiving Zelboraf (vemurafenib), including Grade 4 rash in 1.6% of patients receiving Cotellic (cobimetinib) with Zelboraf (vemurafenib) and 0.8% of the patients receiving Zelboraf (vemurafenib). The incidence of rash resulting in hospitalization was 3.2% in patients receiving Cotellic (cobimetinib) with Zelboraf (vemurafenib) and 2.0% in patients receiving Zelboraf (vemurafenib). In patients receiving Cotellic (cobimetinib), the median time to onset of Grade 3 or 4 rash events was 11 days (range: three days to 2.8 months). Among patients with Grade 3 or 4 rash events, 95% experienced complete resolution with the median time to resolution of 21 days (range four days to 17 months). Cotellic (cobimetinib) should be withheld, dose reduced, or discontinued for severe dermatologic reactions.

Serious Retinopathy and Retinal Vein Occlusion

Ocular toxicities can occur with Cotellic (cobimetinib), including serous retinopathy (fluid accumulation under layers of the retina) (Cotellic prescribing information, 2015). Ophthalmologic examinations, including retinal evaluation, were performed pretreatment, and at regular intervals during treatment in the pivotal trial. Symptomatic and asymptomatic serous retinopathy was identified in 26% of patients receiving Cotellic (cobimetinib) with Zelboraf (vemurafenib). The majority of these events were reported as chorioretinopathy (13%) or retinal detachment (12%). The time to first onset of serous retinopathy events ranged between two days to nine months. The reported duration of serous retinopathy ranged between one day to 15 months. One patient in each arm developed retinal vein occlusion.

Ophthalmological evaluations should be performed at regular intervals and any time a patient reports new or worsening visual disturbances (Cotellic prescribing information, 2015). If serous retinopathy is diagnosed, Cotellic (cobimetinib) therapy should be interrupted until visual symptoms improve. Serious retinopathy should be managed with treatment interruption, dose reduction, or treatment discontinuation.

Hepatotoxicity

Hepatotoxicity can occur with Cotellic (cobimetinib) (Cotellic prescribing information, 2015). Grade 3 or 4 liver laboratory abnormalities amongst the patients in the pivotal trial receiving Cotellic (cobimetinib) with Zelboraf (vemurafenib) compared to patients receiving Zelboraf (vemurafenib) were: 11% vs. 6% for alanine aminotransferase, 7% vs. 2.1% for aspartate aminotransferase, 1.6% vs. 1.2% for total bilirubin, and 7% vs. 3.3% for alkaline phosphatase. Concurrent elevation in ALT > 3 times the upper limit of normal (ULN) and bilirubin > 2 X ULN in the absence of significant alkaline phosphatase > 2 X ULN occurred in one patient (0.4%) receiving Cotellic (cobimetinib) with Zelboraf (vemurafenib), and no patients receiving single-agent Zelboraf (vemurafenib).

Liver laboratory tests should be evaluated and monitored before initiation of Cotellic (cobimetinib), and monthly during treatment, or more frequently as clinically indicated (Cotellic prescribing information, 2015). Grade 3 and 4 liver laboratory abnormalities should be managed with dose interruption, reduction, or discontinuation of Cotellic (cobimetinib).

Rhabdomyolysis

Rhabdomyolysis can occur with Cotellic (cobimetinib) (Cotellic prescribing information, 2015). Grade 3 or 4 creatine phosphokinase (CPK) elevations, including asymptomatic elevations over baseline, occurred in 12% of patients receiving Cotellic (cobimetinib) with Zelboraf (vemurafenib), and 0.4% of patients receiving Zelboraf (vemurafenib) in the pivotal trial. The median time to first occurrence of Grade 3 or 4 CPK elevations was 16 days (range: 12 days to 11 months) in patients receiving Cotellic (cobimetinib) with Zelboraf (vemurafenib), and the median time to complete resolution was 15 days (range: nine days to 11 months). Elevation of serum CPK increase of more than 10 times the baseline value with a concurrent increase in serum creatinine of 1.5 times or greater compared to baseline occurred in 3.6% of patients receiving Cotellic (cobimetinib) with Zelboarf (vemurafenib), and in 0.4% of patients receiving Zelboraf (vemurafenib).

Baseline serum CPK and creatinine levels should be obtained prior to initiating Cotellic (cobimetinib), periodically during treatment, and as clinically indicated (Cotellic prescribing information, 2015). If CPK is elevated, signs and symptoms of rhabdomyolysis should be evaluated, or other causes, and depending on the severity of symptoms or CPK elevation, dose interruption or discontinuation of Cotellic (cobimetinib) may be required.

Severe Photosensitivity

Photosensitivity, including severe cases, can occur with Cotellic (cobimetinib) (Cotellic prescribing information, 2015). Photosensitivity was reported in 47% of patients receiving Cotellic (cobimetinib) with Zelboraf (vemurafenib): 43% of 140 patients with Grades 1 or 2 photosensitivity, and the remaining 4% with Grade 3 photosensitivity in the pivotal trial. Median time to first onset of photosensitivity of any grade was two months (range: one day to 14 months) in patients receiving Cotellic (cobimetinib) with Zelboraf (vemurafenib), and the median duration of photosensitivity was three months (range: two days to 14 months). Among the 47% of patients with photosensitivity reactions on Cotellic (cobimetinib) with Zelboraf (vemurafenib), 63% experienced resolution of photosensitivity reactions.

Patients should be advised to avoid sun exposure, wear protective clothing, and use a broad-spectrum ultra violet (UV)A/UVB sunscreen and lip balm (SPF ≥ 30) when outdoors (Cotellic prescribing information, 2015). Intolerable Grade 2 or greater photosensitivity should be managed with dose modifications.

Embryo-Fetal Toxicity

Based on its mechanism of action and findings from animal reproduction studies, Cotellic (cobimetinib) can cause fetal harm when administered to a pregnant woman (Cotellic prescribing information, 2015). There are no available data on the use of Cotellic (cobimetinib) during pregnancy. There are no available data on the use of Cotellic (cobimetinib) during pregnancy. In animal reproduction studies, oral administration of Cotellic (cobimetinib) in pregnant rats was teratogenic and embryotoxic at maternal exposures that were 0.9 to 1.4-times those observed in humans at the recommended dose of 60 mg. Pregnant women should be advised of the potential risk to the fetus. Females of reproductive potential should be advised to use effective contraception during treatment with Cotellic (cobimetinib), and for two weeks following the final dose of Cotellic (cobimetinib).

Nursing Mothers

There are no data on the presence of cobimetinib in human milk, the effects of cobimetinib on the breastfed child, or the effects of cobimetinib on milk production (Cotellic prescribing information, 2015). Because of the potential for serious adverse events in a breastfed infant, nursing woman should be advised not to breastfeed during treatment with Cotellic (cobimetinib), and for two weeks after the final dose.

Pediatric Use

The safety and efficacy of Cotellic (cobimetinib) in pediatric patients have not been studied (Cotellic prescribing information, 2015).

Drug Interactions

Table 4: Potential Drug Interactions with Cobimetinib

Interacting Agent	Outcome	Recommendation
Strong CYP3A inhibitors (e.g., itraconazole)	↑ cobimetinib exposure by 6.7 fold	Concomitant use should be avoided
Moderate CYP3A inhibitors (e.g., erythromycin, ciprofloxacin)	↑ cobimetinib exposure	Concomitant use should be avoided if possible; otherwise dose of cobimetinib should be reduced
Strong CYP3A inducers*	Potential ↓ cobimetinib exposure by > 80%	Concomitant use should be avoided
Moderate CYP3A inducers*	Potential ↓ cobimetinib exposure	

*E.g., carbamazepine, efavirenz, phenytoin, rifampin, and St. John's Wort
CYP = cytochrome P450 isoenzyme

(Cotellic prescribing information, 2015)

Adverse Events

Permanent discontinuation due to an adverse event occurred in 15% of patients receiving Cotellic (cobimetinib) in the pivotal trial (Cotellic, prescribing information, 2015). Adverse events leading to discontinuation of Cotellic (cobimetinib) were liver laboratory abnormalities defined as increased aspartate aminotransferase (AST) (2.4%), increased gamma glutamyltransferase (GGT) (1.6%), and increased alanine aminotransferase (ALT) (1.6%). Dose interruptions or reductions due to an adverse event occurred in 55% of patients receiving Cotellic (cobimetinib), and included rash (11%), diarrhea (9%), chorioretinopathy (7%), pyrexia (6%), vomiting (6%), nausea (5%), and increased CPK (4.9%).

The most common adverse events occurring with Cotellic (cobimetinib) in the pivotal trial are described in Table 5.

Table 5: Adverse Events in ≥ 10% of Clinical Trial Patients Receiving Cotellic (cobimetinib)*

Adverse Event	Cotellic (cobimetinib) + Zelboraf (vemurafenib) (n = 247)		Placebo + Zelboraf (n = 246)	
	All Grades† (%)	Grade 3 to 4 (%)	All Grades† (%)	Grade 3 to 4 (%)
Gastrointestinal Disorders				
Diarrhea	60	6	31	1
Nausea	41	1	25	1
Vomiting	24	1	13	1
Stomatitis	14	1	8	0
Skin and Subcutaneous Tissue Disorders				
Photosensitivity reaction	46	4	35	0
Acneiform dermatitis	16	2	11	1
General Disorders and Administration Site Conditions				
Pyrexia	28	2	23	0
Chills	10	0	5	0
Vascular Disorders				
Hypertension	15	4	8	2
Hemorrhage	13	1	7	< 1
Eye Disorders				
Vision impaired	15	< 1	4	0
Chorioretinopathy	13	< 1	< 1	0
Retinal detachment	12	2	< 1	0

* ≥ 5% for All Grades or ≥ 2% for Grades 3 to 4 incidence in patients receiving Cotellic (cobimetinib) with Zelboraf (vemurafenib) compared with patients receiving Zelboraf (vemurafenib) as a single agent
† Based on the National Cancer Institute Common Criteria for Adverse Events version 4.0, where Grade 3 is severe and Grade 4 is life-threatening

(Cotellic prescribing information, 2015)

PRODUCT AVAILABILITY

Cotellic (cobimetinib) is supplied as 20 mg tablets in bottles of 63 tablets (Cotellic prescribing information, 2015).

DOSAGE AND ADMINISTRATION

Prior to the initiation of treatment with Cotellic (cobimetinib) with Zelboraf (vemurafenib), the presence of BRAF V600E or V600K mutation in tumor specimens should be confirmed (Cotellic prescribing information, 2015). The recommended dose of Cotellic (cobimetinib) is 60 mg orally once daily for the first 21 days of each 28-day cycle, until disease progression or unacceptable toxicity. No dosage adjustment is required due to mild hepatic impairment or mild to moderate renal impairment. Dosage adjustments due to adverse events are described in Table 6.

If a dose reduction is required, the next lower dose of Cotellic (cobimetinib) is 40 mg per day (Cotellic prescribing information, 2015). If further dose reduction is required, the next lower dose is 20 mg per day. If further dose reduction below 20 mg per day is required, treatment should be discontinued. Prescribers should consult the prescribing information for Zelboraf (vemurafenib) for information regarding dose adjustments for Zelboraf (vemurafenib) due to adverse events.

Table 6: Dosage Adjustments of Cotellic (cobimetinib) Due to Adverse Events and Drug Interactions

Safety Concern	Severity Grade*	Recommendation
New Primary Malignancy (cutaneous and non-cutaneous)	N/A	No dose adjustment required
Hemorrhage	Grade 3	• Withhold Cotellic for up to 4 weeks ▪ If improved to Grade 0 or 1, resume at next lower dose level ▪ If not improved within 4 weeks, permanently discontinue
	Grade 4	Permanently discontinue
Cardiomyopathy	Asymptomatic, absolute ↓ in LVEF from baseline of > 10% and < institutional LLN	• Withhold Cotellic for 2 weeks; repeat LVEF ▪ Resume at next lower dose if all of the following are present o LVEF is ≥ LLN and o Absolute ↓ from baseline LVEF is ≤ 10% ▪ Permanently discontinue if any of the following are present o LVEF is < LLN or o Absolute ↓ from baseline LVEF is > 10%
	Symptomatic LVEF ↓ from baseline	• Withhold Cotellic for up to 4 weeks; repeat LVEF ▪ Resume at next lower dose if all of the following are present o Symptoms resolve and o LVEF is ≥ LLN and o Absolute ↓ from baseline LVEF is ≤ 10% ▪ Permanently discontinue if any of the following are present o Symptoms persist, or, o LVEF is < LLN, or, o Absolute ↓ from baseline LVEF is > 10%
Dermatologic Reactions	Grade 2 (intolerable), Grade 3 or 4	Withhold or reduce dose
Serious Retinopathy or Retinal Vein Occlusion	Serious retinopathy	• Withhold Cotellic for up to 4 weeks ▪ If signs and symptoms improve, resume at next lower dose level ▪ If not improved or symptoms recur at the lower dose within 4 weeks, permanently discontinue
	Retinal vein occlusion	Permanently discontinue Cotellic
Liver Laboratory Abnormality and Hepatotoxicity	First Occurrence Grade 4	• Withhold Cotellic for up to 4 weeks ▪ If improved to Grade 0 or 1, resume at next lower dose level ▪ If not improved to Grade 0 or 1 within 4 weeks, permanently discontinue
	Recurrent Grade 4	Permanently discontinue Cotellic
Rhabdomyolysis and CPK elevations	• Grade 4 CPK Elevation • Any CPK elevation and myalgia	• Withhold Cotellic for up to 4 weeks ▪ If improved to ≤ Grade 3, resume at next lower dose level ▪ If not improved within 4 weeks, permanently discontinue

* Based on National Cancer Institute Common Criteria for Adverse Events version 4.0, where Grade 3 is severe and Grade 4 is life-threatening
† E.g., itraconazole, erythromycin, and ciprofloxacin
CPK = creatine phosphokinase
CYP = cytochrome P450 isoenzyme
LLN = lower limit of normal
LVEF = left ventricular ejection fraction
N/A = not applicable

(Cotellic prescribing information, 2015)

Table 6: Dosage Adjustments of Cotellic (cobimetinib) Due to Adverse Events and Drug Interactions (continued)

Safety Concern	Severity Grade*	Recommendation
Photosensitivity	Grade 2 (intolerable), Grade 3 or Grade 4	• Withhold Cotellic for up to 4 weeks ▪ If improved to Grade 0 or 1, resume at next lower dose level ▪ If not improved within 4 weeks, permanently discontinue
Other	• Grade 2 (intolerable) adverse events • Any Grade 3 adverse events	• Withhold Cotellic for up to 4 weeks ▪ If improved to Grade 0 or 1, resume at next lower dose level ▪ If not improved within 4 weeks, permanently discontinue
	First occurrence of any Grade 4 adverse event	• Withhold Cotellic until adverse event reaction improves to Grade 0 or 1, resume at next lower dose level, *OR* • Permanently discontinue
	Recurrent Grade 4 adverse event	Permanently discontinue Cotellic
Coadministration with moderate strong CYP3A inhibitor†	N/A	• Cotellic dose should be reduced to 20 mg per day if concurrent short term (≤ 14 days) use of moderate inhibitor is unavoidable • After discontinuation of moderate inhibitor, resume previous dose of Cotellic 60mg • Use an alternative to moderate or strong inhibitor in patients already taking a reduced dose of Cotellic (e.g., 20 mg or 40 mg)

* Based on National Cancer Institute Common Criteria for Adverse Events version 4.0, where Grade 3 is severe and Grade 4 is life-threatening
† E.g., itraconazole, erythromycin, and ciprofloxacin
CPK = creatine phosphokinase
CYP = cytochrome P450 isoenzyme
LLN = lower limit of normal
LVEF = left ventricular ejection fraction
N/A = not applicable

(Cotellic prescribing information, 2015)

APPROACHES TO TREATMENT

Melanoma is a heterogenous disease, and it is the most serious form of skin cancer (Nikolaou, 2012 Petrella, 2012). Although melanoma accounts for less than five percent of skin cancer cases, it results in the most deaths (National Cancer Institute [NCI], 2015). In the United States, it is estimated that 73,870 people will be diagnosed with melanoma and 9,940 patients will die from this disease in 2015. Melanoma is the fifth most common form of cancer in males and the seventh most common form of cancer in females (Skin Cancer Foundation [SCF], 2015). Along with liver and esophageal cancer, melanoma is one of the three cancers leading to an increased mortality rate in men. The probability of developing melanoma is higher than any other cancer, except breast cancer, in women 39 years of age and under. The incidence of melanoma has been steadily increasing over the past four decades (NCI, 2015).

Melanoma develops from melanocytes, cells that produce melanin (American Cancer Society [ACS], 2015). Although the most common form is cutaneous melanoma, it can also occur in less common sites where melanocytes are present such as the eye, mouth, genitals, and anal area. In general, the chest and back are the most common sites in men, and the legs are the most common site in women. It is more common in older adults with a median age at diagnosis of 59 years (National Comprehensive Cancer Network [NCCN], 2016). Early signs in a mole that would suggest malignant changes include changes in size, shape or color, itching, tenderness or pain, development of satellites, or a non-healing sore (ACS, 2015). Risk factors for melanoma include family history, prior melanoma, multiple clinical atypical moles or dysplastic nevi, inherited genetic mutations, and sun exposure (ACS, 2015; NCCN, 2016). Individuals with fair skin or with skin that burns easily have a greater risk for developing melanoma (ACS, 2015). Melanoma can occur in an individual of any ethnic background and also in areas without substantial exposure to the sun.

Clinical stage at presentation determines the outcome of melanoma (NCCN, 2015). Increasing tumor thickness, regional lymph node involvement, and distant metastatic disease, can decrease the five-year survival rate to as low as 10%. The American Joint Committee on Cancer (AJCC) provides a Tumor, Node, and Metastasis (TNM) staging system as a standard way of summarizing how far the cancer has spread (ACS; 2015). It is estimated that 2% to 5% of patients will present with metastatic melanoma (NCCN, 2016).

Surgical resection is the primary treatment recommended for early-stage melanoma (NCCN, 2016). Depending on tumor thickness and sentinel node involvement, adjuvant therapy includes a clinical trial, observation, Intron A (interferon alfa-2b), or high-dose Yervoy (ipilimumab). Stage III melanoma treatment with sentinel node involvement includes lymph node dissection as the primary treatment, and adjuvant therapy as used in early-stage melanoma. Excision of the primary tumor and complete lymph node dissection is the primary treatment for Stage III disease with clinically positive node(s). Adjuvant therapy consists of the regimens discussed in early-stage disease, with the additional options of biochemotherapy regimens, and/or radiation therapy (RT). Stage III in-transit melanoma primary treatment consists of clinical trial (preferred), surgical resection, intralesional injections of Imylgic (talimogene laherparepvec), BCG Vaccine (bacillus calmette-guérin vaccine), Intron A (interferon alfa-2b), or Proleukin (aldesleukin), local ablation therapy, topical Aldara (imiquimod), RT, isolated limb infusion/perfusion with Alkeran (melphalan), or systemic therapy utilized in metastatic or unresectable disease as depicted in Table 7. Adjuvant treatment is dependent on primary treatment, and includes clinical trial, observation or Proleukin (aldesleukin).

Primary treatment for Stage IV metastatic, limited disease is surgical resection, or systemic therapy utilized in metastatic or unresectable disease (Table 7). Adjuvant treatment consists of a clinical trial or observation, and if residual disease is present, systemic therapy utilized in metastatic or unresectable disease (Table 7) (NCCN, 2016). Stage IV metastatic, disseminated disease without brain metastases is treated with adjuvant therapy consisting of systemic therapy utilized in metastatic or unresectable disease (Table 7), clinical trial, intralesional Imlygic (talimogene laherparepvec), and/or palliative resection, and/or RT, or best supportive care. Patients with Stage IV metastatic, disseminated disease with brain metastases are managed primarily with palliative resection and/or RT, and adjuvant therapy consists of the regimens discussed in disseminated disease without brain metastases.

Table 7 depicts the treatment recommendations for systemic therapy for metastatic or unresectable melanoma and Table 8 provides the advantages and disadvantages of BRAF-targeted therapies. The treatment landscape for metastatic melanoma is rapidly changing with newly developed, more efficacious immunotherapy, single-agent and combination targeted therapy, intralesional injections, and systemic therapy for unresectable disease (NCCN, 2016; NCI, 2015).

Table 7: NCCN Treatment Algorithm for Systemic Therapy for Metastatic or Unresectable Melanoma

Stage	First-Line Therapy		Performance Status	Second-Line or Subsequent Therapy‡
Metastatic or unresectable disease	• Immunotherapy ▪ Anti PD-1 monotherapy o Keytruda (pembrolizumab) o Opdivo (nivolumab) o Opdivo/Yervoy (ipilimumab)* • Targeted therapy if BRAF-mutated ▪ Combination therapy (preferred if clinically needed for early response) o Tafinlar (dabrafenib)/ Mekinist (trametinib) o Zelboraf (vemurafenib)/ Cotellic (cobimetinib)† ▪ Single agent therapy o Zelboraf o Tafinlar • Clinical Trial	Disease progression or Maximum clinical benefit from *BRAF* targeted therapy	0 to 2	• Immunotherapy ▪ Anti PD-1 monotherapy o Keytruda o Opdivo o Opdivo/Yervoy* o Yervoy • Targeted therapy if BRAF-mutated ▪ Combination therapy (preferred) o Tafinlar/Mekinist o Zelboraf/Cotellic† ▪ Single agent therapy o Zelboraf o Tafinlar • High dose IL-2 • Biochemotherapy§ • Cytotoxic agents‖ • Gleevec (imatinib) for tumors with activating mutations of *C-KIT* • Clinical Trial
			3 to 4	Consider best supportive care

* Opdivo (nivolumab)/Yervoy (ipilimumab) combination therapy is associated with improved relapse-free survival compared with single agent Opdivo (nivolumab) or Yervoy (ipilimumab), at the expense of significantly increased toxicity. Compared to single agent therapy, impact of combination therapy on OS is not known.

† In previously untreated patients with unresectable IIIC or Stage IV disease, the combination of Zelboraf (vemurafenib)/Cotellic (cobimetinib) was associated with improved PFS and response rate when compared to Zelboraf (vemurafenib) alone. The impact on OS compared to single agent therapy is unknown.

‡ Second-line agents should be considered if not used first line, and not of the same class.

§ Biochemotherapy for metastatic melanoma: dacarbazine (e.g., DTIC-Dome) or Temodar (temozolomide), and Platinol (cisplatin) or carboplatin (e.g., Paraplatin), with or without vinblastine (e.g., Velban) or CeeNU (nitrosurea), and IL-2 and Intron-A (interferon alfa-2b); biochemotherapy for adjuvant treatment of high-risk disease: dacarbazine (e.g., DTIC-DOME), Platinol (cisplatin), vinblastine (e.g., Velban), IL-2, and Intron-A (interferon alfa-2b).

‖ Dacarbazine (e.g., DTIC-DOME), Temodar (temozolomide), paclitaxel (e.g., Taxol), Abraxane (albumin-bound paclitaxel), or carboplatin (e.g., Paraplatin)/paclitaxel (e.g., Taxol)

IL-2 = Proleukin (aldesleukin)
NCCN = National Comprehensive Cancer Network
OS = overall survival
PFS = progression free survival
PD-1 = programmed cell death protein 1

(NCCN, 2016)

Table 8: Advantages and Disadvantages of BRAF-Targeted Therapies

Drug	Advantages	Disadvantages
BRAF-Targeted Therapies		
BRAF-Targeted Therapies	• PO administration • Combination therapy with Mekinist (trametinib) + Tafinlar (dabrafenib) and Cotellic (cobimetinib) + Zelboraf (vemurafenib) decrease the incidence of cutaneous secondary cancers than monotherapy, and additional improvements in PFS (NCCN preferred regimens) • Inhibition of both MEK and BRAK kinases might be a strategy to decrease acquired resistance with single-agent BRAF kinase inhibitors	• BRAF gene must be documented by an FDA approved or CLIA-approved facility
Cotellic (cobimetinib)	• NCCN : Preferred regimen as combination therapy with Zelboraf • Demonstrated improvements in PFS in combination with Zelboraf	• Only indicated in patients with BRAF V600E or V600K mutations and in combination with Zelboraf • Not indicated for treatment of patients with wild-type BRAF melanoma • Increased risk of cardiac, ocular, dermatologic, and severe photosensitivity AEs • Requires monitoring of LVEF • Potential for CYP-mediated drug interactions
Mekinist (trametinib)	• NCCN : Preferred regimen as combination therapy with Tafinlar • Demonstrated improvements in PFS and 6-month OS as single therapy compared with chemotherapy, and improvement in PFS in combination with Tafinlar • Low potential for drug interactions	• Only indicated in patients with BRAF V600E or V600K mutations • Not indicated for the treatment of patients who have received prior BRAF-inhibitor therapy • Increased risk of cardiac, ocular, pulmonary, and dermatological AEs • Requires monitoring of LVEF
Tafinlar (dabrafenib)	• NCCN: Preferred regimen as combination therapy with Mekinist • Demonstrated improvements in PFS as single therapy compared with dacarbazine, and improvement in PFS in combination with Mekinist • Appears to cause less SCC toxicity than Zelboraf	• Only indicated in patients with BRAF V600E mutation • Not indicated for treatment of patients with wild-type BRAF melanoma • May cause significant episodic and recurrent fevers • Increased risk of hyperglycemia • Potential for CYP-mediated drug interactions
Zelboraf (vemurafenib)	• NCCN : Preferred regimen as combination therapy with Cotellic • Demonstrated improvements in PFS and OS as single therapy compared with dacarbazine, and improvement in PFS as combination therapy with Cotellic	• Only indicated in patients with BRAF V600E mutation • Increased risk for SCC toxicity, extreme photosensitivity, and dermatological AEs • Potential for CYP-mediated drug interactions

AEs = adverse events
CLIA = Clinical Laboratory Improvement Amendments
CV = cardiovascular
CYP = cytochrome P450 isoenzyme system
FDA = Food and Drug Administration
LVEF = left ventricular ejection fraction
MEK = mitogen-activated extracellular signal-regulated kinase
NCCN = National Comprehensive Cancer Network
OS = overall survival
PFS = progression-free survival
PO = oral
SCC = squamous cell carcinoma

National Institute for Health and Care Excellence (NICE)

It is recommended to manage Stage III melanoma with complete lymphadenectomy/lymph node dissection, adjuvant radiotherapy, or palliative treatment for in-transit metastases (NICE, 2015). Palliative treatments include surgery and systemic therapy, isolated limb infusion or perfusion, radiotherapy, electrochemotherapy, CO2 laser, or a topical agent when palliative surgery is not an option. It is recommended to manage Stage IV melanoma with surgery, stereotactic radiotherapy or radioembolism, or systemic treatment. Systemic treatment is compromised of targeted treatments for patients with BRAF V600 mutation-positive melanoma with Tafinlar (dabrafenib) or Zelboraf (vemurafenib), immunotherapy with Yervoy (ipilimumab), and cytotoxic chemotherapy with dacarbazine (e.g., DTIC-DOME) if immunotherapy or targeted therapy are not treatment options. NICE guidelines with the role of Cotellic (cobimetinib) with Zelboraf (vemurafenib) in BRAF V600, advanced, unresectable, metastatic melanoma are currently under review, and the expected publication date is October 2016.

PRODUCT COMPARISON

Cotellic (cobimetinib) launched on November, 16 2015.

Table 9: Market Share Comparison of Selected Agents for *BRAF*-Mutated Unresectable or Metastatic Melanoma

Product	CVS/caremark		
	Cost (AWP/unit)	Mail and Retail Rxs	Specialty Market Share (Combined Mail/Retail)
Cotellic (cobimetinib) tablets*	$115.46 per 20 mg tablet	48	2.6%
Tafinlar (dabrafenib) capsules	$62.47 per 50 mg capsule $93.70 per 75 mg capsule	750	40.6%
Mekinist (trametinib) tablets	$102.73 per 0.5 mg tablet $410.91 per 2 mg tablet	743	40.2%
Zelboraf (vemurafenib) tablets	$54.25 per 240 mg tablet	308	16.6%

***** Cotellic launched on November 16, 2015
AWP = average wholesale price
Rxs = prescriptions

(Caremark Integrated Utilization File: data source: First National Drug Data File. December 2015 to February 2016; *Medi-Span® Master Drug Data Base v2.5 (MDDB®)*, 13 April 2016, Clinical Drug Information, LLC.)

FORMULARY AND DRUG LIST AVAILABILITY

Table 10: Formulary/Drug List Availability of Selected Agents for BRAF-Mutated Unresectable or Metastatic Melanoma with UM Tools

Product	National Formulary	Prescribing Guide*	Prescribing Guide for Advanced Control Specialty Formulary	Performance Drug List*	Performance Drug List for Advanced Control Specialty Formulary	Advanced Control Formulary	Value Formulary*
Cotellic (cobimetinib) tablets	—						
Mekinist (trametinib) tablets	✓	—					✓†
Tafinlar (dabrafenib) capsules							
Zelboraf (vemurafenib) tablets							

* Advanced Control Specialty Formulary may be applied to Prescribing Guide, Performance Drug List, or Value Formulary
† Prior authorization
UM = utilization management

Table 11: Managed Medicaid Drug List and 2015 Health Exchanges Formularies Availability of Selected Agents for BRAF-Mutated Unresectable or Metastatic Melanoma with UM Tools

Product	Managed Medicaid Drug List	2015 Health Exchanges Template Formulary	2015 Health Exchanges Formulary South Carolina	2015 Health Exchanges Formulary New York
Cotellic (cobimetinib) tablets	—			
Mekinist (trametinib) tablets	✓*	tier 4*		tier 3*
Tafinlar (dabrafenib) capsules				
Zelboraf (vemurafenib) tablets				

* Prior authorization
UM = utilization management

Table 12: 2016 Health Exchanges Formularies Availability of Selected Agents for BRAF-Mutated Unresectable or Metastatic Melanoma with UM Tools

Product	2016 5-Tier Health Exchanges Template Formulary	2016 6-Tier Health Exchanges Template Formulary	2016 4-Tier Health Exchanges Formulary California	2016 3-Tier Health Exchanges Formulary New York	2016 6-Tier Health Exchanges Formulary South Carolina
Cotellic (cobimetinib) tablets	—				
Mekinist (trametinib) tablets	tier 4*	tier 5*	tier 4*	tier 3*	tier 5*
Tafinlar (dabrafenib) capsules					
Zelboraf (vemurafenib) tablets					

* Prior authorization
UM = utilization management

Table 13: 2015 Medicare Part D Drug List Availability of Selected Agents for BRAF-Mutated Unresectable or Metastatic Melanoma Agents with Optional UM Tools*

Product	PDP Drug List	Client Drug Lists						
		Generic Strategy	Generic Strategy Narrow	Standard†	Expanded	Expanded without MSBs	EGWP‡	
	4-Tier	5-Tier		5-Tier	5-Tier		3-Tier/4-Tier	5-Tier
Cotellic (cobimetinib) tablets	—							
Mekinist (trametinib) tablets	tier 4§	tier 5§					tier 3§/tier 4§	tier 5§
Tafinlar (dabrafenib) capsules								
Zelboraf (vemurafenib) tablets	tier 4§‖	tier 5§‖					tier 3§‖/ tier 4§‖	tier 5§‖

***** Centers for Medicare and Medicaid Services class of clinical concern
† Also available as a 2-Tier and 4-Tier MDL. Brands are on tier 2 of the 2-Tier MDL. Generics may be on any tier based on cost. The tier designation for the drugs on the 5-Tier MDL would be one tier lower on the 4-Tier MDL.
‡ Also available as 1-Tier and 2-Tier MDLs. Generics may be on any tier based on cost. Brands are on tier 2 of the 2-Tier MDL.
§ Prior authorization
‖ Limited access
EGWP = Employer Group Waiver Plan
MDL = Medicare Part D Drug List
MSB = multisource brand
PDP = Prescription Drug Plan
UM = utilization management

Table 14: 2016 Medicare Part D Drug List Availability of Selected Agents for BRAF-Mutated Unresectable or Metastatic Melanoma with Optional UM Tools*

Product	PDP Drug List	Client Drug Lists					
		Generic Strategy	Generic Strategy Narrow	Standard†	Expanded	Expanded without MSBs	EGWP
	5-Tier	5-Tier		5-Tier	5-Tier		3-Tier/4-Tier
Cotellic (cobimetinib) tablets	—						
Mekinist (trametinib) tablets	tier 5‡§						tier 3‡§‖/ tier 4‡§‖
Tafinlar (dabrafenib) capsules							
Zelboraf (vemurafenib) tablets							

***** Centers for Medicare and Medicaid Services class of clinical concern
† Also available as a 1-Tier, 2-Tier, and 4-Tier MDL. Brands are on tier 2 of the 2-Tier MDL. The tier designation for the drugs on the 5-Tier MDL would be one tier lower on the 4-Tier MDL.
‡ Prior authorization
§ Limited access
‖ Quantity limit
EGWP = Employer Group Waiver Plan
MDL = Medicare Part D Drug List
MSB = multisource brand
PDP = Prescription Drug Plan
UM = utilization management

FORMULARY CONSIDERATIONS

Cotellic (cobimetinib) is a MEK inhibitor, used in combination with Zelboraf (vemurafenib), a BRAF kinase inhibitor, for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600E or V600K mutation. Results from a randomized, double-blind, placebo-controlled trial demonstrated an improvement in PFS of approximately 3.7 months with the administration of Cotellic (cobimetinib) plus Zelboraf (vemurafenib) vs. Zelboraf (vemurafenib) only. Cotellic (cobimetinib) has warnings regarding cardiac, ocular, photosensitivity reactions and dermatological adverse events. Additional common adverse events include diarrhea, nausea, pyrexia, and vomiting. Cotellic (cobimetinib) offers an additional treatment option in combination with Zelboraf (vemurafenib) for patients with unresectable or metastatic melanoma with a BRAF V600E or V600K mutation, and is one of the preferred combination therapy regimens for BRAF-mutated metastatic or unresectable melanoma recommended by NCCN.

REFERENCES

ADIS R&D Insight. Available with subscription http://bi.adisinsight.com/Login/Login.aspx. Available from Internet. Accessed 2015 November 24.

American Cancer Society. Skin cancer. URL: http://www.cancer.org/cancer/skincancer-basalandsquamouscell/detailedguide/skin-cancer-basal-and-squamous-cell-staging. Available from Internet. Accessed 2015 November 24.

Cotellic prescribing information. San Fransico, CA: Genetech USA, Inc.; 2015 November.

Food and Drug Administration. Drugs@FDA. URL: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/. Available from Internet. Accessed 2015 November 24.

Larkin J, Ascierto PA, Dreno B, et al. Combined Vemurafenib and Cobimetinib in *BRAF*-Mutated Melanoma. *N Engl J Med*. 2014; 371: 1867-76.

Larkin J, Ascierto PA, Dreno B, et al. Update of progression-free survival (PFS) and correlative biomarker analysis from coBRIM: Phase III study of cobimetinib (cobi) plus vemurafenib (vem) in advanced *BRAF*-mutated melanoma. *J Clin Oncol*. 2015; 33: supplement. Abstract 9006.
URL: http://meetinglibrary.asco.org/content/144759-156. Available from Internet. Accessed 2015 December 2.

Medi-Span® Master Drug Data Base v2.5 (MDDB®), 13 April 2016, Clinical Drug Information, LLC.

Mekinist prescribing information. Research Triangle Park, NC: GlaxoSmithKline; 2014, January.

National Cancer Institute. Melanoma. URL: http://www.cancer.gov/cancertopics/types/melanoma. Available from Internet. Accessed 2015 December 2.

National Comprehensive Cancer Network. Melanoma cancer. 2.2016. URL: http://www.nccn.org/professionals/physician_gls/pdf/melanoma.pdf. Available from Internet. Accessed 2015 November 25.

National Institute for Health and Care Excellence. Our Guidance. URL: http://www.nice.org.uk/guidance/index.jsp. Available from Internet. Accessed 2015 December 2.

Nikolaou VA, Stratigos AJ, Flaherty KT et al. Melanoma: new insights and new therapies. *J Invest Dermatol.* 2012;132(3 Pt 2):854-63.

Petrella T. Verma S, Spithoff K et al. Adjuvant interferon therapy for patients at high risk for recurrent melanoma: an updated systematic review and practice guideline. *Clinical Oncology* 2012; 24:413-423.

Skin Cancer Foundation. Skin Cancer Facts, URL: C:\Documents and Settings\ud1jxyb\Desktop\Melanoma TCR\Skin Cancer Facts - SkinCancer_org.mht . Available from the Internet. Accessed 2015 November 24.

Tafinlar prescribing information. Research Triangle Park, NC: GlaxoSmithKline; 2014 January.

Zelboraf prescribing information. South San Francisco: Genentech USA, Inc.; 2015 August.

MONOGRAPH PREPARED BY:

Lisa Raff, Pharm.D., BCPS

December 15, 2015
Update: April 13, 2016

This document includes the clinical opinions of CVS Caremark based on the information available at the time this document was written. The document contains summarized information and is not a substitute for reading the original literature. Economic and other considerations may influence an individual client's formulary decision. The document contains prescription brand name drugs that are registered or trademarks of pharmaceutical manufacturers that are not affiliated with CVS Caremark.

SPECIALTY GUIDELINE MANAGEMENT

COTELLIC (cobimetinib)

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
Cotellic is indicated for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600E or V600K mutation, in combination with vemurafenib.

All other indications are considered experimental/investigational and are not a covered benefit.

II. REQUIRED DOCUMENTATION

The following information is necessary to initiate the prior authorization review: BRAF mutation test results

III. CRITERIA FOR INITIAL APPROVAL

Authorization of 12 months may be granted for treatment of unresectable or metastatic melanoma when all of the following criteria are met:
A. Cotellic is used in combination with vemurafenib
B. Tumor is positive for BRAF V600E or V600K mutation

IV. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must meet ALL initial authorization criteria.

V. DOSAGE AND ADMINISTRATION

Approvals may be subject to dosing limits in accordance with FDA-approved labeling, accepted compendia, and/or evidence-based practice guidelines.

REFERENCES

1. Cotellic [package insert]. South San Francisco, CA: Genentech USA, Inc.; November 2015.

Emend® *(apripitant) oral suspension*

Indication(s)	Treatment of chemotherapy induced nausea and vomiting in combination with other antiemetic agents in patient ≥6 months of age
FDA Approval	December 21th, 2015
Treatment Comparisons for Indications	Emend capsule formulations
Place in Therapy	substance P/neurokinin 1 (NK1) receptor antagonist; brand name suspension formulation with increased pediatric approval for patients unable to swallow pills
Dosage and Administration	***Strengths Available:*** 125 mg ***Dosage Frequency:*** Once daily allow tablet to disintegrate in saliva then swallow; may be taken with or without food
Safety	***Contraindications:*** Hypersensitivity to apripitant or other ingredients in EMEND; Concurrent use of pimozide ***Warnings:*** Do not use in pediatric patients weighing < 6kg; potential for significant drug interactions ***Drug Interactions:*** CYP3A4 inhibitors, warfarin, pimozide, hormone contraceptives
Use in Specific Populations	***Pregnancy:*** category B, no adequate studies in pregnant women, animal data failed to show fetal risk ***Nursing:*** Unknoown if excreted in breast milk; consider benefit & risks ***Pediatric:*** Safety and efficacy in pediatric patients younger than 6 months of age has not been established; not indicated for post-op NV, do not use if < 6kg ***Geriatric:*** has not been studied in the geriatric population; use with caution ***Hepatic:*** Use with caution with severe impairment (Child-Pugh ≥ 9)
Formulary Considerations	***Proposed Formulary Addition*:** Tier 3 with PA and QL No generic substance P/neurokinin 1 (NK1) receptor antagonist on the market Varubi (rolapitant tablets) at Tier 2; Emend (apripitant capsules) at Tier 3; Akynzeo (netupitant/palonosetron capsules) at Tier 3
Utilization	Previously approved as nonformulary; only available via approved formulary exceptions
Conclusion	Accept formulary addition as proposed

PRIOR AUTHORIZATION CRITERIA

BRAND NAME	**EMEND**
(generic)	**(aprepitant capsules) (aprepitant oral suspension) (fosaprepitant dimeglumine injection)**

Status: CVS Caremark Criteria
Type: Post Limit Prior Authorization

POLICY

FDA-APPROVED INDICATIONS

Emend (aprepitant) capsules and oral suspension

Prevention of Chemotherapy Induced Nausea and Vomiting (CINV)

Emend for oral suspension, in combination with other antiemetic agents, is indicated in patients 6 months of age and older for the prevention of:

- acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy (HEC) including high-dose cisplatin.
- nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy (MEC).

Emend capsules, in combination with other antiemetic agents, are indicated in patients 12 years of age and older for the prevention of:

- acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy (HEC) including high-dose cisplatin.
- nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy (MEC).

Prevention of Postoperative Nausea and Vomiting (PONV)

Emend capsules are indicated in adults for the prevention of postoperative nausea and vomiting.

Limitations of Use

Emend has not been studied for the treatment of established nausea and vomiting.

Chronic continuous administration is not recommended because it has not been studied and because the drug interaction profile may change during chronic continuous use.

Emend (fosaprepitant dimeglumine) for injection

Emend for Injection is a substance P/neurokinin-1 (NK1) receptor antagonist indicated in adults for use in combination with other antiemetic agents for the:

- prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy (HEC) including high-dose cisplatin.
- prevention of nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy (MEC).

Limitations of Use

Emend for Injection has not been studied for the treatment of established nausea and vomiting.

Chronic continuous administration is not recommended

COVERAGE CRITERIA

Emend will be covered with prior authorization when the following criteria are met:

- Patient is NOT currently taking pimozide (Orap)

AND

- Emend is being prescribed for the prevention of postoperative nausea and vomiting

OR

- Emend is being prescribed for the prevention of nausea and vomiting associated with highly or moderately emetogenic chemotherapy AND will be used in combination with other antiemetic agents

Quantity Limits apply.

POST LIMIT QUANTITY

Drug	Quantities to approve
Emend 80 mg Capsules	16 capsules / 21 days
Emend 125 mg Capsules	4 capsules / 21 days
Emend Tri-pack (contains one 125mg and two 80mg)	4 packs / 21 days
Emend 125 mg for Oral Suspension (Single-Dose Kit)	12 kits / 21 days
Emend 150 mg Injection	4 vials / 21 days
Emend 40 mg capsule	6 capsules / 6 months

**** This drug is indicated for short-term acute use; therefore, the mail limit will be the same as the retail limit.*** *The duration of 21 days is used for a 28-day fill period.*

REFERENCES

1. Emend capsules and oral suspension [package insert]. Whitehouse Station, NJ: Merck and Co., Inc; December 2015.
2. Emend for injection [package insert]. Whitehouse Station, NJ: Merck and Co., Inc; October 2014.
3. Varubi [package insert]. Waltham, MA: Tesaro, Inc; September 2015.
4. 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 January 2016.
5. Micromedex Solutions [database online]. Greenwood Village, CO: Truven Health Analytics Inc. Updated periodically. www.micromedexsolutions.com [available with subscription]. Accessed January 2016.
6. Basch E, Prestrud AA, Hesketh PJ, et al. Antiemetics: American Society of Clinical Oncology Clinical Practice Guideline Update. *J Clin Oncol* 2011; 29(31);4189-4198.
7. National Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology. Antiemesis. V.2.2015. Available at: www.nccn.org. Accessed January 2016.
8. Roila F, Herrstedt J, Aapro, M, et al. Guideline update for MASCC and ESMO in the prevention of chemotherapy- and radiotherapy-induced nausea and vomiting: results of the Perugia consensus conference. *Ann Oncol* 2010; 21(supplement 5):v232-v243.
9. Albany C, Brames MJ, Fausel C, et. al. Randomized, Double-Blind, Placebo-Controlled, Phase III Cross-Over Study Evaluating the Oral Neurokinin-l Antagonist Aprepitant in Combination With a SHT3 Receptor Antagonist and Dexamethasone in Patients With Germ Cell Tumors Receiving 5-Day Cisplatin Combination Chemotherapy Regimens: A Hoosier Oncology Group Study. *J Clin Oncol* 2012;30:3998-4003.

QUANTITY LIMIT CRITERIA

BRAND NAME	**EMEND**
(generic)	**(aprepitant capsules) (aprepitant oral suspension) (fosaprepitant dimeglumine injection)**
	VARUBI
	(rolapitant)

Status: CVS Caremark Criteria
Type: Quantity Limit

POLICY

FDA-APPROVED INDICATIONS

Emend (aprepitant) capsules and oral suspension

Prevention of Chemotherapy Induced Nausea and Vomiting (CINV)

Emend for oral suspension, in combination with other antiemetic agents, is indicated in patients 6 months of age and older for the prevention of:

- acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy (HEC) including high-dose cisplatin.
- nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy (MEC).

Emend capsules, in combination with other antiemetic agents, are indicated in patients 12 years of age and older for the prevention of:

- acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy (HEC) including high-dose cisplatin.
- nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy (MEC).

Prevention of Postoperative Nausea and Vomiting (PONV)

Emend capsules are indicated in adults for the prevention of postoperative nausea and vomiting.

Limitations of Use

Emend has not been studied for the treatment of established nausea and vomiting.

Chronic continuous administration is not recommended because it has not been studied and because the drug interaction profile may change during chronic continuous use.

Emend (fosaprepitant dimeglumine) for injection

Emend for Injection is a substance P/neurokinin-1 (NK1) receptor antagonist indicated in adults for use in combination with other antiemetic agents for the:

- prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy (HEC) including high-dose cisplatin.
- prevention of nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy (MEC).

Limitations of Use

Emend for Injection has not been studied for the treatment of established nausea and vomiting.

Chronic continuous administration is not recommended

Varubi

Varubi is indicated in combination with other antiemetic agents in adults for the prevention of delayed nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy, including, but not limited to, highly emetogenic chemotherapy.

LIMIT CRITERIA

Drug	4 Weeks Limit and 12 Weeks Limit*
Emend 80 mg Capsule	4 capsules / 21 days
Emend 125 mg Capsule	2 capsule / 21 days
Emend Tri-pack (contains one 125 mg capsule and two 80 mg capsules)	2 packs / 21 days
Emend 125 mg for Oral Suspension (Single-Dose Kit)	6 kits / 21 days
Emend 150 mg Injection	2 vials / 21 days
Emend 40 mg capsule	3 capsules / 6 months

**** This drug is indicated for short-term acute use; therefore, the mail limit will be the same as the retail limit.*** *The duration of 21 days is used for a 28-day fill period.*

LIMIT CRITERIA

The initial quantity limit for Varubi is sufficient to treat 2 chemotherapy cycles per month (each cycle given at no less than 2-week intervals); therefore, no additional quantities are available through a post limit document.

Drug	4 Weeks Limit and 12 Weeks Limit*
Varubi single dose package (contains two 90 mg tablets as one set of twinned blisters)	2 packs/ 21 days

**** This drug is indicated for short-term acute use; therefore, the mail limit will be the same as the retail limit.*** *The duration of 21 days is used for a 28-day fill period.*

REFERENCES

1. Emend capsules and oral suspension [package insert]. Whitehouse Station, NJ: Merck and Co., Inc; December 2015.
2. Emend for injection [package insert]. Whitehouse Station, NJ: Merck and Co., Inc; October 2014.
3. Varubi [package insert]. Waltham, MA: Tesaro, Inc; September 2015.
4. 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 January 2016.
5. Micromedex Solutions [database online]. Greenwood Village, CO: Truven Health Analytics Inc. Updated periodically. www.micromedexsolutions.com [available with subscription]. Accessed January 2016.
6. Basch E, Prestrud AA, Hesketh PJ, et al. Antiemetics: American Society of Clinical Oncology Clinical Practice Guideline Update. *J Clin Oncol* 2011; 29(31);4189-4198.
7. National Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology. Antiemesis. V.2.2015. Available at: www.nccn.org. Accessed January 2016.
8. Roila F, Herrstedt J, Aapro, M, et al. Guideline update for MASCC and ESMO in the prevention of chemotherapy- and radiotherapy-induced nausea and vomiting: results of the Perugia consensus conference. *Ann Oncol* 2010; 21(supplement 5):v232-v243.

CVSHealth

CVS Caremark Pharmacy & Therapeutics
Drug Monograph

Lartruvo™ (olaratumab) intravenous injection
Eli Lilly and Company

INTRODUCTION

Lartruvo (olaratumab) is a platelet-derived growth factor receptor alpha (PDGFR-α) blocking antibody indicated in combination with doxorubicin for the first-line treatment of soft tissue sarcoma (STS) in select patient populations (Lartruvo prescribing information, 2016).

U.S. Food and Drug Administration (FDA)-Review Designation

Lartruvo (olaratumab) was approved by the FDA on October 19, 2016 under a Biologics License Application (BLA) (FDA, 2016a). Lartruvo (olaratumab) is a new molecular entity that underwent priority review and accelerated approval, and was granted orphan drug, fast track and breakthrough therapy designations (FDA, 2016b). An agent may qualify for breakthrough therapy if it treats a serious or life-threatening condition and preliminary clinical evidence indicates that the drug may demonstrate substantial improvement for clinically significant endpoint(s) compared with available therapies (FDA, 2016c).

INDICATION

Lartruvo (olaratumab) is indicated, in combination with doxorubicin, for the treatment of adult patients with STS with a histologic subtype for which an anthracycline-containing regimen is appropriate and which is not amenable to curative treatment with radiotherapy or surgery (Lartruvo prescribing information, 2016). Lartruvo (olaratumab) was approved under accelerated approval, and its continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trial.

CLINICAL PHARMACOLOGY

Mechanism of Action

Olaratumab is a human immunoglobulin G subclass1 (IgG1) monoclonal antibody that inhibits the binding of platelet-derived growth factor (PDGF) ligands with PDGFR-α (Lartruvo prescribing information, 2016). Signaling through the activation of PDGFR-α on cancer cells may contribute to cancer cell proliferation, metastasis, and maintenance of the tumor microenvironment.

Pharmacokinetics

Table 1: Selected Pharmacokinetics of Olaratumab

Route of Administration	Volume of Distribution	Mean Clearance	$T_{1/2}$
Intravenous infusion	7.7 L	0.56 L/day	11 days

$T_{1/2}$ = elimination half-life

(Lartruvo prescribing information, 2016)

Pharmacogenomics

No pharmacogenomics data are available at this time for olaratumab.

CLINICAL EFFICACY

Table 2: Efficacy of Lartruvo (olaratumab) in the Treatment of Soft Tissue Sarcoma

<table>
<tr><th>Study, Treatments, and Groups</th><th>Study Design and Endpoints</th><th>Study Criteria</th><th>Results</th></tr>
<tr>
<td>Tap, 2016
Evidence Level Ib
Lartruvo
15 mg/kg intravenously on day 1 and 8 of each 21-day cycle
plus
doxorubicin
75 mg/m^2 intravenously on day 1 of each 21-day cycle* (n = 66)
vs.
doxorubicin
75 mg/m^2 intravenously on day 1 of each 21-day cycle† (n = 67)</td>
<td>N = 133
Study Design: Phase II, multicenter, open-label, randomized controlled trial
Objective: To assess the efficacy of Lartruvo plus doxorubicin in patients with advanced or metastatic soft tissue sarcoma
Primary Endpoint: PFS
Secondary Endpoints: OS, ORR, safety</td>
<td>Inclusion Criteria: Patients ≥ 18 years of age (median age 58 years; 44% male); histologically confirmed diagnosis of locally advanced or metastatic soft tissue sarcoma not previously treated with an anthracycline‡; ECOG performance status of 0 to 2
Exclusion Criteria: Confirmed Kaposi’s sarcoma; untreated metastases to the CNS; previous therapy targeting PDGF or PDGFR; previous radiation therapy to mediastinal or pericardial area; concurrent anticancer therapy</td>
<td>
<table>
<tr><th>Endpoint</th><th>Lartruvo + doxorubicin (n = 66)</th><th>doxorubicin (n = 67)</th><th>HR (95% CI)[a]</th><th>p-value</th></tr>
<tr><td>Median PFS</td><td>6.6 months (95% CI 4.1 to 8.3)</td><td>4.1 months (95% CI 2.8 to 5.4)</td><td>0.67 (0.44 to 1.02)</td><td>0.0615[b]</td></tr>
<tr><td>Median OS</td><td>26.5 months (95% CI 20.9 to 31.7)</td><td>14.7 months (95% CI 9.2 to 17.1)</td><td>0.46 (0.30 to 0.71)</td><td>0.0003</td></tr>
<tr><td>ORR</td><td>18.2% (95% CI 9.8 to 29.6)</td><td>11.9% (95% CI 5.3 to 22)</td><td rowspan="3">Not available</td><td>0.3421</td></tr>
<tr><td>Complete Response</td><td>3.0%</td><td>1.5%</td><td rowspan="2">Not Available</td></tr>
<tr><td>Partial Response</td><td>15.2%</td><td>10.4%</td></tr>
</table>
a Patients were stratified according to number of lines of prior therapy and histological tumor type
b Protocol-defined significance level was 0.1999

A blinded independent retrospective review of the radiological scans found similar results to investigator assessment for PFS, OS and ORR.
OS was consistent across subgroups including tumor type, number of lines of previous treatment, and PDFR-α status.

Safety

The most common treatment-emergent adverse events with Lartruvo plus doxorubicin were nausea (73%), fatigue (69%), neutropenia (58%), and mucositis (53%). Treatment-related adverse events of Grade 3 or higher and serious adverse events of Grade 3 or higher were more frequent in patients treated with Lartruvo plus doxorubicin than in those treated with doxorubicin. Treatment with Lartruvo was associated with more infusion-related adverse events (13%) compared with patients receiving doxorubin (0%).
Treatment discontinuation due to adverse events occurred in 13% of patients in the Lartruvo plus doxorubicin arm and 18% in the doxorubicin arm, with the most common reason being progression of disease in both groups.

Comments/Study Limitations: There were slightly more women in the Lartruvo plus doxorubicin arm (61%) compared with the doxorubin arm (51%). No investigators, outcome assessors, or patients were blinded to assigned treatment; however, independent radiological reviewers were blinded. Study funded by Eli Lilly and Company.
Conclusions: Lartruvo in combination with doxorubicin demonstrated significant improvements in OS and statistically significant improvements in PFS compared with doxorubicin alone in patients with soft tissue sarcoma without a significant increase in serious adverse events.
</td>
</tr>
</table>

* Administered for up to 8 cycles; after completion of 8 cycles of doxorubicin, patients could receive Lartruvo monotherapy until disease progression
† Administered for up to 8 cycles; after completion of 8 cycles of doxorubicin, patients could receive Lartruvo monotherapy after documented disease progression
‡ 38% of enrolled patients had leiomyosarcoma histology
Ib = evidence from a randomized, controlled trial
CI = confidence interval
CNS = central nervous system
ECOG = Eastern Cooperative Oncology Group
HR = hazard ratio
ORR = objective response rate
OS = overall survival
PDGF = platelet-derived growth factor
PDGFR = platelet-derived growth factor receptor
PFS= Progression-free survival

(Tap, 2016)

SAFETY

Contraindications

Lartruvo (olaratumab) does not have any known contraindications (Lartruvo prescribing information, 2016).

Warnings and Precautions

Infusion-Related Reactions

Infusion-related reactions were reported in 70 of 485 patients (14%) who received at least one dose of Lartruvo (olaratumab) in clinical trials, with the majority of the reactions (97%) occurring during the first or second cycle (Lartruvo prescribing information, 2016). Patients should be monitored for signs and symptoms of infusion-related reactions in a setting with available resuscitation equipment. Lartruvo (olaratumab) should be immediately and permanently discontinued in patients who experience Grade 3 or 4 infusion-related reactions.

Embryo-Fetal Toxicity

Based on animal data and its mechanism of action, olaratumab can cause fetal harm when administered to a pregnant woman and may impair male fertility (Lartruvo prescribing information, 2016). Animal models have demonstrated disruption of PDGFR-α signaling is linked to adverse effects on embryo-fetal development causing malformations and skeletal variations. Pregnant women should be advised of risk to a fetus, and females of reproductive potential should be advised to use effective contraception during treatment with Lartruvo (olaratumab) and for three months after the last dose.

Nursing Mothers

There are no data on the presence of olaratumab in human milk, the effects on the breastfed infant, or the effects on milk production (Lartruvo prescribing information, 2016). Due to the potential for serious adverse events from olaratumab in breastfed infants, nursing women should be advised to discontinue nursing during treatment with Lartruvo (olaratumab) and for three months following the last dose.

Pediatric Use

The safety and efficacy of Lartruvo (olaratumab) in pediatric patients have not been established (Lartruvo prescribing information, 2016).

Geriatric Use

A sufficient number of patients aged 65 years and older where not included in clinical trials to determine whether this population of patients responds differently compared with younger patients (Lartruvo prescribing information, 2016).

Drug Interactions

No clinically relevant drug interactions were observed in clinical trials (Lartruvo prescribing information, 2016).

Adverse Events and Abnormal Laboratory Values

An evaluation of 64 patients with STS who received Lartruvo (olaratumab) for a median duration of six months (range 21 days to 29.4 months) found Lartruvo (olaratumab) was permanently discontinued in 8% of patients due to adverse events, with the most common reason being infusion-related reactions (3%) (Lartruvo prescribing information, 2016). Dose reductions due to adverse events occurred in 25% of patients receiving Lartruvo (olaratumab), with the most common reason due to Grade 3 or 4 neutropenia (20%). Delay in dosing of Lartruvo (olaratumab) due to adverse events occurred in 52% of patients, due to neutropenia (33%), thrombocytopenia (8%), and anemia (5%). The most common adverse events occurring with Lartruvo (olaratumab) are described in Table 3, while the most common laboratory abnormalities are shown in Table 4.

Table 3: Adverse Events for Lartruvo (olaratumab) plus Doxorubicin in 10% or More of Patients and More Commonly than Doxorubicin Alone

Adverse Event	Lartruvo plus Doxorubicin (n = 64)		Doxorubicin (n = 65)	
	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4
Nausea	73%	2%	52%	3%
Asthenia and fatigue	69%	9%	69%	3%
Musculoskeletal pain*	64%	8%	25%	2%
Mucositis	53%	3%	35%	5%
Alopecia	52%	0%	40%	0%
Vomiting	45%	0%	19%	0%
Diarrhea	34%	3%	23%	0%
Decreased appetite	31%	2%	20%	0%
Abdominal pain†	23%	3%	14%	0%
Neuropathy	22%	0%	11%	0%
Headache	20%	0%	9%	0%
Infusion-related reactions	13%	3%	3%	0%
Anxiety	11%	0%	3%	0%
Dry eyes	11%	0%	3%	0%

* Includes arthralgia, back pain, bone pain, flank pain, groin pain, musculoskeletal chest pain, musculoskeletal pain, myalgia, muscle spasms, neck pain, and pain in extremity
† Includes abdominal pain, lower abdominal pain, and upper abdominal pain

(Lartruvo prescribing information, 2016)

Table 4: Abnormal Laboratory Values for Lartruvo (olaratumab) plus Doxorubicin in 10% or More of Patients and More Commonly than Doxorubicin Alone

Adverse Event	Lartruvo plus Doxorubicin*		Doxorubicin*	
	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4
Lymphopenia	77%	44%	73%	37%
Neutropenia	65%	48%	63%	38%
Thrombocytopenia	63%	6%	44%	11%
Hyperglycemia	52%	2%	28%	3%
Increased aPTT	33%	5%	13%	0%
Hypokalemia	21%	8%	15%	3%
Hypophosphatemia	21%	5%	7%	3%
Increased alkaline phosphatase	16%	0%	7%	0%
Hypomagnesemia	16%	0%	8%	0%

* Incidence based on the number of patients who had both baseline and at least one on-study laboratory measurement: Lartruvo plus doxorubicin arm ranged from 60 to 63 patients and doxorubicin arm arranged from 39 to 62 patients
aPTT = activated partial thromboplastin time

(Lartruvo prescribing information, 2016)

Immunogenicity

In clinical trials, 13 of 370 patients (3.5%) of evaluable patients treated with Lartruvo (olaratumab) tested positive for treatment-emergent anti-olaratumab neutralizing antibodies by an enzyme-linked immunosorbent assay (ELISA) (Lartruvo prescribing information, 2016). Due to the limited number of patients testing positive for treatment-emergent anti-olaratumab antibodies, the effects of anti-olaratumab antibodies on efficacy, safety, and exposure could not be assessed.

PRODUCT AVAILABILITY

Lartruvo (olaratumab) is supplied as a 500 mg/50 mL solution in a single-dose vial (Lartruvo prescribing information, 2016).

DOSAGE AND ADMINISTRATION

The recommended dose of Lartruvo (olaratumab) is 15 mg/kg administered as an intravenous infusion over 60 minutes on days one and eight of each 21-day cycle until disease progression or unacceptable toxicity (Lartruvo prescribing information, 2016). Lartruvo (olaratumab) should be administered with doxorubicin for the first eight cycles. Patients should be premedicated with diphenhydramine 25 mg to 50 mg intravenously and dexamethasone 10 mg to 20 mg intravenously prior to administration of Lartruvo (olaratumab) on day one of cycle one.

Dose Modifications

Infusion of Lartruvo (olaratumab) should be interrupted for Grade 1 or 2 infusion-related reactions (Lartruvo prescribing information, 2016). After resolution, Lartruvo (olaratumab) should be resumed at 50% of the initial infusion rate. Lartruvo (olaratumab) should be permanently discontinued for Grade 3 or 4 infusion-related reactions.

For neutropenic fever/infection or Grade 4 neutropenia lasting longer than one week, administration of Lartruvo (olaratumab) should be discontinued until the absolute neutrophil count is ≥ 1,000/µL (Lartruvo prescribing information, 2016). Upon resolution of neutrophil count, the dose of Lartruvo (olaratumab) should be permanently reduced to 12 mg/kg.

APPROACHES TO TREATMENT

Sarcomas are a heterogeneous group of tumors that are derived from mesenchymal cells (National Comprehensive Cancer Network® [NCCN®], 2016). Sarcomas can be divided into soft tissue tumors and bone tumors. There are more than 50 types of STS, including liposarcoma, leiomyosarcoma, synovial sarcoma, gastrointestinal stromal tumors, Kaposi sarcoma, Ewing sarcoma, rhabdomyosarcoma, malignant peripheral nerve sheath tumors, and many others (American Cancer Society [ACS], 2016). Tumors vary in the type of cell affected as well as the location of the tumor.

It is estimated that in 2016 there will be 12,310 people diagnosed with STS as well as 4,990 deaths (ACS, 2016). Sarcomas represent approximately 1% of all adult cancers and 15% of pediatric cancers (NCCN, 2016). The most common types of STS are undifferentiated pleomorphic sarcoma, gastrointestinal stromal tumors (GISTs), liposarcoma, leiomyosarcoma, synovial sarcoma, and malignant peripheral nerve sheath tumors. Liposarcomas are malignant tumors of fat tissue, and the most common locations for these tumors are the thigh, behind the knee, and in the retroperitoneum (ACS, 2016). Liposarcomas are most common in adults between 50 years of age and 65 years of age. Leiomyosarcomas are malignant tumors of the smooth muscle, most commonly the uterus where they are known as fibroids. Leiomyosarcomas represent 30% of uterine sarcomas (National Cancer Institute [NCI], 2015). The peak incidence of leiomyosarcomas occurs around 50 years of age.

Few risk factors have been identified for liposarcomas and leiomyosarcomas (ACS, 2016; NCI, 2015). Prior radiation exposure is a clear risk factor. However, it is thought that radiation exposure only accounts for less than 5% of STSs (ACS, 2016). Tamoxifen increases the risk of leiomyosarcoma as well as the more recognized risk for endometrial cancer (NCI, 2015). Some genetic cancer syndromes, including Li-Fraumeni syndrome, familial adenomatous polyposis, Carney-Stratakis syndrome, neurofibromatosis type 1, and hereditary retinoblastoma increase the risk for certain STSs (NCCN, 2016). Of these, hereditary retinoblastoma is associated with an increased risk of leiomyosarcoma.

Treatment

Surgical resection is the main treatment for STS, sometimes used in conjunction with preoperative or postoperative radiation and/or chemotherapy (NCCN, 2016). For STSs that are advanced, unresectable or metastatic disease, several anthracycline-based combination chemotherapy regimens as well as single-agent regimens are noted to be active against the tumors. Recommendations vary by tumor type. For tumors of non-specific histology, including liposarcomas and the majority of soft-tissue subtypes, anthracycline-based regimens are preferred. Agents that might be used alone or in combination with other agents include doxorubicin, ifosfamide, gemcitabine, dacarbazine, epirubicin, docetaxel, liposomal doxorubicin, temozolomide, vinorelbine, pazopanib, and eribulin. However, the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Soft Tissue Sarcoma note that pazopanib should not be used in liposarcomas and is only recommended for palliative therapy. Votrient (pazopanib) is not indicated in the treatment of liposarcoma (Votrient prescribing information, 2016). Olaratumab has not yet been included in the NCCN Guidelines® for Soft Tissue Sarcoma (NCCN, 2016).

NCCN Guidelines for Uterine Neoplasms also focus on surgery, emphasizing that morcellation should not be used for uterine sarcomas (NCCN, 2017). Chemotherapy with or without radiation therapy is also recommended, and the NCCN Guidelines strongly emphasize the recommendation for participation in a clinical trial for such treatments. Systemic therapies for uterine sarcomas contain the same agents as those recommended for other STSs, either as combination therapy or as a single agent. In addition, trabectedin is an option for uterine leiomyosarcoma that has been previously treated with an anthracycline-containing regimen. Of the regimens included in the guidelines for all uterine sarcomas, docetaxel plus gemcitabine is recommended over other regimens for leiomyosarcoma. Of note, Votrient (pazopanib) is considered active in leiomyosarcoma, unlike in liposarcoma. Olaratumab has also not yet been included in the NCCN Guidelines for Uterine Neoplasms.

