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Proposed Formulary Changes

Effective 4/1/2018 (unless otherwise noted)

Table 1: Summary of Medicaid PDL proposed designation as **Preferred**

Drug Name	Ingredients	Dosage Form	Strength(s)	Notes	P&T Decision
Trulance	Plecanatide	Tablet	3 mg	Prior authorization required for clinical review (diagnosis and OTC trial agents). Quantity limit of 30 tablets per month.	Approved
Xiidra	Lifitegrast	Solution, ophthalmic	5%	Prior authorization required for clinical review (diagnosis and trial of 2 preferred OTC agents). Quantity limit of 60 single use containers per month.	Approved
Xopenex HFA	Levalbuterol	Aerosol, inhalation	45 mcg/actuation (15 g = 200 inhalations)	Quantity limit of 2 inhalers per month.	Approved

Table 2: Summary of Medicaid PDL proposed designation as **Non-Preferred**

Drug Name	Ingredients	Dosage Form	Strength(s)	Notes	P&T Decision
Alevzaol	Clotrimazole	Ointment	1%		Approved
Amitiza	Lubiprostone	Capsule	8 mcg, 24 mcg		Approved
Capcof	Phenylephrine-chlorpheniramine with codeine	Syrup	5 mg-2 mg-10 mg/ 5 mL		Approved
Capmist DM	Pseudoephedrine, Dextromethorphan, Guaifenesin	Tablet	30 mg-30 mg-400 mg		Approved
Capron DM	Dextromethorphan-Pyrilamine	Liquid	7.5 mg-7.5 mg/ 5 mL		Approved
Detrol	Tolterodine	Tablet	1 mg, 2 mg	Grandfather existing utilizers.	Approved
Detrol LA	Tolterodine extended release	Tablet	2 mg, 4 mg	Grandfather existing utilizers.	Approved
Faslodex	Fulvestrant	Solution, intramuscular	250 mg/5 mL	Available through medical benefit.	Approved
Hectorol	Doxercalciferol	Capsule	0.5 mcg, 1 mcg, 2.5 mcg	Grandfather existing utilizers. IV solution on medical benefit.	Approved
Linzess	Linaclotide	Capsule	72 mcg, 145 mcg, 290 mcg		Approved
Sanctura	Trospium	Tablet	20 mg	Grandfather existing utilizers.	Approved
Sanctura XR	Trospium extended release	Tablet	60 mg	Grandfather existing utilizers.	Approved
Zemplar	Paricalcitol	Capsule	1 mcg, 2 mcg, 4 mcg	Grandfather existing utilizers. IV solution on medical benefit.	Approved

New Drugs
Reviewed for P&T Meeting January 4, 2018

Tymlos (abaloparatide)

Therapeutic Class: Parathyroid Hormone Analog
FDA indication: Osteoporosis in postmenopausal women at high risk for fracture
Formulary Recommendations: Non-preferred
Rationale: Tymlos is indicated for the treatment of osteoporosis in postmenopausal womenat high risk of fracture other agents indicated for the treatment of osteoporosis in postmenopausal women at high risk of fracture include Forteo (teriparatide) and Prolia (denosumab). 2016 AACE/ACE guidelines for the treatment of postmenopasal osteoporosis recommend Prolia, Forteo (for up to two years), or Reclast for treatment of women at high fracture list. Tymlos has demonstrated osteoanabolic effects superior to placebo in reducing vertebral and non-vertebral fractures and increasing BMD in postmenopausal women with osteoporosis at high risk of fracture. Overall, Tymlos provides an additional treatment option for postmenopausal women with OP at high fracture risk.
P&T Decision: Approved

Xadago (safinamide)

Therapeutic Class: Anti-Parkinson agent, MAO-B inhibitor
FDA indication: Adjunctive treatment to levodopa/carbidopa in patients with Parkinson's disease experiencing "off" episodes
Formulary Recommendations: Non-preferred
Rationale: Based on the data presented, safinamide is an effective therapy for reduction of "off" episodes in patients who are receiving levodopa/carbidopa for Parkinson's disease.Safinamide is, however, more costly than other medications used for this indication, with other preferred formulary alternatives available. It is comparable to other agents in regards to efficacy and safety parameters and may provide benefit as it does not worsen dyskinesia.
P&T Decision: Approved

Alunbrig (brigatinib)

Therapeutic Class: Tyrosine Kinase Inhibitor
FDA indication: Anaplastic lymphoma kinase – positive, metastatic non-small cell lung cancer who have progressed or are intolerant to Xalkori (crizotinib)
Formulary Recommendations: Non-preferred; previously approved via e-vote 8/30/2017
Rationale: New drug for ALK-positive metastatic non-small cell lung cancer (NSCLC) was reviewed. Criteria for Alunbrig are written based on safety and efficacy data from drug's package insert and evidence-based guidelines from The National Comprehensive Cancer Network (NCCN). It can be considered as treatment option after treatment failure with crizotinib (Xalkori).
P&T Decision: Approved

Austedo (deutetrabenazine)

Therapeutic Class: Vesicular Monoamine transporter 2 (VMAT2) Inhibitor
FDA indication: Chorea associated with Huntington's disease
Formulary Recommendations: Preferred; previously approved via e-vote on 8/30/2017
Rationale: New drug for treatment of chorea associated with Huntington's disease and for treatment of tardive dyskinesia in adults was reviewed. Policy criteria were written based on literature review, clinical trial, and package insert. Formulary status for the drug was recommended based on safety and efficacy of the drug, covered indications of two disease states, and appropriate cost position within alternative agents.
P&T Decision: Approved

Imfinzi (durvalumab)

Therapeutic Class: Anti-PD-L1 Monoclonal Antibody
FDA indication: Locally advanced or metastatic urothelial carcinoma whose disease progressed during or following platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy
Formulary Recommendations: Non-preferred, Medical benefit only; previously approved via e-vote on 8/30/2017
Rationale: New drug for locally advanced or metastatic urothelial carcinoma was reviewed. Criteria for Imfinzi are written based on safety and efficacy data from clinical trials, drug's package insert, and evidence-based guidelines from The National Comprehensive Cancer Network (NCCN). Medication is intended for treatment of those who have disease progression during or following platinum-containing chemotherapy or who have disease progression within 12 months of neoadjuvant treatment with platinum-containing chemotherapy.
P&T Decision: Approved

Ingrezza (valbenazine)

Therapeutic Class: Vesicular monoamine transporter 2 (VMAT2) Inhibitor
FDA indication: Tardive dyskinesia
Formulary Recommendations: Non-preferred; previously approved via e-vote on 9/8/2017
Rationale: Ingrezza is the first and only medication with FDA approved indication for tardive dyskinesia. Because of the absence of other agents on the market, the guidelines have recommended other agents be used when managing patients with tardive dyskinesia. Although these other agents do not have indication for treatment of tardive dyskinesia, the body of literature supports trial with benzodiazepines, second-generation antipsychotics, or tetrabenazine before progressing to more expensive options. Studies suggest that the combination of benzodiazepine, second-generation antipsychotic, and/or tetrabenazine is effective against tardive dyskinesia. Additionally, switching between antipsychotic agents may be effective against tardive dyskinesia symptoms. Due to the high cost of Ingrezza, pursuing potentially effective options available at a much lower cost remains the most cost-effective course of action.
P&T Decision: Approved

Kevzara (sarilumab)

Therapeutic Class: Interleukin-6 receptor antagonist
FDA indication: Rheumatoid Arthritis
Formulary Recommendations: Non-preferred, previously approved via e-vote on 8/30/2017
Rationale: Kevzara is an alternative to DMARDS or TNF-alpha inhibitors. It may be used as monotherapy or in combination with methotrexate or other DMARDS. The rheumatoid arthritis do not currently include Kevzara. The American college of Rheumatology recommends DMARDS as first-line therapy for rheumatoid arthritis with methotrexate being the most commonly used agent. Biologics such as Kevzara are not recommended unless there is a failure of non-biologics DMARDS in moderate to severe rheumatoid arthritis. Current policies include preferred agents such as Enbrel, Actemra, and Humira. In addition, there are no trials comparing Kevzara to Enbrel, Humira, and Actemra.
P&T Decision: Approved

Radicava (Edaravone)

Therapeutic Class: Anti-Parkinson agent, MAO-B inhibitor
FDA indication: Adjunctive treatment to levodopa/carbidopa in patients with Parkinson's disease experiencing "off" episodes
Formulary Recommendations: Non-preferred, Medical benefit only; previously approved via e-vote on 11/1/2017
Rationale: Based on the data presented, edaravone is an effective therapy for ALS in slowing the disease progression allowing for more days with higher functionality. Edaravone is one of two medications available for ALS and is often used in combination with riluzole, as they have two different mechanisms of action. One of the pivotal phase III trials of Radicava found no statistically significant difference in delay of ALS progression, but a post-hoc analysis found that a certain subset of patients may benefit. Based on the post-hoc analysis, the second phase III was performed with a much more strict eligibility criteria and found a statistically significant difference in ALS progression in favor of Radicava.
P&T Decision: Approved

Rydapt (midostaurin)

Therapeutic Class: Tyrosine Kinase Inhibitor
FDA indication: Newly diagnosed acute myeloid leukemia that is FLT3 mutation-positive in combination with standard cytarabine and daunorubicin induction and cytarabine consolidation
Formulary Recommendations: Non-preferred; previously approved via e-vote on 8/30/2017
Rationale: The first agent to treat members with FLT3 mutation-positive AML in combination with standard chemotherapy and the first to treat Aggressive Systemic Mastocytosis (ASM), Systemic Mastocytosis With Associated Hematological Neoplasm (SM-AHN), and Mast Cell Leukemia (MCL). Criteria were written based on package insert of the drug and three studies listed in it. Drug considered safe and effective for targeted indications and would improve clinical outcomes by extending overall survival and event free survival.
P&T Decision: Approved

Brineura (cerliponase)

Therapeutic Class: Hydrolytic lysosomal N-terminal tripeptidyl peptidase
FDA indication: Tripeptidyl peptidase 1 (TPP1) deficiency
Formulary Recommendations: Non-preferred, previously approved via e-vote on 5/31/2017
Rationale: New drug Brineura for treatment of a specific form of Batten disease was reviewed. It is the first FDA-approved treatment to slow loss of walking ability (ambulation) in symptomatic pediatric patients (3 years of age and older) with late infantile neuronal ceroid lipofuscinosis type 2 (CLN2), also known as tripeptidyl peptidase-1 (TPP1) deficiency. Based on available literature, packed insert, and clinical trials date, criteria were written for Brineura policy. Brineura-treated patients were compared to untreated patients from a natural history cohort in clinical trials and demonstrated fewer declines in the Motor domain for Brineura-treated patients.
P&T Decision: Approved

Zejula (niraparib)

Therapeutic Class: PARP Inhibitor
FDA indication: Maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy
Formulary Recommendations: Non-preferred, previously approved via e-vote on 8/30/2017
Rationale: New drug for recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer was reviewed. Criteria for Zejula are written based on drug's package insert and Trial 1 (NOVA) that was included in package insert.
P&T Decision: Approved

Pharmacy &Therapeutics Committee Summary Review
Tymlos (abaloparatide) – Radius Health, Inc.

Prepared by: CVS Health / Andrea Enterline

Presentation Date: **1/4/2018**

Therapeutic Class: Parathyroid hormone analog

FDA Approval Date: 04/28/17

FDA Indication: Treatment of postmenopausal women with osteoporosis at high risk for fracture

Comparable Products: Forteo (teriparatide)

Proposed Designation & Rationale

Recommendation: Non-Preferred

- Diagnosis of Postmenopausal osteoporosis, as indicated by 1 or more of the following:
  - Femoral neck, spine, or total hip bone mineral density T-score minus 2.5 or less
  - Hip or vertebral fragility (ie, low-trauma) fracture in female older than 50 years
  - Risk factors for fracture, as indicated by 1 or more of the following:
  - Alcohol intake of 3 or more drinks per day
  - BMI less than 20
  - Corticosteroid use of more than 6 months duration
  - Current or past history of cigarette smoking
  - Parental hip fracture
  - Personal history of fragility or osteoporotic fracture after age 50 years
- Failure of oral or intravenous bisphosphonates for 90 days (KY MCD = 30 day trial) or inability to tolerate or contraindication
- Approval duration: 1 year

Clinical Implications/ Place in Therapy:
Tymlos is indicated for the treatment of osteoporosis in postmenopausal womenat high risk of fracture other agents indicated for the treatment of osteoporosis in postmenopausal women at high risk of fracture include Forteo (teriparatide) and Prolia (denosumab). 2016 AACE/ACE guidelines for the treatment of postmenopasal osteoporosis recommend Prolia, Forteo (for up to two years), or Reclast for treatment of women at high fracture list. Tymlos has demonstrated osteoanabolic effects superior to placebo in reducing vertebral and non-vertebral fractures and increasing BMD in postmenopausal women with osteoporosis at high risk of fracture. Overall, Tymlos provides an additional treatment option for postmenopausal women with OP at high fracture risk.

Ongoing Clinical Trials:

- There are no current ongoing clinical trials for Tymlos

References:

1. Tymlos [package insert]. Waltham, MA; Radius Health, Inc.: April, 2017.

CVSHealth

CVS Caremark Pharmacy & Therapeutics Drug Monograph

Tymlos™ (abaloparatide) subcutaneous injection Radius Health, Inc.

INDICATION

Tymlos (abaloparatide) is indicated to treat osteoporosis (OP) in postmenopausal women at high risk for fracture (Tymlos prescribing information, 2017).

U.S. FOOD AND DRUG ADMINISTRATION (FDA)-REVIEW DESIGNATION

Tymlos (abaloparatide) was approved by the FDA on April 28, 2017 with a review designation of 1S (FDA, 2017). Tymlos (abaloparatide) is a new molecular entity that underwent a standard review.

DRUG SUMMARY

Tymlos (abaloparatide)	
Place in Therapy	• Tymlos is indicated for the treatment of osteoporosis in postmenopausal women at high risk of fracture. • Other agents indicated for the treatment of osteoporosis in postmenopausal women at high risk of fracture include Forteo (teriparatide) and Prolia (denosumab). Forteo and Tymlos are parathyroid hormone analogs, while Prolia is RANKL inhibitor • 2016 AACE/ACE guidelines for the treatment of postmenopausal osteoporosis recommend Prolia, Forteo (for up to two years), or Reclast (zoledronic acid) for the treatment of women at high fracture risk. The guidelines were updated prior to the approval of Tymlos.
Efficacy	• The efficacy of Tymlos was established in an 18-month, international, double-blind, randomized, controlled trial. • Tymlos (abaloparatide) 80 µg once-daily subcutaneous injections demonstrated significant reductions in the relative risk of new vertebral and nonvertebral fractures compared to placebo. • Tymlos and Forteo were associated with similar rates of vertebral fractures, though the trial was not designed to compare Tymlos for efficacy.
Safety	• Boxed warnings o Not recommended for patients at increased risk of osteosarcoma, as animal studies have shown a dose-dependent increase in the incidence of osteosarcoma. o Cumulative use of Tymlos (abaloparatide) and parathyroid hormone analogs (e.g., teriparatide) for > 2 years during a patient's lifetime is not recommended. • Warnings and Precautions: orthostatic hypotension, hypercalcemia, and hypercalciuria and urolithiasis • Adverse events (≥ 2%) were hypercalciuria, dizziness, nausea, headache, palpitations, fatigue, upper abdominal pain, and vertigo

AACE = American Association of Clinical Endocrinologists
ACE = American College of Endrocrinology
RANKL = receptor activator of nuclear factor kappa-B ligand

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CLINICAL PHARMACOLOGY

Mechanism of Action

Abaloparatide is an analog of human parathyroid hormone related peptide, [PTHrP (1-34)] that acts as an selective agonist at the parathyroid 1 receptor, thereby activating cyclic adenosine monophosphate (cAMP) in target cells and producing increases in bone mineral density (BMD) and bone mineral content (BMC) (Tymlos prescribing information, 2017). Increases in BMD and BMC correlate with increases in bone strength at both vertebral and nonvertebral sites.

Pharmacokinetics

Table 1: Selected Pharmacokinetics of Abaloparatide

Route of Administration	Absolute Bioavailability	T_{max}	Volume of Distribution	Metabolism and Route of Elimination	$T_{1/2}$
Subcutaneous	36%	0.51 hours	50 L	• No specific metabolism or excretion studies have been performed with abaloparatide • The metabolism of is consistent with non-specific proteolytic degradation into smaller peptide fragments, followed by elimination by renal clearance	1.7 hours

$T_{1/2}$ = elimination half-life T_{max} = time to maximum plasma concentration

(Tymlos prescribing information, 2017)

Pharmacokinetics in Geriatric Patients

No age-related differences in abaloparatide pharmacokinetics were observed in postmenopausal women ranging from 49 years to 86 years of age.

Pharmacogenomics

No pharmacogenomic data are available at this time for abaloparatide.

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CLINICAL EFFICACY

Table 2: ACTIVE Study - Efficacy of Tymlos (abaloparatide) in the Treatment of in Postmenopausal Women with Osteoporosis

Study, Treatments, and Groups	Study Design and Endpoints	Study Criteria
Miller, 2016 Evidence Level Ib **Tymlos 80 µg** SC once daily (n = 824) *vs.* **Placebo** SC once daily (n = 821) *vs.* **Forteo (teriparatide) 80 µg** SC once daily for safety analysis (n = 818)	(N = 2,463) **Study Design:** 18-month, multicenter, randomized, double-blinded*, placebo-controlled, phase 3 trial conducted in 10 countries **Objective:** To assess the efficacy and safety of Tymlos in treating OP **Primary Endpoint** Percentage of participants with ≥ 1 incident of new vertebral fractures at 18 months **Key Secondary Endpoints** • Percentage of participants with ≥ 1 incident of new nonvertebral† fractures at 18 months • Percent change in BMD at the total hip, femoral neck, and lumbar spine at 18 months • Incidence of hypercalcemia	**Inclusion Criteria:** Postmenopausal women 49 to 86 years of age (mean age 68.8 years) at high risk for fracture, defined by • T-score‡ of ≤ -2.5 and > -5 at the lumbar spine or femoral neck, *plus* radiologic evidence of ≥ 2 mild vertebral fractures *or* ≥ 1 moderate vertebral fracture *or* a history of a low-trauma fracture of the forearm, humerus, sacrum, pelvis, hip, femur, or tibia in the last 5 years • Women ≥ 65 years meeting fracture criteria with a T-score of ≤ -2.0 and > -5 • Women ≥ 65 years without fracture criteria with a T-score of ≤ -3.0 and > -5 • Normal serum calcium, phosphorous, alkaline phosphatase, intact PTH, and 25(OH)D > 215 ng/mL **Exclusion Criteria:** • ≥ 4 mild, moderate, or severe vertebral fractures • < 2 evaluable lumbar vertebrae • Hip BMD was unevaluable • Evidence of metabolic bone disease, osteosarcoma, or malabsorption, • Receiving medications that interfere with bone metabolism, or use of bisphosphonates for > 3 months in the past 5 years or Prolia in the past year

Efficacy Results: Change from Baseline at Week 18

Endpoint	Tymlos (n =824)	Forteo (n = 818)	Placebo (n = 821)	Tymlos vs. Placebo		
				Difference 95% CI	RR or HR 95% CI	p-value
New Vertebral Fracture	0.58%	0.84%	4.2%	-3.64% (-5.42 to -2.10)	RR 0.14 (0.05 to 0.39)	< 0.001
Nonvertebral Fracture	2.7%	3.3%	4.7%	-2.01% (-4.02 to -0.00)	HR 0.57 (0.32 to 1.00)	0.049
Total Hip BMD change	4.18%	3.26%	-0.10%	4.25% (3.90 to 4.59)	Not applicable	< 0.001
Femoral Neck BMD change	3.60%	2.66	-0.43%	4.01% (3.58 to 4.45)		< 0.001
Lumbar BMD change	11.2%	10.49%	0.63%	10.37% (9.75 to 10.98)		< 0.001

Safety

- A primary safety endpoint was the incidence of albumin-corrected hypercalcemia ≥ 10.7 mg/dL comparing Tymlos with Forteo. Overall incidence was lower in the Tymlos cohort, 3.4% vs. 6.4% with Forteo (risk difference = -2.96 [95% CI: -5.12 to -0.87]; p = 0.006).
- Mild to moderate TEAs that resulted in study drug discontinuation was higher in the Tymlos cohort: nausea (1.6%), dizziness (1.2%), headache (1.0%), and palpitations (0.9%). Serious TEAs leading to study discontinuation were similar in the treatment groups.

Comments: Comparison of Tymlos with Forteo for the primary efficacy end point was not part of the study objectives, because the sample size to obtain 90% power was prohibitively high (22,000/treatment group); however there was no significant difference in the primary endpoint for Tymlos vs. Forteo at 18 months (p = 0.44).

Study Limitations: Enrolled patients were at high risk of fracture; these data cannot determine if Tymlos would have similar effects in patients with lower risk for fracture. In addition, the open-label Forteo group may have resulted in bias in reporting subjective measures, and the study was not powered to compare efficacy of Tymlos vs. Forteo. Study funded by manufacturer of Tymlos.

Conclusions: Tymlos 80 µg was superior to placebo in reducing vertebral and non-vertebral fractures, and increasing BMD.

* After randomization patients in the Forteo branch of the study were unblinded, as Forteo was dispensed in the branded syringe
† Nonvertebral fractures = fractures not located in the spine, sternum, patella, toes, fingers, skull and face; high trauma fractures were excluded (i.e., fall from height ≥ level of a stool, chair, or first rung of a ladder)
‡ T-score = bone density compared to an age and gender based norm; expressed in standard deviations from the norm: ≥ -1 = normal, -1 to -2.4 = osteopenia, ≤ -2.5 = osteoporosis
25(OH)D = serum 25-hydroxy vitamin D
BMD = bone mineral density
CI = confidence interval
FDA = Food and Drug Administration
HR = hazard ratio
OP = osteoporosis
PTH = parathyroid hormone
RR = relative risk
TEA = treatment-emergent adverse event

(Miller, 2017)

Data as of June 23, 2017

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Efficacy Data in the ACTIVExtend Trial

The purpose of the ACTIVExtend trial was to assess the efficacy and safety of 18 months of subcutaneous Tymlos (abaloparatide) or placebo followed by 6 months (and up to 24 months) of oral alendronate (Cosman, 2017). From the participants of the ACTIVE study (Table 2), 1,139 (92%) were enrolled in ACTIVExtend, which was ongoing at the time of the interim printing of results in 2017. The percentages of patients with new morphometric vertebral fractures were 4.4% with placebo/alendronate vs. 0.55% with Tymlos (abaloparatide)/alendronate (relative risk in Tymlos [abaloparatide]/alendronate arms: 0.13; 95% CI: 0.04 to 0.41; $p < 0.001$). BMD percentage changes from ACTIVE baseline for Tymlos (abaloparatide)/alendronate vs. placebo/alendronate were as follows: lumbar spine = 12.8% vs. 3.5% ($p < 0.001$), total hip = 5.5% vs. 1.4% ($p < 0.001$), and femoral neck = 4.5% vs. 0.5% ($p < 0.001$). These data indicate that Tymlos (abaloparatide) for 18 months followed by oral alendronate for 6 months improved bone mineral density and reduced fracture risk throughout the skeleton.