Table 5: Advantages and Disadvantages of Soft Tissue Sarcoma Agents

Drug	Advantages	Disadvantages
Lartruvo (olaratumab)	• Approved for use as first-line treatment in combination with doxorubicin	• Continued approval contingent of confirmatory data
Halaven (eribulin)	• Additional indication for metastatic breast cancer	• STS indication only for use in advanced liposarcomas
Yondelis (trabectedin)	• Indicated as subsequent therapy in both advanced leiomyosarcoma and liposarcoma	• No significant improvement in OS compared with dacarbazine • Administered via intravenous infusion lasting 24 hours • Associated with CYP3A4-mediated drug interactions
Votrient (pazopanib)	• Administered orally • Efficacy established as subsequent therapy in various subtypes of STS, including leiomyosarcoma and synovial sarcoma • NCCN Guidelines note activity in nonspecific STS and GIST • Additional indication for advanced renal cell carcinoma	• No significant improvement in OS compared with placebo • Not indicated for use in liposarcomas • Associated with CYP3A4-mediated drug interactions

CYP = cytochrome P450 isoenzyme
GIST = gastrointestinal stromal tumors
NCCN = National Comprehensive Cancer Network
OS = overall survival
STS = soft tissue sarcoma

National Institute for Health and Care Excellence (NICE)

As of February 2010, NICE recommends trabectedin as a treatment option for patients with advanced STS if treatment with anthracyclines and ifosfamide has failed or if patients cannot tolerate or have contraindications to anthracyclines and ifosfamide (NICE, 2010). NICE guidance for the use of olaratumab has an expected publication date of August 2017 (NICE, 2016).

PRODUCT COMPARISON

Table 6: Market Share Comparison of Agents for Soft Tissue Sarcoma

Product	Cost (AWP)/Unit	CVS Caremark Data	
		Specialty Rxs	Market Share (Combined Mail/Retail)
Lartruvo (olaratumab) injection*†	$2,832.00 per 500 mg/50 mL vial	0	0%
Halaven (eribulin) injection†	$1,260 per 1 mg/2mL vial	0	0%
Votrient (pazopanib) tablets‡	$100.27 per 200 mg tablet	292	100%
Yondelis (trabectedin) injection†	$3,240.00 per 1 mg vial	0	0%

* Launched November 1, 2016

† Agent most likely covered under medical benefit

‡ Includes utilization data only for soft tissue sarcoma

(Caremark Integrated Utilization File: data source: First National Drug Data File. September 2016 to November 2016; *Medi-Span® Master Drug Data Base v2.5 (MDDB®)*, 20 December 2016, Clinical Drug Information, LLC)

FORMULARY AND DRUG LIST AVAILABILITY

Table 7: Formulary/Drug List Availability of Soft Tissue Sarcoma Agents with UM tools

Product	National Formulary	Prescribing Guide*	Prescribing Guide for Advanced Controlled Specialty Formulary	Performance Drug List*	Performance Drug List for Advanced Controlled Specialty Formulary	Advanced Control Formulary	Value Formulary*
Halaven (eribulin) injection	✓	—	—	—	—	—	—
Lartruvo (olaratumab) injection	—	—	—	—	—	—	—
Votrient (pazopanib) tablets	✓	✓	✓	—	✓	✓	✓†
Yondelis (trabectedin) injection	✓	—	—	—	—	—	—

* Advanced Control Specialty Formulary may be applied to Prescribing Guide, Performance Drug List, or Value Formulary
† Prior authorization
UM = utilization management

Table 7: Managed Medicaid and 2016 Health Exchanges Formularies Availability of Soft Tissue Sarcoma Agents with UM Tools

Product	Managed Medicaid Drug List	2016 5-Tier Health Exchanges Template Formulary	2016 6-Tier Health Exchanges Template Formulary	2016 4-Tier Health Exchanges Formulary California	2016 3-Tier Health Exchanges Formulary New York	2016 5-Tier Health Exchanges Formulary New Jersey (Open)	2016 6-Tier Health Exchanges Formulary South Carolina
Halaven (eribulin) injection	—	—	—	—	—	—	—
Lartruvo (olaratumab) injection	—	—	—	—	—	—	—
Votrient (pazopanib) tablets	✓*	**tier 4***	**tier 5***	**tier 4***	**tier 3***	**tier 4***	**tier 5***
Yondelis (trabectedin) injection	—	—	—	—	—	—	—

* Prior authorization
UM = utilization management

Table 8: 2017 Health Exchanges Formularies Availability of Soft Tissue Sarcoma Agents with UM Tools

Product	2017 5-Tier Health Exchanges Template Formulary	2017 6-Tier Health Exchanges Template Formulary	2017 4-Tier Health Exchanges Formulary California	2017 3-Tier Health Exchanges Formulary New York	2017 6-Tier Health Exchanges Formulary South Carolina
Halaven (eribulin) injection	—	—	—	—	—
Lartruvo (olaratumab) injection	—	—	—	—	—
Votrient (pazopanib) tablets	**tier 4***	**tier 5***	**tier 4***	**tier 3***	**tier 5***
Yondelis (trabectedin) injection	—	—	—	—	—

* Prior authorization
UM = utilization management

Table 9: 2016 Medicare Part D Drug List Availability of Soft Tissue Sarcoma Agents with Optional UM Tools*

Product	PDP Drug List	Client Drug Lists						
		Generic Strategy	Generic Strategy Narrow	Standard†	Expanded	Expanded without MSBs	EGWP	
	5-Tier	5-Tier		5-Tier	5-Tier		3-Tier	4-Tier
Halaven (eribulin) injection	—	—	—	—	tier 5‡	tier 5‡	—	—
Lartruvo (olaratumab) injection	—	—	—	—	—	—	—	—
Votrient (pazopanib) tablets	tier 5§	tier 5§	tier 5§	tier 5§	tier 5§	tier 5§	tier 3§‖	tier 4§‖
Yondelis (trabectedin) injection	—	—	—	—	—	—	—	—

* Centers for Medicare and Medicaid Services Class of Clinical Concern
† Also available as a 1-Tier, 2-Tier, and 4-Tier MDL. Brands are on tier 2 of the 2-Tier MDL. The tier designation for the drugs on the 5-Tier MDL would be one tier lower on the 4-Tier MDL.
‡ B vs. D = Medicare Part B versus Part D; PA verifies drug is to be covered by Medicare Part D and not Medicare Part B and requires no clinical determination.
§ Prior authorization
‖ Quantity limit
EGWP = Employer Group Waiver Plan
MDL = Medicare Part D Drug List
MSB = multi-source brand
PDP = Prescription Drug Plan
UM = utilization management

Table 10: 2017 Medicare Part D Drug List Availability of Soft Tissue Sarcoma Agents with Optional UM Tools*

Product	SSI PDP/ PDP Plus Drug List	Client Drug Lists								
		Select†	Generic Strategy Standard†	Generic Strategy Essential	MMP	Standard‡	Expanded	Expanded Performance	EGWP	
	5-Tier	5-Tier			2-Tier	5-Tier	5-Tier		4-Tier	5-Tier
Halaven (eribulin) injection	—	—	—	—	—	—	tier 5§	tier 5§	—	—
Lartruvo (olaratumab) injection	—	—	—	—	—	—	—	—	—	—
Votrient (pazopanib) tablets	tier 5‖	tier 5‖	tier 5‖	tier 5‖	tier 2‖	tier 5‖	tier 5‖	tier 5‖	tier 4‖¶	tier 5‖¶
Yondelis (trabectedin) injection	—	—	—	—	—	—	—	—	—	—

* Centers for Medicare and Medicaid Services Class of Clinical Concern
† Also available as a Single-Source Generic Strategy drug lists
‡ Also available as a 1-Tier and 4-Tier drug list
§ B vs. D = Medicare Part B versus Part D; PA verifies drug is to be covered by Medicare Part D and not Medicare Part B and requires no clinical determination.
‖ Prior authorization
¶ Quantity limit
EGWP = Employer Group Waiver Plan
MMP = Medicare-Medicaid Plan
PDP = Prescription Drug Plan
SSI = Silver Script Insurance
UM = utilization management

FORMULARY CONSIDERATIONS

Lartruvo (olaratumab) is an IgG1 monoclonal antibody that is indicated in combination with doxorubicin as a first-line treatment in patients with soft tissue sarcoma. Preliminary data for Lartruvo (olaratumab) demonstrated improvements in progression-free survival compared with doxorubicin, with significant improvements in median overall survival by 11.8 months in patients with unresectable or advanced STS. Treatment with Lartruvo (olaratumab) plus doxorubicin was associated with more infusion-related adverse events compared with doxorubin alone, which was the leading reason for discontinuation in 3% of patients. Lartruvo (olaratumab) offers a new, tolerable first-line treatment option versus the standard of care, such as doxorubicin plus ifosfamide, for patients with unresectable or advanced STS where few other treatment options are available.

REFERENCES

American Cancer Society. Sarcoma: adult soft tissue cancer. October 2016. URL: http://www.cancer.org/acs/groups/cid/documents/webcontent/003138-pdf.pdf. Available from Internet. Accessed 2016 November.

Food and Drug Administration. Drugs@FDA. URL: http://www.accessdata.fda.gov/scripts/cder/daf/. Available from Internet. Accessed 2016a November.

Food and Drug Administration. Fact sheet: breakthrough therapies. URL: http://www.fda.gov/RegulatoryInformation/Legislation/SignificantAmendmentstotheFDCAct/FDASIA/ucm329491.htm. Available from Internet. Accessed 2016c November.

Food and Drug Administration. FDA grants accelerated approval to new treatment for advanced soft tissue sarcoma. October 2016. URL: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm525878.htm. Available from Internet. Accessed 2016b October.

Lartruvo prescribing information. Indianapolis, IN: Eli Lilly and Company; 2016 October.

Medi-Span® Master Drug Data Base v2.5 (MDDB®), 20 December 2016, Clinical Drug Information, LLC.

National Cancer Institute. Uterine sarcoma treatment-for health professionals (PDQ). July 2015. URL: http://www.cancer.gov/types/uterine/hp/uterine-sarcoma-treatment-pdq. Available from Internet. Accessed 2016 November.

National Comprehensive Cancer Network. Referenced from NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Soft Tissue Sarcoma V.2.2016. © National Comprehensive Cancer Network, Inc 2016. All rights reserved. Accessed November 2016. To view the most recent and complete version of the NCCN Guidelines go to NCCN.org. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, NCCN GUIDELINES®, and all other NCCN Content are trademarks owned by the National Comprehensive Cancer Network, Inc.

National Comprehensive Cancer Network. Referenced from NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Uterine Neoplasms V.1.2017. © National Comprehensive Cancer Network, Inc 2016. All rights reserved. Accessed November 2016. To view the most recent and complete version of the NCCN Guidelines go to NCCN.org. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, NCCN GUIDELINES®, and all other NCCN Content are trademarks owned by the National Comprehensive Cancer Network, Inc.

National Institute for Health and Care Excellence. Olaratumab in combination with doxorubicin for treating advanced soft tissue sarcoma. 2016. URL: http://www.nice.org.uk/guidance/indevelopment/gid-ta10103. Available from Internet. Accessed 2016 November.

National Institute for Health and Care Excellence. Trabectedin for the treatment of advanced soft tissue sarcoma. 2010 February. URL: http://www.nice.org.uk/guidance/ta185. Available from Internet. Accessed 2016 November.

Tap WD, Jones RL, Van Tine Ba, et al. Olaratumab and doxorubicin versus doxorubicin alone for treatment of soft-tissue sarcoma: an open-label phase 1b and randomised phase 2 trial. *Lancet*. 2016; 388:488-97.

Votrient prescribing information. Research Triangle Park, NC: GlaxoSmithKline; 2016 May.

DRUG MONOGRAPH PREPARED BY:

Faon M Bridges, Pharm.D., BCPS
December 20, 2016

This document includes the clinical opinions of CVS Caremark based on the information available at the time this document was written. The document contains summarized information and is not a substitute for reading the original literature. Economic and other considerations may influence an individual client's formulary decision. The document contains prescription brand name drugs that are registered or trademarks of pharmaceutical manufacturers that are not affiliated with CVS Caremark.

CVS/caremark

SPECIALTY GUIDELINE MANAGEMENT

LARTRUVO (olaratumab)

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
Lartruvo is indicated, in combination with doxorubicin, for the treatment of adult patients with soft tissue sarcoma (STS) with a histologic subtype for which an anthracycline-containing regimen is appropriate and which is not amenable to curative treatment with radiotherapy or surgery.

This indication is approved under accelerated approval. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trial.

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 treatment of soft tissue sarcoma (STS) when all of the following criteria are met:
1. Lartruvo is used in combination with doxorubicin.
2. Member has a histologic subtype for which an anthracycline-containing regimen is appropriate.
3. Member's disease is not amenable to curative treatment with radiotherapy or surgery.

III. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must meet all initial authorization criteria.

IV. REFERENCES

1. Lartruvo [package insert]. Indianapolis, IN: Eli Lilly and Company; October 2016.

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use LARTRUVO safely and effectively. See full prescribing information for LARTRUVO.

LARTRUVO (olaratumab) injection, for intravenous use
Initial U.S. Approval: 2016

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

LARTRUVO™ is a platelet-derived growth factor receptor alpha (PDGFR-α) blocking antibody indicated, in combination with doxorubicin, for the treatment of adult patients with soft tissue sarcoma (STS) with a histologic subtype for which an anthracycline-containing regimen is appropriate and which is not amenable to curative treatment with radiotherapy or surgery. (1)

This indication is approved under accelerated approval. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trial. (14)

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

- Administer LARTRUVO at 15 mg/kg as an intravenous infusion over 60 minutes on Days 1 and 8 of each 21-day cycle until disease progression or unacceptable toxicity. (2.1)
- For the first 8 cycles, LARTRUVO is administered with doxorubicin. (2.1)
- Premedicate with diphenhydramine and dexamethasone intravenously, prior to LARTRUVO on Day 1 of cycle 1. (2.2)
- For intravenous infusion only. Do not administer as an intravenous push or bolus. (2.4)

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

Injection: 500 mg/50 mL (10 mg/mL) or 190 mg/19 mL (10 mg/mL) solution in a single-dose vial (3)

---------- CONTRAINDICATIONS ----------

None. (4)

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

- Infusion-Related Reactions: Monitor for signs and symptoms during and following infusion. Discontinue LARTRUVO for Grade 3 or 4 infusion-related reactions. (2.2, 2.3, 5.1)
- Embryo-Fetal Toxicity: Can cause fetal harm. Advise females of potential risk to the fetus and to use effective contraception during treatment with LARTRUVO and for 3 months after the last dose. (5.2, 8.1, 8.3)

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

The most common (≥20%) adverse reactions of LARTRUVO plus doxorubicin are nausea, fatigue, musculoskeletal pain, mucositis, alopecia, vomiting, diarrhea, decreased appetite, abdominal pain, neuropathy, and headache. (6.1)

The most common (≥20%) laboratory abnormalities were lymphopenia, neutropenia, thrombocytopenia, hyperglycemia, elevated aPTT, hypokalemia, and hypophosphatemia. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Eli Lilly and Company at 1-800-LillyRx (1-800-545-5979) 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.

Revised: 02/2017

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

LARTRUVO™ is indicated, in combination with doxorubicin, for the treatment of adult patients with soft tissue sarcoma (STS) with a histologic subtype for which an anthracycline-containing regimen is appropriate and which is not amenable to curative treatment with radiotherapy or surgery.

This indication is approved under accelerated approval *[see Clinical Studies (14)]*. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trial.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

The recommended dose of LARTRUVO is 15 mg/kg administered as an intravenous infusion over 60 minutes on Days 1 and 8 of each 21-day cycle until disease progression or unacceptable toxicity. For the first 8 cycles, LARTRUVO is administered with doxorubicin, *[see Clinical Studies (14)]*.

Refer to doxorubicin prescribing information for dosing, and dose modifications.

2.2 Premedication

- Premedicate with diphenhydramine (25 to 50 mg intravenously) and dexamethasone (10 to 20 mg intravenously) prior to LARTRUVO on Day 1 of cycle 1.

2.3 Dosing Modifications

Infusion-Related Reactions

- Permanently discontinue LARTRUVO for Grade 3 or 4 infusion-related reactions *[see Dosage and Administration (2.2) and Warnings and Precautions (5.1)]*.
- Interrupt infusion of LARTRUVO for Grade 1 or 2 infusion-related reactions (IRR). After resolution, resume LARTRUVO infusion at 50% of the initial infusion rate. *[see Warnings and Precautions (5.1)]*

Neutropenia

- For neutropenic fever/infection or Grade 4 neutropenia lasting longer than 1 week, discontinue administration of LARTRUVO until the absolute neutrophil count is 1,000 /microliter or greater and then permanently reduce the dose to 12 mg/kg.

2.4 Preparation and Administration

Preparation

- Inspect vial contents for particulate matter and discoloration prior to dilution *[see Description (11)]*. Discard the vial if particulate matter or discolorations are identified.
- Withdraw calculated dose and further dilute with 0.9% Sodium Chloride Injection, USP to a final volume of 250 mL for intravenous infusion. **Do not use dextrose-containing or other solutions.**
- Gently invert but do not shake.
- DO NOT FREEZE the diluted solution.
- Store the diluted solution for up to 24 hours under refrigeration at 2°C to 8°C (36°F to 46°F) and for up to an additional 4 hours at room temperature (below 25°C [77°F]). Storage times include the duration of infusion. If refrigerated, allow the diluted solution to come to room temperature prior to administration.
- Discard vial with any unused portion of LARTRUVO.

Administration

- Do not administer LARTRUVO as an intravenous push or bolus. Do not co-infuse with electrolytes or other medications through the same intravenous line.
- Visually inspect the diluted solution for particulate matter and discoloration prior to administration. If particulate matter or discolorations are identified, discard the solution.
- Administer diluted solution as an intravenous infusion over 60 minutes. Flush the line with 0.9% Sodium Chloride Injection, USP at end of infusion.

3 DOSAGE FORMS AND STRENGTHS

Injection: 500 mg/50 mL (10 mg/mL) or 190 mg/19 mL (10 mg/mL) clear to slightly opalescent, colorless to slightly yellow solution in a single-dose vial.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Infusion-Related Reactions

Infusion-related reactions (IRR) occurred in 70 (14%) of 485 patients who received at least one dose of LARTRUVO across clinical trials. For 68 of these 70 patients (97%), the first occurrence of IRR was in the first or second cycle. Grade ≥3 IRR occurred in 11 (2.3%) of 485 patients, with one (0.2%) fatality. Symptoms of IRR included flushing, shortness of breath, bronchospasm, or fever/chills, and in severe cases symptoms manifested as severe hypotension, anaphylactic shock, or cardiac arrest.

Infusion-related reactions required permanent discontinuation in 2.3% of patients and interruption of infusion in 10% of patients. All 59 patients with Grade 1 or 2 IRR resumed LARTRUVO; 12 (20%) of these patients had a Grade 1 or 2 IRR with rechallenge. The incidence of IRR in the overall safety database (N = 485) was similar (18% versus 12%) between those who did (56%) and those who did not (44%) receive premedication.

Monitor patients during and following LARTRUVO infusion for signs and symptoms of IRR in a setting with available resuscitation equipment. Immediately and permanently discontinue LARTRUVO for Grade 3 or 4 IRR *[see Dosage and Administration (2.2, 2.3) and Adverse Reactions (6.1)]*.

5.2 Embryo-Fetal Toxicity

Based on animal data and its mechanism of action, LARTRUVO can cause fetal harm when administered to a pregnant woman. Animal knockout models link disruption of platelet-derived growth factor receptor alpha (PDGFR-α) signaling to adverse effects on embryo-fetal development. Administration of an anti-murine PDGFR-α antibody to pregnant mice during organogenesis caused malformations and skeletal variations. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with LARTRUVO and for 3 months after the last dose *[see Use in Specific Populations (8.1, 8.3)]*.

6 ADVERSE REACTIONS

The following adverse drug reactions are described elsewhere in the labeling:

- Infusion-Related Reactions *[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 data in the Warnings and Precautions section reflect exposure to LARTRUVO in 485 patients from three randomized, open-label, active-controlled clinical trials, which enrolled 256 patients with various tumors who received LARTRUVO in combination with chemotherapy (191 patients) or LARTRUVO as a single agent (65 patients); four open-label single-arm trials which enrolled 96 patients with various tumors who received LARTRUVO as a single agent at doses of 10 to 20 mg/kg; and two trials, including Trial 1, which enrolled 133 patients with soft tissue sarcoma who received LARTRUVO at doses of 15 to 20 mg/kg in combination with doxorubicin (103 patients) or LARTRUVO as a single agent (30 patients). Among the 485 patients, 25% were exposed to LARTRUVO for ≥6 months and 6% were exposed for ≥12 months.

The data described below reflect exposure to LARTRUVO in 64 patients with metastatic soft tissue sarcoma enrolled in Trial 1, a multicenter, randomized (1:1), open-label, active-controlled trial comparing LARTRUVO plus doxorubicin with doxorubicin as a single agent. LARTRUVO was administered at 15 mg/kg as an intravenous infusion on Days 1 and 8 of each 21-day cycle until disease progression or unacceptable toxicity *[see Clinical Studies (14)]*. All patients received doxorubicin 75 mg/m^2 as an intravenous infusion on Day 1 of each 21-day cycle for a maximum of eight cycles and received dexrazoxane, prior to doxorubicin in cycles 5 to 8. In Trial 1, no patients had received a prior anthracycline-containing regimen. The trial excluded patients with an ECOG performance status >2; left ventricular ejection fraction <50%; or unstable angina pectoris, angioplasty, cardiac stenting, or myocardial infarction within 6 months.

Baseline demographics and disease characteristics were: median age 58 years (range 22 to 86); 45% male; 87% White, 8% Black, 3% Asian, 2% Other; 57% ECOG PS 0, 39% ECOG PS 1, and 5% ECOG PS 2. The median duration of exposure to LARTRUVO was 6 months (range: 21 days to 29.4 months) with 36 (56%) patients receiving LARTRUVO for ≥6 months and 10 (16%) patients receiving LARTRUVO for ≥12 months. The median cumulative doxorubicin dose was 488 mg/m^2 in the LARTRUVO plus doxorubicin arm and 300 mg/m^2 in the doxorubicin arm.

In Trial 1, adverse reactions resulting in permanent discontinuation of LARTRUVO occurred in 8% (5/64) of patients. The most common adverse reaction leading to LARTRUVO discontinuation was infusion-related reaction (3%). Dose reductions of LARTRUVO for adverse reactions occurred in 25% (16/64) of patients; the most common adverse

reaction leading to dose reduction was Grade 3 or 4 neutropenia (20%). Dose delays of LARTRUVO for adverse reactions occurred in 52% (33/64) of patients; the most common adverse reactions resulting in dose delays were neutropenia (33%), thrombocytopenia (8%), and anemia (5%).

Table 1 summarizes adverse reactions that occurred in at least 10% of patients receiving LARTRUVO in the randomized portion of the study. The most common adverse reactions reported in at least 20% of patients receiving LARTRUVO plus doxorubicin were nausea, fatigue, musculoskeletal pain, mucositis, alopecia, vomiting, diarrhea, decreased appetite, abdominal pain, neuropathy, and headache.

Table 1: Adverse Reactions Occurring in ≥10% (All Grades) of Patients in the LARTRUVO plus Doxorubicin Arm and at a Higher Incidence than in the Doxorubicin Arm (Between Arm Difference of ≥5% for All Grades or ≥2% for Grades 3 and 4) (Trial 1)

Adverse Reactions	LARTRUVO plus Doxorubicin N=64		Doxorubicin N=65	
	All Grades (%)	Grade 3-4 (%)	All Grades (%)	Grade 3-4 (%)
Gastrointestinal Disorders				
Nausea	73	2	52	3
Mucositis	53	3	35	5
Vomiting	45	0	19	0
Diarrhea	34	3	23	0
Abdominal Pain[a]	23	3	14	0
General Disorders and Administrative Site Conditions				
Fatigue[b]	69	9	69	3
Infusion-Related Reactions	13	3	3	0
Musculoskeletal and Connective Tissue Disorders				
Musculoskeletal Pain[c]	64	8	25	2
Skin and Subcutaneous Tissue Disorders				
Alopecia	52	0	40	0
Metabolic and Nutritional Disorders				
Decreased Appetite	31	2	20	0
Nervous System Disorders				
Neuropathy	22	0	11	0
Headache	20	0	9	0
Psychiatric Disorder				
Anxiety	11	0	3	0
Eye Disorder				
Dry Eyes	11	0	3	0

[a] Abdominal pain includes: abdominal pain, lower abdominal pain, and upper abdominal pain.

[b] Fatigue includes: asthenia and fatigue.

[c] Musculoskeletal pain includes: arthralgia, back pain, bone pain, flank pain, groin pain, musculoskeletal chest pain, musculoskeletal pain, myalgia, muscle spasms, neck pain, and pain in extremity.

In Trial 1, the most common laboratory abnormalities (≥20%) were lymphopenia, neutropenia, thrombocytopenia, hyperglycemia, elevated aPTT, hypokalemia, and hypophosphatemia as shown in Table 2.

Table 2: Laboratory Abnormalities Worsening from Baseline in >10% (All Grades) of Patients in the LARTRUVO plus Doxorubicin Arm and Occurring at a Higher Incidence than in the Doxorubicin Arm (Between Arm Difference ≥5% for All Grades or ≥2% for Grades 3 and 4) (Trial 1)

Laboratory Abnormality	LARTRUVO plus Doxorubicin[a]		Doxorubicin[a]	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Chemistry				
Hyperglycemia	52	2	28	3
Increased aPTT[b]	33	5	13	0
Hypokalemia	21	8	15	3
Hypophosphatemia	21	5	7	3
Increased Alkaline Phosphatase	16	0	7	0
Hypomagnesemia	16	0	8	0
Hematology				

Lymphopenia	77	44	73	37
Neutropenia	65	48	63	38
Thrombocytopenia	63	6	44	11

[a] The incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement: LARTRUVO plus doxorubicin arm (range 60 to 63 patients) and doxorubicin arm (range 39 to 62 patients).

[b] aPTT = activated partial thromboplastin time

6.2 Immunogenicity

As with all therapeutic proteins, there is the potential for immunogenicity. In clinical trials, 13/370 (3.5%) of evaluable LARTRUVO-treated patients tested positive for treatment-emergent anti-olaratumab antibodies by an enzyme-linked immunosorbent assay (ELISA). Neutralizing antibodies were detected in all patients who tested positive for treatment-emergent anti-olaratumab antibodies. The effects of anti-olaratumab antibodies on efficacy, safety, and exposure could not be assessed due to the limited number of patients with treatment-emergent anti-olaratumab antibodies.

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 incidence of antibodies to LARTRUVO with the incidences of antibodies to other products may be misleading.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on animal data and its mechanism of action, LARTRUVO can cause fetal harm *[see Clinical Pharmacology (12.1)]*. There are no available data on LARTRUVO use in pregnant women. No animal studies using olaratumab have been conducted to evaluate its effect on female reproduction and embryo-fetal development. Animal knockout models link disruption of platelet-derived growth factor receptor alpha (PDGFR-α) signaling to adverse effects on embryo-fetal development. Administration of an anti-murine PDGFR-α antibody to pregnant mice during organogenesis at exposures less than the exposure at the maximum recommended human dose caused malformations and skeletal variations *[see 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.

Data

Animal Data

No animal studies have been conducted using olaratumab to evaluate the effect of blocking PDGFR-α signaling on reproduction and embryo-fetal development. In PDGFR-α knockout mice, disruption of PDGFR-α signaling resulted in embryo-fetal lethality and teratogenicity, including cleft face and spina bifida. Intravenous administration of an anti-murine PDGFR-α antibody once every 3 days to pregnant mice during organogenesis at 50 and 150 mg/kg resulted in increased malformations (abnormal eyelid development) and skeletal variations (additional ossification sites in the frontal/parietal skull). Increased post-implantation loss occurred at a dose of 5 mg/kg. The effects on fetal development in mice administered this antibody occurred at exposures less than the AUC exposure at the maximum recommended human dose of 15 mg/kg LARTRUVO.

8.2 Lactation

Risk Summary

There are no data on the presence of olaratumab in human milk, or its effects on the breastfed infant or on milk production. Because of the potential risk for serious adverse reactions in breastfeeding infants from olaratumab, advise women not to breastfeed during treatment with LARTRUVO and for 3 months following the last dose.

8.3 Females and Males of Reproductive Potential

Contraception

Females

Based on its mechanism of action, LARTRUVO can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)]*. Advise females of reproductive potential to use effective contraception during treatment with LARTRUVO and for 3 months after the last dose.

Infertility

Males

Based on animal models, LARTRUVO may impair male fertility *[see Nonclinical Toxicology (13.1)]*.

8.4 Pediatric Use

The safety and effectiveness of LARTRUVO in pediatric patients have not been established.

8.5 Geriatric Use

Clinical studies of LARTRUVO did not include sufficient numbers of patients aged 65 years and older to determine whether they respond differently from younger patients.

11 DESCRIPTION

Olaratumab is a recombinant human IgG1 monoclonal blocking antibody that binds specifically to human platelet-derived growth factor receptor alpha (PDGFR-α). LARTRUVO has an approximate molecular weight of 154 kDa. LARTRUVO is produced in genetically engineered mammalian NS0 cells.

LARTRUVO is a sterile, preservative-free, clear to slightly opalescent, and colorless to slightly yellow solution. LARTRUVO injection is supplied in single-dose vials for intravenous use following dilution. Each vial contains 500 mg LARTRUVO in 50 mL (10 mg/mL) or 190 mg LARTRUVO in 19 mL (10 mg/mL). Each mL contains 10 mg olaratumab, glycine (7.5 mg), L-histidine (0.3 mg), L-histidine monohydrochloride (1.7 mg), mannitol (13.7 mg), polysorbate 20 (0.2 mg), sodium chloride (2.9 mg), and water for injection, USP, pH 5.2 to 5.8.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Olaratumab is a human IgG1 antibody that binds platelet-derived growth factor receptor alpha (PDGFR-α). PDGFR-α is a receptor tyrosine kinase expressed on cells of mesenchymal origin. Signaling through this receptor plays a role in cell growth, chemotaxis, and mesenchymal stem cell differentiation. The receptor has also been detected on some tumor and stromal cells, including sarcomas, where signaling can contribute to cancer cell proliferation, metastasis, and maintenance of the tumor microenvironment. The interaction between olaratumab and PDGFR-α prevents binding of the receptor by the PDGF-AA and -BB ligands as well as PDGF-AA, -BB, and -CC-induced receptor activation and downstream PDGFR-α pathway signaling. Olaratumab exhibits in vitro and in vivo anti-tumor activity against selected sarcoma cell lines and disrupted the PDGFR-α signaling pathway in in vivo tumor implant models.

12.2 Pharmacodynamics

Olaratumab exposure-response relationships and the time course of the pharmacodynamics response are unknown.

12.3 Pharmacokinetics

Distribution

The volume of distribution (CV%) at steady-state (V_{ss}) is 7.7 L (16%).

Elimination

The mean clearance (CV%) for olaratumab was 0.56 L/day (33%). The estimated elimination half-life was approximately 11 days (range 6 to 24 days).

Specific Populations

Age (22 to 85 years), sex (47% females), race (86% Whites), mild to moderate renal impairment [calculated creatinine clearance (CLcr) 30-89 mL/min as estimated by the Cockcroft-Gault formula (C-G)], and mild [total bilirubin within upper limit of normal (ULN) and AST greater than ULN or total bilirubin greater than 1.0 and up to 1.5 times ULN and any AST] to moderate (total bilirubin greater than 1.5 and up to 3.0 times ULN and any AST) hepatic impairment had no clinically important effect on the pharmacokinetics of olaratumab. The pharmacokinetics of olaratumab in patients with severe renal impairment (CLcr 15-29 mL/min as estimated by C-G) or with severe hepatic impairment (total bilirubin greater than 3.0 times ULN and any AST) are unknown. Body weight (range 37 to 151 kg) correlates with clearance and volume of distribution of olaratumab.

Drug Interaction Studies

No clinically relevant changes in the exposure of either olaratumab or doxorubicin were observed when LARTRUVO 15 mg/kg and doxorubicin 75 mg/m^2 were co-administered in patients with solid tumors.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No studies have been performed to assess the potential of olaratumab for carcinogenicity or genotoxicity.

Fertility studies have not been performed with olaratumab; however, in animal knockout models, loss of PDGFR-α pathway signaling resulted in progressive reduction in testicular size, Leydig cell loss, and spermatogenic arrest.

14 CLINICAL STUDIES

The efficacy of LARTRUVO was demonstrated in Trial 1, an open-label, randomized, active-controlled study. Eligible patients were required to have soft tissue sarcoma not amenable to curative treatment with surgery or radiotherapy, a histologic type of sarcoma for which an anthracycline-containing regimen was appropriate but had not been administered, ECOG PS of 0-2, and tumor specimen available for assessment of PDGFR-α expression by an investigational use assay. Patients were randomized (1:1) to receive LARTRUVO in combination with doxorubicin or doxorubicin as a single agent. PDGFR-α expression (positive versus negative), number of previous lines of treatment (0 versus 1 or more), histological tumor type (leiomyosarcoma versus synovial sarcoma versus all others), and ECOG PS (0 or 1 versus 2) were used to allocate patients in the randomization. LARTRUVO was administered at 15 mg/kg as an intravenous infusion on Days 1 and 8 of each 21-day cycle until disease progression or unacceptable toxicity. All patients received doxorubicin 75 mg/m^2 as an intravenous infusion on Day 1 of each 21-day cycle for a maximum of eight cycles and were permitted to receive dexrazoxane prior to doxorubicin in Cycles 5 to 8. Patients randomized to receive doxorubicin as a single agent were offered LARTRUVO at the time of disease progression. The efficacy outcome measures were overall survival (OS), and progression-free survival (PFS) and objective response rate (ORR) as assessed by investigator and by independent review according to RECIST v1.1.

A total of 133 patients were randomized, 66 patients to the LARTRUVO plus doxorubicin arm and 67 patients to the doxorubicin arm. Baseline demographics and disease characteristics were: median age of 58 years (range 22 to 86); 44% men; 86% White, 8% Black, 3% Asian, and 2% Other; 56% ECOG PS 0 and 39% ECOG PS 1; 65% no prior chemotherapy (excluding adjuvant and neoadjuvant therapy); 38% leiomyosarcoma, 1.5% synovial sarcoma, and 61% other histologies [17% liposarcoma (8% dedifferentiated, 4% myxoid, 3% well-differentiated, 1.5% pleomorphic, 1% liposarcoma not otherwise specified (NOS)), 11% undifferentiated pleomorphic sarcoma, 5% angiosarcoma, 5% undifferentiated sarcoma NOS, 3% extraskeletal myxoid chondrosarcoma, 2% malignant peripheral nerve sheath tumor, 2% myxofibrosarcoma, 2% malignant solitary fibrous tumor, 2% endometrial stromal sarcoma, 1.5% chondrosarcoma, 1.5% epithelioid sarcoma, 1.5% fibrosarcoma, 1.5% low-grade fibromyxoid sarcoma, and 5% other histologies with one patient each]. All patients had metastatic disease and were enrolled at U.S. sites. Among patients randomized to doxorubicin, 30 (45%) patients received LARTRUVO as a single agent at the time of disease progression.

Trial 1 demonstrated a significant improvement in overall survival. The efficacy results are summarized in Table 3 and Figure 1.

Table 3: Efficacy Results in Trial 1

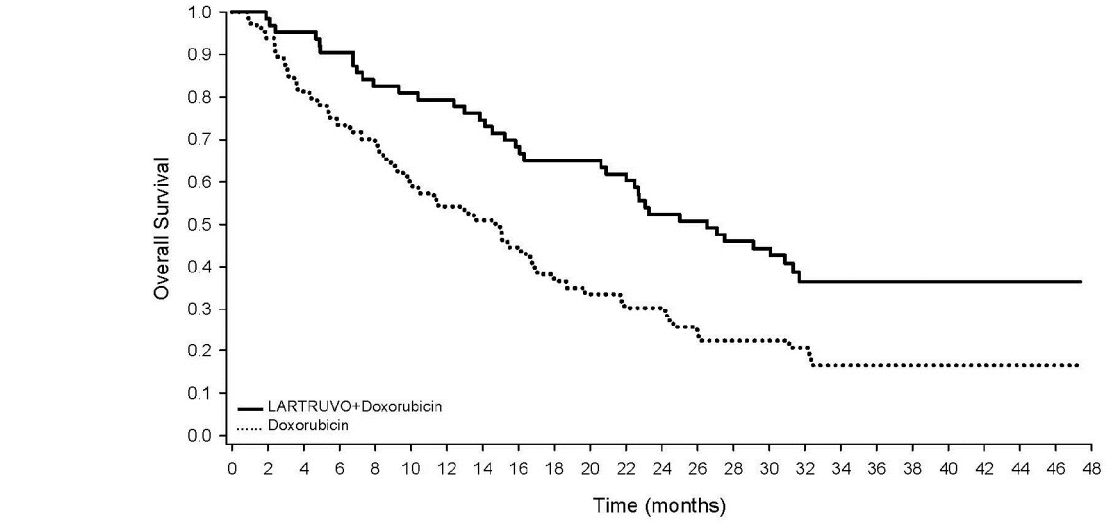
	LARTRUVO + Doxorubicin N=66	**Doxorubicin N=67**
Overall Survival		
Number of deaths (%)	39 (59%)	52 (78%)
Median, months (95% CI)	26.5 (20.9, 31.7)	14.7 (9.2, 17.1)
Hazard Ratio (95% CI)[a]	0.52 (0.34, 0.79)	
p-value	p<0.05	
Progression-Free Survival[b]		
Number of events (%)	37 (56%)	34 (51%)
Median, months (95% CI)	8.2 (5.5, 9.8)	4.4 (3.1, 7.4)
Hazard Ratio (95% CI)[a]	0.74 (0.46, 1.19)	
Objective Response Rate (CR + PR)[b]		
(95% CI)	18.2% (9.8, 29.6)	7.5% (2.5, 16.6)
CR, n (%)	3 (4.5%)	1 (1.5%)
PR, n (%)	9 (13.6%)	4 (6%)

Abbreviations: CI = confidence interval, CR = complete response, PR = partial response

[a] Unstratified Cox model.

[b] Based on independent review.

Figure 1: Kaplan-Meier Curves of Overall Survival



Number at Risk

LARTRUVO+Doxorubicin	66	62	60	57	52	51	50	47	43	41	41	39	33	32	29	26	16	16	15	8	3	3	1	1	0
Doxorubicin	67	61	51	46	43	37	34	32	28	23	21	19	19	15	13	13	10	7	6	6	5	3	2	1	0

16 HOW SUPPLIED/STORAGE AND HANDLING

LARTRUVO is supplied in single-dose vials as a sterile, preservative-free, clear to slightly opalescent and colorless to slightly yellow solution.

- NDC 0002-7190-01
  190 mg/19 mL (10 mg/mL) single-dose vial, individually packaged in a carton
- NDC 0002-8926-01
  500 mg/50 mL (10 mg/mL) single-dose vial, individually packaged in a carton

Store vials in a refrigerator at 2°C to 8°C (36°F to 46°F) until time of use. Keep the vial in the outer carton to protect from light. **DO NOT FREEZE OR SHAKE** the vial.

17 PATIENT COUNSELING INFORMATION

Infusion-Related Reactions

Advise patients to report signs and symptoms of infusion reactions *[see Dosage and Administration (2.2) and Warnings and Precautions (5.1)]*.

Embryo-Fetal Toxicity

Advise pregnant women of the potential risk to the fetus. Advise females of reproductive potential of the potential risk to the fetus, to use effective contraception during treatment with LARTRUVO and for 3 months after the last dose, and to inform their healthcare provider of a known or suspected pregnancy *[see Use in Specific Populations (8.1, 8.3)]*.

Lactation

Advise patients not to breastfeed during treatment with LARTRUVO and for 3 months after the last dose *[see Use in Specific Populations (8.2)]*.

Eli Lilly and Company, Indianapolis, IN 46285, USA

US License No. 1891

LAR-0002-USPI-20170213

Kyprolis (carfilzomib)

Click on the associated hyperlinks to view the source of information used.

Indication	Kyprolis is a proteasome inhibitor that is indicated: • in combination with dexamethasone or with lenalidomide plus dexamethasone for the treatment of patients with relapsed or refractory multiple myeloma who have received one to three lines of therapy. (1,14) • as a single agent for the treatment of patients with relapsed or refractory multiple myeloma who have received one or more lines of therapy. (1,14) **FDA Approval Date:** July 20, 2012
Treatment Comparisons for Indications	Velcade (bortezomib), alternate MM inidicated immunomodulatory drugs (lenolidomide, pomalidomide); alternate MM indicate monoclonal antibodies (elotuzumab, daratumumab)
Place in Therapy	Second generation selective proteasome inhibitor; Prospective trials demonstrated response rates of 40 to 50 percent on bortezomib-naïve cases and 15 to 20 percent in bortezomib-refractory cases. Higher response rates have been seen with combination therapy, such as carfilzomib, lenalidomide, dexamethasone (KRd).
Pharmacology	Intravenous carfilzomib administration resulted in suppression of proteasome chymotrypsin-like (CT-L) activity when measured in blood 1 hour after the first dose. Doses of carfilzomib ≥ 15 mg/m2with or without lenalidomide and dexamethasone induced a ≥ 80% inhibition of the CT-L activity of the proteasome. In addition, carfilzomib, 20 mg/m2intravenously as a single agent, resulted in a mean inhibition of the low molecular mass polypeptide 2 (LMP2) and multicatalytic endopeptidase complex-like 1 (MECL1) subunits of the proteasome ranging from 26% to 32% and 41% to 49%, respectively. Proteasome inhibition was maintained for ≥ 48 hours following the first dose of carfilzomib for each week of dosing.
Dosage and Administration	**Strengths Available:** For injection: 30 mg or 60 mg, lyophilized powder in single-dose vial for reconstitution (3) **Dosage Frequency:** • See Full Prescribing Information for dosing. (2.2) • Hydrate prior to and following Kyprolis administration as needed. (2.1)

	• Premedicate Kyprolis infusions with dexamethasone prior to all Cycle 1 doses and if infusion reaction symptoms develop or reappear. (2.1) • Administer the 20/56 mg/m2regimen by 30-minute infusion and the 20/27 mg/m2regimen by 10-minute infusion. (2.2)
Safety	The most common adverse reactions occurring in at least 20% of patients treated with Kyprolis in monotherapy trials: anemia, fatigue, thrombocytopenia, nausea, pyrexia, dyspnea, diarrhea, headache, cough, edema peripheral. (6) The most common adverse reactions occurring in at least 20% of patients treated with Kyprolis in the combination therapy trials: anemia, neutropenia, diarrhea, dyspnea, fatigue, thrombocytopenia, pyrexia, insomnia, muscle spasm, cough, upper respiratory tract infection, hypokalemia. (6) To report SUSPECTED ADVERSE REACTIONS, contact Amgen Medical Information at 1-800-77-AMGEN (1-800-772-6436) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch. **Contraindications:** None (4)
Use in Specific Populations	• Geriatric use: In the Kyprolis clinical trials, the incidence of adverse events was greater in patients ≥ 75 years of age. (8.5) • Hepatic impairment: Reduce the dose of Kyprolis by 25% in patients with mild or moderate hepatic impairment. (2.4) • Patients on hemodialysis: Administer Kyprolis after the hemodialysis procedure. (2.1)
Formulary Considerations	***Proposed Formulary Addition*:** Tier 6 Revlimid (enalidomide) at Tier 5; Pomalyst (pomalidomide), Darzalex (daratumumab), Empliciti (elotuzumab) at Tier 6
Utilization	Previously approved as nonformulary; only available via approved formulary exceptions
Conclusion	Accept formulary addition as proposed

CVS/caremark

SPECIALTY GUIDELINE MANAGEMENT

KYPROLIS (carfilzomib)

POLICY

A. 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

- Kyprolis in combination with lenalidomide and dexamethasone is indicated for the treatment of patients with relapsed multiple myeloma who have received one to three prior lines of therapy
- Kyprolis is indicated for the treatment of patients with multiple myeloma who have received at least two prior therapies, including Velcade (bortezomib) and an immunomodulatory agent, and have demonstrated disease progression on or within 60 days of completion of the last therapy.

Compendial Uses

- Waldenström's macroglobulinemia/lymphoplasmacytic lymphoma

All other indications are considered experimental/investigational and are not a covered benefit.

B. CRITERIA FOR APPROVAL

1. Multiple Myeloma

Authorization of 12 months may be granted to members who are prescribed Kyprolis for the treatment of multiple myeloma.

2. Waldenström's macroglobulinemia/lymphoplasmacytic lymphoma

Authorization of 12 months may be granted to members who are prescribed Kyprolis as a component of CaRD (carfilzomib, rituximab, and dexamethasone) regimen.

C. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must meet ALL initial authorization criteria.

D. DOSAGE AND ADMINISTRATION

Approvals may be subject to dosing limits in accordance with FDA-approved labeling, accepted compendia, and/or evidence-based practice guidelines.

REFERENCES

1. Kyprolis [package insert]. South San Francisco, CA: Onyx Pharmaceuticals, Inc.; July 2015.
2. The NCCN Drugs & Biologics Compendium™ © 2015 National Comprehensive Cancer Network, Inc. http://www.nccn.org. Accessed October 15, 2015.
3. The NCCN Practice Guidelines in Oncology™ Multiple Myeloma (Version 2.2016). ©2015 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed October 15, 2015.
4. The NCCN Practice Guidelines in Oncology™ Waldenström's Macroglobulinemia/Lymphoplasmacytic Lymphoma (Version 2.2016). ©2015 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed October 27, 2015.
5. Treon SP, Tripsas CK, Meid K, et al. Carfilzomib, rituximab and dexamethasone (CaRD) is active and offers a neuropathy-sparing approach for proteasome-inhibitor based therapy in Waldenström's macroglobulinemia. *Blood*. 2014; 124(4):503-510.

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use KYPROLIS safely and effectively. See full prescribing information for KYPROLIS.

KYPROLIS® (carfilzomib) for injection, for intravenous use
Initial U.S. Approval: 2012

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

Indications and Usage (1)	01/2016
Dosage and Administration (2)	11/2016
Warnings and Precautions (5)	08/2016

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

Kyprolis is a proteasome inhibitor that is indicated:

- in combination with dexamethasone or with lenalidomide plus dexamethasone for the treatment of patients with relapsed or refractory multiple myeloma who have received one to three lines of therapy. (1, 14)
- as a single agent for the treatment of patients with relapsed or refractory multiple myeloma who have received one or more lines of therapy. (1, 14)

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

- See Full Prescribing Information for dosing. (2.2)
- Hydrate prior to and following Kyprolis administration as needed. (2.1)
- Premedicate Kyprolis infusions with dexamethasone prior to all Cycle 1 doses and if infusion reaction symptoms develop or reappear. (2.1)
- Administer the 20/56 mg/m^2 regimen by 30-minute infusion and the 20/27 mg/m^2 regimen by 10-minute infusion. (2.2)

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

For injection: 30 mg or 60 mg, lyophilized powder in single-dose vial for reconstitution (3)

----------CONTRAINDICATIONS----------

None (4)

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

- Cardiac Toxicities: Monitor for signs and symptoms of cardiac failure or ischemia. Withhold Kyprolis and evaluate promptly. (5.1)
- Acute Renal Failure: Monitor serum creatinine regularly. (5.2)
- Tumor Lysis Syndrome (TLS): Administer pre-treatment hydration. (2.1) Monitor for TLS, including uric acid levels and treat promptly. (5.3)
- Pulmonary Toxicity, including Acute Respiratory Distress Syndrome, Acute Respiratory Failure, and Acute Diffuse Infiltrative Pulmonary Disease: Withhold Kyprolis and evaluate promptly. (5.4)
- Pulmonary Hypertension: Withhold Kyprolis and evaluate. (5.5)
- Dyspnea: For severe or life threatening dyspnea, withhold Kyprolis and evaluate. (5.6)
- Hypertension Including Hypertensive Crisis: Monitor blood pressure regularly. If hypertension cannot be controlled, interrupt treatment with Kyprolis. (5.7)
- Venous Thrombosis: Thromboprophylaxis is recommended. (5.8)
- Infusion Reactions: Premedicate with dexamethasone. (2.1, 5.9)
- Hemorrhage: Fatal or serious cases of hemorrhage may occur, including gastrointestinal, pulmonary, and intracranial hemorrhage. Promptly evaluate signs and symptoms of blood loss. (5.10)
- Thrombocytopenia: Monitor platelet counts; interrupt or reduce Kyprolis dosing as clinically indicated. (2.3, 5.11)
- Hepatic Toxicity and Hepatic Failure: Monitor liver enzymes regularly. Withhold Kyprolis if suspected. (5.12)
- Thrombotic Microangiopathy: Monitor for signs and symptoms. Discontinue Kyprolis if suspected. (5.13)
- Posterior Reversible Encephalopathy Syndrome (PRES): Consider neuro-radiological imaging (MRI) for onset of visual or neurological symptoms; discontinue Kyprolis if suspected. (5.14)
- Embryo-Fetal Toxicity: Kyprolis can cause fetal harm. Females of reproductive potential should avoid becoming pregnant while being treated. (5.15, 8.1)

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

The most common adverse reactions occurring in at least 20% of patients treated with Kyprolis in monotherapy trials: anemia, fatigue, thrombocytopenia, nausea, pyrexia, dyspnea, diarrhea, headache, cough, edema peripheral. (6)

The most common adverse reactions occurring in at least 20% of patients treated with Kyprolis in the combination therapy trials: anemia, neutropenia, diarrhea, dyspnea, fatigue, thrombocytopenia, pyrexia, insomnia, muscle spasm, cough, upper respiratory tract infection, hypokalemia. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Amgen Medical Information at 1-800-77-AMGEN (1-800-772-6436) or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

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

- Geriatric use: In the Kyprolis clinical trials, the incidence of adverse events was greater in patients ≥ 75 years of age. (8.5)
- Hepatic impairment: Reduce the dose of Kyprolis by 25% in patients with mild or moderate hepatic impairment. (2.4)
- Patients on hemodialysis: Administer Kyprolis after the hemodialysis procedure. (2.1)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 11/2016

FULL PRESCRIBING INFORMATION: CONTENTS*

***Sections or subsections omitted from the Full Prescribing Information are not listed.**

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Relapsed or Refractory Multiple Myeloma

- Kyprolis is indicated in combination with dexamethasone or with lenalidomide plus dexamethasone for the treatment of patients with relapsed or refractory multiple myeloma who have received one to three lines of therapy *[see Clinical Studies (14.1)]*.
- Kyprolis is indicated as a single agent for the treatment of patients with relapsed or refractory multiple myeloma who have received one or more lines of therapy *[see Clinical Studies (14.2, 14.3)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Administration Precautions

- **Hydration** - Adequate hydration is required prior to dosing in Cycle 1, especially in patients at high risk of tumor lysis syndrome or renal toxicity. The recommended hydration includes both oral fluids (30 mL per kg at least 48 hours before Cycle 1, Day 1) and intravenous fluids (250 mL to 500 mL of appropriate intravenous fluid prior to each dose in Cycle 1). If needed, give an additional 250 mL to 500 mL of intravenous fluids following Kyprolis administration. Continue oral and/or intravenous hydration, as needed, in subsequent cycles. Monitor patients for evidence of volume overload and adjust hydration to individual patient needs, especially in patients with or at risk for cardiac failure *[see Warnings and Precautions (5.1, 5.3)]*.
- **Electrolyte Monitoring** - Monitor serum potassium levels regularly during treatment with Kyprolis.
- **Premedications** - Premedicate with the recommended dose of dexamethasone for monotherapy or the recommended dexamethasone dose if on combination therapy *[see Dosage and Administration (2.2)]*. Administer dexamethasone orally or intravenously at least 30 minutes but no more than 4 hours prior to all doses of Kyprolis during Cycle 1 to reduce the incidence and severity of infusion reactions *[see Warnings and Precautions (5.9)]*. Reinstate dexamethasone premedication if these symptoms occur during subsequent cycles.

- **Administration** - Infuse over 10 or 30 minutes depending on the Kyprolis dose regimen *[see Dosage and Administration (2.2)]*. Do not administer as a bolus. Flush the intravenous administration line with normal saline or 5% dextrose injection, USP immediately before and after Kyprolis administration. Do not mix Kyprolis with or administer as an infusion with other medicinal products.
- **Dose Calculation** - Calculate the Kyprolis dose *[see Dosage and Administration (2.2)]* using the patient's actual body surface area at baseline. In patients with a body surface area greater than 2.2 m^2, calculate the dose based upon a body surface area of 2.2 m^2.
- **Thromboprophylaxis** - Thromboprophylaxis is recommended for patients being treated with the combination of Kyprolis with dexamethasone or with lenalidomide plus dexamethasone. The thromboprophylaxis regimen should be based on an assessment of the patient's underlying risks *[see Warnings and Precautions (5.8)]*.
- **Infection Prophylaxis** - Consider antiviral prophylaxis for patients being treated with Kyprolis to decrease the risk of herpes zoster reactivation.
- **Patients on Hemodialysis** - Administer Kyprolis after the hemodialysis procedure.

2.2 Recommended Dosing

Kyprolis in Combination with Lenalidomide and Dexamethasone

For the combination regimen with lenalidomide and dexamethasone, administer Kyprolis intravenously as a 10-minute infusion on two consecutive days, each week for three weeks followed by a 12-day rest period as shown in Table 1. Each 28-day period is considered one treatment cycle. The recommended starting dose of Kyprolis is 20 mg/m^2 in Cycle 1 on Days 1 and 2. If tolerated, escalate the dose to 27 mg/m^2 on Day 8 of Cycle 1. From Cycle 13, omit the Day 8 and 9 doses of Kyprolis. Discontinue Kyprolis after Cycle 18. Lenalidomide 25 mg is taken orally on Days 1–21 and dexamethasone 40 mg by mouth or intravenously on Days 1, 8, 15, and 22 of the 28-day cycles.

Table 1: Kyprolis (10-Minute Infusion) in Combination with Lenalidomide and Dexamethasone

	Cycle 1										
	Week 1			**Week 2**			**Week 3**			**Week 4**	
	Day 1	**Day 2**	**Days 3–7**	**Day 8**	**Day 9**	**Days 10–14**	**Day 15**	**Day 16**	**Days 17–21**	**Day 22**	**Days 23-28**
Kyprolis (mg/m^2)	20	20	-	27	27	-	27	27	-	-	-
Dexamethasone (mg)	40	-	-	40	-	-	40	-	-	40	-
Lenalidomide	25 mg daily on Days 1-21									-	-
	Cycles 2 to 12										
	Week 1			**Week 2**			**Week 3**			**Week 4**	
	Day 1	**Day 2**	**Days 3–7**	**Day 8**	**Day 9**	**Days 10–14**	**Day 15**	**Day 16**	**Days 17–21**	**Day 22**	**Days 23-28**
Kyprolis (mg/m^2)	27	27	-	27	27	-	27	27	-	-	-
Dexamethasone (mg)	40	-	-	40	-	-	40	-	-	40	-
Lenalidomide	25 mg daily on Days 1-21									-	-
	Cycles 13 and later[a]										
	Week 1			**Week 2**			**Week 3**			**Week 4**	
	Day 1	**Day 2**	**Days 3–7**	**Day 8**	**Day 9**	**Days 10–14**	**Day 15**	**Day 16**	**Days 17–21**	**Day 22**	**Days 23-28**
Kyprolis (mg/m^2)	27	27	-	-	-	-	27	27	-	-	-
Dexamethasone (mg)	40	-	-	40	-	-	40	-	-	40	-
Lenalidomide	25 mg daily on Days 1-21									-	-

[a] Kyprolis is administered through Cycle 18; lenalidomide and dexamethasone continue thereafter.

Continue treatment until disease progression or unacceptable toxicity occurs *[see Dosage and Administration (2.3)]*. Refer to the lenalidomide and dexamethasone Prescribing Information for other concomitant medications, such as the use of anticoagulant and antacid prophylaxis, that may be required with those agents.

Kyprolis in Combination with Dexamethasone

For the combination regimen with dexamethasone, administer Kyprolis intravenously as a 30-minute infusion on two consecutive days, each week for three weeks followed by a 12-day rest period as shown in Table 2. Each 28-day period is considered one treatment cycle. Administer Kyprolis by 30-minute infusion at a starting dose of 20 mg/m^2 in Cycle 1 on Days 1 and 2. If tolerated, escalate the dose to 56 mg/m^2 on Day 8 of Cycle 1. Dexamethasone 20 mg is taken by mouth or intravenously on Days 1, 2, 8, 9, 15, 16, 22, and 23 of each 28-day cycle. Administer dexamethasone 30 minutes to 4 hours before Kyprolis.

Table 2: Kyprolis (30-Minute Infusion) in Combination with Dexamethasone

	Cycle 1											
	Week 1			**Week 2**			**Week 3**			**Week 4**		
	Day 1	**Day 2**	**Days 3–7**	**Day 8**	**Day 9**	**Days 10–14**	**Day 15**	**Day 16**	**Days 17–21**	**Day 22**	**Day 23**	**Days 24-28**
Kyprolis (mg/m^2)	20	20	-	56	56	-	56	56	-	-	-	-
Dexamethasone (mg)	20	20	-	20	20	-	20	20	-	20	20	-
	Cycles 2 and later											
	Week 1			**Week 2**			**Week 3**			**Week 4**		
	Day 1	**Day 2**	**Days 3–7**	**Day 8**	**Day 9**	**Days 10–14**	**Day 15**	**Day 16**	**Days 17–21**	**Day 22**	**Day 23**	**Days 24-28**
Kyprolis (mg/m^2)	56	56	-	56	56	-	56	56	-	-	-	-
Dexamethasone (mg)	20	20	-	20	20	-	20	20	-	20	20	-

Treatment may be continued until disease progression or unacceptable toxicity occurs *[see Dosage and Administration (2.3)]*. Refer to the dexamethasone Prescribing Information for other concomitant medications.

Kyprolis Monotherapy

For monotherapy, administer Kyprolis intravenously as a 10-minute or 30-minute infusion depending on the regimen as described below.

20/27 mg/m^2 regimen by 10-minute infusion

For monotherapy using the 20/27 mg/m^2 regimen, administer Kyprolis intravenously as a 10-minute infusion *[see Clinical Studies (14.3)]*. In Cycles 1 through 12, administer Kyprolis on two consecutive days, each week for three weeks followed by a 12-day rest period as shown in Table 3. Each 28-day period is considered one treatment cycle. From Cycle 13, omit the Day 8 and 9 doses of Kyprolis (see Table 3). Premedicate with dexamethasone 4 mg orally or intravenously 30 minutes to 4 hours before each Kyprolis dose in Cycle 1, then as needed to help prevent infusion reactions *[see Dosage and Administration (2.1)]*. The recommended starting dose of Kyprolis is 20 mg/m^2 in Cycle 1 on Days 1 and 2. If tolerated, escalate the dose to 27 mg/m^2 on Day 8 of Cycle 1. Treatment may continue until disease progression or unacceptable toxicity occurs.

Table 3: Kyprolis Monotherapy (10-Minute Infusion)

	Cycle 1									
	Week 1			**Week 2**			**Week 3**			**Week 4**
	Day 1	**Day 2**	**Days 3–7**	**Day 8**	**Day 9**	**Days 10–14**	**Day 15**	**Day 16**	**Days 17–21**	**Days 22–28**
Kyprolis (mg/m^2)[a]	20	20	-	27	27	-	27	27	-	-
	Cycles 2 to 12									
	Week 1			**Week 2**			**Week 3**			**Week 4**
	Day 1	**Day 2**	**Days 3–7**	**Day 8**	**Day 9**	**Days 10–14**	**Day 15**	**Day 16**	**Days 17–21**	**Days 22–28**
Kyprolis (mg/m^2)	27	27	-	27	27	-	27	27	-	-
	Cycles 13 and later									
	Week 1			**Week 2**			**Week 3**			**Week 4**
	Day 1	**Day 2**	**Days 3–7**	**Day 8**	**Day 9**	**Days 10–14**	**Day 15**	**Day 16**	**Days 17–21**	**Days 22–28**
Kyprolis (mg/m^2)	27	27	-	-	-	-	27	27	-	-

[a] Dexamethasone premedication is required for each Kyprolis dose in Cycle 1.

20/56 mg/m^2 regimen by 30-minute infusion

For monotherapy using the 20/56 mg/m^2 regimen, administer Kyprolis intravenously as a 30-minute infusion *[see Clinical Studies (14.3)]*. In Cycles 1 through 12, administer Kyprolis on two consecutive days, each week for three weeks followed by a 12-day rest period as shown in Table 4. Each 28-day period is considered one treatment cycle. From Cycle 13, omit the Day 8 and 9 doses of Kyprolis (see Table 4). Premedicate with dexamethasone 8 mg orally or intravenously 30 minutes to 4 hours before each Kyprolis dose in Cycle 1, then as needed to help prevent infusion reactions *[see Dosage and Administration (2.1)]*. The recommended starting dose of Kyprolis is 20 mg/m^2 in Cycle 1 on Days 1 and 2. If tolerated, escalate the dose to 56 mg/m^2 on Day 8 of Cycle 1. Treatment may continue until disease progression or unacceptable toxicity occurs.

Table 4: Kyprolis Monotherapy (30-Minute Infusion)

	Cycle 1									
	Week 1			**Week 2**			**Week 3**			**Week 4**
	Day 1	**Day 2**	**Days 3–7**	**Day 8**	**Day 9**	**Days 10–14**	**Day 15**	**Day 16**	**Days 17–21**	**Days 22–28**
Kyprolis (mg/m^2)[a]	20	20	-	56	56	-	56	56	-	-
	Cycles 2 to 12									
	Week 1			**Week 2**			**Week 3**			**Week 4**
	Day 1	**Day 2**	**Days 3–7**	**Day 8**	**Day 9**	**Days 10–14**	**Day 15**	**Day 16**	**Days 17–21**	**Days 22–28**
Kyprolis (mg/m^2)	56	56	-	56	56	-	56	56	-	-
	Cycles 13 and later									
	Week 1			**Week 2**			**Week 3**			**Week 4**
	Day 1	**Day 2**	**Days 3–7**	**Day 8**	**Day 9**	**Days 10–14**	**Day 15**	**Day 16**	**Days 17–21**	**Days 22–28**
Kyprolis (mg/m^2)	56	56	-	-	-	-	56	56	-	-

[a] Dexamethasone premedication is required for each Kyprolis dose in Cycle 1.

2.3 Dose Modifications Based on Toxicities

Modify dosing based on toxicity. Recommended actions and dose modifications for Kyprolis are presented in Table 5. Dose level reductions are presented in Table 6. See the

lenalidomide and dexamethasone Prescribing Information respectively for dosing recommendations.

Table 5: Dose Modifications for Toxicity[a] during Kyprolis Treatment

Hematologic Toxicity	Recommended Action
• ANC less than 0.5×10^9/L	• Withhold dose • If recovered to greater than or equal to 0.5×10^9/L, continue at the same dose level • For subsequent drops to less than 0.5×10^9/L, follow the same recommendations as above and consider 1 dose level reduction when restarting Kyprolis[a]
• Febrile neutropenia ANC less than 0.5×10^9/L and an oral temperature more than 38.5°C or two consecutive readings of more than 38.0°C for 2 hours	• Withhold dose • If ANC returns to baseline grade and fever resolves, resume at the same dose level
• Platelets less than 10×10^9/L or evidence of bleeding with thrombocytopenia *[see Warnings and Precautions (5)]*	• Withhold dose • If recovered to greater than or equal to 10×10^9/L and/or bleeding is controlled, continue at the same dose level • For subsequent drops to less than 10×10^9/L, follow the same recommendations as above and consider 1 dose level reduction when restarting Kyprolis[a]
Renal Toxicity	**Recommended Action**
• Serum creatinine greater than or equal to 2 × baseline, or • Creatinine clearance less than 15 mL/min, or creatinine clearance decreases to less than or equal to 50% of baseline, or need for hemodialysis *[see Warnings and Precautions (5)]*	• Withhold dose and continue monitoring renal function (serum creatinine or creatinine clearance) • If attributable to Kyprolis, resume when renal function has recovered to within 25% of baseline; start at 1 dose level reduction[a] • If not attributable to Kyprolis, dosing may be resumed at the discretion of the physician • For patients on hemodialysis receiving Kyprolis, the dose is to be administered after the hemodialysis procedure
Other Non-hematologic Toxicity	**Recommended Action**
• All other severe or life-threatening[b] non-hematological toxicities	• Withhold until resolved or returned to baseline • Consider restarting the next scheduled treatment at 1 dose level reduction[a]

ANC = absolute neutrophil count

[a] See Table 6 for dose level reductions.

[b] CTCAE Grades 3 and 4.

Table 6: Dose Level Reductions for Kyprolis

Regimen	Dose	First Dose Reduction	Second Dose Reduction	Third Dose Reduction
Kyprolis, Lenalidomide, and Dexamethasone, or Monotherapy (20/27 mg/m^2)	27 mg/m^2	20 mg/m^2	15 mg/m^2[a]	—
Kyprolis and Dexamethasone, or Monotherapy (20/56 mg/m^2)	56 mg/m^2	45 mg/m^2	36 mg/m^2	27 mg/m^2[a]

Note: Infusion times remain unchanged during dose reduction(s).

[a] If toxicity persists, discontinue Kyprolis treatment.

2.4 Dose Modifications for Use in Hepatic Impairment

For patients with mild or moderate hepatic impairment, reduce the dose of Kyprolis by 25%. Dosing recommendation cannot be made in patients with severe hepatic impairment *[see Use in Specific Populations (8.6), Clinical Pharmacology (12.3)]*.

2.5 Dosing in Patients with End Stage Renal Disease

For patients with end stage renal disease who are on dialysis, administer Kyprolis after the hemodialysis procedure.

2.6 Reconstitution and Preparation for Intravenous Administration

Kyprolis vials contain no antimicrobial preservatives and are intended for single use only. Unopened vials of Kyprolis are stable until the date indicated on the package when stored in the original package at 2°C to 8°C (36°F to 46°F). The reconstituted solution contains carfilzomib at a concentration of 2 mg/mL.

Read the complete preparation instructions prior to reconstitution. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Reconstitution/Preparation Steps:

1. Remove vial from refrigerator just prior to use.
2. Calculate the dose (mg/m^2) and number of vials of Kyprolis required using the patient's body surface area (BSA) at baseline. Patients with a BSA greater than 2.2 m^2 should receive a dose based upon a BSA of 2.2 m^2. Dose adjustments do not need to be made for weight changes of less than or equal to 20%.

3. Use a 21-gauge or larger gauge needle (0.8 mm or smaller external diameter needle) to aseptically reconstitute each vial by slowly injecting **29 mL** (for 60 mg vial) or **15 mL** (for 30 mg vial) Sterile Water for Injection, USP, through the stopper and directing the solution onto the INSIDE WALL OF THE VIAL to minimize foaming.

4. Gently swirl and/or invert the vial slowly for about 1 minute, or until complete dissolution. DO NOT SHAKE to avoid foam generation. If foaming occurs, allow the solution to settle in the vial until foaming subsides (approximately 5 minutes) and the solution is clear.
5. Visually inspect for particulate matter and discoloration prior to administration. The reconstituted product should be a clear, colorless solution and should not be administered if any discoloration or particulate matter is observed.
6. Discard any unused portion left in the vial. DO NOT pool unused portions from the vials. DO NOT administer more than one dose from a vial.
7. Optionally, Kyprolis can be administered in an intravenous bag.
8. When administering in an intravenous bag, use a 21-gauge or larger gauge needle (0.8 mm or smaller external diameter needle) to withdraw the calculated dose *[see Dosage and Administration (2)]* from the vial and dilute into 50 mL or 100 mL intravenous bag containing 5% Dextrose Injection, USP (based on the calculated total dose and infusion time).

The stabilities of reconstituted Kyprolis under various temperature and container conditions are shown in Table 7.

Table 7: Stability of Reconstituted Kyprolis

Storage Conditions of Reconstituted Kyprolis	Stability[a] per Container		
	Vial	Syringe	Intravenous Bag (D5W[b])
Refrigerated (2°C to 8°C; 36°F to 46°F)	24 hours	24 hours	24 hours
Room Temperature (15°C to 30°C; 59°F to 86°F)	4 hours	4 hours	4 hours

[a] Total time from reconstitution to administration should not exceed 24 hours.

[b] 5% Dextrose Injection, USP.

3 DOSAGE FORMS AND STRENGTHS

Kyprolis is supplied as follows:

- For injection: 30 mg lyophilized cake or powder in single-dose vial for reconstitution
- For injection: 60 mg lyophilized cake or powder in single-dose vial for reconstitution

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Cardiac Toxicities

New onset or worsening of pre-existing cardiac failure (e.g., congestive heart failure, pulmonary edema, decreased ejection fraction), restrictive cardiomyopathy, myocardial ischemia, and myocardial infarction including fatalities have occurred following administration of Kyprolis. Some events occurred in patients with normal baseline ventricular function. In clinical studies with Kyprolis, these events occurred throughout the course of Kyprolis therapy. Death due to cardiac arrest has occurred within one day of Kyprolis administration. In a randomized, open-label, multicenter trial evaluating Kyprolis in combination with lenalidomide and dexamethasone (KRd) *versus* lenalidomide/dexamethasone (Rd), the incidence of cardiac failure events was 6% in the KRd arm *versus* 4% in the Rd arm. In a randomized, open-label, multicenter trial of Kyprolis plus dexamethasone (Kd) *versus* bortezomib plus dexamethasone (Vd), the incidence of cardiac failure events was 8% in the Kd arm *versus* 3% in the Vd arm.

Monitor patients for clinical signs or symptoms of cardiac failure or cardiac ischemia. Evaluate promptly if cardiac toxicity is suspected. Withhold Kyprolis for Grade 3 or 4 cardiac adverse events until recovery, and consider whether to restart Kyprolis at 1 dose level reduction based on a benefit/risk assessment *[see Dosage and Administration (2.3)]*.

While adequate hydration is required prior to each dose in Cycle 1, all patients should also be monitored for evidence of volume overload, especially patients at risk for cardiac failure. Adjust total fluid intake as clinically appropriate in patients with baseline cardiac failure or who are at risk for cardiac failure *[see Dosage and Administration (2.1)]*.

In patients ≥ 75 years of age, the risk of cardiac failure is increased compared to patients < 75 years of age. Patients with New York Heart Association Class III and IV heart failure, recent myocardial infarction, conduction abnormalities, angina, or arrhythmias uncontrolled by medications were not eligible for the clinical trials. These patients may be at greater risk for cardiac complications and should have a comprehensive medical assessment (including blood pressure and fluid management) prior to starting treatment with Kyprolis and remain under close follow-up *[see Use in Specific Populations (8.5)]*.

5.2 Acute Renal Failure

Cases of acute renal failure have occurred in patients receiving Kyprolis. Renal insufficiency adverse events (including renal failure) have occurred in approximately 10% of patients treated with Kyprolis. Acute renal failure was reported more frequently in patients with advanced relapsed and refractory multiple myeloma who received Kyprolis monotherapy. This risk was greater in patients with a baseline reduced estimated creatinine clearance (calculated using Cockcroft and Gault equation). Monitor renal function with regular measurement of the serum creatinine and/or estimated creatinine clearance. Reduce or withhold dose as appropriate *[see Dosage and Administration (2.3)]*.

5.3 Tumor Lysis Syndrome

Cases of tumor lysis syndrome (TLS), including fatal outcomes, have been reported in patients who received Kyprolis. Patients with multiple myeloma and a high tumor burden should be considered to be at greater risk for TLS. Ensure that patients are well hydrated before administration of Kyprolis in Cycle 1, and in subsequent cycles as needed *[see Dosage and Administration (2.1)]*. Consider uric acid-lowering drugs in patients at risk for TLS. Monitor for evidence of TLS during treatment and manage promptly, including interruption of Kyprolis until TLS is resolved *[see Dosage and Administration (2.1)]*.

5.4 Pulmonary Toxicity

Acute Respiratory Distress Syndrome (ARDS), acute respiratory failure, and acute diffuse infiltrative pulmonary disease such as pneumonitis and interstitial lung disease have occurred in less than 1% of patients receiving Kyprolis. Some events have been fatal. In the event of

drug-induced pulmonary toxicity, discontinue Kyprolis *[see Dosage and Administration (2.3)]*.

5.5 Pulmonary Hypertension

Pulmonary arterial hypertension was reported in approximately 1% of patients treated with Kyprolis and was Grade 3 or greater in less than 1% of patients. Evaluate with cardiac imaging and/or other tests as indicated. Withhold Kyprolis for pulmonary hypertension until resolved or returned to baseline, and consider whether to restart Kyprolis based on a benefit/risk assessment *[see Dosage and Administration (2.3)]*.

5.6 Dyspnea

Dyspnea was reported in 28% of patients treated with Kyprolis and was Grade 3 or greater in 4% of patients. Evaluate dyspnea to exclude cardiopulmonary conditions including cardiac failure and pulmonary syndromes. Stop Kyprolis for Grade 3 or 4 dyspnea until resolved or returned to baseline. Consider whether to restart Kyprolis based on a benefit/risk assessment *[see Dosage and Administration (2.3), Warnings and Precautions (5.1 and 5.4), and Adverse Reactions (6.1)]*.

5.7 Hypertension

Hypertension, including hypertensive crisis and hypertensive emergency, has been observed with Kyprolis. In a randomized, open-label, multicenter trial evaluating Kyprolis in combination with KRd *versus* Rd, the incidence of hypertension events was 16% in the KRd arm *versus* 8% in the Rd arm. In a randomized, open-label, multicenter trial of Kd *versus* Vd, the incidence of hypertension events was 26% in the Kd arm *versus* 10% in the Vd arm. Some of these events have been fatal. Monitor blood pressure regularly in all patients. If hypertension cannot be adequately controlled, withhold Kyprolis and evaluate. Consider whether to restart Kyprolis based on a benefit/risk assessment *[see Dosage and Administration (2)]*.

5.8 Venous Thrombosis

Venous thromboembolic events (including deep venous thrombosis and pulmonary embolism) have been observed with Kyprolis. In a randomized, open-label, multicenter trial

evaluating KRd *versus* Rd (with thromboprophylaxis used in both arms), the incidence of venous thromboembolic events in the first 12 cycles was 13% in the KRd arm *versus* 6% in the Rd arm. In a randomized, open-label, multicenter trial of Kd *versus* Vd, the incidence of venous thromboembolic events in months 1–6 was 9% in the Kd arm *versus* 2% in the Vd arm. With Kyprolis monotherapy, the incidence of venous thromboembolic events was 2%.

Thromboprophylaxis is recommended for patients being treated with the combination of Kyprolis with dexamethasone or with lenalidomide plus dexamethasone. The thromboprophylaxis regimen should be based on an assessment of the patient's underlying risks.

Patients using oral contraceptives or a hormonal method of contraception associated with a risk of thrombosis should consider an alternative method of effective contraception during treatment with Kyprolis in combination with dexamethasone or lenalidomide plus dexamethasone *[see Use in Specific Population (8.3)]*.

5.9 Infusion Reactions

Infusion reactions, including life-threatening reactions, have occurred in patients receiving Kyprolis. Symptoms include fever, chills, arthralgia, myalgia, facial flushing, facial edema, vomiting, weakness, shortness of breath, hypotension, syncope, chest tightness, or angina. These reactions can occur immediately following or up to 24 hours after administration of Kyprolis. Administer dexamethasone prior to Kyprolis to reduce the incidence and severity of infusion reactions *[see Dosage and Administration (2)]*. Inform patients of the risk and of symptoms and to contact a physician immediately if symptoms of an infusion reaction occur.

5.10 Hemorrhage

Fatal or serious cases of hemorrhage have been reported in patients treated with Kyprolis. Hemorrhagic events have included gastrointestinal, pulmonary, and intracranial hemorrhage and epistaxis. The bleeding can be spontaneous, and intracranial hemorrhage has occurred without trauma. Hemorrhage has been reported in patients having either low or normal platelet counts. Hemorrhage has also been reported in patients who were not on antiplatelet therapy or anticoagulation. Promptly evaluate signs and symptoms of blood loss. Reduce or

withhold dose as appropriate *[see Dosage and Administration (2.3) and Adverse Reactions (6.1)]*.

5.11 Thrombocytopenia

Kyprolis causes thrombocytopenia with platelet nadirs observed between Day 8 and Day 15 of each 28-day cycle, with recovery to baseline platelet count usually by the start of the next cycle *[see Adverse Reactions (6.1)]*. Thrombocytopenia was reported in approximately 40% of patients in clinical trials with Kyprolis. Monitor platelet counts frequently during treatment with Kyprolis. Reduce or withhold dose as appropriate *[see Dosage and Administration (2.3)]*. Hemorrhage may occur *[see Adverse Reactions (6.1) and Warnings and Precautions (5.10)]*.

5.12 Hepatic Toxicity and Hepatic Failure

Cases of hepatic failure, including fatal cases, have been reported (< 1%) during treatment with Kyprolis. Kyprolis can cause increased serum transaminases. Monitor liver enzymes regularly, regardless of baseline values. Reduce or withhold dose as appropriate *[see Dosage and Administration (2.3) and Adverse Reactions (6.1)]*.

5.13 Thrombotic Microangiopathy

Cases of thrombotic microangiopathy, including thrombotic thrombocytopenic purpura/hemolytic uremic syndrome (TTP/HUS), have been reported in patients who received Kyprolis. Some of these events have been fatal. Monitor for signs and symptoms of TTP/HUS. If the diagnosis is suspected, stop Kyprolis and evaluate. If the diagnosis of TTP/HUS is excluded, Kyprolis may be restarted. The safety of reinitiating Kyprolis therapy in patients previously experiencing TTP/HUS is not known *[see Dosage and Administration (2.3)]*.

5.14 Posterior Reversible Encephalopathy Syndrome

Cases of posterior reversible encephalopathy syndrome (PRES) have been reported in patients receiving Kyprolis. PRES, formerly termed Reversible Posterior Leukoencephalopathy Syndrome (RPLS), is a neurological disorder which can present with seizure, headache, lethargy, confusion, blindness, altered consciousness, and other visual and

neurological disturbances, along with hypertension, and the diagnosis is confirmed by neuro-radiological imaging (MRI). Discontinue Kyprolis if PRES is suspected and evaluate. The safety of reinitiating Kyprolis therapy in patients previously experiencing PRES is not known.

5.15 Embryo-Fetal Toxicity

Kyprolis can cause fetal harm when administered to a pregnant woman based on its mechanism of action and findings in animals. There are no adequate and well-controlled studies in pregnant women using Kyprolis.

Advise females of reproductive potential to avoid becoming pregnant while being treated with Kyprolis. Advise males of reproductive potential to avoid fathering a child while being treated with Kyprolis. Advise women who use Kyprolis during pregnancy or become pregnant during treatment with Kyprolis of the potential hazard to the fetus *[see Use in Specific Populations (8.1, 8.3)]*.

6 ADVERSE REACTIONS

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

- Cardiac Toxicities *[see Warnings and Precautions (5.1)]*
- Acute Renal Failure *[see Warnings and Precautions (5.2)]*
- Tumor Lysis Syndrome *[see Warnings and Precautions (5.3)]*
- Pulmonary Toxicity *[see Warnings and Precautions (5.4)]*
- Pulmonary Hypertension *[see Warnings and Precautions (5.5)]*
- Dyspnea *[see Warnings and Precautions (5.6)]*
- Hypertension *[see Warnings and Precautions (5.7)]*
- Venous Thrombosis *[see Warnings and Precautions (5.8)]*
- Infusion Reactions *[see Warnings and Precautions (5.9)]*
- Hemorrhage *[see Warnings and Precautions (5.10)]*
- Thrombocytopenia *[see Warnings and Precautions (5.11)]*
- Hepatic Toxicity and Hepatic Failure *[see Warnings and Precautions (5.12)]*

- Thrombotic Microangiopathy *[see Warnings and Precautions (5.13)]*
- Posterior Reversible Encephalopathy Syndrome *[see Warnings and Precautions (5.14)]*

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 with rates in the clinical trials of another drug, and may not reflect the rates observed in medical practice.

Safety Experience with Kyprolis in Combination with Lenalidomide and Dexamethasone in Patients with Multiple Myeloma

The safety of Kyprolis in combination with lenalidomide and dexamethasone (KRd) was evaluated in an open-label randomized study in patients with relapsed multiple myeloma. Details of the study treatment are described in Section 14.1. The median number of cycles initiated was 22 cycles for the KRd arm and 14 cycles for the Rd arm.

Deaths due to adverse reactions within 30 days of the last dose of any therapy in the KRd arm occurred in 27/392 (7%) patients compared with 27/389 (7%) patients who died due to adverse events within 30 days of the last dose of any Rd therapy. The most common cause of deaths occurring in patients (%) in the two arms (KRd *versus* Rd) included cardiac 10 (3%) *versus* 7 (2%), infection 9 (2%) *versus* 10 (3%), renal 0 (0%) *versus* 1 (< 1%), and other adverse reactions 9 (2%) *versus* 10 (3%). Serious adverse reactions were reported in 60% of the patients in the KRd arm and 54% of the patients in the Rd arm. The most common serious adverse reactions reported in the KRd arm as compared with the Rd arm were pneumonia (14% *versus* 11%), respiratory tract infection (4% *versus* 1.5%), pyrexia (4% *versus* 2%), and pulmonary embolism (3% *versus* 2%). Discontinuation due to any adverse reaction occurred in 26% in the KRd arm *versus* 25% in the Rd arm. Adverse reactions leading to discontinuation of Kyprolis occurred in 12% of patients and the most common reactions included pneumonia (1%), myocardial infarction (0.8%), and upper respiratory tract infection (0.8%).

Common Adverse Reactions (≥ 10%)

The adverse reactions in the first 12 cycles of therapy that occurred at a rate of 10% or greater in the KRd arm are presented in Table 8.

Table 8: Most Common Adverse Reactions (≥ 10% in the KRd Arm) Occurring in Cycles 1–12 (20/27 mg/m^2 Regimen In Combination with Lenalidomide and Dexamethasone)

	KRd Arm (N = 392) n (%)		Rd Arm (N = 389) n (%)	
Adverse Reactions by Body System	**Any Grade**	**≥ Grade 3**	**Any Grade**	**≥ Grade 3**
Blood and Lymphatic System Disorders				
Anemia	138 (35)	53 (14)	127 (33)	47 (12)
Neutropenia	124 (32)	104 (27)	115 (30)	89 (23)
Thrombocytopenia	100 (26)	58 (15)	75 (19)	39 (10)
Gastrointestinal Disorders				
Diarrhea	115 (29)	7 (2)	105 (27)	12 (3)
Constipation	68 (17)	0	53 (14)	1 (0)
Nausea	60 (15)	1 (0)	39 (10)	3 (1)
General Disorders and Administration Site Conditions				
Fatigue	109 (28)	21 (5)	104 (27)	20 (5)
Pyrexia	93 (24)	5 (1)	64 (17)	1 (0)
Edema peripheral	63 (16)	2 (1)	57 (15)	2 (1)
Asthenia	53 (14)	11 (3)	46 (12)	7 (2)
Infections and Infestations				
Upper respiratory tract infection	85 (22)	7 (2)	52 (13)	3 (1)
Nasopharyngitis	63 (16)	0	43 (11)	0
Bronchitis	54 (14)	5 (1)	39 (10)	2 (1)
Pneumonia[a]	54 (14)	35 (9)	43 (11)	27 (7)
Metabolism and Nutrition Disorders				
Hypokalemia	78 (20)	22 (6)	35 (9)	12 (3)
Hypocalcemia	55 (14)	10 (3)	39 (10)	5 (1)
Hyperglycemia	43 (11)	18 (5)	33 (9)	15 (4)
Musculoskeletal and Connective Tissue Disorders				
Muscle spasms	88 (22)	3 (1)	73 (19)	3 (1)
Nervous System Disorders				
Peripheral neuropathies[b]	43 (11)	7 (2)	37 (10)	4 (1)

Psychiatric Disorders				
Insomnia	63 (16)	6 (2)	50 (13)	8 (2)
Respiratory, Thoracic, and Mediastinal Disorders				
Cough[c]	91 (23)	2 (1)	52 (13)	0
Dyspnea[d]	70 (18)	9 (2)	58 (15)	6 (2)
Skin and Subcutaneous Tissue Disorders				
Rash	45 (12)	5 (1)	53 (14)	5 (1)
Vascular Disorders				
Embolic and thrombotic events venous[e]	49 (13)	16 (4)	22 (6)	9 (2)
Hypertension[f]	41 (11)	12 (3)	15 (4)	4 (1)

KRd = Kyprolis, lenalidomide, and dexamethasone; Rd = lenalidomide and dexamethasone

[a] Pneumonia includes pneumonia and bronchopneumonia.

[b] Peripheral neuropathies includes peripheral neuropathy, peripheral sensory neuropathy, and peripheral motor neuropathy.

[c] Cough includes cough and productive cough.

[d] Dyspnea includes dyspnea and dyspnea exertional.

[e] Embolic and thrombotic events, venous include deep vein thrombosis, pulmonary embolism, thrombophlebitis superficial, thrombophlebitis, venous thrombosis limb, post thrombotic syndrome, venous thrombosis.

[f] Hypertension includes hypertension, hypertensive crisis.

There were 274 (70%) patients in the KRd arm who received treatment beyond Cycle 12. There were no new clinically relevant adverse reactions that emerged in the later treatment cycles.

Adverse Reactions Occurring at a Frequency of < 10%

- **Blood and lymphatic system disorders:** febrile neutropenia, lymphopenia
- **Cardiac disorders:** cardiac arrest, cardiac failure, cardiac failure congestive, myocardial infarction, myocardial ischemia, pericardial effusion
- **Eye disorders:** cataract, vision blurred
- **Gastrointestinal disorders:** abdominal pain, abdominal pain upper, dyspepsia, gastrointestinal hemorrhage, toothache
- **General disorders and administration site conditions:** chills, infusion site reaction, multi-organ failure, pain
- **Infections and infestations:** influenza, lung infection, rhinitis, sepsis, urinary tract infection, viral infection
- **Metabolism and nutrition disorders:** dehydration, hyperkalemia, hyperuricemia, hypoalbuminemia, hyponatremia, tumor lysis syndrome
- **Musculoskeletal and connective tissue disorders:** muscular weakness, myalgia
- **Nervous system disorders:** hypoesthesia, intracranial hemorrhage, paresthesia, deafness

- **Psychiatric disorders:** anxiety, delirium
- **Renal and urinary disorders:** renal failure, renal failure acute, renal impairment
- **Respiratory, thoracic and mediastinal disorders:** dysphonia, epistaxis, oropharyngeal pain, pulmonary embolism, pulmonary edema, pulmonary hemorrhage
- **Skin and subcutaneous tissue disorders:** erythema, hyperhidrosis, pruritus
- **Vascular disorders:** deep vein thrombosis, hemorrhage, hypotension

Grade 3 and higher adverse reactions that occurred during Cycles 1–12 with a substantial difference (≥ 2%) between the two arms were neutropenia, thrombocytopenia, hypokalemia, and hypophosphatemia.

Laboratory Abnormalities

Table 9 describes Grade 3–4 laboratory abnormalities reported at a rate of ≥ 10% in the KRd arm for patients who received combination therapy.

Table 9: Grade 3–4 Laboratory Abnormalities (≥ 10% in the KRd Arm) in Cycles 1–12 (20/27 mg/m^2 Regimen In Combination with Lenalidomide and Dexamethasone)

Laboratory Abnormality	KRd (N = 392) n (%)	Rd (N = 389) n (%)
Decreased lymphocytes	182 (46)	119 (31)
Decreased absolute neutrophil count	152 (39)	140 (36)
Decreased phosphorus	122 (31)	106 (27)
Decreased platelets	101 (26)	59 (15)
Decreased total white blood cell count	97 (25)	71 (18)
Decreased hemoglobin	58 (15)	68 (18)
Decreased potassium	41 (11)	23 (6)

KRd = Kyprolis, lenalidomide, and dexamethasone; Rd = lenalidomide and dexamethasone

Safety Experience with Kyprolis in Combination with Dexamethasone in Patients with Multiple Myeloma

The safety of Kyprolis in combination with dexamethasone was evaluated in an open-label, randomized trial of patients with relapsed multiple myeloma. The study treatment is described in Section 14.2. Patients received treatment for a median duration of 40 weeks in

the Kyprolis/dexamethasone (Kd) arm and 27 weeks in the bortezomib/dexamethasone (Vd) arm.

Deaths due to adverse reactions within 30 days of last study treatment occurred in 22/463 (5%) patients in the Kd arm and 21/456 (5%) patients in the Vd arm. The causes of death occurring in patients (%) in the two arms (Kd *versus* Vd) included cardiac 7 (2%) *versus* 5 (1%), infections 5 (1%) *versus* 8 (2%), disease progression 6 (1%) *versus* 4 (1%), pulmonary 3 (1%) *versus* 2 (< 1%), renal 1 (< 1%) *versus* 0 (0%), and other adverse events 2 (< 1%) *versus* 2 (< 1%). Serious adverse reactions were reported in 48% of the patients in the Kd arm and 36% of the patients in the Vd arm. In both treatment arms, pneumonia was the most commonly reported serious adverse reaction (6% *versus* 9%). Discontinuation due to any adverse reaction occurred in 20% in the Kd arm *versus* 21% in the Vd arm. The most common reaction leading to discontinuation was cardiac failure in the Kd arm (n = 6, 1.3%) and peripheral neuropathy in the Vd arm (n = 19, 4.2%).

Common Adverse Reactions (≥ 10%)

Adverse reactions in the first 6 months of therapy that occurred at a rate of 10% or greater in the Kd arm are presented in Table 10.

Table 10: Most Common Adverse Reactions (≥ 10% in the Kd Arm) Occurring in Months 1–6 (20/56 mg/m^2 Regimen In Combination with Dexamethasone)

	Kd (N = 463) n (%)		**Vd (N = 456) n (%)**	
Adverse Reaction by Body System	**Any Grade**	**≥ Grade 3**	**Any Grade**	**≥ Grade 3**
Blood and Lymphatic System Disorders				
Anemia	160 (35)	57 (12)	112 (25)	43 (9)
Thrombocytopenia[a]	127 (27)	46 (10)	112 (25)	65 (14)
Gastrointestinal Disorders				
Diarrhea	111 (24)	14 (3)	150 (33)	26 (6)
Nausea	69 (15)	4 (1)	66 (15)	3 (1)
Constipation	58 (13)	1 (0)	109 (24)	6 (1)
Vomiting	45 (10)	5 (1)	32 (7)	3 (1)
General Disorders and Administration Site Conditions				
Fatigue	112 (24)	13 (3)	124 (27)	25 (6)

Pyrexia	102 (22)	9 (2)	52 (11)	3 (1)
Peripheral edema	75 (16)	3 (1)	73 (16)	3 (1)
Asthenia	71 (15)	9 (2)	66 (14)	13 (3)
Infections and Infestations				
Upper respiratory tract infection	66 (14)	4 (1)	54 (12)	3 (1)
Bronchitis	54 (12)	5 (1)	26 (6)	2 (0)
Nasopharyngitis	45 (10)	0 (0)	42 (9)	1 (0)
Musculoskeletal and Connective Tissue Disorders				
Muscle spasms	66 (14)	1 (0)	22 (5)	3 (1)
Back pain	58 (13)	7 (2)	60 (13)	8 (2)
Nervous System Disorders				
Headache	68 (15)	4 (1)	38 (8)	2 (0)
Peripheral neuropathies[b,c]	54 (12)	7 (2)	167 (37)	23 (5)
Psychiatric Disorders				
Insomnia	103 (22)	5 (1)	113 (25)	10 (2)
Respiratory, Thoracic and Mediastinal Disorders				
Dyspnea[d]	123 (27)	23 (5)	66 (15)	8 (2)
Cough[e]	91 (20)	0 (0)	61 (13)	2 (0)
Vascular Disorders				
Hypertension[f]	80 (17)	29 (6)	33 (7)	12 (3)

Kd = Kyprolis and dexamethasone; Vd = bortezomib and dexamethasone

[a] Thrombocytopenia includes platelet count decreased and thrombocytopenia.

[b] Peripheral neuropathies include peripheral neuropathy, peripheral sensory neuropathy, and peripheral motor neuropathy.

[c] See Clinical Studies (14.2).

[d] Dyspnea includes dyspnea and dyspnea exertional.

[e] Cough includes cough and productive cough.

[f] Hypertension includes hypertension, hypertensive crisis, and hypertensive emergency.

The event rate of ≥ Grade 2 peripheral neuropathy in the Kd arm was 6% (95% CI: 4, 8) *versus* 32% (95% CI: 28, 36) in the Vd arm.

Adverse Reactions Occurring at a Frequency of < 10%

- **Blood and lymphatic system disorders:** febrile neutropenia, leukopenia, lymphopenia, neutropenia, thrombotic microangiopathy, thrombotic thrombocytopenic purpura
- **Cardiac disorders:** atrial fibrillation, cardiac arrest, cardiac failure, cardiac failure congestive, myocardial infarction, myocardial ischemia, palpitations, tachycardia
- **Eye disorders:** cataract, vision blurred

- **Gastrointestinal disorders:** abdominal pain, abdominal pain upper, dyspepsia, gastrointestinal hemorrhage, toothache
- **General disorders and administration site conditions:** chest pain, chills, infusion site reactions (including inflammation, pain, and erythema), pain
- **Hepatobiliary disorders:** cholestasis, hepatic failure, hyperbilirubinemia
- **Immune system disorders:** drug hypersensitivity
- **Infections and infestations:** bronchopneumonia, influenza, lung infection, pneumonia, rhinitis, sepsis, urinary tract infection, viral infection
- **Metabolism and nutrition disorders:** decreased appetite, dehydration, hypercalcemia, hyperkalemia, hyperuricemia, hypoalbuminemia, hypocalcemia, hypomagnesemia, hyponatremia, hypophosphatemia, tumor lysis syndrome
- **Musculoskeletal and connective tissue disorders:** muscular weakness, musculoskeletal chest pain, musculoskeletal pain, myalgia
- **Nervous system disorders:** cerebrovascular accident, dizziness, hypoesthesia, paresthesia, posterior reversible encephalopathy syndrome
- **Psychiatric disorders:** anxiety
- **Renal and urinary disorders:** renal failure, renal failure acute, renal impairment
- **Respiratory, thoracic and mediastinal disorders:** acute respiratory distress syndrome, dysphonia, epistaxis, interstitial lung disease, oropharyngeal pain, pneumonitis pulmonary embolism, pulmonary edema, pulmonary hypertension, wheezing
- **Skin and subcutaneous tissue disorders:** erythema, hyperhidrosis, pruritus, rash
- **Vascular disorders:** deep vein thrombosis, flushing, hypotension

Laboratory Abnormalities

Table 11 describes Grades 3–4 laboratory abnormalities reported at a rate of ≥ 10% in the Kd arm.

Table 11: Grades 3–4 Laboratory Abnormalities (≥ 10%) in Months 1–6 (20/56 mg/m^2 Regimen In Combination with Dexamethasone)

Laboratory Abnormality	Kd (N = 463) n (%)	Vd (N = 456) n (%)
Decreased lymphocytes	248 (54)	180 (40)
Increase uric acid	243 (53)	198 (43)
Decreased hemoglobin	79 (17)	68 (15)

Decreased platelets	85 (18)	77 (17)
Decreased phosphorus	73 (16)	61 (13)
Decreased creatinine clearance[a]	65 (14)	49 (11)
Increased potassium	55 (12)	21 (5)

Kd = Kyprolis and dexamethasone; Vd = bortezomib and dexamethasone
[a] Calculated using the Cockcroft-Gault formula.

Safety Experience with Kyprolis in Patients with Multiple Myeloma who Received Monotherapy

The safety of Kyprolis, dosed at 20/27 mg/m^2 by up to 10-minute infusion, was evaluated in clinical trials in which 598 patients with relapsed and/or refractory myeloma received Kyprolis monotherapy starting with the 20 mg/m^2 dose in Cycle 1, Day 1 and escalating to 27 mg/m^2 on Cycle 1, Day 8 or Cycle 2, Day 1. Premedication with dexamethasone 4 mg was required before each dose in Cycle 1 and was optional for subsequent cycles. The median age was 64 years (range 32–87), and approximately 57% were male. The patients received a median of 5 (range 1–20) prior regimens. The median number of cycles initiated was 4 (range 1–35).

Serious adverse reactions, regardless of causality, were reported in 50% of patients in the pooled Kyprolis monotherapy studies (N = 598). The most common serious adverse reactions were: pneumonia (8%), acute renal failure (5%), disease progression (4%), pyrexia (3%), hypercalcemia (3%), congestive heart failure (3%), multiple myeloma (3%), anemia (2%), and dyspnea (2%). In patients treated with Kyprolis, the incidence of serious adverse reactions was higher in those ≥ 65 years old and those ≥ 75 years old *[see Geriatric Use (8.5)]*.

Deaths due to adverse reactions within 30 days of the last dose of Kyprolis occurred in 30/598 (5%) patients receiving Kyprolis monotherapy. These adverse reactions were related to cardiac disorders in 10 (2%) patients, infections in 8 (1%) patients, renal disorders in 4 (< 1%) patients, and other adverse reactions in 8 (1%) patients. In a randomized trial comparing Kyprolis as a single agent *versus* corticosteroids with optional oral cyclophosphamide for patients with relapsed and refractory multiple myeloma, mortality was higher in the patients treated with Kyprolis in comparison to the control arm in the subgroup

of 48 patients ≥ 75 years of age. The most common cause of discontinuation due to an adverse reaction was acute renal failure (2%).

Safety of Kyprolis monotherapy dosed at 20/56 mg/m^2 by 30-minute infusion was evaluated in a multicenter, open-label study in patients with relapsed and/or refractory multiple myeloma. The study treatment is described in Section 14.3. The patients received a median of 4 (range 1–10) prior regimens.

The common adverse reactions occurring at a rate of 20% or greater with Kyprolis monotherapy are presented in Table 12.

Table 12: Most Common Adverse Reactions (≥ 20%) with Kyprolis Monotherapy

	20/56 mg/m^2 by 30-minute infusion (N = 24)		**20/27 mg/m^2 by 2- to 10-minute infusion (N = 598)**	
Adverse Reaction	**Any Grade n (%)**	**Grades 3 - 5 n (%)**	**Any Grade n (%)**	**Grades 3 - 5 n (%)**
Fatigue	14 (58)	2 (8)	238 (40)	25 (4)
Dyspnea[a]	14 (58)	2 (8)	202 (34)	21 (4)
Pyrexia	14 (58)	0	177 (30)	11 (2)
Thrombocytopenia	13 (54)	13 (54)	220 (37)	152 (25)
Nausea	13 (54)	0	211 (35)	7 (1)
Anemia	10 (42)	7 (29)	291 (49)	141 (24)
Hypertension[b]	10 (42)	3 (13)	90 (15)	22 (4)
Chills	9 (38)	0	73 (12)	1 (< 1)
Headache	8 (33)	0	141 (24)	7 (1)
Cough[c]	8 (33)	0	134 (22)	2 (< 1)
Vomiting	8 (33)	0	104 (17)	4 (1)
Lymphopenia	8 (33)	8 (33)	85 (14)	73 (12)
Insomnia	7 (29)	0	75 (13)	0
Dizziness	7 (29)	0	64 (11)	5 (1)
Diarrhea	6 (25)	1 (4)	160 (27)	8 (1)
Blood creatinine increased	6 (25)	1 (4)	103 (17)	15 (3)
Peripheral edema	5 (21)	0	118 (20)	1 (< 1)
Back pain	5 (21)	1 (4)	115 (19)	19 (3)
Upper respiratory tract infection	5 (21)	1 (4)	112 (19)	15 (3)
Decreased appetite	5 (21)	0	89 (15)	2 (< 1)

Muscle spasms	5 (21)	0	62 (10)	2 (< 1)
Chest pain	5 (21)	0	20 (3)	1 (< 1)

[a] Dyspnea includes preferred terms of dyspnea and dyspnea exertional.

[b] Hypertension includes hypertension, hypertensive crisis, and hypertensive emergency.

[c] Cough includes cough and productive cough.

Adverse Reactions Occurring at a Frequency of < 20%

- **Blood and lymphatic system disorders:** febrile neutropenia, leukopenia, neutropenia
- **Cardiac disorders:** cardiac arrest, cardiac failure, cardiac failure congestive, myocardial infarction, myocardial ischemia
- **Eye disorders:** cataract, blurred vision
- **Gastrointestinal disorders:** abdominal pain, abdominal pain upper, constipation, dyspepsia, gastrointestinal hemorrhage, toothache
- **General disorders and administration site conditions:** asthenia, infusion site reaction, multi-organ failure, pain
- **Hepatobiliary disorders:** hepatic failure
- **Infections and infestations:** bronchitis, bronchopneumonia, influenza, lung infection, pneumonia, nasopharyngitis, respiratory tract infection, rhinitis, sepsis, urinary tract infection
- **Metabolism and nutrition disorders:** hypercalcemia, hyperglycemia, hyperkalemia, hyperuricemia, hypoalbuminemia, hypocalcemia, hypokalemia, hypomagnesemia, hyponatremia, hypophosphatemia, tumor lysis syndrome
- **Musculoskeletal and connective tissue disorders:** arthralgia, musculoskeletal pain, musculoskeletal chest pain, myalgia, pain in extremity
- **Nervous system disorders:** hypoesthesia, intracranial hemorrhage, paresthesia, peripheral motor neuropathy, peripheral neuropathy, peripheral sensory neuropathy
- **Psychiatric disorders:** anxiety
- **Renal and urinary disorders:** acute renal failure, renal failure, renal impairment
- **Respiratory, thoracic and mediastinal disorders:** dysphonia, epistaxis, oropharyngeal pain, pulmonary edema, pulmonary hemorrhage
- **Skin and subcutaneous tissue disorders:** erythema, hyperhidrosis, pruritus, rash
- **Vascular disorders:** embolic and thrombotic events, venous (including deep vein thrombosis and pulmonary embolism), hemorrhage, hypotension

Grade 3 and higher adverse reactions occurring at an incidence of > 1% include febrile neutropenia, cardiac arrest, cardiac failure congestive, pain, sepsis, urinary tract infection, hyperglycemia, hyperkalemia, hyperuricemia, hypoalbuminemia, hypocalcemia, hyponatremia, hypophosphatemia, renal failure, renal failure acute, renal impairment, pulmonary edema, and hypotension.

Laboratory Abnormalities

Table 13 describes Grade 3–4 laboratory abnormalities reported at a rate of > 10% for patients who received Kyprolis monotherapy.

Table 13: Grade 3–4 Laboratory Abnormalities (> 10%) with Kyprolis Monotherapy

Laboratory Abnormality	Kyprolis 20/56 mg/m^2 (N = 24)	Kyprolis 20/27 mg/m^2 (N = 598)
Decreased lymphocytes	15 (63)	151 (25)
Decreased platelets	11 (46)	184 (31)
Decreased hemoglobin	7 (29)	132 (22)
Decreased total white blood cell count	3 (13)	71 (12)
Decreased sodium	2 (8)	69 (12)
Decreased absolute neutrophil count	2 (8)	67 (11)

6.2 Postmarketing Experience

The following additional adverse reactions were reported in the postmarketing experience with Kyprolis. 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: hemolytic uremic syndrome (HUS), gastrointestinal perforation, pericarditis.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Kyprolis can cause fetal harm based on findings from animal studies *[see Data]* and the drug's mechanism of action *[see Clinical Pharmacology (12.1)]*. There are no adequate and well-controlled studies in pregnant women using Kyprolis.

Females of reproductive potential should be advised to avoid becoming pregnant while being treated with Kyprolis. Males of reproductive potential should be advised to avoid fathering a child while being treated with Kyprolis. Consider the benefits and risks of Kyprolis and possible risks to the fetus when prescribing Kyprolis to a pregnant woman. If Kyprolis is used during pregnancy, or if the patient becomes pregnant while taking this drug, apprise the patient of the potential hazard to the fetus. 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

Carfilzomib administered intravenously to pregnant rats and rabbits during the period of organogenesis was not teratogenic at doses up to 2 mg/kg/day in rats and 0.8 mg/kg/day in rabbits. Carfilzomib was not teratogenic at any dose tested. In rabbits, there was an increase in pre-implantation loss at ≥ 0.4 mg/kg/day and an increase in early resorptions and post-implantation loss and a decrease in fetal weight at the maternally toxic dose of 0.8 mg/kg/day. The doses of 0.4 and 0.8 mg/kg/day in rabbits are approximately 20% and 40%, respectively, of the recommended dose in humans of 27 mg/m^2 based on body surface area.

8.2 Lactation

Risk Summary

There is no information regarding the presence of Kyprolis in human 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 Kyprolis and any potential adverse effects on the breastfed infant from Kyprolis or from the underlying maternal condition.

8.3 Females and Males of Reproductive Potential

Contraception

Kyprolis can cause fetal harm *[see Use in Specific Populations (8.1)]*. Advise female patients of reproductive potential to use effective contraceptive measures or abstain from sexual activity to prevent pregnancy during treatment with Kyprolis and for at least 30 days following completion of therapy. Advise male patients of reproductive potential to use effective contraceptive measures or abstain from sexual activity to prevent pregnancy during treatment with Kyprolis and for at least 90 days following completion of therapy.

8.4 Pediatric Use

The safety and effectiveness of Kyprolis in pediatric patients have not been established.

8.5 Geriatric Use

Of 598 patients in clinical studies of Kyprolis monotherapy dosed at 20/27 mg/m^2 by up to 10-minute infusion, 49% were 65 and over, while 16% were 75 and over. The incidence of serious adverse events was 44% in patients < 65 years of age, 55% in patients 65 to 74 years of age, and 56% in patients ≥ 75 years of age *[see Warnings and Precautions (5.1)]*. In a single-arm, multicenter clinical trial of Kyprolis monotherapy dosed at 20/27 mg/m^2 (N = 266), no overall differences in effectiveness were observed between older and younger patients.

Of 392 patients treated with Kyprolis in combination with lenalidomide and dexamethasone, 47% were 65 and over and 11% were 75 years and over. The incidence of serious adverse events was 50% in patients < 65 years of age, 70% in patients 65 to 74 years of age, and 74% in patients ≥ 75 years of age *[see Warnings and Precautions (5.1)]*. No overall differences in effectiveness were observed between older and younger patients.

Of 463 patients treated with Kyprolis dosed at 20/56 mg/m^2 by 30-minute infusion in combination with dexamethasone, 52% were 65 and over and 17% were 75 and over. The incidence of serious adverse events was 44% in patients < 65 years of age, 50% in patients 65 to 74 years of age, and 57% in patients ≥ 75 years of age *[see Warnings and*

Precautions (5.1)]. No overall differences in effectiveness were observed between older and younger patients.

8.6 Hepatic Impairment

Reduce the dose of Kyprolis by 25% in patients with mild or moderate hepatic impairment. Dosing recommendation cannot be made for patients with severe hepatic function *[see Dosage and Administration (2.4), Clinical Pharmacology (12.3)]*.

The pharmacokinetics and safety of Kyprolis were evaluated in patients with advanced malignancies who had either normal hepatic function, or mild (bilirubin > 1 to 1.5×ULN or AST > ULN), moderate (bilirubin > 1.5 to 3×ULN), or severe (bilirubin > 3×ULN) hepatic impairment. The AUC of carfilzomib increased by approximately 50% in patients with mild and moderate hepatic impairment compared to patients with normal hepatic function. PK data were not collected in patients with severe hepatic impairment. The incidence of serious adverse events was higher in patients with mild, moderate, and severe hepatic impairment combined (22/35 or 63%) than in patients with normal hepatic function (3/11 or 27%) *[see Warnings and Precautions (5.12), Clinical Pharmacology (12.3)]*.

Monitor liver enzymes regularly, regardless of baseline values, and modify dose based on toxicity *[see Dosage and Administration (2.3)]*.

8.7 Renal Impairment

No starting dose adjustment is required in patients with baseline mild, moderate, or severe renal impairment or patients on chronic hemodialysis. The pharmacokinetics and safety of Kyprolis were evaluated in a Phase 2 trial in patients with normal renal function and those with mild, moderate, and severe renal impairment and patients on chronic hemodialysis. In addition, a pharmacokinetic study was conducted in patients with normal renal function and end-stage renal disease (ESRD) *[see Clinical Pharmacology (12.3)]*.

In these studies, the pharmacokinetics of Kyprolis was not influenced by the degree of baseline renal impairment, including the patients on hemodialysis. Since dialysis clearance of Kyprolis concentrations has not been studied, the drug should be administered after the hemodialysis procedure *[see Clinical Pharmacology (12.3)]*.

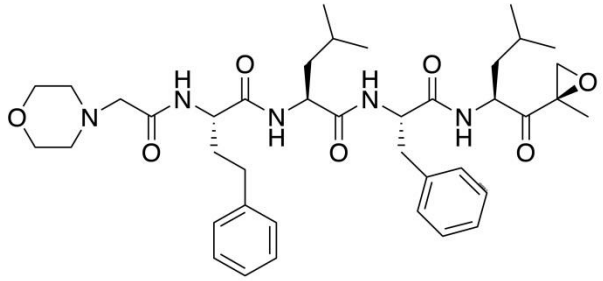
10 OVERDOSAGE

Acute onset of chills, hypotension, renal insufficiency, thrombocytopenia, and lymphopenia has been reported following a dose of 200 mg of Kyprolis administered in error.

There is no known specific antidote for Kyprolis overdosage. In the event of overdose, the patient should be monitored, specifically for the side effects and/or adverse reactions listed in *Adverse Reactions (6).*

11 DESCRIPTION

Carfilzomib is a modified tetrapeptidyl epoxide, isolated as the crystalline free base. The chemical name for carfilzomib is (2S)-N-((S)-1-((S)-4-methyl-1-((R)-2-methyloxiran-2-yl)-1-oxopentan-2-ylcarbamoyl)-2-phenylethyl)-2-((S)-2-(2-morpholinoacetamido)-4-phenylbutanamido)-4-methylpentanamide. Carfilzomib has the following structure:



Carfilzomib is a crystalline substance with a molecular weight of 719.9. The molecular formula is $C_{40}H_{57}N_5O_7$. Carfilzomib is practically insoluble in water and very slightly soluble in acidic conditions.

Kyprolis is a sterile, white to off-white lyophilized powder and is available as a single-dose 30 mg or 60 mg vial. Each 30 mg vial contains 30 mg of carfilzomib, 1500 mg sulfobutylether beta-cyclodextrin, and 28.9 mg anhydrous citric acid and sodium hydroxide for pH adjustment (target pH 3.5). Each 60 mg vial contains 60 mg of carfilzomib, 3000 mg sulfobutylether beta-cyclodextrin, 57.7 mg citric acid, and sodium hydroxide for pH adjustment (target pH 3.5).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Carfilzomib is a tetrapeptide epoxyketone proteasome inhibitor that irreversibly binds to the N-terminal threonine-containing active sites of the 20S proteasome, the proteolytic core particle within the 26S proteasome. Carfilzomib had antiproliferative and proapoptotic activities *in vitro* in solid and hematologic tumor cells. In animals, carfilzomib inhibited proteasome activity in blood and tissue and delayed tumor growth in models of multiple myeloma, hematologic, and solid tumors.

12.2 Pharmacodynamics

Intravenous carfilzomib administration resulted in suppression of proteasome chymotrypsin-like (CT-L) activity when measured in blood 1 hour after the first dose. Doses of carfilzomib $\geq$ 15 mg/m^2 with or without lenalidomide and dexamethasone induced a $\geq$ 80% inhibition of the CT-L activity of the proteasome. In addition, carfilzomib, 20 mg/m^2 intravenously as a single agent, resulted in a mean inhibition of the low molecular mass polypeptide 2 (LMP2) and multicatalytic endopeptidase complex-like 1 (MECL1) subunits of the proteasome ranging from 26% to 32% and 41% to 49%, respectively. Proteasome inhibition was maintained for $\geq$ 48 hours following the first dose of carfilzomib for each week of dosing.

12.3 Pharmacokinetics

The mean (CV%) C_{max} and AUC following a 2- to 10-minute intravenous infusion of 27 mg/m^2 of carfilzomib were 4232 ng/mL (49%) and 379 ng•hr/mL (25%), respectively. Following repeated doses of carfilzomib at 15 and 20 mg/m^2, systemic exposure (AUC) and half-life were similar on Days 1 and 15 or 16 of Cycle 1, suggesting there was no systemic carfilzomib accumulation.

Following a 30-minute infusion of the 56 mg/m^2 dose, the mean (CV%) AUC of 948 ng•hr/mL (34%) was approximately twice that observed following a 2- to 10-minute infusion at the 27 mg/m^2 dose with a mean (CV%) of 379 ng•hr/mL (25%). The mean (CV%) C_{max} of 2079 ng/mL (44%) following a 30-minute infusion of the 56 mg/m^2 dose was

lower compared to that of 27 mg/m^2 over the 2- to 10-minute infusion with a mean (CV%) of 4232 ng/mL (49%).

At doses between 20 and 56 mg/m^2, there was a dose-dependent increase in exposure at either infusion duration.

Distribution: The mean steady-state volume of distribution of a 20 mg/m^2 dose of carfilzomib was 28 L. When tested *in vitro*, the binding of carfilzomib to human plasma proteins averaged 97% over the concentration range of 0.4 to 4 micromolar.

Metabolism: Carfilzomib was rapidly and extensively metabolized. The predominant metabolites measured in human plasma and urine, and generated *in vitro* by human hepatocytes, were peptide fragments and the diol of carfilzomib, suggesting that peptidase cleavage and epoxide hydrolysis were the principal pathways of metabolism. Cytochrome P450-mediated mechanisms played a minor role in overall carfilzomib metabolism. The metabolites have no known biologic activity.

Elimination: Following intravenous administration of doses ≥ 15 mg/m^2, carfilzomib was rapidly cleared from the systemic circulation with a half-life of ≤ 1 hour on Day 1 of Cycle 1. The systemic clearance ranged from 151 to 263 L/hour, and exceeded hepatic blood flow, suggesting that carfilzomib was largely cleared extrahepatically. In 24 hours, approximately 25% of the administered dose of carfilzomib was excreted in urine as metabolites. Urinary and fecal excretion of the parent compound was negligible (0.3% of total dose).

Specific Populations

Age, Gender, and Race: Clinically significant differences were not observed in the pharmacokinetics of carfilzomib based on age (35-88 years), gender, and race.

Hepatic Impairment: The pharmacokinetics of carfilzomib was studied in patients with relapsed or progressive advanced malignancies with mild (bilirubin > 1 to 1.5×ULN or AST > ULN) or moderate (bilirubin > 1.5 to 3×ULN) chronic hepatic impairment relative to those with normal hepatic function.

Compared to patients with normal hepatic function, patients with mild and moderate hepatic impairment had approximately 50% higher carfilzomib AUC. The pharmacokinetics of carfilzomib has not been evaluated in patients with severe hepatic impairment (bilirubin > 3×ULN and any AST).

Renal Impairment: The pharmacokinetics of carfilzomib was studied in relapsed multiple myeloma patients with normal renal function; mild, moderate or severe renal impairment; and patients with ESRD requiring hemodialysis. Exposures of carfilzomib (AUC and C_{max}) in patients with mild, moderate, and severe renal impairment were similar to those with normal renal function. Relative to patients with normal renal function, ESRD patients on hemodialysis showed 33% higher carfilzomib AUC. No starting dose adjustment is required in patients with baseline renal impairment.

Drug Interactions

Carfilzomib is primarily metabolized via peptidase and epoxide hydrolase activities, and as a result, the pharmacokinetic profile of carfilzomib is unlikely to be affected by concomitant administration of cytochrome P450 inhibitors and inducers. Carfilzomib is not expected to influence exposure of other drugs.

Cytochrome P450: In an *in vitro* study using human liver microsomes, carfilzomib showed modest direct (Ki = 1.7 micromolar) and time-dependent inhibition (Ki = 11 micromolar) of human cytochrome CYP3A4/5. *In vitro* studies indicated that carfilzomib did not induce human CYP1A2 and CYP3A4 in cultured fresh human hepatocytes. Cytochrome P450-mediated mechanisms play a minor role in the overall metabolism of carfilzomib. A clinical trial of 17 patients using oral midazolam as a CYP3A probe demonstrated that the pharmacokinetics of midazolam were unaffected by concomitant carfilzomib administration. Kyprolis is not expected to inhibit CYP3A4/5 activities and/or affect the exposure to CYP3A4/5 substrates.

P-gp: Carfilzomib is a P-glycoprotein (P-gp) substrate. *In vitro*, carfilzomib inhibited the efflux transport of P-gp substrate digoxin by 25% in a Caco-2 monolayer system. However,

given that Kyprolis is administered intravenously and is extensively metabolized, the pharmacokinetics of Kyprolis is unlikely to be affected by P-gp inhibitors or inducers.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been conducted with carfilzomib.

Carfilzomib was clastogenic in the *in vitro* chromosomal aberration test in peripheral blood lymphocytes. Carfilzomib was not mutagenic in the *in vitro* bacterial reverse mutation (Ames) test and was not clastogenic in the *in vivo* mouse bone marrow micronucleus assay.

Fertility studies with carfilzomib have not been conducted. No effects on reproductive tissues were noted during 28-day repeat-dose rat and monkey toxicity studies or in 6-month rat and 9-month monkey chronic toxicity studies.

13.2 Animal Toxicology and/or Pharmacology

Monkeys administered a single bolus intravenous dose of carfilzomib at 3 mg/kg (approximately 1.3 times recommended dose in humans of 27 mg/m^2 based on body surface area) experienced hypotension, increased heart rate, and increased serum levels of troponin-T. The repeated bolus intravenous administration of carfilzomib at ≥ 2 mg/kg/dose in rats and 2 mg/kg/dose in monkeys using dosing schedules similar to those used clinically resulted in mortalities that were due to toxicities occurring in the cardiovascular (cardiac failure, cardiac fibrosis, pericardial fluid accumulation, cardiac hemorrhage/degeneration), gastrointestinal (necrosis/hemorrhage), renal (glomerulonephropathy, tubular necrosis, dysfunction), and pulmonary (hemorrhage/inflammation) systems. The dose of 2 mg/kg/dose in rats is approximately half the recommended dose in humans of 27 mg/m^2 based on body surface area. The dose of 2 mg/kg/dose in monkeys is approximately equivalent to the recommended dose in humans based on body surface area.

14 CLINICAL STUDIES

14.1 In Combination with Lenalidomide and Dexamethasone for the Treatment of Patients with Relapsed or Refractory Multiple Myeloma (Study 1)

Study 1 was a randomized, open-label, multicenter superiority trial which evaluated the combination of Kyprolis with lenalidomide and dexamethasone (KRd) *versus* lenalidomide and dexamethasone alone (Rd) in patients with relapsed or refractory multiple myeloma who had received 1 to 3 lines of therapy (A line of therapy is a planned course of treatment [including sequential induction, transplantation, consolidation, and/or maintenance] without an interruption for lack of efficacy, such as for relapse or progressive disease). Patients who had the following were excluded from the trial: refractory to bortezomib in the most recent regimen, refractory to lenalidomide and dexamethasone in the most recent regimen, not responding to any prior regimen, creatinine clearance < 50 mL/min, ALT/AST > 3.5 × ULN and bilirubin > 2 × ULN, New York Heart Association Class III to IV congestive heart failure, or myocardial infarction within the last 4 months. In the KRd arm, Kyprolis was evaluated at a starting dose of 20 mg/m^2, which was increased to 27 mg/m^2 on Cycle 1, Day 8 onward. Kyprolis was administered as a 10-minute infusion on Days 1, 2, 8, 9, 15, and 16 of each 28-day cycle for Cycle 1 through 12. Kyprolis was dosed on Days 1, 2, 15, and 16 of each 28-day cycle from Cycle 13 through 18. Dexamethasone 40 mg was administered orally or intravenously on Days 1, 8, 15 and 22 of each cycle. Lenalidomide was given 25 mg orally on Days 1 to 21 of each 28-day cycle. The Rd treatment arm had the same regimen for lenalidomide and dexamethasone as the KRd treatment arm. Kyprolis was administered for a maximum of 18 cycles unless discontinued early for disease progression or unacceptable toxicity. Lenalidomide and dexamethasone administration could continue until progression or unacceptable toxicity. Concurrent use of thromboprophylaxis and a proton pump inhibitor were required for both arms, and antiviral prophylaxis was required for the KRd arm.

The 792 patients in Study 1 were randomized 1:1 to the KRd or Rd arm. The demographics and baseline characteristics were well-balanced between the two arms (see Table 14). Only 53% of the patients had testing for genetic mutations; a high-risk genetic mutation was identified for 12% of patients in the KRd arm and in 13% in the Rd arm.

Table 14: Demographics and Baseline Characteristics in Study 1 (Combination Therapy for Relapsed or Refractory Multiple Myeloma)

Characteristic	KRd Combination Therapy	
	KRd Arm (N = 396)	Rd Arm (N = 396)
Age, Median, Years (min, max)	64 (38, 87)	65 (31, 91)
Age ≥ 75 Years, n (%)	43 (11)	53 (13)
Males, n (%)	215 (54)	232 (59)
Race, n (%)		
White	377 (95)	377 (95)
Black	12 (3)	11 (3)
Other or Not Reported	7 (2)	8 (2)
Number of Prior Regimens, n (%)		
1	184 (46)	157 (40)
2	120 (30)	139 (35)
3[a]	92 (23)	100 (25)
Prior Transplantation	217 (55)	229 (58)
ECOG Performance Status		
0	165 (42)	175 (44)
1	191 (48)	186 (47)
2	40 (10)	35 (9)
ISS Stage at Study Baseline, n (%)		
I	167 (42)	154 (39)
II	148 (37)	153 (39)
III	73 (18)	82 (21)
Unknown	8 (2)	7 (2)
CrCL, mL/min, Median (min, max)	79 (39, 212)	79 (30, 208)
30 to < 50, n (%)	19 (5)	32 (8)
50 to < 80, n (%)	185 (47)	170 (43)
Refractory to Last Therapy, n (%)	110 (28)	119 (30)
Refractory at Any Time to, n (%):		
Bortezomib	60 (15)	58 (15)
Lenalidomide	29 (7)	28 (7)
Bortezomib + immunomodulatory agent	24 (6)	27 (7)

ECOG = Eastern Cooperative Oncology Group; CrCL = creatinine clearance; IgG = immunoglobulin G; ISS = International Staging System; KRd = Kyprolis, lenalidomide, and dexamethasone; Rd = lenalidomide and dexamethasone

[a] Including 2 patients with 4 prior regimens.

Patients in the KRd arm demonstrated improved progression-free survival (PFS) compared with those in the Rd arm (HR = 0.69, with 2-sided P-value = 0.0001) as determined using standard International Myeloma Working Group (IMWG)/European Blood and Marrow Transplantation (EBMT) response criteria by an Independent Review Committee (IRC).

The median PFS was 26.3 months in the KRd arm *versus* 17.6 months in the Rd arm (see Table 15 and Figure 1).

The OS results were not significantly different at the interim analysis (Figure 2).

Table 15: Efficacy Outcomes in Study 1 (Combination Therapy for Relapsed or Refractory Multiple Myeloma)[a]

	Combination Therapy	
	KRd Arm (N = 396)	**Rd Arm (N = 396)**
PFS[b]		
Median[c], Months (95% CI)	26.3 (23.3, 30.5)	17.6 (15.0, 20.6)
HR (95% CI)[d]	0.69 (0.57, 0.83)	
P-value (2-sided)[e]	0.0001	
Overall Response, n (%)[b]	345 (87)	264 (67)
Response Category, n (%)		
sCR	56 (14)	17 (4)
CR	70 (18)	20 (5)
VGPR	151 (38)	123 (31)
PR	68 (17)	104 (26)

CI = confidence interval; CR = complete response; KRd = Kyprolis, lenalidomide, and dexamethasone; PFS = progression-free survival; Rd = lenalidomide and dexamethasone; sCR = stringent CR; VGPR = very good partial response

[a] Eligible patients had 1-3 prior lines of therapy.

[b] As determined by an Independent Review Committee.

[c] Based on Kaplan Meier estimates.

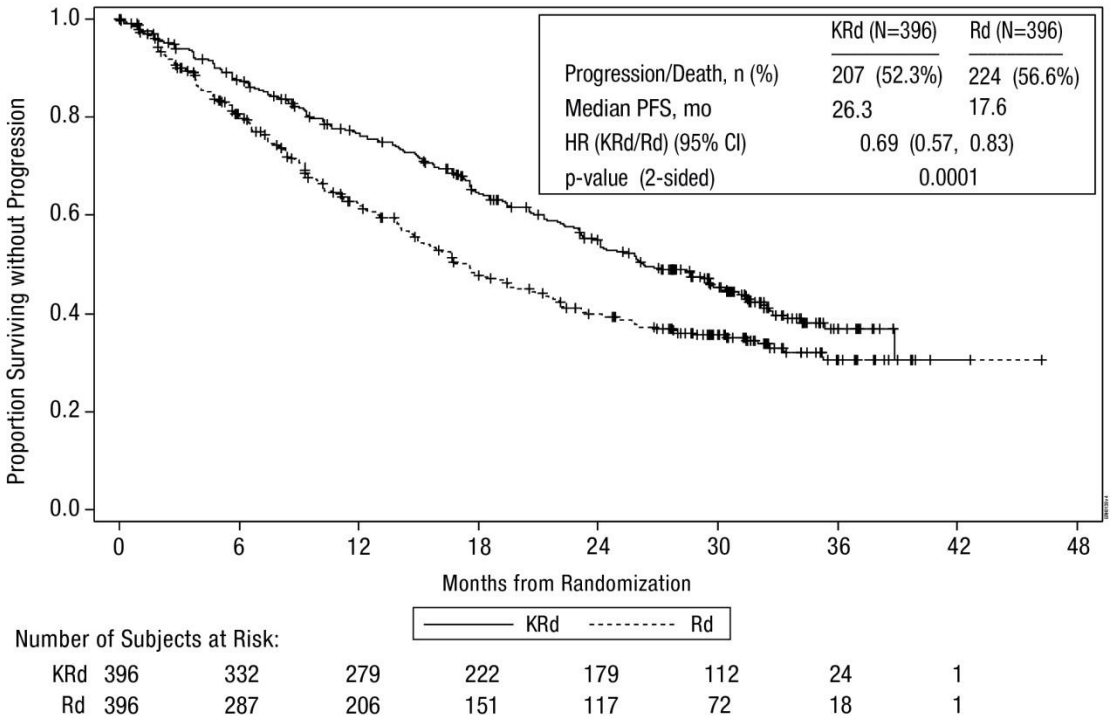
[d] Based on stratified Cox's model.

[e] The P-value was derived using stratified log-rank test.

The median duration of response (DOR) was 28.6 months (95% CI: 24.9, 31.3) for the 345 patients achieving a response in the KRd arm and 21.2 months (95% CI: 16.7, 25.8) for the 264 patients achieving a response in the Rd arm. The median time to response was

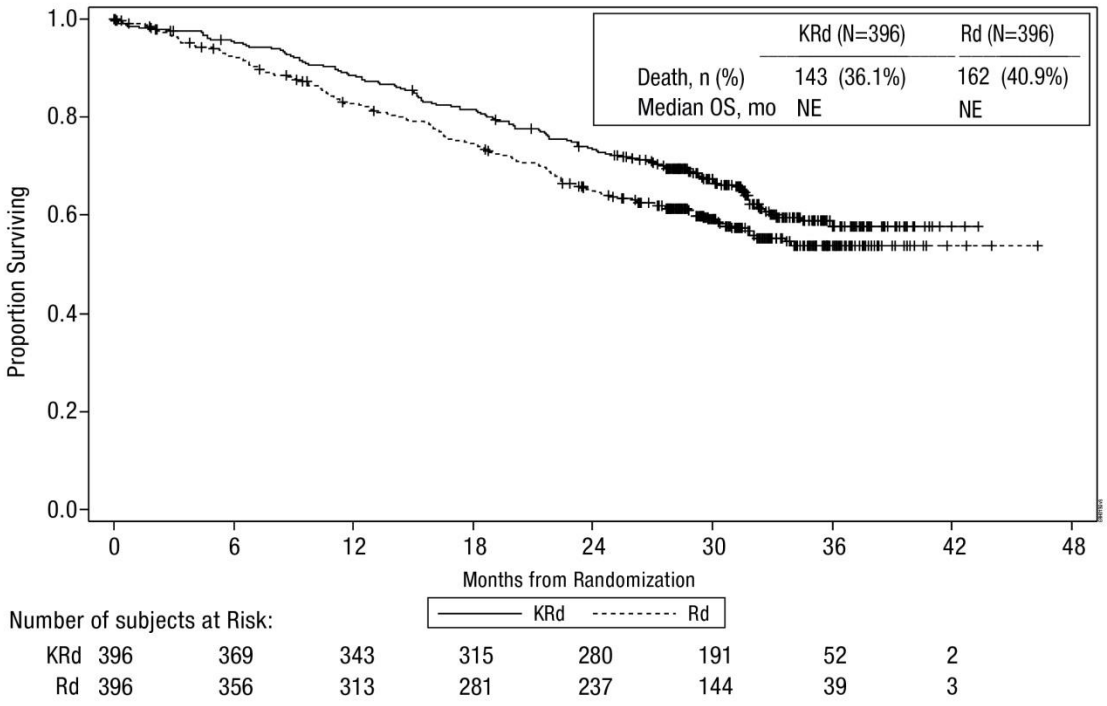
1 month (range 1 to 14 months) in the KRd arm and 1 month (range 1 to 16 months) in the Rd arm.

Figure 1: Kaplan-Meier Curve of Progression-Free Survival in Study 1



CI = confidence interval; EBMT = European Blood and Marrow Transplantation; HR = hazard ratio; IMWG = International Myeloma Working Group; KRd = Kyprolis, lenalidomide, and dexamethasone; mo = months; PFS = progression-free survival; Rd = lenalidomide and dexamethasone arm
Note: The response and PD outcomes were determined using standard objective IMWG/EBMT response criteria.

Figure 2: Kaplan-Meier Curve of Interim Overall Survival in Study 1



KRd = Kyprolis, lenalidomide, and dexamethasone; NE = not estimable; OS = overall survival; PFS = progression-free survival; Rd = lenalidomide and dexamethasone arm

Note: The interim OS analysis did not meet the protocol-specified early stopping boundary for OS.