Efficacy Data in the Elderly

No dose adjustment is required for elderly patients (Tymlos prescribing information, 2017). Of the total number of patients in the postmenopausal OP clinical studies of Tymlos (abaloparatide), 82% were age 65 years and over, and 19% were age 75 years and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, but greater sensitivity of some older individuals cannot be ruled out.

SAFETY

Boxed Warning

RISK OF OSTEOSARCOMA

Tymlos (abaloparatide) caused a dose-dependent increase in the incidence of osteosarcoma in animal studies (Tymlos prescribing information, 2017). The effect was observed at systemic exposures to abaloparatide ranging from 4 to 28 times the exposure in humans receiving the 80 µg dose. It is unknown if Tymlos (abaloparatide) will cause osteosarcoma in humans. The use of Tymlos (abaloparatide) is not recommended in patients at increased risk of osteosarcoma, including those with Paget's disease of bone or unexplained elevations of alkaline phosphatase, open epiphyses, bone metastases or skeletal malignancies, hereditary disorders predisposing to osteosarcoma, or prior external beam or implant radiation therapy involving the skeleton. Cumulative use of Tymlos (abaloparatide) and parathyroid hormone analogs (e.g., teriparatide) for more than two years during a patient's lifetime is not recommended.

Contraindications

Tymlos (abaloparatide) has no known contraindications e (Tymlos prescribing information, 2017).

Warnings and Precautions

Orthostatic Hypotension

Tymlos (abaloparatide) may cause orthostatic hypotension; this typically occurs within four hours of injection (Tymlos prescribing information, 2017). Associated symptoms may include dizziness, palpitations, tachycardia or nausea, and may resolve by having the patient lie down. For the first several doses, Tymlos (abaloparatide) should be administered where the patient can sit or lie down if necessary.

Hypercalcemia

Tymlos (abaloparatide) may cause hypercalcemia and is not recommended in patients with pre-existing hypercalcemia or in patients who have an underlying hypercalcemic disorder such as primary hyperparathyroidism (Tymlos prescribing information, 2017).

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Hypercalciuria and Urolithiasis

Tymlos (abaloparatide) may cause hypercalciuria, though it is unknown if the drug will exacerbate urolithiasis (Tymlos prescribing information, 2017). Measurement of urinary calcium excretion should be considered in patients with suspected active urolithiasis or pre-existing hypercalciuria.

Reproductive Risk and/or Nursing Mothers

Tymlos (abaloparatide) is not indicated for use in females of reproductive potential (Tymlos prescribing information, 2017). There are no human or animal data with abaloparatide to inform any drug associated risks in pregnancy or lactation.

Pediatric Use

The safety and effectiveness of Tymlos (abaloparatide) have not been established in pediatric patients, and Tymlos (abaloparatide) is not recommended for use in pediatric patients with open epiphyses or hereditary disorders predisposing to osteosarcoma because of an increased baseline risk of osteosarcoma (Tymlos prescribing information, 2017).

Drug Interactions

No specific drug-drug interaction studies have been performed with abaloparatide (Tymlos prescribing information, 2017).

Adverse Events

Table 3: Adverse Events for Tymlos (abaloparatide) with an Incidence of ≥ 2%

Adverse Event	Tymlos (n = 822)	Placebo (n = 820)
Hypercalciuria	11%	9%
Dizziness	10%	6%
Nausea	8%	3%
Headache	8%	6%
Palpitations	5%	0.4%
Fatigue	3%	2%
Upper abdominal pain	3%	2%
Vertigo	2%	2%

(Tymlos prescribing information, 2017)

PRODUCT AVAILABILITY

Tymlos (abaloparatide) is available in a pre-assembled, single-patient-use, disposable pen that delivers 30 once daily doses of 80 µg in 40 µL (Tymlos prescribing information, 2017). Sterile needles are not included. Before the first use, Tymlos (abaloparatide) should be refrigerated between 2°C to 8°C (36°F to 46°F). After the first use, Tymlos (abaloparatide) should be stored for up to 30 days at 20°C to 25°C (68°F to 77°F).

DOSAGE AND ADMINISTRATION

The recommended dosage of Tymlos (abaloparatide) is 80 µg administered subcutaneously once daily in the periumbilical region of the abdomen (Tymlos prescribing information, 2017). Tymlos (abaloparatide) should not be administered intravenously or intramuscularly. No dosage adjustment is required in renal impairment, though those with severe renal impairment may have a higher risk for adverse events. Cumulative use of Tymlos (abaloparatide) and parathyroid hormone analogs (e.g., teriparatide) for more than two years during a patient's lifetime is not recommended. Patients should receive supplemental calcium and vitamin D if dietary intake is inadequate.

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APPROACHES TO TREATMENT

OP is a public health problem that impacts quality and quantity of life (American Association of Clinical Endocrinologists and American College of Endocrinology [AACE/ACE], 2016). OP is characterized by low bone mass, microarchitecture deterioration of bone tissue, bone fragility, and an increase in fracture risk (National Osteoporosis Foundation [NOF], 2014), Osteoporotic fractures often result in loss of function, significant costs, and increased mortality (Jeremiah, 2015). Fractures related to OP are estimated to cause more than 432,000 hospital admissions, nearly 2.5 million medical office visits, and approximately 180,000 nursing home admissions per year in the United States (NOF, 2014). OP and low bone mass at the femoral neck or lumbar spine affected an estimated 53.6 million older US adults in 2010 (Wright, 2014). Over 2 million osteoporosis-related fractures occur annually in the Unites States, more than 70% of these occur in women (Burge, 2007).

All postmenopausal women aged ≥ 50 years should be evaluated for osteoporosis risk (AACE/ACE, 2016). Risk factors for OP include white or Asian race, excessive alcohol and/or caffeine intake, tobacco use, family history of osteoporotic fracture, gonadal hormone deficiency, immobilization, inadequate activity, increasing age, low body weight, low calcium or vitamin D intake, low level of physical activity, and personal history of fracture (Jeremiah, 2015). The Fracture Risk Assessment Tool (FRAX®) should be utilized in the initial evaluation for OP (AACE/ACE, 2016). BMD should be assessed via axial dual-energy X-ray absorptiometry (DXA) measurement of the spine and hip based on clinical risk profile. Normal spinal or hip BMD is within 1.0 standard deviation (SD) below the young adult female reference mean (T-score ≥ –1.0) (Jeremiah, 2015). Osteopenia is defined as a spinal or hip BMD between 1.0 and 2.5 SDs below the young adult female reference mean (T-score < –1.0 and > –2.5), while osteoporosis is defined as a spinal or hip BMD ≥ 2.5 SDs below the young adult female reference mean (T-score ≤ –2.5), Severe/established osteoporosis is defined as a BMD ≥ 2.5 SDs below the young adult female reference mean and the presence of one or more fragility fractures. According to the 2016 AACE/ACE guidelines for the treatment of postmenopausal osteoporosis, pharmacologic treatment of osteoporosis in postmenopausal women is strongly recommended for patients with any of the following clinical presentations: osteopenia or low bone mass and a history of fragility fracture of the hip or spine; T-score of –2.5 or lower in the spine, femoral neck, total hip or 33% radius; or T-score between –1.0 and –2.5 if the FRAX 10-year probability for major osteoporotic fracture is ≥ 20% or the 10-year probability of hip fracture is ≥ 3% (AACE/ACE, 2016).

According to the AACE/ACE guidelines, first-line treatment to prevent fractures consists of fall prevention, smoking cessation, moderation of alcohol intake, and bisphosphonate therapy (AACE/ACE, 2016). For women with no prior fragility fractures or moderate fracture risk, recommended treatments include Fosamax (alendronate), Prolia (denosumab), Actonel (risedronate), or Reclast (zoledronic acid). Alternative options include Boniva (ibandronate) or Evista (raloxifene). For initial therapy for patients at especially high fracture risk (i.e., prior fragility fracture or high fracture risk), Reclast (zoledronic acid), Forteo (teriparatide), or Prolia (denosumab) should be considered. Alternative therapies include Fosamax (alendronate) or Actonel (risedronate). The guidelines note that Forteo (teriparatide) should be administered for up to two years, and then patients should be switched to another agent. Patients receiving Reclast (zoledronic acid) should have a drug holiday after six years or receive another agent. For patients who experience progressive bone loss or recurrent fractures while receiving Prolia (denosumab), add-on therapy with Forteo (teriparatide) should be considered. For patients who experience progressive bone loss or recurrent fractures while receiving Reclast (zoledronic acid), a switch to Forteo (teriparatide) should be considered. Tymlos (abaloparatide) was not reviewed in these guidelines, as it was approved after their publication. Advantages and disadvantages of Tymlos (abaloparatide) compared with Forteo (teriparatide) and Prolia (denosumab) are described in Table 4.

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National Institute for Health and Care Excellence (NICE)

As of 2011, NICE guidance for secondary prevention of OP related fractures in postmenopausal women recommends alendronate for women with a BMD T-score of -2.5 standard deviations (SD) or below (NICE, 2011). Risedronate or etidronate is recommended as an alternative agent for selected women who cannot receive alendronate based a combination of factors including T-score, age and number of independent clinical risk factors for fracture. Raloxifene or strontium ranelate (not available in the United States) are alternatives for selected women who cannot receive bisphosphonate. Forteo (teriparatide) is recommended as an alternative agent for patients who are unable to receive other agents or who have had an unsatisfactory response to bisphosphonates and who are ≥ 65 years of age and have a BMD T-score of –4.0 SD or below, or a T-score of –3.5 SD or below plus more than two fractures, or who are aged 55–64 years and have a T-score of –4 SD or below plus more than two fractures. Guidance is not yet available for Tymlos (abaloparatide).

PRODUCT COMPARISON

Table 4: Advantages and Disadvantages of Agents Indicated for Postmenopausal Women at High Fracture Risk

Drug	Advantages	Disadvantages
Forteo (teriparatide) SC injection	• Recommended in AACE/ACE guidelines for postmenopausal women with a prior fracture or at high fracture risk • Recommended in AACE/ACE guidelines as add-on therapy to Prolia in some women • Additional indications in men with osteoporosis and in patients with steroid-induced osteoporosis	• Boxed warning for increased risk of osteosarcoma • Risk for hypercalcemia • Cumulative lifetime use > 2 years is not recommended • Use with caution in patients receiving digoxin • Must be refrigerated at all times • Administered once daily
Tymlos (abaloparatide) SC injection	• After first use, may be stored at controlled room temperature for up to 30 days	• Boxed warning for increased risk of osteosarcoma • Risk for hypercalcemia (appears to be less than with teriparatide) • Cumulative lifetime use > 2 years is not recommended • Administered once daily
Prolia (denosumab) SC injection	• Recommended in AACE/ACE guidelines for postmenopausal women with or without a prior fracture or at moderate to high fracture • Administered every 6 months • Additional indications in men with osteoporosis, in selected men with prostate cancer, and in selected women with breast cancer • No cumulative lifetime dose	• Risk for hypocalcemia, serious infection, and osteonecrosis of the jaw • Atypical femoral fractures may occur • Must be administered by a healthcare provider

AACE = American Association of Clinical Endocrinologists SC = subcutaneous
ACE = American College of Endocrinology
(Prescribing information: Forteo prescribing information, 2013; Prolia, 2016; Tymlos prescribing information, 2017)

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PRODUCT COMPARISON

Table 5: Market Share Comparison of Agents Indicated for Postmenopausal Women at High Fracture Risk

Product	Cost (AWP)/Unit	CVS Caremark Data	
		Mail/Retail Utilizers	Market Share (Combined Mail/Retail)
Tymlos (abaloparatide) SC injection*	$1,950.00 per 30-dose pen	—	—
Prolia (denosumab) SC injection	$1,293.06 per single-dose prefilled syringe	22,588	71.59%
Forteo (abaloparatide) SC injection	$3,597.48 per 28-dose pen	8,963	28.41%

* Tymlos launched on May 26, 2017
AWP = average wholesale price
Rx = prescription
SC = subcutaneous

(CVS Administrative Claims Data. March 2017 to May 2017; *Medi-Span® Master Drug Data Base v2.5 (MDDB®)*, June 8, 2017, Clinical Drug Information, LLC)

FORMULARY AND DRUG LIST AVAILABILITY

Table 6: Formulary/Drug List Availability of Agents Indicated for Postmenopausal Women at High Fracture Risk

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*
Injectable Agents							
Forteo (abaloparatide) SC injection	✓	✓	✓	✓	✓	✓	—
Prolia (denosumab) SC injection	✓	—	**Excluded**	—	**Excluded**	**Excluded**	—
Tymlos (abaloparatide) SC injection	—	—	—	—	—	—	—

Boldface Indicates generic availability
* Advanced Control Specialty Formulary may be applied to Prescribing Guide, Performance Drug List, or Value Formulary
† Excluded for some clients
SC = subcutaneous

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Table 7: Managed Medicaid Drug List and 2017 Health Exchanges Formularies Availability of Agents Indicated for Postmenopausal Women at High Fracture Risk with UM Tools

Product	Managed Medicaid Drug List	2017 5-Tier Health Exchanges Template Formulary	2017 6-Tier Health Exchanges Template Formulary	2017 3-Tier Health Exchanges Formulary New York	2017 4-Tier Health Exchanges Formulary California	2017 6-Tier Health Exchanges Formulary South Carolina
Forteo (abaloparatide) SC injection	—	tier 4*	tier 5*	tier 3*	tier 4*	tier 5*
Prolia (denosumab) SC injection	—	tier 4*	tier 5*	tier 3*	tier 4*	tier 5*
Tymlos (abaloparatide) SC injection	—	—	—	—	—	—

* Prior authorization
UM = utilization management

Table 8: 2018 Health Exchanges Formularies Availability of Agents Indicated for Postmenopausal Women at High Fracture Risk with UM Tools

Product	2018 5-Tier Health Exchanges Template Formulary	2018 6-Tier Health Exchanges Template Formulary	2018 3-Tier Health Exchanges Formulary New York	2018 4-Tier Health Exchanges Formulary California	2018 6-Tier Health Exchanges Formulary South Carolina
Forteo (abaloparatide) SC injection	tier 4*	tier 5*	tier 3*	tier 4*	tier 5*
Prolia (denosumab) SC injection	—	—	—	—	—
Tymlos (abaloparatide) SC injection	—	—	—	—	—

* Prior authorization
UM = utilization management

Table 9: 2017 Medicare Part D Drug List Availability of Agents Indicated for Postmenopausal Women at High Fracture Risk with Optional UM Tools

Product	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
Forteo (abaloparatide) SC injection	tier 5‡§	tier 5‡§	tier 5‡§	tier 5‡§	tier 2‡§	tier 5‡§	tier 5‡	tier 5‡	tier 4‡§	tier 5‡§
Prolia (denosumab) SC injection	tier 4§	tier 4§	tier 4§	tier 4§	tier 2§	tier 4§	tier 4§	tier 4§	tier 3‡§	tier 4‡§
Tymlos (abaloparatide) SC injection	—	—	—	—	—	—	—	—	—	—

* Also available as a Single-Source Generic Strategy drug lists
† Also available as a 1-Tier and 4-Tier drug list
‡ Prior authorization
§ Quantity limit
EGWP = Employer Group Waiver Plan
MMP = Medicare-Medicaid Plan
PDP = Prescription Drug Plan
UM = utilization management

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Table 10: 2018 Medicare Part D Drug List Availability of Agents Indicated for Postmenopausal Women at High Fracture Risk with Optional UM Tools

Product	PDP Choice/ PDP Plus Drug List	Client Drug Lists									
		Select*	Generic Strategy Standard*	Generic Strategy Essential	MMP	Standard†	Expanded	Performance	Core	EGWP	
	5-Tier	5-Tier			2-Tier	5-Tier	5-Tier			4-Tier	5-Tier
Forteo (abaloparatide) SC injection	—	—	—	—	—	—	tier 5‡	tier 5‡	—	—	—
Prolia (denosumab) SC injection	tier 4§	tier 4§	tier 4§	tier 4§	tier 2§	tier 4§	tier 4§	tier 4§	tier 4§	tier 3‡§	tier 4‡§
Tymlos (abaloparatide) SC injection	—	—	—	—	—	—	—	—	—	—	—

* Also available as a Single-Source Generic Strategy drug lists
† Also available as a 1-Tier and 4-Tier drug list
‡ Prior authorization
§ Quantity limit
EGWP = Employer Group Waiver Plan
MMP = Medicare-Medicaid Plan
PDP = Prescription Drug Plan
UM = utilization management

FORMULARY CONSIDERATIONS

Tymlos (abaloparatide) is an analog of PTHrP (1-34) indicated to treat OP in postmenopausal women at high risk for fracture. It has demonstrated osteoanabolic effects superior to placebo in reducing vertebral and non-vertebral fractures and increasing BMD in postmenopausal women with osteoporosis at high risk of fracture. In comparison to Forteo (teriparatide), Tymlos (abaloparatide) has the same boxed warning regarding the risk of osteosarcoma and limit of two years of administration per lifetime. However, based on indirect comparison, Tymlos (abaloparatide) has a lower risk for hypercalcemia and it can be stored at controlled room temperature for 30 days once opened. Prolia has a higher number of warnings and precautions than either Tymlos (abaloparatide) or Forteo (teriparatide). Overall, Tymlos provides an additional treatment option for postmenopausal women with OP at high fracture risk.

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DRUG MONOGRAPH PREPARED BY:

Carrie Allen, Pharm.D.
June 23, 2017

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Pharmacy &Therapeutics Committee Summary Review
Xadago® (safinamide) – US WorldMeds, LLC

Prepared by: Sarah Winey

Presentation Date: January 4, 2018

Therapeutic Class: Anti-Parkinson agent, MAO-B Inhibitor[1]

FDA Approval Date: March 21, 2017

FDA Indication: Adjunctive treatment to levodopa/carbidopa in patients with Parkinson's disease experiencing "off" episodes[1]

Comparable Formulary Products: Rasagiline, Selegiline, Entacapone, Pramipexole, Ropinirole

Proposed Designation & Rationale

Recommendation: Non-preferred

- Criteria for use:
  - Member has a diagnosis of Parkinson's disease
  - Member had a documented inadequate response or adverse reaction to: Rasagiline AND selegiline (per chart notes)
  - Member has claims AND is currently using carbidopa/levodopa
- Approval duration:
  - 1 year

Clinical Implications/Place in Therapy:
Based on the data presented, safinamide is an effective therapy for reduction of "off" episodes in patients who are receiving levodopa/carbidopa for Parkinson's disease.[1-6] Safinamide is, however, more costly than other medications used for this indication, with other preferred formulary alternatives available.[14-17] It is comparable to other agents in regards to efficacy and safety parameters and may provide benefit as it does not worsen dyskinesia.[2-6]

Clinical Pharmacology: Monoamine oxidase B (MAO-B) Inhibitor[1]

- High selective inhibition of MAO-B with complete inhibition seen at doses >20 mg
- Blocks catabolism of dopamine
- Causes increased dopamine levels and activity in the brain
- Precise mechanism for Parkinson's Disease unknown

Notable Pharmacokinetics[1]:

- *Absorption:*
  - T_{max}: 2-3 hours under fasting conditions
  - Absolute bioavailability: 95% (negligible first pass metabolism)
  - Food caused a slight delay in T_{max} but did not affect $AUC_{0-\infty}$ or C_{max}
- *Distribution:*
  - Volume of distribution: 165 L
  - Not highly protein bound
- *Metabolism:*
  - 3 main metabolic pathways yield metabolites with no pharmacologic activity
  - Non-microsomal enzymes responsible for most metabolism
- *Elimination:*
  - Half-life: 20-26 hours

  Kidneys are primary route of excretion

Efficacy:

Trial Design/ Population	Groups	Outcomes	Results
Borgohain R et al. *Mov Disord*. 2014;29(2):229-37.[5] Phase 3 RCT ▪ 4 Phases - 10 day screening period - 4 week L-dopa stabilization period (required 28 day fixed-dose period) - 24 week treatment period - Optional 1 week taper period ▪ 18 month extension study N= 669 patients ▪ Age: 30-80 years ▪ Diagnosis: Idiopathic PD of ≥3 years' duration ▪ Hoehn and Yahr stage I-IV during off ▪ Motor fluctuations (>1.5 hours' off time/day) ▪ Ability to accurately maintain a diary ▪ Exclusion criteria: late-stage PD with severe, disabling peak-dose or biphasic dyskinesia or unpredictable or widely swinging symptom fluctuations; Evidence of dementia, major psychiatric illnesses, and/or severe and progressive medical illnesses	Double-blind randomization (1:1:1) ▪ Safinamide 100 mg/day ▪ Safinamide 50 mg/day ▪ Placebo During trial, doses of PD therapies were to remain as stable as possible. ▪ If a patient experienced deterioration in motor symptoms, the dose could be increased, or additional PD drugs could be used as "rescue medication" (e.g. COMT) inhibitors, amantadine, and/or anticholinergic; not MAO-B inhibitors). ▪ The l-dopa dose could be decreased based upon the patient's condition or occurrence of adverse events. ▪ Patients in the safinamide 100 mg/day group could have their dose reduced to 50 mg/day if they did not tolerate the higher dose.	*Primary:* Change in mean daily total "on" time with no or nontroublesome dyskinesia as recorded in patient diaries *Secondary* ▪ Total daily "off" time ▪ UPDRS (Unified Parkinson's Disease Rating Scale) Part III (motor) scores during "on" time ▪ CGI-C (Clinical Global Impression-Change) scores ▪ "Off" time following the first morning l-dopa dose ▪ DRS (Dyskinesia Rating Scale) scores during "on" time ▪ UPDRS Part II (activities of daily living) scores during "on" time ▪ CGI-S (Clinical Global Impression-Severity) scores ▪ Percentage change in l-dopa dose *Safety* ▪ Treatment-emergent AEs (TEAEs) ▪ Laboratory data ▪ Ophthalmological and dermatological examinations ▪ Electrocardiogram (ECG) ▪ Vital signs	*Primary* Both doses of safinamide showed a significantly greater mean increase in total "on" time with no or nontroublesome dyskinesia compared with placebo (50 mg/day: LS mean difference, 0.51 hours; 95% CI, 0.07 to 0.94; P = 0.0223; 100 mg/day: LS mean difference, 0.55 hours; 95% CI, 0.12 to 0.99; P = 0.0130). ▪ Safinamide 50 mg/day: +0.2-1.0 (±1.96-3.24) hours on time ▪ Safinamide 100 mg/day: +0.1-1.1 (±2.07-2.86) hours on time ▪ Placebo: +0.2-0.6 (±1.92-2.98) hours on time *Secondary* ▪ Both doses of safinamide showed significant improvements in the following outcomes compared with placebo: total daily "off" time, UPDRS Part III score, CGI-C score, CGI-S score, and "off" time following the morning l-dopa dose. ▪ Only the 100 mg/day safinamide showed significant improvement in UPDRS-II compared with placebo. ▪ No differences were present between groups for the following outcomes: DRS scores during "on" time or percent change in l-dopa dose (all groups had small percent reduction). *Safety* TEAEs were reported by 67% of patients with no group having a significantly different incidence of TEAEs or of TEAEs leading to discontinuation (P=0.5293; 0.8497). The following occurred in >5% of patients. ▪ Dyskinesia: safinamide>placebo (100 mg/day: 41%; 50 mg/day: 47%; placebo: 28%) ▪ Worsening PD: placebo>safinamide (100 mg/day: 9%; 50 mg/day: 12%; placebo: 18%) ▪ Cataract: about equivalent among groups (100 mg/day: 14%; 50 mg/day: 11%; placebo: 13%) ▪ Depression: placebo>safinamide (100 mg/day: 4%; 50 mg/day: 2%; placebo: 12%) ▪ Headache: safinamide>placebo (100 mg/day: 11%; 50 mg/day: 13%; placebo: 10%) ▪ Hypertension: safinamide>placebo (100 mg/day: 10%; 50 mg/day: 13%; placebo: 8%) SAEs did not follow a pattern and were higher in the placebo and safinamide 100 mg/day groups compared to safinamide 50 mg/day. ▪ 7 deaths o 5 in the safinamide 100 mg/day group ▪ 2 considered unrelated to study drug ▪ 2 unknown cause ▪ 1 occurred 49 days after discontinuation from study due to posttraumatic subdural hematoma (reported as SAE) o 2 in the placebo group