14.2 In Combination with Dexamethasone for the Treatment of Patients with Relapsed or Refractory Multiple Myeloma (Study 2)

Study 2 was a randomized, open-label, multicenter superiority trial of Kyprolis plus dexamethasone (Kd) *versus* bortezomib plus dexamethasone (Vd) in patients with relapsed or refractory multiple myeloma who had received 1 to 3 lines of therapy. A total of 929 patients were enrolled and randomized (464 in the Kd arm; 465 in the Vd arm). Randomization was stratified by prior proteasome inhibitor therapy (yes *versus* no), prior lines of therapy (1 *versus* 2 or 3), current International Staging System stage (1 *versus* 2 or 3), and planned route of bortezomib administration. Patients were excluded if they had less than PR to all prior regimens; creatinine clearance < 15 mL/min; hepatic transaminases ≥ 3 × ULN; or left-ventricular ejection fraction < 40% or other significant cardiac conditions. This trial evaluated Kyprolis at a starting dose of 20 mg/m^2, which was increased to 56 mg/m^2 on Cycle 1, Day 8 onward. Kyprolis was administered twice weekly as a 30-minute infusion on

Days 1, 2, 8, 9, 15, and 16 of each 28-day cycle. Dexamethasone 20 mg was administered orally or intravenously on Days 1, 2, 8, 9, 15, 16, 22, and 23 of each cycle. In the Vd arm, bortezomib was dosed at 1.3 mg/m^2 intravenously or subcutaneously on Days 1, 4, 8, and 11 of a 21-day cycle, and dexamethasone 20 mg was administered orally or intravenously on Days 1, 2, 4, 5, 8, 9, 11, and 12 of each cycle. Concurrent use of thromboprophylaxis was optional, and prophylaxis with an antiviral agent and proton pump inhibitor was required. Of the 465 patients in the Vd arm, 381 received bortezomib subcutaneously. Treatment continued until disease progression or unacceptable toxicity.

The demographics and baseline characteristics are summarized in Table 16.

Table 16: Demographics and Baseline Characteristics in Study 2 (Combination Therapy for Relapsed or Refractory Multiple Myeloma)

Characteristics	Kd Arm (N = 464)	Vd Arm (N = 465)
Age, Years		
Median (min, max)	65 (35, 89)	65 (30, 88)
< 65, n (%)	223 (48)	210 (45)
65–74, n (%)	164 (35)	189 (41)
≥ 75, n (%)	77 (17)	66 (14)
Sex, n (%)		
Female	224 (48)	236 (51)
Male	240 (52)	229 (49)
Race, n (%)		
White	348 (75)	353 (76)
Black	8 (2)	9 (2)
Asian	56 (12)	57 (12)
Other or Not Reported	52 (11)	46 (10)
ECOG Performance Status, n (%)		
0	221 (48)	232 (50)
1	211 (46)	203 (44)
2	32 (7)	30 (6)
Creatinine Clearance (mL/min)		
Median (min, max)	73 (14, 185)	72 (12, 208)
< 30, n (%)	28 (6)	28 (6)
30 – < 50, n (%)	57 (12)	71 (15)

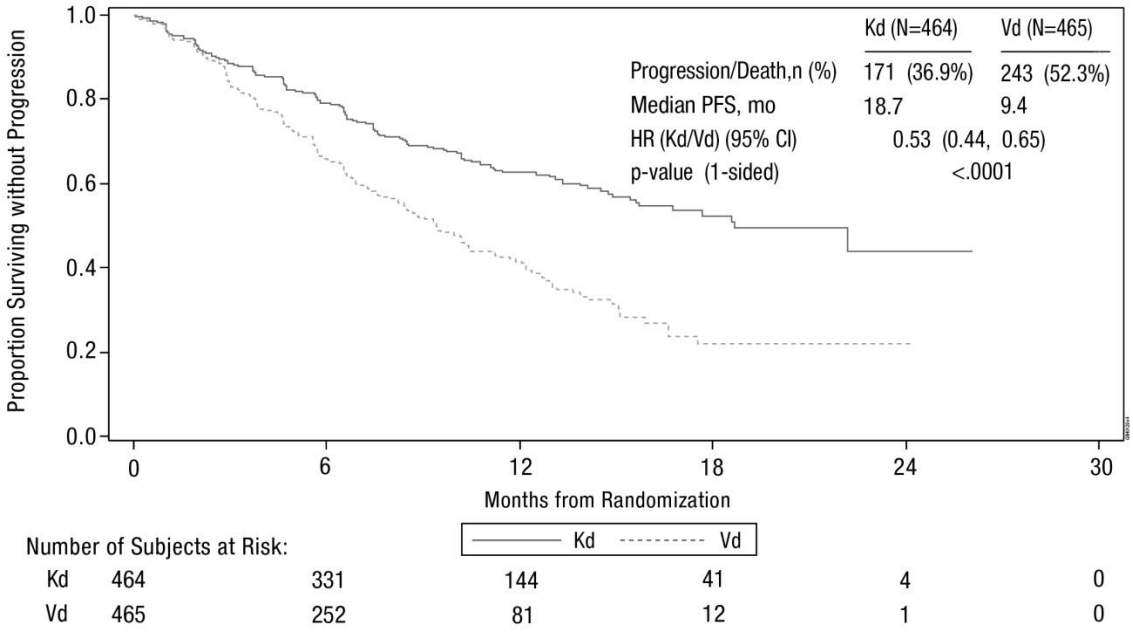
50 – < 80, n (%)	186 (40)	177 (38)
≥ 80, n (%)	193 (42)	189 (41)
FISH, n (%)		
High-risk	97 (21)	113 (24)
Standard-risk	284 (61)	291 (63)
Unknown-risk	83 (18)	61 (13)
ISS Stage at Study Baseline, n (%)		
ISS I	212 (46)	205 (44)
ISS II	138 (30)	151 (33)
ISS III	114 (25)	109 (23)
Number of Prior Regimens		
1	232 (50)	232 (50)
2	157 (34)	145 (31)
3	75 (16)	87 (19)
4	0 (0)	1 (0)
Prior Therapies, n (%)	464 (100)	465 (100)
Bortezomib	250 (54)	252 (54)
Transplant for Multiple Myeloma	266 (57)	272 (59)
Thalidomide	211 (46)	247 (53)
Lenalidomide	177 (38)	177 (38)
Bortezomib + immunomodulatory agent	158 (34)	167 (36)
Refractory to last prior therapy, n (%)[a]	184 (40)	188 (40)

ECOG = Eastern Cooperative Oncology Group; FISH = Fluorescence in situ hybridization; ISS = International Staging System; Kd = Kyprolis plus dexamethasone; Vd = bortezomib and dexamethasone

[a] Refractory = disease not achieving a minimal response or better, progressing during therapy, or progressing within 60 days after completion of therapy.

The efficacy of Kyprolis was evaluated by PFS as determined by an IRC using IMWG response criteria. The trial showed a median PFS of 18.7 months in the Kd arm *versus* 9.4 months in the Vd arm (see Table 17 and Figure 3).

Figure 3: Kaplan-Meier Plot of Progression-Free Survival in Study 2



HR = hazard ratio; Kd = Kyprolis plus dexamethasone; PFS = progression-free survival; Vd = bortezomib and dexamethasone

Other endpoints included OS and overall response rate (ORR). At the time of analysis, OS data were not mature. ORR was 77% for patients in the Kd arm and 63% for patients in the Vd arm (see Table 17).

Table 17: Summary of Key Results in Study 2 (Intent-to-Treat Population)[a]

	Kd Arm (N = 464)	**Vd Arm (N = 465)**
PFS[b]		
Median[c], Months (95% CI)	18.7 (15.6, —)	9.4 (8.4, 10.4)
Hazard Ratio (Kd/Vd) (95% CI)[d]	0.53 (0.44, 0.65)	
P-value (1-sided)[e]	< 0.0001	
Overall Response[b]		
N with Response	357	291
ORR (%) (95% CI)[f]	77 (73, 81)	63 (58, 67)
P-value (1-sided)[g]	< 0.0001	
Response Category, n (%)		
sCR	8 (2)	9 (2)

CR	50 (11)	20 (4)
VGPR	194 (42)	104 (22)
PR[h]	105 (23)	158 (34)

CI = confidence interval; CR = complete response; Kd = Kyprolis and dexamethasone; ORR = overall response rate; PFS = progression-free survival; sCR = stringent CR; Vd = bortezomib and dexamethasone; VGPR = very good partial response

[a] Eligible patients had 1-3 prior lines of therapy.
[b] PFS and ORR were determined by an Independent Review Committee.
[c] Based on Kaplan Meier estimates.
[d] Based on a stratified Cox's model.
[e] The P-value was derived using stratified log-rank test.
[f] Exact confidence interval.
[g] The P-value was derived using Cochran Mantel Haenszel test.
[h] Includes one patient in each arm with a confirmed PR which may not have been the best response.

The median DOR in subjects achieving PR or better was 21.3 months (95% CI: 21.3, not estimable) in the Kd arm and 10.4 months (95% CI: 9.3, 13.8) in the Vd arm. The median time to response was 1 month (range < 1 to 8 months) in both arms.

14.3 Monotherapy for the Treatment of Patients with Relapsed or Refractory Multiple Myeloma (Study 3, Study 4, and Study 5)

Study 3

Study 3 was a multicenter, open-label, dose escalation, single-arm trial that evaluated the safety of carfilzomib monotherapy as a 30-minute infusion in patients with relapsed or refractory multiple myeloma after 2 or more lines of therapy. Patients were excluded if they had a creatinine clearance < 20 mL/min; ALT ≥ 3 × upper limit of normal (ULN), bilirubin ≥ 1.5 × ULN; New York Heart Association class III or IV congestive heart failure; or other significant cardiac conditions. A total of 24 subjects with multiple myeloma were enrolled at the maximum tolerated dose level of 20/56 mg/m^2. Carfilzomib was administered twice-weekly for 3 consecutive weeks (Days 1, 2, 8, 9, 15, and 16) of a 28-day cycle. In Cycle 13 onward, the Day 8 and 9 carfilzomib doses could be omitted. Patients received carfilzomib at a starting dose of 20 mg/m^2 on Days 1 and 2 of Cycle 1, which was increased to 56 mg/m^2 for all subsequent doses. Dexamethasone 8 mg orally or intravenously was required prior to each carfilzomib dose in Cycle 1 and was optional in subsequent cycles. Treatment was continued until disease progression or unacceptable toxicity.

Efficacy was evaluated by ORR and DOR. ORR by investigator assessment was 50% (95% CI: 29, 71) per IMWG criteria (see Table 18). The median DOR in subjects who achieved a PR or better was 8.0 months (Range: 1.4, 32.5).

Table 18: Response Categories in Study 3 (20/56 mg/m^2 Monotherapy Regimen)

Characteristic	Study Patients[a] n (%)
Number of Patients (%)	24 (100)
Overall Response[b]	12 (50)
95% CI[c]	(29, 71)
Response Category	
sCR	1 (4)
CR	0 (0)
VGPR	4 (17)
PR	7 (29)

sCR = stringent complete response; VGPR = very good partial response

[a] Eligible patients had 2 or more prior lines of therapy.

[b] Per investigator assessment.

[c] Exact confidence interval.

Study 4

Study 4 was a single-arm, multicenter clinical trial of Kyprolis monotherapy by up to 10-minute infusion. Eligible patients were those with relapsed and refractory multiple myeloma who had received at least two prior therapies (including bortezomib and thalidomide and/or lenalidomide) and had ≤ 25% response to the most recent therapy or had disease progression during or within 60 days of the most recent therapy. Patients were excluded from the trial if they were refractory to all prior therapies or had a total bilirubin ≥ 2 × ULN; creatinine clearance < 30 mL/min; New York Heart Association Class III to IV congestive heart failure; symptomatic cardiac ischemia; myocardial infarction within the last 6 months; peripheral neuropathy Grade 3 or 4, or peripheral neuropathy Grade 2 with pain; active infections requiring treatment; or pleural effusion.

Kyprolis was administered intravenously up to 10 minutes on two consecutive days each week for three weeks, followed by a 12-day rest period (28-day treatment cycle), until

disease progression, unacceptable toxicity, or for a maximum of 12 cycles. Patients received 20 mg/m^2 at each dose in Cycle 1, and 27 mg/m^2 in subsequent cycles. Dexamethasone 4 mg orally or intravenously was administered prior to Kyprolis doses in the first and second cycles.

A total of 266 patients were enrolled. Baseline patient and disease characteristics are summarized in Table 19.

Table 19: Demographics and Baseline Characteristics in Study 4 (20/27 mg/m^2 Monotherapy Regimen for Relapsed and Refractory Multiple Myeloma)

Characteristic	Number of Patients (%)
Patient Characteristics	
Enrolled patients	266 (100)
Median age, years (range)	63 (37, 87)
Age group, < 65 / ≥ 65 (years)	146 (55) / 120 (45)
Gender (male / female)	155 (58) / 111 (42)
Race (White / Black / Asian / Other)	190 (71) / 53 (20) / 6 (2) / 17 (6)
Disease Characteristics	
Number of Prior Regimens (median)	5[a]
Prior Transplantation	198 (74)
Refractory Status to Most Recent Therapy[b]	
Refractory: Progression during most recent therapy	198 (74)
Refractory: Progression within 60 days after completion of most recent therapy	38 (14)
Refractory: ≤ 25% response to treatment	16 (6)
Relapsed: Progression after 60 days post treatment	14 (5)
Years since diagnosis, median (range)	5.4 (0.5, 22.3)
Plasma cell involvement (< 50% / ≥ 50% / unknown)	143 (54) / 106 (40) / 17 (6)
ISS Stage at Study Baseline	
I	76 (29)
II	102 (38)
III	81 (31)
Unknown	7 (3)
Cytogenetics or FISH analyses	
Normal/Favorable	159 (60)
Poor Prognosis	75 (28)
Unknown	32 (12)
Creatinine clearance < 30 mL/min	6 (2)

FISH = Fluorescence in situ hybridization; ISS = International Staging System

[a] Range: 1, 20.

[b] Categories for refractory status are derived by programmatic assessment using available laboratory data.

Efficacy was evaluated by ORR as determined by IRC assessment using IMWG criteria. The median number of cycles started was four. The ORR (PR or better) was 23% (95% CI: 18, 28) (see Table 20). The median DOR was 7.8 months (95%CI: 5.6, 9.2).

Table 20: Response Categories in Study 4 (20/27 mg/m^2 Monotherapy Regimen)

Characteristic	Study Patients[a] n (%)
Number of Patients (%)	266 (100)
Overall Response[b]	61 (23)
95% CI[c]	(18, 28)
Response Category	
CR	1 (< 1)
VGPR	13 (5)
PR	47 (18)

CR = complete response; VGPR = very good partial response

[a] Eligible patients had 2 or more prior lines of therapy and were refractory to the last regimen.

[b] As assessed by the Independent Review Committee.

[c] Exact confidence interval.

Study 5

Study 5 was a single-arm, multicenter clinical trial of Kyprolis monotherapy by up to 10-minute infusion. Eligible patients were those with relapsed or refractory multiple myeloma who were bortezomib-naïve, had received one to three prior lines of therapy and had ≤ 25% response or progression during therapy or within 60 days after completion of therapy. Patients were excluded from the trial if they were refractory to standard first-line therapy or had a total bilirubin ≥ 2 × ULN; creatinine clearance < 30 mL/min; New York Heart Association Class III to IV congestive heart failure; symptomatic cardiac ischemia; myocardial infarction within the last 6 months; active infections requiring treatment; or pleural effusion.

Kyprolis was administered intravenously up to 10 minutes on two consecutive days each week for three weeks, followed by a 12-day rest period (28-day treatment cycle), until disease progression, unacceptable toxicity, or for a maximum of 12 cycles. Patients received 20 mg/m^2 at each dose in Cycle 1, and 27 mg/m^2 in subsequent cycles. Dexamethasone 4 mg orally or intravenously was administered prior to Kyprolis doses in the first and second cycles.

A total of 70 patients were treated with this 20/27 mg/m^2 regimen. Baseline patient and disease characteristics are summarized in Table 21.

Table 21: Demographics and Baseline Characteristics in Study 5 (20/27 mg/m^2 Monotherapy Regimen for Relapsed or Refractory Multiple Myeloma)

Characteristic	Number of Patients (%)
Patient Characteristics	
Enrolled patients	70 (100)
Median age, years (range)	66 (45, 85)
Age group, < 65 / ≥ 65 (years)	31 (44) / 39 (56)
Gender (male / female)	44 (63) / 26 (37)
Race (White / Black / Asian / Hispanic / Other)	52 (74) / 12 (17) / 3 (4) / 2 (3) / 1 (1)
Disease Characteristics	
Number of Prior Regimens (median)	2[a]
Prior Transplantation	47 (67)
Refractory Status to Most Recent Therapy[b]	
Refractory: Progression during most recent therapy	28 (40)
Refractory: Progression within 60 days after completion of most recent therapy	7 (10)
Refractory: ≤ 25% response to treatment	10 (14)
Relapsed: Progression after 60 days post treatment	23 (33)
No Signs of Progression	2 (3)
Years since diagnosis, median (range)	3.6 (0.7, 12.2)
Plasma cell involvement (< 50% / ≥ 50% / unknown)	54 (77) / 14 (20) / 1 (1)
ISS Stage at Study Baseline, n (%)	
I	28 (40)
II	25 (36)
III	16 (23)
Unknown	1 (1)
Cytogenetics or FISH analyses	
Normal/Favorable	57 (81)

Poor Prognosis	10 (14)
Unknown	3 (4)
Creatinine clearance < 30 mL/min	1 (1)

FISH = Fluorescence in situ hybridization; ISS = International Staging System

[a] Range: 1, 4.

[b] Categories for refractory status are derived by programmatic assessment using available laboratory data.

Efficacy was evaluated by ORR as determined by IRC assessment using IMWG criteria. The median number of cycles started was seven. The ORR (PR or better) was 50% (95% CI: 38, 62) (see Table 22). The median DOR was not reached.

Table 22: Response Categories in Study 5 (20/27 mg/m^2 Monotherapy Regimen)

Characteristic	Study Patients[a] n (%)
Number of Patients (%)	70 (100)
Overall Response[b]	35 (50)
95% CI[c]	(38 - 62)
Response Category	
CR	1 (1)
VGPR	18 (26)
PR	16 (23)

CR = complete response; VGPR = very good partial response

[a] Eligible patients had 1-3 prior lines of therapy and were refractory to the last regimen.

[b] As assessed by an Independent Review Committee.

[c] Exact confidence interval.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Kyprolis (carfilzomib) is supplied as:

- An individually packaged single-dose vial containing 30 mg of carfilzomib as a white to off-white lyophilized cake or powder: NDC 76075-102-01.
- An individually packaged single-dose vial containing 60 mg of carfilzomib as a white to off-white lyophilized cake or powder: NDC 76075-101-01.

16.2 Storage and Handling

Unopened vials should be stored refrigerated (2°C to 8°C; 36°F to 46°F). Retain in original package to protect from light.

17 PATIENT COUNSELING INFORMATION

Discuss the following with patients prior to treatment with Kyprolis:

Cardiac Toxicities: Advise patients of the risks and symptoms of cardiac failure and ischemia *[see Warnings and Precautions (5.1)]*.

Dehydration: Counsel patients to avoid dehydration, since patients receiving Kyprolis therapy may experience vomiting and/or diarrhea. Instruct patients to seek medical advice if they experience symptoms of dehydration *[see Warnings and Precautions (5.3)]*.

Respiratory: Advise patients that they may experience cough or shortness of breath (dyspnea) during treatment with Kyprolis. This most commonly occurs within a day of dosing. Advise patients to contact their physician if they experience shortness of breath *[see Warnings and Precautions (5.6)]*.

Venous Thrombosis: Inform patients of the risk of venous thromboembolism and discuss the options for prophylaxis. Advise patients to seek immediate medical attention for symptoms of venous thrombosis or embolism *[see Warnings and Precautions (5.8)]*.

Infusion Reactions: Advise patients of the risk of infusion reactions, and discuss the common signs and symptoms of infusion reactions with the patients *[see Warnings and Precautions (5.9)]*.

Bleeding: Inform patients that they may bruise or bleed more easily or that it may take longer to stop bleeding and to report to their physician any prolonged, unusual or excessive bleeding. Instruct patients on the signs of occult bleeding *[see Warnings and Precautions (5.10)]*.

Hepatic: Inform patients of the risk of developing hepatic failure. Advise patients to contact their physician if they experience jaundice *[see Warnings and Precautions (5.12)]*.

Other: Inform patients to contact their physician if they experience neurologic symptoms such as headaches, confusion, seizures, or visual loss *[see Adverse Reactions (6) and Warnings and Precautions (5)]*.

Driving/Operating Machines: Advise patients that Kyprolis may cause fatigue, dizziness, fainting, and/or drop in blood pressure. Advise patients not to drive or operate machinery if they experience any of these symptoms *[see Adverse Reactions (6.1)]*.

Pregnancy/Nursing: Counsel females of reproductive potential to use effective contraceptive measures to prevent pregnancy during and for at least 30 days after treatment with Kyprolis. Counsel males of reproductive potential to use effective contraceptive measures to prevent pregnancy during and for at least 90 days after treatment with Kyprolis. Advise the patient to contact their physician immediately if pregnancy does occur during these times. Advise patients not to take Kyprolis treatment while pregnant or breastfeeding. If a patient wishes to restart breastfeeding after treatment, advise her to discuss the appropriate timing with her physician *[see Warnings and Precautions (5.15) and Use in Specific Populations (8.1, 8.3)]*.

Concomitant Medications: Advise patients to discuss with their physician any medication they are currently taking prior to starting treatment with Kyprolis, or prior to starting any new medication(s) during treatment with Kyprolis.

AMGEN®

Kyprolis® (carfilzomib)

Manufactured for:
Onyx Pharmaceuticals, Inc.
Thousand Oaks, CA 91320-1799 U.S.A
Patent: http://pat.amgen.com/kyprolis

1XXXXXX – v14

Impavido® *(miltefosine) capsules*

Indication(s)	Treatment of: visceral leishmaniasis due to *L. donovani*; cutaneous leishmaniasis due to *L. braziliensis, L guyanensis* and *L panamensis*; mucosal leishmanisis due to *L. braziliensis* in adults and adolescents ≥ 12 years
FDA Approval	March 19, 2014
Treatment Comparisons for Indications	Antiparisitic azole agents (ketoconazole), parenteral antiparisitic agents
Place in Therapy	Oral alkylphosphocholine agent with activity against leishamaniasis
Dosage and Administration	***Strengths Available:*** 50 mg ***Dosage Frequency:*** 50mg given up to 3 times daily based on patient weight
Safety	***Contraindications:*** Hypersensitivity to miltefosine products or other ingredients in IMPAVIDO; Use in pregnancy; Use in Sjögren-Larsson syndrome ***Warnings:*** Fertility effects, renal toxicity, Stevens-Johnson syndrome, hepatic effects and GI effects ***Drug Interactions:*** No known significant interactions
Use in Specific Populations	***Pregnancy:*** category D, may cause fetal harm, do not administer ***Nursing:*** Breastfeeding not recommended ***Pediatric:*** Safety and efficacy in patients younger than 12years of age have not been established ***Geriatric:*** has not been studied in the geriatric population
Formulary Considerations	***Proposed Formulary Addition*:** Tier 3 No generic on the market, limited oral options for indication
Utilization	Previously approved as nonformulary; only available via approved formulary exceptions
Conclusion	Accept formulary addition as proposed

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use IMPAVIDO safely and effectively. See full prescribing information for IMPAVIDO.

IMPAVIDO (miltefosine) capsules, for oral use
Initial U.S. Approval: 2014

WARNING: EMBRYO-FETAL TOXICITY

See full prescribing information for complete boxed warning.

IMPAVIDO may cause fetal harm. Fetal death and teratogenicity, occurred in animals administered miltefosine at doses lower than the recommended human dose. Do not administer IMPAVIDO to pregnant women. Obtain a serum or urine pregnancy test in females of reproductive potential prior to prescribing IMPAVIDO.
Advise females of reproductive potential to use effective contraception during therapy and for 5 months after therapy (4.1, 5.1, 8.1, 8.8, 13.1).

INDICATIONS AND USAGE

IMPAVIDO is an antileishmanial drug indicated in adults and adolescents ≥12 years of age weighing ≥30 kg (66 lbs) for treatment of:

- Visceral leishmaniasis due to *Leishmania donovani* (1).
- Cutaneous leishmaniasis due to *Leishmania braziliensis, Leishmania guyanensis,* and *Leishmania panamensis* (1).
- Mucosal leishmaniasis due to *Leishmania braziliensis* (1).

Limitations of use: *Leishmania* species evaluated in clinical trials were based on epidemiologic data. There may be geographic variation in the response of the same *Leishmania* species to IMPAVIDO (1, 14). The efficacy of IMPAVIDO in the treatment of other *Leishmania* species has not been evaluated.

DOSAGE AND ADMINISTRATION

Administer with food to ameliorate gastrointestinal adverse reactions.

- 30 to 44 kg: one 50 mg capsule twice daily for 28 consecutive days (2).
- 45 kg or greater: one 50 mg capsule three times daily for 28 consecutive days (2).

DOSAGE FORMS AND STRENGTHS

Each IMPAVIDO capsule for oral use contains 50 mg miltefosine (3).

CONTRAINDICATIONS

- Pregnancy (4.1,8.1, 8.8, 13.1).
- Sjögren-Larsson-Syndrome (4.2, 12.3).
- Hypersensitivity to miltefosine or any of its excipients (4.3).

WARNINGS AND PRECAUTIONS

- Embryo-Fetal Toxicity. Do not use in pregnant women. Obtain a urine or serum pregnancy test prior to initiation of therapy. Advise use of effective contraception in females of reproductive potential (Boxed Warning, 5.1, 8.1, 8.8, 13.1).
- Reproductive effects. Miltefosine caused testicular atrophy and impaired fertility in male rats and impaired fertility in female rats. Advise patients of reproductive toxicities in animal studies and that the potential effects on human fertility have not been adequately evaluated (13.1).
- Renal Effects. Monitor serum creatinine during therapy and for 4 weeks after end of therapy (5.3, 6.1).
- Hepatic Effects. Monitor transaminases and bilirubin during therapy (5.4, 6.1).
- Gastrointestinal Effects. Encourage fluid intake (5.5).
- Thrombocytopenia. Monitor platelet count during therapy for visceral leishmaniasis (5.6, 6.1).
- Absorption of Oral Contraceptives. Advise use of alternative method of contraception if vomiting and/or diarrhea occur (5.7).
- Stevens-Johnson syndrome. Discontinue IMPAVIDO (5.8).

ADVERSE REACTIONS

- Adverse reactions occurring in ≥2% of patients include nausea, vomiting, diarrhea, headache, decreased appetite, dizziness, abdominal pain, pruritus, somnolence, elevated transaminases, and elevated creatinine (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Profounda, Inc. at 1-866-588-5405 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- IMPAVIDO did not inhibit human cytochrome P450 enzymes in vitro.
- IMPAVIDO did not induce cytochrome 3A activity in rats(7, 12.3).

USE IN SPECIFIC POPULATIONS

- Pregnancy: IMPAVIDO should not be used during pregnancy. Obtain a urine or serum pregnancy test in females of reproductive potential prior to prescribing (4.1, 5.1, 8.1, 8.8, 13.1).
- Nursing Mothers: Discontinue drug or nursing depending on importance of drug to mother. Avoid breastfeeding for 5 months after IMPAVIDO therapy (8.3).
- Females and Males of Reproductive Potential: Advise females to use effective contraception during therapy and for 5 months after therapy. Advise patients of reproductive toxicities in animals, and that the potential for impaired fertility in humans has not been adequately evaluated (5.1, 5.2, 8.8).

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 10/2015

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: EMBRYO-FETAL TOXICITY

IMPAVIDO may cause fetal harm. Fetal death and teratogenicity occurred in animals administered miltefosine at doses lower than the recommended human dose. Do not administer IMPAVIDO to pregnant women. Obtain a serum or urine pregnancy test in females of reproductive potential prior to prescribing IMPAVIDO. Females of reproductive potential should be advised to use effective contraception during IMPAVIDO therapy and for 5 months after therapy *[see Contraindications (4.1), Warnings and Precautions (5.1), Use in Specific Populations (8.1, 8.8) and Nonclinical Toxicology (13.1)].*

1 INDICATIONS AND USAGE

IMPAVIDO (miltefosine) capsules are indicated in adults and adolescents ≥12 years of age weighing ≥ 30 kg for the treatment of:

- Visceral leishmaniasis caused by *Leishmania donovani [see Clinical Trials (14.1)]*.
- Cutaneous leishmaniasis caused by *Leishmania braziliensis*, *Leishmania guyanensis*, and *Leishmania panamensis [see Clinical Trials (14.2)]*.
- Mucosal leishmaniasis caused by *Leishmania braziliensis [see Clinical Trials (14.3)]*.

Limitations of Use:

- *Leishmania* species studied in clinical trials evaluating IMPAVIDO were based on epidemiologic data *[see Clinical Trials (14.1, 14.2)]*.
- There may be geographic variation in clinical response of the same *Leishmania* species to IMPAVIDO *[see Clinical Trials (14.1, 14.2)]*.
- The efficacy of IMPAVIDO in the treatment of other *Leishmania* species has not been evaluated.

2 DOSAGE AND ADMINISTRATION

The treatment duration is 28 consecutive days. Administer with food to ameliorate gastrointestinal adverse reactions.

Table 1: Miltefosine Dosage

Weight	Dosage and Administration
30 kg to 44 kg	One 50 mg capsule twice daily with food (breakfast and dinner)
45 kg or greater	One 50 mg capsule three times daily with food (breakfast, lunch, and dinner)

3 DOSAGE FORMS AND STRENGTHS

IMPAVIDO® (miltefosine) oral capsules are opaque, red, hard gelatin capsules with "PLB" imprinted on the capsule body and "MILT 50" imprinted on the cap using a white ink. Each capsule contains 50 mg miltefosine *[see Description (11), How Supplied/Storage and Handling (16)]*.

4 CONTRAINDICATIONS

4.1 Pregnancy

IMPAVIDO may cause fetal harm. IMPAVIDO is contraindicated in pregnant women. Obtain a urine or serum pregnancy test prior to prescribing IMPAVIDO *[see Boxed Warning and Use in Specific Populations (8.1)]*.

4.2 Sjögren-Larsson-Syndrome

IMPAVIDO is contraindicated in patients who have Sjögren-Larsson-Syndrome *[see Clinical Pharmacology (12.3)]*.

4.3 Hypersensitivity

IMPAVIDO is contraindicated in patients who are hypersensitive to miltefosine or any IMPAVIDO excipients.

5 WARNINGS AND PRECAUTIONS

5.1 Embryo-Fetal Toxicity

Miltefosine may cause fetal harm. Embryo-fetal toxicity, including death and teratogenicity, was observed in animals administered miltefosine prior to mating, during early pregnancy, and during organogenesis at doses lower than the maximum recommended human dose (MRHD). Do not use IMPAVIDO in pregnant women. Obtain a urine or serum pregnancy test prior to prescribing IMPAVIDO to females of reproductive potential. Advise females of reproductive potential to use effective contraception during IMPAVIDO therapy and for 5 months after completion of therapy *[see Boxed Warning, Contraindications (4.1) and Use in Specific Populations (8.1, 8.8)]*.

5.2 Reproductive Effects

Females

Miltefosine caused impaired fertility in rats and reversible follicular atresia and diestrus in dogs at doses approximately 1.0 and 0.2 times respectively the MRHD based on body surface area comparisons *[see Nonclinical Toxicology (13.1)]*. Effects on human female fertility have not been formally studied.

Males

Miltefosine caused reduced viable sperm counts and impaired fertility in rats at doses approximately 0.4 times the MRHD *[see Nonclinical Toxicology (13.1)]*. A higher dose in rats, approximately 1.0 times the MRHD, caused testicular atrophy and impaired fertility that did not fully reverse 10 weeks after drug administration ended.

Scrotal pain and decreased or absent ejaculation during therapy have been reported during IMPAVIDO therapy *[see Adverse Reactions (6.2)]*. The effects of IMPAVIDO on human male fertility have not been adequately studied.

Advise women and men of the animal fertility findings, and that the potential for impaired fertility with IMPAVIDO therapy in humans has not been adequately evaluated.

5.3 Renal Effects

Elevations of serum creatinine (Cr) were noted in clinical trials evaluating IMPAVIDO in the treatment of cutaneous, mucosal and visceral leishmaniasis. Monitor renal function weekly in patients receiving IMPAVIDO during therapy and for 4 weeks after end of therapy *[see Adverse Reactions (6.1)]*.

5.4 Hepatic Effects

Elevations in liver transaminases (ALT, AST) and bilirubin were noted in clinical trials evaluating IMPAVIDO in the treatment of visceral leishmaniasis. Monitor liver transaminases (ALT, AST) and bilirubin during therapy in patients receiving IMPAVIDO *[see Adverse Reactions (6.1)]*.

5.5 Gastrointestinal Effects

Vomiting and/or diarrhea commonly occur during IMPAVIDO administration and may result in volume depletion. Encourage fluid intake to avoid volume depletion *[see Adverse Reactions (6.1)]*.

5.6 Thrombocytopenia

Thrombocytopenia during therapy has been reported in patients treated for visceral leishmaniasis. Monitor platelet count during therapy for visceral leishmaniasis *[see Adverse Reactions (6.1, 6.2)]*.

5.7 Absorption of Oral Contraceptives

Vomiting and/or diarrhea occurring during IMPAVIDO therapy may affect the absorption of oral contraceptives, and therefore compromise their efficacy. If vomiting and/or diarrhea occur during IMPAVIDO therapy, advise females to use additional non-hormonal or alternative method(s) of effective contraception.

5.8 Stevens-Johnson Syndrome

Stevens-Johnson syndrome has been reported during IMPAVIDO therapy. Discontinue IMPAVIDO if an exfoliative or bullous rash is noted during therapy *[see Adverse Reactions (6.1)]*.

6 ADVERSE REACTIONS

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.

6.1 Clinical Trials Experience

Visceral Leishmaniasis

One Phase 3 trial was conducted in patients ≥ 12 years of age in India. Two-hundred and ninety-nine (299) patients (211 men and 88 women) received oral IMPAVIDO at a target dose of 2.5 mg/kg/day for 28 days (50 mg capsule once daily if weight was less than 25 kg and 50 mg capsule twice daily if weight was 25 kg or greater). Patients ranged between 12 and 64 years of age. Weight ranged between 15 and 67 kg (mean weight 38.6 kg) and BMI ranged between 8.2 and 24 (mean 16.1). Ninety-nine (99) patients received 1 mg/kg/day amphotericin B deoxycholate intravenously every other day for 15 doses. A statistically significant higher percentage of men received IMPAVIDO compared to amphotericin B.

Less than 1% of patients who received IMPAVIDO died (2/299) and no patient who received amphotericin B died. Serious adverse reactions were reported in 2% of IMPAVIDO recipients (6/299) and 1% of amphotericin B recipients (1/99). Approximately 3% of patients discontinued treatment in each treatment arm due to an adverse reaction. Serious adverse reactions and adverse reactions leading to drug discontinuation that were thought to be related or possibly related to IMPAVIDO included Stevens-Johnson syndrome, melena and thrombocytopenia, arthritis and skin rash, CTCAE[1] Grade 4 diarrhea (≥10 stools per day) and CTCAE Grade 4 hyperbilirubinemia (≥10x upper limit of normal ULN).

Table 2: Treatment Emergent Adverse Reactions Occurring in ≥2% of Visceral Leishmaniasis Patients Receiving IMPAVIDO

System Organ Class Preferred Term	IMPAVIDO N = 299	Amphotericin B Deoxycholate N = 99
Gastrointestinal Disorders		
Diarrhea	61 (20.4%)	6 (6.1%)
Vomiting	113 (37.8%)	20 (20.0%)

General Disorders		
Asthenia	19 (6.3%)	4 (4.0%)
Metabolism and Nutrition Disorders		
Decreased Appetite	69 (23.1%)	22 (22.2%)

In this study, creatinine (Cr) elevations ≥ 1.5 times above baseline occurred in approximately 10% of IMPAVIDO recipients and in 40% of amphotericin B recipients at the end of therapy. Ten percent of subjects in each arm had Cr elevations ≥1.5 times above baseline at 6 months follow up. No IMPAVIDO recipient discontinued therapy due to Cr elevation.

Elevations of transaminases during therapy occurred in up to half of IMPAVIDO recipients and up to a third of amphotericin B recipients. The elevations were mild (< 3x ULN) or moderate (3-5x ULN) in 94% and 6% respectively of IMPAVIDO-treated patients who experienced an elevation. No patient discontinued therapy due to elevations in transaminases.

At the end of therapy, 62% and 2.4% of IMPAVIDO recipients and 54% and 2% of amphotericin B recipients had platelet count < 150,000 and < 50,000 respectively.

Cutaneous Leishmaniasis

The efficacy of IMPAVIDO in the treatment of cutaneous leishmaniasis was evaluated in one placebo-controlled trial conducted in Colombia and Guatemala and in two comparative trials conducted in Bolivia and Brazil respectively. In the placebo-controlled trial, eighty-nine (89) patients ≥12 years of age received a target IMPAVIDO dose of 2.5 mg/kg/day for 28 days and forty-four (44) received placebo. In the comparative trials, one hundred and twenty (120) patients ≥12 years of age received a target IMPAVIDO dose of 2.5 mg/kg/day for 28 days and fifty eight (58) patients received 20 mg/kg/day pentavalent antimony (meglumine) parenterally for 20 days.

Table 3: Adverse Reactions Occurring in ≥2% of IMPAVIDO-Treated Patients ≥12 Years of Age with Cutaneous Leishmaniasis in the Placebo-Controlled Trial

System Organ Class **Preferred Term**	**IMPAVIDO** **N = 89**	**Placebo** **N = 44**
Ear and Labyrinth Disorders		
Motion Sickness	26 (29.2%)	10 (22.7%)
Gastrointestinal Disorders		
Abdominal Pain	10 (11.2%)	3 (6.8%)
Diarrhea	7 (7.9%)	2 (4.5%)
Nausea	32 (35.9%)	5 (11.1%)
Vomiting	4 (4.5%)	0
General and Administration Site Disorders		
Malaise	3 (3.4%)	1 (2.3%)
Pyrexia	5 (5.6%)	2 (4.5%)
Nervous System Disorders		
Dizziness	4 (4.5%)	0
Headache	25 (28.1%)	10 (22.7%)
Somnolence	3 (3.4%)	0
Skin and Subcutaneous Tissue Disorders		
Pruritus	4 (4.5%)	0

Table 4: Adverse Reactions Occurring in ≥2% of IMPAVIDO-Treated Patients ≥ 12 Years of Age with Cutaneous Leishmaniasis in Two Comparative Trials

System Organ Class Preferred Term	IMPAVIDO N = 120	Meglumine N = 58
Gastrointestinal Disorders		
Abdominal Pain	9 (7.5%)	3 (5.2%)
Diarrhea	18 (15.0%)	3 (5.2%)
Nausea	50 (41.7%)	3 (5.2%)
Vomiting	33 (27.5%)	0
Infections and Infestations		
Lymphangitis	7 (5.8%)	0
Metabolism and Nutrition Disorders		
Decreased Appetite	13 (10.8%)	4 (5.8%)
Nervous System Disorders		
Dizziness	15 (12.5%)	4 (6.9%)
Skin and Subcutaneous Tissue Disorders		
Pruritus	7 (5.8%)	0

In the placebo controlled trial, 12/89 (13.4%) IMPAVIDO subjects had Cr increases of 1.5-3 times above baseline, compared to 2/44 (4.5%) placebo subjects at end of therapy. In the comparative trial, a similar percentage of subjects who received IMPAVIDO or pentavalent antimony had Cr elevations above baseline at 3 and 6 months after therapy (approximately 5%). Approximately 25% of IMPAVIDO subjects and 11% of pentavalent antimony subjects had Cr elevations 1.5-3 times above baseline at the end of therapy in the two active controlled trials. The frequency of AST and ALT increase above upper limit of normal at end of therapy was similar in IMPAVIDO and placebo recipients (approximately 5%).

Other adverse events seen at <2% incidence in the IMPAVIDO group included anemia, lymphadenopathy, abdominal distension, constipation, dysphagia, flatulence, fatigue, malaise, abscess, cellulitis, ecthyma, paresthesia, testicular pain, testicular swelling, Stevens-Johnson syndrome, urticaria, rash, pyoderma.

---

1 Common Terminology Criteria for Adverse Events

6.2 Postmarketing Experience

The following adverse reactions have been identified during use of IMPAVIDO worldwide. 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.

Blood and Lymphatics Disorders: thrombocytopenia, agranulocytosis

Gastrointestinal Disorders: melena

General Disorders: generalized edema, peripheral edema

Hepatobiliary Disorders: jaundice

Nervous System Disorders: seizure

Reproductive System and Breast Disorders: scrotal pain, decreased ejaculate volume, absent ejaculation.

Vascular Disorders: epistaxis

7 DRUG INTERACTIONS

In vitro and animal metabolism studies showed that miltefosine did not markedly induce or inhibit the activity of the major human cytochrome P450 enzymes *[see Clinical Pharmacology (12.3)]*. The potential of miltefosine to interact with drug transporters has not been evaluated.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category D

Risk Summary

IMPAVIDO may cause fetal harm. Human pregnancy data are not available, however, embryo-fetal toxicity including death and teratogenicity, was observed in embryo-fetal studies in rats and rabbits administered oral miltefosine during organogenesis at doses that were respectively 0.06 and 0.2 times the maximum recommended human dose (MRHD), based on body surface area (BSA) comparison. Numerous visceral and skeletal fetal malformations were observed in a fertility study in female rats administered miltefosine prior to mating through day 7 of pregnancy at doses 0.3 times the MRHD. Do not administer IMPAVIDO to pregnant women.

Clinical Considerations

During pregnancy, visceral leishmaniasis may be life-threatening for the mother and may result in adverse fetal outcomes, including spontaneous abortion, congenital disease due to vertical transmission, small for gestational age newborn, and severe anemia. During pregnancy, cutaneous leishmaniasis may manifest with larger and atypical appearing lesions and may be associated with increased risk for adverse fetal outcomes, including preterm births and stillbirths.

Animal Data

Miltefosine administration in rat embryo-fetal toxicity studies during early embryonic development (Day 6 to Day 15 of gestation) caused embryo-fetal toxicity including death and teratogenicity at dosages of $\geq$ 1.2 mg/kg/day (0.06 times the MRHD based on BSA comparison). Teratogenic effects included undeveloped cerebrum, hemorrhagic fluid filling the lumina of the skull, cleft palate and generalized edema. Embryo-fetal toxicity was also observed in rabbits after oral administration of miltefosine during organogenesis (Day 6 to Day 18 of gestation) at doses $\geq$ 2.4 mg/kg/day (0.2 times the MRHD based on BSA comparison). In both rats and rabbits, there were no viable litters at miltefosine doses $\geq$ 6.0 mg/kg/day (0.3 or 0.6 times the MRHD based on BSA comparisons for rats and rabbits respectively).

In a separate female fertility study in rats, miltefosine doses $\geq$ 6.81 mg/kg/day (0.3 times the MRHD based on BSA comparison) administered for four weeks before mating and up to Day 7 of pregnancy produced numerous visceral (misshapen cerebral structures, dilated ventricles filled with brown masses, misshapen spinal cord, misshapen and malpositioned eyes, hypophysis, and absent inner ear) and skeletal (cleft palate, dumbbell-shaped ossification of thoracic vertebral centers, markedly enlarged skull bones, and markedly dilated suturae) fetal malformations. *[see Contraindications (4.1), Nonclinical Toxicology (13.1)]*.

8.3 Nursing Mothers

It is not known whether IMPAVIDO is present in human milk. Because many drugs are present in human milk and because of the potential for serious adverse reactions in nursing infants from IMPAVIDO, a decision should be made whether to discontinue nursing or discontinue the drug, taking

into account the importance of the drug to the mother. Breastfeeding should be avoided for 5 months after IMPAVIDO therapy.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients < 12 years have not been established. Juvenile rats were more sensitive to the miltefosine-induced effects, especially retinal and kidney effects, than adult rats *[see Indications and Usage (1)]*.

8.5 Geriatric Use

Clinical studies of IMPAVIDO did not include sufficient numbers of subjects 65 years of age and over to determine if they respond differently than younger subjects.

8.6 Renal Impairment

Patients with serum creatinine or BUN levels ≥1.5 times the upper limit of normal were excluded from the clinical studies. Miltefosine pharmacokinetics have not been studied in patients with renal impairment.

8.7 Hepatic Impairment

Patients with serum levels of ALT or AST ≥3 times the upper limit of normal and bilirubin levels ≥2 times the upper limit of normal were excluded from the clinical studies. Miltefosine pharmacokinetics have not been studied in patients with hepatic impairment.

8.8 Females and Males of Reproductive Potential

Contraception

IMPAVIDO may cause fetal harm when used during pregnancy. Advise females of reproductive potential to use effective contraception during IMPAVIDO therapy and for 5 months after therapy is completed *[see Boxed Warning, Warnings and Precautions (5.1) and Use in Specific Populations (8.1)]*.

Vomiting and/or diarrhea occurring during IMPAVIDO therapy may affect absorption of oral contraceptives and therefore may compromise their efficacy. Advise females who use oral contraceptives to use additional non-hormonal or alternative method(s) of effective contraception during IMPAVIDO therapy if vomiting and/or diarrhea occurs during therapy *[see Warnings and Precautions (5.7)]*.

Infertility

Females

Miltefosine caused impaired fertility in rats and caused reversible follicular atresia and diestrus in dogs at doses approximately 1.0 and 0.2 times respectively the MRHD *[see Warnings and Precautions (5.2), Nonclinical Toxicology (13.1)]*. The effects of IMPAVIDO on human female fertility have not been formally studied.

Males

Miltefosine caused reduced viable sperm counts and impaired fertility in rats at doses approximately 0.4 times the MRHD *[see Warnings and Precautions (5.2), Nonclinical Toxicology (13.1)]*. A higher dose in rats, approximately 1.0 times the MRHD, caused testicular atrophy and impaired fertility that did not fully reverse 10 weeks after drug administration ended. The effects of IMPAVIDO on human male fertility have not been adequately studied.

Advise women and men of the animal fertility findings, and that the potential for impaired fertility with IMPAVIDO therapy has not been adequately evaluated.

10 OVERDOSAGE

The common adverse effects of vomiting, diarrhea, and abdominal pain are likely in case of overdose. Institute adequate hydration to prevent the risk of impaired renal function, and replace electrolytes as necessary. Because miltefosine is only slightly excreted in the urine, forced diuresis will not increase miltefosine excretion. Gastrointestinal lavage is of unknown value. A specific antidote to treat miltefosine overdose is not known.

11 DESCRIPTION

IMPAVIDO capsules contain the active ingredient miltefosine, an antileishmanial agent. The chemical name of miltefosine is 2-[[(hexadecyloxy)hydroxyphosphenyl]oxy]-N,N,N-trimethylethylammonium inner salt. Miltefosine is a white powder that is freely soluble in water, 0.1 N HCl or NaOH, methanol, and ethanol. It has the empirical formula of $C_{21}H_{46}NO_4P$ with a molecular weight of 407.6 and the following structural formula:

Structural Formula

The inactive ingredients are colloidal silicon dioxide, microcrystalline cellulose, lactose monohydrate, talc, and magnesium stearate. The capsule shell contains gelatin, titanium dioxide, ferric oxide, and purified water.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Miltefosine is an anti-leishmanial agent *[see Clinical Pharmacology (12.4)]*.

12.3 Pharmacokinetics

The pharmacokinetic parameters of miltefosine in patients with visceral and cutaneous leishmaniasis treated for 28 days with IMPAVIDO are listed in Table 5. Due to the long half-life of miltefosine (> 6 days), trough plasma concentrations did not appear to reach a steady state at the end of treatment (i.e., Day 28).

Table 5: Mean (%CV) Pharmacokinetic Parameters for Miltefosine Following Oral Capsule Administration to Adult Patients with Visceral and Cutaneous Leishmaniasis

	Dose	C_{max} (µg/mL)	T_{max}[d] (hr)	AUC_{tau}[e] (µg·hr/mL)	$t_{1/2,\alpha}$[f] (day)	$t_{1/2,\beta}$[g] (day)
Visceral Leishmaniasis (on Day 23)	50 mg BID (4 wks)[a]	66.2 (28.5)	7(2-12)	636 (26.7)	6.4 (31.1)	
	50 mg BID (1 wk)/ 50 mg TID (3 wks)[b]	75.9 (17.6)	4 (2-8)	486 (18.1)	8.5 (28.9)	
Cutaneous Leishmaniasis[c] (on Day 27)	50 mg TID (4 wks)	37.3 (22)[f]		295 (22)[f]	6.8 (5.8) [g,h]	30.7 (18.3) [g,h]

a: Adolescent (≥12 years)/Adults, mean dose per kg was 3.1 mg/kg/day
b: Adolescent (≥12 years)/Adults, mean dose per kg was 3.6 mg/kg/day
c: Adults, mean dose per kg was 1.8 mg/kg/day
d: median (range)
e: $AUC_{0\text{-}12h}$ for BID, $AUC_{0\text{-}8h}$ for TID
f: $t_{1/2,\alpha}$ = distribution phase half-life; $t_{1/2,\beta}$ = terminal elimination phase half-life
g: Estimates based on a population PK model
h: mean (% standard error)

Absorption

Absolute bioavailability of miltefosine has not been determined. In patients with visceral leishmaniasis, maximum miltefosine concentrations following oral administration of IMPAVIDO capsules were reached right before the next dose in many patients, indicating that the absorption of miltefosine may proceed throughout the dosing interval.

Distribution

The distribution of miltefosine has not been studied in humans. Human plasma protein binding of miltefosine, evaluated by an ultracentrifugation method, was 98% over the drug concentration range from 0.1 to 10 µg/mL. In rats, radioactivity of [^{14}C] miltefosine is widely distributed after both single and repeated oral administration with highest uptake of radioactivity in kidney, liver, and spleen. Placental transfer and excretion into milk have not been investigated.

Metabolism and Excretion

No *in vitro* oxidative metabolism by 15 different human cytochrome P450 enzymes (1A1, 1A2, 1B1, 2A6, 2B6, 2C8, 2C9, 2C18, 2C19, 2D6, 2E1, 3A4, 3A5, 3A7, and 4A1) was observed.

A slow metabolic breakdown could be shown in human hepatocytes, resulting in the release of choline by phospholipase D-like cleavage of the miltefosine molecule. The fatty alcohol-containing fragment of miltefosine can enter the metabolism of fatty acids after being oxidized to palmitic acid. This oxidation is blocked in patients with Sjögren-Larsson syndrome, which is caused by a genetic defect in fatty aldehyde dehydrogenase activity. IMPAVIDO is contraindicated in patients who have Sjögren-Larsson-Syndrome *[see Contraindications (4.2)]*.

There was little or no evidence of time or metabolism dependent inhibition of the cytochrome P450 enzymes examined at up to approximately 40 µg/mL miltefosine.

Oral administration of miltefosine did not markedly induce the content of hepatic CYP3A assayed by demethylation activity of erythromycin in rats.

In visceral leishmaniasis patients, <0.2% of the administered dose was excreted into the urine.

12.4 Microbiology

Mechanism of Action

The specific mode of action of miltefosine against *Leishmania* species is unknown. The mechanism of action of miltefosine is likely to involve interaction with lipids (phospholipids and sterols), including membrane lipids, inhibition of cytochrome c oxidase (mitochondrial function), and apoptosis-like cell death.

Activity *In Vitro* and *In Vivo*

Miltefosine has anti-leishmanial activity *in vitro* and in clinical infections *[see Clinical Studies (14)]*. Sensitivity of different *Leishmania* species as well as different strains of a *Leishmania* species to miltefosine may vary in different geographic regions.

Drug Resistance

In vitro studies show a potential for development of resistance to miltefosine. Some strains of *L. braziliensis* with intrinsic resistance to miltefosine have been identified. However, the clinical relevance of these observations is not known.

Drug resistance could be due to a decrease in miltefosine accumulation within *Leishmania* parasite which is thought to be due to either an increase in drug efflux, mediated by the overexpression of the ABC transporter P-glycoprotein and/or a decrease in drug uptake by the inactivation of the miltefosine transport machinery that consists of the miltefosine transporter and its beta subunit. Mutation in the transporter gene was reported in the isolates from a relapsed patient in one study. However, the clinical relevance of these findings is not known.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Mutagenicity/Carcinogenicity: Miltefosine tested negative in the AMES-Salmonella test, DNA-amplification test, chromosomal aberration test *in vitro*, UDS-test *in vivo/in vitro*, and oral mouse micronucleus test *in vivo*. The V 79 mammalian cell HPRT gene mutation test showed an increase in mutant frequency without dose dependency. In view of all mutagenicity test results, the single positive finding in the V 79 HPRT test is considered to be not of toxicological relevance with respect to a mutagenic risk to humans.

Carcinogenicity studies were not performed. In a 52-week oral rat toxicity study, testicular Leydig cell adenoma was observed in 3 of 30 male rats with daily administration of 21.5 mg/kg/day miltefosine (1.0 times the MRHD based on BSA comparison). The carcinogenic potential of miltefosine in humans is unknown.

In a Segment I fertility study in male rats, testicular atrophy, reduced numbers of viable sperm, and impaired fertility were observed in rats following daily oral doses of ≥ 8.25 mg/kg (0.4 times the MRHD based on BSA comparison). These findings were reversible within a recovery period of 10 weeks except at the highest dose tested, 21.5 mg/kg/day (1.0 times the MRHD based on BSA comparison), where effects were not fully reversible.

In a female fertility study in rats, estrus cycle arrest in the metestrus or diestrus phases occurred with the high-dose of 21.5 mg/kg (1.0 times the MRHD based on BSA comparison). At doses of 6.81 and 21.5 mg/kg (0.3 and 1.0 times the MRHD respectively based on BSA comparison) increased numbers of embryonic and fetal resorptions and dead fetuses were observed. In a 52-week toxicology study in dogs, increased numbers of atretic follicles in the ovaries, and cycle arrest in the uterus, vagina, and mammary

gland with morphology consistent with anestrus or diestrus was observed at doses ≥ 1 mg/kg/day (0.2 times the MRHD based on BSA comparison). The effects in dogs were fully reversible after a recovery period of 6 weeks.

13.2 Animal Toxicology and/or Pharmacology

Toxicological studies with miltefosine have been performed in mice, rats, dogs, and rabbits. Adverse reactions not observed in clinical studies but seen in animals at exposure levels similar to clinical exposure levels and with possible relevance to clinical use were as follows:

Acute and chronic toxicity: The oral administration of miltefosine in rats was associated with lesions affecting the eyes (retinal degeneration). Retinal degeneration was observed after 8-weeks treatment at doses of 10 mg/kg/day (0.5 times the MRHD based on BSA comparison). Juvenile rats were more sensitive to the miltefosine-induced effects, especially on eyes and kidneys, than adult rats with retinal degeneration occurring at doses ≥ 2.15 mg/kg/day (0.1 times the MRHD based on BSA comparison), and reversible damage to proximal tubule epithelium occurring at doses ≥ 4.64 mg/kg/day (0.2 times the MRHD based on BSA comparison).

14 CLINICAL STUDIES

14.1 Treatment of Visceral Leishmaniasis

One randomized, open-label, active-controlled study was conducted to evaluate the efficacy of IMPAVIDO in the treatment of visceral leishmaniasis in Bihar, India, an area where *L. donovani* is known epidemiologically to be the prevalent infecting species. Patients ≥ 12 years of age with clinical signs and symptoms compatible with visceral leishmaniasis (fever, splenomegaly, and cytopenia) confirmed by the presence of *Leishmania* amastigotes in aspirates of spleen or bone marrow were randomized to receive oral IMPAVIDO or intravenous amphotericin B deoxycholate in a 3:1 ratio. Patients weighing ≥ 25 kg received an IMPAVIDO 50 mg capsule with meals twice a day. Patients weighing < 25 kg received an IMPAVIDO 50 mg capsule with meals once a day in the morning. Weight ranged between 15 and 67 kg (mean weight 38.6 kg) and BMI ranged between 8.2 and 24 (mean 16.1). No patient weighed more than 70kg. Amphotericin B was administered intravenously over 6 continuous hours at 1 mg/kg every other day for 15 doses. Patients were hospitalized for the duration of therapy.

Exclusion criteria included platelet count $<50 \times 10^9$/L, white cell count $<1 \times 10^9$/L, hemoglobin <6 g/100 mL, AST or ALT ≥3 times upper limit of the normal range, bilirubin ≥2 times upper limit of the normal range, serum creatinine or BUN >1.5 times upper limit of the normal range, prothrombin time >5 seconds above control, and any non-compensated or uncontrolled condition including human immunodeficiency virus (HIV) infection. Women of reproductive potential were required to use effective contraception for the duration of therapy and for 2 months post therapy.

Final cure was defined as initial cure at end of therapy plus absence of signs and symptoms of visceral leishmaniasis at 6 months follow up. Initial cure at the end of therapy was evaluated by repeat spleen or bone marrow aspiration. Patients with initial parasitologic cure were followed for 6 months; patients without absence of clinical signs and symptoms of visceral leishmaniasis were to be evaluated with repeat spleen or bone marrow aspiration to determine final cure.

Two hundred and ninety nine (299) patients received IMPAVIDO and 99 patients received amphotericin B. Approximately, 70% of patients in each arm had previously failed treatment with pentavalent antimony. Initial cure was achieved in 98% of patients in each treatment arm. At 6 months after therapy, 88 (29.5%) IMPAVIDO recipients and 12 (12.1%) amphotericin B recipients continued to have signs and symptoms suggestive of visceral leishmaniasis. These signs or symptoms were attributed to alternative diagnosis in 73 patients. The remaining 27 patients, all in the IMPAVIDO arm, underwent

evaluation with splenic or bone marrow aspiration, and 9 (3.0%) were positive for *Leishmania* amastigotes, indicating relapse. The final cure rates for IMPAVIDO and amphotericin B were 94% and 97%, respectively.

Table 6: Efficacy of IMPAVIDO in Visceral Leishmaniasis in Patients ≥12 years of Age in India

	IMPAVIDO N = 299	Amphotericin B Deoxycholate N = 99
	End of therapy	
Initial Cure	293 (98%)	97 (98%)
	6 months after therapy	
Final Cure*	282 (94%)	96 (97%)
Treatment Failure	9 (3%)	0 (0)
Not Assessable	8 (3%)	3 (3%)

* The 95% exact confidence interval for the difference (IV Amphotericin B – IMPAVIDO) in final cure is (-3.0%, 6.8%).

14.2 Treatment of Cutaneous Leishmaniasis

A placebo controlled study was performed in Colombia where *L. panamensis* and *L. braziliensis* are epidemiologically known to be the prevalent infecting *Leishmania* species, and in Guatemala where *L. braziliensis* is epidemiologically known to be the prevalent infecting species. The study included male and female patients older than 12 years of age who had newly diagnosed or relapsing cutaneous leishmaniasis without mucosal involvement, parasitologically confirmed, presenting with at least one skin ulcer with minimum area of 50 mm^2. Exclusion criteria were AST or ALT ≥2 times upper limit of normal range, bilirubin ≥1.5 times upper limit of normal range, and serum creatinine or BUN >1.5 times upper limit of normal range. Women of reproductive potential were required to use effective contraception for the duration of therapy and for 2 months post therapy.

Patients were randomized to receive IMPAVIDO or placebo in a 2:1 allocation. Patients who weighed < 45 kg received IMPAVIDO 50 mg capsule twice a day, and patients who weighed ≥45 kg received IMPAVIDO 50 mg capsule three times a day. No patient weighed more than 84 kg. Definite cure was defined as apparent (complete epithelialization of all lesions) or partial cure (incomplete epithelialization, no enlargement by > 50% in lesions, no appearance of new lesions, and negative parasitology if done) at 2 weeks after end of therapy and complete epithelialization of all ulcers at 6 months after end of therapy. The definite cure rate for IMPAVIDO was statistically significantly higher than the cure rate for placebo.

Table 7: Efficacy of IMPAVIDO Compared to Placebo in the Treatment of Cutaneous Leishmaniasis in Colombia and Guatemala

	IMPAVIDO	Placebo
Definite Cure*	59/89 (66%)	13/44 (30%)
Colombia	40/49 (82%)	9/24 (38%)
Guatemala	19/40 (48%)	4/20 (20%)

* The difference (95% CI) between groups is 36.8% (20.1%, 53.4%) with P-value<0.0001.

An additional study of IMPAVIDO was conducted in Bahia and Manaus, two regions in Brazil where respectively *L. braziliensis* and *L. guyanensis* are epidemiologically the prevalent infecting pathogens. Adolescent/adult patients aged 12-65 years received IMPAVIDO orally for 28 days. IMPAVIDO target dose was 2.5 mg/kg/day: patients weighing 15-29 kg received 50 mg once daily, patients weighing 30-45 kg received 50 twice mg daily and patients weighing > 46 kg received 50 mg three times daily. The efficacy criteria were initial cure (complete re-epithelialization of the ulcer at 2 months after the end of therapy) followed by definite cure (complete re-epithelialization at 6 months after the end of therapy). Definite cure rate in patients aged ≥12 years was 27/40 (67.5%) for Manaus, Brazil and 34/40 (85%) for Bahia, Brazil.

14.3 Treatment of Mucosal Leishmaniasis

A single arm study was conducted to evaluate the efficacy of IMPAVIDO capsules for the treatment of mucosal leishmaniasis. The study was conducted in Bolivia where *L. braziliensis* is epidemiologically the prevalent species.

Seventy nine (79) patients ≥18 years of age with a cutaneous leishmaniasis scar plus parasites observed or cultured from lesion material or a positive skin test, andno clinically significant concomitant disease received miltefosine at a target dose of 2.5 mg/kg/day for 28 days.By 12 months after the end of therapy, 49 of the patients (62%) had complete resolution of edema, erythema, infiltration and erosion from the involved mucosal sites.

16 HOW SUPPLIED/STORAGE AND HANDLING

Each IMPAVIDO capsule contains 50 mg miltefosine in an opaque, red, hard gelatin capsule. IMPAVIDO capsules are supplied in a folded peel/push-through child-resistant blister card. Each blister card contains 14 capsules. Each carton contains two blister cards (NDC 69051-300-01).

Store at 20-25 °C (68-77 °F); excursions permitted to 15-30 °C (59-86 °F). [See USP Controlled Room Temperature]. Protect from moisture.

Dispense only in the original carton.

17 PATIENT COUNSELING INFORMATION

See the FDA-approved Medication Guide

17.1 Dosing Instructions

- IMPAVIDO is administered with food to ameliorate gastrointestinal side effects.
- Instruct the patient to swallow the capsule whole and not to chew it or break it apart. Instruct the patient to complete the full course of therapy.
- Inform the patient that abdominal pain, nausea, vomiting, and diarrhea are common side effects of therapy with IMPAVIDO and instruct the patient to inform their healthcare provider if these gastrointestinal side effects are severe or persistent. Instruct the patient to consume sufficient fluids to avoid dehydration and, consequently, the risk of kidney injury.

17.2 Females and Males of Reproductive Potential

- Advise women of reproductive potential to use effective contraception during IMPAVIDO therapy and for 5 months after therapy ends *[see Boxed Warning and Use in Specific Populations (8.1, 8.8)]*.

- Advise women who use oral contraceptives to use additional non-hormonal or alternative method (s) of effective contraception during IMPAVIDO therapy if vomiting and/or diarrhea occurs *[see Warnings and Precautions (5.7) and Use in Specific Populations (8.8)].*
- Advise nursing mothers not to breastfeed during IMPAVIDO therapy and for 5 months after therapy is completed *[see Use in Specific Populations (8.3)].*
- Advise women and men that IMPAVIDO caused infertility in male rats, impaired fertility in female rats, and caused atresia in ovarian follicles in female dogs. Advise patients that the potential of impaired fertility in humans has not been adequately evaluated *[see Warnings and Precautions (5.2) and Use in Specific Populations (8.8)].*

Distributed by:
Profounda, Inc.
5790 Hoffner Avenue, Suite 507
Orlando, FL 32822
USA

PR033

Medication Guide

IMPAVIDO® (Im-PA-vee-do)
(miltefosine)
Capsules

Read this Medication Guide before you receive IMPAVIDO. This information does not take the place of talking to your healthcare provider about you medical condition or treatment.

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

IMPAVIDO may cause serious risks to pregnancy:

- Do not take IMPAVIDO if you are pregnant. If you take IMPAVIDO during pregnancy, your baby is at risk for death or serious birth defects.
- Women who can become pregnant should use effective birth control (contraception) during IMPAVIDO treatment and for 5 months after stopping IMPAVIDO treatment. Discuss with your healthcare provider which birth control method is right for you.
- If you become pregnant while taking IMPAVIDO, tell your healthcare provider right away. Talk to your healthcare provider about taking part in the IMPAVIDO Pregnancy Registry. This is a study to learn how IMPAVIDO affects pregnancy and babies. You can enroll in this registry by calling 1-866-588-5405.

What is IMPAVIDO?

IMPAVIDO is prescription medicine used to treat certain types of leishmaniasis:

- visceral leishmaniasis (affecting your internal organs)
- cutaneous leishmaniasis (affecting the skin)
- mucosal leishmaniasis (affecting the nose, mouth and throat)

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

Who should not take IMPAVIDO? Do not take IMPAVIDO if you:

- are pregnant

- have Sjögren-Larsson-Syndrome
- are allergic to miltefosine or any of the ingredients in IMPAVIDO. See the end of this leaflet for a list of the ingredients in IMPAVIDO.
- are a woman who can become pregnant and have not had a pregnancy test. Women who can get pregnant must have a urine or blood pregnancy test before taking IMPAVIDO.
- are a woman who can become pregnant and you are not willing to use effective birth control during IMPAVIDO treatment and for 5 months after treatment

Before you take IMPAVIDO, tell your healthcare provider about all of your medical conditions, including if you:

- have kidney or liver problems. Your healthcare provider should do blood tests to check your kidneys and liver before you start, during and after your treatment with IMPAVIDO.
- are pregnant or planning to become pregnant. IMPAVIDO may harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if IMPAVIDO passes into your breast milk. Talk to your healthcare provider about the best way to feed your baby if you take IMPAVIDO. You should avoid breastfeeding while you take IMPAVIDO and for 5 months after you stop taking IMPAVIDO.

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 IMPAVIDO?

- Take IMPAVIDO exactly as your healthcare provider tells you to.
- Complete your full 28 day IMPAVIDO treatment.
- Take IMPAVIDO capsules whole. Do not break, crush, dissolve, or chew IMPAVIDO before swallowing.
- Take IMPAVIDO with food to help reduce stomach problems.