Schapira AH et al. *JAMA Neurol*. 2017;74(2):216-224.[6] Phase 3 RCT ▪ Phases - 10 day screening period- therapy adjusted to minimize motor fluctuations - 4 week observation phase- observe unchanging regimen - 24 week treatment period N= 549 patients ▪ Age: 30-80 years ▪ Diagnosis of idiopathic PD by clinical evaluation and Queen Square Brain Bank criteria ▪ Duration since diagnosis > 3 years ▪ Hoehn and Yahr rating of stages 1-4 during "off" phase and daily off time >1.5 hours (excluded morning akinesia) ▪ Pharmacotherapy: Levodopa responsive with current and stable (at least 4 weeks) oral regimen - Regimen could include: COMT inhibitor, dopamine agonist, anticholinergic and/or amantadine ▪ Exclusion criteria: severe, disabling peak-dose or biphasic dyskinesia and/or wide or unpredictable symptom fluctuations	Double-blind randomization (1:1) ▪ Safinamide 50mg once daily for 2 weeks, then titrated up to 100mg daily if tolerating for remainder of study period (24 weeks total) ▪ Placebo	*Primary:* Change from baseline to week 24 in mean daily "on" time without troublesome dyskinesia (recorded in patient diary) *Secondary:* ▪ Mean change in daily off time ▪ Mean change in UPDRS Part III (motor examination) score during on phase ▪ Mean change in UPDRS Part II (activities of daily living) score during on phase ▪ Proportion of patients with an improved CGI-C rating ▪ Mean change in PDQ-39 summary index score *Safety:* ▪ TEAEs ▪ Serious adverse events (SAEs) ▪ Discontinuations due to TEAEs ▪ Physical, neurologic, ophthalmologic, and dermatologic exams ▪ 12-lead ECG ▪ Clinical laboratory tests	*Primary:* Safinamide showed a significantly greater mean increase in total daily "on" time without troublesome dyskinesia compared with placebo (LS mean difference, 0.96 hour; 95% CI, 0.56 to 1.37 hours; P<0.001). ▪ Safinamide: +1.42 (±2.80) hours on time ▪ Placebo: +0.57 (±2.47) hours on time *Secondary:* ▪ Safinamide showed significant improvements in the following outcomes compared with placebo: total daily "off" time, UPDRS Part III score, CGI-C score, PDQ-39 score. ▪ No differences were present between groups for the following outcomes: UPDRS Part II score. *Safety:* TEAEs were reported by 67.9% of patients in the safinamide group and 69.1% of patients in the placebo group. The following occurred in >5% of patients. ▪ Dyskinesia: safinamide>placebo (14.6%; 5.5%); considered severe in 5 safinamide patients and 1 placebo patient ▪ Fall: safinamide>placebo (6.6%; 3.6%) ▪ UTI: safinamide>placebo (6.2%; 4.4%) ▪ Nausea: safinamide>placebo (5.8%; 5.5%) ▪ Headache: placebo>safinamide (6.2%; 4.4%) ▪ Back pain: placebo>safinamide (5.1%; 3.3%) SAEs were reported by 6.6% of patients in the safinamide group and 9.5% of patients in the placebo group. ▪ Both groups: breast cancer, hallucinations ▪ Placebo only: diarrhea, myocardial ischemia Discontinuation due to TEAEs occurred in 5.1% of patients in the safinamide group and 4.4% of patients in the placebo group. ▪ Nervous system events (both) ▪ Dyskinesia (safinamide) ▪ PD worsening (safinamide) ▪ Paraesthesia (safinamide) ▪ Dizziness (placebo) ▪ 3 deaths o 1 in the safinamide group (PD worsening considered unlikely to be related to study medication) o 2 in the placebo group (myocardial ischemia and acute lymphocytic leukemia).

Conclusion[5,6]*:*

- Overall increased "on" time and decreased "off" time.
- Does not seem to worsen dyskinesia when added on to levodopa/carbidopa, other agents have conflicting data (e.g. rasigiline).
- Improvement in PD symptom scores
- Well tolerated with generally low rates of adverse events.

Ongoing Clinical Trials[7]: No new studies for safinamide are ongoing or in recruitment phase.

Contraindications[1]:

- Concomitant use of other drugs that inhibit MAO due to risk of increased blood pressure
- Concomitant use of opioids, SNRIs, tricyclic/tetracyclic/triazolopyridine antidepressants, cyclobenzaprine, methylphenidate, amphetamine/amphetamine derivatives, or St. John's wort due to risk of serotonin syndrome
- Concomitant use of dextromethorphan due to reports of episodes of psychosis or abnormal behavior
- History of hypersensitivity to safinamide
- Severe hepatic impairment

Warnings/Precautions[1]:

- *Hypertension:*
  - May cause new onset hypertension or exacerbate existing hypertension
  - Doses above 100 mg daily (maximum recommended dose) increase hypertension risk due to loss of selectivity
  - Dietary restriction of tyramine is not required with recommended doses, but patients should be counselled to avoid foods that are very high in tyramine
- *Serotonin Syndrome:*
  - Use is contraindicated with drugs that have high serotonergic activity
  - Use lowest effective dose of concomitant SSRI
- *Falling Asleep During Activities of Daily Living*
  - Seen in clinical trials with higher dose of 100 mg daily
  - Xadago should be discontinued if patient falls asleep during activities requiring full attention
- *Dyskinesia*
  - May cause dyskinesia or exacerbate existing dyskinesia
  - Mitigation strategies include dose reduction of levodopa or other dopaminergic drugs
- *Hallucinations/Psychotic Behavior*
  - Patients with major psychotic disorder should not be treated with Xadago
  - Mitigation strategies include dose reduction or discontinuation of Xadago
- *Impulse Control/Impulsive Behaviors*
  - Mitigation strategies include dose reduction or discontinuation of Xadago
- *Withdrawal-Emergent Hyperpyrexia and Confusion*
  - Symptoms resembling neuroleptic malignant syndrome (NMS) may occur with rapid dose reduction, withdrawal or other changes in drugs affecting dopaminergic tone
- *Retinal Pathology*
  - Retinal degeneration, scarring and cataracts were observed in rat studies at all doses
  - Monitor patients for vision changes with any history of retinal conditions of albinism

Drug Interactions[1]:

- MAO Inhibitors
- Opioid drugs: Allow at least 14 days between therapies
- Serotonergic drugs: Allow at least 14 days between therapies
- Dextromethorphan
- Sympathomimetic Medications
- Tyramine
- Substrates of Breast Cancer Resistance Protein (BCRP): BCRP may be inhibited by Xadago and its major metabolite
- Dopaminergic antagonists

Common Adverse Effects[1]:

- Common (≥2%)
  - Dyskinesia (21% 50 mg/day, 17% 100 mg/day, 9% placebo)
  - Fall
  - Nausea
  - Insomnia
  - Orthostatic hypotension
  - Anxiety
  - Cough
  - Dyspepsia

Safety:

- No major safety issues identified by ISMP[8-10]
- No REMS requirement[11]
- Current known safety concerns reported in the manufacturer package insert[1]

Dosage/Administration[1]:

- Recommended starting dose of 50 mg PO once daily (at the same time of day)
- May be increased after 2 weeks to 100 mg PO once daily based on patient need and tolerability
- Effective only when used in combination with levodopa/carbidopa
- Can be taken with or without food
- Hepatic impairment
    - Moderate (Child-Pugh B): Dose should not exceed 50 mg PO once daily
    - Severe (Child-Pugh C): Contraindicated

Special Drug Monitoring[1]:

- Efficacy: decreased "off" time relative to baseline
- Toxicity: visual disturbances

Handling and Preparation[1]:

- Available as 50 mg and 100 mg tablet
- Supplied in 30 and 90 count bottles
- Should be stored at room temperature (25°C; 77°F) with excursions permitted to 15 to 30°C (59 to 86°F)

Financial Impact:

Safinamide is currently approved as an adjunctive treatment to levodopa/carbidopa in patients with Parkinson's disease who are experiencing "off" episodes. The prevalence of the disease is difficult to estimate, but some have estimated it to be 0.3% in the general population. Many factors contribute to the increasing cost burden of PD in the US, including the increasing elderly population and the lack of curative treatment. PD patients are high utilizers of healthcare. According to a recent 2010 survey, these patients had a total of 1.9 million hospital days, and 15% reside in nursing home facilities. In 2010, the medical expenses for individuals with PD amounted to about 14 billion dollars; this was about 8.1 billion dollars more than similar demographics without a PD diagnosis. Indirect costs, such as reduced employment, are also important considerations in this population; these were estimated to be 6.3 billion dollars in 2010.[12]
Additionally, PD has a tremendous impact on quality of life (QOL). A recent systematic review reports the following factors as negatively impacting QOL: psychosocial function, mobility limitations, depression, and fear, among others. This systematic review, along with others, showed that nonmotor symptoms often affect QOL more strongly than motor symptoms.[13]

The following details the breakdown of direct monthly and yearly drug costs for potential add-on therapies for PD:

Drug	Xadago (safinamide)[14]	Rasagiline[15]	Pramipexole[16]	Entacapone[17]
WAC (30 day supply)	$669.90	$402.25	$236.10	$480
Maintenance cost	$8,038.80/yr	$4,827/yr	$2,833.20/yr	$5,760/yr

Three pharmacologic classes carry guideline recommendations for their use to reduce "off" time: non-ergot-derived dopamine agonists, MAO-B inhibitors, and COMT inhibitors.[2,3] Of these recommended treatments, dopamine agonists may have the greatest impact in "off" time reduction, with MAO-B inhibitors and COMT inhibitors also showing significant reduction compared to placebo. MAO-B inhibitors are considered to have the fewest adverse events.[2] The 2006 American Academy of Neurology guidelines cites entacapone and rasagiline as being the most effective for "off" time reduction.[3] Entacapone is dosed alongside the levodopa/carbidopa up to 8 times per day, making cost difficult to estimate (the maximum dose is used above). Head to head studies of agents are needed to better determine proper use of these agents.[4]

No trials have been published concerning pharmacoeconomic parameters related to safinamide.

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Pharmacy &Therapeutics Committee Summary Review
Alunbrig (brigatinib) – ARAID Pharmaceuticals, Inc

Prepared by: CVS Health / Irina Yaroshenko

Presentation Date: 1/4/18

Therapeutic Class: Tyrosine kinase inhibitor

FDA Approval Date: 04/28/17

FDA Indication: Indicated for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib.

Comparable Products: Xalkori (preferred), Zykadia (preferred), Alecensa (non-preferred)

Proposed Designation & Rationale

Recommendation: Non-Preferred, approved via e-vote on 08/30/17

- Criteria for use / Approval duration: See policy for criteria for use and approval durations.
  - For reference, Ohio Medicaid version of policy can be found at: Alunbrig.
  - All other state specific policies can be found under Pharmacy Policies by clicking on the appropriate state.

Clinical Implications/ Place in Therapy:
New drug for ALK-positive metastatic non-small cell lung cancer (NSCLC) was reviewed. Criteria for Alunbrig are written based on safety and efficacy data from drug's package insert and evidence-based guidelines from The National Comprehensive Cancer Network (NCCN). It can be considered as treatment option after treatment failure with crizotinib (Xalkori).

Ongoing Clinical Trials:

- There are 5 clinical trials (recruiting; enrolling by invitation; active, not recruiting): https://clinicaltrials.gov/ct2/results?cond=&term=brigatinib&cntry1=&state1=&Search=Search&recrs=a&recrs=d&recrs=f

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CVSHealth

CVS Caremark Pharmacy & Therapeutics Drug Monograph

Alunbrig™ (brigatinib) tablets
ARIAD Pharmaceuticals, Inc.

INDICATION

Alunbrig (brigatinib) is indicated for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive, metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to Xalkori (crizotinib) (Alunbrig prescribing information, 2017).

U.S. FOOD AND DRUG ADMINISTRATION (FDA)-REVIEW DESIGNATION

Alunbrig (brigatinib) was approved by the FDA under an accelerated approval on April 28, 2017 with a review designation of 1P (FDA, 2017a, FDA, 2017b). Alunbrig (brigatinib) is a new molecular entity that received breakthrough therapy and priority review designations. An agent may qualify for a breakthrough therapy program 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, 2014).

DRUG SUMMARY

	Alunbrig (brigatinib)
Place in Therapy	• Alunbrig is an ALK TKI that is FDA-approved for the subsequent treatment of patients with ALK-positive NSCLC who experience progression on or are intolerant to Xalkori (crizotinib). • Additional ALK TKIs FDA-approved for the treatment of ALK-positive NSCLC include Xalkori, Zykadia (ceritinib), and Alecensa (alectinib). Similar to Alunbrig, Alecensa is only indicated for use in patients who are refractory to treatment with Xalkori. • NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for NSCLC recommend first-line treatment with crizotinib or ceritinib. Treatment with ceritinib, alectinib, or brigatinib is recommended as subsequent therapy in patients who progress on crizotinib.
Efficacy	• The efficacy and safety of Alunbrig was evaluated in a phase II, two-arm, open-label, randomized trial that studied two doses of Alunbrig: 90 mg once daily and 180 mg once daily following a 7-day lead-in with 90 mg. • The trial included adult patients with ALK-positive advanced or metastatic NSCLC who were refractory to treatment with Xalkori. • Alunbrig demonstrated improvements in objective response rate of 45% and 54% for the 90 mg and 180 mg doses, respectively, as measured by trial investigators.
Safety	• Warnings and precautions: interstitial lung disease/pneumonitis, hypertension, bradycardia, visual disturbance, creatine phosphokinase elevation, pancreatic enzymes elevation, hyperglycemia, and embryo-fetal toxicity • Common adverse events (≥ 25%): nausea, diarrhea, fatigue, cough, and headache

ALK = anaplastic lymphoma kinase
FDA = Food and Drug Administration
NCCN = National Comprehensive Cancer Network®
NSCLC = non-small cell lung cancer
TKI = tyrosine kinase inhibitor

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CLINICAL PHARMACOLOGY

Mechanism of Action

Brigatinib is a tyrosine kinase inhibitor (TKI) that targets multiple kinases including ALK, ROS1, insulin-like growth factor-1 receptor (IGF-1R), and FLT-3, as well as epidermal growth factor receptor (EGFR) deletion and point mutations (Alunbrig prescribing information, 2017). Brigatinib inhibits proliferation of cell lines that express mutated ALK proteins, including mutant forms associated with resistance to other ALK inhibitors.

Pharmacokinetics

Table 1: Selected Pharmacokinetics of Brigatinib

Route of Administration	T_{max}	Volume of Distribution	Protein Binding	In Vitro Metabolism	Route of Elimination	$T_{1/2}$
Oral	1 hour to 4 hours	153 L	66%	CYP2C8 and CYP3A4	Feces: 65% Urine: 25%	25 hours

CYP = cytochrome P450 isoenzyme
$T_{1/2}$ = elimination half-life
T_{max} = time to maximum plasma concentration
(Alunbrig prescribing information, 2017)

Pharmacogenomics

A number of driver mutations that induce and sustain tumorigenesis in NSCLC have been identified and serve as predictive biomarkers of treatment benefit with targeted therapies over standard chemotherapy (National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology [NCCN Guidelines®], 2017). A few of the key mutations with targeted treatments approved in NSCLC include EGFR mutations found in 10% to 35% of patients, ALK gene rearrangements found in 2% to 7% of all NSCLCs, and ROS1 gene arrangements found in approximately 1% to 2% of all NSCLCs (Lovly, 2016; NCCN Guidelines®, 2017). These mutations do not typically overlap within a tumor and are more commonly found in non-smokers. ALK gene rearrangements are more likely to be found in men and younger patients (NCCN Guidelines, 2017). One of the limitations of targeted therapies is the development of resistance either through a secondary mutation of the initial mutation or through a secondary pathway (National Cancer Institute, 2017). Secondary mutations within ALK are believed to be the cause of resistance in patients with ALK-positive NSCLC (Liao, 2015).

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CLINICAL EFFICACY

Table 2: Efficacy of Alunbrig (brigatinib) in the Treatment of ALK-Positive NSCLC

Study, Treatments, and Groups	Study Design and Endpoints	Study Criteria	Results		
ALK in Lung Cancer Trial of AP26113 (ALTA) Trial; Kim, 2017 Evidence Level IIa **Arm A** **Alunbrig 90 mg** once daily (n = 112) **Arm B** **Alunbrig 180 mg** once daily following 7-day lead in with 90 mg once daily (n = 110)	N = 222 **Study Design:** Phase II, two-arm, open-label, randomized trial **Objective:** To evaluate the efficacy and safety of two doses of Alunbrig in patients with Xalkori (crizotinib)-refractory advanced ALK-positive NSCLC **Primary Endpoint:** Investigator-assessed confirmed ORR according to RECIST v1.1* **Secondary Endpoints:** • IRC-assessed confirmed ORR according to RECIST v1.1* • Median DOR • Median PFS	**Inclusion Criteria:** • Patients ≥ 18 years of age with locally advanced or metastatic ALK-positive NSCLC (median age 54 years; 57% female; 31% Asian) • Documented ALK rearrangement based on FDA-approved test • ECOG Performance Status† ≤ 2 • Progression on Xalkori and no treatment with any other ALK TKI **Exclusion Criteria:** • History of ILD or drug-related pneumonitis • Received Xalkori within 3 days; cytotoxic chemotherapy, investigational agents, or radiation therapy within 14 days; or monoclonal antibodies within 30 days of first dose of Alunbrig • Symptomatic central nervous system metastases	**Endpoint**	**Arm A** Alunbrig 90 mg once daily (n = 112)	**Arm B** Alunbrig 180 mg once daily (n = 110)
			Investigator-Assessed Endpoints		
			ORR (97.5% CI)	45% (34 to 56)	54% (43 to 65)
			Complete Response	1%	4%
			Partial Response	44%	50%
			Median DOR (95% CI)	13.8 months (5.6 to 13.8)	11.1 months (9.2 to 13.8)
			Median PFS (95% CI)	9.2 months (7.4 to 15.6)	12.9 months (11.1 to not reached)
			IRC-Assessed Endpoints		
			ORR (95% CI)	48% (39 to 58)	53% (43 to 62)
			Complete Response	4%	5%
			Partial Response	45%	48%
			Median DOR (95% CI)	13.8 months (7.4 to not reached)	13.8 months (9.3 to not reached)
			Median PFS (95% CI)	9.2 months (7.4 to not reached)	15.6 months (11.0 to not reached)
			Safety • Most commonly reported adverse events (≥ 25% overall) in both treatment arms included nausea, diarrhea, headache, and cough. Grade 3 or higher adverse events (≥ 3%) included increased creatine phosphokinase, hypertension, pneumonia, and increased lipase. • Early onset pneumonitis (2 day median onset) occurred in 6% of patients (14 of 219 treated patients‡), 3% of which were Grade 3 or higher. Half of patients were successfully retreated and no events occurred after dose escalation to 180 mg in Arm B. **Comments/Study Limitations:** Patients were stratified based on best prior response to Xalkori and brain metastases. Trial included 8 months of median follow-up. Twenty-six patients in Arm A and 18 patients in Arm B had measurable brain metastases at baseline. IRC-assessed intracranial ORR in these patients was 42% (95% CI 23 to 63) in Arm A and 67% (95% CI 41 to 87) in Arm B. Investigators did not perform statistical analysis comparing each treatment arm. **Conclusions:** Both doses of Alunbrig demonstrated improvements in ORR and median PFS, with indirect comparison favoring the 180 mg dose, and both doses were well tolerated in patients with ALK-positive NSCLC who were refractory to treatment with Xalkori.		

* Standardized tool to evaluate tumor shrinkage (objective response) and time to development of disease progression
† ECOG performance status scale rates a patients level of function from 0 to 5 where 0 = fully active, able to carry on all pre-disease performance without restriction and 5 = dead
‡ Three patients in Arm A were never treated and were included in the intent-to-treat analyses
ALK = anaplastic lymphoma kinase
CI = confidence interval
DOR = duration of response
ECOG = Eastern Cooperative Oncology Group
FDA = Food and Drug Administration
ILD = interstitial lung disease
IRC = independent review committee
NSCLC = non-small cell lung cancer
ORR = objective response rate
PFS = progression-free survival
RECIST = Response Evaluation Criteria in Solid Tumors
TKI = tyrosine kinase inhibitor

(Kim, 2017)

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Data as of June 16, 2017
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SAFETY

Contraindications

There are no known contraindications for Alunbrig (brigatinib) (Alunbrig prescribing information, 2017).

Warnings and Precautions

Interstitial Lung Disease (ILD)/Pneumonitis

Severe, life-threatening, and fatal pulmonary adverse events consistent with ILD/pneumonitis have occurred in patients receiving Alunbrig (brigatinib), usually occurring early after treatment initiation (Alunbrig prescribing information, 2017). Patients should be monitored for new or worsening respiratory symptoms, especially during the first week after initiating treatment. Treatment should be withheld and patient evaluated for ILD/pneumonitis or other causes of respiratory symptoms if symptoms occur. Alunbrig (brigatinib) should be permanently discontinued in patients who develop Grade 3 or Grade 4 ILD/pneumonitis or recurrence of Grade 1 or Grade 2 ILD/pneumonitis.

Hypertension

In clinical trials, hypertension was reported in patients receiving Alunbrig (brigatinib) (Alunbrig prescribing information, 2017). Prior to initiating treatment with Alunbrig (brigatinib), blood pressure should be controlled and then monitored two weeks after treatment initiation and monitored at least monthly during treatment. Alunbrig (brigatinib) should be withheld for Grade 3 hypertension despite optimal antihypertensive therapy and resumed at a reduced dose once resolution or improvement to Grade 1 severity occurs. Permanent discontinuation of Alunbrig (brigatinib) should be considered in patients who experience Grade 4 hypertension or recurrence of Grade 3 hypertension.

Bradycardia

Bradycardia may occur with Alunbrig (brigatinib) (Alunbrig prescribing information, 2017). Heart rate and blood pressure should be monitored during treatment with Alunbrig (brigatinib) and should be monitored more frequently if coadministration with a drug known to cause bradycardia cannot be avoided. Alunbrig (brigatinib) should be withheld for symptomatic bradycardia and medications adjusted after review and resolution of symptoms. Alunbrig (brigatinib) should be discontinued for life-threatening bradycardia when no contributing concomitant medication is identified.

Visual Disturbance

Treatment with Alunbrig (brigatinib) was associated with visual disturbances, including blurred vision, diplopia, and reduced visual acuity, in clinical trials (Alunbrig prescribing information, 2017). Patients should be advised to report any visual symptoms, and treatment with Alunbrig (brigatinib) should be withheld and an ophthalmologic evaluation obtained in patients with new or worsening visual symptoms of Grade 2 or higher. Alunbrig (brigatinib) should be resumed at a reduced dose upon recovery in patients who experience Grade 2 or Grade 3 visual disturbances and permanently discontinued in patients who experience Grade 4 visual disturbances.

Creatine Phosphokinase (CPK) Elevation

Elevations in CPK occurred in patients receiving Alunbrig (brigatinib) in clinical trials (Alunbrig prescribing information, 2017). Patients should be advised to report any unexplained muscle pain, tenderness, or weakness and CPK levels should be monitored during treatment. Treatment with Alunbrig (brigatinib) should be withheld for Grade 3 or Grade 4 CPK elevation and resumed at an appropriate dose following recovery.

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Pancreatic Enzyme Elevation

Elevations in amylase and lipase were observed in patients receiving Alunbrig (brigatinib) in clinical trials (Alunbrig prescribing information, 2017). Amylase and lipase levels should be monitored during treatment with Alunbrig (brigatinib) and treatment withheld for Grade 3 or Grade 4 pancreatic enzyme elevation. Alunbrig (brigatinib) should be resumed at an appropriate dose following recovery.

Hyperglycemia

New or worsening hyperglycemia was reported in patients receiving Alunbrig (brigatinib) in clinical trials (Alunbrig prescribing information, 2017). Fasting serum glucose should be assessed before initiation of Alunbrig (brigatinib) and monitored periodically thereafter. Antihyperglycemic therapy should be initiated or optimized as needed. Alunbrig (brigatinib) should be withheld if adequate hyperglycemic control cannot be achieved with optimal medical management, and dose reductions or discontinuation should be considered.

Embryo-Fetal Toxicity

There are no data on the use of brigatinib in pregnant women (Alunbrig prescribing information, 2017). Based on animal data and its mechanism of action, brigatinib may cause fetal harm when administered to a pregnant woman and may reduce male fertility. Animal models have demonstrated dose-related skeletal anomalies, increased implantation loss, malformations, and decreased fetal body weight. Pregnant women should be advised of the risk to a fetus, and females of reproductive potential should be advised to use effective contraception during treatment with Alunbrig (brigatinib) and for four months after the last dose. Males with female partners of reproductive potential should be advised to use effective contraception during treatment and for at least three months following the last dose of Alunbrig (brigatinib).

Nursing Mothers

There are no data on the presence of brigatinib in human milk, the effects on the breastfed infant, or the effects on milk production (Alunbrig prescribing information, 2017). Due to the potential for serious adverse events from brigatinib in breastfed infants, nursing women should be advised to discontinue nursing during treatment with Alunbrig (brigatinib) and for one week following the last dose.

Pediatric Use

The safety and efficacy of Alunbrig (brigatinib) have not been established in pediatric patients (Alunbrig prescribing information, 2017).

Geriatric Use

A sufficient number of patients aged 65 years and older were not included in clinical trials to determine whether this population of patients responds differently compared with younger patients (Alunbrig prescribing information, 2017). No clinically relevant differences in safety and efficacy were observed between younger patients and patients aged 65 years and older.

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Drug Interactions

Table 3: Potential Drug Interactions with Brigatinib

Interacting Agent	Outcome	Recommendation
Strong CYP3A Inhibitors	May increase plasma concentrations of brigatinib resulting in increased adverse events	Avoid concomitant use with strong CYP3A inhibitors, grapefruit, or grapefruit juice; reduce dose of brigatinib by approximately 50% if coadministration cannot be avoided
Strong CYP3A Inducers	May decrease plasma concentrations of brigatinib resulting in decreased efficacy	Avoid concomitant use
CYP3A Substrates	May alter plasma concentrations of CYP3A substrates, including hormonal contraceptives, resulting in loss of efficacy of CYP3A substrate	Use non-hormonal method of contraception

CYP = cytochrome P450 isoenzyme

(Alunbrig prescribing information, 2017)

Adverse Events

Table 4: All Grades of Adverse Events and Laboratory Abnormalities for Alunbrig (brigatinib) in 20% or More of Patients

Adverse Event	Alunbrig 90 mg (n = 109)		Alunbrig 180 mg with 90 mg Lead-In (n = 110)	
	All Grades	Grade 3 to 4	All Grades	Grade 3 to 4
Increased aspartate aminotransferase	38%	0.9%	65%	0%
Hyperglycemia	38%	3.7%	49%	3.6%
Increased creatine phosphokinase	27%	2.8%	48%	12%
Increased lipase	21%	4.6%	45%	5.5%
Increased alanine aminotransferase	34%	0%	40%	2.7%
Nausea	33%	0.9%	40%	0.9%
Anemia	23%	0.9%	40%	0.9%
Increased amylase	27%	3.7%	39%	2.7%
Diarrhea	19%	0%	38%	0%
Fatigue	29%	1.8%	36%	0%
Cough	18%	0%	34%	0%
Increased alkaline phosphatase	15%	0.9%	29%	0.9%
Headache	28%	0%	27%	0.9%
Lymphopenia	19%	2.8%	27%	4.5%
Rash	15%	1.8%	24%	3.6%
Vomiting	24%	1.8%	23%	0%
Decreased phosphorous	15%	1.8%	23%	3.6%
Dyspnea	27%	2.8%	21%	1.8%*
Hypertension	11%	5.5%	21%	6.4%
Prolonged activated partial thromboplastin time	22%	1.8%	20%	0.9%
Decreased appetite	22%	0.9%	15%	0.9%

* Includes one Grade 5 adverse event

(Alunbrig prescribing information, 2017)

PRODUCT AVAILABILITY

Alunbrig (brigatinib) is available as 30 mg and 90 mg tablets (Alunbrig prescribing information, 2017).

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DOSAGE AND ADMINISTRATION

The recommended starting dose of Alunbrig (brigatinib) is 90 mg once daily for the first seven days (Alunbrig prescribing information, 2017). If the initial dose is tolerated during the first seven days, the dose may be increased to 180 mg once daily. Treatment with Alunbrig (brigatinib) should be administered until disease progression or unacceptable toxicity. The dose of Alunbrig (brigatinib) should be modified based on adverse events such as increases in laboratory values, ILD/pneumonitis, and bradycardia, with details of dose modifications provided in the prescribing information. Alunbrig (brigatinib) should be permanently discontinued if a patient is not able to tolerate a reduced dose of 60 mg once daily.

APPROACHES TO TREATMENT

Lung cancer is the second most common cancer among both men and women and is the leading cause of cancer deaths in the United States (American Cancer Society [ACS], 2016). It is estimated that 222,500 new cases will be diagnosed in 2017 and there will be 155,870 deaths due to lung cancer. Lung cancer typically occurs at an older age; with an estimated two out of every three lung cancers occurring in patients ages 65 years or older. Smoking is the greatest risk factor for the development of lung cancer, including secondhand smoke, and is associated with at least 80% of lung cancer deaths. Since smoking is the greatest risk factor for developing lung cancer, never smoking is the best way to prevent its development. Smokers who quit before 50 years of age can reduce their risk of dying from lung cancer in the next 15 years by half.

Symptoms of lung cancer typically do not present until the cancer has spread too far to be cured (ACS, 2016). Common signs and symptoms of lung cancer include a cough that does not resolve or gets worse over time, chest pain, especially on deep breathing, hoarseness, weight loss, decreased appetite, and coughing up blood. Patients may also be short of breath, fatigued, and prone to infections such as bronchitis and pneumonia. The diagnosis of lung cancer is made via history and physical examination, laboratory evaluations including biopsy, imaging tests including chest x-ray, computed tomography (CT) scans, positron emission tomography (PET) scans and ultrasound, and bronchoscopy.

Lung cancer can be classified into two major types: NSCLC and small cell lung cancer (SCLC) (ACS, 2016). NSCLC accounts for approximately 80% to 85% of all lung cancers. The treatment of NSCLC is guided by tumor histology and may include traditional chemotherapy and/or newer targeted agents (NCCN Guidelines, 2017). The identification of predictive biomarkers, such as ALK rearrangements, using genetic testing has drastically changed the landscape of the treatment of NSCLC and may guide the selection of therapy using targeted agents.

A number of targeted therapies have been developed that specifically target changes in the cells of NSCLC that help it to grow (ACS, 2016). Targeted therapies are most often used in advanced lung cancers and are typically associated with less severe adverse events than chemotherapy. Targeted agents for ALK rearrangements include the ALK TKIs Alecensa (alectinib), Alunbrig (brigatinib), Xalkori (crizotinib) and Zykadia (ceritinib). NCCN Guidelines recommend first-line therapy with crizotinib or ceritinib in patients with ALK-positive NSCLC, and subsequent therapy with ceritinib if not previously given, or alectinib or brigatinib in patients who have progressed on crizotinib (NCCN Guidelines, 2017). Alunbrig (brigatinib) is currently in phase III development for the first-line treatment of ALK-positive NSCLC (AdisInsight, 2017; Kim, 2017).

National Institute for Health and Care Excellence (NICE)

NICE Guidelines for the treatment of NSCLC were last updated in 2011 and provide separate guidance for each of the ALK TKIs (NICE, 2011). Xalkori (crizotinib) is recommended as an option in adult patients with untreated or previously treated ALK-positive advanced NSCLC, and Zykadia (ceritinib) is recommended as an option in adult patients with ALK-positive advanced NSCLC previously treated with Xalkori (crizotinib) (NICE, 2016a; NICE, 2016b; NICE, 2016c). NICE was unable to make a recommendation for the use of Alecensa (alectinib) due to no evidence being submitted from the manufacturer (NICE, 2017). The use of Alunbrig (brigatinib) has not yet been evaluated by NICE.

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Table 5: Advantages and Disadvantages of ALK-Positive NSCLC Agents

Drug	Advantages	Disadvantages
All Agents	• Oral administration	• Associated with cardiac and pulmonary adverse events
Alecensa (alectinib) capsules	• Additional activity against RET • No reports of QT interval prolongation	• Approved only for use as subsequent therapy following Xalkori • May be associated with severe myalgia and creatine phosphokinase elevation • No additional activity against ROS1
Alunbrig (brigatinib) tablets	• Administered once daily • No reports of QT interval prolongation	• Approved only for use as subsequent therapy following Xalkori • May cause hyperglycemia, hypertension, and elevations in creatine phosphokinase and pancreatic enzymes • CYP3A-mediated drug interactions
Xalkori (crizotinib) capsules	• Indicated and recommended as first-line treatment option • Additional FDA-approved indication for ROS1 mutation-positive NSCLC • Additional activity against MET	• May cause severe visual loss • CYP3A-mediated drug interactions
Zykadia (ceritinib) capsules	• Indicated and recommended as first-line treatment option • Administered once daily	• May cause hyperglycemia and pancreatitis • Associated with severe or persistent gastrointestinal toxicity • CYP3A- and CYP2C9-mediated drug interactions

ALK = anaplastic lymphoma kinase
CYP = cytochrome P450 isoenzyme
FDA = Food and Drug Administration
NSCLC = non-small cell lung cancer

PRODUCT COMPARISON

Table 6: Market Share Comparison of ALK-Positive NSCLC Agents

Product	AWP	CVS Caremark Data	
		Mail/Retail Rxs	Market Share (Combined Mail/Retail)
Alunbrig (brigatinib) tablets*	$95.00 per 30 mg tablet	—	—
Xalkori (crizotinib) capsules	$296.92 per 200 mg and 250 mg capsule	999	53.1%
Alecensa (alectinib) capsules	$66.57 per 150 mg capsule	665	35.4%
Zykadia (ceritinib) capsules	$120.64 per 150 mg capsule	216	11.5%

* Alunbrig launched May 9, 2017
ALK = anaplastic lymphoma kinase
AWP = average wholesale price
NSCLC = non-small cell lung cancer

(CVS Administrative Claims Data. February 2017 to April 2017; *Medi-Span® Master Drug Data Base v2.5 (MDDB®)*, June 2017, Clinical Drug Information, LLC)

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FORMULARY AND DRUG LIST AVAILABILITY

Table 7: Formulary/Drug List Availability of ALK-Positive NSCLC Agents

Product	National Formulary	Prescribing Guide*	Performance Drug List*	Advanced Control Formulary	Value Formulary*
Alunbrig (brigatinib) tablets	—	New-to-Market Block			—
Alecensa (alectinib) capsules	✓	New-to-Market Block			—
Xalkori (crizotinib) capsules	✓	—	—	—	✓†
Zykadia (ceritinib) capsules	✓	—	—	—	✓†

* Advanced Control Specialty Formulary may be applied to Prescribing Guide, Performance Drug List, or Value Formulary
† Prior authorization
ALK = anaplastic lymphoma kinase
NSCLC = non-small cell lung cancer

Table 8: 2017 Health Exchanges Formularies Availability of ALK-Positive NSCLC Agents with UM Tools

Product	Managed Medicaid Drug List	2017 5-Tier Health Exchanges Template Formulary	2017 6-Tier Health Exchanges Template Formulary	2017 3-Tier Health Exchanges Formulary New York	2017 4-Tier Health Exchanges Formulary California	2017 6-Tier Health Exchanges Formulary Blue Cross Blue Shield South Carolina
Alunbrig (brigatinib) tablets	—	—	—	—	—	—
Alecensa (alectinib) capsules	—	—	—	—	—	—
Xalkori (crizotinib) capsules	—	tier 4*	tier 5*	tier 3*	tier 4*	tier 5*
Zykadia (ceritinib) capsules	✓	tier 4*	tier 5*	tier 3*	tier 4*	tier 5*

* Prior authorization
ALK = anaplastic lymphoma kinase
NSCLC = non-small cell lung cancer
UM = utilization management

Table 9: 2018 Health Exchanges Formularies Availability of ALK-Positive NSCLC Agents with UM Tools

Product	2018 5-Tier Health Exchanges Template Formulary	2018 6-Tier Health Exchanges Template Formulary	2018 3-Tier Health Exchanges Formulary New York	2018 4-Tier Health Exchanges Formulary California	2018 6-Tier Health Exchanges Formulary South Carolina
Alunbrig (brigatinib) tablets	—	—	—	—	—
Alecensa (alectinib) capsules	—	—	—	—	—
Xalkori (crizotinib) capsules	tier 4*	tier 5*	tier 3*	tier 4*	tier 5*
Zykadia (ceritinib) capsules	tier 4*	tier 5*	tier 3*	tier 4*	tier 5*

* Prior authorization
ALK = anaplastic lymphoma kinase
NSCLC = non-small cell lung cancer
UM = utilization management

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Table 10: 2017 Medicare Part D Drug Lists Availability of ALK-Positive NSCLC Agents with Optional UM Tools*

Product	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
Alunbrig (brigatinib) tablets	—	—	—	—	—	—	—	—	—	—
Alecensa (alectinib) capsules	tier 5§	tier 5§	tier 5§	tier 5§	tier 2§	tier 5§	tier 5§	tier 5§	tier 4§‖	tier 5§‖
Xalkori (crizotinib) capsules	tier 5§	tier 5§	tier 5§	tier 5§	tier 2§	tier 5§	tier 5§	tier 5§	tier 4§‖	tier 5§‖
Zykadia (ceritinib) capsules	tier 5§	tier 5§	tier 5§	tier 5§	tier 2§	tier 5§	tier 5§	tier 5§	tier 4§‖	tier 5§‖

* 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
§ Prior authorization
‖ Quantity limit
ALK = anaplastic lymphoma kinase
EGWP = Employer Group Waiver Plan
MMP = Medicare-Medicaid Plan
NSCLC = non-small cell lung cancer
PDP = Prescription Drug Plan
UM = utilization management

Table 11: 2018 Medicare Part D Drug Lists Availability of ALK-Positive NSCLC Agents with Optional UM Tools*

Product	PDP Choice/ PDP Plus Drug List	Client Drug Lists									
		Select†	Generic Strategy Standard†	Generic Strategy Essential	MMP	Standard‡	Expanded	Performance	Core	EGWP	
	5-Tier	5-Tier			2-Tier	5-Tier	5-Tier			4-Tier	5-Tier
Alunbrig (brigatinib) tablets	—	—	—	—	—	—	—	—	—	—	—
Alecensa (alectinib) capsules	tier 5§	tier 5§	tier 5§	tier 5§	tier 2§	tier 5§	tier 5§	tier 5§	tier 5§	tier 4§‖	tier 5§‖
Xalkori (crizotinib) capsules	tier 5§	tier 5§	tier 5§	tier 5§	tier 2§	tier 5§	tier 5§	tier 5§	tier 5§	tier 4§‖	tier 5§‖
Zykadia (ceritinib) capsules	tier 5§	tier 5§	tier 5§	tier 5§	tier 2§	tier 5§	tier 5§	tier 5§	tier 5§	tier 4§‖	tier 5§‖

* 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
§ Prior authorization
‖ Quantity limit
ALK = anaplastic lymphoma kinase
EGWP = Employer Group Waiver Plan
MMP = Medicare-Medicaid Plan
NSCLC = non-small cell lung cancer
PDP = Prescription Drug Plan
UM = utilization management

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FORMULARY CONSIDERATIONS

Alunbrig (brigatinib) is a second-generation ALK TKI that is FDA-approved for the treatment of patients with ALK-positive, metastatic NSCLC who have progressed on or are intolerant to Xalkori (crizotinib). The efficacy of Alunbrig (brigatinib) was established in a phase II, two-arm, open-label trial that evaluated Alunbrig (brigatinib) 90 mg and 180 mg (following a 7-day 90 mg lead-in) in adult patients with ALK-positive NSCLC who were refractory to therapy with Xalkori (crizotinib). Both doses of Alunbrig (brigatinib) demonstrated improvements in objective response rate (ORR) and progression-free survival as assessed by the investigators. Improvement in intracranial ORR measured by an independent review committee was also observed in patients who had measurable brain metastases at baseline. Adverse events most commonly reported in the clinical trial included nausea, diarrhea, headache, and cough. Early onset of pulmonary adverse events, including Grade 3 or higher, were observed with a median onset of two days, with half of patients being successfully retreated and no occurrence following dose escalation to 180 mg. Alunbrig (brigatinib) provides an additional safe and effective treatment option for patients with ALK-positive NSCLC who are refractory to treatment with Xalkori (crizotinib).

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DRUG MONOGRAPH PREPARED BY:

Faon M Bridges, Pharm.D., BCPS
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Pharmacy &Therapeutics Committee Summary Review
Austedo (deutetrabenazine) – Teva Pharmaceuticals

Prepared by: CVS Health / Irina Yaroshenko

Presentation Date: 1/4/18

Therapeutic Class: VMAT2 inhibitor

FDA Approval Date: 04/03/17

FDA Indication: Indicated for chorea associated with Huntington's disease and for tardive dyskinesia in adults.

Comparable Products: Xenazine (preferred)

Proposed Designation & Rationale

Recommendation: Preferred, approved via e-vote on 08/30/17

- Criteria for use / Approval duration: See policy for criteria for use and approval durations.
  - For reference, Ohio Medicaid version of policy can be found at: Austedo.
  - All other state specific policies can be found under Pharmacy Policies by clicking on the appropriate state.

Clinical Implications/ Place in Therapy:

New drug for treatment of chorea associated with Huntington's disease and for treatment of tardive dyskinesia in adults was reviewed. Policy criteria were written based on literature review, clinical trial, and package insert. Formulary status for the drug was recommended based on safety and efficacy of the drug, covered indications of two disease states, and appropriate cost position within alternative agents.

Ongoing Clinical Trials:

- There is 1 clinical trial (recruiting; enrolling by invitation; active, not recruiting): https://clinicaltrials.gov/ct2/results?cond=&term=deutetrabenazine&cntry1=&state1=&Search=Search&recrs=a&recrs=d&recrs=f

References:

1. Austedo [package insert]. North Wales, PA; Teva Pharmaceuticals, Inc. April 2017.
2. Huntington Study group. Effect of deutetrabenazine on chorea among patients with huntington disease: a randomized clinical trial. JAMA. 2016; 316(1):40-50. doi: 10.1001/jama.2016.8655.
3. Claassen DO, Carroll B, De Boer LM, et al. Indirect tolerability comparison of deutetrabenazine and tetrabenazine for huntington disease. J Clin Mov Dis 2017(4):3. doi: 10.1186/s40734-017-0051-5.

CVSHealth

CVS Caremark Pharmacy & Therapeutics Drug Monograph

Austedo™ (deutetrabenazine) tablets
Teva Pharmaceuticals USA, Inc.

INDICATION

Austedo (deutetrabenazine) is indicated for the treatment of chorea associated with Huntington's disease (Austedo prescribing information, 2017).

U.S. FOOD AND DRUG ADMINISTRATION (FDA)-REVIEW DESIGNATION

Austedo (deutetrabenazine) was approved by the FDA on April 3, 2017 with a review designation of 1S (FDA, 2017). Austedo (deutetrabenazine) is a new molecular entity that underwent standard review.