What are the possible side effects of IMPAVIDO?

IMPAVIDO may cause serious side effects, including:

See "What is the most important information I should know about IMPAVIDO?"

- **Fertility problems in male and female rats and abnormal menstrual cycle in female dogs.** It is not known if IMPAVIDO causes fertility problems in men or women
- **Testicular pain and absent or decreased ejaculation**
- **Kidney and liver problems**
- **Stomach problems**. IMPAVIDO can cause vomiting, diarrhea, and dehydration. Call your healthcare provider right away if you have severe vomiting and diarrhea that does not go away. Drink a lot of water to help prevent dehydration while you are having vomiting and diarrhea.
- **Decreased effectiveness of oral contraceptive pills**. Vomiting and diarrhea may cause your birth control pills to be less effective at preventing pregnancy. Use an extra method of birth control, such as male condoms with spermicide, until you are no longer having vomiting and diarrhea.
- **Decrease in platelets** (which are blood cells that help blood clot).
- **Serious Skin Problems.** IMPAVIDO can cause a serious skin problem called Stevens-Johnson Syndrome. If you develop a skin rash with blisters while taking IMPAVIDO, stop taking IMPAVIDO right away and call your healthcare provider.

The most common side effects of IMPAVIDO include: nausea, vomiting and diarrhea. Other side effects include abdominal pain, decreased appetite, dizziness, headache, sleepiness, skin itching, and abnormalities in liver or kidney tests.

Tell your healthcare provider if you have any side effect that bothers you or that does not go away. These are not all the possible side effects of IMPAVIDO. For more information, ask your healthcare provider.

You may report side effects to FDA at 1-800-FDA-1088.

How should I store IMPAVIDO?

- Store IMPAVIDO at room temperature between 68°F to 77°F (20°C to 25°C).
- Protect IMPAVIDO from moisture.

Keep IMPAVIDO and all medicines out of the reach of children.

General information about the safe and effective use of IMPAVIDO.

Medicines are sometimes prescribed for purposes other than those listed in this Medication Guide. Do not use IMPAVIDO for a condition for which it was not prescribed. This Medication Guide summarizes the most important information about IMPAVIDO. If you would like more information, talk to your healthcare provider or pharmacist. You can ask your healthcare or pharmacist for information about IMPAVIDO that is written for health professionals. Do not give IMPAVIDO to other people, even if they have the same symptoms that you have. For more information, go to www.IMPAVIDO.com or www.dailymed.nlm.nih.gov, or call 1-866-588-5405.

What are the ingredients in IMPAVIDO?

Active ingredient: miltefosine

Inactive ingredients: colloidal silicon dioxide, microcrystalline cellulose, lactose monohydrate, talc, and magnesium stearate. The capsule shell contains gelatin, titanium dioxide, ferric oxide, and purified water.

Distributed by: Profounda, Inc.

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

Issued: Oct 2015

PR034

PRINCIPAL DISPLAY PANEL - CARTON

NDC 69051-300-01 28 Capsules

Impavido®
(miltefosine) capsules
50 mg per Capsule

Rx only PROFOUNDA

Contains 2 blister cards, 14 blisters per card, 1 capsule per blister.
Active ingredient: miltefosine
Inactive ingredients: colloidal silicon dioxide, lactose monohydrate, magnesium stearate, microcrystalline cellulose, talc. The capsule shell contains gelatin, titanium dioxide, ferric oxide and purified water.

Usual dosage: see enclosed package insert for complete prescribing information.

Keep out of reach of children.

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

Distributed by:
Profounda, Inc.
5790 Hoffner Avenue, Suite 507
Orlando, Florida 32822 USA

IMPAVIDO
miltefosine capsule

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:69051-300
Route of Administration	ORAL	**DEA Schedule**	

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
MILTEFOSINE (UNII: 53EY29W7EC) (MILTEFOSINE - UNII:53EY29W7EC)	MILTEFOSINE	50 mg

Inactive Ingredients

Ingredient Name	Strength
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
CELLULOSE, MICROCRYSTALLINE (UNII: OP1R32D61U)	
LACTOSE MONOHYDRATE (UNII: EWQ57Q8I5X)	
TALC (UNII: 7SEV7J4R1U)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
GELATIN (UNII: 2G86QN327L)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
FERRIC OXIDE RED (UNII: 1K09F3G675)	
WATER (UNII: 059QF0KO0R)	

Product Characteristics

Color	RED (opaque)	**Score**	no score
Shape	CAPSULE	**Size**	18mm

Flavor		**Imprint Code**	
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:69051-300-01	2 in 1 CARTON		
1		14 in 1 BLISTER PACK; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA204684	10/29/2015	

Labeler - Profounda, Inc. (078862060)

Establishment

Name	Address	ID/FEI	Business Operations
BASF Pharma SA		480143502	API MANUFACTURE(69051-300)

Establishment

Name	Address	ID/FEI	Business Operations
Haupt Pharma Amareg GmbH		331334909	MANUFACTURE(69051-300)

Establishment

Name	Address	ID/FEI	Business Operations
Bertin Pharma		262319480	ANALYSIS(69051-300)

Establishment

Name	Address	ID/FEI	Business Operations
Carton Service, Inc.		928861723	PACK(69051-300)

Revised: 10/2015

Profounda, Inc.

CVS Caremark Pharmacy & Therapeutics
Condensed Drug Monograph

Vemlidy® (tenofovir alafenamide) tablets
Gilead Sciences Inc.

INDICATION

Vemlidy (tenofovir alafenamide) is indicated for the treatment of chronic hepatitis B virus (HBV) infection in adults with compensated liver disease.

KEY POINTS

Vemlidy (tenofovir alafenamide) is a new prodrug of tenofovir for the treatment of HBV. It is similar to Viread (tenofovir disoproxil fumarate), another prodrug of tenofovir, but with a lower risk of renal and bone adverse events. Vemlidy (tenofovir alafenamide) may be administered in patients with creatinine clearance as low as 15 mL/minute, while the administered dose of Viread (tenofovir disoproxil fumarate) should be adjusted in patients with a creatinine clearance < 50 mL/minute (Prescribing information: Vemlidy, 2016; Viread, 2013).

Vemlidy (tenofovir alafenamide) is not recommended in patients with renal impairment with an estimated creatinine clearance less than 15 mL/minute, nor in patients with decompensated hepatic impairment (Child-Pugh of B or C).

Vemlidy (tenofovir alafenamide) was approved by the Food and Drug Administration (FDA) on November 10, 2016, with a review designation of 5S, as a new formulation that underwent a standard review (FDA, 2016).

CLINICAL EFFICACY

Table 1: Efficacy of Vemlidy (TAF) in the Treatment of Adults with Chronic HBV Infection with Compensated Liver Disease*

Study/Size (Evidence Level Ib)		**Study 108 (N = 425) (Buti, 2016)**		**Study 110 (N = 873) (Chan, 2016)**	
Design		Phase 3, non-inferiority, 48-week, randomized, double-blind, active-controlled studies			
Inclusion Criteria		Adults with chronic HBV infection, HBV DNA ≥ 2 x 10^4 IU/mL, ALT level > 60 U/L (males) or > 38 U/L (females) and ≤ 10 x the ULN, adequate renal function†, normal ECG			
		HBeAg-negative and HBeAb-positive patients		HBeAg-positive patients	
Exclusion Criteria		Co-infection with HCV, HIV, or HDV; evidence of hepatocellular carcinoma; received solid organ or bone marrow transplant; history of malignancy; receiving immunomodulators, investigational agents, nephrotoxic agents, or agents capable of modifying renal excretion			
Baseline Characteristics		Mean age: 46 years, 68% male, 21% treatment experienced, mean plasma HBV DNA: 5.8 $\log_{10}$ IU/mL, mean serum ALT: 94 U/L, history of cirrhosis: 9%		Mean age: 38 years, 64% male, 26% treatment experienced, mean plasma HBV DNA: 7.6 $\log_{10}$ IU/mL, mean serum ALT: 120 U/L, history of cirrhosis: 7%	
Treatment		**Vemlidy (TAF) 25 mg PO QD** (N = 285)	**TDF 300 mg PO QD** (N = 140)	**Vemlidy (TAF) 25 mg PO QD** (N = 581)	**TDF 300 mg PO QD** (N = 292)
Primary Endpoints	**% of patients with HBV DNA < 29 IU/mL at 48 weeks**	94%	93%	64%	67%
	Treatment Difference	1.8% (95% CI: -3.6% to 7.2%; p = 0.47)		-3.6% (95% CI: -9.8% to 2.6%; p = 0.25)	
	Normalized ALT: Central lab‡	83%	75%	72%	67%
	Normalized ALT: AASLD§	50%	32%	45%	36%
	Treatment Difference	p = NS		p = NS	
Secondary Endpoints	**Hip BMD, % change (g/cm^2)²**	-0.29 (2.14)	-2.16 (2.17)	-0.10 (2.29)	-1.72 (2.57)
	Spine BMD, % change (g/cm^2)²	-0.88 (2.86)	-2.51 (3.36)	-0.42 (2.93)	-2.29 (3.13)
	Treatment Difference	p < 0.001		p < 0.001	
	Renal Function	In a pooled analysis of both studies, the patient's mean serum creatinine increased < 0.1 mg/dL in both treatment groups.			
Comments		The studies were funded by Gilead Sciences Inc.			
Conclusion		The studies demonstrated TAF to be noninferior in efficacy compared with TDF, with a virologic response rate of 94% vs. 92.2%, respectively. However, patients on TAF experienced statistically significant less decline in spine and hip BMD. Additional primary endpoint of ALT normalized showed no statistical difference in either treatment groups.			

* Child-Pugh A classification
† Defined as creatinine clearance of > 15 mL/minute
‡ ULN defined as > 43 U/L for males aged 18 to < 69 years and > 35 U/L for males ≥ 69 years; > 34 U/L for females 18 to < 69 years and > 32 U/L for females ≥ 69 years
§ ULN defined as > 30 U/L for males and > 19 U/L for females
Evidence Level Ib = randomized controlled trial
AASLD = American Association for the Study of Liver Disease
ALT = serum alanine aminotransferase
BMD = bone mineral density
CI = confidence interval
DNA = deoxyribonucleic acid
ECG = electrocardiogram
HBeAb = hepatitis B e antibody
HBeAg = hepatitis B e antigen
HBV = hepatitis B virus
HCV = hepatitis C virus
HDV = hepatitis D virus
HIV = human immunodeficiency virus
IU = international units
NS = not statistically significant
PO = by mouth
QD = once daily
TAF = tenofovir alafenamide
TDF = tenofovir disoproxil fumarate
U = units
ULN = upper limit of the normal range

(Buti, 2016; Chan, 2016; Seto, 2016; Vemlidy prescribing information, 2016)

SAFETY

Vemlidy (tenofovir alafenamide) has boxed warnings for lactic acidosis, severe hepatomegaly with steatosis, and severe acute exacerbation of hepatitis B after discontinuation of treatment. Vemlidy (tenofovir alafenamide) has no contraindications. Warnings and precautions for Vemlidy (tenofovir alafenamide) include new onset or worsening renal impairment and risk of developing human immunodeficiency virus (HIV)-1 resistance in patients coinfected with HBV and HIV-1. The most commonly reported adverse events are headache, abdominal pain, fatigue, cough, nausea, and back pain.

PRODUCT AVAILABILITY

Vemlidy (tenofovir alafenamide) is available in bottles of 30 tablets, each containing 25 mg of tenofovir alafenamide. Vemlidy (tenofovir alafenamide) launched on November 14, 2016 (RxPipeline, 2016). The average wholesale price (AWP) of Vemlidy (tenofovir alafenamide) is $39.91 per tablet (Medi-Span, 2016).

DOSAGE AND ADMINSTRATION

The recommended dosage of Vemlidy (tenofovir alafenamide) is one 25 mg oral tablet administered once daily with food. Patients should be tested for HIV infection prior to the initiation of Vemlidy (tenofovir alafenamide). Vemlidy (tenofovir alafenamide) is not recommended in patients with renal impairment with an estimated creatinine clearance less than 15 mL/minute, nor in patients with decompensated hepatic impairment (Child-Pugh of B or C).

PLACE IN THERAPY

- Vemlidy (tenofovir alafenamide) offers an additional once-daily, single-tablet treatment option for the treatment of chronic hepatitis B infection. Viread (tenofovir disoproxil fumarate) 300 mg once-daily oral tablet is another prodrug of tenofovir currently available for the treatment of chronic hepatitis B infection (Terrault, 2015; Viread prescribing information, 2013).
- Chronic hepatitis B infection is a life-threatening infection of the liver that affects up to 2.2 million patients in the United States, and approximately 240 million patients globally (Centers for Disease Control and Prevention [CDC], 2016; Gilead Sciences, 2016). An estimated 786,000 patients die each year worldwide due to hepatitis B complications, including cirrhosis and liver cancer (CDC, 2016; World Health Organization [WHO], 2016).
- Vemlidy (tenofovir alafenamide) was shown to be noninferior compared with Viread (tenofovir disoproxil fumarate) for efficacy and is associated with a lower risk of renal and bone adverse events (Buti, 2016; Chan, 2016).
- Vemlidy (tenofovir alafenamide) is more stable in plasma with improved delivery of tenofovir intracellularly, while lowering circulating levels of tenofovir by approximately 90% compared with Viread (tenofovir disoproxil fumarate) (Sax, 2015).
- Tenofovir alafenamide is also available in combination products, including Descovy (emtricitabine/tenofovir alafenamide), Odefsey (emtricitabine/rilpivirine/tenofovir alafenamide), and Genvoya (elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide) for the treatment of HIV infection (FDA, 2016).
- Viread (tenofovir disoproxil fumarate) is projected to become generically available in the fourth quarter of 2017 (Gilead Sciences, 2013; RxPipeline, 2016).
- The 2015 American Association for the Study of Liver Diseases (AASLD) guidelines recommend Baraclude (entecavir) solution or tablets, Viread (tenofovir disoproxil) tablets, or Pegasys (peginterferon α-2a) injection as preferred initial therapy for adults with immune-active chronic hepatitis B infection (Terrault, 2016). The guidelines have not been updated since the approval of Vemlidy (tenofovir alafenamide).

REFERENCES

Data were compiled using the prescribing information of Vemlidy (tenofovir alafenamide) unless otherwise notated.

ADIS R&D Insight. Available with subscription at http://bi.adisinsight.com/_mem_bin/formsLoginReal.asp. Accessed 2016 November 31.

Buti M, Gane E et al. A Phase 3 study of tenofovir alafenamide compared with tenofovir disoproxil fumarate in patients with HBeAg-negative, chronic hepatitis BL week 48 efficacy and safety results. *J Hepatol*. 2016; 64:s133-s151, Abstract GS06.

Chan HL, Fung S et al. A Phase 3 study of tenofovir alafenamide compared with tenofovir disoproxil fumarate in patients with HBeAg-positive, chronic hepatitis B: week 48 efficacy and safety results. *J Hepatol*. 2016; 64:s133-s151, Abstract GS12.

Centers for Disease Control and Prevention. Viral hepatitis: hepatitis B information. 2016 August 14. URL: http://www.cdc.gov/hepatitis/hbv/hbvfaq.htm#overview. Accessed 2016 November 31.

Food and Drug Administration. Drugs@FDA. URL: http://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=BasicSearch.process. Available from Internet. Accessed 2016 Nov 23.

Gilead Sciences. Gilead and Teva reach settlement agreement in Viread® patent litigation. 2013. URL: http://www.gilead.com/news/press-releases/2013/2/gilead-and-teva-reach-settlement-agreement-in-viread-patent-litigation. Available from Internet. Accessed 2016 Dec 1.

Gilead Sciences. U.S. Food and Drug Administration Approves Gilead's Vemlidy® (Tenofovir Alafenamide) for the treatment of chronic hepatitis B virus infection. 2016 November 11. URL: http://www.gilead.com/news/press-releases/2016/11/us-food-and-drug-administration-approves-gileads-vemlidy-tenofovir-alafenamide-for-the-treatment-of-chronic-hepatitis-b-virus-infection. Available from Internet. Accessed 2016 November 23.

Medi-Span® Master Drug Data Base v2.5 (MDDB®), 19 December 2016, Clinical Drug Information, LLC.

RxPipeline. Available with subscription at https://www.caremark.com/wps/portal/client. Accessed 2016 Dec 1.

Sax PE, Wohl D, Yin MT et al. Tenofovir alafenamide versus tenofovir disoproxil fumarate, coformulated with elvitegravir, cobicistat, and emtricitabine, for initial treatment of HIV-1 infection: two randomized, double-blind, phase 3, non-inferiority trials. *Lancet*. 2015;385:2606-15.

Seto W, Asahina Y et al. Reduced changes in bone mineral density in CHB patients receiving tenofovir alafenamide (TAF) compared with tenofovir disoproxil fumarate. Liver Meeting of American Association for the Study of Liver Diseases, Boston; 11-15 Nov 2016. Abstract 67.

Terrault NA, Bzowej NA, Chang K et al. AASLD guidelines for treatment of chronic hepatitis B. *Hepatology*. 2016; 63(1):261-83.

Vemlidy prescribing information. Foster City, CA: Gilead Sciences, Inc.; 2016 November.

Viread prescribing information. Foster City, CA: Gilead Sciences, Inc.; 2013 October.

World Health Organization. Hepatitis B. 2016 July. URL: http://www.who.int/mediacentre/factsheets/fs204/en/. Accessed 2016 November 31.

CONDENSED DRUG MONOGRAPH PREPARED BY:

Jessica Toma, Pharm.D. Candidate 2017
Amy Schwalm, Pharm.D.
December 20, 2016

This document includes the clinical opinions of CVS Caremark based on the information available at the time this document was written. The document contains summarized information and is not a substitute for reading the original literature. Economic and other considerations may influence an individual client's formulary decision. The document contains prescription brand name drugs that are registered or trademarks of pharmaceutical manufacturers that are not affiliated with CVS Caremark.

Adzenys XR-ODT® *(amphetamine extended release oral dis tablets)*

Indication(s)	Treatment of Attention Deficit Hyperactivity Disorder (ADHD) in patients 6 years and older
FDA Approval	January 27th, 2016
Treatment Comparisons for Indications	Central nervous system stimulants (amphetamine, methylphenidate, dextroamphetamine)
Place in Therapy	CNS stimulant; brand name ODT tablet formulation
Dosage and Administration	***Strengths Available:*** 3.1 mg, 6.3 mg, 9.4 mg, 12.5 mg, 15.7mg, 18.8mg tablets ***Dosage Frequency:*** Once daily allow tablet to disintegrate in saliva then swallow; may be taken with or without food
Safety	***Contraindications:*** Hypersensitivity to amphetamine products or other ingredients in ADZENYS XR-ODT; Use of monoamine oxidase inhibitor (MAOI) or within 14 days of the last MAOI dose ***Warnings:*** Do not substitute for other amphetamine products on a mg-per-mg basis; Potential for abuse or dependence; Psychiatric Symptoms; Cardiovascular Disease; Serotonin Syndrome; Long-term suppression of growth; Raynaud's phenomenon; Potential medication error related overdose ***Drug Interactions:*** MAO inhibitors, serotonergic agents, tricyclic antidepressants, alkalinizing agents (sodium bicarbonate, acetazolamide), acidifying agents (ascorbic acid, reserpine) Monitor with concomitant PPIs (eg, omeprazole). May interfere with urinary steroid tests.
Use in Specific Populations	***Pregnancy:*** category C, based on animal data. May cause fetal harm ***Nursing:*** Breastfeeding not recommended ***Pediatric:*** Safety and efficacy in pediatric patients younger than 6 years of age with ADHD have not been established ***Geriatric:*** has not been studied in the geriatric population
Formulary Considerations	**Proposed Formulary Addition: Tier 3 with prior authorization and quantity limits** No generic ODT tablet formulations on the market Dyanavel XR (amphetamine base extended release suspension) at Tier 3 Multiple extended release ADHD agents available at Tier 1 and Tier 2
Utilization	Previously approved as nonformulary; only available via approved formulary exceptions
Conclusion	Accept formulary addition as proposed

Quillichew ER® *(methylphenidate extended release chewable tablets)*

Indication(s)	Treatment of Attention Deficit Hyperactivity Disorder (ADHD) for patients 6 years and above
FDA Approval	December 4th, 2015
Treatment Comparisons for Indications	Central nervous system stimulants (amphetamine, methylphenidate, dextroamphetamine)
Place in Therapy	CNS stimulant; extended release chewable formulation
Dosage and Administration	***Strengths Available:*** 20 mg, 30 mg scored tablets ***Dosage Frequency:*** Chew tablet once daily in the morning; may be taken with or without food; Titrate in increments of 10mg, 15mg or 20mg per day, maximum recommended daily dose of 60mg
Safety	***Contraindications:*** Known sensitivity to methylphenidate or other ingredients in QuilliChew ER; Use of monoamine oxidase inhibitor (MAOI) or within 14 days of the last MAOI dose ***Warnings:*** Potential for abuse or dependence; Psychiatric Symptoms; Cardiovascular Disease; Priapism; Seizure disorder; Potential medication error related overdose ***Drug Interactions:*** MAO inhibitors, tricyclic antidepressants, alkalinizing agents (sodium bicarbonate, acetazolamide), acidifying agents (ascorbic acid, reserpine) Monitor with concomitant PPIs (eg, omeprazole) and vitamin K antagonist (warfarin).
Use in Specific Populations	***Pregnancy:*** category C, based on animal data. May cause fetal harm ***Nursing:*** Breastfeeding not recommended ***Pediatric:*** Safety and efficacy in pediatric patients younger than 6 years of age with ADHD have not been established ***Geriatric:*** has not been studied in the geriatric population
Formulary Considerations	**Proposed Formulary Addition: Tier 3 with prior authorization and quantity limits** No generic extended release chewable tablet formulations on the market Quillivant XR (methylphenidate extended release suspension) at Tier 3 Multiple extended release ADHD agents available at Tier 1 and Tier 2
Utilization	Previously approved as nonformulary & only available via approved formulary exceptions
Conclusion	Accept formulary addition as proposed

DRUG CLASS	**ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD) AGENTS**
BRAND NAME (generic)	**ADDERALL (amphetamine mixture)** **ADDERALL XR (amphetamine extended-release mixture)** **ADZENYS XR-ODT (amphetamine extended-release orally disintegrating tablets)** **APTENSIO XR (methylphenidate extended-release)** **CONCERTA (methylphenidate extended-release)** **DAYTRANA (methylphenidate transdermal system)** **DESOXYN (methamphetamine)** **DEXTROAMPHETAMINE PRODUCTS (dextroamphetamine)** **DEXEDRINE SPANSULE (dextroamphetamine sustained-release)** **DYANAVEL XR (amphetamine extended-release oral suspension)** **EVEKEO (amphetamine sulfate)** **FOCALIN (dexmethylphenidate)** **FOCALIN XR (dexmethylphenidate extended-release)** **METADATE CD (methylphenidate extended-release)** **METHYLIN CHEWABLE TABLET (methylphenidate chewable tablet)**

METHYLPHENIDATE PRODUCTS
(methylphenidate)

METHYLPHENIDATE EXTENDED-RELEASE PRODUCTS
(methylphenidate extended-release)

PROCENTRA
(dextroamphetamine sulfate oral solution)

QUILLICHEW ER
(methylphenidate extended-release chewable tablets)

QUILLIVANT XR
(methylphenidate extended-release oral suspension)

RITALIN LA
(methylphenidate extended-release)

STRATTERA
(atomoxetine)

VYVANSE
(lisdexamfetamine)

Type: Quantity Limit, Post Limit Prior Authorization

POLICY

FDA-APPROVED INDICATIONS

Adderall
Adderall is indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) and Narcolepsy.

Adderall XR
Adderall XR is indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD).

Adzenys XR-ODT
Adzenys XR-ODT is a central nervous system (CNS) stimulant indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in patients 6 years and older.

Aptensio XR
Aptensio XR is indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD).

Concerta
Concerta is indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in children 6 years of age and older, adolescents, and adults up to the age of 65.

Daytrana

Daytrana is indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD).

Desoxyn
Desoxyn is indicated for Attention Deficit Disorder with Hyperactivity and Exogenous Obesity.

Dextroamphetamine
Dextroamphetamine is indicated for the treatment of Narcolepsy and Attention Deficit Disorder with Hyperactivity.

Dexedrine Spansule
Dexedrine Spansules are indicated for the treatment of Narcolepsy and Attention Deficit Disorder with Hyperactivity.

Dyanavel XR
Dyanavel XR is a central nervous system (CNS) stimulant indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD).

Evekeo
Evekeo is indicated for Narcolepsy, Attention Deficit Disorder with Hyperactivity, and Exogenous Obesity.

Focalin
Focalin is indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD).

Focalin XR
Focalin XR is indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in patients aged six years and older.

Metadate CD
Metadate CD is indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD).

Methylin Chewable Tablets
Methylin Chewable Tablets are indicated for Attention Deficit Disorders and Narcolepsy.

Methylphenidate/Methylphenidate Extended-release
Methylphenidate and methylphenidate extended-release are indicated for Attention Deficit Disorders and Narcolepsy.

ProCentra
ProCentra is indicated for the treatment of Narcolepsy and Attention Deficit Disorder with Hyperactivity.

QuilliChew ER
QuilliChew ER is indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD).

Quillivant XR
Quillivant XR is indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD).

Ritalin LA
Ritalin LA is indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD).

Strattera
Strattera is indicated for the treatment of Attention-Deficit/Hyperactivity Disorder (ADHD).

Vyvanse
Vyvanse is indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) and moderate to severe Binge-Eating Disorder (BED).

Zenzedi
Zenzedi is indicated for Narcolepsy and Attention Deficit Disorder with Hyperactivity.
For all ADHD Agents:

Attention Deficit Hyperactivity Disorder (ADHD)

A diagnosis of Attention Deficit Hyperactivity Disorder (ADHD; DSM-IV) implies the presence of hyperactive-impulsive or inattentive symptoms that caused impairment and were present before age 7 years. The symptoms must cause clinically significant impairment, e.g., in social, academic, or occupational functioning, and be present in two or more settings, e.g., school (or work) and at home. The symptoms must not be better accounted for by another mental disorder. For the Inattentive Type, at least six of the following symptoms must have persisted for at least 6 months: lack of attention to details/careless mistakes; lack of sustained attention; poor listener; failure to follow through on tasks; poor organization; avoids tasks requiring sustained mental effort; loses things; easily distracted; forgetful. For the Hyperactive-Impulsive Type, at least six of the following symptoms must have persisted for at least 6 months: fidgeting/squirming; leaving seat; inappropriate running/climbing; difficulty with quiet activities; "on the go;" excessive talking; blurting answers; can't wait turn; intrusive. The Combined Type requires both inattentive and hyperactive-impulsive criteria to be met.

LIMIT CRITERIA

One limit allowed per each strength

	1 Month Limit*	**3 Month Limit***
Adderall 5 mg, 7.5 mg, 10 mg, 12.5 mg	90 tabs/25 days	270 tabs/75 days
Adderall 15 mg, 20 mg	60 tabs/25 days	180 tabs/75 days
Adderall 30 mg	30 tabs/25 days	90 tabs/75 days
Adderall XR 5 mg, 10 mg	90 caps/25 days	270 caps/75 days
Adderall XR 15 mg, 20 mg, 25 mg, 30 mg	30 caps/25 days	90 caps/75 days
Adzenys XR-ODT 3.1 mg, 6.3 mg, 9.4 mg	60 tabs/25 days	180 tabs/75 days
Adzenys XR-ODT 12.5 mg, 15.7 mg. 18.8 mg	30 tabs/25 days	90 tabs/75 days
Aptensio XR 10 mg, 15 mg, 20 mg, 30 mg	60 caps/25 days	180 caps/75 days
Aptensio XR 40 mg, 50 mg, 60 mg	30 caps/25 days	90 caps/75 days
Concerta 18 mg, 27 mg, 36 mg	60 tabs/25 days	180 tabs/75 days
Concerta 54 mg	30 tabs/25 days	90 tabs/75 days
Daytrana Patch 10 mg, 15 mg, 20 mg, 30 mg	30 patches/25 days	90 patches/75 days
Desoxyn 5 mg	150 tabs/25 days	450 tabs/75 days
Dextroamphetamine 2.5 mg, 5 mg, 7.5 mg, 10 mg	120 tabs/25 days	360 tabs/75 days
Dextroamphetamine 15 mg, 20 mg	60 tabs/25 days	180 tabs/75 days
Dextroamphetamine 30 mg	30 tabs/25 days	90 tabs/75 days
Dexedrine Spansule 5 mg, 10 mg	120 caps/25 days	360 caps/75 days
Dexedrine Spansule 15 mg	60 caps/25 days	180 caps/75 days
Dyanavel XR oral suspension 2.5 mg/mL	240 mL/25 days	720 mL/75 days
Evekeo 5 mg, 10 mg	120 tabs/25 days	360 tabs/75 days

Focalin 2.5 mg, 5 mg	120 tabs/25 days	360 tabs/75 days
Focalin 10 mg	60 tabs/25 days	180 tabs/75 days
Focalin XR 5 mg, 10 mg, 15 mg, 20 mg	60 caps/25 days	180 caps/75 days
Focalin XR 25 mg, 30 mg, 35 mg, 40 mg	30 caps/25 days	90 caps/75 days
Metadate CD 10 mg, 20 mg, 30 mg	60 caps/25 days	180 caps/75 days
Metadate CD 40 mg, 50 mg, 60 mg	30 caps/25 days	90 caps/75 days
Methylin Chewable Tablets 2.5 mg, 5 mg or 10 mg	180 tabs/25 days	540 tabs/75 days
Methylphenidate 5 mg, 10 mg	180 tabs/25 days	540 tabs/75 days
Methylphenidate 20 mg	90 tabs/25 days	270 tabs/75 days
Methylphenidate oral solution 5 mg/5 mL	1800 mL/25 days	5400 mL/75 days
Methylphenidate oral solution 10 mg/5 mL	900 mL/25 days	2,700 mL/75 days
Methylphenidate ER 10 mg, 20 mg	90 tabs/25 days	270 tabs/75 days
ProCentra oral solution 5 mg/5 mL	1200 mL/25 days	3600 mL/75 days
QuilliChew ER 20 mg, 30 mg	60 tabs/25 day	180 tabs/75 days
QuilliChew ER 40 mg	30 tabs/25 days	90 tabs/75 days
Quillivant XR oral suspension 25 mg/5 mL (5 mg/1 mL)	360 mL/25 days	1080mL/75 days
Ritalin LA 10 mg, 20 mg, 30 mg	60 caps/25 days	180 caps/75 days
Ritalin LA 40 mg, 60 mg	30 caps/25 days	90 caps/75 days
Strattera 10 mg, 18 mg, 25 mg	120 caps/25 days	360 caps/75 days
Strattera 40 mg	60 caps/25 days	180 caps/75 days
Strattera 60 mg, 80 mg, 100 mg	30 caps/25 days	90 caps/75 days
Vyvanse 10 mg, 20 mg, 30 mg	60 caps/25 days	180 caps/75 days
Vyvanse 40 mg, 50 mg, 60 mg, 70 mg	30 caps/25 days	90 caps/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.*

COVERAGE CRITERIA

- Prior authorization will be required for age greater than or equal to 19 years for methylphenidates, Strattera, and amphetamines.
- ADHD/Narcolepsy Agents will be covered with prior authorization when the following criteria are met:
    - The patient has a diagnosis of Attention-Deficit Hyperactivity Disorder (ADHD) or Attention Deficit Disorder (ADD) **AND**
    - The diagnosis has been appropriately documented (i.e., evaluated by a complete clinical assessment, using DSM-5, standardized rating scales, interviews/questionnaires).

    OR
    - The patient has a diagnosis of narcolepsy confirmed by a sleep study **AND**
    - This request is NOT for amphetamine extended-release mixture (Adderall XR, Adzenys XR-ODT), methylphenidate immediate release, methylphenidate extended-release (Aptensio XR, Concerta, Metadate CD, QuilliChew ER, Quillivant XR, Ritalin LA), dexmethylphenidate (Focalin), dexmethylphenidate extended-release (Focalin XR) or methylphenidate chewable tablet (Methylin chewable tablet)

POST LIMIT QUANTITY FOR APPROVAL

Quantity for Approval - Quantity Chart for ADHD		
Drug	**Quantity/25 days***	**Quantity/75 days***
Adderall 5 mg, 7.5 mg, 10 mg, 12.5 mg	120 tablets	360 tablets
Adderall 15 mg, 20 mg	90 tablets	270 tablets
Adderall 30 mg	60 tablets	180 tablets
Adderall XR 5 mg, 10 mg	120 tablets	360 tablets
Adderall XR 15 mg, 20 mg, 25 mg, 30 mg	60 capsules	180 capsules
Adzenys XR-ODT 3.1 mg, 6.3 mg, 9.4 mg	120 tablets	360 tablets
Adzenys XR-ODT 12.5 mg, 15.7 mg. 18.8 mg	60 capsules	180 capsules
Aptensio XR** 10 mg, 15 mg, 20 mg, 30 mg	90 capsules	270 capsules
Aptensio XR** 40 mg, 50 mg	60 capsules	180 capsules
Concerta 18 mg, 27 mg, 36 mg	90 tablets	270 tablets
Concerta 54 mg	60 tablets	180 tablets
Dextroamphetamine 2.5 mg, 5 mg, 7.5 mg, 10 mg	180 tablets	540 tablets
Dextroamphetamine 15 mg	120 tablets	360 tablets
Dextroamphetamine 20 mg	90 tablets	270 tablets
Dextroamphetamine 30 mg	60 tablets	180 tablets
Dexedrine Spansule 5 mg, 10 mg	150 capsules	450 capsules
Dexedrine Spansule 15 mg	120 capsules	360 capsules
Evekeo 5 mg, 10 mg	180 tablets	540 tablets
Focalin 2.5 mg, 5 mg, 10 mg	150 tablets	450 tablets
Focalin XR** 5 mg, 10 mg, 15 mg	90 capsules	270 capsules
Focalin XR** 20 mg, 25 mg	60 capsules	180 capsules
Metadate CD** 40 mg, 50 mg	60 capsules	180 capsules
Methylin chewable tablets 2.5 mg, 5 mg, 10 mg	300 tablets	900 tablets
Methylphenidate 5 mg, 10 mg	210 tablets	630 tablets
Methylphenidate 20 mg	150 tablets	450 tablets
Methylphenidate oral solution 10mg/5ml	1,500 mL	4,500 mL
Methylphenidate ER 10 mg, 20 mg	150 tablets	450 tablets
ProCentra oral solution 5mg/5ml	1,800 mL	5,400 mL
QuilliChew ER 20 mg	150 tablets	450 tablets

QuilliChew ER 30 mg	90 tablets	270 tablets
QuilliChew ER 40 mg	60 tablets	180 tablets
Quillivant XR oral suspension 25 mg/5 mL (5 mg/1 mL)	600 mL	1, 800 mL
Ritalin LA 10 mg, 20 mg,	150 capsules	450 capsules
Ritalin LA 30 mg	90 capsules	270 capsules
Ritalin LA 40 mg	60 capsules	180 capsules
**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.*		

**Focalin XR 30 mg, 35 mg, and 40 mg, Metadate CD 60 mg, Aptensio XR 60 mg, and Ritalin LA 60 mg strengths are not included in the post limit because taking more than one capsule per day would result in exceeding the off-label maximum daily dose.

Quantity for Approval - Quantity Chart for Narcolepsy**		
Drug	**Quantity/25 days***	**Quantity/75 days***
Adderall 5 mg, 7.5 mg, 10 mg, 12.5 mg	120 tablets	360 tablets
Adderall 15 mg, 20 mg	90 tablets	270 tablets
Adderall 30 mg	60 tablets	180 tablets
Dextroamphetamine 2.5 mg, 5 mg, 7.5 mg, 10 mg	180 tablets	540 tablets
Dextroamphetamine 15 mg	120 tablets	360 tablets
Dextroamphetamine 20 mg	90 tablets	270 tablets
Dextroamphetamine 30 mg	60 tablets	180 tablets
Dexedrine Spansule 5 mg, 10 mg	150 capsules	450 capsules
Dexedrine Spansule 15 mg	120 capsules	360 capsules
Evekeo 5 mg, 10 mg	180 tablets	540 tablets
ProCentra oral solution 5mg/5ml	1,800 mL	5,400 mL
**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 initial limits for methylphenidate, methylphenidate extended-release, and Methylin chewable tablet are set at the FDA maximum approved daily doses for narcolepsy; therefore, no post limit quantities will be available for these drugs for the diagnosis of narcolepsy.

REFERENCES

1. Adderall [package insert]. Horsham, PA: Teva Pharmaceuticals USA; August 2015.
2. Adderall XR [package insert]. Wayne, PA: Shire US Inc.; May 2015.
3. Adzenys XR-ODT [package insert]. Grand Prairie, TX: Neos Therapeutics, LP.; January 2016.
4. Aptensio XR [package insert]. Coventry, RI: Rhodes Pharmaceuticals L.P.; May 2015.
5. Concerta [package insert]. Titusville, NJ: Janssen Pharmaceuticals, Inc.; September 2015.
6. Daytrana [package insert]. Miami, FL: Noven Therapeutics, LLC; September 2015.
7. Desoxyn [package insert]. Lebanon, NJ: Recordati Rare Diseases Inc.; February 2015.
8. Dexedrine Spansule [package insert]. Horsham, PA: Amedra Pharmaceuticals, LLC; February 2015.
9. Dextroamphetamine sulfate [package insert]. Dayton, NJ: Aurolife Pharma LLC; February 2015.
10. Dyanavel XR [package insert]. Monmouth Junction, NJ: Tris Pharma, Inc.; October 2015.
11. Evekeo [package insert]. Atlanta, GA: Arbor Pharmaceuticals, LLC; February 2015.
12. Focalin [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; April 2015.
13. Focalin XR [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; June 2015.
14. Metadate CD [package insert]. Smyrna, GA: UCB, Inc.; April 2015.
15. Metadate ER [package insert]. Smyrna, GA: UCB, Inc.; January 2014.
16. Ritalin/Ritalin SR [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; April 2015.
17. Methyphenidate/Methylphenidate ER Tablets [package insert]. Hazelwood, MO: Mallinckrodt Inc.; June 2015.
18. Methylin Chewable Tablets [package insert]. Florham Park, NJ: Shionogi Inc.; December 2013.
19. Methylin Solution [package insert]. Florham Park, NJ: Shionogi Inc.; February 2015.
20. ProCentra [package insert]. Newport, KY: Independence Pharmaceuticals, LLC; August 2015.

21. Quillivant XR [package insert]. Cupertino, CA: NextWave Pharmaceuticals, Inc.; March 2015.
22. QuilliChew ER [package insert]. Monmouth Junction, NJ: Tris Pharma, Inc.; December 2015.
23. Ritalin LA [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; July 2015.
24. Strattera [package insert]. Indianapolis, IN: Eli Lilly and Company; June 2015.
25. Vyvanse [package insert]. Wayne, PA: Shire US Inc.; April 2015.
26. Zenzedi [package insert]. Atlanta, GA: Arbor Pharmaceuticals, LLC; May 2015.
27. 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 November 2015.
28. Micromedex Solutions [database online]. Greenwood Village, CO: Truven Health Analytics Inc. Updated periodically. www.micromedexsolutions.com [available with subscription]. Accessed November 2015.
29. Practice Parameter for the Assessment and Treatment of Children and Adolescents with Attention-Deficit/Hyperactivity Disorder. *J Am Acad Child Adolesc Psychiatry*. 2007; 46(7):894-921. http://www.jaacap.com/article/S0890-8567%2809%2962182-1/pdf. Accessed November 2015.

American Academy of Pediatrics. ADHD: Clinical Practice Guideline for the Diagnosis, Evaluation, and Treatment of Attention-Deficit/Hyperactivity Disorder in Children and Adolescents. *Pediatrics.* 2011; 128(5):1007-1022. http://pediatrics.aappublications.org/content/early/2011/10/14/peds.2011-2654. Accessed November 2015.

Onzetra Xsail® *(sumatriptan nasal powder)*

Indication(s)	Treatment of migraine with or without aura in adults; not indicated for migraine prophylaxis or treatment of cluster headaches
FDA Approval	January 27th, 2016
Treatment Comparisons for Indications	Multiple generic and preferred brand 5-HT1B/1D (triptan) receptor agonists
Place in Therapy	Anti-migraine 5-HT1B/1D receptor agonist (triptan); brand name nasal powder delivery formulation
Dosage and Administration	***Strengths Available:*** 11 mg capsule in disposable breath-powered nosepiece delivery device ***Dosage Frequency:*** Use one 11mg nosepiece in each nostril for 22mg total dose; do not exceed two doses (44mg) per 24 hour period with each dose separated by a minimum of 2 hours
Safety	• ***Contraindications:*** Hypersensitivity to sumatriptan products or other ingredients in Onzentra Xsail; History of coronary artery disease, stroke, transient ischemic attack, coronary vasospasm, uncontrolled hypertension or hemiplegic or basilar migraine; Wolff-Parkinson-White syndrome or other cardiac accessory conduction pathway disorders, Peripheral vascular disease, Ischemic bowel disease; Recent (within 24 hours) use of another 5-HT1agonist (e.g., another triptan) or of an ergotamine-containing medication; Concurrent or recent (past 2 weeks) use of monoamine oxidase-A inhibitor; Severe hepatic impairment ***Warnings:*** Only indicated for acute treatment, use greater than 10 days per month may lead to worsening of headaches and withdrawal treatment may be necessary with overuse ; Not indicated for migraine prophylaxis; Cerebrovascular events; Cardiovascular Disease; Serotonin Syndrome; seizure disorders ***Drug Interactions:*** MAO inhibitors, serotonergic agents, antipsychotic agents, tricyclic antidepressants, antiemetic (5HT3 antagonists), ergot derivatives, dapoxetine
Use in Specific Populations	***Pregnancy:*** category C, based on animal data. May cause fetal harm ***Nursing:*** Breastfeeding not recommended ***Pediatric:*** has not been studied in the pediatric population ***Hepatic:*** Contraindicated in severe hepatic impairment
Formulary Considerations	**Proposed: Add Tier 3 with prior authorization, step therapy and quantity limits** Only nasal powder formulation; alts include sumatriptan nasal spray 20mg/act Tier 2, Imitrex nasal spray 20mg/act Tier 3, multiple oral triptan agents
Utilization	Previously approved as nonformulary; requires approved formulary exception

Zembrace® SymTouch

(sumatriptan succinate) injection, for subcutaneous use

Indication(s)	Acute treatment of migraine with or without aura in adults; Limits: use only with a clear diagnosis of migraine, not for prophylactic therapy
FDA Approval	Jan 29, 2016 (1992 – sumatriptan)
Treatment Comparisons for Indications	Triptans (various formulations), combo analgesics (aspirin, caffeine, and acetaminophen), NSAIDs, intravenous metoclopramide
Place in Therapy	Triptans are the drug of choice for treating acute migraines; subcutaneous formulation may result in quicker on set of action
Dosage and Administration	***Strengths Available:*** 3 mg prefilled, ready-to-use, single-dose disposable autoinjector ***Dosage Frequency:*** maximum dose in a 24-hour period: 12 mg. Separate doses by at least 1 hour
Safety	***Contraindications:*** history of coronary artery disease or coronary vasospasm, Wolff-Parkinson-White syndrome or other cardiac accessory conduction pathway disorders, history of stroke, transient ischemic attack, or hemiplegic or basilar migraine Peripheral vascular disease Ischemic bowel disease Uncontrolled hypertension Recent (within 24 hours) use of another 5-HT1 agonist (e.g., another triptan) or of an ergotamine-containing medication Concurrent or recent (past 2 weeks) use of monoamine oxidase-A inhibitor ***Warnings:*** myocardial ischemia/infarction and Prinzmetal's angina, arrhythmias, Chest/throat/neck/jaw pain, tightness, pressure, or heaviness, gastrointestinal ischemia and reactions, peripheral vasospastic reactions, serotonin syndrome, seizures ***Drug Interactions:*** ergot-containing drugs, MAO-A inhibitors, other 5-HT_1 agonists, SSRIs, SNRIs, TCAs
Use in Specific Populations	***Pregnancy:*** category C ***Nursing:*** is excreted in breast milk, avoid breastfeeding for 12 hours after use ***Pediatric:*** safety and effectiveness has not been established ***Geriatric:*** cardiovascular evaluation is recommended
Formulary Considerations	Availability of generic triptans in multiple formulations including sumatriptan succinate tablets, ODT tablets, injections, and nasal spray
Conclusion	Zembrace® SymTouch adds an additional option for treating acute migraines that may provide rapid onset of action in a novel disposable injection device if oral formulations cannot be taken due to nausea.

North Carolina State Health Plan
FOR TEACHERS AND STATE EMPLOYEES
A Division of the Department of State Treasurer

PRIOR AUTHORIZATION CRITERIA

DRUG CLASS	**5-HT$_1$ AGONISTS, COMBINATIONS (ALL DOSAGE FORMS)**		
BRAND NAME (generic)	**ALSUMA (sumatriptan)**	**AMERGE (naratriptan)**	**AXERT (almotriptan)**
	FROVA (frovatriptan)	**IMITREX (sumatriptan)**	**MAXALT/ MAXALT-MLT (rizatriptan)**
	ONZETRA XSAIL (sumatriptan)	**RELPAX (eletriptan)**	**SUMAVEL DosePro (sumatriptan)**
	TREXIMET (sumatriptan/naproxen)	**ZEMBRACE SYMTOUCH (sumatriptan)**	**ZOMIG / ZOMIG-ZMT (zolmitriptan)**

Type: Initial Step Therapy; Post Step Therapy Prior Authorization; Quantity Limit; Post Limit Prior Authorization

POLICY

FDA-APPROVED INDICATIONS

Alsuma

Alsuma (sumatriptan injection) is indicated in adults for the acute treatment of migraine, with or without aura, and the acute treatment of cluster headache.

Use only if a clear diagnosis of migraine or cluster headache has been established. If a patient has no response to the first migraine attack treated with Alsuma, reconsider the diagnosis of migraine before Alsuma is administrated to treat any subsequent attacks.

Alsuma is not indicated for the prevention of migraine attacks.

Amerge

Amerge tablets are indicated for the acute treatment of migraine attacks with or without aura in adults.

Amerge tablets are not intended for the prophylactic therapy of migraine or for use in the management of hemiplegic or basilar. Safety and effectiveness of Amerge tablets have not been established for cluster headache, which is present in an older, predominantly male population.

Axert

Adults: Axert (almotriptan malate) is indicated for the acute treatment of migraine attacks in patients with a history of migraine with or without aura.

Adolescents Age 12 to 17 Years: Axert is indicated for the acute treatment of migraine headache pain in patients with a history of migraine attacks with or without aura usually lasting 4 hours or more (when untreated).

Axert should only be used where a clear diagnosis of migraine has been established. If a patient has no response for the first migraine attack treated with Axert , the diagnosis of migraine should be reconsidered before Axert is administered to treat any subsequent attacks.

In adolescents age 12 to 17 years, efficacy of Axert on migraine-associated symptoms (nausea, photophobia, and phonophobia) was not established. Axert is not intended for the prophylactic therapy of migraine or for use in the management of hemiplegic or basilar migraine.

Safety and effectiveness of Axert have not been established for cluster headache which is present in an older, predominantly male population.

Frova
Frova tablets are indicated for the acute treatment of migraine attacks with or without aura in adults.
Frova is not intended for the prophylactic therapy of migraine or for use in the management of hemiplegic or basilar migraine. The safety and effectiveness of Frova have not been established for cluster headache, which is present in an older, predominately male, population.

Imitrex Injection
Imitrex Injection is indicated for the acute treatment of migraine attacks, with or without aura, and the acute treatment of cluster headache episodes.
Use only if a clear diagnosis of migraine or cluster headache has been established. If a patient has no response to the first migraine attack treated with Imitrex, reconsider the diagnosis of migraine before Imitrex is administered to treat any subsequent attacks. Imitrex is not indicated for the prevention of migraine attacks.

Imitrex Nasal Spray and Imitrex Tablets
Imitrex Nasal Spray and Imitrex Tablets are indicated for the acute treatment of migraine attacks with or without aura in adults.
Imitrex Nasal Spray and Tablets are not intended for the prophylactic therapy of migraine or for use in the management of hemiplegic or basilar migraine. Safety and effectiveness of Imitrex Nasal Spray and Tablets have not been established for cluster headache, which is present in an older, predominantly male population.

Maxalt-MLT and Maxalt Tablets
Maxalt-MLT and Maxalt Tablets are indicated for the acute treatment of migraine attacks with or without aura in adults.
Maxalt should only be used where a clear diagnosis of migraine has been established. If a patient has no response for the first migraine attack treated with Maxalt, the diagnosis of migraine should be reconsidered before Maxalt is administered to treat any subsequent attacks. Maxalt is not indicated for use in the management of hemiplegic or basilar migraine.
Maxalt is not indicated for the prevention of migraine attacks. Safety and effectiveness of Maxalt have not been established for cluster headache.

Onzetra Xsail
Onzetra Xsail is indicated for the acute treatment of migraine with or without aura in adults.
Use only if a clear diagnosis of migraine has been established. If a patient has no response to the first migraine attack treated with Onzetra Xsail, reconsider the diagnosis of migraine before treatment of subsequent attacks with Onzetra Xsail.
Onzetra Xsail is not indicated for the prevention of migraine attacks.
Safety and effectiveness of Onzetra Xsail have not been established for the treatment of cluster headache.

Relpax
Relpax tablets are indicated for the acute treatment of migraine attacks with or without aura in adults.
Relpax is not intended for the prophylactic therapy of migraine or for use in the management of hemiplegic or basilar migraine. Safety and effectiveness of Relpax Tablets have not been established for cluster headache, which is present in an older, predominantly male population.

Sumavel DosePro
Sumavel DosePro is indicated in adults for (1) the acute treatment of migraine, with or without aura, and (2) the acute treatment of cluster headache.
Use only if a clear diagnosis of migraine or cluster headache has been established.
If a patient has no response to the first migraine attack treated with Sumavel DosePro, reconsider the diagnosis of migraine before Sumavel DosePro is administered to treat any subsequent attacks.
Sumavel DosePro is not indicated for the prevention of migraine attacks.

Treximet
Treximet is indicated for the acute treatment of migraine with or without aura in adults and pediatric patients 12 years of age and older.
Use only if a clear diagnosis of migraine headache has been established. If a patient has no response to the first migraine attack treated with Treximet, reconsider the diagnosis of migraine before Treximet is administered to treat any subsequent attacks.
Treximet is not indicated for the prevention of migraine attacks.
Safety and effectiveness of Treximet have not been established for cluster headache.

Zembrace SymTouch
Zembrace SymTouch is indicated for the acute treatment of migraine with or without aura in adults.
Use only if a clear diagnosis of migraine has been established. If a patient has no response to the first migraine attack treated with Zembrace SymTouch, reconsider the diagnosis before Zembrace SymTouch is administered to treat any subsequent attacks. Zembrace SymTouch injection is not indicated for the prevention of migraine attacks.

Zomig Nasal Spray, **Tablets, and Zomig-ZMT**
Zomig is indicated for the acute treatment of migraine with or without aura in adults.
Zomig should only be used if a clear diagnosis of migraine has been established. If a patient has no response to Zomig treatment for the first migraine attack, reconsider the diagnosis of migraine before Zomig is administered to treat any subsequent attacks. Zomig is not indicated for the prevention of migraine attacks. Safety and effectiveness of Zomig have not been established for cluster headache. Zomig nasal spray is not recommended in patients with moderate or severe hepatic impairment.

COMPENDIAL USE
Imitrex Nasal Spray
Acute treatment of cluster headache
Zomig Nasal Spray
Acute treatment of cluster headache

INITIAL STEP THERAPY
If the patient has filled a prescription for at least a 30 day supply of a generic 5HT-1 Agonist (triptan) drug within the past 180 days under a prescription benefit administered by CVS Caremark, then the requested branded drug will be paid under that prescription benefit. If the patient does not meet the initial step therapy criteria, then the system will reject with a message indicating that a prior authorization (PA) is required. The prior authorization criteria would then be applied to requests submitted for evaluation to the PA unit.

COVERAGE CRITERIA
Branded triptans will be covered with post step therapy prior authorization when the following criteria are met:

- Patient has experienced an inadequate treatment response, intolerance, or contraindication to at least one generic triptan product.

RATIONALE
If the patient has filled a prescription for at least a 30 day supply of a generic 5HT 1 Agonist (triptan) drug within the past 180 days under a prescription benefit administered by CVS Caremark, then the requested branded drug will be paid under that prescription benefit.

If the patient does not meet the initial step therapy criteria, then prior authorization is required.

If the patient has a documented contraindication to or a potential drug interaction with a generic drug, then the requested brand drug will be covered. If the patient is intolerant to at least one of the generic drugs, then the requested brand drug will be covered. If the patient has tried one of the generic drugs for at least 30 days and had an inadequate treatment response, or requires a dosage form that is not available generically, then the requested brand drug will be covered. If these requirements are met, then the approval duration is 24 months.

LIMIT CRITERIA
The intent is for the patient to receive only one drug from this drug class at a time.
PLEASE NOTE: Since manufacturer package sizes may vary, it is the discretion of the dispensing pharmacy to fill quantities per package size up to these quantity limits. In such cases the filling limit and day supply may be less than what is indicated.
Zecuity is not included and clients should implement the Specialty UM if they so desire.

Medication	Strength	Dose per headache	Maximum dose per 24 hours	Package Size	1 Month Limit * 3 Months Limit *
Alsuma (sumatriptan)	6 mg	1-2 injections	2 injections 12 mg	2 autoinjectors 0.5mL each	12 injectors / 25 days 36 injectors / 75 days
Amerge (naratriptan)	1 mg	1-2 tablets	2 tablets	9 tablets	12 tablets / 25 days 36 tablets / 75 days
	2.5 mg	1-2 tablets	2 tablets 5 mg		
Axert (almotriptan)	6.25 mg	1-2 tablets	2 tablets	6 tablets	12 tablets / 25 days 36 tablets / 75 days
	12.5 mg	1-2 tablets	2 tablets 25 mg	6 tablets 12 tablets	

Frova (frovatriptan)	2.5 mg	1-2 tablets	3 tablets 7.5 mg	9 tablets	18 tablets / 25 days 54 tablets / 75 days
Imitrex Injection (sumatriptan) vials	6 mg	1-2 injections	2 injections 12 mg	5 single dose vials 0.5mL each	12 vials / 25 days 40 vials / 75 days
Imitrex Injection (sumatriptan) syringes	4 mg	1-2 injections	3 injections	2 prefilled syringes 0.5mL each	18 syringes / 25 days 54 syringes / 75 days
	6 mg	1-2 injections	2 injections 12 mg		12 syringes / 25 days 36 syringes / 75 days
Imitrex Nasal Spray (sumatriptan)	5 mg	1-4 sprays	4 sprays	6 nasal spray units	24 units / 25 days 72 units / 75 days
	20 mg	1-2 sprays	2 sprays 40 mg		12 units / 25 days 36 units / 75 days
Imitrex Tablets (sumatriptan)	25mg, 50mg	1-2 tablets	2 tablets	9 tablets	12 tablets / 25 days 36 tablets / 75 days
	100 mg	1-2 tablets	2 tablets 200 mg		
Maxalt / Maxalt-MLT (rizatriptan)	5 mg	1-2 tablets	3 tablets	12 tablets 18 tablets	18 tablets / 25 days 54 tablets / 75 days
	10 mg	1-2 tablets	3 tablets 30 mg		
Onzetra Xsail (sumatriptan)	11mg	2 nosepieces	4 nosepieces 44mg	8 pouches per kit 2 nosepieces per pouch	1 kit / 25 days (8 pouches, 16 nosepieces) 3 kits / 75 days (24 pouches, 48 nosepieces)
Relpax (eletriptan)	20 mg	1-2 tablets	2 tablets	6 tablets	12 tablets / 25 days 36 tablets / 75 days
	40 mg	1-2 tablets	2 tablets 80 mg	6 tablets 12 tablets	
Sumavel DosePro (sumatriptan)	4 mg	1-2 injections	3 injections	6 injections 0.5mL each	18 injections / 25 days 54 injections / 75 days
	6 mg	1-2 injections	2 injections 12 mg		12 injections / 25 days 36 injections / 75 days
Treximet (sumatriptan/naproxen)	10mg/60mg	1 tablet	1 tablet	9 tablets dispensed in original bottle	9 tablets / 25 days 18 tablets / 75 days
	85mg/500mg	1-2 tablets	1-2 tablets 170mg/1000mg		9 tablets / 25 days 36 tablets / 75 days
Zembrace SymTouch (sumatriptan)	3 mg	1-4 injections	4 injections 12mg	4 autoinjectors 0.5mL each	24 injectors / 25 days 72 injectors / 75 days
Zomig / Zomig-ZMT (zolmitriptan)	2.5 mg	1/2-2 tablets	2 tablets	6 tablets	12 tablets / 25 days 36 tablets / 75 days
	5 mg	1-2 tablets	2 tablets 10 mg	3 tablets 6 tablets	
Zomig Nasal Spray (zolmitriptan)	2.5 mg	1-2 sprays	2 sprays	6 nasal spray units	12 units / 25 days 36 units / 75 days
	5 mg	1-2 sprays	2 sprays 10 mg		

** 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.*

POST LIMIT COVERAGE CRITERIA

5-HT1 Agonists will be covered with prior authorization when the following criteria are met:

- The patient does not have confirmed or suspected cardiovascular or cerebrovascular disease, or uncontrolled hypertension.
- The patient is not treating more than eight headaches per month with a 5-HT1 agonist.

AND

- The patient has a diagnosis of migraine headache.
  - The patient is currently using migraine prophylactic therapy or unable to take migraine prophylactic therapies due to inadequate response, intolerance or contraindication.
    [Note: examples of prophylactic therapy are divalproex sodium, topiramate, valproate sodium, metoprolol, propranolol, timolol, atenolol, nadolol, amitriptyline, venlafaxine.].
  - Medication overuse headache has been considered and ruled out.

OR

- The patient has a diagnosis of cluster headache.
  - The request is for Alsuma, Imitrex (sumatriptan) Injection, Imitrex (sumatriptan) Nasal Spray, Sumavel DosePro, or Zomig Nasal Spray.

POST LIMIT QUANTITY FOR APPROVAL

The post limit quantity chart below should be used to determine the quantity for approval for each prescribed medication.

✱POST LIMIT QUANTITY

PLEASE NOTE: Since manufacturer package sizes may vary, it is the discretion of the dispensing pharmacy to fill quantities per package size up to these quantity limits. In such cases the filling limit and day supply may be less than what is indicated. **Zecuity is not included and clients should implement the Specialty UM if they so desire.**

Medication	Strength	1 Month Limit*	3 Month Limit*
Alsuma Injection (sumatriptan)	6mg / 0.5mL	18 auto-injectors	54 auto-injectors
Amerge Tablets (naratriptan)	1mg, 2.5mg	18 tablets	54 tablets
Axert Tablets (almotriptan)	6.25mg, 12.5mg	18 tablets	54 tablets
Frova Tablets (frovatriptan)	2.5mg	27 tablets	81 tablets
Imitrex single-dose vial (sumatriptan)	6mg/0.5mL	18 vials	55 vials
Imitrex prefilled syringe (sumatriptan)	4mg/0.5mL	27 syringe cartridges	81 syringe cartridges
Imitrex prefilled syringe (sumatriptan)	6mg/0.5mL	18 syringe cartridges	54 syringe cartridges
Imitrex Nasal Spray (sumatriptan)	5mg	36 nasal units	108 nasal units
Imitrex Nasal Spray (sumatriptan)	20mg	18 nasal units	54 nasal units
Imitrex Tablets (sumatriptan)	25mg, 50mg, 100mg	18 tablets	54 tablets
Maxalt/Maxalt-MLT Tablets (rizatriptan)	5mg, 10 mg	27 tablets	81 tablets
Onzetra Xsail Nosepiece (sumatriptan)	11mg	2 kits (16 pouches, 32 nosepieces)	6 kits (48 pouches, 96 nosepieces)
Relpax Tablets (eletriptan)	20mg, 40mg	18 tablets	54 tablets
Sumavel DosePro (sumatriptan)	4mg / 0.5mL	27 syringes	81 syringes
Sumavel DosePro (sumatriptan)	6mg / 0.5mL	18 syringes	54 syringes
Treximet Tablets (sumatriptan)	10mg / 60mg	18 tablets	27 tablets
Treximet Tablets (sumatriptan)	85mg / 500mg	18 tablets	54 tablets
Zembrace SymTouch (sumatriptan)	3mg / 0.5mL	36 auto-injectors	108 auto-injectors
Zomig/Zomig-ZMT Tablets (zolmitriptan)	2.5mg, 5mg	18 tablets	54 tablets
Zomig Nasal Spray (zolmitriptan)	2.5mg,5mg	18 nasal units	54 nasal units

***** *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.*

REFERENCES

1. Alsuma [package insert]. Columbia, MD: Meridian Medical Technologies, Inc.; April 2014.
2. Amerge [package insert]. Research Triangle Park, NC: GlaxoSmithKline; October 2013.
3. Axert [package insert]. Titusville, NJ: Ortho-McNeil Pharmaceutical, Inc.; August 2014.
4. Frova [package insert]. Chadds Ford, PA: Endo Pharmaceuticals Inc.; October 2013.
5. Imitrex Injection [package insert]. Research Triangle Park, NC: GlaxoSmithKline; October 2012.
6. Imitrex Nasal Spray [package insert]. Research Triangle Park, NC: GlaxoSmithKline; November 2013.
7. Imitrex Tablets [package insert]. Research Triangle Park, NC: GlaxoSmithKline; November 2013.
8. Maxalt and Maxalt-MLT [package insert]. Whitehouse Station, NJ: Merck & Co., Inc; January 2013.
9. Onzetra Xsail [package insert]. Aliso Viejo, CA: Avanir Pharmaceuticals, Inc.; January 2016.
10. Relpax [package insert]. New York, NY: Roerig, Division of Pfizer, Inc.; March 2014.
11. Sumavel DosePro [package insert]. San Diego, CA: Zogenix, Inc.; February 2014.
12. Treximet [package insert]. Research Triangle Park, NC: GlaxoSmithKline; May 2015.
13. Zembrace SymTouch [package insert]. San Diego, CA: Ajinomoto Althea Inc.; January 2016.
14. Zomig and Zomig-ZMT [package insert]. Hayward, CA: Impax Pharmaceuticals Inc.; September 2012.
15. Zomig Nasal Spray [package insert]. Hayward, CA: Impax Pharmaceuticals Inc.; September 2013.

16. 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 2015.
17. Micromedex Solutions [database online]. Greenwood Village, CO: Truven Health Analytics Inc. Updated periodically. www.micromedexsolutions.com [available with subscription]. Accessed May 2015.
18. Beithon J, Gallenberg M, Johnson K, et al. Institute for Clinical Systems Improvement. Diagnosis and Treatment of Headache. https://www.icsi.org/_asset/qwrznq/Headache.pdf. Updated January 2013. Accessed May 2015.
19. Silberstein S, Holland S, Freitag F, et al. Evidence-Based Guideline Update: Pharmacologic Treatment for Episodic Migraine Prevention in Adults: Report of the Quality and the American Headache Society Standards Subcommittee of the American Academy of Neurology. *Neurology* 2012;78;1337-1346.
20. Lewis D, Ashwal S, Hershey A, et al. Practice Parameter: Pharmacological treatment of migraine headache in children and adolescents: Report of the American Academy of Neurology Quality Standards Subcommittee and the Practice Committee of the Child Neurology Society. *Neurology* 2004;63;2215-2224.
21. Law S, Derry S, and Moore RA. Triptans for acute cluster headache (Review). The Cochrane Collaboration; *Cochrane Database of Systematic Reviews* 2010; Issue 4.
22. Francis G, Becker W, Pringsheim T. Acute and Preventive Pharmacologic Treatment of Cluster Headache. *Neurology* August 3, 2010 75:463-473.
23. Van Vliet, J, Bahra, A, Martin V, et al. Intranasal Sumatriptan in Cluster Headache, Randomized Placebo-Controlled Double-Blind Study. *Neurology* 2003;60:630-633.
24. Rapoport A, Mathew N, Silberstein S. et al. Zolmitriptan Nasal Spray in the Acute Treatment of Cluster Headache, A double-blind study. *Neurology* 2007;69:821-826.
25. Elizabeth Cittadini, MD; Arne May, MD; Andreas Straube, Effectiveness of Intranasal Zolmitriptan in Acute Cluster Headache, A Randomized, Placebo-Controlled, Double-blind Crossover Study. *ArchNeurol*.2006;63. http://www.archneurol.com/.

Keveyis®
(dichlorphenamide) tablets, for oral use

Indication(s)	Treatment of primary hyperkalemic periodic paralysis, primary hypokalemic periodic paralysis, and related variants
FDA Approval	Aug 10, 2015 (1958 – dichlorphenamide)
Treatment Comparisons for Indications	Hypokalenic periodic paralyses: Oral potassium chloride supplementation, intravenous potassium, acetazolamide, potassium-sparing diretics, Hyperkalemic periodic paralyses: high carb foods, inhaled salbutamol, thiazide diuretics, carbonic anhydrase inhibitors
Place in Therapy	Prophylactic treatment if attacks are frequent; first line agent in acute primary hyperkalemic periodic paralysis, though treatment is often not needed
Dosage and Administration	***Strengths Available:*** 50 mg tablets ***Dosage Frequency:*** initial dose: 50 mg twice daily, titrate based on individual response, maximum dose is 200 mg daily
Safety	***Contraindications:*** hepatic insufficiency, severe pulmonary obstruction, hypersensitivity to dichlorphenamide or other sulfonamides, concomitant use with high dose aspirin ***Warnings:*** hypersensitivity, hypokalemia, metabolic acidosis, falls ***Drug Interactions:*** aspirin and salicylates
Use in Specific Populations	***Pregnancy:*** category C ***Nursing:*** caution, unknown if excreted in human milk ***Pediatric:*** safety and effectiveness has not been established ***Geriatric:*** risk of falls and of metabolic acidosis are greater
Formulary Considerations	The other treatment options are available mostly in generic formulations, only FDA-approved treatment for this condition
Conclusion	First line option for patients experiencing frequent attacks of hyperkalemic, hypokalemic, and related variants of Primary Periodic Paralysis if other treatments are unsuccessful.