DRUG SUMMARY

Austedo (deutetrabenazine)	
Place in Therapy	• Austedo is the second FDA-approved agent for the treatment of chorea associated with Huntington's disease. • Xenazine (tetrabenazine) has been the only FDA-approved agent for this indication and is recommended for use in the 2012 American Academy of Neurology (AAN) guidelines. The AAN guidelines also recommend the off-label use of amantadine and Rilutek (riluzole) and note that adverse events should be considered when selecting therapy. Xenazine is associated with increased depression and suicidality, and Parkinsonism. • Austedo is a VMAT2 inhibitor that is structurally related to Xenazine but contains deuterium, which prolongs the half-life of the active metabolites through attenuation of the metabolism by CYP2D6. • When compared indirectly with Xenazine, Austedo is associated with a lower incidence of adverse events including somnolence and depression.
Efficacy	• The efficacy of Austedo was established in a 12-week, phase 3, randomized, double-blind, placebo-controlled trial in 90 ambulatory adult patients diagnosed with Huntington's disease • Austedo provided greater improvements compared with placebo in chorea motor signs at 12 weeks as measured by the Total Maximal Chorea Score, with a mean between-group treatment difference of -2.5 ($p < 0.001$).
Safety	• Contraindications: patients who are suicidal or have untreated or inadequately controlled depression; patients with hepatic impairment; and patients taking MAOIs, reserpine, or Xenazine (tetrabenazine) • Boxed Warning: increased risk of depression and suicidal thoughts and behavior (suicidality) • Warnings/Precautions: clinical worsening and adverse events; depression and suicidality; neuroleptic malignant syndrome; akathisia, agitation, and restlessness; parkinsonism; sedation and somnolence; QTc prolongation; hyperprolactinemia; and binding to melanin-containing tissues • Adverse Events (≥ 8%): somnolence, diarrhea, dry mouth, fatigue

FDA = Food and Drug Administration
CYP = cytochrome P450
MAOIs = monoamine oxidase inhibitors
VMAT2 = vesicular monoamine transporter 2

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CLINICAL PHARMACOLOGY

Mechanism of Action

Deutetrabenazine is a vesicular monoamine transporter type 2 (VMAT2) inhibitor that is a deuterated form of tetrabenazine (Huntington Study Group, 2016). Deuterium is a nontoxic form of hydrogen. The addition of deuterium is believed to prolong plasma half-life and reduce metabolic variability due to cytochrome P450 (CYP) 2D6 metabolism, allowing for less frequent and lower daily dosing and improving the risk-benefit profile compared with tetrabenazine.

The anti-chorea effects of deutetrabenazine are believed to be related to the reversible depletion of monoamines (e.g., dopamine, serotonin, norepinephrine, and histamine) from nerve terminals by the major metabolites of deutetrabenazine (α-dihydrotetrabenazine [HTBZ] and β-HTBZ), although the precise mechanism is unknown (Austedo prescribing information, 2017).

Pharmacokinetics

Table 1: Selected Pharmacokinetics of Deutetrabenazine*

Route of Administration	Absolute Bioavailability	T_{max}	Volume of Distribution	Protein Binding	Metabolism	Route of Elimination	$T_{1/2}$
Oral	≥ 80%	3 hours to 4 hours	500 L to 730 L	59% to 68%	CYP2D6	Urine: 75% to 86% Feces: 8% to 11%	9 hours to 10 hours

* Deutetrabenazine undergoes extensive metabolism following oral administration to the active deuterated dihydro metabolites (HTBZ), α-HTBZ and β-HTBZ. Data represent pharmacokinetics for these metabolites.

CYP = cytochrome P450

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

T_{max} = time to maximum plasma concentration

(Austedo prescribing information, 2017)

Pharmacogenomics

No pharmacogenomics data are available at this time for deutetrabenazine.

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CLINICAL EFFICACY

Table 2: Efficacy of Austedo (deutetrabenazine) in the Treatment of Chorea Associated with Huntington's Disease

Study, Treatments, and Groups	Study Design and Endpoints	Study Criteria	Results
FIRST time use of deutetrabenazine in Huntington's Disease **(FIRST HD); Huntington Study Group, 2016** Evidence Level Ib **Austedo** (n = 45) vs. **Placebo** (n = 45) Doses were administered twice daily and titrated to optimal dose level over eight weeks and maintained for four weeks, followed by a one week washout	N = 90 **Study Design:** 12-week, multicenter, phase 3, randomized, double-blind, placebo-controlled trial **Objective:** To evaluate the efficacy and safety of Austedo treatment to control chorea associated with Huntington's disease **Primary Endpoint:** UHDRS total maximal chorea score* change from baseline (day 0) to maintenance therapy† **Secondary Endpoints:** • Treatment success as measured by PGIC and CGIC‖ • SF-36 physical functioning score¶ • Berg Balance Test¶	**Inclusion Criteria:** • Ambulatory adult patients diagnosed with manifest Huntington's disease‡ (mean age 53.7 years; 44.4% women) • UHDRS total maximal chorea score* ≥ 8 at screening and baseline • UHDRS total functional capacity score§ ≥ 5 **Exclusion Criteria:** • Serious untreated or undertreated psychiatric illness • Scored ≥ 11 on the depression subscale of the HADS or had a history of significant suicidal thoughts or behavior • Certain cardiac conditions • Hepatic or renal impairment • Use of tetrabenazine within 6 months or antipsychotics or amine modifying agents within 30 days	

Endpoint	Austedo (n = 45)	Placebo (n = 45)	Treatment Difference
Change in Total Maximal Chorea Score	-4.4 (95% CI -5.3 to -3.6)	-1.9 (95% CI -2.8 to -1.1)	-2.5 (95% CI -3.7 to -1.3; p < 0.001)
PGIC	51%	20%	31.1 (95% CI 12.4 to 49.8; p = 0.002)
CGIC	42%	13%	28.9 (95% CI 11.4 to 46.4; p = 0.002)
SF-36	0.7 (95% CI -2.0 to 3.4)	-3.6 (95% CI -6.4 to 0.8)	4.34 (95% CI 0.4 to 2.2; p= 0.03)
Berg Balance Test	2.2 (95% CI 1.3 to 3.1)	1.3 (95% CI 0.4 to 2.2)	1.0 (95% CI -0.3 to 2.3; p = 0.14)

Safety
- Adverse events in both treatment groups were generally mild to moderate and led to discontinuation in 3 patients (6.7%) in each group.
- Somnolence was the most commonly reported adverse event for Austedo-treated patients (11.1%) compared with placebo (4.4%), which generally resolved without dose reduction.
- Reports of depression or agitated depression were not significantly different between patients receiving Austedo (4.4%) and those receiving placebo (6.7%).

Comments/Study Limitations: The mean dose at the end of the treatment period for patients receiving Austedo was 39.7 mg and 43.3 mg for patients receiving placebo. A minimal clinically important difference in UHDRS has not yet been established. Study authors used a treatment effect of 2.7 units that was consistent with previously published clinical trials for Xenazine (tetrabenazine) for Huntington's Disease.

Conclusions: In patients with Huntington's disease, Austedo demonstrated improvements in chorea, motor functioning, and treatment success but not balance vs. placebo. Austedo was not associated with any significant safety concerns compared with placebo.

* The total maximal chorea score is a standardized, reliable chorea assessment based on frequency and severity in seven body regions, with a range of 0 to 28, where 0 is defined as no chorea and lower scores indicate less chorea
† Maintenance therapy was defined as the average of values from week 9 and week 12 visits
‡ As indicated by characteristic motor examination and an expanded *HTT* CAG repeat sequence (≥ 36)
§ The total functional capacity is a 13-point standardized disease staging scale that assesses an individual's ability to perform tasks in 5 functional areas; a score of 5 or higher indicates that patients are in stages I through III and have had Huntington's disease diagnosis for approximately 15 years
‖ Rated on a 7-point Likert scale ranging from "very much improved" to "very much worse"; treatment success was defined as "much" or "very much" improved at week 12
¶ Analyzed as changes from day 0 to week 12
CAG = cytosine-adenine-guanine
CGIC = Clinical Global Impression of Change
CI = confidence interval
HADS = Hospital Anxiety and Depression Scale
HTT = huntingtin
PGIC = Patient Global Impression of Change
SF-36 = 36-Item Short Form Health Survey
UHDRS = United Huntington's Disease Rating Scale

(Huntington Study Group, 2016)

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SAFETY

Contraindications

Austedo (deutetrabenazine) is contraindicated in patients who are suicidal or have untreated or inadequately treated depression, and in patients with hepatic impairment (Austedo prescribing information, 2017).

Austedo (deutetrabenazine) is also contraindicated in patients taking monoamine oxidase inhibitors (MAOIs), reserpine, or Xenazine (tetrabenazine) (Austedo prescribing information, 2017). At least 20 days should elapse between the discontinuation of reserpine, an irreversible VMAT2 inhibitor, and the initiation of therapy with Austedo (deutetrabenazine) in order to reduce the risk of overdosage and major depletion of serotonin and norepinephrine in the central nervous system. Therapy with Austedo (deutetrabenazine) should not be initiated within 14 days of discontinuation of a MAOI, and may be initiated the day following the discontinuation of Xenazine (tetrabenazine).

Boxed Warning

DEPRESSION AND SUICIDALITY

The risk of use of Austedo (deutetrabenazine) should be considered against the clinical need for the treatment of chorea due to an increased risk of depression and suicidal thoughts and behavior (suicidality) in patients with Huntington's disease (Austedo prescribing information, 2017). Patients should be closely monitored for the emergence or worsening of depression, suicidality, or unusual changes in behavior. Patients, their caregivers, and families should be informed of the risk of depression and suicidality and instructed to report behaviors of concern promptly to the treating physician.

Extra caution should be exercised when administering Austedo (deutetrabenazine) to patients with a history of depression or prior suicide attempts or ideation, which are increased in frequency in Huntington's disease (Austedo prescribing information, 2017).

Warnings and Precautions

Clinical Worsening and Adverse Events

Austedo (deutetrabenazine) may cause worsening in the progressive characteristics of Huntington's disease including mood, cognition, rigidity, and function capacity (Austedo prescribing information, 2017). The need for Austedo (deutetrabenazine) should be periodically re-evaluated by assessing the effects on chorea and possible adverse events.

Depression and Suicidality

Patients with Huntington's disease have an increased risk for depression, and suicidal ideation or behaviors (suicidality) and treatment with Austedo (deutetrabenazine) may increase this risk (Austedo prescribing information, 2017). Depression occurred in 4% of patients receiving Austedo (deutetrabenazine) in clinical trials. Suicidal ideation was reported in 2% of patients in clinical trials, and there were no reports of suicide attempts or completed suicides. Patients treated with Austedo (deutetrabenazine) should be observed for new or worsening depression or suicidality, and discontinuation of treatment should considered if depression or suicidality does not resolve.

Neuroleptic Malignant Syndrome (NMS)

NMS is a potentially fatal symptom complex that has been reported in association with drugs that reduce dopaminergic transmission, including neuroleptic drugs such as dopamine antagonists or antipsychotics (Austedo prescribing information, 2017). NMS has not been observed in patients receiving Austedo (deutetrabenazine), but has been observed in patients receiving Xenazine (tetrabenazine), a closely related VMAT2 inhibitor. Prescribers should be aware of the signs and symptoms of NMS and ensure proper management if a patient develops these signs and symptoms.

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Akathisia, Agitation, and Restlessness

Patients should be monitored for the signs and symptoms of restlessness and agitation when receiving Austedo (deutetrabenazine), as these may indicate the development of akathisia (Austedo prescribing information, 2017). Austedo (deutetrabenazine) may increase the risk of akathisia, agitation, and restlessness in patients with Huntington's disease, and the dose should be reduced or discontinued in patients who develop akathisia. The concomitant us of Austedo (deutetrabenazine) with neuroleptic drugs such as dopamine agonists or antipsychotics may also increase this risk.

Parkinsonism

Rigidity may develop as an underlying disease process in Huntington's disease, and distinguishing between drug-induced adverse event related to Austedo (deutetrabenazine) and progression of the underlying disease process may be difficult (Austedo prescribing information, 2017). The dose of Austedo (deutetrabenazine) should be reduced, or may require discontinuation, in patients who develop Parkinsonism during treatment. The concomitant us of Austedo (deutetrabenazine) with neuroleptic drugs such as dopamine agonists or antipsychotics may also increase this risk.

Sedation and Somnolence

Patients receiving Austedo (deutetrabenazine) should not perform activities requiring mental alertness until they are on a maintenance dose of Austedo (deutetrabenazine) and are aware of how the drug affects them due to dose-limiting sedation commonly associated with Austedo (deutetrabenazine) (Austedo prescribing information, 2017). The administration of Austedo (deutetrabenazine) with alcohol or other sedating drugs may have additive effects and worsen sedation and somnolence.

Corrected QT (QTc) Prolongation

Xenazine (tetrabenazine) has been associated with an increase in the QTc interval, and a clinically relevant QT prolongation may occur in some patients receiving Austedo (deutetrabenazine) who are poor CYP2D6 metabolizers or are receiving concomitant administration of a strong CYP2D6 inhibitor (Austedo prescribing information, 2017). The administration of Austedo (deutetrabenazine) should be avoided in combination with other drugs that are known to prolong QTc, and in patients with congenital long QT syndrome or a history of cardiac arrhythmias.

Hyperprolactinemia

Although serum prolactin levels were not evaluated in patients receiving Austedo (deutetrabenazine), elevations in prolactin concentrations have been observed with Xenazine (tetrabenazine) (Austedo prescribing information, 2017). Appropriate laboratory testing should be conducted if there is a clinical suspicion of symptomatic hyperprolactinemia, and discontinuation of Austedo (deutetrabenazine) should be considered.

Binding to Melanin-Containing Tissues

The accumulation of deutetrabenazine or its metabolites in melanin-containing tissues could occur over time due to binding (Austedo prescribing information, 2017). Although the clinical relevance of the binding of deutetrabenazine to melanin-containing tissues is unknown, there may be a possibility of toxicity in these tissues after extended use. Prescribers should be aware of the possibility of long-term ophthalmologic effects; however, there are no specific recommendations for periodic monitoring.

Reproductive Risk

Adequate data are not available to for deutetrabenazine in pregnant women to inform on drug-associated risk of major birth defects and miscarriage (Austedo prescribing information, 2017). Animal reproduction studies for tetrabenazine in rats resulted in an increase in stillbirths and postnatal offspring mortality.

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Nursing Mothers

There are no data to assess the effect of deutetrabenazine or its metabolites on milk production, presence in milk, or effects on the breastfed infant (Austedo prescribing information, 2017).

Pediatric Use

The safety and efficacy of Austedo (deutetrabenazine) have not been established in pediatric patients (Austedo prescribing information, 2017).

Geriatric Use

A sufficient number of patients aged 65 years and older were not included in clinical trials to determine whether these patients respond differently from younger patients (Austedo prescribing information, 2017).

Adverse Events

Table 3: Adverse Events for Austedo (deutetrabenazine) in 4% or More of Patients and More Common than with Placebo*

Adverse Event	Austedo (n = 45)	Placebo (n = 45)
Somnolence	11%	4%
Diarrhea	9%	0%
Dry mouth	9%	7%
Fatigue	9%	4%
Urinary tract infection	7%	2%
Insomnia	7%	4%
Anxiety	4%	2%
Constipation	4%	2%
Contusion	4%	2%

* Because clinical trials are conducted under widely varying conditions, adverse event 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 (Austedo prescribing information, 2017)

PRODUCT AVAILABILITY

Austedo (deutetrabenazine) is available as 6 mg, 9 mg, and 12 mg tablets in bottles of 60 tablets that should be stored protected from light and moisture (Austedo prescribing information, 2017).

DOSAGE AND ADMINISTRATION

The dose of Austedo (deutetrabenazine) is dependent upon individual patient response in reduction of chorea, and tolerability (Austedo prescribing information, 2017). A dose conversion chart should be consulted for the initial dose when switching patients from Xenazine (tetrabenazine) to Austedo (deutetrabenazine). For patients not being switched from Xenazine (tetrabenazine), the recommended starting dose is 6 mg once daily with food. For all patients, the dose may be titrated up at weekly intervals in increments of 6 mg per day to a maximum daily dose of 48 mg. Daily dosages of 12 mg or above should be administered in two divided doses. In patients who have a treatment interruption for greater than one week, therapy should be re-titrated upon resuming therapy.

Dose Modifications

An increase in systemic exposure to the active dihydro-metabolites of deutetrabenazine has been observed to occur with concomitant use of Austedo (deutetrabenazine) and strong CYP2D6 inhibitors (Austedo prescribing information, 2017). The maximum daily dose of Austedo (deutetrabenazine) should not exceed 36 mg (maximum single dose of 18 mg) in patients who are receiving strong CYP2D6 inhibitors or who are poor CYP2D6 metabolizers.

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APPROACHES TO TREATMENT

Huntington's disease is an inherited disorder caused by an exon 1 cytosine-adenine-guanine (CAG) trinucleotide expansion in the huntingtin (*HTT*) gene (Huntington Study Group, 2016). This expansion in the *HTT* gene causes progressive breakdown of neurons in motor control regions of the brain, in addition to other areas (National Institute of Neurological Disorders and Stroke [NINDS], 2017). Symptoms of Huntington's disease include uncontrolled movements referred to as chorea, abnormal body postures, and changes in behavior, emotion, judgment, and cognition, that progressively worsen over time causing severe disability. Patients with Huntington's disease may develop additional symptoms including impaired coordination, slurred speech, and difficulty feeding and swallowing. Huntington's disease is estimated to affect more than 30,000 individuals in the United States, with most individuals first developing symptoms between 30 years and 50 years of age. Some individuals may develop Huntington's disease under the age of 20 years, and this early onset of disease is referred to as juvenile Huntington's disease. Patients usually die within 15 years to 20 years following diagnosis with Huntington's disease.

There is no available treatment to reverse the course of Huntington's disease (NINDS, 2017). Chorea often develops early and is considered a hallmark of Huntington's disease, in addition to cognitive decline and psychiatric impairment (Armstrong, 2012). The 2012 American Academy of Neurology (AAN) guidelines for the treatment of chorea in Huntington's disease recommend treatment with Xenazine (tetrabenazine) or the off-label use of amantadine or Rilutek (riluzole). The selection of agent should be based on discussion of related adverse events with patients. Adverse events should be monitored during treatment, especially depression/suicidality and Parkinsonism with Xenazine (tetrabenazine), and elevated liver enzymes with Rilutek (riluzole). The AAN guidelines also note that while the Unified Huntington's Disease Rating Scale (UHDRS) is the main outcome measure for Huntington's disease studies, a clinically important change on the UHDRS has not been established.

National Institute for Health and Care Excellence (NICE)

NICE does not provide guidance for the treatment of Huntington's disease.

Advantages and Disadvantages of Agents for Huntington's Disease Associated Chorea

Austedo (deutetrabenazine) and Xenazine (tetrabenazine) have similar safety and efficacy profiles when compared indirectly; however, Austedo (deutetrabenazine) is associated with a lower incidence of adverse events, including somnolence and depression. The attenuation of the metabolism of Austedo (deutetrabenazine) allows for less frequent dosing of Austedo (deutetrabenazine) at a lower dose compared with Xenazine (tetrabenazine).

PRODUCT COMPARISON

Table 4: Market Share Comparison of Agents for Huntington's Disease Associated Chorea

Product	Cost (AWP)/Unit	CVS Caremark Data	
		Mail/Retail Rxs	Market Share (Combined Mail/Retail)
Austedo (deutetrabenazine) tablets*	$66.76 per 6 mg tablet $73.98 per 9 mg tablet $98.64 per 12 mg tablet	—	—
tetrabenazine tablets	$77.19 per 12.5 mg tablet $154.39 per 25 mg tablet	3,525	65.3%
Xenazine (tetrabenazine) tablets	$125.07 per 12.5 mg tablet $250.15 per 25 mg tablet	1,875	34.7%

Boldface indicates generic availability
* Austedo launched April 13, 2017
AWP = average wholesale price
Rx = prescription
(CVS Administrative Claims Data. January 2017 to March 2017; *Medi-Span® Master Drug Data Base v2.5 (MDDB®)*, April 2017, Clinical Drug Information, LLC)

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FORMULARY AND DRUG LIST AVAILABILITY

Table 5: Formulary/Drug List Availability of Huntington's Disease Associated Chorea Agents

Product	National Formulary	Prescribing Guide*	Performance Drug List*	Advanced Control Formulary	Value Formulary*
Austedo (deutetrabenazine) tablets	—	—	—	—	—
Xenazine (tetrabenazine) tablets	✓	Excluded†	Excluded†	Excluded	—
tetrabenazine tablets	✓	✓	✓	✓	—

Boldface indicates generic availability
* Advanced Control Specialty Formulary may be applied to Prescribing Guide, Performance Drug List, or Value Formulary
† Excluded for some clients

Table 6: 2017/2018 Health Exchanges Formularies Availability of Huntington's Disease Associated Chorea Agents with UM Tools

Product	Managed Medicaid Drug List	2017/2018 5-Tier Health Exchanges Template Formulary	2017/2018 6-Tier Health Exchanges Template Formulary	2017/2018 3-Tier Health Exchanges Formulary New York	2017/2018 4-Tier Health Exchanges Formulary California	2017/2018 6-Tier Health Exchanges Formulary South Carolina
Austedo (deutetrabenazine) tablets	—	—	—	—	—	—
Xenazine (tetrabenazine) tablets	—	—	—	—	—	—
tetrabenazine tablets	—	**tier 4***	**tier 5***	**tier 3***	**tier 4***	**tier 5***

Boldface indicates generic availability
* Prior authorization
UM = utilization management

Table 7: 2017 Medicare Part D Drug List Availability of Huntington's Disease Associated Chorea Agents with Optional UM Tools

Product	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
Austedo (deutetrabenazine) tablets	—	—	—	—	—	—	—	—	—	—
Xenazine (tetrabenazine) tablets	—	—	—	—	—	—	tier 5‡§	—	—	—
tetrabenazine tablets	tier 5‡§	tier 5‡§	tier 5‡§	tier 5‡§	tier 2‡§	tier 5‡§	tier 5‡§	tier 5‡§	tier 4‡§	tier 5‡§

Boldface indicates generic availability
* Also available as a Single-Source Generic Strategy drug lists
† Also available as a 1-Tier and 4-Tier drug list
‡ Prior authorization
§ Quantity limit
EGWP = Employer Group Waiver Plan
MMP = Medicare-Medicaid Plan
PDP = Prescription Drug Plan
UM = utilization management

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Table 8: 2018 Medicare Part D Drug List Availability of Huntington's Disease Associated Chorea Agents with Optional UM Tools

Product	PDP Choice/ PDP Plus Drug List	Client Drug Lists									
		Select*	Generic Strategy Standard*	Generic Strategy Essential	MMP	Standard†	Expanded	Performance	Core	EGWP	
	5-Tier	5-Tier			2-Tier	5-Tier	5-Tier			4-Tier	5-Tier
Austedo (deutetrabenazine) tablets	—	—	—	—	—	—	—	—	—	—	—
Xenazine (tetrabenazine) tablets	—	—	—	—	—	—	tier 5‡§	—	—	—	—
tetrabenazine tablets	tier 5‡§	tier 5‡§	tier 5‡§	tier 5‡§	tier 2‡§	tier 5‡§	tier 5‡§	tier 5‡§	tier 5‡§	tier 4‡§	tier 5‡§

Boldface indicates generic availability
* Also available as a Single-Source Generic Strategy drug lists
† Also available as a 1-Tier and 4-Tier drug list
‡ Prior authorization
§ Quantity limit
EGWP = Employer Group Waiver Plan
MMP = Medicare-Medicaid Plan

PDP = Prescription Drug Plan
UM = utilization management

FORMULARY CONSIDERATIONS

Austedo (deutetrabenazine) is the second agent FDA-approved for the treatment of chorea associated with Huntington's disease. The efficacy of Austedo (deutetrabenazine) was established in a 12-week, phase III, randomized controlled trial in 90 patients where Austedo (deutetrabenazine) provided greater improvements compared with placebo in chorea motor signs at 12 weeks as measured the Total Maximal Chorea Score. Austedo (deutetrabenazine) was well tolerated in clinical trials and was associated with a greater incidence of somnolence compared with placebo, and no significant difference in depression or agitated depression. Austedo (deutetrabenazine) is pending FDA review for the treatment of chorea associated with tardive dyskinesia, and has an expected review in August 2017 (AdisInsight, 2017). Austedo (deutetrabenazine) provides an efficacious and possibly safer alternative option for patients with chorea associated Huntington's disease.

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DRUG MONOGRAPH PREPARED BY:

Faon M Bridges, Pharm.D., BCPS
May 17, 2017

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.

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Pharmacy &Therapeutics Committee Summary Review
Imfinzi (durvalumab) – AstraZeneca

Prepared by: CVS Health / Irina Yaroshenko

Presentation Date: 1/4/18

Therapeutic Class: PD-L1 inhibitor

FDA Approval Date: 05/01/17

FDA Indication: Treatment of patient with locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-containing chemotherapy or who have disease progression within 12 months of neoadjuvant treatment with platinum-containing chemotherapy.

Comparable Products: Keytruda (non-preferred), Tecentriq (non-preferred), Opdivo (non-prefrred)

Proposed Designation & Rationale

Recommendation: Non-Preferred, approved via e-vote on 08/30/17

- Criteria for use / Approval duration: See policy for criteria for use and approval durations.
  - For reference, Ohio Medicaid version of policy can be found at: Imfinzi.
  - All other state specific policies can be found under Pharmacy Policies by clicking on the appropriate state.

Clinical Implications/ Place in Therapy:
New drug for locally advanced or metastatic urothelial carcinoma was reviewed. Criteria for Imfinzi are written based on safety and efficacy data from clinical trials, drug's package insert, and evidence-based guidelines from The National Comprehensive Cancer Network (NCCN). Medication is intended for treatment of those who have disease progression during or following platinum-containing chemotherapy or who have disease progression within 12 months of neoadjuvant treatment with platinum-containing chemotherapy.

Ongoing Clinical Trials:

- There are 170 clinical trials (recruiting; enrolling by invitation; active, not recruiting): https://clinicaltrials.gov/ct2/results?term=durvalumab&Search=Apply&recrs=a&recrs=f&recrs=d&age_v=&gndr=&type=&rslt=

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1. Imfinzi [package inset]. Wilmington, DE; AstraZeneca Pharmaceuticals: May 2017.

CVSHealth

CVS Caremark Pharmacy & Therapeutics Drug Monograph

Imfinzi™ (durvalumab) intravenous injection AstraZeneca Pharmaceuticals LP

INDICATION

Imfinzi (durvalumab) is indicated for the treatment of patients with locally advanced or metastatic urothelial carcinoma whose disease progressed during or following platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy (Imfinzi prescribing information, 2017). This indication is approved under accelerated approval based on tumor response rate and duration of response. Continued approval of Imfinzi (durvalumab) may be contingent upon verification and description of clinical benefit in confirmatory trials.

U.S. FOOD AND DRUG ADMINISTRATION (FDA)-REVIEW DESIGNATION

Imfinzi (durvalumab) was approved by the FDA on May 1, 2017 as a new biologic with priority review and Breakthrough Therapy Designation for patients with locally advanced or metastatic urothelial carcinoma (FDA, 2017a). An agent may qualify for breakthrough therapy if it treats a serious condition and preliminary clinical evidence indicates that the drug may demonstrate substantial improvement for clinically significant endpoint(s) compared with available therapies (FDA, 2017b).

DRUG SUMMARY

	Imfinzi (durvalumab)
Place in Therapy	• Imfinzi is FDA-approved for the treatment of locally advanced or metastatic UC in patients with disease progression during or following platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant platinum-containing chemotherapy. • NCCN Clinical Practice Guidelines in Oncology® for UC recommend chemotherapy with gemcitabine and cisplatin or DDMVAC with growth factor support as first-line therapy in the setting of metastatic urothelial bladder cancer. Second-line therapy options include pembrolizumab (Keytruda), atezolizumab (Tecentriq), nivolumab (Opdivo), avelumab (Bavencio), durvalumab (Imfinzi), paclitaxel or docetaxel, gemcitabine, or pemetrexed.
Efficacy	• FDA approval for Imfinzi was based on an open-label, single-arm, multi-center, phase I/II trial demonstrating favorable clinical activity and an acceptable safety profile in patients with locally advanced or metastatic urothelial carcinoma including patients with 2 or more previous lines of therapy in post-platinum metastatic UC. • In the population considered for FDA approval, ORR was 17.6%, with a higher ORR among patients with tumors having high expression of PD-L1 compared with low expression of PD-L1 (27.4% vs. 4.1%). • Median PFS was 1.5 months, and median OS was 18.2 months.
Safety	• Warnings and precautions: infusion-related reactions, embryo-fetal toxicity, infection, and immune-mediated adverse events. • Common AEs (≥ 15%): fatigue, musculoskeletal pain, constipation, decreased appetite, peripheral edema, and urinary tract infection

AE = adverse event
FDA = Food and Drug Administration
NCCN = National Comprehensive Cancer Network
ORR = overall response rate
OS = overall survival
PD-L1 = programmed death ligand-1
PFS = progression-free survival
UC = urothelial carcinoma

CLINICAL PHARMACOLOGY

Mechanism of Action

Durvalumab is a human immunoglobulin G1 kappa (IgG1κ) monoclonal antibody that blocks the interaction of programmed death ligand-1 (PD-L1) with programmed death 1 (PD-1) and cluster of differentiation 80 (CD80) (Imfinzi prescribing information, 2017). This interaction releases the PD-L1/PD-1 mediated inhibition of the immune responses, including cytotoxic T-cell activity, proliferation, and cytokine production, without inducing antibody dependent cell-mediated cytotoxicity.

Pharmacokinetics

Table 1: Selected Pharmacokinetics of Durvalumab

Route of Administration	Volume of Distribution	$T_{1/2}$
Intravenous infusion	5.6 L	17 days

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

(Imfinzi prescribing information, 2017)

Pharmacogenomics

No pharmacogenomic data are available at this time for durvalumab.

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CLINICAL EFFICACY

Table 2: Efficacy of Imfinzi (durvalumab) in the Treatment of Metastatic Urothelial Carcinoma

Study, Treatments, and Groups	Study Design and Endpoints	Study Criteria	Results
Hahn, 2017 Evidence Level IIa **Imfinzi** 10 mg/kg IV every 2 weeks until unacceptable toxicity or disease progression (N = 191)	**Study Design:** Open-label, single-arm, multicenter, phase I/II trial **Objective:** To evaluate the efficacy and safety of Imfinzi in patients with locally advanced or metastatic UC during or after platinum-containing chemotherapy or who had disease progression within 12 months of treatment with a platinum-containing neoadjuvant or adjuvant chemotherapy regimen **Primary Endpoint(s):** ORR **Secondary Endpoint(s):** DoR, PFS, OS	**Inclusion Criteria:** • Adult patients with metastatic UC (median age 67 years [range: 34 to 88 years of age], 7% male, 64% Caucasian) **Exclusion Criteria:** • History of immunodeficiency • Conditions requiring immunosuppression • History of autoimmune disease • Untreated CNS metastases • Concurrent HIV • Active TB, hepatitis B or C infection	See nested table below

Efficacy Endpoint	All Patients (N = 191)	PD-L1 High* (N = 98)	PD-L1 Low/negative (N = 79)	PD-L1 unknown (N = 14)
ORR (95% CI)	17.8% (12.7 to 24.0)	27.6% (19.0 to 37.5)	5.1% (1.4 to 12.5)	21.4% (4.7 to 50.8)
CR rate	3.7%	4.1%	2.5%	7.1%
PR rate	14.1%	23.5%	2.5%	14.3%
Median DoR (months) (95% CI)	NR (0.9 to 19.9)	NR (0.9 to 19.9)	12.25 (1.9 to 12.3)	NR (2.3 to 2.6)
Second-line or Greater Post-Platinum UC Patients†				
Number of patients	N = 182	N = 95	N = 73	N = 14
ORR (95% CI)	17.6% (12.3 to 23.9	27.4% (18.7 to 37.5)	4.1% (0.9 to 11.5)	21.4% (4.7 to 50.8)

- Median follow up was 6.87 months.
- Median time to response was 1.41 months.
- Median PFS and OS were 1.5 months (95% CI 1.4 months to 1.9 months) and 18.2 months (95% CI 8.1 months to not estimable), respectively.
- OS at 1 year was 55.0% (95% CI, 43.9 to 64.7%)

Safety

- Infections occurred in 29.7% of patients
- Grade 3/4 TEAEs occurred in 6.8% of patients.
- Grade 3/4 immune mediated AEs occurred in 4 patients with 2 patients permanently discontinuing due to acute kidney injury and autoimmune hepatitis

Comments/Study Limitations: The study is not published; single-arm trial; short duration of follow up.

Conclusions: Imfinzi demonstrated favorable clinical activity and an acceptable safety profile in patients with locally advanced or metastatic urothelial carcinoma including patients with 2 or more previous lines of therapy in post-platinum metastatic UC.

* Defined as ≥ 25% PD-L1 expression on tumor or immune cells

† Patients who had progressed during or after platinum-based therapy including those who progressed within 12 months of receiving at least one drug therapy regimen in a neo-adjuvant or adjuvant setting.

AEs = adverse events
CNS = central nervous system
CR = complete response
DoR = duration of response
HIV = human immunodeficiency virus
NR = not reached
ORR = objective response rate
OS = overall survival
PFS = progression free survival
PR = partial response
TB = tuberculosis
TEAEs = treatment emergent adverse events
UC = urothelial carcinoma

(Hahn, 2017; Imfinzi prescribing information 2017)

Data as of June 16, 2017

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SAFETY

Contraindications

There are no known contraindications for Imfinzi (durvalumab) (Imfinzi prescribing information, 2017).

Warnings and Precautions

Immune-Mediated Pneumonitis

Immune-mediated pneumonitis was reported in 2.3% of patients receiving Imfinzi (durvalumab) across clinical trials, with 0.4% permanently discontinuing due to severe pneumonitis (Imfinzi prescribing information, 2017). There was one case of Grade 5 immune-mediated pneumonitis. The median time to onset reported was 55.5 days (range: 24 days to 423 days). Patients with suspected pneumonitis should be evaluated with radiographic imaging. Corticosteroids should be administered with treatment modifications as clinically indicated for immune-mediated pneumonitis.

Immune-Mediated Hepatitis

Immune-mediated hepatitis was reported in 1.1% of patients receiving Imfinzi (durvalumab) across clinical trials, with permanent discontinuation in 0.2% of patients (Imfinzi prescribing information, 2017). There was one case of fatal hepatitis. The median time to onset reported was 51.5 days (range: 15 days to 312 days), and the median duration was 2.5 months (range: 1 day to > 7.4 months). Patients should be monitored for abnormal liver tests each cycle during treatment with Imfinzi (durvalumab). Corticosteroids should be administered with treatment modifications as clinically indicated for immune-mediated hepatitis.

Immune-Mediated Colitis

Immune-mediated colitis or diarrhea was reported in 1.3% of patients receiving Imfinzi (durvalumab) across clinical trials, with 0.4% of patients permanently discontinuing Imfinzi (durvalumab) due to severe colitis (Imfinzi prescribing information, 2017). The median time to onset reported was 73 days (range: 13 days to 345 days). Corticosteroids and anti-diarrheal agents should be administered with treatment modifications as clinically indicated for immune-mediated colitis.

Immune-Mediated Endocrinopathies

Thyroid Disorders (Hypothyroidism/Hyperthyroidism)

Immune-mediated thyroid disorders were reported in 15.3% of patients receiving Imfinzi (durvalumab) across clinical trials (Imfinzi prescribing information, 2017). Hypothyroidism occurred in 9.6% of patients, hyperthyroidism occurred in 5.7% of patients. The median time to first onset was 42 days (range: 15 days to 239 days). Thyroid function should be monitored prior to and periodically during treatment with Imfinzi (durvalumab). Asymptomatic patients with abnormal thyroid function tests can receive Imfinzi (durvalumab). Patients with abnormal thyroid function tests should be managed with hormone replacement (if indicated) and treatment modifications.

Adrenal Insufficiency

Immune-mediated adrenal insufficiency was reported in 0.9% of patients receiving Imfinzi (durvalumab) across clinical trials (Imfinzi prescribing information, 2017). Corticosteroids and hormone replacement should be administered as clinically indicated for adrenal insufficiency.

Type 1 Diabetes Mellitus

Imfinzi (durvalumab) can cause new onset type 1 diabetes mellitus (Imfinzi prescribing information, 2017). New onset type 1 diabetes without an alternative etiology was reported to have occurred in < 0.1% of patients receiving Imfinzi (durvalumab) in clinical trials. Insulin should be initiated with treatment modifications for type 1 diabetes.

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Hypophysitis

Hypopituitarism leading to adrenal insufficiency and diabetes insipidus was reported to have occurred in < 0.1% of patients receiving Imfinzi (durvalumab) in clinical trials (Imfinzi prescribing information, 2017). Corticosteroids and hormone replacement therapy should be initiated as clinically indicated for hypophysitis.

Other Immune-Mediated Adverse Reactions

Imfinzi (durvalumab) has caused immune-mediated rash (Imfinzi prescribing information, 2017). Other immune-related adverse reactions, including aseptic meningitis, hemolytic anemia, immune thrombocytopenic purpura, myocarditis, myositis, nephritis, and ocular inflammatory toxicity including uveitis and keratitis, have occurred in ≤ 1.0% of patients treated with Imfinzi (durvalumab). Immune-mediated rash occurred in 15.6% of patients receiving Imfinzi (durvalumab) in clinical trials, with 0.3% of patients developing vitiligo. Immune thrombocytopenic purpura led to death in < 0.1% of patients receiving Imfinzi (durvalumab). Immune-mediated nephritis occurred in 0.2%, resulting in permanent discontinuation for these patients. Patients should be monitored for abnormal renal function tests prior to and each cycle during treatment with Imfinzi (durvalumab) and managed with treatment modifications and corticosteroids

Infection

Imfinzi (durvalumab) can cause severe infections, including sepsis, necrotizing fasciitis, and osteomyelitis (Imfinzi prescribing information, 2017). Anti-infectives should be administered for suspected or confirmed infections. Infections occurred in 37.6% of patients receiving Imfinzi (durvalumab) in clinical trials.

Infusion-Related Reactions

Imfinzi (durvalumab) can cause severe infusion-related reactions (Imfinzi prescribing information, 2017). Across clinical trials, infusion-related reactions were reported in 1.8% of patients receiving Imfinzi (durvalumab). Infusion rates should be slowed or interrupted in patients with mild to moderate infusion reactions and permanently discontinued in patients with Grade 3 or 4 infusion reactions.

Reproductive Risk

Durvalumab can cause fetal harm based on its mechanism of action and data from animal studies (Imfinzi prescribing information, 2017). Animal models have noted premature delivery, fetal loss, and premature neonatal death after administration of durvalumab. Females of reproductive potential should be advised of the potential risk to a fetus and use effective contraception during treatment and for at least three months after the last dose of Imfinzi (durvalumab).

Nursing Mothers

There is no information regarding the presence of durvalumab in human milk, the effects on the breastfed infant, or the effects on milk production (Imfinzi prescribing information, 2017). Durvalumab was found to be present in the milk of lactating cynomolgus monkeys and was associated with premature neonatal death. Due to the potential for adverse reactions in breastfed infants from durvalumab, lactating women should be advised to not breastfeed during treatment and for at least three months after the last dose of Imfinzi (durvalumab).

Pediatric Use

The safety and effectiveness of Imfinzi (durvalumab) have not established in pediatric patients (Imfinzi prescribing information, 2017).

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Geriatric Use

Of the 182 patients receiving Imfinzi (durvalumab) in the treatment of locally advanced or metastatic urothelial carcinoma in clinical trials, 112 patients were ≥ 65 years of age, and 34 patients were ≥ 75 years of age (Imfinzi prescribing information, 2017). The overall response rate (ORR) in patients ≥ 65 years of age was 15.2% (17 of 112) and was 11.8% (4 of 24) in patients ≥ 75 years of age. Grade 3 or 4 adverse events occurred in 38% (42 of 112) of patients aged ≥ 65 years and in 35% (12 of 34) of patients ≥ 75 years of age. Study outcomes in patients ≥ 65 years of age should be viewed with caution given the small number of patients in this cohort of patients.

Adverse Events

Table 3: Adverse Events Reported in ≥ 10% of Patients with Urothelial Carcinoma Receiving Imfinzi (durvalumab)

Adverse Event	Imfinzi (durvalumab) N = 182	
	All Grades	Grades 3 or 4
All Adverse Events	96 %	43 %
General Disorders and Administration		
Fatigue	39 %	6 %
Peripheral edema	15 %	2 %
Pyrexia/Tumor associated fever	14 %	1 %
Musculoskeletal and Connective Tissue Disorders		
Musculoskeletal pain	24 %	4 %
Gastrointestinal Disorders		
Constipation	21 %	1 %
Nausea	16 %	2 %
Abdominal pain	14 %	3 %
Diarrhea/Colitis	13 %	1 %
Metabolism and Nutrition Disorders		
Decreased appetite/Hypophagia	19 %	1 %
Infections		
Urinary tract infection	15 %	4 %
Respiratory, Thoracic, and Mediastinal Disorders		
Dyspnea/Exertional dyspnea	13 %	2 %
Cough/Productive cough	10 %	0 %
Skin and Subcutaneous Tissue Disorders		
Rash	11 %	1 %

(Imfinzi prescribing information, 2017)

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Table 4: Grade 3 or 4 Laboratory Abnormalities Worsened from Baseline Occurring in ≥ 1% of Patients with Urothelial Carcinoma Receiving Imfinzi (durvalumab)

Laboratory Test	Grade 3-4
Hyponatremia	12 %
Lymphopenia	11 %
Anemia	8 %
Increased alkaline phosphatase (ALP)	4 %
Hypermagnesemia	4 %
Hypercalcemia	3 %
Hyperglycemia	3 %
Increased aspartate aminotransferase (AST)	2 %
Increased alanine aminotransferase (ALT)	1 %
Hyperbilirubinemia	1 %
Increased creatinine	1 %
Neutropenia	1 %
Hyperkalemia	1 %
Hypokalemia	1 %
Hypoalbuminemia	1 %

(Imfinzi prescribing information, 2017)

Immunogenicity

In clinical trials, 3.3% of patients receiving Imfinzi (durvalumab) tested positive for treatment-emergent anti-drug antibodies (Imfinzi prescribing information, 2017). The clinical significance of anti-durvalumab antibodies is unknown.

PRODUCT AVAILABILITY

Imfinzi (durvalumab) is supplied as a 500 mg/10 mL or 120 mg/2.4 mL solution in a single-dose vial for intravenous infusion (Imfinzi prescribing information, 2017). Imfinzi (durvalumab) should be stored refrigerated at 2°C to 8°C (36°F to 46°F) protected from light.

DOSAGE AND ADMINISTRATION

The recommended dose of Imfinzi (durvalumab) is 10 mg/kg administered as an intravenous infusion over 60 minutes every two weeks until disease progression or unacceptable toxicity (Imfinzi prescribing information, 2017). Table 5 summarizes recommendations for withholding or permanently discontinuing Imfinzi (durvalumab). No dose reductions of Imfinzi (durvalumab) are recommended. Additional treatments recommended for the management of specific adverse events are described in the prescribing information.

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Table 5: Recommendations for Withholding or Permanently Discontinuing Imfinzi (durvalumab)

Warnings and Precautions	Recommendation	
	Withhold	Permanently Discontinue
Pneumonitis	Grade 2	Grade 3 or 4
Hepatitis	Grade 2 AST or ALT > 3 and ≤ 5 x ULN or total bilirubin > 1.5 and ≤ 3 x ULN Or Grade 3 AST or ALT ≤ 8 x ULN or total bilirubin ≤ 5 x ULN	AST or ALT > 8 x ULN or total bilirubin > 5 x ULN Or Concurrent ALT or AST > 3 x ULN and total bilirubin > 2 x ULN with no other cause
Colitis of Diarrhea	Grade 2	Grade 3 or 4
Endocrinopathies*	Grade 2 to 4	NA
Nephritis	Grade 2 serum creatinine > 1.5 and ≤ 3 x ULN	Grade 3 serum creatinine > 3 and ≤ 6 x ULN Or Grade 4 serum creatinine > 6 x ULN
Rash or dermatitis	Grade 2 for > 1 week Or Grade 3	Grade 4
Infection	Grade 3 or 4	NA
Infusion-Related Reactions	Grade 1 or 2	Grade 3 or 4
Other Adverse Events	Grade 3	Grade 4

* Including but not limited to thyroid disorders, adrenal insufficiency, and hyperglycemia
† Including but not limited to myocarditis, myositis, psoriasis, dermatitis, erythema multiforme, pemphigoid, and hypopituitarism
ALT = alanine aminotransferase NA = not applicable
AST = aspartate aminotransferase ULN = upper limit of normal

(Imfinzi prescribing information, 2017)

APPROACHES TO TREATMENT

Bladder cancer is the sixth most common cancer in the United States, with 16,870 deaths estimated for 2017 (12,240 in men and 4,630 in women) due to bladder cancer (American Cancer Society [ACS], 2017; National Comprehensive Cancer Network [NCCN], 2017; National Cancer Institute [NCI], 2017). Bladder cancer accounts for about 5% of all new cases of cancer. It is estimated that 76,030 new cases of bladder cancer are will occur (of which 60,490 in men and 18,540 in women) in 2017 (ACS, 2017). The 5-year survival among all stages of bladder cancer is estimated to be 77% (ACS, 2016a). Overall, the death rates due to bladder cancer have been stable for the past decade.

Men are three to four times more likely during their lifetime compared with women to be diagnosed with bladder cancer, and it is the third most common cancer in men (ACS, 2017; NCI, 2017). Ninety percent of patients with bladder cancer are older than 55 years of age. The mean age at the time of diagnosis of bladder cancer is 73 years (ACS, 2017). When compared with African Americans, white patients are diagnosed with bladder cancer approximately twice as often. Cigarette smoking is the most common risk factor for bladder cancer, and other risk factors include family history, arsenic exposure, and cyclophosphamide use (ACS, 2016b). Interestingly, it's been found drinking more water can to lead to lower rates of bladder cancer.