CVSHealth

CVS Caremark Pharmacy & Therapeutics
Drug Monograph

Exondys 51™ (eteplirsen) for intravenous infusion
Sarepta Therapeutics, Inc.

INTRODUCTION

Exondys 51 (eteplirsen) is the first agent approved by the Food and Drug Administration (FDA) for the treatment of Duchenne muscular dystrophy (DMD) (FDA, 2016a). Approximately 13% of patients with DMD are candidates for treatment with Exondys 51 (eteplirsen).

U.S. FDA-Review Designation

Exondys 51 (eteplirsen) was approved by the FDA on September 19, 2016 with a review designation of 1P (FDA, 2016b). Exondys 51 (eteplirsen) is a new molecular entity that underwent a priority review and received fast track designation and orphan drug designation (FDA, 2016a).

INDICATIONS

Exondys 51 (eteplirsen) is indicated for the treatment of DMD in patients who have a confirmed mutation of the DMD gene that is amenable to exon 51 skipping (Exondys 51 prescribing information, 2016).

Exondys 51 (eteplirsen) was approved under the accelerated approval pathway, which was based on showing the drug has an effect on a surrogate endpoint (i.e., dystrophin increase in skeletal muscle) that is reasonably likely to predict clinical benefit to patients (FDA, 2016a). The manufacturer must conduct clinical trials to verify the predicted clinical benefit (i.e., improved motor function) in order to receive continued approval.

CLINICAL PHARMACOLOGY

Mechanism of Action

Eteplirsen is designed to bind to exon 51 of dystrophin precursor messenger ribonucleic acid (pre-mRNA), resulting in exclusion of this exon during mRNA processing in patients with genetic mutations that are amenable to exon 51 skipping (Exondys prescribing information, 2016). Exon skipping is intended to allow for production of an internally truncated dystrophin protein.

Pharmacokinetics

Table 1: Selected Pharmacokinetics of Eteplirsen

Route of Administration	Protein Binding	Volume of Distribution	Metabolism	Elimination	$T_{1/2}$
IV	6% to 17%	600 mL/kg	Not via hepatic microsomes	~2/3 renal excretion within 24 hours of administration	3 to 4 hours

IV = intravenous
$T_{1/2}$ = half life

(Exondys 51 prescribing information, 2016)

Pharmacogenomics

Due to the mechanism of action eteplirsen is effective in patients with a confirmed mutation of the dystrophin gene that is amenable to exon 51 skipping (Exondys 51 prescribing information, 2016). This consists of deletions that include exons 50 or 52 (Mendell, 2016).

CLINICAL EFFICACY

The efficacy of Exondys 51 (eteplirsen) was assessed in a 24-week, single-center, double-blind, randomized, controlled trial of 12 boys with DMD (Evidence level Ib) (Mendell, 2013). The patients, were aged seven years to 13 years of age and had DMD with confirmed out-of-frame deletions that were potentially correctable by skipping exon 51. The patients were required to walk 200 m to 400 m on the six-minute walk test (6MWT), and patients were also required to have been receiving a stable dose of corticosteroids (i.e. prednisone or deflazacort) for at least 24 weeks prior to enrollment. The mean age at enrollment was 9.4 years, and mean baseline 6MWT distance was 363 m (Exondys 51 prescribing information; Mendell, 2016). The 6MWT is a test that measures the distance walked in six minutes and is commonly used in patients with muscular dystrophy (Goemans, 2013). This test is used to follow ambulatory capacity and disease progression, and 6MWT values peak by approximately seven years of age in boys with DMD.

Patients were randomized to receive intravenous Exondys 51 (eteplirsen) 30 mg/kg/week (n = 4), Exondys 51 (eteplirsen) 50 mg/kg/week (n = 4), or placebo (n = 4) (Mendell, 2013). After 24 weeks of treatment, patients in the placebo arm were crossed over to receive open-label Exondys 51 (eteplirsen) 30 mg/kg/week (n = 2) or Exondys 51 (eteplirsen) 50 mg/kg/week (n = 2). The primary endpoint was dystrophin production, as assessed by immunohistochemistry, and change in 6MWT distance was a key secondary endpoint. Table 2 summarizes the study results. There was no significant difference between Exondys 51 (eteplirsen)-treated patients and placebo-treated patients for dystrophin at week 48.

Table 2: Efficacy of Exondys 51 (eteplirsen) in Patients with Duchenne Muscular Dystrophy

Endpoint	Exondys 51 30 mg/kg/week (n= 4)	Exondys 51 50 mg/kg/week (n = 4)	Placebo/ Delayed Exondys 51 (n = 4)
Change in % dystrophin-positive fibers in biopsy from baseline to week 48	51.7% ($p \leq 0.001$ vs. baseline)	42.9% ($p \leq 0.008$ vs. baseline)	37.7% ($p \leq 0.009$ vs. baseline)
Change in 6MWT from baseline to week 24	-128.2 m* (p = not provided)	-0.3 m (p = not provided)	-25.8 m (p = not provided)
Change in 6MWT from baseline to week 48	-153.4 m* (p = not provided)	21 m (p = not provided)	-68.4 m (p = not provided)

* The authors attributed the large decrease to two patients who had rapid disease progression immediately after enrollment in the trial; excluding these patients yields a positive change in 6MWT at both 24 weeks and 48 weeks
6MWT = six-minute walk test

(Mendell, 2013)

All of the patients in the trial described above were enrolled in a long-term open-label extension study (Evidence level III) (Mendel, 2016). Mean 6MWT distances were compared with those of 11 matched historical controls. There was no significant difference between the patients and historical controls for mean 6MWT at 12 months or 24 months from the start of therapy, but there was a statistically significant difference at 36 months favoring the patients receiving Exondys 51 (eteplirsen) (difference of 151 m; $p < 0.01$). However, after 48 months, there was no significant difference between the Exondys 51 (eteplirsen)-treated patients and historical controls (Exondys 51 prescribing information, 2016). Of note, after three years, 16.7% of Exondys 51 (eteplirsen)-treated patients lost the ability to walk compared with 46.2% of historical controls.

An additional unpublished study analyzed dystrophin using Western blot in 12 additional patients with DMD who had received Exondys 51 (eteplirsen) for 48 weeks (Exondys 51 prescribing information, 2016). The percentage of dystrophin vs. levels in healthy children increased from 0.16% to 0.44% from baseline to 48 weeks ($p = 0.008$). Of note, in the 12 patients in the randomized, controlled trial, the mean percentage of dystrophin vs. healthy children was 0.93% after 180 weeks of treatment with Exondys 51 (eteplirsen), though baseline dystrophin levels using Western blot were not available.

Efficacy and Safety Data in the Elderly

DMD is largely a disease of children and young adults; therefore, there is no experience with Exondys 51 (eteplirsen) in elderly patients (Exondys 51 prescribing information, 2016).

SAFETY

There are no known contraindications, warnings and precautions, or drug interactions for Exondys 51 (eteplirsen) (Exondys 51 prescribing information, 2016).

Pregnancy

There are no human or animal data available to assess the use of Exondys 51 (eteplirsen) during pregnancy (Exondys 51 prescribing information, 2016).

Nursing Mothers

There are no human or animal data to assess the effect of eteplirsen on milk production, the presence of eteplirsen in milk, or the effects of eteplirsen on the breastfed infant (Exondys 51 prescribing information, 2016).

Pediatric Use

Exondys 51 (eteplirsen) is indicated in pediatric patients (Exondys 51 prescribing information). Studies in juvenile male rats found renal tubular necrosis at doses that resulted in exposure higher than that in humans at recommended doses, and there was decreased bone mineral density at all doses.

Adverse Events

Table 3: Adverse Events Reported in Patients with DMD Treated with Exondys 51 (eteplirsen) with an Incidence of ≥ 25% More than with Placebo

Adverse Event	Exondys 51 (N = 8)	Placebo (N = 4)
Balance disorder	38%	0%
Vomiting	38%	0%
Contact dermatitis	25%	0%

DMD = Duchenne muscular dystrophy

(Exondys 51 prescribing information, 2016)

PRODUCT AVAILABILITY

Exondys 51 (eteplirsen) is available as single-dose vials containing 100 mg/2 mL or 500 mg/10 mL (Exondys 51 prescribing information, 2016). Vials should be stored refrigerated at 2 °C to 8 °C (36 °F to 46 °F).

DOSAGE AND ADMINISTRATION

The recommended dose of Exondys 51 (eteplirsen) is 30 mg/kg administered once weekly as a 35-minute to 60-minute intravenous infusion (Exondys 51 prescribing information, 2016). Exondys 51 (eteplirsen) should be diluted in 0.9% sodium chloride to make a total volume of 100 mL to 150 mL, and administration should be completed within four hours of dilution.

APPROACHES TO TREATMENT

Epidemiology and Clinical Presentation

DMD is a progressive, fatal, X-linked genetic condition that affects approximately one in 3,500 live male births (National Organization for Rare Disorders [NORD], 2016). Approximately 10% of female carriers also have mild symptoms. Signs and symptoms typically become apparent between three years and six years of age and include weakness and wasting of muscles in the pelvis, thighs, and shoulders; waddling gait, difficulty standing up independently, difficulty climbing stairs, and frequent falls. As the disease progresses, muscles of the calves, forearms, neck, and trunk are affected, and scoliosis and decreased respiratory function are common. Late manifestations may include cardiomyopathy and gastrointestinal dysmotility. Approximately one-third of patients with DMD also have some degree of cognitive impairment. Most affected children require leg braces by nine years of age and require a wheelchair by 12 years of age. The mean age at death is approximately 19 years and is often due to heart or respiratory failure (Bushby, 2010). Nonpharmacologic interventions such as mechanical ventilation and gastrostomy may prolong life into the fourth decade but do not prevent disease progression.

Pathophysiology and Genetics

DMD is caused by mutations in the dystrophin gene that lead to absence or near absence of dystrophin (Bushby, 2010). Dystrophin connects actin muscle fibers to connective tissue that surrounds muscle fibers, acting to absorb the force of muscle movement (Aartsma-Rus, 2016). Lack of dystrophin causes muscle fibers to be easily damaged by repeated contraction, and inflammation of muscle fibers and replacement of muscle fibers by fat and fibrotic tissue result.

The dystrophin gene is the largest known human gene and has a high mutation rate (Aartsma-Rus, 2016). Due to the high mutation rate, one-third of DMD cases arise from de novo mutations, and there is a wide variety of mutations that lead to DMD. Approximately two-thirds of patients with DMD have mutations that cause a deletion of one or more of the 79 exons in the gene, while one-third have exon duplication mutations or small mutations. Deletions tend to occur in exons 45 to 55. The disease phenotype depends on the nature of the deletion or duplication. If the number of nucleotides affected is not divisible by three, the RNA reading frame is disrupted during protein translation, and truncated proteins are usually formed due to premature stop codons that are created. The truncated protein lacks the domain that connects to beta-dystroglycan, leading to nonfunctional dystrophin. Patients with such mutations have DMD. In contrast, if the number of nucleotides affected is divisible by three, the RNA reading frame will not be disrupted, and a mutated but semi-functional dystrophin protein results. Patients with these mutations typically have Becker muscular dystrophy, which is associated with milder symptoms and a later disease onset than DMD. Small mutations in the dystrophin gene may be associated with DMD or Becker muscular dystrophy.

Diagnosis

Diagnosis of DMD should be performed by a neuromuscular specialist (Bushby, 2010). DMD should be suspected in children not walking by 18 months of age or who display Gower's sign (i.e., standing up by walking hand up the legs due to a lack of hip and thigh strength) if there is no family history of DMD. Any abnormal muscle function should lead to suspicion of DMD in children with a family history of the condition, and unexplained transaminase levels should also lead to screening for DMD in all children. An elevated creatine kinase level is considered to be a positive screening for DMD, and a positive diagnosis involves genetic testing for mutations in the dystrophin gene with or without a muscle biopsy demonstrating the effective absence of dystrophin. It is estimated that 13% of patients with DMD have mutations that are amenable to exon 51 skipping (Aartsma-Rus, 2009).

Treatment

DMD treatment guidelines from the American Academy of Neurology recommend that prednisone 0.75 mg/kg/day should be used to improved strength and pulmonary function in patients with DMD (Gloss, 2016). Prednisone may also reduce the need for scoliosis surgery and delay the onset of cardiomyopathy. Deflazacort is an alternative corticosteroid option that may improve strength, delay the age of loss of ambulation, improve pulmonary function, reduce the need for scoliosis surgery, delay the onset of cardiomyopathy, and increase survival. Corticosteroids delay the loss of ambulation by approximately two years to three years (Bushby, 2010).

Eteplirsen is a splice switching oligomer that converts frameshift mutations to in-frame mutations by causing the skipping of exon 51 during the formation of the final dystrophin mRNA (Cirak, 2012). Exondys 51 (eteplirsen) was approved following several delays in review by the FDA (AdisInsight, 2016). The agent received a negative vote by an FDA Advisory Committee, and additional data was requested regarding dystrophin measurements using Western blot (Sarepta Therapeutics, 2016). The FDA review document noted concerns with immunohistochemistry to measure dystrophin, a potential lack of clinical meaningfulness of the dystrophin levels demonstrated, a lack of significant benefit in 6MWT in the randomized, controlled trial, and problems with using historical controls to measure drug efficacy (FDA, 2016c).

Another exon 51-skipping antisense agent, Kyndrisa (drisapersen) received a complete response letter from the FDA due to lack of persuasive efficacy data, and development of this agent has been discontinued (RxPipeline, 2016). Several other agents to treat DMD are in clinical development, including agents to skip exons 45 or 53. Deflazacort is pending FDA review for the treatment of DMD, with an anticipated review date of February 9, 2017.

National Institute for Health and Care Excellence (NICE)

NICE does not currently provide guidance on the use of eteplirsen (NICE, 2016a). NICE recommends the use of ataluren for treating DMD resulting from a nonsense mutation in the dystrophin gene in patienst aged five years and older who can walk (NICE, 2016b).

PRODUCT COMPARISON

Exondys 51 (eteplirsen) launched on September 23, 2016. The average wholesale price of Exondys 51 (eteplirsen) is $1,920.00 per 100 mg/2 mL vial and $9,600.00 per 500 mg/10 mL vial ((*Medi-Span® Master Drug Data Base v2.5 (MDDB®)*, 18 October 2016, Clinical Drug Information, LLC). There are currently no agents available that are comparable to Exondys 51 (eteplirsen). Exondys 51 (eteplirsen) is not currently listed on the CVS Caremark National Formulary or any other drug list.

FORMULARY CONSIDERATIONS

Exondys 51 (eteplirsen) is the first FDA-approved treatment for patients with DMD who have a confirmed mutation of the DMD gene that is amenable to exon 51 skipping. Limited data are available to support the efficacy of Exondys 51 (eteplirsen), including conflicting data regarding the effect on ambulation. Unpublished data from 12 patients found a significant improvement in dystrophin levels after 48 weeks of treatment with Exondys 51 (eteplirsen). Limited safety data are available for Exondys 51 (eteplirsen). Despite these limitations, Exondys 51 (eteplirsen) represents the only available treatment option for a subset of patients with DMD, which is a progressive and fatal condition.

REFERENCES

AdisInsight. Available with subscription at http://adisinsight.springer.com/. Accessed 2016 October 4.

Aartsma-Rus A, Fokkema I, Verschuuren J et al. Theoretic applicability of antisense-mediated exon skipping for Duchenne muscular dystrophy mutations. *Hum Mutat*. 2009; 30(3):293-9.

Aartsma-Rus A, Ginjaar IE, Bushby K. The importance of genetic diagnosis for Duchenne muscular dystrophy. *J Med Genet.* 2016; 53(3):145-51.

Bushby K, Finkel R, Birnkrant DJ et al. Diagnosis and management of Duchenne muscular dystrophy, part 1: diagnosis, and pharmacological and psychosocial management. *Lancet Neurol.* 2010; 9(1):77-93.

Cirak S, Feng L, Anthony K et al. Restoration of the dystrophin-associated glycoprotein complex after exon skipping therapy in Duchenne muscular dystrophy. *Mol Ther.* 2012; 20(2):462-7.

Exondys 51 prescribing information. Cambridge, MA: Sarepta Therapeutics, Inc.; 2016 September.

Food and Drug Administration. Drugs@FDA. URL: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/. Available from Internet. Accessed 2016b October 3.

Food and Drug Administration. FDA grants accelerated approval to first drug for Duchenne muscular dystrophy. 2016a September 19. URL: http://www.fda.gov/newsevents/newsroom/pressannouncements/ucm521263.htm. Available from Internet. Accessed 2016 October 3.

Food and Drug Administration. Summary review for eteplirsen. URL: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/206488_summary%20review_Redacted.pdf . Available from Internet. Accessed 2016c October 7.

Gloss D, Moxley RT, Ashwal S et al. Practice guideline update summary: corticosteroid treatment of Duchenne muscular dystrophy. *Neurology.* 2016; 86(5):465-72.

Goemans N, van den Hauwe M, Wilson R et al. Ambulatory capacity and disease progression as measured by the 6-minute-walk-distance in Duchenne muscular dystrophy subjects on daily corticosteroids. *Neuromuscul Disord.* 2013; 23(8):618-23.

Medi-Span® Master Drug Data Base v2.5 (MDDB®), 18 October 2016, Clinical Drug Information, LLC.

Mendell JR, Goemans N, Lowes LP et al. Longitudinal effect of eteplirsen vs. historical control on ambulation in DMD. *Ann Neurol.* 2016; 79(2):257-71.

Mendell JR, Rodino-Klapac LR, Sahenk Z et al. Eteplirsen for the treatment of Duchenne muscular dystrophy. *Ann Neurol.* 2013; 74(5):637-47.

National Institute for Health and Care Excellence. URL: https://www.nice.org.uk/. Available from Internet. Accessed 2016a October 3.

National Institute for Health and Care Excellence. Ataluren for treating Duchenne muscular dystrophy with a nonsense mutation in the dystrophin gene. 2016b July 20. URL: https://www.nice.org.uk/guidance/hst3. Available from Internet. Accessed 2016 October 3.

National Organization for Rare Disorders. Duchenne muscular dystrophy. URL: https://rarediseases.org/rare-diseases/duchenne-muscular-dystrophy/. Available from Internet. Accessed 2016 October 7.

RxPipeline. Available with subscription at https://client.caremark.com/wps/portal/client. Accessed 2016 October 4.

Sarepta Therapeutics, Inc. 2016 news releases. URL: http://investorrelations.sarepta.com/phoenix.zhtml?c=64231&p=irol-news&nyo=0. Available from Internet. Accessed 2016 October 4.

MONOGRAPH PREPARED BY:

Eve Hindin, Pharm.D.
October 18, 2016

This document includes the clinical opinions of CVS Caremark based on the information available at the time this document was written. The document contains summarized information and is not a substitute for reading the original literature. Economic and other considerations may influence an individual client's formulary decision. The document contains prescription brand name drugs that are registered or trademarks of pharmaceutical manufacturers that are not affiliated with CVS Caremark.

SPECIALTY GUIDELINE MANAGEMENT

EXONDYS 51 (eteplirsen)

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
Exondys 51 is indicated for the treatment of Duchenne muscular dystrophy (DMD) in patients who have a confirmed mutation of the *DMD* gene that is amenable to exon 51 skipping.

This indication is approved under accelerated approval based on an increase in dystrophin in skeletal muscle observed in some patients treated with Exondys 51. A clinical benefit of Exondys 51 has not been established. Continued approval for this indication may be contingent upon verification of a clinical benefit in confirmatory trials.

All other indications are considered experimental/investigational and are not a covered benefit.

II. REQUIRED DOCUMENTATION

The following information is necessary to initiate the prior authorization review:

Laboratory confirmation of DMD diagnosis with a *DMD* gene mutation that is amenable to exon 51 skipping (refer to Appendix)

III. CRITERIA FOR INITIAL APPROVAL

Duchenne Muscular Dystrophy
Indefinite authorization may be granted for treatment of DMD when all of the following criteria are met:
1. Genetic testing was conducted to confirm the diagnosis of DMD and to identify the specific type of *DMD* gene mutation
2. The *DMD* gene mutation is amenable to exon 51 skipping (refer to Appendix)

IV. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must meet all initial authorization criteria.

V. DOSAGE AND ADMINISTRATION

Approvals may be subject to dosing limits in accordance with FDA-approved labeling, accepted compendia, and/or evidence-based practice guidelines.

VI. APPENDIX

Examples of *DMD* gene mutations (exon deletions) amenable to exon 51 skipping
1. Deletion of exon 50
2. Deletion of exon 52
3. Deletion of exons 45-50
4. Deletion of exons 47-50
5. Deletion of exons 48-50
6. Deletion of exons 49-50

VII. REFERENCES

1. Exondys 51 [package insert]. Cambridge, MA: Sarepta Therapeutics, Inc.; September 2016.
2. Mendell JR, Rodino-Klapac LR, Sahenk Z, et al. Eteplirsen for the treatment of Duchenne muscular dystrophy. *Ann Neurol*. 2013;74(5):637-47.
3. Cirak S, Arechavala-Gomeza V, Guglieri M, et al. Exon skipping and dystrophin restoration in patients with Duchenne muscular dystrophy after systemic phosphorodiamidate morpholino oligomer treatment: an open-label, phase 2, dose-escalation study. *Lancet*. 2011;378(9791):595-605.

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use EXONDYS 51™ safely and effectively. See full prescribing information for EXONDYS 51.

EXONDYS 51 (eteplirsen) injection, for intravenous use
Initial U.S. Approval: 2016

INDICATIONS AND USAGE

EXONDYS 51 is an antisense oligonucleotide indicated for the treatment of Duchenne muscular dystrophy (DMD) in patients who have a confirmed mutation of the DMD gene that is amenable to exon 51 skipping. This indication is approved under accelerated approval based on an increase in dystrophin in skeletal muscle observed in some patients treated with EXONDYS 51 *[see Clinical Studies (14)]*. A clinical benefit of EXONDYS 51 has not been established. Continued approval for this indication may be contingent upon verification of a clinical benefit in confirmatory trials. (1)

DOSAGE AND ADMINISTRATION

- 30 milligrams per kilogram of body weight once weekly (2.1)
- Administer as an intravenous infusion over 35 to 60 minutes (2.1, 2.3)
- Dilution required prior to administration (2.2)

DOSAGE FORMS AND STRENGTHS

Injection:
- 100 mg/2 mL (50 mg/mL) in single-dose vial (3)
- 500 mg/10 mL (50 mg/mL) in single-dose vial (3)

CONTRAINDICATIONS

None (4)

ADVERSE REACTIONS

The most common adverse reactions (incidence ≥35% and higher than placebo) were balance disorder and vomiting (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Sarepta Therapeutics, Inc. at 1-888-SAREPTA (1-888-727-3782) or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

Revised: 09/2016

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

EXONDYS 51 is indicated for the treatment of Duchenne muscular dystrophy (DMD) in patients who have a confirmed mutation of the DMD gene that is amenable to exon 51 skipping. This indication is approved under accelerated approval based on an increase in dystrophin in skeletal muscle observed in some patients treated with EXONDYS 51 *[see Clinical Studies (14)]*. A clinical benefit of EXONDYS 51 has not been established. Continued approval for this indication may be contingent upon verification of a clinical benefit in confirmatory trials.

2 DOSAGE AND ADMINISTRATION

2.1 Dosing Information

The recommended dose of EXONDYS 51 is 30 milligrams per kilogram administered once weekly as a 35 to 60 minute intravenous infusion.

If a dose of EXONDYS 51 is missed, it may be administered as soon as possible after the scheduled time.

2.2 Preparation Instructions

EXONDYS 51 is supplied in single-dose vials as a preservative-free concentrated solution that requires dilution prior to administration. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Use aseptic technique.

a. Calculate the total dose of EXONDYS 51 to be administered based on the patient's weight and the recommended dose of 30 milligrams per kilogram. Determine the volume of EXONDYS 51 needed and the correct number of vials to supply the full calculated dose.

b. Allow vials to warm to room temperature. Mix the contents of each vial by gently inverting 2 or 3 times. Do not shake.

c. Visually inspect each vial of EXONDYS 51. EXONDYS 51 is a clear, colorless solution that may have some opalescence. Do not use if the solution in the vials is discolored or particulate matter is present.

d. With a syringe fitted with a 21-gauge or smaller non-coring needle, withdraw the calculated volume of EXONDYS 51 from the appropriate number of vials.

e. Dilute the withdrawn EXONDYS 51 in 0.9% Sodium Chloride Injection, USP, to make a total volume of 100-150 mL. Visually inspect the diluted solution for particulates.

f. EXONDYS 51 contains no preservatives and should be administered immediately after dilution. Complete infusion of diluted EXONDYS 51 solution within 4 hours of dilution. If immediate use is not possible, the diluted solution may be stored for up to

24 hours at 2ºC to 8ºC (36ºF to 46ºF). Do not freeze. Discard unused EXONDYS 51.

2.3 Administration Instructions

Application of a topical anesthetic cream to the infusion site prior to administration of EXONDYS 51 may be considered.

EXONDYS 51 is administered via intravenous infusion. Flush the intravenous access line with 0.9% Sodium Chloride Injection, USP, prior to and after infusion.

Infuse the diluted EXONDYS 51 solution over 35 to 60 minutes. Do not mix other medications with EXONDYS 51 or infuse other medications concomitantly via the same intravenous access line.

3 DOSAGE FORMS AND STRENGTHS

EXONDYS 51 is a clear and colorless solution that may have some opalescence, and is available as follows:

- Injection: 100 mg/2 mL (50 mg/mL) solution in a single-dose vial
- Injection: 500 mg/10 mL (50 mg/mL) solution in a single-dose vial

4 CONTRAINDICATIONS

None.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in 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 the EXONDYS 51 clinical development program, 107 patients received at least one intravenous dose of EXONDYS 51, ranging between 0.5 mg/kg (0.017 times the recommended dosage) and 50 mg/kg (1.7 times the recommended dosage). All patients were male and had genetically confirmed Duchenne muscular dystrophy. Age at study entry was 4 to 19 years. Most (89%) patients were Caucasian.

EXONDYS 51 was studied in a double-blind, placebo-controlled study for 24 weeks (Study 1), followed by an open label extension (Study 2). In Study 1, 12 patients were randomized to receive weekly intravenous infusions of EXONDYS 51 (n=8) or placebo (n=4) for 24 weeks. All 12 patients continued in Study 2 and received open-label EXONDYS 51 weekly for up to 208 weeks.

In Study 1, 4 patients received placebo, 4 patients received EXONDYS 51 30 mg/kg, and 4 patients received EXONDYS 51 50 mg/kg (1.7 times the recommended dosage). In Study 2, 6

patients received EXONDYS 51 30 mg/kg/week and 6 patients received EXONDYS 51 50 mg/kg/week *[see Clinical Studies (14)]*.

Adverse reactions that occurred in 2 or more patients who received EXONDYS 51 and were more frequent than in the placebo group in Study 1 are presented in Table 1 (the 30 and 50 mg/kg groups are pooled). Because of the small numbers of patients, these represent crude frequencies that may not reflect the frequencies observed in practice. The 50 mg/kg once weekly dosing regimen of EXONDYS 51 is not recommended *[see Dosage and Administration (2.1)]*.

The most common adverse reactions were balance disorder and vomiting.

Table 1. Adverse Reactions in DMD Patients Treated with 30 or 50 mg/kg/week[1] EXONDYS 51 with Incidence at Least 25% More than Placebo (Study 1)

Adverse Reactions	EXONDYS 51 (N=8) %	Placebo (N=4) %
Balance disorder	38	0
Vomiting	38	0
Contact dermatitis	25	0

[1] 50 mg/kg/week = 1.7 times the recommended dosage

In the 88 patients who received ≥30 mg/kg/week of EXONDYS 51 for up to 208 weeks in clinical studies, the following events were reported in ≥10% of patients and occurred more frequently than on the same dose in Study 1: vomiting, contusion, excoriation, arthralgia, rash, catheter site pain, and upper respiratory tract infection.

There have been reports of transient erythema, facial flushing, and elevated temperature occurring on days of EXONDYS 51 infusion.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no human or animal data available to assess the use of EXONDYS 51 during pregnancy. In the U.S. general population, major birth defects occur in 2 to 4% and miscarriage occurs in 15 to 20% of clinically recognized pregnancies.

8.2 Lactation

Risk Summary

There are no human or animal data to assess the effect of EXONDYS 51 on milk production, the presence of eteplirsen in milk, or the effects of EXONDYS 51 on the breastfed infant.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for EXONDYS 51 and any potential adverse effects on the breastfed infant from EXONDYS 51 or from the underlying maternal condition.

8.4 Pediatric Use

EXONDYS 51 is indicated for the treatment of Duchenne muscular dystrophy (DMD) in patients who have a confirmed mutation of the DMD gene that is amenable to exon 51 skipping, including pediatric patients *[see Clinical Studies (14)]*.

Intravenous administration of eteplirsen (0, 100, 300, or 900 mg/kg) to juvenile male rats once weekly for 10 weeks beginning on postnatal day 14 resulted in renal tubular necrosis at the highest dose tested and decreased bone densitometry parameters (mineral density, mineral content, area) at all doses. The kidney findings were associated with clinical pathology changes (increased serum urea nitrogen and creatinine, decreased urine creatinine clearance). No effects were observed on the male reproductive system, neurobehavioral development, or immune function. An overall no-effect dose was not identified. Plasma eteplirsen exposure (AUC) at the lowest dose tested (100 mg/kg) was similar to that in humans at the recommended human dose (30 mg/kg).

8.5 Geriatric Use

DMD is largely a disease of children and young adults; therefore, there is no geriatric experience with EXONDYS 51.

8.6 Patients with Renal or Hepatic Impairment

EXONDYS 51 has not been studied in patients with renal or hepatic impairment.

10 OVERDOSAGE

There is no experience with overdose of EXONDYS 51.

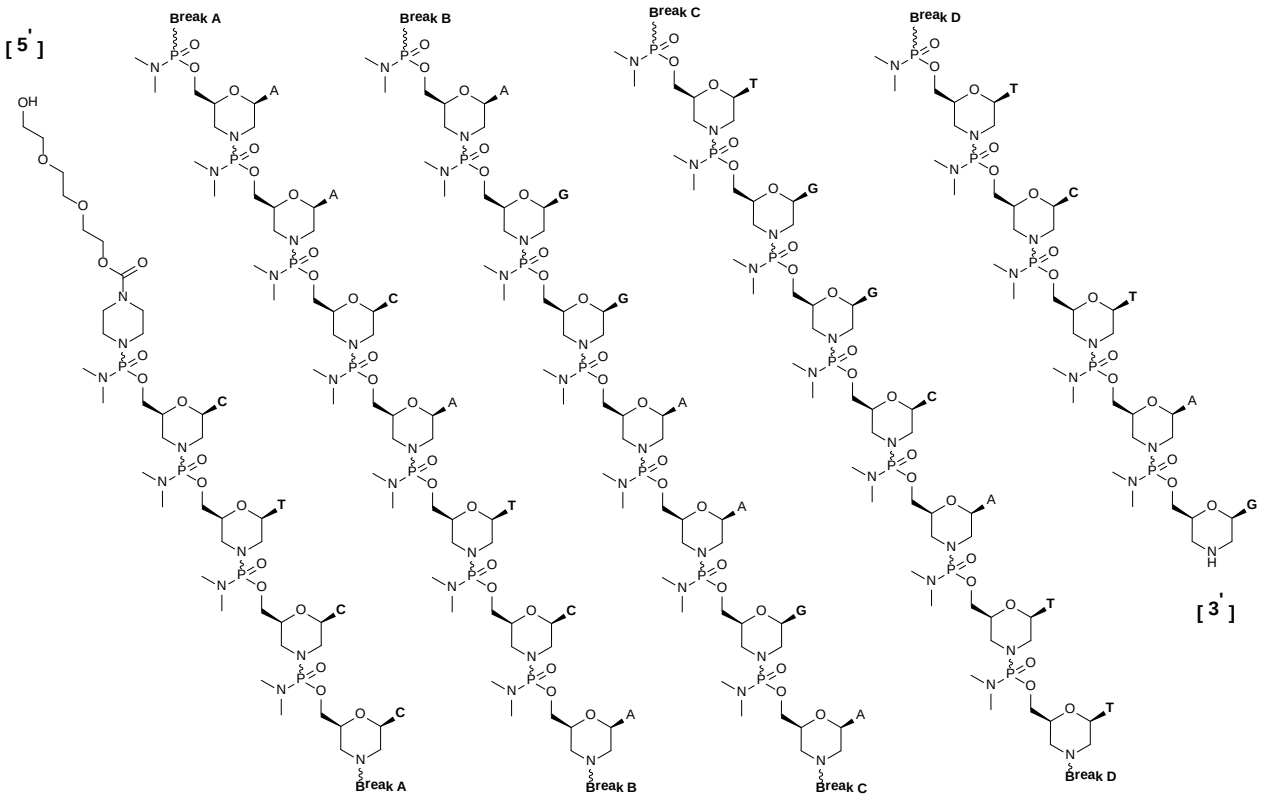
11 DESCRIPTION

EXONDYS 51 (eteplirsen) injection is a sterile, aqueous, preservative-free, concentrated solution for dilution prior to intravenous administration. EXONDYS 51 is clear and colorless, and may have some opalescence. EXONDYS 51 is supplied in single dose vials containing 100 mg or 500 mg eteplirsen (50 mg/mL). EXONDYS 51 is formulated as an isotonic, phosphate buffered saline solution with an osmolality of 260 to 320 mOsm and a pH of 7.5. Each milliliter of EXONDYS 51 contains 50 mg eteplirsen; 0.2 mg potassium chloride, 0.2 mg potassium phosphate monobasic, 8 mg sodium chloride, and 1.14 mg sodium phosphate dibasic, anhydrous, in water for injection. The product may contain hydrochloric acid or sodium hydroxide to adjust pH.

Eteplirsen is an antisense oligonucleotide of the phosphorodiamidate morpholino oligomer (PMO) subclass. PMOs are synthetic molecules in which the five-membered ribofuranosyl rings

found in natural DNA and RNA are replaced by a six-membered morpholino ring. Each morpholino ring is linked through an uncharged phosphorodiamidate moiety rather than the negatively charged phosphate linkage that is present in natural DNA and RNA. Each phosphorodiamidate morpholino subunit contains one of the heterocyclic bases found in DNA (adenine, cytosine, guanine, or thymine). Eteplirsen contains 30 linked subunits. The molecular formula of eteplirsen is $C_{364}H_{569}N_{177}O_{122}P_{30}$ and the molecular weight is 10305.7 daltons.

The structure and base sequence of eteplirsen are:



The sequence of bases from the 5' end to the 3' end is:
CTCCAACATCAAGGAAGATGGCATTTCTAG

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Eteplirsen is designed to bind to exon 51 of dystrophin pre-mRNA, resulting in exclusion of this exon during mRNA processing in patients with genetic mutations that are amenable to exon 51 skipping. Exon skipping is intended to allow for production of an internally truncated dystrophin protein, which was evaluated in Study 2 and Study 3 [*see Clinical studies (14)*].

12.2 Pharmacodynamics

All EXONDYS 51-treated patients evaluated (n=36) were found to produce messenger ribonucleic acid (mRNA) for a truncated dystrophin protein by reverse transcription polymerase chain reaction.

In Study 2, the average dystrophin protein level in muscle tissue after 180 weeks of treatment with EXONDYS 51 was 0.93% of normal (i.e., 0.93% of the dystrophin level in healthy subjects). Because of insufficient information on dystrophin protein levels before treatment with EXONDYS 51 in Study 1, it is not possible to estimate dystrophin production in response to EXONDYS 51 in Study 1.

In Study 3, the average dystrophin protein level was 0.16% of normal before treatment, and 0.44% of normal after 48 weeks of treatment with EXONDYS 51 *[see Clinical studies (14)]*. The median increase in truncated dystrophin in Study 3 was 0.1% *[see Clinical Studies (14)]*.

12.3 Pharmacokinetics

Following single or multiple intravenous infusions of EXONDYS 51 in male pediatric DMD patients, plasma concentration-time profiles of eteplirsen were generally similar and showed multi-phasic decline. The majority of drug elimination occurred within 24 hours. Approximate dose-proportionality and linearity in PK properties were observed following multiple-dose studies (0.5 mg/kg/week [0.017 times the recommended dosage] to 50 mg/kg/week [1.7 times the recommended dosage]). There was no significant drug accumulation following weekly dosing across this dose range. The inter-subject variability for eteplirsen C_{max} and AUC range from 20 to 55%.

Following single or multiple intravenous infusions of EXONDYS 51, the peak plasma concentrations (C_{max}) of eteplirsen occurred near the end of infusion (i.e., 1.1 to 1.2 hours across a dose range of 0.5 mg/kg/week to 50 mg/kg/week).

Distribution

In vitro investigation suggested that plasma protein binding of eteplirsen in human ranges between 6 to 17%. The mean apparent volume of distribution (Vss) of eteplirsen was 600 mL/kg following weekly intravenous infusion of EXONDYS 51 at 30 mg/kg.

Twenty-four hours after the end of the infusion, mean concentrations of eteplirsen were 0.07% of C_{max}. Accumulation of eteplirsen during once weekly dosing has not been observed.

Elimination

The total clearance of eteplirsen was 339 mL/hr/kg following 12 weeks of therapy with 30 mg/kg/week.

Metabolism

Eteplirsen did not appear to be metabolized by hepatic microsomes of any species tested, including humans.

Excretion

Renal clearance of eteplirsen accounts for approximately two-thirds of the administered dose within 24 hours of intravenous administration. Elimination half-life ($t_{1/2}$) of eteplirsen was 3 to 4 hours.

Specific Populations

Age:

The pharmacokinetics of eteplirsen have been evaluated in male pediatric DMD patients. There is no experience with the use of EXONDYS 51 in patients 65 years of age or older.

Sex:

Sex effects have not been evaluated; EXONDYS 51 has not been studied in female patients.

Race:

Potential impact of race is not known because 89% of the patients in studies were Caucasians.

Renal or Hepatic Impairment:

EXONDYS 51 has not been studied in patients with renal or hepatic impairment.

Drug Interaction Studies

In vitro data showed that eteplirsen did not significantly inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A4/5. Eteplirsen did not induce CYP2B6 or CYP3A4, and induction of CYP1A2 was substantially less than the prototypical inducer, omeprazole. Eteplirsen was not a substrate nor did it have any major inhibitory potential for any of the key human transporters tested (OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3, P-gp, BCRP, MRP2 and BSEP). Based on *in vitro* data on plasma protein binding, CYP or drug transporter interactions, and microsomal metabolism, eteplirsen is expected to have a low potential for drug-drug interactions in humans.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Carcinogenicity studies have not been conducted with eteplirsen.

Mutagenesis

Eteplirsen was negative in *in vitro* (bacterial reverse mutation and chromosomal aberration in CHO cells) and *in vivo* (mouse bone marrow micronucleus) assays.

Impairment of Fertility

Fertility studies in animals were not conducted with eteplirsen. No effects on the male reproductive system were observed following intravenous administration of eteplirsen (0, 5, 40, or 320 mg/kg) to male monkeys once weekly for 39 weeks. Plasma eteplirsen exposure (AUC)

in monkeys at the highest dose tested was 20 times that in humans at recommended human dose (30 mg/kg).

14 CLINICAL STUDIES

EXONDYS 51 was evaluated in three clinical studies in patients who have a confirmed mutation of the DMD gene that is amenable to exon 51 skipping.

In Study 1, patients were randomized to receive weekly infusions of EXONDYS 51 (30 mg/kg, n=4); EXONDYS 51 (50 mg/kg, n=4), or placebo (n=4) for 24 weeks. The primary endpoint was dystrophin production; a clinical outcome measure, the 6-minute walk test (6MWT), was also assessed. The 6MWT measures the distance that a patient can walk on a flat, hard surface in a period of 6 minutes. Patients had a mean age of 9.4 years, a mean 6-minute walk distance (6MWD) at baseline of 363 meters, and were on a stable dose of corticosteroids for at least 6 months. There was no significant difference in change in 6MWD between patients treated with EXONDYS 51 and those treated with placebo.

All 12 patients who participated in Study 1 continued treatment with open-label EXONDYS 51 weekly for an additional 4 years in Study 2. The 4 patients who had been randomized to placebo were re-randomized 1:1 to EXONDYS 30 or 50 mg/kg/week such that there were 6 patients on each dose. Patients who participated in Study 2 were compared to an external control group. The primary clinical efficacy outcome measure was the 6MWT. Eleven patients in Study 2 had a muscle biopsy after 180 weeks of treatment with EXONDYS 51, which was analyzed for dystrophin protein level by Western blot. Study 2 failed to provide evidence of a clinical benefit of EXONDYS 51 compared to the external control group. The average dystrophin protein level after 180 weeks of treatment with EXONDYS 51 was 0.93% of the dystrophin level in healthy subjects. Because of insufficient information on dystrophin protein levels before treatment with EXONDYS 51 in Study 1, it is not possible to estimate dystrophin production in response to EXONDYS 51 in Study 1.

In Study 3, 13 patients were treated with open-label EXONDYS 51 (30 mg/kg) weekly for 48 weeks and had a muscle biopsy at baseline and after 48 weeks of treatment. Patients had a mean age of 8.9 years and were on a stable dose of corticosteroids for at least 6 months. Dystrophin levels in muscle tissue were assessed by Western blot. In the 12 patients with evaluable results, the pre-treatment dystrophin level was 0.16% ± 0.12% (mean ± standard deviation) of the dystrophin level in a healthy subject and 0.44% ± 0.43% after 48 weeks of treatment with EXONDYS 51 ($p < 0.05$). The median increase after 48 weeks was 0.1%.

Individual patient dystrophin levels from Study 3 are shown in Table 2.

Table 2. Western Blot Results: EXONDYS 51-Treated (Week 48) vs Pre-treatment Baseline (% Normal Dystrophin) (Study 301)

Patient Number	Baseline % normal dystrophin	Week 48 % normal dystrophin	Change from Baseline % normal dystrophin

1	0.13	0.26	0.13
2	0.35	0.36	0.01
3	0.06	0.37	0.31
4	0.04	0.10	0.06
5	0.17	1.02	0.85
6	0.37	0.30	-0.07
7	0.17	0.42	0.25
8	0.24	1.57	1.33
9	0.11	0.12	0.01
10	0.05	0.47	0.43
11	0.02	0.09	0.07
12	0.18	0.21	0.03
Mean	0.16	0.44	0.28; p=0.008

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

EXONDYS 51 injection is supplied in single-dose vials. The solution is clear and colorless, and may have some opalescence.

- Single-dose vials containing 100 mg/2 mL (50 mg/mL) eteplirsen NDC 60923-363-02
- Single-dose vials containing 500 mg/10 mL (50 mg/mL) eteplirsen NDC 60923-284-10

16.2 Storage and Handling

Store EXONDYS 51 at 2°C to 8°C (36°F to 46°F). Do not freeze. Protect from light and store EXONDYS 51 in the original carton until ready for use.

Manufactured for:
Sarepta Therapeutics, Inc.
Cambridge, MA 02142 USA

Rayaldee®

(calcifediol) extended-release capsules, for oral use

Indication(s)	Vitamin D_3 analog indicated for the treatment of secondary hyperparathyroidism in adults with stage 3 or 4 chronic kidney disease and serum total 25-hydroxyvitamin D levels less than 30 ng/mL
FDA Approval	Jan 21, 2016
Treatment Comparisons for Indications	Low-dose vitamin D, phosphate binders, cinacalcet, calcitriol, doxercalciferol, paricalcitol
Place in Therapy	Adjunctive therapy; first product to receive FDA approval for this indication; current treatment is high dose vitamin D supplementation
Dosage and Administration	***Strengths Available:*** 30 mcg extended-release capsules ***Dosage Frequency:*** once daily at bedtime, serum calcium < 9.8 mg/dL; increase to 60 mcg after 3 months if intact PTH is above the treatment goal.
Safety	***Contraindications:*** none ***Warnings:*** hypercalcemia, digitalis toxicity, adynamic bone disease ***Drug Interactions:*** CYP3A inhibitors, thiazides, cholestyramine, phenobarbital or other anticonvulsants
Use in Specific Populations	***Pregnancy:*** category C ***Nursing:*** caution, unknown if excreted in human milk ***Pediatric:*** safety and effectiveness has not been established ***Geriatric:*** clinical experience has not identified differences in elderly vs younger
Formulary Considerations	Other treatment options range from generics (PhosLo, calcium acetate) to specialty medications (Sensipar, cinacalcet)
Conclusion	Use is limited to stage 3 or 4 chronic kidney disease with serum total 25-hydroxyvitamin D levels less than 30 ng/mL; cannot be used in stage 5 CKD or end-stage renal disease on dialysis.

Veltassa®

(patiromer) suspension, for oral use

Indication(s)	Potassium binder for the treatment of hyperkalemia, not to be used in life threatening hyperkalemia due to its delayed onset of action
FDA Approval	Oct 21, 2015
Treatment Comparisons for Indications	Low-potassium diets, discontinuing medications that may precipitate hyperkalemia, loop diuretics or fludrocortisone, sodium bicarbonate supplementation
Place in Therapy	Adjunctive therapy for patients with chronic unstable hyperkalemia refractory to other treatment options
Dosage and Administration	***Strengths Available:*** 8.4. 16.8, and 25.2 gram powder packets ***Dosage Frequency:*** 8.4 grams once daily with food, titrate at one week intervals by 8.4 grams to obtain desired potassium target range
Safety	***Contraindications:*** hypersensitivity to patiromer or any of its components ***Warnings:*** worsening of gastrointestinal motility, hypomagnesemia ***Drug Interactions:*** binding to other oral medications; administer at least 3 hours before or 3 hours after Veltassa
Use in Specific Populations	***Pregnancy:*** category A, not absorbed systemically ***Nursing:*** not excreted in human milk ***Pediatric:*** safety and effectiveness has not been established ***Geriatric:*** clinical experience has not identified differences in elderly vs younger; more gastrointestinal adverse reactions were reported in patient > 65 yo
Formulary Considerations	Most other pharmacotherapies are generic or over-the-counter
Conclusion	Veltassa provides another alternative to treating chronic non-life threatening hyperkalemia.

Corlanor® *(ivabradine) tablets*

Indication(s)	To reduce rick of hospitalization for worsening heart failure in patient with stable, symptomatic chronic heart failure with NSR, LVEF ≤ 35%, resting heart rate of at least 70 bpm and on maximum tolerated beta blocker dosing (or contraindicated)
FDA Approval	April 15, 2015
Treatment Comparisons for Indications	Beta blockers
Place in Therapy	Selective hyperpolarization-activated cyclic nucleotide-gated (HCN) channel inhibitor agent; unique MOA
Dosage and Administration	***Strengths Available:*** 5mg, 7mg tablets ***Dosage Frequency:*** Initial dose of 5mg or 2.5 mg twice daily; adjust dose after 2 weeks to achieve a resting heart rate between 50 to 60 bpm; maximum recommend dosage of 7.5mg twice daily
Safety	***Contraindications:*** Acute decompensated heart failure, BP < 80/50 mmHg, sick sinus syndrome, SA block, third-degree AV block unless patient has functioning pacemaker, baseline resting heart rate < 60 bpm, severe hepatic impairment, exclusive pacemaker dependence ***Warnings:*** Atrial fibrillation, bradycardia, conduction disturbances, visual phosphenes ***Drug Interactions:*** Significant potential interactions, CYP 3A4 major and minor substrates;
Use in Specific Populations	***Pregnancy:*** category D, may cause fetal harm, do not administer ***Nursing:*** Breastfeeding not recommended ***Pediatric:*** Safety and efficacy in pediatric patients has not been established ***Geriatric:*** Reduce dose to 2.5mg twice daily in patients ≥ 75 years old ***Hepatic:*** Use is contraindicated in severe impairment (Child-Pugh C)
Formulary Considerations	***Proposed Formulary Addition*:** Tier 3 No generic on the market
Utilization	Previously approved as nonformulary; only available via approved formulary exceptions
Conclusion	Accept formulary addition as proposed

PRIOR AUTHORIZATION CRITERIA

BRAND NAME	**CORLANOR**
(generic)	**(ivabradine)**

Type: Initial Prior Authorization

POLICY

FDA-APPROVED INDICATIONS

Corlanor (ivabradine) is a hyperpolarization-activated cyclic nucleotide-gated channel blocker indicated to reduce the risk of hospitalization for worsening heart failure in patients with stable, symptomatic chronic heart failure with left ventricular ejection fraction ≤ 35%, who are in sinus rhythm with resting heart rate ≥ 70 beats per minute and either are on maximally tolerated doses of beta-blockers or have a contraindication to beta-blocker use.

COVERAGE CRITERIA

Corlanor will be covered with prior authorization when the following criteria are met:

- The patient has all of the following: A) Stable, symptomatic chronic heart failure, B) Left ventricular ejection fraction less than or equal to 35 percent, C) Sinus rhythm with resting heart rate greater than or equal to 70 beats per minute, D) Using maximally tolerated doses of beta-blockers or has a contraindication to beta-blocker use
  AND
- The patient does not have any of the following: A) Blood pressure less than 90/50 mmHg, B) Sick sinus syndrome, sinoatrial block, or 3rd degree AV block, unless a functioning demand pacemaker is present, C) Severe hepatic impairment, D) Pacemaker dependence (heart rate maintained exclusively by the pacemaker)

REFERENCES

1. Corlanor [package insert]. Thousand Oaks, California: Amgen Inc.; April 2015.
2. Swedberg K, Komajda M, Böhm M, et al. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study. *Lancet*. 2010 Sep 11;376(9744):875-85.
3. Ceconi C1, Freedman SB, Tardif JC, et al. Effect of heart rate reduction by ivabradine on left ventricular remodeling in the echocardiographic substudy of BEAUTIFUL.Int *J Cardiol*. 2011 Feb 3;146(3):408-14.
4. Fox K, Ford I, Steg PG, et al. Ivabradine in stable coronary artery disease without clinical heart failure. *N Engl J Med*. 2014 Sep 18;371(12):1091-9.
5. McMurray JJ, Adamopoulos S, Anker SD, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. *Eur Heart J* 2012; 33:1787.
6. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. *Circulation* 2013; 128:1810.
7. Micromedex Solutions [database online]. Greenwood Village, CO: Truven Health Analytics Inc. Updated periodically. www.micromedexsolutions.com [available with subscription]. Accessed March 2016.

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use CORLANOR® safely and effectively. See full prescribing information for CORLANOR.

CORLANOR (ivabradine) tablets, for oral use
Initial U.S. Approval: 2015

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

- Warning and Precautions (5.3) 01/2017

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

Corlanor (ivabradine) is a hyperpolarization-activated cyclic nucleotide-gated channel blocker indicated to reduce the risk of hospitalization for worsening heart failure in patients with stable, symptomatic chronic heart failure with left ventricular ejection fraction ≤ 35%, who are in sinus rhythm with resting heart rate ≥ 70 beats per minute and either are on maximally tolerated doses of beta-blockers or have a contraindication to beta-blocker use. (1)

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

- Starting dose is 5 mg twice daily. After 2 weeks of treatment, adjust dose based on heart rate. The maximum dose is 7.5 mg twice daily. (2)
- In patients with conduction defects or in whom bradycardia could lead to hemodynamic compromise, initiate dosing at 2.5 mg twice daily. (2)

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

Tablets: 5 mg, 7.5 mg (3)

---------- CONTRAINDICATIONS ----------

- Acute decompensated heart failure (4)
- Blood pressure less than 90/50 mmHg (4)
- Sick sinus syndrome, sinoatrial block or 3rd degree AV block, unless a functioning demand pacemaker is present (4)
- Resting heart rate less than 60 bpm prior to treatment (4)
- Severe hepatic impairment (4)
- Pacemaker dependence (heart rate maintained exclusively by the pacemaker) (4)
- In combination with strong cytochrome CYP3A4 inhibitors (4)

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

- Fetal toxicity: Females should use effective contraception. (5.1)
- Monitor patients for atrial fibrillation. (5.2)
- Monitor heart rate decreases and bradycardia symptoms during treatment. (5.3)
- Not recommended in patients with 2nd degree AV block. (5.3)

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

Most common adverse reactions occurring in ≥ 1% of patients are bradycardia, hypertension, atrial fibrillation and luminous phenomena (phosphenes). (6)

To report SUSPECTED ADVERSE REACTIONS, contact Amgen Medical Information at 1-800-772-6436 (1-800-77-AMGEN) or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

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

- CYP3A4 inhibitors increase Corlanor plasma concentrations and CYP3A4 inducers decrease Corlanor plasma concentrations. (7.1)
- Negative chronotropes: Increased risk of bradycardia, monitor heart rate. (7.2)
- Pacemakers: Not recommended for use with demand pacemakers set to rates ≥ 60 beats per minute. (7.3)

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

- Lactation: Breastfeeding not recommended. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 01/2017

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1. INDICATIONS AND USAGE

Corlanor is indicated to reduce the risk of hospitalization for worsening heart failure in patients with stable, symptomatic chronic heart failure with left ventricular ejection fraction ≤ 35%, who are in sinus rhythm with resting heart rate ≥ 70 beats per minute and either are on maximally tolerated doses of beta-blockers or have a contraindication to beta-blocker use.

2. DOSAGE AND ADMINISTRATION

The recommended starting dose of Corlanor is 5 mg twice daily with meals. Assess patient after two weeks and adjust dose to achieve a resting heart rate between 50 and 60 beats per minute (bpm) as shown in Table 1. Thereafter, adjust dose as needed based on resting heart rate and tolerability. The maximum dose is 7.5 mg twice daily.

In patients with a history of conduction defects, or other patients in whom bradycardia could lead to hemodynamic compromise, initiate therapy at 2.5 mg twice daily before increasing the dose based on heart rate *[see Warnings and Precautions (5.3)]*.

Table 1. Dose Adjustment

Heart Rate	**Dose Adjustment**
> 60 bpm	Increase dose by 2.5 mg (given twice daily) up to a maximum dose of 7.5 mg twice daily
50-60 bpm	Maintain dose
< 50 bpm or signs and symptoms of bradycardia	Decrease dose by 2.5 mg (given twice daily); if current dose is 2.5 mg twice daily, discontinue therapy*

**[see Warnings and Precautions (5.3)]*

3. DOSAGE FORMS AND STRENGTHS

Corlanor 5 mg: salmon-colored, oval-shaped, film-coated tablet, scored on both edges, debossed with “5” on one face and bisected on the other face. The tablet is scored and can be divided into equal halves to provide a 2.5 mg dose.

Corlanor 7.5 mg: salmon-colored, triangular-shaped, film-coated tablet debossed with "7.5" on one face and plain on the other face.

4. CONTRAINDICATIONS

Corlanor is contraindicated in patients with:

- Acute decompensated heart failure
- Blood pressure less than 90/50 mmHg
- Sick sinus syndrome, sinoatrial block, or 3rd degree AV block, unless a functioning demand pacemaker is present
- Resting heart rate less than 60 bpm prior to treatment *[see Warnings and Precautions (5.3)]*
- Severe hepatic impairment *[see Use in Specific Populations (8.6)]*
- Pacemaker dependence (heart rate maintained exclusively by the pacemaker) *[see Drug Interactions (7.3)]*
- Concomitant use of strong cytochrome P450 3A4 (CYP3A4) inhibitors *[see Drug Interactions (7.1)]*

5. WARNINGS AND PRECAUTIONS

5.1 Fetal Toxicity

Corlanor may cause fetal toxicity when administered to a pregnant woman based on findings in animal studies. Embryo-fetal toxicity and cardiac teratogenic effects were observed in fetuses of pregnant rats treated during organogenesis at exposures 1 to 3 times the human exposures ($AUC_{0\text{-}24hr}$) at the maximum recommended human dose (MRHD) *[see Use in Specific Populations (8.1)]*. Advise females to use effective contraception when taking Corlanor *[see Use in Specific Populations (8.3)]*.

5.2 Atrial Fibrillation

Corlanor increases the risk of atrial fibrillation. In SHIFT, the rate of atrial fibrillation was 5.0% per patient-year in patients treated with Corlanor and 3.9% per patient-year in patients treated with placebo *[see Clinical Studies (14)]*. Regularly monitor cardiac rhythm. Discontinue Corlanor if atrial fibrillation develops.

5.3 Bradycardia and Conduction Disturbances

Bradycardia, sinus arrest, and heart block have occurred with Corlanor. The rate of bradycardia was 6.0% per patient-year in patients treated with Corlanor (2.7% symptomatic; 3.4% asymptomatic) and 1.3% per patient-year in patients treated with placebo. Risk factors for bradycardia include sinus node dysfunction, conduction defects (e.g., 1st or 2nd degree atrioventricular block, bundle branch block), ventricular

dyssynchrony, and use of other negative chronotropes (e.g., digoxin, diltiazem, verapamil, amiodarone). Bradycardia may increase the risk of QT prolongation which may lead to severe ventricular arrhythmias, including torsade de pointes, especially in patients with risk factors such as use of QTc prolonging drugs *[see Adverse Reactions (6.2)]*.

Concurrent use of verapamil or diltiazem will increase Corlanor exposure, may themselves contribute to heart rate lowering, and should be avoided *[see Clinical Pharmacology (12.3)]*. Avoid use of Corlanor in patients with 2nd degree atrioventricular block, unless a functioning demand pacemaker is present *[see Contraindications (4) and Dosage and Administration (2)]*.

6. ADVERSE REACTIONS

Clinically significant adverse reactions that appear in other sections of the labeling include:

- Fetal Toxicity *[see Warnings and Precautions (5.1)]*
- Atrial Fibrillation *[see Warnings and Precautions (5.2)]*
- Bradycardia and Conduction Disturbances *[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.

In the Systolic Heart failure treatment with the I_f inhibitor ivabradine Trial (SHIFT), safety was evaluated in 3260 patients treated with Corlanor and 3278 patients given placebo. The median duration of Corlanor exposure was 21.5 months.

The most common adverse drug reactions in the SHIFT trial are shown in Table 2 *[see also Warnings and Precautions (5.2), (5.3)]*.

Table 2. Adverse Drug Reactions with Rates ≥ 1.0% Higher on Ivabradine than Placebo occurring in > 1% on Ivabradine in SHIFT

	Ivabradine N=3260	**Placebo N=3278**
Bradycardia	10%	2.2%

Hypertension, blood pressure increased	8.9%	7.8%
Atrial fibrillation	8.3%	6.6%
Phosphenes, visual brightness	2.8%	0.5%

Luminous Phenomena (Phosphenes)

Phosphenes are phenomena described as a transiently enhanced brightness in a limited area of the visual field, halos, image decomposition (stroboscopic or kaleidoscopic effects), colored bright lights, or multiple images (retinal persistency). Phosphenes are usually triggered by sudden variations in light intensity. Corlanor can cause phosphenes, thought to be mediated through Corlanor's effects on retinal photoreceptors *[see Clinical Pharmacology (12.1)]*. Onset is generally within the first 2 months of treatment, after which they may occur repeatedly. Phosphenes were generally reported to be of mild to moderate intensity and led to treatment discontinuation in < 1% of patients; most resolved during or after treatment.

6.2 Postmarketing Experience

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.

The following adverse reactions have been identified during post-approval use of Corlanor: syncope, hypotension, torsade de pointes, ventricular fibrillation, ventricular tachycardia, angioedema, erythema, rash, pruritus, urticaria, vertigo, diplopia, and visual impairment.

7. DRUG INTERACTIONS

7.1 Cytochrome P450-Based Interactions

Corlanor is primarily metabolized by CYP3A4. Concomitant use of CYP3A4 inhibitors increases ivabradine plasma concentrations, and use of CYP3A4 inducers decreases them. Increased plasma concentrations may exacerbate bradycardia and conduction disturbances.

The concomitant use of strong CYP3A4 inhibitors is contraindicated *[see Contraindications (4) and Clinical Pharmacology (12.3)]*. Examples of strong CYP3A4 inhibitors include azole antifungals (e.g., itraconazole), macrolide antibiotics (e.g., clarithromycin, telithromycin), HIV protease inhibitors (e.g., nelfinavir), and nefazodone.

Avoid concomitant use of moderate CYP3A4 inhibitors when using Corlanor. Examples of moderate CYP3A4 inhibitors include diltiazem, verapamil, and grapefruit juice *[see Warnings and Precautions (5.3) and Clinical Pharmacology (12.3)]*.

Avoid concomitant use of CYP3A4 inducers when using Corlanor. Examples of CYP3A4 inducers include St. John's wort, rifampicin, barbiturates, and phenytoin *[see Clinical Pharmacology (12.3)]*.

7.2 Negative Chronotropes

Most patients receiving Corlanor will also be treated with a beta-blocker. The risk of bradycardia increases with concomitant administration of drugs that slow heart rate (e.g., digoxin, amiodarone, beta-blockers). Monitor heart rate in patients taking Corlanor with other negative chronotropes.

7.3 Pacemakers

Corlanor dosing is based on heart rate reduction, targeting a heart rate of 50 to 60 beats per minute *[see Dosage and Administration (2)]*. Patients with demand pacemakers set to a rate ≥ 60 beats per minute cannot achieve a target heart rate < 60 beats per minute, and these patients were excluded from clinical trials *[see Clinical Studies (14)]*. The use of Corlanor is not recommended in patients with demand pacemakers set to rates ≥ 60 beats per minute.

8. USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on findings in animals, Corlanor may cause fetal harm when administered to a pregnant woman. There are no adequate and well-controlled studies of Corlanor in pregnant women to inform any drug-associated risks. In animal reproduction studies, oral administration of ivabradine to pregnant rats during organogenesis at a dosage providing 1 to 3 times the human exposure ($AUC_{0\text{-}24hr}$) at the MRHD resulted in embryo-fetal toxicity and teratogenicity manifested as abnormal shape of the heart, interventricular septal defect, and complex anomalies of primary arteries. Increased postnatal mortality was associated with these teratogenic effects in rats. In pregnant rabbits, increased post-implantation loss was noted at an exposure ($AUC_{0\text{-}24hr}$) 5 times the human exposure at the MRHD. Lower doses were not tested in rabbits. The background risk of major birth defects for the indicated population is unknown. The estimated background risk of major birth defects in the U.S. general population is 2 to 4%, however, and the estimated risk of miscarriage is 15 to 20% in clinically recognized pregnancies. Advise a pregnant woman of the potential risk to the fetus.

Clinical Considerations

Disease-associated maternal and/or embryo/fetal risk

Stroke volume and heart rate increase during pregnancy, increasing cardiac output, especially during the first trimester. Pregnant patients with left ventricular ejection fraction less than 35% on maximally tolerated doses of beta-blockers may be particularly heart-rate dependent for augmenting cardiac output. Therefore, pregnant patients who are started on Corlanor, especially during the first trimester, should be followed closely for destabilization of their congestive heart failure that could result from heart rate slowing.

Monitor pregnant women with chronic heart failure in 3rd trimester of pregnancy for preterm birth.

Data

Animal Data

In pregnant rats, oral administration of ivabradine during the period of organogenesis (gestation day 6-15) at doses of 2.3, 4.6, 9.3, or 19 mg/kg/day resulted in fetal toxicity and teratogenic effects. Increased intrauterine and post-natal mortality and cardiac malformations were observed at doses ≥ 2.3 mg/kg/day (equivalent to the human exposure at the MRHD based on $AUC_{0\text{-}24hr}$). Teratogenic effects including interventricular septal defect and complex anomalies of major arteries were observed at doses ≥ 4.6 mg/kg/day (approximately 3 times the human exposure at the MRHD based on $AUC_{0\text{-}24hr}$).

In pregnant rabbits, oral administration of ivabradine during the period of organogenesis (gestation day 6-18) at doses of 7, 14, or 28 mg/kg/day resulted in fetal toxicity and teratogenicity. Treatment with all doses ≥ 7 mg/kg/day (equivalent to the human exposure at the MRHD based on $AUC_{0\text{-}24hr}$) caused an increase in post-implantation loss. At the high dose of 28 mg/kg/day (approximately 15 times the human exposure at the MRHD based on $AUC_{0\text{-}24hr}$), reduced fetal and placental weights were observed, and evidence of teratogenicity (ectrodactylia observed in 2 of 148 fetuses from 2 of 18 litters) was demonstrated.

In the pre- and postnatal study, pregnant rats received oral administration of ivabradine at doses of 2.5, 7, or 20 mg/kg/day from gestation day 6 to lactation day 20. Increased postnatal mortality associated with cardiac teratogenic findings was observed in the F1 pups delivered by dams treated at the high dose (approximately 15 times the human exposure at the MRHD based on $AUC_{0\text{-}24hr}$).

8.2 Lactation

Risk Summary

There is no information regarding the presence of ivabradine in human milk, the effects of ivabradine on the breastfed infant, or the effects of the drug on milk production. Animal studies have shown, however, that ivabradine is present in rat milk *[see Data]*. Because of the potential risk to breastfed infants from exposure to Corlanor, breastfeeding is not recommended.

Data

Lactating rats received daily oral doses of [^{14}C]-ivabradine (7 mg/kg) on post-parturition days 10 to 14; milk and maternal plasma were collected at 0.5 and 2.5 hours post-dose on day 14. The ratios of total radioactivity associated with [^{14}C]-ivabradine or its metabolites in milk vs. plasma were 1.5 and 1.8, respectively, indicating that ivabradine is transferred to milk after oral administration.

8.3 Females and Males of Reproductive Potential

Contraception

Females

Corlanor may cause fetal harm, based on animal data. Advise females of reproductive potential to use effective contraception during Corlanor treatment *[see Use in Specific Populations (8.1)]*.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

No pharmacokinetic differences have been observed in elderly (≥ 65 years) or very elderly (≥ 75 years) patients compared to the overall population. However, Corlanor has only been studied in a limited number of patients ≥ 75 years of age.

8.6 Hepatic Impairment

No dose adjustment is required in patients with mild or moderate hepatic impairment. Corlanor is contraindicated in patients with severe hepatic impairment (Child-Pugh C) as it has not been studied in this population and an increase in systemic exposure is anticipated *[see Contraindications (4) and Clinical Pharmacology (12.3)]*.

8.7 Renal Impairment

No dosage adjustment is required for patients with creatinine clearance 15 to 60 mL/min. No data are available for patients with creatinine clearance below 15 mL/min *[see Clinical Pharmacology (12.3)]*.

10. OVERDOSAGE

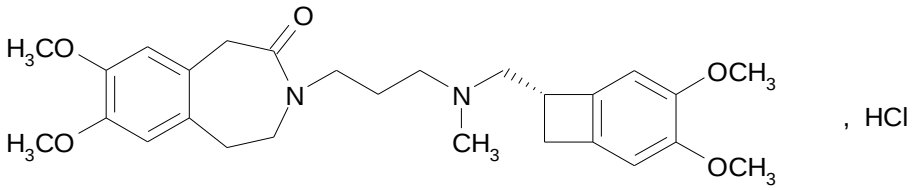
Overdose may lead to severe and prolonged bradycardia. In the event of bradycardia with poor hemodynamic tolerance, temporary cardiac pacing may be required. Supportive treatment, including intravenous (IV) fluids, atropine, and intravenous beta-stimulating agents such as isoproterenol, may be considered.

11. DESCRIPTION

Corlanor (ivabradine) is a hyperpolarization-activated cyclic nucleotide-gated channel blocker that reduces the spontaneous pacemaker activity of the cardiac sinus node by selectively inhibiting the I_f-current (I_f), resulting in heart rate reduction with no effect on ventricular repolarization and no effects on myocardial contractility.

The chemical name for ivabradine is 3-(3-{[((7*S*)-3,4-Dimethoxybicyclo[4.2.0]octa-1,3,5-trien-7-yl)methyl] methyl amino} propyl)-1,3,4,5-tetrahydro-7,8-dimethoxy-2H-3-benzazepin-2-one, hydrochloride. The molecular formula is $C_{27}H_{36}N_2O_5$, HCl, and the molecular weight (free base + HCl) is 505.1 (468.6 + 36.5). The chemical structure of ivabradine is shown in Figure 1.

Figure 1. Chemical Structure of Ivabradine



Corlanor tablets are formulated as salmon-colored, film-coated tablets for oral administration in strengths of 5 mg and 7.5 mg of ivabradine as the free base equivalent.

Inactive Ingredients

Core

Lactose monohydrate, maize starch, maltodextrin, magnesium stearate, colloidal silicon dioxide

Film Coating

Hypromellose, titanium dioxide, glycerol, magnesium stearate, polyethylene glycol 6000, yellow iron oxide, red iron oxide

12. CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Corlanor blocks the hyperpolarization-activated cyclic nucleotide-gated (HCN) channel responsible for the cardiac pacemaker I_f current, which regulates heart rate. In clinical electrophysiology studies, the cardiac effects were most pronounced in the sinoatrial (SA) node, but prolongation of the AH interval has occurred on the surface ECG, as has PR interval prolongation. There was no effect on ventricular repolarization and no effects on myocardial contractility *[see Clinical Pharmacology (12.2)]*.

Corlanor can also inhibit the retinal current I_h. I_h is involved in curtailing retinal responses to bright light stimuli. Under triggering circumstances (e.g., rapid changes in luminosity), partial inhibition of I_h by Corlanor may underlie the luminous phenomena experienced by patients. Luminous phenomena (phosphenes) are described as a transient enhanced brightness in a limited area of the visual field *[see Adverse Reactions (6.1)]*.

12.2 Pharmacodynamics

Corlanor causes a dose-dependent reduction in heart rate. The size of the effect is dependent on the baseline heart rate (i.e., greater heart rate reduction occurs in subjects with higher baseline heart rate). At recommended doses, heart rate reduction is approximately 10 bpm at rest and during exercise. Analysis of heart rate reduction vs. dose indicates a plateau effect at doses > 20 mg twice daily. In a study of subjects with preexisting conduction system disease (first- or second-degree AV block or left or right bundle branch block) requiring electrophysiologic study, IV ivabradine (0.20 mg/kg) administration slowed the overall heart rate by approximately 15 bpm, increased the PR interval (29 msec), and increased the AH interval (27 msec).

Corlanor does not have negative inotropic effects. Ivabradine increases the uncorrected QT interval with heart rate slowing but does not cause rate-corrected prolongation of QT.

12.3 Pharmacokinetics

Absorption and Bioavailability

Following oral administration, peak plasma ivabradine concentrations are reached in approximately 1 hour under fasting conditions. The absolute oral bioavailability of ivabradine is approximately 40% because of first-pass elimination in the gut and liver.

Food delays absorption by approximately 1 hour and increases plasma exposure by 20% to 40%. Corlanor should be taken with meals *[see Dosage and Administration (2)]*.

Ivabradine is approximately 70% plasma protein bound, and the volume of distribution at steady state is approximately 100 L.

Metabolism and Excretion

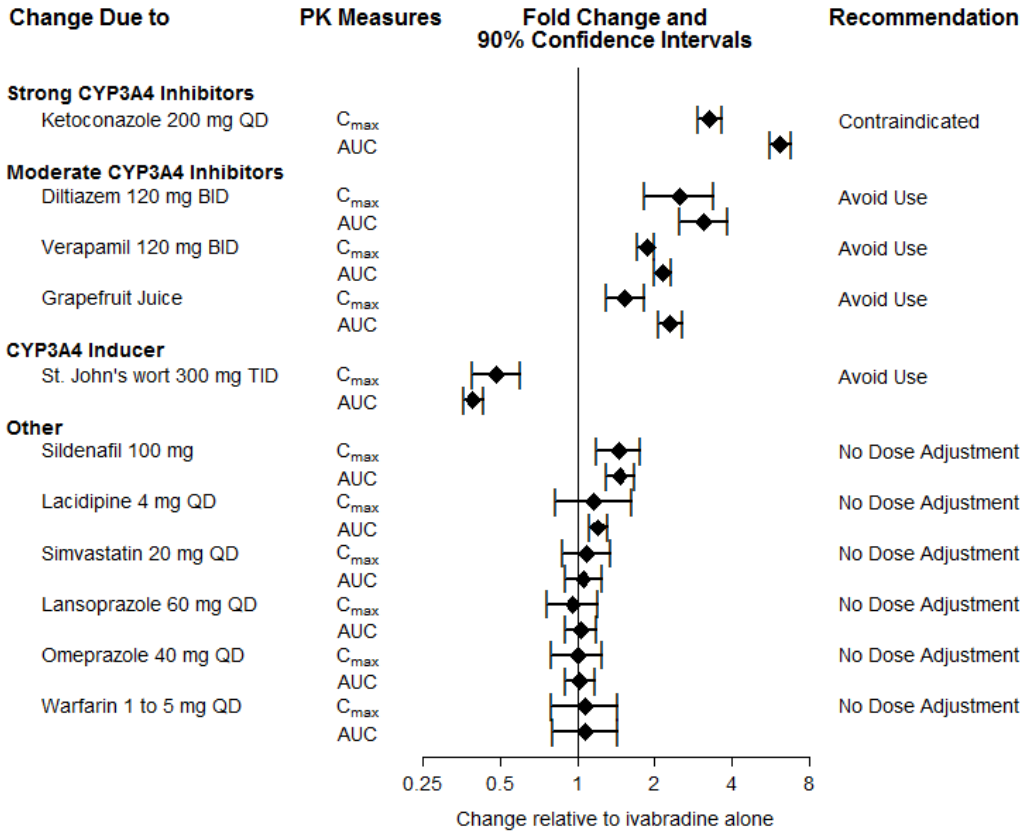
The pharmacokinetics of ivabradine are linear over an oral dose range of 0.5 mg to 24 mg. Ivabradine is extensively metabolized in the liver and intestines by CYP3A4-mediated oxidation. The major metabolite is the N-desmethylated derivative (S 18982), which is equipotent to ivabradine and circulates at concentrations approximately 40% that of ivabradine. The N-desmethylated derivative is also metabolized by CYP3A4. Ivabradine plasma levels decline with a distribution half-life of 2 hours and an effective half-life of approximately 6 hours.

The total clearance of ivabradine is 24 L/h, and renal clearance is approximately 4.2 L/h, with ~ 4% of an oral dose excreted unchanged in urine. The excretion of metabolites occurs to a similar extent via feces and urine.

Drug Interactions

The effects of coadministered drugs (CYP3A4 inhibitors, substrates, inducers, and other concomitantly administered drugs) on the pharmacokinetics of Corlanor were studied in several single- and multiple-dose studies. Pharmacokinetic measures indicating the magnitude of these interactions are presented in Figure 2.

Figure 2. Impact of Coadministered Drugs on the Pharmacokinetics of Corlanor



Digoxin exposure did not change when concomitantly administered with ivabradine. No dose adjustment is required when ivabradine is concomitantly administered with digoxin.

Effect of Ivabradine on Metformin Pharmacokinetics

Ivabradine, dosed at 10 mg twice daily to steady state, did not affect the pharmacokinetics of metformin (an organic cation transporter [OCT2] sensitive substrate). The geometric mean (90% confidence interval [CI]) ratios of C_{max} and AUC_{inf} of metformin, with and without ivabradine were 0.98 [0.83-1.15] and 1.02 [0.86-1.22], respectively. No dose adjustment is required for metformin when administered with Corlanor.

Specific Populations

Age

No pharmacokinetic differences (AUC or C_{max}) have been observed between elderly (≥ 65 years) or very elderly (≥ 75 years) patients and the overall patient population *[see Use in Specific Populations (8.5)]*.

Hepatic Impairment

In patients with mild (Child-Pugh A) and moderate (Child-Pugh B) hepatic impairment, the pharmacokinetics of Corlanor were similar to that in patients with normal hepatic function. No data are available in patients with severe hepatic impairment (Child-Pugh C) *[see Contraindications (4)]*.

Renal Impairment

Renal impairment (creatinine clearance from 15 to 60 mL/min) has minimal effect on the pharmacokinetics of Corlanor. No data are available for patients with creatinine clearance below 15 mL/min.

Pediatrics

The pharmacokinetics of Corlanor have not been investigated in patients < 18 years of age.

13. NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

There was no evidence of carcinogenicity when mice and rats received ivabradine up to 104 weeks by dietary administration. High doses in these studies were associated with mean ivabradine exposures of at least 37 times higher than the human exposure ($AUC_{0\text{-}24hr}$) at the MRHD.

Ivabradine tested negative in the following assays: bacterial reverse mutation (Ames) assay, *in vivo* bone marrow micronucleus assay in both mouse and rat, *in vivo* chromosomal aberration assay in rats, and *in vivo* unscheduled DNA synthesis assay in rats. Results of the *in vitro* chromosomal aberration assay were equivocal at concentrations approximately 1,500 times the human C_{max} at the MRHD. Ivabradine tested positive in the mouse lymphoma assays and *in vitro* unscheduled DNA synthesis assay in rat hepatocytes at concentrations greater than 1,500 times the human C_{max} at the MRHD.

Reproduction toxicity studies in animals demonstrated that ivabradine did not affect fertility in male or female rats at exposures 46 to 133 times the human exposure ($AUC_{0\text{-}24hr}$) at the MRHD.

13.2 Animal Toxicology and/or Pharmacology

Reversible changes in retinal function were observed in dogs administered oral ivabradine at total doses of 2, 7, or 24 mg/kg/day (approximately 0.6 to 50 times the human exposure at the MRHD based on $AUC_{0\text{-}24hr}$) for 52 weeks. Retinal function assessed by electroretinography demonstrated reductions in cone system responses, which reversed within a week post-dosing, and were not associated with damage to ocular structures as evaluated by light microscopy. These data are consistent with the pharmacological

effect of ivabradine related to its interaction with hyperpolarization-activated I_h currents in the retina, which share homology with the cardiac pacemaker I_f current.

14. CLINICAL STUDIES

SHIFT

The Systolic Heart failure treatment with the I_f inhibitor ivabradine Trial (SHIFT) was a randomized, double-blind trial comparing Corlanor and placebo in 6558 adult patients with stable NYHA class II to IV heart failure, left ventricular ejection fraction ≤ 35%, and resting heart rate ≥ 70 bpm. Patients had to have been clinically stable for at least 4 weeks on an optimized and stable clinical regimen, which included maximally tolerated doses of beta-blockers and, in most cases, ACE inhibitors or ARBs, spironolactone, and diuretics, with fluid retention and symptoms of congestion minimized. Patients had to have been hospitalized for heart failure within 12 months prior to study entry.

The underlying cause of CHF was coronary artery disease in 68% of patients. At baseline, approximately 49% of randomized subjects were NYHA class II, 50% were NYHA class III, and 2% were NYHA class IV. The mean left ventricular ejection fraction was 29%. All subjects were initiated on Corlanor 5 mg (or matching placebo) twice daily and the dose was increased to 7.5 mg twice daily or decreased to 2.5 mg twice daily to maintain the resting heart rate between 50 and 60 bpm, as tolerated. The primary endpoint was a composite of the first occurrence of either hospitalization for worsening heart failure or cardiovascular death.

Most patients (89%) were taking beta-blockers, with 26% on guideline-defined target daily doses. The main reasons for not receiving the target beta-blocker doses at baseline were hypotension (45% of patients not at target), fatigue (32%), dyspnea (14%), dizziness (12%), history of cardiac decompensation (9%), and bradycardia (6%). For the 11% of patients not receiving any beta-blocker at baseline, the main reasons were chronic obstructive pulmonary disease, hypotension, and asthma. Most patients were also taking ACE inhibitors and/or angiotensin II antagonists (91%), diuretics (83%), and anti-aldosterone agents (60%). Few patients had an implantable cardioverter-defibrillator (ICD) (3.2%) or a cardiac resynchronization therapy (CRT) device (1.1%). Median follow-up was 22.9 months. At 1 month, 63%, 26%, and 8% of Corlanor-treated patients were taking 7.5, 5, and 2.5 mg BID, whereas 3% had withdrawn from the drug, primarily for bradycardia.

SHIFT demonstrated that Corlanor reduced the risk of the combined endpoint of hospitalization for worsening heart failure or cardiovascular death based on a time-to-event analysis (hazard ratio: 0.82, 95% confidence interval [CI]: 0.75, 0.90, $p < 0.0001$) (Table 3). The treatment effect reflected only a reduction in the risk of hospitalization for worsening heart failure; there was no favorable effect on the mortality

component of the primary endpoint. In the overall treatment population, Corlanor had no statistically significant benefit on cardiovascular death.

Table 3. SHIFT – Incidence of the Primary Composite Endpoint and Components

	Corlanor (N = 3241)			Placebo (N = 3264)					
Endpoint	**n**	**%**	**% PY**	**n**	**%**	**% PY**	**Hazard Ratio**	**[95% CI]**	**p-value**
Primary composite endpoint: Time to first hospitalization for worsening heart failure or cardiovascular death[a]	793	24.5	14.5	937	28.7	17.7	0.82	[0.75 , 0.90]	< 0.0001
Hospitalization for worsening heart failure	505	15.6	9.2	660	20.2	12.5			
Cardiovascular death as first event	288	8.9	4.8	277	8.5	4.7			
Subjects with events at any time									
Hospitalization for worsening heart failure[b]	514	15.9	9.4	672	20.6	12.7	0.74	[0.66 , 0.83]	
Cardiovascular death[b]	449	13.9	7.5	491	15.0	8.3	0.91	[0.80 , 1.03]	

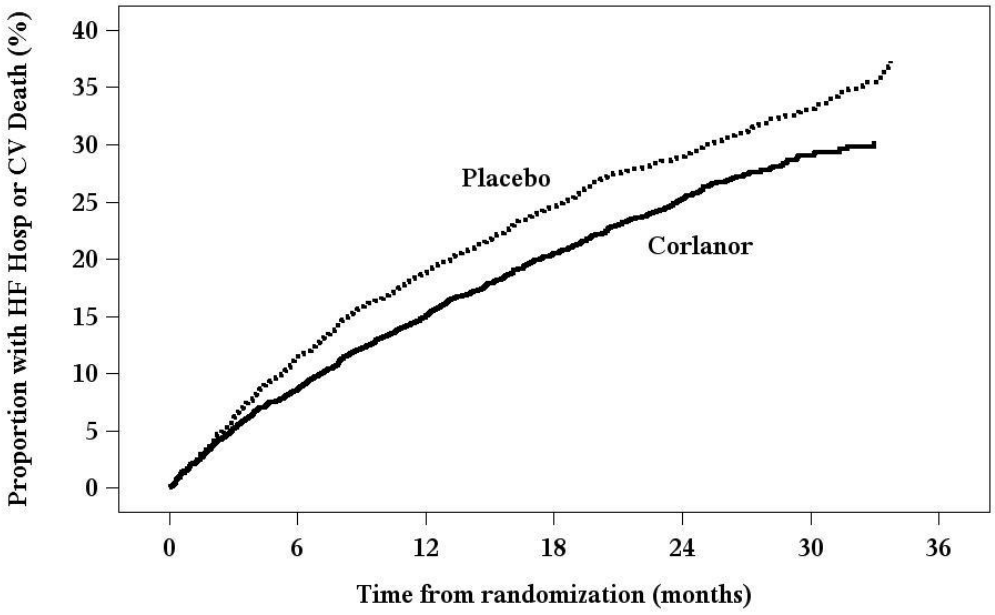
[a] Subjects who died on the same calendar day as their first hospitalization for worsening heart failure are counted under cardiovascular death.

[b] Analyses of the components of the primary composite endpoint were not prospectively planned to be adjusted for multiplicity.

N: number of patients at risk; n: number of patients having experienced the endpoint; %: incidence rate = (n/N) x 100; % PY: annual incidence rate = (n/number of patient-years) x 100; CI: confidence interval
The hazard ratio between treatment groups (ivabradine/placebo) was estimated based on an adjusted Cox proportional hazards model with beta-blocker intake at randomization (yes/no) as a covariate; p-value: Wald test

The Kaplan-Meier curve (Figure 3) shows time to first occurrence of the primary composite endpoint of hospitalization for worsening heart failure or cardiovascular death in the overall study.

Figure 3. SHIFT: Time to First Event of Primary Composite Endpoint

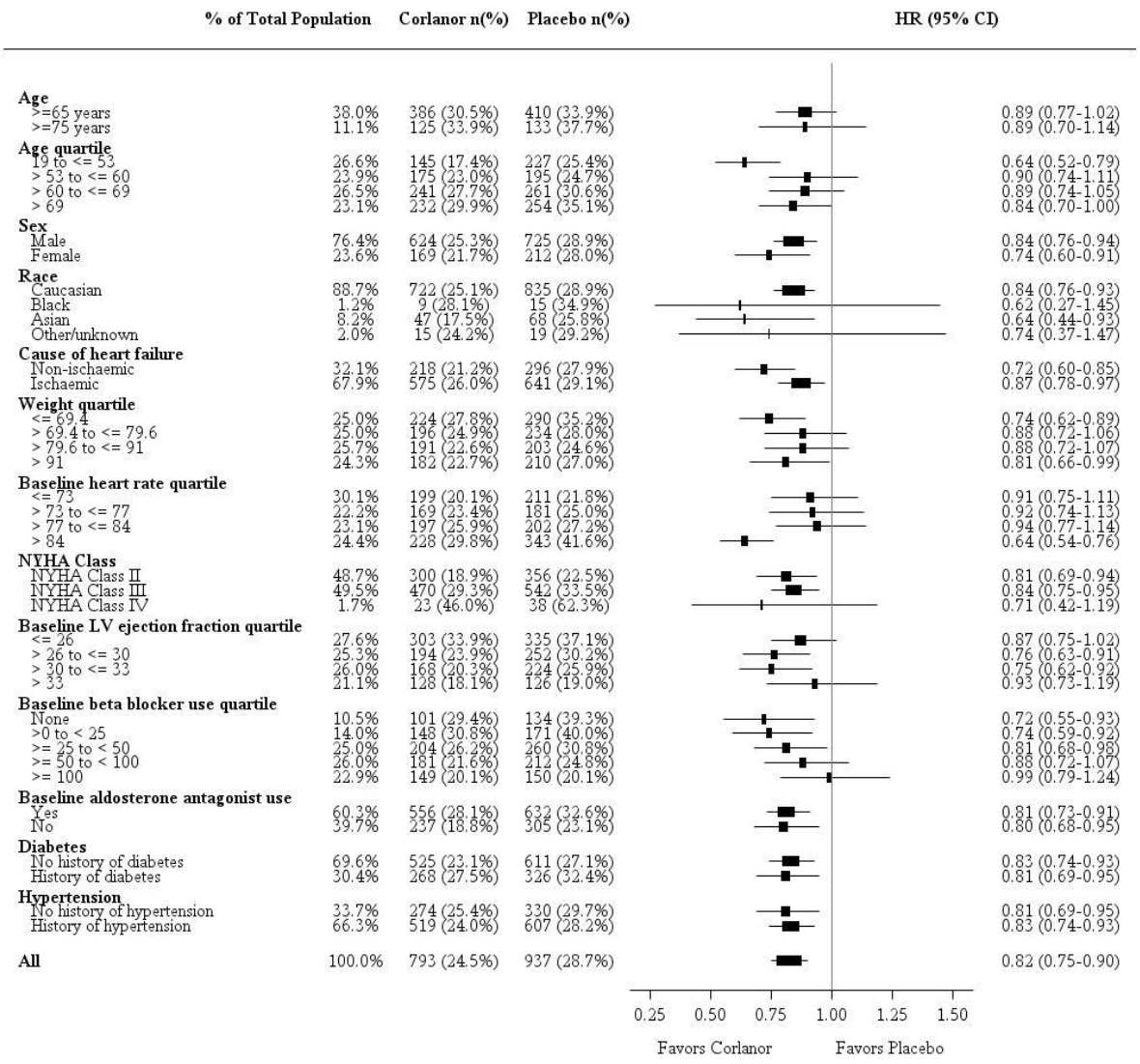


Number of Subjects at Risk:							
Placebo	3264	2868	2489	2061	1089	439	17
Corlanor	3241	2928	2600	2173	1191	447	16

A wide range of demographic characteristics, baseline disease characteristics, and baseline concomitant medications were examined for their influence on outcomes. Many of these results are shown in Figure 4. Such analyses must be interpreted cautiously, as differences can reflect the play of chance among a large number of analyses.

Most of the results show effects consistent with the overall study result. Corlanor's benefit on the primary endpoint in SHIFT appeared to decrease as the dose of beta-blockers increased, with little if any benefit demonstrated in patients taking guideline-defined target doses of beta-blockers.

Figure 4. Effect of Treatment on Primary Composite Endpoint in Subgroups



Note: The figure above presents effects in various subgroups, all of which are baseline characteristics. The 95% confidence limits that are shown do not take into account the number of comparisons made, and may not reflect the effect of a particular factor after adjustment for all other factors. Apparent homogeneity or heterogeneity among groups should not be over-interpreted.

<u>BEAUTIFUL and SIGNIFY: No benefit in stable coronary artery disease with or without stable heart failure</u>

BEAUTIFUL was a randomized, double-blind, placebo-controlled trial in 10,917 adult patients with coronary artery disease, impaired left ventricular systolic function (ejection fraction < 40%) and resting heart rate ≥ 60 bpm. Patients had stable symptoms of heart failure and/or angina for at least 3 months, and were receiving conventional cardiovascular medications at stable doses for at least 1 month. Beta-blocker

therapy was not required, nor was there a protocol mandate to achieve any specific dosing targets for patients who were taking beta-blockers. Patients were randomized 1:1 to Corlanor or placebo at an initial dose of 5 mg twice daily with the dose increased to 7.5 mg twice daily depending on resting heart rate and tolerability. The primary endpoint was the composite of time to first cardiovascular death, hospitalization for acute myocardial infarction, or hospitalization for new-onset or worsening heart failure. Most patients were NYHA class II (61.4%) or class III (23.2%) - none were class IV. Through a median follow-up of 19 months, Corlanor did not significantly affect the primary composite endpoint (HR 1.00, 95% CI = 0.91, 1.10).

SIGNIFY was a randomized, double-blind trial administering Corlanor or placebo to 19,102 adult patients with stable coronary artery disease but without clinically evident heart failure (NYHA class I). Beta-blocker therapy was not required. Corlanor was initiated at a dose of 7.5 mg twice daily and the dose could be increased to as high as 10 mg twice daily or down-titrated to 5.0 mg twice daily to achieve a target heart rate of 55 to 60 bpm. The primary endpoint was a composite of the first occurrence of either cardiovascular death or myocardial infarction. Through a median follow-up of 24.1 months, Corlanor did not significantly affect the primary composite endpoint (HR 1.08, 95% CI = 0.96, 1.20).

16. HOW SUPPLIED/STORAGE AND HANDLING

Corlanor 5 mg tablets are formulated as salmon-colored, oval-shaped, film-coated tablets scored on both edges, marked with “5” on one face and bisected on the other face. They are supplied as follows:

- Bottles of 60 tablets (NDC 55513-800-60)
- Bottles of 180 tablets (NDC 55513-800-80)

Corlanor 7.5 mg tablets are formulated as salmon-colored, triangular-shaped, film-coated tablets debossed with “7.5” on one face and plain on the other face. They are supplied as follows:

- Bottles of 60 tablets (NDC 55513-810-60)
- Bottles of 180 tablets (NDC 55513-810-80)

Storage

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

17. PATIENT COUNSELING INFORMATION

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

- Fetal Toxicity

  Advise pregnant women of the potential risks to a fetus.

  Advise females of reproductive potential to use effective contraception and to notify their healthcare provider with a known or suspected pregnancy *[see Warnings and Precautions (5.1) and Use in Specific Populations (8.1, 8.3)]*.

- Low Heart Rate

  Advise patients to report significant decreases in heart rate or symptoms such as dizziness, fatigue, or hypotension *[see Warnings and Precautions (5.3)]*.

- Atrial fibrillation

  Advise patients to report symptoms of atrial fibrillation, such as heart palpitations or racing, chest pressure, or worsened shortness of breath *[see Warnings and Precautions (5.2)]*.

- Phosphenes

  Advise patients about the possible occurrence of luminous phenomena (phosphenes). Advise patients to use caution if they are driving or using machines in situations where sudden changes in light intensity may occur, especially when driving at night. Advise patients that phosphenes may subside spontaneously during continued treatment with Corlanor *[see Adverse Reactions (6.1)]*.

- Drug Interactions

  Advise patients to avoid ingestion of grapefruit juice and St. John's wort *[see Drug Interactions (7.1)]*.

- Intake with Food

  Advise patients to take Corlanor twice daily with meals *[see Dosage and Administration (2)]*.

AMGEN®

Corlanor® (ivabradine)
Manufactured for:
Amgen Inc.
One Amgen Center Drive
Thousand Oaks, California 91320-1799

Patent: http://pat.amgen.com/Corlanor/

v2

MEDICATION GUIDE
Corlanor® (core' lan ore)
(ivabradine)
Tablets

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

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

Corlanor may cause serious side effects, including:

- **Harm to your unborn baby.** You should not become pregnant while taking Corlanor. Women who are able to get pregnant must use birth control when taking Corlanor. If you become pregnant while taking Corlanor, tell your doctor right away.
- **Increased risk of irregular or rapid heartbeat (atrial fibrillation or heart rhythm problems).** Tell your doctor if you have symptoms of an irregular or rapid heartbeat, such as feeling that your heart is pounding or racing (palpitations), chest pressure, worsened shortness of breath, near fainting or fainting.
- **Low heart rate (bradycardia).** Tell your doctor if you have a slowing of your heart rate or if you have symptoms of a low heart rate such as dizziness, fatigue, lack of energy, or have low blood pressure. Low heart rate is a common side effect of Corlanor and can be serious.

What is Corlanor?
Corlanor is a prescription medicine that is used to reduce the risk of hospitalization for worsening heart failure in people who have chronic heart failure.

- It is not known if Corlanor is safe and effective in children.

Who should not take Corlanor?

Do not take Corlanor if:

- You have symptoms of heart failure that recently worsened.
- You have low blood pressure (less than 90/50 mmHg).
- You have a certain heart condition called sick sinus syndrome, sinoatrial block, or 3rd degree atrioventricular block.
- You have a slow resting heart rate (less than 60 beats per minute) before treatment with Corlanor.
- You are taking medicines that can change how much Corlanor gets into your body after it is swallowed. Your doctor can advise you if you are taking a medicine that should not be used with Corlanor.

What should I tell my doctor before taking Corlanor?

Before you take Corlanor, tell your doctor about all of your medical conditions, including if you:

- Have any other heart problems, including heart rhythm problems, a slow heart rate, or a heart conduction problem.
- Are breastfeeding or plan to breastfeed. It is not known if Corlanor passes into your breast milk. You and your doctor should decide if you will take Corlanor or breastfeed. You should not do both.

Tell your doctor about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Corlanor may affect the way other medicines work, and other medicines may affect how Corlanor works, and could cause serious side effects.

How should I take Corlanor?

- Take Corlanor exactly as your doctor tells you to take it.
- Your doctor may change your dose of Corlanor during treatment.
- If you take too much Corlanor, call your doctor or go to the nearest emergency room right away.
- If you forget to take a dose of Corlanor, take the next dose at the usual time. Do not take a double dose to make up for the forgotten dose.

What should I avoid while taking Corlanor?

Avoid drinking grapefruit juice and taking St. John's wort during treatment with Corlanor. These can affect the way Corlanor works and may cause serious side effects.

What are the possible side effects of Corlanor?

See **"What is the most important information I should know about Corlanor?"**

The most common side effects of Corlanor are:

- Increased blood pressure.
- Temporary brightness in your field of vision, usually caused by sudden changes in light (luminous phenomena). This brightness usually happens within the first 2 months of treatment with Corlanor and usually goes away during or after treatment with Corlanor. Use caution when driving or operating machinery where sudden changes in light can happen, especially when driving at night.

These are not all the side effects of Corlanor. 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 Corlanor?

- Store Corlanor at room temperature between 68°F to 77°F (20°C to 25°C).
- Safely throw away medicine that is out of date or no longer needed.

Keep Corlanor and all medicines out of the reach of children.

General information about the safe and effective use of Corlanor

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use Corlanor for a condition for which it was not prescribed. Do not give Corlanor to other people, even if they have the same symptoms that you have. It may harm them. You can ask your doctor or pharmacist for information about Corlanor that is written for health professionals.

What are the ingredients in Corlanor?

Active ingredient: ivabradine

Inactive ingredients:

Core: Lactose monohydrate, maize starch, maltodextrin, magnesium stearate, colloidal silicon dioxide

Film Coating: Hypromellose, titanium dioxide, glycerol, magnesium stearate, polyethylene glycol 6000, yellow iron oxide, red iron oxide

AMGEN®

Corlanor® (ivabradine)

Manufactured for:

Amgen Inc.
One Amgen Center Drive
Thousand Oaks, California 91320-1799

Patent: http://pat.amgen.com/Corlanor/

For more information, go to www.Corlanor.com or call 1-800-772-6436.
Medication Guide has been approved by the U.S. Food and Drug Administration.
Issued: 01/2017

v2

Linzess® *(linaclotide) capsules*

Indication(s)	Treatment of irritable bowel syndrome with constipation, chronic idiopathic constipation in adult patients
FDA Approval	August 30, 2012
Treatment Comparisons for Indications	Amitiza (lubiprostone), osmotic laxatives
Place in Therapy	Guanylate cyclase agonist; unique MOA
Dosage and Administration	***Strengths Available:*** 72mcg, 145mcg, 290 mcg capsules ***Dosage Frequency:*** Take once daily on empty stomach at least 30 minutes prior to first meal
Safety	***Contraindications:*** mechanical GI obstruction, patients < 6 years old ***Warnings:*** Diarrhea, potentially severe ***Drug Interactions:*** No known significant drug interactions
Use in Specific Populations	***Pregnancy:*** category C, based on animal data. May cause fetal harm ***Nursing:*** Breastfeeding not recommended ***Pediatric:*** Safety and efficacy in pediatric patients < 6 years old has not been established ***Geriatric:*** Use with caution
Formulary Considerations	***Proposed Formulary Addition*****:** Tier 2 Amitiza (lubiprostone) at Tier 2; multiple generic osmotic laxatives at Tier 1
Utilization	Previously approved as nonformulary; only available via approved formulary exceptions
Conclusion	Accept formulary addition as proposed

Obredon®

(hydrocodone bitartrate and guaifenesin) oral solution

Indication(s)	Opioid antitussive and expectorant for symptomatic relief of cough and to loosen mucus associated with the common cold in patients > 18 years of age
FDA Approval	Nov 14, 2014
Treatment Comparisons for Indications	Decongestants, cough suppressants, expectorants, antihistamines, anticholinergics, NSAIDs
Place in Therapy	Last line after all non-pharmacotherapy and over-the-counter treatments have failed
Dosage and Administration	***Strengths Available:*** 2.5 mg hydrocodone & 200 mg guaifenesin per 5 mL ***Dosage Frequency:*** 10 mL every 4 to 6 hours, not to exceed 6 doses (60 mL) in 24 hours
Safety	***Contraindications:*** hypersensitivity to any of the active or inactive ingredients, MAOI therapy ***Warnings:*** dose-related respiratory depression, drug dependence, head injury & increased intracranial pressure, activities requiring mental alertness, acute abdominal conditions, coexisting conditions ***Drug Interactions:*** opioids, antihistamines, antipsychotics, anti-anxiety agents, or other CNS depressants (including alcohol), MAOIs, TCAs, anticholinergics
Use in Specific Populations	***Pregnancy:*** category C ***Nursing:*** caution, is excreted in human milk ***Pediatric:*** safety and effectiveness has not been established ***Geriatric:*** clinical experience has not identified differences in elderly vs younger
Formulary Considerations	Expansive availability of generic first line agents
Conclusion	Additional low dose opioid option for refractory cough due to the common cold

Belsomra®

(suvorexant) tablets, for oral use

Indication(s)	Orexin receptor antagonist used for the treatment of insomnia, characterized by difficulties with sleep onset and/or sleep maintenance
FDA Approval	Aug 13, 2014
Treatment Comparisons for Indications	Non-medical, benzodiazepines, nonbenzodiazepines, melatonin agonists, antidepressants, diphenhydramine, antipsychotics, barbiturates, over-the-counter (herbals, melatonin, homeopathic)
Place in Therapy	Novel therapy with similar characteristics to other sedatives; use in refractory insomnia cases
Dosage and Administration	***Strengths Available:*** 5, 10, 15, or 20 mg tablets ***Dosage Frequency:*** 10 mg once per night 30 minutes prior to sleep, titrate to a maximum of 20 mg once daily
Safety	***Contraindications:*** narolepsy ***Warnings:*** daytime somnolence, evaluate for co-morbidities, nighttime sleep driving, depression, compromised respiratory function, sleep paralysis ***Drug Interactions:*** CNS-active agents (alcohol), CYP3A inhibitors & Inducers, digoxin
Use in Specific Populations	***Pregnancy:*** category C ***Nursing:*** caution, unknown if excreted in human milk ***Pediatric:*** safety and effectiveness has not been established ***Geriatric:*** clinical experience has not identified differences in elderly vs younger
Formulary Considerations	There is other generic and brand named availability of additional options for insomnia
Conclusion	Additional option for patients suffering from insomnia, that may or may not have failed other established therapies

North Carolina State Health Plan
FOR TEACHERS AND STATE EMPLOYEES
A Division of the Department of State Treasurer

PRIOR AUTHORIZATION CRITERIA

DRUG CLASS	**INSOMNIA AGENTS**
BRAND NAME	**BELSOMRA**
(generic)	**(suvorexant)**

Type: Initial Prior Authorization; Initial Step Therapy; Post Step Therapy Prior Authorization

POLICY

FDA-APPROVED INDICATIONS
Belsomra (suvorexant) is indicated for the treatment of insomnia characterized by difficulties with sleep onset and/or sleep maintenance.

INITIAL STEP THERAPY
If the patient has filled a prescription for a least a 30 day supply of a generic non-benzodiazepine hypnotic within the past 180 days under a prescription benefit administered by CVS Caremark, then the requested branded drug will be paid under that prescription benefit. If the patient does not meet the initial step therapy criteria, then a prior authorization (PA) is required. The prior authorization criteria would then be applied to requests submitted for evaluation to the PA unit.

COVERAGE CRITERIA
Belsomra (suvorexant) will be covered with prior authorization when the following criteria are met:

- The drug is being prescribed for the treatment of insomnia characterized by difficulties with sleep onset and/or sleep maintenance
  AND
- Potential causes of sleep disturbances have been addressed (e.g., inappropriate sleep hygiene and sleep environment issues or treatable medical/psychological causes of chronic insomnia)
  AND
- The patient does not have a diagnosis of narcolepsy
  AND
- If the patient is 65 years of age or older, the patient experienced an inadequate treatment response, intolerance or contraindication to Rozerem, Silenor or trazodone
  OR
- If the patient is less than 65 years of age, the patient experienced an inadequate treatment response, intolerance or contraindication to a generic non-benzodiazepine sedative-hypnotic (e.g., zolpidem) and a short acting benzodiazepine (e.g., temazepam)

RATIONALE
If the patient has filled a prescription for a least a 30 day supply of a generic non-benzodiazepine hypnotic within the past 180 days under a prescription benefit administered by CVS Caremark, then the requested branded drug will be paid under that prescription benefit.

If the patient does not meet the initial step therapy criteria, then prior authorization is required.

If the patient has a documented contraindication to or a potential drug interaction with a generic drug, then the requested brand drug will be covered. If the patient is intolerant to at least one of the generic drugs, then the requested brand drug will be covered. If the patient has tried one of the generic drugs for at least 30 days and had an inadequate treatment response, then the requested brand drug will be covered. If these requirements are met, then the approval duration is 24 months.

Quantity Limits may apply.

REFERENCES

1. Belsomra [package insert]. Whitehouse Station, NY: Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.; August 2014.
2. National Institutes of Health. NIH State-of-the Science Conference Statement on Manifestations and Management of Chronic Insomnia in Adults. Volume 22, Number 2. June 13-15, 2005.
3. Silber, MH. Chronic Insomnia. *N Engl J Med*. 2005; 353: 803-810.
4. Krystal, AD. The Changing Perspective on Chronic Insomnia Management. *J Clin Psychiatry.* 2004; 65(S8): 20-25.
5. Ramakrishnan K, Scheid DC. Treatment Options for Insomnia. *American Family Physician*. August 15, 2007; 76(4):517-527.
6. Schutte-Rodin S; Broch L; Buysse D; Dorsey C; Sateia M. Clinical guideline for the evaluation and management of chronic insomnia in adults. *J Clin Sleep Med 2008*;4(5):487-504.
7. Morgenthaler T; Kramer M; Alessi C et al. Practice parameters for the psychological and behavioral treatment of insomnia: an update. An American Academy of Sleep Medicine report. *SLEEP* 2006;29(11):1415-1419.
8. Micromedex Solutions [database online]. Greenwood Village, CO: Truven Health Analytics Inc. Updated periodically. www.micromedexsolutions.com [available with subscription]. Accessed May 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 2016.
10. NCQA. 2015. (on line) www.ncqa.org. Accessed May 2016.
11. Steven, A., Colombi, A., et al. Potentially Inappropriate Medications and Risk of Hospitalization in Retirees. Drugs. Aging. 2010 May; 27(5):407-415.
12. Patient Safety Analysis: HRM Measures – Report User Guide. July 2015. Acumen LLC.
13. The American Geriatrics Society 2015 Beers Criteria Update Expert Panel. American Geriatrics Society 2015 Updated Beers Criteria for Potentially Inappropriate Medication Use in Older Adults. American Geriatrics Society. 2015.
14. Hanlon, Joseph T, PharmD, MS, Semla, Todd P. MS, PharmD and Schmader, Kenneth E. MD. Alternative Medications for Medications in the Use of High-Risk Medications in the Elderly and Potentially Harmful Drug–Disease Interactions in the Elderly Quality Measures. Journal of American Geriatrics Society.2015.
15. Qaseem A, Kansagara D, Forciea MA, Cooke M, Denberg TD, for the Clinical Guidelines Committee of the American College of Physicians. Management of Chronic Insomnia Disorder in Adults: A Clinical Practice Guideline From the American College of Physicians. *Ann Intern Med*. Epub ahead of print May 3, 2016. doi:10.7326/M15-2175.

BINDER DIVIDER

"Utilization Management"

PRIOR AUTHORIZATION CRITERIA

DRUG CLASS	**NARCOLEPSY AGENTS**
BRAND NAME	**PROVIGIL**
(generic)	**(modafinil)**

Status: CVS Caremark
Type: Initial Prior Authorization

POLICY

FDA-APPROVED INDICATIONS
Provigil is indicated to improve wakefulness in adult patients with excessive sleepiness associated with narcolepsy, obstructive sleep apnea, and shift work disorder.

In OSA, Provigil is indicated as an adjunct to standard treatment(s) for the underlying obstruction. If continuous positive airway pressure (CPAP) is the treatment of choice for a patient, a maximal effort to treat with CPAP for an adequate period of time should be made prior to initiating Provigil. If Provigil is used adjunctively with CPAP, the encouragement of and periodic assessment of CPAP compliance is necessary.

In all cases, careful attention to the diagnosis and treatment of the underlying sleep disorder(s) is of utmost importance. Prescribers should be aware that some patients may have more than one sleep disorder contributing to their excessive sleepiness.

The effectiveness of modafinil in long-term use (greater than 9 weeks in Narcolepsy clinical trials and 12 weeks in OSA and SWD clinical trials) has not been systematically evaluated in placebo-controlled trials. The physician who elects to prescribe Provigil for an extended time in patients with Narcolepsy, OSA, or SWD should periodically reevaluate long-term usefulness for the individual patient.

COVERAGE CRITERIA
PROVIGIL will be covered with prior authorization when the following criteria are met:

- The patient has a diagnosis of narcolepsy confirmed by sleep lab evaluation

OR

- The patient has a diagnosis of Shift Work Disorder (SWD).

OR

- The patient has a diagnosis of obstructive sleep apnea (OSA) confirmed by polysomnography.

REFERENCES

1. Provigil [package insert]. Frazer, PA: Cephalon, Inc.; January 2015.
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 May 2016.
3. Micromedex Solutions [database online]. Greenwood Village, CO: Truven Health Analytics Inc. Updated periodically. www.micromedexsolutions.com [available with subscription]. Accessed May 2016.
4. Morgenthaler TJ, Kapur VK, Brown T, et al. Practice parameters for the treatment of narcolepsy and other hypersomnias of central origin. *Sleep* 2007;30(12):1705-11.
5. Kushida, C, Morgenthaler, T, et al. Practice parameters for the treatment of snoring and obstructive sleep apnea with oral appliances: an update for 2005. *Sleep* 2006;29(2):240-243.
6. Czeisler, CA et al. Modafinil for excessive sleepiness associated with shift work sleep disorder. *New England Journal of Medicine*. 2005: 353; 476-486.

PRIOR AUTHORIZATION CRITERIA

DRUG CLASS	**NARCOLEPSY AGENTS**
BRAND NAME	**NUVIGIL**
(generic)	**(armodafinil)**

Status: CVS Caremark Criteria
Type: Initial Prior Authorization

FDA-APPROVED INDICATIONS

Nuvigil is indicated to improve wakefulness in adult patients with excessive sleepiness associated with obstructive sleep apnea (OSA), narcolepsy, or shift work disorder (SWD).

In OSA, Nuvigil is indicated to treat excessive sleepiness and not as treatment for the underlying obstruction. If continuous positive airway pressure (CPAP) is the treatment of choice for a patient, a maximal effort to treat with CPAP for an adequate period of time should be made prior to initiating Nuvigil for excessive sleepiness. If Nuvigil is used adjunctively with CPAP, the encouragement of and periodic assessment of CPAP compliance is necessary.

In all cases, careful attention to the diagnosis and treatment of the underlying sleep disorder(s) is of utmost importance. Prescribers should be aware that some patients may have more than one sleep disorder contributing to their excessive sleepiness.

The effectiveness of Nuvigil in long-term use (greater than 12 weeks) has not been systematically evaluated in placebo-controlled trials. The physician who elects to prescribe Nuvigil for an extended time in patients should periodically re-evaluate long-term usefulness for the individual patient.

COVERAGE CRITERIA

Nuvigil will be covered with prior authorization when the following criteria are met:

- The patient has a diagnosis of narcolepsy confirmed by sleep lab evaluation

OR

- The patient has a diagnosis of Shift Work Disorder (SWD).

OR

- The patient has a diagnosis of obstructive sleep apnea (OSA) confirmed by polysomnography.

REFERENCES

1. Nuvigil [package insert]. Frazer, PA: Cephalon, Inc; April 2015.
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 May 2016.
3. Micromedex Solutions [database online]. Greenwood Village, CO: Truven Health Analytics Inc. Updated periodically. www.micromedexsolutions.com [available with subscription]. Accessed May 2016.
4. Morgenthaler TJ, Kapur VK, Brown T, et al. Practice parameters for the treatment of narcolepsy and other hypersomnias of central origin. *Sleep* 2007;30(12):1705-11.
5. Kushida, C, Morgenthaler, T, et al. Practice parameters for the treatment of snoring and obstructive sleep apnea with oral appliances: an update for 2005. *Sleep* 2006;29(2):240-243.
6. Czeisler CA, Walsh JK, Wesnes KA, Arora S, Roth T. Armodafinil for Treatment of Excessive Sleepiness Associated with Shift Work Disorder: A Randomized Controlled Study. *Mayo Clin Proc*. 2009; 84(11):958-972.

North Carolina State Health Plan
FOR TEACHERS AND STATE EMPLOYEES
A Division of the Department of State Treasurer

PRIOR AUTHORIZATION CRITERIA

DRUG CLASS	**SHORT ACTING BETA2-ADRENERGIC AGONIST ORAL INHALATION**		
BRAND NAME (generic)	**ACCUNEB (albuterol)**	**albuterol inhalation solution**	
	PROAIR HFA (albuterol)	**PROAIR RESPICLICK (albuterol)**	
	PROVENTIL HFA (albuterol)	**VENTOLIN HFA (albuterol)**	
	XOPENEX (levalbuterol)	**XOPENEX CONCENTRATE (levalbuterol)**	**XOPENEX HFA* (levalbuterol)**
Type: Quantity Limit, Initial Step Therapy*; Post Step Therapy Prior Authorization*			

POLICY

FDA-APPROVED INDICATIONS

Accuneb

AccuNeb is indicated for the relief of bronchospasm in patients 2 to 12 years of age with asthma (reversible obstructive airway disease).

Albuterol Inhalation Solution 0.083%, 0.5%

Albuterol sulfate inhalation solution is indicated for the relief of bronchospasm in patients 2 years of age and older with reversible obstructive airway disease and acute attacks of bronchospasm.

ProAir HFA

Bronchospasm

Proair HFA Inhalation Aerosol is indicated for the treatment or prevention of bronchospasm in patients 4 years of age and older with reversible obstructive airway disease.

Exercise-Induced Bronchospasm

Proair HFA Inhalation Aerosol is indicated for the prevention of exercise induced bronchospasm in patients 4 years of age and older.

ProAir RespiClick

Bronchospasm

ProAir RespiClick (albuterol sulfate) inhalation powder is indicated for the treatment or prevention of bronchospasm in patients 12 years of age and older with reversible obstructive airway disease.

Exercise-Induced Bronchospasm

ProAir RespiClick is indicated for the prevention of exercise-induced bronchospasm in patients 12 years of age and older.

Proventil HFA

Proventil HFA Inhalation Aerosol is indicated in adults and children 4 years of age and older for the treatment or prevention of bronchospasm with reversible obstructive airway disease and for the prevention of exercise-induced bronchospasm.

Ventolin HFA

Bronchospasm

Ventolin HFA is indicated for the treatment or prevention of bronchospasm in patients 4 years of age and older with reversible obstructive airway disease.

Exercise-Induced Bronchospasm

Ventolin HFA is indicated for the prevention of exercise-induced bronchospasm in patients 4 years of age and older.

Xopenex Solution

Xopenex (levalbuterol HCl) Inhalation Solution is indicated for the treatment or prevention of bronchospasm in adults, adolescents, and children 6 years of age and older with reversible obstructive airway disease.

Xopenex Concentrate

PRIOR AUTHORIZATION CRITERIA

Xopenex (levalbuterol HCl) Inhalation Solution Concentrate is indicated for the treatment or prevention of bronchospasm in adults, adolescents, and children 6 years of age and older with reversible obstructive airway disease.

Xopenex HFA

XopenexHFA is indicated for the treatment or prevention of bronchospasm in adults, adolescents, and children 4 years of age and older with reversible obstructive airway disease.

LIMIT CRITERIA

PLEASE NOTE: Since manufacturer package sizes may vary, it is the discretion of the dispensing pharmacy to fill quantities per package size up to these quantity limits. In such cases the filling limit and day supply may be less than what is indicated.

Medication*	Maintenance Dose	Maximum Daily Dose	Package Size	1 Month Limit* 3 Months Limit*
AccuNeb 0.63mg, 1.25mg / 3mL Albuterol Inhalation Solution	nebulization of 1 vial (3mL) three-four times daily	4 vials (3mL each)	25 vials (3mL each) per carton 30 vials (3mL each) per carton	5 packages (125 vials x 3mL) / 25 days 15 packages (375 vials x 3mL) / 75 days 4 packages (120 vials x 3mL) / 25 days 12 packages (360 vials x 3mL) / 75 days
Albuterol 0.083% Inhalation Solution	nebulization of 1 vial (3mL) three-four times daily	4 vials (3mL each)	25 vials (3mL each) per carton 30 vials (3mL each) per carton 60 vials (3mL each) per carton	5 packages (125 vials x 3mL) / 25 days 15 packages (375 vials x 3mL) / 75 days 4 packages (120 vials x 3mL) / 25 days 12 packages (360 vials x 3mL) / 75 days 2 packages (120 vials x 3mL) / 25 days 6 packages (360 vials x 3mL) / 75 days
Albuterol 0.5% Inhalation Solution	nebulization of 0.2mL-0.5mL three-four times daily	2mL	20mL per bottle 30 vials (0.5mL each) per carton	3 packages (20mL each) / 25 days 9 packages (20mL each) / 75 days 4 packages (120 vials x 0.5mL) / 25 days 12 packages (360vials x 0.5mL) / 75 days
ProAir HFA	1-2 inhalations every 4-6 hours	12 inhalations	200 inhalations per 8.5gm canister	2 packages (8.5gm each) / 25 days 6 packages (8.5gm each) / 75 days
ProAir RespiClick	1-2 inhalations every 4-6 hours	12 inhalations	200 inhalations per inhaler	2 packages / 25 days 6 packages / 75 days
Proventil HFA	1-2 inhalations every 4-6 hours	12 inhalations	200 inhalations per 6.7gm canister	2 packages (6.7gm each) / 25 days 6 packages (6.7gm each) / 75 days
Ventolin HFA	1-2 inhalations every 4-6 hours	12 inhalations	60 inhalations per 8gm canister 200 inhalations per 18gm canister	6 packages (8gm each) / 25 days 18 packages (8gm each) / 75 days 2 packages (18gm each) / 25 days 6 packages (18gm each) / 75 days
Xopenex 0.31mg,0.63mg, 1.25 mg / 3 mL Levalbuterol Inhalation Solution	nebulization of 1 vial (3mL) three times daily	3 vials (3mL each)	24 vials (3mL each) per carton 25 vials (3mL each) per carton	4 packages (96 vials x 3mL) / 25 days 12 packages (288 vials x 3mL) / 75 days 4 packages (100 vials x 3mL) / 25 days 12 packages (300 vials x 3mL) / 75 days
Xopenex Concentrate 1.25mg / 0.5mL	nebulization of 1 vial (0.5mL) three times daily	3 vials (0.5mL each)	30 vials (0.5mL each) per carton	3 package (90 vials x 0.5mL) / 25 days 9 packages (270 vials x 0.5mL) / 75 days
Xopenex HFA	1-2 inhalations every 4 to 6 hours	12 inhalations	200 inhalations per 15gm canister	2 packages (15gm each) / 25 days 6 packages (15gm 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.*

INITIAL STEP THERAPY CRITERIA:

If the patient has filled a prescription for at least a 30 day supply of ProAir HFA, Proventil HFA, or Ventolin HFA within the past 365 days under a prescription benefit administered by CVS Caremark, then the requested branded drug will be paid under that prescription benefit. If the patient does not meet the initial step therapy criteria, then the system will reject with a message indicating that a prior authorization (PA) is required. The prior authorization criteria would then be applied to requests submitted for evaluation to the PA unit.

COVERAGE CRITERIA

Branded SABAs will be covered with post step therapy prior authorization when the following criteria are met:

- Patient has experienced an inadequate treatment response, intolerance, or contraindication to at least one preferred SABA drug.

RATIONALE

If the patient has filled a prescription for at least a 30 day supply of ProAir HFA, Proventil HFA, or Ventolin HFA within the past 365 days under a prescription benefit administered by CVS Caremark, then the requested branded drug will be paid under that prescription benefit.

If the patient does not meet the initial step therapy criteria, then prior authorization is required.

If the patient has a documented contraindication to or a potential drug interaction with a preferred drug, then the requested brand drug will be covered. If the patient is intolerant to at least one of the preferred drugs, then the requested brand drug will be covered. If the patient has tried one of the preferred drugs for at least 30 days and had an inadequate treatment response, then the requested brand drug will be covered. If these requirements are met, then the approval duration is 24 months.

REFERENCES

1. AccuNeb [package insert]. Napa, CA: Dey Pharmaceuticals; March 2011.
2. Albuterol 0.021% and 0.042% inhalation solution [package insert]. Orlando, FL: Nephron Pharmaceuticals Corporation; March 2011.
3. Albuterol 0.083% inhalation solution [package insert]. Princeton, NJ: Sandoz Inc.; October 2012.
4. Albuterol 0.5% inhalation solution [package insert]. Tampa, FL: Bausch & Lomb Incorporated; August 2013.
5. ProAir HFA [package insert]. Horsham, PA: Teva Respiratory; May 2012.
6. ProAir RespiClick [package insert]. Horsham, PA: Teva Respiratory; March 2015.
7. Proventil HFA [package insert]. Whitehouse Station, NJ: Merck&Co., Inc.; June 2012.
8. Ventolin HFA [package insert]. Research Triangle Park, NC: GlaxoSmithKline; December 2014.
9. Xopenex inhalation solution [package insert]. Marlborough, MA: Sunovion Pharmaceuticals, Inc.; March 2014.
10. Xopenex inhalation solution, concentrate [package insert]. Marlborough, MA: Sunovion Pharmaceuticals, Inc.; March 2014.
11. Xopenex HFA [package insert]. Marlborough, MA: Sunovion Pharmaceuticals, Inc.; March 2015.

DRUG CLASS **LONG ACTING BETA2-ADRENERGIC AGONIST, COMBINATIONS ORAL INHALATION**

LONG-ACTING BETA2-ADRENERGIC AGONISTS:

BRAND NAME (generic)	**ARCAPTA NEOHALER (indacaterol)**	**BROVANA (arformoterol tartrate)**
	FORADIL AEROLIZER (formoterol)	**PERFOROMIST (formoterol)**
	SEREVENT DISKUS (salmeterol)	**STRIVERDI RESPIMAT (olodaterol)**

LONG-ACTING BETA2-ADRENERGIC AGONIST / ANTICHOLINERGIC:

ANORO ELLIPTA (umeclidinium/vilanterol)	**BEVESPI AEROSPHERE (glycopyrrolate/formoterol)**
STIOLTO RESPIMAT (tiotropium bromide/olodaterol)	**UTIBRON NEOHALER (glycopyrrolate/indacaterol)**

LONG-ACTING BETA2-ADRENERGIC AGONIST / CORTICOSTEROID:

ADVAIR DISKUS (fluticasone propionate/salmeterol)	**ADVAIR HFA (fluticasone propionate/salmeterol)**
BREO ELLIPTA (fluticasone furoate/vilanterol)	**DULERA (mometasone/formoterol)**
SYMBICORT (budesonide/formoterol)	

Type: Quantity Limit

POLICY

FDA-APPROVED INDICATIONS

Long-Acting Beta2-Adrenergic Agonists:

Arcapta Neohaler

Arcapta Neohaler is a long-acting beta2-agonist indicated for long-term, once-daily maintenance bronchodilator treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema.

Arcapta Neohaler is not indicated to treat asthma. The safety and effectiveness of Arcapta Neohaler in asthma have not been established.

Brovana

Brovana (arformoterol tartrate) Inhalation Solution is indicated for the long-term, twice daily (morning and evening) maintenance treatment of bronchoconstriction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema. Brovana Inhalation Solution is for use by nebulization only.

Brovana Inhalation Solution is not indicated to treat asthma. The safety and effectiveness of Brovana Inhalation Solution in asthma have not been established.

Foradil Aerolizer

Treatment of Asthma
Foradil Aerolizer is indicated for the treatment of asthma and in the prevention of bronchospasm only as concomitant therapy with a long-term asthma control medication, such as an inhaled corticosteroid, in adults and children 5 years of age and older with reversible obstructive airways disease, including patients with symptoms of nocturnal asthma.
Prevention of Exercise-Induced Bronchospasm
Foradil Aerolizer is also indicated for the acute prevention of exercise-induced bronchospasm in adults and children 5 years of age and older, when administered on an occasional, as-needed basis. Use of Foradil Aerolizer as a single agent for the prevention of exercise-induced bronchospasm may be clinically indicated in patients who do not have persistent asthma. In patients with persistent asthma, use of Foradil Aerolizer for the prevention of exercise-induced bronchospasm may be clinically indicated, but the treatment of asthma should include a long-term asthma control medication, such as an inhaled corticosteroid.
Maintenance Treatment of Chronic Obstructive Pulmonary Disease
Foradil Aerolizer is indicated for the long-term, twice daily (morning and evening) administration in the maintenance treatment of bronchoconstriction in patients with Chronic Obstructive Pulmonary Disease including chronic bronchitis and emphysema.
Perforomist
Perforomist (formoterol fumarate) Inhalation Solution is indicated for the long-term, twice daily (morning and evening) administration in the maintenance treatment of bronchoconstriction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema.
Perforomist Inhalation Solution is not indicated to treat asthma. The safety and effectiveness of Perforomist Inhalation Solution in asthma have not been established.
Serevent Diskus
Treatment of Asthma
Serevent Diskus is indicated for the treatment of asthma and in the prevention of bronchospasm only as concomitant therapy with a long-term asthma control medication, such as an inhaled corticosteroid, in patients aged 4 years and older with reversible obstructive airway disease, including patients with symptoms of nocturnal asthma.
Prevention of Exercise-Induced Bronchospasm
Serevent Diskus is also indicated for prevention of exercise-induced bronchospasm (EIB) in patients aged 4 years and older. Use of Serevent Diskus as a single agent for the prevention of EIB may be clinically indicated in patients who do not have persistent asthma. In patients with persistent asthma, use of Serevent Diskus for the prevention of EIB may be clinically indicated, but the treatment of asthma should include a long-term asthma control medication, such as an inhaled corticosteroid.
Maintenance Treatment of Chronic Obstructive Pulmonary Disease
Serevent Diskus is indicated for the long-term twice-daily administration in the maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD) (including emphysema and chronic bronchitis).
Striverdi Respimat
Striverdi Respimat is a long-acting beta2-agonist indicated for long-term, once-daily maintenance bronchodilator treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema.
Striverdi Respimat is not indicated to treat asthma. The safety and effectiveness of Striverdi Respimat in asthma have not been established.

Long-Acting Beta2-Adrenergic Agonist / Anticholinergic:
Anoro Ellipta
Anoro Ellipta is a combination anticholinergic/long-acting beta2-adrenergic agonist (anticholinergic/LABA) indicated for the long-term, once-daily, maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema.
Anoro ELlipta is not indicated for the treatment of asthma.

Bevespi Aerosphere
Bevespi Aerosphere is a combination of glycopyrrolate and formoterol fumarate indicated for the long-term, maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema.
Bevespi Aerosphere is not indicated for the relief of acute bronchospasm or for the treatment of asthma.

Stiolto Respimat

Stiolto Respimat is a combination of tiotropium and olodaterol indicated for long-term, once-daily maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema.
Stiolto Respimat is not indicated to treat asthma. The safety and effectiveness of Stiolto Respimat in asthma have not been established.
Utibron Neohaler
Utibron Neohaler is a combination of indacaterol and glycopyrrolate indicated for the long-term, maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema.
Utibron Neohaler is not indicated for the treatment of asthma.

Long-Acting Beta2-Adrenergic Agonist / Corticosteroids:
Advair Diskus
Treatment of Asthma
Advair Diskus is indicated for the treatment of asthma in patients aged 4 years and older.
Maintenance Treatment of Chronic Obstructive Pulmonary Disease
Advair Diskus 250/50 is indicated for the twice-daily maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema. Advair Diskus 250/50 is also indicated to reduce exacerbations of COPD in patients with a history of exacerbations. Advair Diskus 250/50 twice daily is the only approved dosage for the treatment of COPD because an efficacy advantage of the higher strength Advair Diskus 500/50 over Advair Diskus 250/50 has not been demonstrated.
Advair HFA
Advair HFA is indicated for the treatment of asthma in patients aged 12 years and older.
Breo Ellipta
Breo Ellipta is a combination inhaled corticosteroid/long-acting beta2-adrenergic agonist (ICS/LABA) indicated for the long-term, once-daily, maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema. Breo Ellipta is also indicated to reduce exacerbations of COPD in patients with a history of exacerbations.
Breo Ellipta is NOT indicated for the treatment of asthma.
Dulera
Dulera is indicated for the treatment of asthma in patients 12 years of age and older.
Symbicort
Treatment of Asthma
Symbicort is indicated for the treatment of asthma in patients 12 years of age and older.
Maintenance Treatment of Chronic Obstructive Pulmonary Disease (COPD)
Symbicort 160/4.5 is indicated for the twice daily maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD) including chronic bronchitis and emphysema. Symbicort 160/4.5 is the only approved dosage for the treatment of airflow obstruction in COPD.

Important Limitations of Use
LABAs are NOT indicated for the relief of acute bronchospasm.
LABAs are not indicated to treat acute deteriorations of chronic obstructive pulmonary disease

Long-acting beta2-adrenergic agonists (LABAs) increase the risk of asthma-related death. Available data from controlled clinical trials suggest that LABAs increase the risk of asthma-related hospitalization in pediatric and adolescent patients. Therefore, when treating patients with asthma, physicians should only prescribe LABAs for patients not adequately controlled on a long-term asthma control medication, such as an inhaled corticosteroid, or whose disease severity clearly warrants initiation of treatment with both an inhaled corticosteroid and a LABA. Once asthma control is achieved and maintained, assess the patient at regular intervals and step down therapy (e.g., discontinue LABAs) if possible without loss of asthma control and maintain the patient on a long-term asthma control medication, such as an inhaled corticosteroid. Do not use LABAs for patients whose asthma is adequately controlled on low- or medium-dose inhaled corticosteroids.