Patients with bladder cancer commonly present with symptoms such as microscopic or gross hematuria, urinary tract infections, pain or burning during urination, and/or upper tract obstruction or pain (NCCN, 2017). It is recommended for patients to be evaluated with office cystoscopy as well as urine cytology. A positive urine cytology result may indicate urothelial tumor anywhere in the urinary tract. Transurethral resection of the bladder tumor (TURBT) is conducted to confirm the diagnosis and the extent of disease.

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Staging for bladder cancer follows the seventh edition of the American Joint Committee on Cancer tumor node metastasis (TNM) staging system (American Society of Clinical Oncology [ASCO], 2016; NCCN, 2017). The "T" or "Tumor," represents how large the tumor is and where it is located; the "N" or "Node" indicates whether the tumor has spread to the lymph nodes; and "M" or "Metastasis," indicates whether the cancer has metastasized to other parts of the body and to what extent. The TNM classifications are combined to assign the stage of bladder cancer, Stages 0 to IV. Table 6 summarizes the different stages of bladder cancer and their associated 5-year survival rates.

Table 6: Stages of Bladder Cancer and Associated Five-Year Survival Rates

Stage	Description	5-Year Survival Rates
0	Abnormal cells found in tissue lining the inside of the bladder 0a: papillary carcinoma 0is: carcinoma in situ	98%
I	Formed and spread to the layers of the connective tissue next to the lining of the bladder	88%
II	Spread to the layers of muscle tissue of the bladder	63%
III	Spread from the bladder to the layer of fat surrounding it and may spread to prostate, seminal vesicles, uterus, or vagina	46%
IV	Has ≥ 1 of the following: • Spread from the bladder to the wall of the abdomen or pelvis • Spread to one or more lymph nodes • Spread to other parts of the body, such as the lung, bone or liver	15%

(ACS, 2016a; ACS, 2016c)

The three types of bladder cancer include transitional cell carcinoma (or urothelial carcinoma), squamous cell carcinoma, and adenocarcinoma (NCI, 2017). Urothelial carcinoma is the most common histologic type in the United States (NCCN, 2017). Urothelial carcinoma involves the bladder and related organs (from the renal pelvis to the ureter, bladder, and proximal two thirds of the urethra), but more than 90% of tumors originate in the urinary bladder. There may be cases with a mixed histology (non-urothelial cell tumors and urothelial cell tumors), which can reflect an increased risk of disease progression. Oftentimes this can create difficulties in treatment as systemic chemotherapy regimens may only target cells of urothelial origin and the non-urothelial tumor cells can remain and continue to grow.

Bladder cancer is divided into three categories: non-muscle invasive tumors, muscle-invasive lesions, and metastatic lesions (NCCN, 2017). The prognosis and management vary across the different types of bladder cancer. Approximately 70% of all new cases of bladder cancer are categorized as non-muscle invasive tumors and are generally confined to the mucosa or submucosa.

Urothelial carcinoma of the prostate is also another type of urothelial cancer that can arise from urothelial carcinomas from the bladder wall invading into the prostate. The disease can also occur de novo, concurrently or after treatment of bladder cancer (NCCN, 2017). Urothelial carcinoma of the prostate is evaluated by a digital rectal examination, cystoscopy with bladder biopsy, and transurethral resection of the prostate (TURP). Management of prostatic urothelial carcinomas is based on the extent of the disease in reference to the urethra, duct, acini, and stroma.

Treatment of Bladder Cancer

Bladder cancer management is dependent upon the histology, stage, grade, and depth of invasion of the tumor (NCCN, 2017). These factors can help estimate the probability of recurrence and degree of progression into advanced stages. Treatment options for bladder cancer consist of surgery, radiation therapy, chemotherapy, and biologic therapy. The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) recommend surgical excision of the tumor, as standard of therapy and initial treatment for both non-invasive and muscle-invasive disease.

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Non-muscle-invasive Disease

TURBT, combined with a bimanual examination under anesthesia, is the standard therapy for non-invasive disease. The process involves resecting the visible tumor and obtaining muscle samples to analyze the extent of the disease within the bladder (NCCN, 2017). Although the tumors are managed endoscopically with complete resection, 31% to 78% of patients with a confined tumor in the mucosa or submucosa experience recurrence or a new occurrence of urothelial carcinoma within five years. To decrease the risk of recurrence, intravesical instillation of chemotherapy with mitomycin C is recommended within 24 hours of TURBT. Tumors with intermediate or high risk of progression require subsequent treatment with intravesical induction (e.g. mitomycin C or gemcitabine) or Bacillus Calmette-Guerin (BCG). Maintenance therapy with BCG for one year is preferred for patients at intermediate risk and three years for patients with high-risk disease. BCG is a weakened, live bacterium, intravesical immunotherapy that has demonstrated reduced risk of recurrence, with an estimated 70% of bladder cancer patients achieving remission after BCG therapy (Cancer Research Institute [CRI], 2016).

Muscle-invasive and Metastatic/Advanced Disease

Although TURBT is the initial treatment recommended in patients with muscle-invasive bladder cancer, further treatment is required (NCCN, 2017). Treatments, such as bladder-preserving approaches, neoadjuvant or adjuvant therapy, radical cystectomy, and partial cystectomy, may be used following TURBT. Standard regimens for neoadjuvant and adjuvant chemotherapy include DDMVAC (dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin) with growth factor, gemcitabine and cisplatin, and CMV (cisplatin, methotrexate, and vinblastine). Chemotherapy is recommended in advanced disease, with the specific regimen partially dependent on patient characteristics (such as cardiac disease, renal dysfunction, and the extent of disease). Table 7 summarizes the 2016 NCCN Clinical Practice Guidelines In Oncology® (NCCN Guidelines®) recommendations for systemic therapy in locally advanced or metastatic bladder cancer. Bavencio (avelumab) and Opdivo (nivolumab) are also FDA-approved to treat locally advanced or metastatic urothelial carcinoma in patients whose disease has worsened during or following platinum-containing chemotherapy, or had disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy (Prescribing information: Opdivo, 2017; Bavencio, 2017). Tecentriq (atezolizumab) and Keytruda (pembrolizumab) also carry this indication with the added indication of treatment in patients with locally advanced or metastatic urothelial carcinoma who are cisplatin-ineligible (Tecentriq prescribing information, 2017; Keytruda prescribing information, 2017). Of note, the NCCN guidelines consider pembrolizumab (Keytruda) as the only category 1 recommendation for second-line systemic therapy for locally advanced or metastatic bladder cancer (NCCN, 2017).

Table 7: NCCN Clinical Practice Guidelines® for the Systemic Treatment of Locally Advanced or Metastatic Bladder Cancer

First-Line Chemotherapy	
• Cisplatin-eligible†: o Cisplatin + gemcitabine o DDMVAC with growth factor support	• Cisplatin-ineligible‡: o Carboplatin + gemcitabine o Atezolizumab (Tecentriq)
Second-Line Systemic Therapy	
• Participation in clinical trials of new agents preferred • Other options include pembrolizumab (Keytruda)†, atezolizumab (Tecentriq), avelumab (Bavencio), nivolumab (Opdivo), durvalumab (Imfinzi), paclitaxel or docetaxel, gemcitabine, or pemetrexed	

* All recommendations are Category 2A (based on lower-level evidence and there is uniform NCCN consensus that the intervention is appropriate) unless otherwise noted

† Category 1 recommendations are based on high-level evidence and there is uniform NCCN consensus that the intervention is appropriate

‡ Cisplatin ineligible with poor kidney function or poor performance status

DDMVAC = dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin

NCCN = National Comprehensive Cancer Network®

(NCCN, 2017)

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Urothelial Carcinoma of the Prostate

Tumors limited to the prostatic urethra can be managed with TURP and intraprostatic BCG as primary treatment (NCCN, 2017). Upon local recurrence, cystoprostatectomy with or without urethrectomy is recommended. Neoadjuvant chemotherapy is recommended in patients with stromal invasion. Adjuvant chemotherapy may be considered after primary treatment if neoadjuvant chemotherapy was not administered.

National Institute for Health and Care Excellence (NICE)

As of February 2015, NICE guidelines recommend a cisplatin-based chemotherapy regimen (e.g., cisplatin in combination with gemcitabine, or accelerated [high-dose] methotrexate, vinblastine, doxorubicin and cisplatin [MVAC] in combination with granulocyte-colony stimulating factor [G-CSF]) as first-line therapy for patients with locally advanced or metastatic urothelial bladder cancer who have a ECOG 0 or 1 and have adequate renal function (defined as a glomerular filtration rate of 60 ml/min/1.73m^2) (NICE, 2015). If cisplatin-based chemotherapy is unsuitable, the guidelines recommend carboplatin in combination with gemcitabine in patients with an ECOG 0 to 2.

As second-line therapy, NICE recommends gemcitabine in combination with cisplatin, or accelerated (high-dose) MVAC in combination with Granulocyte – Colony Stimulating Factor (G-CSF) for patients with incurable, locally advanced or metastatic urothelial bladder cancer which has progressed following first-line chemotherapy (NICE, 2015). In patients who are considered unsuitable for cisplatin-based chemotherapy, the guidelines recommend carboplatin in combination with paclitaxel or gemcitabine in combination with paclitaxel. Vinflunine is approved in Europe as second-line therapy, yet NICE does not recommend vinflunine for advanced or metastatic urothelial cancer (NICE, 2013).

Guidance regarding the use of Imfinzi (durvalumab) in the setting of urothelial carcinoma has not yet been published and an anticipated publication date is not available.

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Table 8: Comparison of the PD-1 and PD-L1 Checkpoint Inhibitors Indicated for the Treatment of Urothelial Carcinoma

Drug	Advantages	Disadvantages
All Agents	• Overall ORR in clinical trials range from 15% to 29%	• Warnings and precautions include infusion reaction, embryo-fetal toxicity and immune-mediated adverse events*
Bavencio (avelumab)	• Also indicated in the treatment of metastatic Merkel cell carcinoma	• Requires premedication with antihistamine and acetaminophen prior to infusions
Imfinzi (durvalumab)	• None identified	• No additional indications • Associated with increased risk of infection
Keytruda (pembrolizumab)	• Also indicated in the treatment of melanoma, NSCLC, HNSCC, CHL, and MSI-H cancer • Can treat cisplatin ineligible patients with metastatic UC • Dosing interval is every 3 weeks	• Associated with increased risk of complications after allogeneic HSCT
Opdivo (nivolumab)	• Multiple additional indications, including BRAF V600 wild-type or mutation positive unresectable or metastatic melanoma, metastatic NSCLC, advanced renal cell carcinoma, classical Hodgkin lymphoma, and recurrent or metastatic squamous cell carcinoma of head and neck	• Associated with increased risk of complications after allogeneic HSCT
Tecentriq (atezolizumab)	• Also indicated in the treatment of metastatic NSCLC • Can treat cisplatin ineligible patients with metastatic UC • Dosing interval is every 3 weeks	• Possible ocular toxicity • Risk of pancreatitis

* Including colitis, endocrinopathies, hepatitis, nephritis, and pneumonitis
AE = adverse event
CHL = classical Hodgkin lymphoma
HNSCC = head and neck squamous cell cancer
HSCT = hematopoietic stem cell transplant
NSCLC = non-small cell lung cancer
MSI-H = microsatellite instability-high
ORR = objective response rate
PD-1 = programmed death 1
PD-L1 = programmed death ligand 1
UC = urothelial carcinoma
(prescribing information: Bavencio, 2017; Imfinzi, 2017; Keytruda, 2017; Opdivo, 2017; Tecentriq, 2017)

PRODUCT COMPARISON

Imfinzi (durvalumab) launched on May 2, 2017 (RxPipeline, 2017). All of the urothelial carcinoma agents may be adjudicated through the medical benefit. The average wholesale price for Imfinzi (durvalumab) is $4,174.60 per 10 mL vial and $1,001.90 per 2.4 mL vial (*Medi-Span® Master Drug Data Base v2.5 [MDDB®]*, 9 June 2017, Clinical Drug Information, LLC).

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FORMULARY AND DRUG LIST AVAILABILITY

Table 9: Formulary/Drug List Availability of Agents for Metastatic Urothelial Carcinoma

Product	National Formulary	Prescribing Guide*	Performance Drug List*	Advanced Control Formulary	Value Formulary*
Bavencio (avelumab) intravenous injection	✓	—	—	—	—
Imfinzi (durvalumab) intravenous injection	—	NTMB			—
Keytruda (pembrolizumab) intravenous injection	✓	—	—	—	—
Opdivo (nivolumab) intravenous injection	✓	—	—	—	—
Tecentriq (atezolizumab) intravenous injection	✓	—	—	—	—

* Advanced Control Specialty Formulary may be applied to Prescribing Guide, Performance Drug List, or Value Formulary
NTMB = new-to-market block

Table 10: 2017 Health Exchanges Formularies Availability of Agents for Metastatic Urothelial Carcinoma with UM Tools

Product	Managed Medicaid Drug List	5-Tier Health Exchanges Template Formulary	6-Tier Health Exchanges Template Formulary	3-Tier Health Exchanges Formulary New York	4-Tier Health Exchanges Formulary California	6-Tier Health Exchanges Formulary South Carolina
Bavencio (avelumab) intravenous injection	—	—	—	—	—	—
Imfinzi (durvalumab) intravenous injection	—	—	—	—	—	—
Keytruda (pembrolizumab) intravenous injection	—	tier 4*	tier 5*	tier 3*	tier 4*	tier 5*
Opdivo (nivolumab) intravenous injection	—	—	—	—	—	—
Tecentriq (atezolizumab) intravenous injection	—	—	—	—	—	—

* Prior authorization
UM = utilization management

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Table 11: 2018 Health Exchanges Formularies Availability of Agents for Metastatic Urothelial Carcinoma with UM Tools

Product	5-Tier Health Exchanges Template Formulary	6-Tier Health Exchanges Template Formulary	3-Tier Health Exchanges Formulary New York	4-Tier Health Exchanges Formulary California	6-Tier Health Exchanges Formulary South Carolina
Bavencio (avelumab) intravenous injection	—	—	—	—	—
Imfinzi (durvalumab) intravenous injection	—	—	—	—	—
Keytruda (pembrolizumab) intravenous injection	tier 4*	tier 5*	tier 3*	tier 4*	tier 5*
Opdivo (nivolumab) intravenous injection	—	—	—	—	—
Tecentriq (atezolizumab) intravenous injection	—	—	—	—	—

* Prior authorization
UM = utilization management

Table 12: 2017 Medicare Part D Drug List Availability of Agents for Metastatic Urothelial Carcinoma with Optional UM Tools*

Product	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
Bavencio (avelumab) intravenous injection	—	—	—	—	—	—	—	—	—	—
Imfinzi (durvalumab) intravenous injection	—	—	—	—	—	—	—	—	—	—
Keytruda (pembrolizumab) intravenous injection	tier 5§	tier 5§	tier 5§	tier 5§	tier 2§	tier 5§	tier 5§	tier 5§	tier 4§	tier 5§
Opdivo (nivolumab) intravenous injection	—	—	—	—	—	—	—	—	—	—
Tecentriq (atezolizumab) intravenous injection	tier 5§	tier 5§	tier 5§	tier 5§	tier 2§	tier 5§	tier 5§	tier 5§	tier 4§	tier 5§

* 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
§ Prior authorization
EGWP = Employer Group Waiver Plan
MMP = Medicare-Medicaid Plan
PDP = Prescription Drug Plan
UM = utilization management

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Table 13: 2018 Medicare Part D Drug List Availability of Agents for Metastatic Urothelial Carcinoma with Optional UM Tools*

Product	PDP Choice/ PDP Plus Drug List	Client Drug Lists									
		Select†	Generic Strategy Standard†	Generic Strategy Essential	MMP	Standard‡	Expanded	Performance	Core	EGWP	
	5-Tier	5-Tier			2-Tier	5-Tier	5-Tier			4-Tier	5-Tier
Bavencio (avelumab) intravenous injection	–	–	–	–	–	–	–	–	–	–	–
Imfinzi (durvalumab) intravenous injection	–	–	–	–	–	–	–	–	–	–	–
Keytruda (pembrolizumab) intravenous injection	tier 5§	tier 5§	tier 5§	tier 5§	tier 2§	tier 5§	tier 5§	tier 5§	tier 5§	tier 4	tier 5§
Opdivo (nivolumab) intravenous injection	–	–	–	–	–	–	–	–	–	–	–
Tecentriq (atezolizumab) intravenous injection	tier 5§	tier 5§	tier 5§	tier 5§	tier 2§	tier 5§	tier 5§	tier 5§	tier 5§	tier 4	tier 5§

* 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
§ Prior authorization
EGWP = Employer Group Waiver Plan
MMP = Medicare-Medicaid Plan
PDP = Prescription Drug Plan
UM = utilization management

FORMULARY CONSIDERATIONS

Imfinzi (durvalumab) is indicated to treat patients with locally advanced or metastatic urothelial carcinoma whose disease progressed during or following platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy (Imfinzi prescribing information, 2017). In an open-label, single-arm, multi-center, phase I/II trial, Imfinzi (durvalumab) showed acceptable tolerability and a strong response in patients with metastatic urothelial carcinoma. Of note, response rates were considerably higher in patients with high PD-L1 expression compared to those with low or negative PD-L1 expression. In general, Imfinzi (durvalumab) has a similar efficacy and safety profile when compared with other FDA-approved agents in the second-line treatment of metastatic urothelial carcinoma. Warnings and precautions associated with Imfinzi (durvalumab) include infusion reactions, embryo-fetal toxicity, infection, and various immune-related events. Ultimately, Imfinzi (durvalumab) serves as a safe and efficacious additional treatment option for locally advanced or metastatic urothelial carcinoma.

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DRUG MONOGRAPH PREPARED BY:

Elias Pittos, Pharm.D.
June 16, 2017

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Pharmacy &Therapeutics Committee Summary Review
Ingrezza® (valbenazine) – Neurocrine Biosciences

Prepared by: Sara Evans

Presentation Date: January 4, 2018

Therapeutic Class: Vesicular monoamine transporter 2 (VMAT2) inhibitor

FDA Approval Date: April 11, 2017

FDA Indication: Tardive dyskinesia

Comparable Formulary Products: Xenazine® (tetrabenazine)

Proposed Designation & Rationale

Recommendation: Non-preferred, Previously approved via e-vote on 9/8/2017
Approval Criteria:

- For initial authorization:
  - Member is 18 years of age and older and medication is prescribed by neurologist or psychiatrist; AND
  - Member has clinical diagnosis of moderate to severe neuroleptic-induced TD as determined by clinical
  - observation and documented in chart notes; AND
  - Member must try and fail at least 2 other guideline recommended treatments first: clonazepam, ginkgo
  - biloba, amantadine, or tetrabenazine; AND
  - Member has one of the following clinical diagnoses for at least 3 months documented in chart notes:
  - Schizophrenia or Schizoaffective Disorder, or Mood Disorder; AND
  - Chart notes confirming that member does not have risk for suicidal or violent behavior and has stable psychiatric symptoms; AND
  - Member has a negative urine drug screen for all of the following: amphetamines, barbiturates,
  - benzodiazepine, phencyclidine, cocaine, opiates, and cannabinoids; AND
  - If member has a history of substance dependence, substance (drug) or alcohol abuse, chart notes confirming that member is in sustained remission for at least 12 months must be provided; AND
  - Member's The Abnormal Involuntary Movement Scale (AIMS) score is documented in chart notes; AND
  - Member does not have ANY of the following:
    - History of neuroleptic malignant syndrome;
    - History of long QT syndrome or cardiac arrhythmia;
    - Allergy, hypersensitivity, or intolerance to tetrabenazine.
  - Dosage allowed: 40 mg once daily. After one week, increase the dose to the recommended dose of 80 mg once daily.
  - Approval duration: 2 months
- For reauthorization:
  - Documentation that the member's TD symptoms have improved due to Ingrezza use as evidenced by AIMS score showing reduction of score from baseline.
  - Approval duration: 12 months

Clinical Implications/Place in Therapy:
Ingrezza is the first and only medication with FDA approved indication for tardive dyskinesia. Because of the absence of other agents on the market, the guidelines have recommended other agents be used when managing patients with tardive dyskinesia. Although these other agents do not have indication for treatment of tardive dyskinesia, the body of literature supports trial with benzodiazepines, second-generation antipsychotics, or tetrabenazine before progressing to more expensive options. Studies suggest that the combination of benzodiazepine, second-generation antipsychotic, and/or tetrabenazine is effective against tardive dyskinesia. Additionally, switching between antipsychotic agents may be effective against tardive dyskinesia symptoms. Due to the high cost of Ingrezza, pursuing potentially effective options available at a much lower cost remains the most cost-effective course of action.

Clinical Pharmacology:
Valbenazine is a vesicular monoamine transporter (VMAT) 2 inhibitor. VMAT2 is responsible for regulating monoamine uptake from the cytoplasm of the synaptic vesicle. Inhibition of this transporter leads to depletion of the synaptic pool of monoamines reducing hyperkinetic movements.

Notable Pharmacokinetics:

- Absorption: T_{max} 0.5-1 hours with steady state reached within 1 week. T_{max} of the active metabolite ([+]-α-HTBZ) is 4-8 hours. Eating a high fat meal will reduce the C_{max} of the parent drug without affecting the active metabolite.
- Distribution: Both the parent drug and the active metabolite are highly protein bound (>99% and 64%).
- Metabolism: Hydrolyzed to form the active metabolite and oxidized (primarily by CYP3A4/5) to other metabolites. The active metabolite is metabolized further by CYP2D6.
- Elimination: $T_{1/2}$ 15-22 hours. Excreted in the urine and feces.