LIMIT CRITERIA LONG-ACTING BETA2-ADRENERGIC AGONISTS:				
Medication*	**Maintenance Dose**	**Maximum Daily Dose**	**Package Size**	**1 Month Limit* 3 Months Limit***
Arcapta Neohaler	inhalation of the powder contents of 1 capsule once daily	1 capsule	30 capsules per box	1 package (30 capsules) / 25 days 3 packages (30 capsules each) / 75 days
Brovana	nebulization of 1 vial (2mL) twice daily	2 vials (2mL each)	30 vials (2mL each) per carton 60 vials (2mL each) per carton	2 packages (60 vials x 2mL) / 25 days 6 packages (180 vials x 2mL) / 75 days 1 package (60 vials x 2mL) / 25 days 3 packages (180 vials x 2mL) / 75 days
Foradil Aerolizer	inhalation of the powder contents of 1 capsule every 12 hours	2 capsules	60 capsules per box	1 package (60 capsules) / 25 days 3 packages (60 capsules each)/ 75 days
Perforomist	nebulization of 1 vial (2 mL) twice daily	2 vials (2mL each)	30 vials (2mL each) per carton 60 vials (2mL each) per carton	2 package (60 vials x 2mL) / 25 days 6 packages (180 vials x 2mL) / 75 days 1 package (60 vials x 2mL) / 25 days 3 packages (180 vials x 2mL) / 75 days
Serevent Diskus	1 inhalation twice daily	2 inhalations	60 blisters per device	1 package (60 blisters) / 25 days 3 packages (60 blisters each) / 75 days
Striverdi Respimat	2 inhalations once daily	2 inhalations	60 inhalations per cartridge (4gm each)	1 package (4gm) / 25 days 3 packages (4gm each) / 75 days

LIMIT CRITERIA LONG-ACTING BETA2-ADRENERGIC AGONIST / ANTICHOLINERGIC:				
Medication*	**Maintenance Dose**	**Maximum Daily Dose**	**Package Size**	**1 Month Limit* 3 Months Limit***
Anoro Ellipta	1 inhalation once daily	1 inhalation	30 inhalations/60 blisters per inhaler	1 package / 25 days 3 packages / 75 days
Bevespi Aerosphere	2 inhalations twice daily	4 inhalations	120 inhalations per canister	1 package / 25 days 3 packages / 75 days
Stiolto Respimat	2 inhalations once daily	2 inhalations	60 inhalations per inhaler	1 package / 25 days 3 packages / 75 days
Utibron Neohaler	1 inhalation twice daily	2 inhalations	60 capsules per box	1 package (60 capsules) / 25 days 3 packages (180 capsules / 75 days

LIMIT CRITERIA LONG-ACTING BETA2-ADRENERGIC AGONIST / CORTICOSTEROIDS:				
Medication*	**Maintenance Dose**	**Maximum Daily Dose**	**Package Size**	**1 Month Limit* 3 Months Limit***
Advair Diskus	1 inhalation twice daily	2 inhalations	60 blisters per device	1 package (60 blisters) / 25 days 3 packages (60 blisters each) / 75 days
Advair HFA	2 inhalations twice daily	4 inhalations	120 inhalations per 12gm canister	1 package (12gm) / 25 days 3 packages (12gm each) / 75 days
Breo Ellipta	1 inhalation once daily	1 inhalation	30 inhalations/60 blisters per inhaler	1 package / 25 days 3 packages / 75 days
Dulera	2 inhalations twice daily	4 inhalations	120 inhalations per 13gm canister	1 package (13gm) / 25 days 3 packages (13gm each) / 75 days
Symbicort	2 inhalations twice daily	4 inhalations	120 inhalations per 10.2gm canister	1 package (10.2gm) / 25 days 3 packages (10.2gm 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.*

REFERENCES

1. Advair Diskus [package insert]. Research Triangle Park, NC: GlaxoSmithKline; July 2014.
2. Advair HFA [package insert]. Research Triangle Park, NC: GlaxoSmithKline; December 2014.
3. Anoro Ellipta [package insert]. Research Triangle Park, NC: GlaxoSmithKline; May 2014.
4. Arcapta Neohaler [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; September, 2012.
5. Breo Ellipta [package insert]. Research Triangle Park, NC: GlaxoSmithKline; September 2015.
6. Brovana [package insert]. Marlborough, MA: Sunovion Pharmaceuticals, Inc.; February 2014.
7. Dulera [package insert]. Whitehouse Station, NJ: Schering Corp/MSD; January 2015.
8. Foradil Aerolizer [package insert]. Whitehouse Station, NJ: Schering Corp.; November 2012.
9. Perforomist [package insert]. Napa, CA: Dey Pharmaceuticals; March 2013.
10. Serevent Diskus [package insert]. Research Triangle Park, NC: GlaxoSmithKline; February 2015.
11. Stiolto Respimat [package insert]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc.; June 2015.
12. Striverdi Respimat [package insert.] Ridgefield, CT; Boehringer Ingelheim Pharmaceuticals, Inc.: August 2014.
13. Symbicort [package insert]. Wilmington, DE: AstraZeneca. May 2012.
14. Utibron Neohaler [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; October 2015.
15. Bevespi Aerosphere [package insert]. Wilmington, DE: AstraZeneca; April 2016.

BINDER DIVIDER

"Other Topics"

FORMULARY OMISSIONS

Drug Name	Tier
DISPOSABLE INSULIN DELIVERY DEVICES	
OMNIPOD	3
V-GO 20	3
V-GO 30	3
V-GO 40	3
IV INJECTABLES	
ABELCET	3
ABILIFY	2
ABLAVAR	3
ABRAXANE	3
ACETADOTE	3
ACETAZOLAMIDE SODIUM	1
ACETYLCYSTEINE	1
ACTHAR HP	6
ACTHIB	3
ACTHREL	3
ACTIMMUNE	6
ACTIVASE	3
ACYCLOVIR SODIUM	1
ADACEL	3
ADAGEN	3
ADCETRIS	6
ADENOCARD	3
ADENOSCAN	3
ADENOSINE	1
ADRENACLICK	3
ADREVIEW	3
ADRIAMYCIN	1
ADRUCIL	1
ADVATE	5
AK-FLUOR	1
AK-FLUOR	3
ALBUKED 25	1
ALBUKED 5	1
ALBUMIN HUMAN	1
ALBUMINAR-25	1
ALBUMINAR-5	1
ALBUMIN-ZLB	1
ALBURX	1
ALBUTEIN	1
ALDURAZYME	6
ALFENTANIL	1
ALFENTANIL HCL	3
ALFERON N	6
ALIMTA	3
ALKERAN	3
ALLOPURINOL SODIUM	1
ALOPRIM	3
ALOXI	3
ALPHANATE	6
ALPHANINE SD	6
ALPROSTADIL	1
AMBISOME	3
AMIDATE	3
AMIFOSTINE	1
AMIKACIN SULFATE	1
AMINOCAPROIC ACID	1
AMINOHIPPURATE SODIUM	3
AMINOPHYLLINE	1
AMINOSYN	3
AMINOSYN 7%/ELECTROLYTES	3
AMINOSYN 8.5%/ELECTROLYTE	1
AMINOSYN II	3
AMINOSYN II 8.5%/ELECTROL	1
AMINOSYN M	3
AMINOSYN-HBC	3
AMINOSYN-PF	3
AMINOSYN-PF 7%	3
AMINOSYN-RF	3
AMIODARONE HCL	1
AMMONIUM MOLYBDATE	1
AMMONUL	3
AMPHADASE	3
AMPHOTEC	3
AMPHOTERICIN B	1
AMPICILLIN SODIUM	1
AMPICILLIN-SULBACTAM	1
AMVISC	3
AMVISC PLUS	3
AMYTAL SODIUM	3
AMYVID	3
ANASCORP	3
ANECTINE	3
ANGIOMAX	3
ANTIVENIN LATRODECTUS MAC	3
ANTIZOL	3
ANZEMET	3
APIDRA	3
APLISOL	3
APOKYN	6
AQUASOL A PARENTERAL	3
ARALAST NP	6
ARCALYST	6
ARGATROBAN	1
ARGATROBAN	3
ARGENTUM-D20	3
ARISTADA	2
ARIXTRA	2
ARRANON	3
ARZERRA	6
ASCLERA	3
ASCORBIC ACID	1
ASPERGILLUS FUMIGATIS	3
ATGAM	2
ATIVAN	3
ATROPEN	3
ATROPINE SULFATE	1
AUVI-Q	3
AVASTIN	6

Drug Name	Tier
IV INJECTABLES	
MIOCHOL-E	3
MIOSTAT	3
MITOMYCIN	1
MITOXANTRONE	4
M-M-R II	3
MONOCLATE-P	6
MONOJECT BONE MARROW BIOP	3
MONOJECT PHARMA GRADE FLU	1
MONOJECT PREFILL ADVANCED	1
MONONINE	6
MORPHINE SULFATE	1
MORPHINE SULFATE	3
MORRHUATE SODIUM	1
MOZOBIL	6
MULTIHANCE	3
MULTITRACE-4	3
MULTITRACE-4 CONCENTRATE	1
MULTITRACE-4 NEONATAL	3
MULTITRACE-4 PEDIATRIC	3
MULTITRACE-5	3
MULTITRACE-5 CONCENTRATE	1
MUSTARGEN	3
MYCAMINE	3
MYCOPHENOLATE MOFETIL	1
MYOBLOC	6
MYOVIEW 30ML	3
NABI-HB	6
NAFCILLIN	3
NAFCILLIN SODIUM	1
NAGLAZYME	6
NALBUPHINE HCL	1
NALOXONE HCL	1
NAROPIN	3
NATPARA	6
NATRECOR	3
NAVELBINE	3
NEMBUTAL SODIUM	3
NEOPROFEN	3
NEOSTIGMINE METHYLSULFATE	1
NEPHRAMINE	3
NESACAINE	3
NEUMEGA	6
NEURALGO-RHEUM	3
NEUT	3
NEUTREXIN	3
NEXAVIR	3
NEXIUM I.V.	3
NEXPLANON	6
NEXTERONE	3
NICARDIPINE HCL	1
NIPENT	3
NITHIODOTE	3
NITROGLYCERIN	3
NITROGLYCERIN IN 5% DEXTR	1
NITROGLYCERIN IN DEXTROSE	1
NITROPRESS	3
NOREPINEPHRINE BITARTRATE	1
NORMOSOL -R	3
NORMOSOL-M IN D5W	3
NORMOSOL-R	3
NORMOSOL-R IN D5W	3
NOVAREL	4
NOVOEIGHT	5
NOVOLIN 70/30	2
NOVOLIN 70/30 RELION	3
NOVOLIN N	3
NOVOLIN R	3
NOVOLOG	2
NOVOLOG MIX 70/30	2
NOVOSEVEN	6
NPLATE	6
NUCALA	6
NULOJIX	2
NUTRILIPID	1
NUTRILYTE	1
NUTRILYTE II	1
NUWIQ	5
OCTAGAM	6
OCTREOSCAN	3
OCTREOTIDE	4
OCTREOTIDE ACETATE	4
OCUCOAT VISCOADHERENT	1
OFIRMEV	3
OLANZAPINE	1
OMNIPAQUE	3
OMNISCAN	3
OMNISCAN/SODIUM CHLORIDE	3
ONCASPAR	6
ONDANSETRON HCL	1
ONIVYDE	3
OPANA	3
OPTIMARK	3
OPTIRAY 240	3
OPTIRAY 300	3
OPTIRAY 320	3
OPTIRAY 350	3
OPTISON	3
ORPHENADRINE CITRATE	1
ORTHO-CS 250	1
OSMITROL VIAFLEX	1
OTREXUP	6
OVIDREL	5
OXACILLIN SODIUM	1
OXALIPLATIN	1
OXYTOCIN	1
OZURDEX	6
PACLITAXEL	1
PAMIDRONATE	1

AVELOX	3
AZACITIDINE	4
AZACTAM	3
AZATHIOPRINE	2
AZITHROMYCIN	1
AZTREONAM	1
BACIIM	1
BACITRACIN	1
BACTERIOSTATIC WATER FOR	1
BACTERIOSTATIC WATER PARA	3
BACTOCILL IN DEXTROSE	3
BAL IN OIL	3
BALANCED SALT	1
BALANCED SALT SOLUTION	1
B-COMPLEX 100	1
BD PUDENDAL/LOCAL BLOCK	3
BEBULIN	6
BENLYSTA	6
BENTYL	3
BENZTROPINE MESYLATE	1
BERINERT	6
BETAMETHASONE SODIUM PHOS	1
BICILLIN C-R	3
BICILLIN L-A	3
BICNU	3
BIOTHRAX	3
BIVALIRUDIN	1
BIVIGAM	6
BLEOMYCIN	1
BONIVA	3
BOOSTRIX	3
BOTOX	6
BOTOX COSMETIC	3
BREVIBLOC	3
BREVITAL SODIUM	3
BRIVIACT	3
BSS	1
BSS PLUS	3
BUMETANIDE	1
BUMINATE	1
BUPIVACAINE HCL	1
BUPIVACAINE SPINAL	1
BUPIVACAINE/DEXTROSE SPIN	1
BUPIVACAINE/EPINEPHRINE	1
BUPRENEX	3
BUPRENORPHINE HCL	1
BUSULFEX	3
BUTORPHANOL TARTRATE	1
CAFCIT	3
CAFFEINE CITRATE	1
CAFFEINE/SODIUM BENZOATE	1
CALCITRIOL	1
CALCIUM CHLORIDE	1
CALCIUM GLUCONATE	1
CALDOLOR	3
CAMPATH	3
CAMPTOSAR	3
CANCIDAS	3
CANDIDA ALBICANS	1
CANDIN	3
CAPASTAT SULFATE	3
CARBOCAINE	3
CARBOPLATIN	1
CARDENE IV	3
CARIMUNE	6
CARNITOR	3
CARTICEL	3
CATHFLO ACTIVASE	3
CAVERJECT	3
CAVERJECT IMPULSE	3
CEFAZOLIN SODIUM	1
CEFAZOLIN SODIUM	3
CEFAZOLIN SODIUM/DEXTROSE	3
CEFEPIME	3
CEFEPIME	1
CEFEPIME/DEXTROSE	3
CEFOTAN	3
CEFOTAXIME SODIUM	1
CEFOTETAN	1
CEFOTETAN/DEXTROSE	3
CEFOXITIN SODIUM	1
CEFOXITIN SODIUM	3
CEFTAZIDIME	1
CEFTAZIDIME/DEXTROSE	3
CEFTRIAXONE IN ISO-OSMOTI	1
CEFTRIAXONE SODIUM	1
CEFTRIAXONE/DEXTROSE	3
CEFUROXIME SODIUM	1
CEFUROXIME SODIUM	3
CELESTONE-SOLUSPAN	3
CELLCEPT	2
CELLUGEL	3
CEPROTIN	6
CEREBYX	3
CERETEC	3
CEREZYME	6
CERVARIX	3
CETROTIDE	5
CHIRHOSTIM	3
CHLORAMPHENICOL SODIUM SU	1
CHLOROMAG	1
CHLOROTHIAZIDE SODIUM	1
CHLORPROMAZINE HCL	3
CHOLETEC	3
CHOLOGRAFIN MEGLUMINE	3
CHORIONIC GONADOTROPIN	4
CIDOFOVIR	1
CINRYZE	6
CIPRO I.V.-IN D5W	3
CIPROFLOXACIN	1
CIPROFLOXACIN I.V.-IN D5W	1
CISPLATIN	1
CLAFORAN	3
PANCURONIUM BROMIDE	1
PANHEMATIN	3
PANTOPRAZOLE SODIUM	1
PAPAVERINE HCL	1
PARICALCITOL	1
PEDIARIX	3
PEG-INTRON	5
PENICILLIN G POTASSIUM	1
PENICILLIN G POTASSIUM IN	3
PENICILLIN G PROCAINE	3
PENICILLIN G SODIUM	1
PENTACEL	3
PENTAM 300	3
PENTETATE CALCIUM TRISODI	3
PERJETA	6
PFIZERPEN-G	1
PH 12 STERILE DILUENT FOR	6
PHENERGAN	3
PHENOBARBITAL SODIUM	3, 1
PHENTOLAMINE MESYLATE	3
PHENYLEPHRINE HCL	1, 3
PHENYTOIN SODIUM	1
PHOTOFRIN	3
PHYSOSTIGMINE SALICYLATE	3
PHYTONADIONE	1
PIPERACILLIN SODIUM/ TAZO	1
PIPERACILLIN SODIUM/TAZOB	1
PIPERACILLIN/TAZOBACTAM	1
PITOCIN	3
PLASBUMIN-25	1
PLASBUMIN-5	1
PLASMA-LYTE A	3
PLASMA-LYTE-148	3
PLASMA-LYTE-56/D5W	3
PLASMANATE	3
PLENAMINE	1
PNEUMOVAX 23	3
PNEUMOVAX 23/1 DOSE	3
PNEUMOVAX 23/5 DOSE	3
POLOCAINE	1
POLOCAINE-MPF	1
POLYMYXIN B SULFATE	1
POTASSIUM ACETATE	1
POTASSIUM CHLORIDE	1
POTASSIUM CHLORIDE 0.15%	1
POTASSIUM CHLORIDE 0.22%	1
POTASSIUM CHLORIDE 0.224%	1
POTASSIUM CHLORIDE/DEXTRO	1
POTASSIUM CHLORIDE/SODIUM	1
PRECEDEX	3
PREGNYL	4
PREMARIN	3
PREMASOL	1
PRE-PEN	3
PREVNAR 13	3
PRIALT	3
PRIMAXIN IV	3
PRIMAXIN IV ADD-VANTAGE	3
PRIVIGEN	6
PROCAINAMIDE HCL	1
PROCALAMINE	3
PROCHLORPERAZINE EDISYLAT	1
PROFILNINE SD	6
PROGESTERONE	1
PROGESTERONE IN OIL	1
PROGRAF	2
PROHANCE	3
PROLASTIN-C	6
PROLEUKIN	6
PROMETHAZINE HCL	1
PROPRANOLOL HCL	1
PROQUAD	3
PROSOL	3
PROSTASCINT	3
PROSTIN VR PEDIATRIC	3
PROTAMINE SULFATE	1
PROTONIX	3
PROTOPAM CHLORIDE	3
PROVENGE	3
PROVISC	3
PYRIDOXINE HCL	1
QUADRACEL	3
QUADRAMET	3
QUELICIN	3
QUINIDINE GLUCONATE	3
RABAVERT	3
RANITIDINE HCL	1
READYSHARP LIDOCAINE	3
RECLAST	6
RECOMBINATE	6
RECOMBIVAX HB	3
RELISTOR	3
REMODULIN	6
REOPRO	3
RETISERT	6
RETROVIR	2
REVONTO	1
R-GENE 10	3
RIASTAP	6
RIFADIN	3
RIFAMPIN	1
RINGERS INJECTION	1
RISPERDAL CONSTA	2
RIXUBIS	6
ROBINUL	3
ROCURONIUM BROMIDE	1
ROPIVACAINE	1
ROPIVACAINE HCL	1
SALINE/PHENOL	3
SANDIMMUNE	2
SANDOSTATIN	6
SARAPIN	3
SASH KIT FOR FLUSHING VAS	1

CLAFORAN/D5W	3
CLEOCIN	3
CLEOCIN IN D5W	3
CLEOCIN PHOSPHATE	3
CLEVIPREX	3
CLINDAMYCIN	1
CLINDAMYCIN PHOSPHATE	1
CLINDAMYCIN PHOSPHATE IN	1
CLINDAMYCIN PHOSPHATE PHA	1
CLINIMIX 4.25%/DEXTROSE 1	3
CLINIMIX 4.25%/DEXTROSE 2	3
CLINIMIX 4.25%/DEXTROSE 5	3
CLINIMIX 5%/DEXTROSE 15%	3
CLINIMIX 5%/DEXTROSE 20%	3
CLINIMIX 5%/DEXTROSE 25%	3
CLINIMIX E 2.75%/DEXTROSE	3
CLINIMIX E 4.25%/DEXTROSE	3
CLINIMIX E 5%/DEXTROSE 15	3
CLINIMIX E 5%/DEXTROSE 20	3
CLINIMIX E 5%/DEXTROSE 25	3
CLINISOL SF 15%	1
CLOLAR	3
CLONIDINE HCL	1
COAGADEX	3
COGENTIN	3
COLISTIMETHATE SODIUM	1
COLY-MYCIN M	3
COMVAX	3
CONRAY	3
CONRAY 30	3
CONRAY 43	3
CONSTANT TRICHOPHYTON	3
COPPER SULFATE	3
COPPER TRACE METAL	1
CORIFACT	6
CORLOPAM	3
CORTROSYN	3
CORVERT	3
COSMEGEN	3
COSYNTROPIN	1
CRESEMBA	3
CROFAB	3
CUBICIN	3
CUBICIN RF	3
CYANOCOBALAMIN	1
CYANOKIT	3
CYCLOPHOSPHAMIDE	1
CYCLOSPORINE	1
CYSTEINE HCL	1
CYTARABINE	1
CYTOGAM	6
CYTOVENE	3
D.H.E. 45	2
DACARBAZINE	1
DACOGEN	6
DANTRIUM IV	3
DAPTACEL	3
DAPTOMYCIN	1
DATSCAN	3
DAUNORUBICIN	1
DAUNOXOME	3
DDAVP	3
DECITABINE	4
DEFEROXAMINE	4
DEFINITY	3
DEHYDRATED ALCOHOL	1
DELESTROGEN	3
DELFLEX-LC/1.5% DEXTROSE	3
DELFLEX-LC/4.25% DEXTROSE	3
DELFLEX-LM/1.5% DEXTROSE	1
DELFLEX-LM/2.5% DEXTROSE	3
DELFLEX-LM/4.25% DEXTROSE	3
DELFLEX-SM/1.5% DEXTROSE	3
DELFLEX-SM/2.5% DEXTROSE	3
DELFLEX-SM/4.25% DEXTROSE	3
DEMEROL	3
DEPACON	3
DEPOCYT	3
DEPO-ESTRADIOL	3
DEPO-MEDROL	3
DEPO-PROVERA	3
DEPO-PROVERA CONTRACEPTIV	2
DESFERAL	6
DESMOPRESSIN ACETATE	1
DEXAMETHASONE SODIUM PHOS	1
DEXFERRUM	1
DEXMEDETOMIDINE HCL	1
DEXPANTHENOL	3
DEXRAZOXANE	1
DEXTROSE 10%/NACL 0.45%	1
DEXTROSE 5%	3
DEXTROSE 10%	1
DEXTROSE 10%/NACL 0.2%	3
DEXTROSE 10%/NACL 0.225%	3
DEXTROSE 2.5%/NACL 0.45%	1
DEXTROSE 20%	3
DEXTROSE 25%	1
DEXTROSE 30%	1
DEXTROSE 40%	3
DEXTROSE 5%	1
DEXTROSE 5%/LACTATED RING	1
DEXTROSE 5%/NACL 0.2%	1
DEXTROSE 5%/NACL 0.225%	1
DEXTROSE 5%/NACL 0.3%	3
DEXTROSE 5%/NACL 0.33%	1
DEXTROSE 5%/NACL 0.45%	1
DEXTROSE 5%/NACL 0.9%	1
DEXTROSE 50%	1
DEXTROSE 70%	1
DIAGNOSTIC KIT	3
DIANEAL LOW CALCIUM/1.5%	3
DIANEAL LOW CALCIUM/2.5%	3
DIANEAL LOW CALCIUM/4.25%	3
SCLEROSOL INTRAPLEURAL	3
SECREFLO	3
SELENIUM	1
SENSORCAINE	1
SENSORCAINE/EPINEPHRINE	1
SENSORCAINE-MPF	1
SENSORCAINE-MPF SPINAL	1
SENSORCAINE-MPF/EPINEPHRI	1
SEROSTIM	6
SHELLGEL	3
SIGNIFOR LAR	6
SILDENAFIL CITRATE	4
SIMULECT	2
SINOGRAFIN	3
SODIUM ACETATE	1
SODIUM BICARBONATE	1
SODIUM CHLORIDE	1
SODIUM CHLORIDE 0.9%	1
SODIUM CHLORIDE 0.45%	1
SODIUM CHLORIDE 0.9%	1
SODIUM CHLORIDE BACTERIOS	1
SODIUM DIURIL	3
SODIUM EDECRIN	3
SODIUM FERRIC GLUCONATE C	1
SODIUM LACTATE	3
SODIUM NITRITE	3
SODIUM NITROPRUSSIDE	1
SODIUM PHENYLACETATE/SODI	1
SODIUM PHOSPHATE	1
SODIUM THIOSULFATE	1
SOLESTA	6
SOLIRIS	6
SOLU-MEDROL	3
SOMATULINE DEPOT	6
SOMAVERT	6
SOTALOL HYDROCHLORIDE	3
SOTRADECOL	3
SPASCUPREEL	3
STERILE DILUENT FOR EPOPR	4
STERILE DILUENT FOR REMOD	6
STERILE TALC POWDER	3
STERILE WATER FOR INJECTI	1
STREPTOMYCIN SULFATE	1
SUFENTANIL CITRATE	1
SULFAMETHOXAZOLE/TRIMETHO	1
SUMATRIPTAN SUCCINATE	1
SUPPRELIN LA	6
SYLATRON	6
SYNAGIS	6
SYNERCID	3
TALTZ	5
TALWIN	3
TAXOTERE	3
TAZICEF	1
TECENTRIQ	6
TEFLARO	3
TEMODAR (INJECTABLE)	6
TENIPOSIDE	3
TENIVAC	3
TERBUTALINE SULFATE	1
TESTOPEL	3
TETANUS/DIPHTHERIA TOXOID	3
TETRACAINE HCL	1
THALLOUS CHLORIDE TL 201	3
THAM	3
THEOPHYLLINE/D5W	3
THIAMINE HCL	1
THIOTEPA	3
THROMBATE III	3
THROMBATE III W/10 ML STE	3
THROMBATE III W/20 ML STE	3
THYMOGLOBULIN	2
THYROGEN	6
TIGAN	3
TIGECYCLINE	3
TNKASE	3
TOBRAMYCIN SULFATE	1
TOPOTECAN HCL	3
TORISEL	6
TORSEMIDE	3
TPN ELECTROLYTES	1
TRACE ELEMENTS 4/PEDIATRI	3
TRAUMEEL	3
TRAVASOL	3
TREANDA	6
TRELSTAR DEPOT	5
TRELSTAR LA	5
TRELSTAR MIXJECT	5
TRICHOPHYTON	3
TRIESENCE	3
TRIOSTAT	3
TRISENOX	3
TROPHAMINE	3
TUBERSOL	3
TURKEL PARACENTESIS PROCE	3
TWINRIX	3
TYGACIL	3
TYPHIM VI	3
TYSABRI	6
ULTIVA	3
ULTRABAG/DIANEAL LOW CALC	3
ULTRABAG/DIANEAL PD-2/1.5	3
ULTRAVIST	3
UNASYN	3
UNASYN BULK PACK	3
UVADEX	3
VALPROATE SODIUM	1
VANCOMYCIN HCL	1
VANCOMYCIN HCL IN DEXTROS	3
VANTAS	6
VAPRISOL	3
VAQTA	3
VARIVAX	3

DIANEAL PD-2/1.5% DEXTROS	**3**
DIANEAL PD-2/2.5% DEXTROS	**3**
DIANEAL PD-2/4.25% DEXTRO	**3**
DIAZEPAM	**1**
DICYCLOMINE HCL	**1**
DIGIFAB	**3**
DIGOXIN	**1**
DIHYDROERGOTAMINE MESYLAT	**1**
DILAUDID	**3**
DILAUDID-HP	**3**
DILTIAZEM HCL	**1**
DILTIAZEM HCL	**3**
DIMENHYDRINATE	**3**
DIPHENHYDRAMINE HCL	**1**
DIPHTHERIA/TETANUS TOXOID	**3**
DIPYRIDAMOLE	**1**
DISCOVISC	**3**
DMSA	**3**
DOBUTAMINE HCL	**1**
DOBUTAMINE HCL/D5W	**1**
DOBUTAMINE/DEXTROSE 5%	**1**
DOCEFREZ	**3**
DOCETAXEL	**3**
DOCETAXEL	**1**
DOPAMINE HCL	**1**
DOPAMINE/D5W	**1**
DOPAMINE/DEXTROSE	**1**
DOPRAM	**3**
DORIBAX	**3**
DORIPENEM	**1**
DOXERCALCIFEROL	**1**
DOXIL	**3**
DOXORUBICIN	**1**
DOXY 100	**1**
DOXYCYCLINE HYCLATE	**1**
DRAX IMAGE DTPA	**3**
DROPERIDOL	**1**
DUOVISC	**3**
DURACLON	**3**
DURAMORPH	**1**
DURASAFE SPINAL/EPIDURAL	**3**
DYSPORT	**6**
EDEX	**3**
EGRIFTA	**6**
ELAPRASE	**6**
ELELYSO	**3**
ELIGARD	**6**
ELITEK	**3**
ELLENCE	**3**
ELLIOTTS B	**3**
ELOXATIN	**3**
EMEND	**3**
EMPLICITI	**6**
ENALAPRILAT	**1**
ENGERIX-B	**3**
ENGYSTOL	**3**
ENLON	**3**
ENLON-PLUS	**3**
ENOXAPARIN SODIUM	**1**
EOVIST	**3**
EPHEDRINE SULFATE	**1**
EPINEPHRINE	**1**
EPINEPHRINE HCL	**1**
EPIPEN	**2**
EPIPEN 2-PAK	**2**
EPIRUBICIN	**1**
EPOGEN	**6**
EPOPROSTENOL	**4**
EPTIFIBATIDE	**1**
ERAXIS	**3**
ERBITUX	**6**
ERYTHROCIN LACTOBIONATE	**3**
ESMOLOL HCL	**1**
ESOMEPRAZOLE SODIUM	**1**
ESTRADIOL VALERATE	**1**
ETHACRYNATE SODIUM	**1**
ETHAMOLIN	**3**
ETHYOL	**3**
ETOMIDATE	**1**
ETOPOPHOS	**3**
EXPAREL	**3**
EYLEA	**6**
FABRAZYME	**6**
FAMOTIDINE PREMIXED	**1**
FASLODEX	**3**
FEIBA NF	**6**
FERAHEME	**3**
FERRIC GLUCONATE COMPLEX	**1**
FERRLECIT	**3**
FIRAZYR	**6**
FIRMAGON	**6**
FLEBOGAMMA DIF	**6**
FLEXBUMIN	**1**
FLOLAN	**2**
FLOXURIDINE	**1**
FLUCONAZOLE IN DEXTROSE	**1**
FLUCONAZOLE IN NACL	**3**
FLUCONAZOLE IN NACL	**1**
FLUDARABINE	**1**
FLUMAZENIL	**1**
FLURESCITE	**3**
FLUOROURACIL	**1**
FLUPHENAZINE DECANOATE	**1**
FLUPHENAZINE HCL	**1**
FOLIC ACID	**1**
FOLLISTIM AQ	**5**
FOLOTYN	**6**
FOMEPIZOLE	**1**
FONDAPARINUX SODIUM	**1**
FORTAZ	**3**
FORTEO	**5**
FOSPHENYTOIN SODIUM	**1**
FRAGMIN	**2**
VASOPRESSIN	**1**
VECTIBIX	**6**
VECURONIUM BROMIDE	**1**
VELCADE	**6**
VELETRI	**6**
VENOFER	**3**
VENOMIL WHITE FACED HORNE	**3**
VERAPAMIL HCL	**1**
VFEND IV	**3**
VIBATIV	**3**
VIDAZA	**6**
VIMPAT	**2**
VINBLASTINE	**1**
VINCASAR	**1**
VINCRISTINE	**1**
VINORELBINE	**1**
VISCOAT	**3**
VISIPAQUE	**3**
VISTIDE	**3**
VISUDYNE	**6**
VITAJECT	**3**
VITAMIN B-COMPLEX 100	**1**
VITAMIN C 222MG	**1**
VITAMIN K1	**1**
VITRASE	**3**
VIVITROL	**6**
VOLUVEN	**3**
VORAXAZE	**3**
VORICONAZOLE	**1**
VPRIV	**6**
WILATE	**6**
WINRHO SDF	**6**
XEOMIN	**6**
XGEVA	**6**
XIAFLEX	**3**
XOLAIR	**6**
XYLOCAINE	**3**
XYLOCAINE DENTAL	**1**
XYLOCAINE/EPINEPHRINE	**3**
XYLOCAINE-MPF	**3**
XYLOCAINE-MPF/EPINEPHRINE	**3**
XYNTHA	**5**
YERVOY	**6**
YF-VAX	**3**
YONDELIS	**6**
ZALTRAP	**6**
ZANOSAR	**3**
ZANTAC	**3**
ZARXIO	**5**
ZEEL	**3**
ZEMAIRA	**6**
ZEMPLAR	**3**
ZEMURON	**3**
ZEVALIN Y-90	**3**
ZINACEF	**3**
ZINC SULFATE	**1**
ZINC TRACE METAL	**1**
ZINECARD	**3**
ZITHROMAX	**3**
ZOLADEX	**5**
ZOLEDRONIC ACID	**4, 6**
ZOMETA	**6**
ZORBTIVE	**6**
ZOSTAVAX	**3**
ZOSYN	**3**
ZYPREXA	**3**
ZYPREXA RELPREVV	**3**
HIGH COST-GENERICS	
AMOXICILLIN & K CLAVULANATE FOR SUSP 250-62.5 MG/5ML	**2**
AMOXICILLIN & K CLAVULANATE TAB SR 12HR 1000-62.5 MG	**2**
CEFACLOR FOR SUSP 375 MG/5ML	**2**
CEFIXIME FOR SUSP 100 MG/5ML	**2**
CEFIXIME FOR SUSP 200 MG/5ML	**2**
ERYTHROMYCIN TAB 250 MG	**2**
ERYTHROMYCIN TAB 500 MG	**2**
ERYTHROMYCIN TAB DELAYED RELEASE 333 MG	**2**
ERYTHROMYCIN ETHYLSUCCINATE FOR SUSP 200 MG/5ML	**2**
DEMECLOCYCLINE HCL TAB 150 MG	**2**
DOXYCYCLINE HYCLATE TAB DELAYED RELEASE 50 MG	**2**
DOXYCYCLINE HYCLATE TAB DELAYED RELEASE 150 MG	**2**
DOXYCYCLINE HYCLATE TAB DELAYED RELEASE 200 MG	**2**
MINOCYCLINE HCL TAB SR 24HR 90 MG	**2**
TETRACYCLINE HCL CAP 500 MG	**2**
RIFABUTIN CAP 150 MG	**2**
GRISEOFULVIN MICROSIZE TAB 500 MG	**2**
GRISEOFULVIN ULTRAMICROSIZE TAB 250 MG	**2**
VALGANCICLOVIR HCL TAB 450 MG (BASE EQUIVALENT)	**2**
ACYCLOVIR SUSP 200 MG/5ML	**2**
OSELTAMIVIR PHOSPHATE CAP 75 MG (BASE EQUIV)	**2**
VANCOMYCIN HCL CAP 125 MG	**2**
VANCOMYCIN HCL CAP 250 MG	**2**
ATOVAQUONE SUSP 750 MG/5ML	**2**
CYCLOPHOSPHAMIDE CAP 50 MG	**2**
EXEMESTANE TAB 25 MG	**2**
LEUCOVORIN CALCIUM TAB 25 MG	**2**
BUDESONIDE DELAYED RELEASE PARTICLES CAP 3 MG	**2**
PREDNISOLONE SOD PHOS ORALLY DISINTEGR TAB 10 MG (BASE EQ)	**2**
TESTOSTERONE TD GEL 25 MG/2.5GM (1%)	**2**
TESTOSTERONE TD GEL 50 MG/5GM (1%)	**2**
TESTOSTERONE TD GEL 12.5 MG/ACT (1%)	**2**
TESTOSTERONE TD GEL 10MG/ACT (2%)	**2**
ESTRADIOL TD PATCH TWICE WEEKLY 0.1 MG/24HR	**2**
ESTRADIOL TD PATCH WEEKLY 0.1 MG/24HR	**2**
MEGESTROL ACETATE SUSP 625 MG/5ML	**2**
METFORMIN HCL TAB SR 24HR OSMOTIC 500 MG	**2**
METFORMIN HCL TAB SR 24HR OSMOTIC 1000 MG	**2**
METFORMIN HCL TAB SR 24HR MODIFIED RELEASE 500 MG	**2**
METFORMIN HCL TAB SR 24HR MODIFIED RELEASE 1000 MG	**2**
PIOGLITAZONE HCL-GLIMEPIRIDE TAB 30-2 MG	**2**
PIOGLITAZONE HCL-GLIMEPIRIDE TAB 30-4 MG	**2**
METHYLERGONOVINE MALEATE TAB 0.2 MG	**2**
DESMOPRESSIN ACETATE INJ 4 MCG/ML	**2**
DESMOPRESSIN ACETATE NASAL SPRAY SOLN 0.01% (REFRIGERATED)	**2**

FREAMINE HBC 6.9%	3
FREAMINE III	3
FUROSEMIDE	1
FUSILEV	6
FUZEON	5
GABLOFEN	3
GADAVIST	3
GAMASTAN S/D	6
GAMMAGARD LIQUID	5
GAMMAGARD S/D	5
GAMMAKED	5
GAMMAPLEX	6
GAMUNEX-C	5
GANCICLOVIR	1
GANIRELIX ACETATE	6
GARDASIL	3
GEMCITABINE	1
GEMZAR	3
GENTAMICIN SULFATE	1
GENTAMICIN SULFATE PEDIAT	1
GENTAMICIN SULFATE/0.9% S	1
GENTAMICIN SULFATE/0.9% S	3
GEODON	3
GLASSIA	6
GLIADEL WAFER	3
GLOFIL-125	3
GLUCAGEN HYPOKIT	2
GLUCAGON EMERGENCY KIT	2
GLYCOPYRROLATE	1
GRANISETRON HCL	1
HALAVEN	6
HALDOL	3
HALDOL DECANOATE 100	3
HALDOL DECANOATE 50	3
HALOPERIDOL	1
HALOPERIDOL DECANOATE	1
HALOPERIDOL LACTATE	1
HAVRIX	3
HEALON	3
HEALON GV	3
HEALON5	3
HECTOROL	3
HEMABATE	3
HEMOFIL-M	6
HEPAGAM B	6
HEPARIN I.V. FLUSH 5/12ML	1
HEPARIN LOCK FL/NACL LUERLOK F	1
HEPARIN LOCK FLUSH	1
HEPARIN LOCK FLUSH 5/12ML	1
HEPARIN LOCK FLUSH FOR FL	1
HEPARIN LOCK FLUSH/NACL F	1
HEPARIN SODIUM	1
HEPARIN SODIUM LOCK FLUSH	1
HEPARIN SODIUM LOCK FLUSH/ F	1
HEPARIN SODIUM/D5W	1
HEPARIN SODIUM/D5W	3
HEPARIN SODIUM/NACL 0.45%	3
HEPARIN SODIUM/NACL 0.9%	1
HEPARIN SODIUM/SODIUM CHL	1
HEPATAMINE	1
HERCEPTIN	6
HESPAN	3
HETASTARCH 6%/NACL	1
HEXTEND	3
HISTATROL	3
HIZENTRA	5
HSA STERILE DILUENT	3
HUMALOG	3
HUMALOG MIX 50/50	3
HUMALOG MIX 75/25	3
HUMAN ALBUMIN GRIFOLS	1
HUMATE-P	6
HUMATROPE	5
HUMULIN 500 R-U500	2
HUMULIN 70/30	3
HUMULIN N	3
HUMULIN R	3
HYALGAN	5
HYCAMTIN	3
HYDRALAZINE HCL	1
HYDROCHLORIDE	1
HYDROMORPHONE HCL	1
HYDROMORPHONE HCL DOSETTE	1
HYDROXOCOBALAMIN	1
HYDROXYZINE HCL	1
HYLENEX	3
HYMENOPTERA VENOM/VENOM P	3
HYPERHEP B	6
HYPERLYTE-CR	1
HYPERTET S/D	3
IBANDRONATE SODIUM	1
IBUPROFEN LYSINE	1
IBUTILIDE FUMARATE	1
IC GREEN	3
IDAMYCIN	3
IDARUBICIN	1
IFEX	3
IFOSFAMIDE	1
IFOSFAMIDE	3
ILARIS	6
IMIPENEM/CILASTATIN	1
IMITREX	3
IMLYGIC	6
IMOVAX RABIES (H.D.C.V.)	3
INCRELEX	6
INDICLOR	3
INDIGO CARMINE	1
INDIUM IN 111 DTPA	3
INDIUM IN 111 OXYQUINOLIN	3
INDOCYANINE GREEN	1
INDOMETHACIN	1
INFANRIX	3
INFED	3
DESMOPRESSIN ACETATE NASAL SPRAY SOLN 0.01%	2
NITROGLYCERIN TL SOLN 0.4 MG/SPRAY (400 MCG/SPRAY)	2
DILTIAZEM HCL CAP SR 12HR 120 MG	2
NISOLDIPINE TAB SR 24HR 8.5 MG	2
MEXILETINE HCL CAP 150 MG	2
PROPAFENONE HCL CAP SR 12HR 225 MG	2
PROPAFENONE HCL CAP SR 12HR 325 MG	2
AMIODARONE HCL TAB 100 MG	2
OLMESARTAN MEDOXOMIL TAB 40 MG	2
EPLERENONE TAB 50 MG	2
OLMESARTAN MEDOXOMIL-HYDROCHLOROTHIAZIDE TAB 40-12.5 MG	2
OLMESARTAN MEDOXOMIL-HYDROCHLOROTHIAZIDE TAB 40-25 MG	2
OLMESARTAN-AMLODIPINE-HYDROCHLOROTHIAZIDE TAB 20-5-12.5 MG	2
OLMESARTAN-AMLODIPINE-HYDROCHLOROTHIAZIDE TAB 40-5-12.5 MG	2
OLMESARTAN-AMLODIPINE-HYDROCHLOROTHIAZIDE TAB 40-5-25 MG	2
OLMESARTAN-AMLODIPINE-HYDROCHLOROTHIAZIDE TAB 40-10-12.5 MG	2
OLMESARTAN-AMLODIPINE-HYDROCHLOROTHIAZIDE TAB 40-10-25 MG	2
ACETAZOLAMIDE TAB 125 MG	2
METHAZOLAMIDE TAB 50 MG	2
EPINEPHRINE SOLUTION AUTO-INJECTOR 0.15 MG/0.15ML (1:1000)	2
EPINEPHRINE SOLUTION AUTO-INJECTOR 0.3 MG/0.3ML (1:1000)	2
EZETIMIBE TAB 10 MG	2
FLUVASTATIN SODIUM TAB SR 24 HR 80 MG	2
NIACIN TAB CR 750 MG (ANTIHYPERLIPIDEMIC)	2
AMLODIPINE BESYLATE-ATORVASTATIN CALCIUM TAB 5-20 MG	2
AMLODIPINE BESYLATE-ATORVASTATIN CALCIUM TAB 5-40 MG	2
AMLODIPINE BESYLATE-ATORVASTATIN CALCIUM TAB 10-40 MG	2
PROMETHAZINE HCL SUPPOS 25 MG	2
MOMETASONE FUROATE NASAL SUSP 50 MCG/ACT	2
ALBUTEROL SULFATE TAB 2 MG	2
LEVALBUTEROL HCL SOLN NEBU 0.63 MG/3ML (BASE EQUIV)	2
BUDESONIDE INHALATION SUSP 0.25 MG/2ML	2
BUDESONIDE INHALATION SUSP 0.5 MG/2ML	2
BUDESONIDE INHALATION SUSP 1 MG/2ML	2
ZAFIRLUKAST TAB 10 MG	2
CHLORDIAZEPOXIDE HCL-CLIDINIUM BROMIDE CAP 5-2.5 MG	2
ESOMEPRAZOLE MAGNESIUM CAP DELAYED RELEASE 20 MG (BASE EQ)	2
ESOMEPRAZOLE MAGNESIUM CAP DELAYED RELEASE 40 MG (BASE EQ)	2
SUCRALFATE SUSP 1 GM/10ML	2
OMEPRAZOLE-SODIUM BICARBONATE CAP 20-1100 MG	2
OMEPRAZOLE-SODIUM BICARBONATE CAP 40-1100 MG	2
DRONABINOL CAP 5 MG	2
DRONABINOL CAP 10 MG	2
URSODIOL CAP 300 MG	2
CROMOLYN SODIUM ORAL CONC 100 MG/5ML	2
MESALAMINE ENEMA 4 GM	2
ALOSETRON HCL TAB 0.5 MG (BASE EQUIV)	2
ALOSETRON HCL TAB 1 MG (BASE EQUIV)	2
*METHENAMINE-HYOSC-METH BLUE-SOD PHOS-PHEN SAL CAP 118 MG***	2
*METHENAMINE-HYOSC-METH BLUE-SOD PHOS-PHEN SAL TAB 81 MG***	2
DARIFENACIN HYDROBROMIDE TAB SR 24HR 15 MG (BASE EQUIV)	2
OXYBUTYNIN CHLORIDE TAB SR 24HR 5 MG	2
TOLTERODINE TARTRATE CAP SR 24HR 2 MG	2
TOLTERODINE TARTRATE CAP SR 24HR 4 MG	2
METRONIDAZOLE VAGINAL GEL 0.75%	2
ESTRADIOL VAGINAL TAB 10 MCG	2
POTASSIUM CITRATE TAB CR 5 MEQ (540 MG)	2
NEFAZODONE HCL TAB 100 MG	2
NEFAZODONE HCL TAB 200 MG	2
FLUOXETINE HCL TAB 60 MG	2
FLUVOXAMINE MALEATE CAP SR 24HR 100 MG	2
PAROXETINE HCL TAB SR 24HR 37.5 MG	2
DULOXETINE HCL ENTERIC COATED PELLETS CAP 40 MG	2
VENLAFAXINE HCL TAB SR 24HR 225 MG (BASE EQUIVALENT)	2
CLOMIPRAMINE HCL CAP 25 MG	2
CLOMIPRAMINE HCL CAP 50 MG	2
CLOMIPRAMINE HCL CAP 75 MG	2
DESIPRAMINE HCL TAB 100 MG	2
DESIPRAMINE HCL TAB 150 MG	2
IMIPRAMINE PAMOATE CAP 75 MG	2
IMIPRAMINE PAMOATE CAP 100 MG	2
PALIPERIDONE TAB SR 24HR 1.5 MG	2
PALIPERIDONE TAB SR 24HR 3 MG	2
PALIPERIDONE TAB SR 24HR 9 MG	2
RISPERIDONE ORALLY DISINTEGRATING TAB 0.25 MG	2
QUETIAPINE FUMARATE TAB SR 24HR 50 MG	2
QUETIAPINE FUMARATE TAB SR 24HR 150 MG	2
QUETIAPINE FUMARATE TAB SR 24HR 200 MG	2
QUETIAPINE FUMARATE TAB SR 24HR 300 MG	2
QUETIAPINE FUMARATE TAB SR 24HR 400 MG	2
OLANZAPINE ORALLY DISINTEGRATING TAB 5 MG	2
CHLORPROMAZINE HCL TAB 50 MG	2
CHLORPROMAZINE HCL TAB 100 MG	2
CHLORPROMAZINE HCL TAB 200 MG	2
FLUPHENAZINE HCL TAB 5 MG	2
PERPHENAZINE TAB 8 MG	2
ARIPIPRAZOLE TAB 2 MG	2
ARIPIPRAZOLE TAB 5 MG	2
ARIPIPRAZOLE TAB 10 MG	2
ARIPIPRAZOLE TAB 15 MG	2
ARIPIPRAZOLE TAB 20 MG	2
ARIPIPRAZOLE TAB 30 MG	2
ARIPIPRAZOLE ORAL SOLUTION 1 MG/ML	2
DEXTROAMPHETAMINE SULFATE TAB 2.5 MG	2
DEXTROAMPHETAMINE SULFATE ORAL SOLUTION 5 MG/5ML	2
DEXTROAMPHETAMINE SULFATE CAP SR 24HR 15 MG	2
AMPHETAMINE-DEXTROAMPHETAMINE CAP SR 24HR 10 MG	2
CLONIDINE HCL TAB SR 12HR 0.1 MG	2
ARMODAFINIL TAB 50 MG	2
ARMODAFINIL TAB 150 MG	2
ARMODAFINIL TAB 200 MG	2
ARMODAFINIL TAB 250 MG	2
DEXMETHYLPHENIDATE HCL CAP SR 24 HR 40 MG	2
METHYLPHENIDATE HCL CAP CR 50 MG (CD)	2
METHYLPHENIDATE HCL TAB CR 10 MG	2
METHYLPHENIDATE HCL TAB SA OSM 18 MG	2
METHYLPHENIDATE HCL TAB SA OSM 27 MG	2
METHYLPHENIDATE HCL TAB SA OSM 36 MG	2
METHYLPHENIDATE HCL TAB SA OSM 54 MG	2
METHYLPHENIDATE HCL SOLN 5 MG/5ML	2
METHYLPHENIDATE HCL CAP SR 24HR 40 MG (LA)	2
METHYLPHENIDATE HCL TAB SR 24HR 36 MG	2
METHYLPHENIDATE HCL TAB SR 24HR 54 MG	2

INFUMORPH 200	3
INFUMORPH 500	3
INFUVITE	3
INFUVITE ADULT	3
INFUVITE PEDIATRIC	3
INTEGRILIN	3
INTRALIPID	1
INTRALIPID	3
INTRON A	6
INULIN	3
INVANZ	3
INVEGA SUSTENNA	3
IODOPEN	3
IONOSOL-B/DEXTROSE 5%	3
IONOSOL-MB/DEXTROSE 5%	3
IPOL INACTIVATED IPV	3
IPRIVASK	3
IRINOTECAN	1
ISCAR MALI	3
ISOLYTE-P/DEXTROSE 5%	3
ISOLYTE-S	3
ISOLYTE-S PH 7.4	3
ISONIAZID	1
ISOSULFAN BLUE	1
ISOTONIC GENTAMICIN	1
ISOVUE-200	3
ISOVUE-250	3
ISOVUE-250 MULTIPACK	3
ISOVUE-300	3
ISOVUE-300 MULTIPACK	3
ISOVUE-370	3
ISOVUE-370 MULTIPACK	3
ISOVUE-M 200	3
ISOVUE-M 300	3
ISTODAX	6
ISUPREL	3
IXEMPRA	6
IXIARO	3
IXINITY	6
JEVTANA	6
KALBITOR	6
KANUMA	3
KCL 0.075%/D5W/NACL 0.45%	1
KCL 0.15%/D5W/ NACL 0.3%	1
KCL 0.15%/D5W/NACL 0.2%	1
KCL 0.15%/D5W/NACL 0.225%	3
KCL 0.15%/D5W/NACL 0.45%	1
KCL 0.15%/D5W/NACL 0.9%	1
KCL 0.3%/D5W/NACL 0.45%	1
KCL 0.3%/D5W/NACL 0.9%	3
KEDBUMIN	1
KENALOG-10	3
KENALOG-40	3
KEPIVANCE	3
KEPPRA	3
KETALAR	3
KETALAR	1
KETAMINE HCL	1
KETOROLAC TROMETHAMINE	1
KINEVAC	3
KINRIX	3
KIT FOR THE PREPARATION O	3
KOATE	6
KOATE-DVI	6
KOGENATE FS	5
KOVALTRY	5
KRYSTEXXA	6
KYPROLIS	6
LABETALOL HCL	1
LACTATED RINGERS	1
LACTATED RINGERS VIAFLEX	1
LANOXIN	3
LANOXIN PEDIATRIC	3
LANTUS	3
L-CYSTEINE HCL	1
LEUCOVORIN	1
LEUKINE	6
LEUPROLIDE ACETATE	4
LEVAQUIN	3
LEVEMIR	2
LEVETIRACETAM	1
LEVETIRACETAM	3
LEVOCARNITINE	1
LEVOFLOXACIN	1
LEVOFLOXACIN IN 5% DEXTRO	1
LEVOFLOXACIN IN D5W	1
LEVOLEUCOVORIN CALCIUM	4
LEVOPHED	3
LEVOTHYROXINE SODIUM	1
LEVSIN	3
LEXISCAN	3
LIDOCAINE HCL	1
LIDOCAINE HCL IN D5W	1
LIDOCAINE HCL/DEXTROSE	1
LIDOCAINE HCL/DEXTROSE	3
LIDOCAINE/EPINEPHRINE	1
LINCOCIN	3
LINCOMYCIN HCL	1
LIORESAL INTRATHECAL	3
LIOTHYRONINE SODIUM	1
LIPODOX	1
LMD 10% DEXTROSE 5%	1
LMD 10% SODIUM CHLORIDE 0	1
LOPRESSOR	3
LORAZEPAM	1
LOVENOX	2
LOVENOX	3
LUCENTIS	6
LUMIZYME	6
LUPRON DEPOT	5
LUPRON DEPOT-PED	5
LYMPHOMYOSOT X	3
M.V.I. ADULT	3

DONEPEZIL HYDROCHLORIDE TAB 23 MG	2
RIVASTIGMINE TD PATCH 24HR 9.5 MG/24HR	2
RIVASTIGMINE TD PATCH 24HR 13.3 MG/24HR	2
FLUOXETINE HCL (PMDD) CAP 20 MG	2
ACAMPROSATE CALCIUM TAB DELAYED RELEASE 333 MG	2
OLANZAPINE-FLUOXETINE HCL CAP 6-50 MG	2
SALSALATE TAB 750 MG	2
HYDROMORPHONE HCL TAB ER 24HR DETER 16 MG	2
HYDROMORPHONE HCL TAB ER 24HR DETER 32 MG	2
LEVORPHANOL TARTRATE TAB 2 MG	2
MORPHINE SULFATE CAP SR 24HR 60 MG	2
MORPHINE SULFATE CAP SR 24HR 100 MG	2
MORPHINE SULFATE BEADS CAP SR 24HR 90 MG	2
OXYCODONE HCL TAB ER 12HR DETER 10 MG	2
OXYCODONE HCL TAB ER 12HR DETER 20 MG	2
OXYCODONE HCL TAB ER 12HR DETER 40 MG	2
OXYCODONE HCL TAB 30 MG	2
OXYMORPHONE HCL TAB 10 MG	2
OXYMORPHONE HCL TAB SR 12HR 10 MG	2
OXYMORPHONE HCL TAB SR 12HR 15 MG	2
OXYMORPHONE HCL TAB SR 12HR 20 MG	2
OXYMORPHONE HCL TAB SR 12HR 40 MG	2
TRAMADOL HCL CAP SR 24HR BIPHASIC RELEASE 300 MG	2
BUTALBITAL-ACETAMINOPHEN-CAFF W/ COD CAP 50-300-40-30 MG	2
HYDROCODONE-ACETAMINOPHEN TAB 7.5-300 MG	2
HYDROCODONE-ACETAMINOPHEN TAB 10-300 MG	2
HYDROCODONE-ACETAMINOPHEN SOLN 7.5-325 MG/15ML	2
HYDROCODONE-IBUPROFEN TAB 10-200 MG	2
FENOPROFEN CALCIUM CAP 400 MG	2
NAPROXEN SUSP 125 MG/5ML	2
NAPROXEN SODIUM TAB SR 24HR 500 MG (BASE EQUIV)	2
ALMOTRIPTAN MALATE TAB 12.5 MG	2
FROVATRIPTAN SUCCINATE TAB 2.5 MG (BASE EQUIVALENT)	2
SUMATRIPTAN NASAL SPRAY 20 MG/ACT	2
SUMATRIPTAN SUCCINATE SOLUTION AUTO-INJECTOR 4 MG/0.5ML	2
SUMATRIPTAN SUCCINATE SOLUTION AUTO-INJECTOR 6 MG/0.5ML	2
SUMATRIPTAN SUCCINATE SOLUTION CARTRIDGE 6 MG/0.5ML	2
SUMATRIPTAN SUCCINATE INJ 6 MG/0.5ML	2
ISOMETHEPTENE-DICHLORAL-ACETAMINOPHEN CAP 65-100-325 MG	2
ERGOTAMINE W/ CAFFEINE SUPPOS 2-100 MG	2
COLCHICINE TAB 0.6 MG	2
LIDOCAINE HCL LOCAL PRESERVATIVE FREE (PF) INJ 2%	2
FELBAMATE TAB 400 MG	2
FELBAMATE TAB 600 MG	2
TIAGABINE HCL TAB 2 MG	2
TIAGABINE HCL TAB 4 MG	2
ETHOSUXIMIDE CAP 250 MG	2
ETHOSUXIMIDE SOLN 250 MG/5ML	2
CARBAMAZEPINE TAB SR 12HR 400 MG	2
LAMOTRIGINE ORALLY DISINTEGRATING TAB 25 MG	2
LAMOTRIGINE ORALLY DISINTEGRATING TAB 200 MG	2
LAMOTRIGINE TAB SR 24HR 25 MG	2
LAMOTRIGINE TAB SR 24HR 50 MG	2
LAMOTRIGINE TAB SR 24HR 100 MG	2
LAMOTRIGINE TAB SR 24HR 200 MG	2
LAMOTRIGINE TAB SR 24HR 250 MG	2
LAMOTRIGINE TAB SR 24HR 300 MG	2
TOPIRAMATE CAP ER 24HR SPRINKLE 50 MG	2
TOPIRAMATE CAP ER 24HR SPRINKLE 100 MG	2
TOPIRAMATE CAP ER 24HR SPRINKLE 200 MG	2
ENTACAPONE TAB 200 MG	2
BROMOCRIPTINE MESYLATE CAP 5 MG (BASE EQUIVALENT)	2
PRAMIPEXOLE DIHYDROCHLORIDE TAB SR 24HR 0.375 MG	2
PRAMIPEXOLE DIHYDROCHLORIDE TAB SR 24HR 0.75 MG	2
ROPINIROLE HYDROCHLORIDE TAB SR 24HR 8 MG (BASE EQUIVALENT)	2
ROPINIROLE HYDROCHLORIDE TAB SR 24HR 12 MG (BASE EQUIVALENT)	2
CARBIDOPA-LEVODOPA-ENTACAPONE TABS 18.75-75-200 MG	2
CARBIDOPA-LEVODOPA-ENTACAPONE TABS 31.25-125-200 MG	2
CARBIDOPA-LEVODOPA-ENTACAPONE TABS 50-200-200 MG	2
RASAGILINE MESYLATE TAB 1 MG (BASE EQUIV)	2
CARBIDOPA TAB 25 MG	2
METAXALONE TAB 800 MG	2
PYRIDOSTIGMINE BROMIDE TAB CR 180 MG	2
POTASSIUM CHLORIDE ORAL SOLN 10% (20 MEQ/15ML)	2
POTASSIUM CHLORIDE ORAL SOLN 20% (40 MEQ/15ML)	2
POTASSIUM CHLORIDE POWDER PACKET 20 MEQ	2
ENOXAPARIN SODIUM INJ 60 MG/0.6ML	2
ENOXAPARIN SODIUM INJ 100 MG/ML	2
ENOXAPARIN SODIUM INJ 150 MG/ML	2
FONDAPARINUX SODIUM SUBCUTANEOUS INJ 7.5 MG/0.6ML	2
FONDAPARINUX SODIUM SUBCUTANEOUS INJ 10 MG/0.8ML	2
ANAGRELIDE HCL CAP 1 MG	2
ASPIRIN-DIPYRIDAMOLE CAP SR 12HR 25-200 MG	2
GENTAMICIN SULFATE OPHTH SOLN 0.3%	2
TOBRAMYCIN-DEXAMETHASONE OPHTH SUSP 0.3-0.1%	2
BRIMONIDINE TARTRATE OPHTH SOLN 0.15%	2
BROMFENAC SODIUM OPHTH SOLN 0.09% (BASE EQUIV) (ONCE-DAILY)	2
FLUOCINOLONE ACETONIDE (OTIC) OIL 0.01%	2
HYDROCORTISONE ACETATE SUPPOS 25 MG	2
HYDROCORTISONE ACETATE SUPPOS 30 MG	2
ADAPALENE CREAM 0.1%	2
ADAPALENE GEL 0.3%	2
BENZOYL PEROXIDE LIQ 7%	2
BENZOYL PEROXIDE FOAM 9.8%	2
ISOTRETINOIN CAP 20 MG	2
ISOTRETINOIN CAP 30 MG	2
ISOTRETINOIN CAP 40 MG	2
TRETINOIN CREAM 0.05%	2
TRETINOIN CREAM 0.1%	2
TRETINOIN GEL 0.05%	2
TRETINOIN MICROSPHERE GEL 0.04%	2
TRETINOIN MICROSPHERE GEL 0.1%	2
CLINDAMYCIN PHOSPHATE FOAM 1%	2
BENZOYL PEROXIDE-ERYTHROMYCIN GEL 5-3%	2
CLINDAMYCIN PHOSPHATE-BENZOYL PEROXIDE GEL 1-5%	2
CLINDAMYCIN PHOSPHATE-TRETINOIN GEL 1.2-0.025%	2
SULFACETAMIDE SODIUM W/ SULFUR WASH 9-4%	2
SULFACETAMIDE SODIUM W/ SULFUR CLEANSER 9.8-4.8%	2
SULFACETAMIDE SODIUM W/ SULFUR CLEANSER 10-2%	2
SULFACETAMIDE SODIUM W/ SULFUR SUSP 8-4%	2
SULFACETAMIDE SODIUM W/ SULFUR CREAM 10-2%	2
SULFACETAMIDE SODIUM W/ SULFUR CREAM 10-5%	2
DOXYCYCLINE (ROSACEA) CAP DELAYED RELEASE 40 MG	2

M.V.I. PEDIATRIC	**3**
M.V.I.-12 WITHOUT VITAMIN	**3**
MACUGEN	**6**
MAGNESIUM CHLORIDE	**1**
MAGNESIUM SULFATE	**1**
MAGNESIUM SULFATE IN D5W	**3**
MAGNESIUM SULFATE IN D5W	**1**
MAGNEVIST	**3**
MAKENA	**6**
MANGANESE SULFATE	**1**
MANGANESE TRACE METAL	**1**
MANNITOL	**1**
MARCAINE	**3**
MARCAINE SPINAL	**3**
MARCAINE/EPINEPHRINE	**3**
MAXIPIME	**3**
MD-76 R	**3**
MEDROXYPROGESTERONE ACETA	**1**
MEGA-C/A PLUS	**1**
MELPHALAN HYDROCHLORIDE	**1**
MENACTRA	**3**
MENOMUNE-A/C/Y/W-135	**3**
MENOPUR	**6**
MENVEO	**3**
MEPERIDINE HCL	**1**
MEROPENEM	**1**
MERREM	**3**
MESNA	**1**
MESNEX	**3**
METASTRON	**3**
METHADONE HCL	**3**
METHOTREXATE	**1**
METHYLDOPATE HCL	**1**
METHYLENE BLUE	**1**
METHYLERGONOVINE MALEATE	**1**
METHYLPREDNISOLONE ACETAT	**1**
METHYLPREDNISOLONE SODIUM	**1**
METOCLOPRAMIDE HCL	**1**
METOPROLOL TARTRATE	**1**
METRO IV	**3**
METRONIDAZOLE	**1**
METRONIDAZOLE IN NACL 0.7	**1**
MIACALCIN	**2**
MIDAZOLAM HCL	**1**
MINOCIN	**3**
METRONIDAZOLE GEL 1%	**2**
MUPIROCIN CALCIUM CREAM 2%	**2**
CICLOPIROX GEL 0.77%	**2**
NAFTIFINE HCL CREAM 1%	**2**
OXICONAZOLE NITRATE CREAM 1%	**2**
NYSTATIN-TRIAMCINOLONE CREAM 100000-0.1 UNIT/GM-%	**2**
NYSTATIN-TRIAMCINOLONE OINT 100000-0.1 UNIT/GM-%	**2**
DICLOFENAC SODIUM SOLN 1.5%	**2**
DICLOFENAC SODIUM GEL 1%	**2**
CALCIPOTRIENE CREAM 0.005%	**2**
CALCIPOTRIENE OINT 0.005%	**2**
CALCITRIOL OINT 3 MCG/GM	**2**
ACITRETIN CAP 10 MG	**2**
ACITRETIN CAP 25 MG	**2**
SULFACETAMIDE SODIUM SHAMPOO 10%	**2**
ACYCLOVIR OINT 5%	**2**
BETAMETHASONE VALERATE AEROSOL FOAM 0.12%	**2**
CLOBETASOL PROPIONATE CREAM 0.05%	**2**
CLOBETASOL PROPIONATE FOAM 0.05%	**2**
CLOBETASOL PROPIONATE LOTION 0.05%	**2**
CLOBETASOL PROPIONATE OINT 0.05%	**2**
CLOBETASOL PROPIONATE SHAMPOO 0.05%	**2**
CLOBETASOL PROPIONATE EMULSION FOAM 0.05%	**2**
CLOCORTOLONE PIVALATE CREAM 0.1%	**2**
DESONIDE CREAM 0.05%	**2**
DESONIDE LOTION 0.05%	**2**
DESOXIMETASONE CREAM 0.05%	**2**
DESOXIMETASONE OINT 0.05%	**2**
DESOXIMETASONE OINT 0.25%	**2**
FLUOCINOLONE ACETONIDE OIL 0.01% (BODY OIL)	**2**
FLUOCINOLONE ACETONIDE OIL 0.01% (SCALP OIL)	**2**
FLUOCINONIDE CREAM 0.1%	**2**
FLUOCINONIDE GEL 0.05%	**2**
FLUOCINONIDE OINT 0.05%	**2**
FLURANDRENOLIDE LOTION 0.05%	**2**
HYDROCORTISONE VALERATE OINT 0.2%	**2**
HYDROCORTISONE BUTYRATE HYDROPHILIC LIPO BASE CREAM 0.1%	**2**
TRIAMCINOLONE ACETONIDE AEROSOL SOLN 0.147 MG/GM	**2**
CALCIPOTRIENE-BETAMETHASONE DIPROPIONATE OINT 0.005-0.064%	**2**
UREA CREAM 40%	**2**
UREA IN ZINC UNDECYLENATE-LACTIC ACID VEHICLE EMULSION 50%	**2**
SALICYLIC ACID FILM FORMING LIQUID 27.5%	**2**
SALICYLIC ACID SHAMPOO 6%	**2**
TACROLIMUS OINT 0.1%	**2**
LIDOCAINE OINT 5%	**2**
MALATHION LOTION 0.5%	**2**
SPINOSAD SUSP 0.9%	**2**

North Carolina State Health Plan
FOR TEACHERS AND STATE EMPLOYEES
A Division of the Department of State Treasurer
3200 Atlantic Avenue • Raleigh, NC 27604 • Phone: 919-814-4400 • Fax: 919-855-5817 • www.shpnc.org

Address: 3200 Atlantic Avenue
Raleigh, NC 27604

Phone: 919-814-4400

THE NC STATE HEALTH PLAN IS LOCATED IN THE LONGLEAF BUILDING

Directions to the State Health Plan from Downtown Raleigh

Take US-401 N / S. McDowell Street

Take the Wake Forest Road exit toward Atlantic Ave

Use the left 2 lanes to turn left onto Wake Forest Rd

Continue onto Atlantic Avenue

Cross Highwoods Boulevard and take the first or second right into the office complex.

Follow the signs to the Longleaf Building.

Street level/handicapped parking can be found on the opposite side of the building from where the flags are flying.

Directions to the State Health Plan from RDU Airport

Take I-40 East

Use the right 2 lanes to take exit 289 for Wade Avenue toward I-440/US-1 N

Continue onto Wade Avenue

Take exit onto 1-440E/US-1 N toward Wake Forest/Rocky Mt/Wilson

Take exit 11 to merge onto US-1 N/US-401 N/Capital Boulevard toward Wake Forest/Louisburg

Stay in the left lane and turn left at Highwoods Boulevard

Turn right on Atlantic Avenue and take the first or second right into the office complex.

Follow the signs to the Longleaf Building

Street level/handicapped parking can be found on the opposite side of the building from where the flags are flying