Efficacy:

NBI-98854 for tardive dyskinesia[1]	
Trial Design/ Population	Randomized, double-blind, placebo-controlled Patients age 18-85 with schizophrenia, schizoaffective disorder, or mood disorder with neuroleptic-induced tardive dyskinesia (TD) or with a gastrointestinal disorder with metoclopramide-induced TD
Groups	NBI-98854 (valbenazine) started at 25mg once daily which could be titrated up by 25mg every 2 weeks to a maximum of 75mg daily or placebo once daily titrated in the same way
Outcomes	• *Primary efficacy endpoint*: change in Abnormal Involuntary Movement Scale (AIMS) score from baseline at week 6 • *Secondary efficacy endpoints*: Clinical Global Impression of Change-TD (CGI-TD) scale score, Patient Global Impression of Change (PGIC) scale score • *Safety endpoints*: Barnes Akathisia Rating Scale, Simpson Angus Scale, Calgary Depression Scale for Schizophrenia (CDSS), Positive and Negative Syndrome Scale (PANSS), Young Mania Rating Scale, Columbia Suicide Severity Rating Scale, Montgomery-Asberg Depression Rating Scale and standard clinical chemistry, hematology, electrocardiogram, and urine drug screen assessments.
Results	• Significantly greater improvement in AIMS score from baseline with NBI-98854 versus placebo (95% CI -3.7, -1.1; p=0.0005) • Significantly more patients with “very much improved” or “much improved” CGI-TD responses with NBI-98854 versus placebo (p < 0.0001) • More patients experienced treatment emergent adverse events with NBI-988574 versus placebo (49.0% vs. 32.7%) with no clinically relevant impact on clinical laboratory values and no concerns related to other safety scales.
KINECT 3 Trial[2]	
Trial Design/ Population	Randomized, double-blind, placebo-controlled trial Patients age 18-85 with schizophrenia, schizoaffective disorder, or mood disorder with moderate-severe TD
Groups	Valbenazine 40 mg/day, valbenazine 80 mg/day, or placebo
Outcomes	• *Primary efficacy endpoint*: change in AIMS score from baseline at week 6 • *Secondary efficacy endpoint*: CGI-TD • *Safety endpoints*: adverse event monitoring, laboratory tests, ECG, and psychiatric measures [as described above]
Results	• Significantly greater improvement in AIMS score with valbenazine 80 mg/day versus placebo (p < 0.001)

[1] O’Brien C, Jimenez R, Hauser RA, et. al. NBI-98854, a selective monoamine transport inhibitor for the treatment of tardive dyskinesia: a randomized, double-blind, placebo-controlled study. *Mov Disord.* 2015;30(12):1681-1687. Doi: 10.1002.mds.26330.
[2] Hauser R, Factor SA, Marder SR, et. al. KINECT 3: a phase 3 randomized, double-blind, placebo-controlled trial of valbenazine for tardive dyskinesia. *Am J Psychiatry.* 2017;174(5):476-484. Doi: 10.1176/appi.ajp.2017.16091037.

	• No significant difference in CGI-TD between valbenazine 80 mg/day, valbenazine 40 mg/day, and placebo in the intent-to-treat population (p = 0.074) • Treatment-emergent adverse events were more common in the valbenazine 80 mg/day group than placebo (50.6% versus 43.4%). Serious events were also more common (7.6% versus 3.9%). The most common event was somnolence (5.1% in valbenazine 80 mg/day).

Conclusion: Ingrezza (valbenazine) is an effective and reasonably safe agent for the treatment of moderate-severe dopamine receptor blocker-induced tardive dyskinesia in patients with schizophrenia, schizoaffective disorder, or mood disorders who are medically and psychiatrically stable.

Ongoing Clinical Trials:

- NCT02736955 – Rollover Study for Continuing Valbenazine (NBI-98854) Administration for the Treatment of Tardive Dyskinesia
- NCT02879578 – Safety and Tolerability Study of NBI-98854 for the Treatment of Subjects with Tourette Syndrome
- NCT02581865 – Safety and Efficacy Study of NBI-9854 in Adults with Tourette Syndrome
- NCT02679079 – Safety and Efficacy Study of NBI-98854 in Children and Adolescents with Tourette Syndrome

Contraindications: None

Warnings/Precautions: Somnolence, QT prolongation

Drug Interactions:

- *Monoamine oxidase inhibitors (MAOIs)* – avoid concomitant use due to increased risk of adverse reactions
- *Strong CYP3A4 inhibitors* – reduce valbenazine dose when co-administered due to increased exposure to valbenazine and its active metabolite
- *Strong CYP2D6 inhibitors* – consider reducing valbenazine dose based on tolerability due to possible increased exposure to valbenazine's active metabolite
- *Strong CYP3A4 inducers* – avoid concomitant use due to decreased exposure to valbenazine and its active metabolite
- *Digoxin* – monitor digoxin concentrations due to potential for increased levels

Common Adverse Effects:

Adverse Reaction	% Observed with Valbenazine	Adverse Reaction	% Observed with Valbenazine
Somnolence	10.9%	Akathisia	2.7%
Anticholinergic effects	5.4%	Vomiting	2.6%
Balance disorders/fall	4.1%	Nausea	2.3%
Headache	3.4%	Arthralgia	2.3%

Adverse effects with an incidence ≥1% and greater than placebo: increased blood glucose, increased weight, respiratory infections, drooling, dyskinesia, extrapyramidal symptoms (non-akathisia), anxiety, insomnia, dose-related increase in prolactin, dose-related increase in alkaline phosphatase and bilirubin

Safety:

- *Sound Alike Look Alike:* None
- *REMs Program Requirement:* None
- *Known safety issues (ISMP safety alerts):* None
- *Pregnancy*: May cause fetal harm
- *Breastfeeding*: Present in breastmilk, avoid breastfeeding during therapy and for 5 days after discontinuation

Dosage/Administration:

- Initial dose: 40mg once daily with or without food for one week then increase
- Maintenance dose: After one week of initial dose, 80mg once daily with or without food
- Hepatic impairment (moderate or severe): 40mg once daily with or without food
- Renal impairment (CrCl 30-90 mL/min): No dose adjustment necessary; not recommended in CrCl <30 mL/min.

- CYP2D6 poor metabolizers: Consider dose reduction

Special Drug Monitoring: Monitor ECG for QT prolongation

Handling and Preparation: No special instructions.

Financial Impact:

- *Prevalence of tardive dyskinesia*
  - 13.1% in adult patients taking atypical antipsychotics
  - 32.4% in adult patients taking first-generation antipsychotics
- *Acquisition cost and annual budget impact (PMPM)*
  - Monthly cost: $12,660/utilizer
  - PMPM:
- *Manage-care costs*
  - Potential increased risk for exacerbation of mental health condition (e.g. schizophrenia)
- *Pharmacoeconomic data*
  - None published
  - In process: Institute for Clinical and Economic Review "Tardive Dyskinesia" [review scheduled to be released in December 2017]

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Pharmacy &Therapeutics Committee Summary Review
Kevzara® (Sarilumab) – Sanofi Genzyme

Prepared by: Karim Maharem, PharmD Candidate 2018

Presentation Date: January 4, 2018

Therapeutic Class[2]: Interleukin-6 receptor antagonist

FDA Approval Date[1]: May 22, 2017

FDA Indication[2]: Rheumatoid Arthritis

Comparable Formulary Products: Preferred: Tocilizumab (Actemra), Adalimumab (Humira), Etanercept (Enbrel); Non-preferred: Siltuximab (Sylvant)

Proposed Designation & Rationale[2]

Recommendation: Non-preferred, previously approved via e-vote on 8/30/2017
Approval Criteria:

- For initial authorization:
  - Member must be 18 years of age or older; AND
  - Must have a documented negative TB test (i.e. tuberculosis skin test (PPD), an interferon-release assay (IGRA), or a chest x-ray) within 6 months prior to starting therapy; AND
  - Medication must be prescribed by a rheumatologist; AND
  - Member has at least 8 tender and 6 swollen joints at baseline; AND
  - Member does not have ANC less than 2000/mm3, platelets less than 150,000/mm3 or liver transaminases above 1.5 times ULN; AND
  - Member must have tried and failed treatment with at least two non-biologic DMARDS (i.e. methotrexate, hydroxychloroquine, sulfasalazine (pregnancy category B), and leflunomide) or must have documented contraindication to all non-biologic DMARDS. Treatment trial duration with each non-biologic DMARD agent must have been at least 12 weeks; AND
  - Member has tried and failed treatment with Enbrel, Humira and Actemra.
  - Dosage allowed: 200 mg once every two weeks given as a subcutaneous injection.
  - Approval duration = 6 months
- For reauthorization:
  - Must have been retested for TB with a negative result within the past 12 months; AND
  - Member must be in compliance with all other initial criteria; AND
  - Chart notes have been provided that show the member has shown improvement of signs and symptoms of disease.
  - Reauthorization duration = 12 months

Clinical Implications/Place in Therapy[3]: Kevzara (sarilumab) belongs to a class of medications called IL-6 receptor antagonists. The efficacy and safety of Kevzara was evaluated in two randomized, double-blind, placebo-controlled trials in adults over 18 years old. Participants were treated with 200mg or 150mg every 2 weeks plus methotrexate/DMARD and achieved a low level of disease and higher response rates versus placebo plus methotrexate/DMARD- treated patients at week 24. Kevzara is appropriate if a patient is not controlled on other DMARDS or TNF-alpha inhibitors. It may be used as monotherapy or in combination with methotrexate or other DMARDS. The current rheumatoid arthritis guidelines have not been updated to include Kevzara. The American college of Rheumatology recommends DMARDS as first-line therapy for rheumatoid arthritis with methotrexate being the most commonly used agent. Biologics such as Kevzara are not recommended unless there is a failure of non-biologics DMARDS in moderate to severe rheumatoid arthritis. Current policies include preferred agents such as Enbrel, Actemra, and Humira which have been on the market for several years. In addition, there are no trials comparing Kevzara to Enbrel, Humira, and Actemra.

Clinical Pharmacology: Sarilumab, an IL-6 receptor antagonist and its inhibition leads to a reduction in CRP levels. It is a human recombinant monoclonal antibody which binds to soluble and membrane-bound IL-6 receptors. This inhibition decreases production of IL-6 in joints causing less inflammatory process. Moreover, inhibition of IL-6 leads to less inflammation in synovial and endothelial cells.[2]

Notable Pharmacokinetics:

Absorption:

- Median Tmax:2-4 days
- At steady state, exposure over the dosing interval measured by AUC increased 2-fold with an increase in dose from 150 to 200mg every two weeks. Steady states was reached in 14-16 weeks with a 2-3 fold accumulation in comparison to single dose exposure

Distribution:

- Vdss- 7.3L
- Half-life: concentration-dependent
  200mg once every 2 weeks-10 days 150mg once every 2 weeks-8 days

Metabolism:

- Degradation into small peptides and amino acids via catabolic pathways but no information about metabolism has been identified.

Excretion:

- At high concentrations, elimination is mostly through linear, non-saturable proteolytic pathway. At lower concentrations, elimination is mostly through non-linear saturable target-mediated pathway.

Efficacy[6,7,8]:

Trial Design/ Population	Groups	Outcomes	Results
Mobility Part A Clinical Trial: Phase-2 randomized double-blind placebo-controlled multi-center trial Objective: To validate that combining Sarilumab with methotrexate and once weekly or once every 2 weeks decreases the signs and symptoms of rheumatoid arthritis at week 12 and 24 weeks *Physical function and disability and radiographic responses were evaluated in the study.	Population: Adults with a diagnosis of rheumatoid arthritis > 3 months duration, have active disease defined as at least 8/68 tender joints and 6/66 swollen joints, high sensitivity CPR >6mg/l, and continuous treatment with MTX for at least 12 weeks prior to baseline visit and on stable dose for at least 6 weeks prior to screening visit. Groups: 306 patients were randomized to receive placebo or 5 different regimens of subcutaneous Sarilumab plus methotrexate: 100 mg weekly, 150 mg weekly, 100 mg every 2 weeks, 150 mg every 2 weeks, or 200 mg every 2 weeks.	Primary outcome: patients achieving American College of Rheumatology (ACR) as more than 20% improvement in tender joint count and swollen joint count and >20% improvement in at least 3 of 5 following: C-Reactive Protein (CRP), Participant assessment of pain; Participant's global assessment of disease activity; Physician global assessment of disease activity; Health Assessment Question-Disability Index (HAQ-DI). Missing data imputed by Last Observation Carried Forward (LOCF). Also, percentage of patients reaching ACR20 response in 24 weeks was also assessed and change from baseline in HAQ-DI at week 16.	72% of patients who received sarilumab 150 mg once weekly achieved an ACR20 response compared with 46.2% of patients who received placebo (multiplicity adjusted *P* = .0203) at week 12. Furthermore, 67% of patients who received Sarilumab 150 mg every 2 weeks achieved ACR20 (unadjusted *P* = .0363), and 65% of patients who received Sarilumab 200 mg every 2 weeks achieved ACR20 (unadjusted *P* = .0426) compared with patients who received placebo. 43% to 72% of patients on Sarilumab experienced adverse events vs. only 47% with placebo.

Mobility part B Clinical Trial: Phase 3 Objective: To show that Sarilumab in addition to MTX was effective in reducing the signs and symptoms of rheumatoid arthritis at 24 weeks, stopping the progression of structural damage at 52 weeks, and improving the physical function at 16 weeks. Secondary objectives: To show that Sarilumab added to MTX was effective in causing a clinical response at 52 weeks and to evaluate the safety of Sarilumab when added to MTX.	Population: same as from Part A trial Groups: 2 cohorts- cohort 1 (N = 172) included patients from the dose-finding, MOBILITY Part A study who were randomized to receive placebo or 1 of 5 subcutaneous doses of sarilumab, and cohort 2 (N = 1197) included patients who were randomized in a 1:1:1 ratio to receive placebo, sarilumab 150 mg every 2 weeks, or sarilumab 200 mg every 2 weeks, in combination with weekly methotrexate.	Part B: Percentage of Participants Achieving ACR20 Response at Week 24. Part B: Change From Baseline in Health Assessment Question Disability Index (HAQ-DI) at Week 16. Part B: Change From Baseline in Van Der Heijde Modified Total Sharp Score (mTSS) at Week 52.	Patients who received sarilumab 150 mg or 200 mg every 2 weeks achieved significant improvements in all 3 coprimary end points. The ACR20 response at week 24 for placebo plus MTX was only 33.4% whereas for sarilumab 150mg plus MTX was 58.0% and for sarilumab 200mg plus MTX was 66.4%. The mean change from baseline in HAQ-DI scores at week 16 was –0.53 with sarilumab 150 mg plus methotrexate and –0.55 with sarilumab 200 mg plus methotrexate versus –0.29 with placebo plus methotrexate (P <.0001). The mean change from baseline in mTSS at week 52 was 2.78 with placebo plus methotrexate (P <.0001). Moreover, it was 0.90 with sarilumab 150 mg plus methotrexate and 0.25 with sarilumab 200 mg plus methotrexate.
Phase 3 Target Clinical Trial: Objective: To show that sarilumab added to DMARDS are effective in reducing signs and symptoms at week 24 and improving physical function at week 12 in patients who didn't have an adequate response or were intolerant to 1 or more TNF-alpha antagonists. Secondary objectives: To examine the effects of sarilumab when added to DMARD therapy in selected RA patients for reducing signs and symptoms at week 12, improving in physical function at week 24, and improvement in ACR score at weeks 12 and 24.	Population: adults who had a diagnosis of RA >6 months duration, have an ACR class I-III functional status, had inadequate response to at least TNF-alpha inhibitors after being treated for at least 3 months, have moderate-severe active rheumatoid arthritis. Groups: Participants were randomized 1:1:1 (placebo q2w : sarilumab 150 mg q2w : sarilumab 200 mg q2w	Percentage of Participants who achieved at least 20% improvement in the ACR20 score at week 24 Change From Baseline in the Health Assessment Questionnaire-Disability Index (HAQ-DI) at Week 12.	The ACR20 response rate at week 24 was much higher with sarilumab 150 mg and sarilumab 200 mg every 2 weeks compared with placebo (55.8%, 60.9%, and 33.7%, respectively and P < 0.0001). The mean change from baseline in the HAQ DI score at week 12 was significantly greater for sarilumab (least squares mean change: for 150 mg, -0.46 [P = 0.0007]; for 200 mg, -0.47 [P = 0.0004]) versus placebo (-0.26).

Conclusion: The efficacy and safety of Kevzara were evaluated in two randomized, double-blind, placebo

Ongoing Clinical Trials:

- An open-label, ascending, repeated dose-finding study of sarilumab in children and adolescents with polyarticular-course juvenile idiopathic arthritis (pcJIA)
- A repeated dose-finding study of Sarilumab in children and adolescents with systemic juvenile idiopathic arthritis(sJIA).

Contraindications[1]:

- Hypersensitivity to sarilumab or any component of the formulation.

Warnings/Precautions[2]:

- GI Perforation when concomitant use of NSAIDS or corticosteroid therapy
- Neutropenia and thrombocytopenia can occur: Possible interruption of treatment, dose modification or discontinuation.
- Hepatotoxicity: Increase in AST/ALT: Monitor liver function tests before initiation and during treatment
- Hyperlipidemia: Increase in triglycerides, LDL, and HDL. Monitor lipids every 4-8 weeks after starting therapy, and then roughly every 6 months.
- Hypersensitivity reactions: Hypersensitivity reactions such as injection-site rash, rash, and urticaria have been reported.
- Infections: active tuberculosis, invasive fungal, bacterial, viral, and other opportunistic infections have been reported.
- Viral reactivation: Has been observed with biologics (zoster)

Drug Interactions[2]:

- CYP3A4 substrate drugs(oral contraceptives, lovastatin, atorvastatin)
- Tacrolimus: Tacrolimus increases the adverse/toxic effect of sarilumab
- Inactivated Vaccines: Sarilumab may diminish the effect of vaccines
- Live Vaccines: Immunosuppresants like Sarilumab may enhance the adverse/toxic effect of live vaccines
- Leflunomide: Sarilumab may increase adverse effects of Leflunomide
- Natalizumab: Sarilumab may increase adverse effects of Natalizumab
- Nivolumab: Sarilumab may increase adverse effects of Nivolumab

Common Adverse Effects[1,2]:

- Increased ALT and AST
- Injection-site pruritus
- Hypertriglyceridemia
- Neutropenia
- Antibody development
- Upper respiratory tract infection
- Nasopharyngitis

Safety[1,2,4,9]:

- Sarilumab may be confused with adalimumab, certolizumab pegol, golimumab, siltuximab, tocilizumab.

Dosage/Administration[1,2]:

- Sarilumab injection is supplied as a colorless to pale yellow solution in a single-dose pre-filled syringe.
- SubQ: 200 mg once every 2 weeks. It can be used as monotherapy or in combination with *nonbiologic* DMARDs.
- Do not use in combination with *biologic* DMARDs
- Renal impairment: CrCl 30 to 90 mL/minute: No dosage adjustment necessary.
  CrCl <30 mL/minute: There are no dosage adjustments provided in the manufacturer's labeling (has not been studied).
- Hepatic impairment prior to treatment initiation: There are no dosage adjustments provided in the manufacturer's labeling (has not been studied). Sarilumab is not recommended for use in patients with active hepatic disease or hepatic impairment.
  Hepatotoxicity during treatment:
  ALT >1 to ≤3 x ULN: Adjust concomitant DMARDs as appropriate.
  ALT >3 to ≤5 x ULN: Interrupt therapy; when ALT is <3 x ULN, resume at 150 mg once every 2 weeks (may increase to 200 mg once every 2 weeks as clinically appropriate).
  ALT >5 x ULN: Discontinue.

Special Drug Monitoring[2]:

- ALT/AST, neutrophils, and platelets prior to use, 4-8weeks after start of therapy, and every 3 months thereafter
- Lipid panel (4 to 8 weeks following initiation and every 6 months during therapy).
- Signs and symptoms of infection (prior to, during, and after therapy)
- Latent tuberculosis screening prior to therapy initiation

- Hypersensitivity reactions
- GI perforation

Handling and Preparation[2]:

- Refrigerate at 36F to 46F in original carton to protect from light. Do not freeze or shake.
- Sarilumab can be stored at room temperature up to 77F up to 14 days in outer carton.
- Must be used within 14 days after removal from the refrigerator.

Financial Impact[5,10,11]:

- Commonality of disease drug is used to treat
  - Onset between 30-50 years old
  - 3:1 women to men ratio
  - Annual incidence of rheumatoid arthritis is 40 per 100,000
- Acquistion cost:
  - ❖ Kevzara
    - AWP unit price: $1578.94
    - $37,894.56 per year
  - ❖ Enbrel
    - AWP unit Enbrel 25mg is $653.24 and Enbrel 50mg is $1332.60
    - 25 mg: $31,355.52 per year
    - 50 mg: $63,964.8 per year
  - ❖ Humira
    - AWP of Humira for 10mg/0.2ml, 20mg/0.4ml, and 40mg/0.8ml is $2664.74
    - $63,953.76 per year
  - ❖ Actemra
    - AWP unit price for Actemra single use vial is $119.32 and $1094.14 for prefilled syringe
    - $13,129.68 - $26,263.68 per year

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Pharmacy &Therapeutics Committee Summary Review
Radicava® (Edaravone) – MT Pharma America, Inc.

Prepared by: Natalie Lennartz

Presentation Date: January 4, 2018

Therapeutic Class: Free radical scavenger[1]

FDA Approval Date: May 5, 2017[2]

FDA Indication: Amyotrophic lateral sclerosis (ALS)[3]

Comparable Formulary Products: Rilutek® (Riluzole)[4]

Proposed Designation & Rationale

Recommendation: Non-preferred; Previously approved via e-vote on 11/1/2017

- Medical Benefit Only
- Criteria for use:
  - Provider detailed chart notes confirming member's definite or probable ALS based on El Escorial revised criteria
  - Member has disease duration of 2 years or less (documented in chart notes)
  - Member can eat a meal, excrete, or move with oneself alone, and does not need assistance in everyday life (documented in chart notes)
  - Member does not have Parkinson's disease, schizophrenia, dementia, renal failure, or hypersensitivity to Radicava (edaravone)
  - Member's %FVC ≥80% (documentation required)
  - Member's functionality retained most activities of daily living and defined as scores of 2 points or better on each individual item of the ALS Functional Rating Scale – Revised (ALSFRS-R), and submitted with chart notes (i.e., scores for speech, salivation, swallowing, handwriting, walking, etc.)
  - Dosage allowed: 60 mg administered as an intravenous infusion over 60 minutes as follows: initial treatment cycle: daily dosing for 14 days followed by a 14-day drug-free period; subsequent treatment cycles: daily dosing for 10 days out of 14-day periods, followed by 14-day drug-free periods.
  - Approval duration: 6 months
- Reauthorization
  - Member must be in compliance with all initial criteria
  - Chart notes have been provided that show the member has shown improving signs and symptoms of disease
  - Documented member's ALSFRS-R score improvement
  - Reauthorization approval duration: 6 months

Clinical Implications/Place in Therapy:
Based on the data presented, edaravone is an effective therapy for ALS in slowing the disease progression allowing for more days with higher functionality. Edaravone is one of two medications available for ALS and is often used in combination with riluzole, as they have two different mechanisms of action. One of the pivotal phase III trials of Radicava found no statistically significant difference in delay of ALS progression, but a post-hoc analysis found that a certain subset of patients may benefit. Based on the post-hoc analysis, the second phase III was performed with a much more strict eligibility criteria and found a statistically significant difference in ALS progression in favor of Radicava.

*El Escorial revised criteria: signs of lower motor neuron (LMN) degeneration by clinical, electrophysiological or neuropathologic examination; signs of upper motor neuron (UMN) degeneration by clinical examination; and progressive spread of signs within a region or to other regions, together with the absence of electrophysiological evidence of other disease processes that might explain the signs of LMN and/or UMN degeneration and neuroimaging evidence of other disease processes that might explain the observed clinical and electrophysiological signs[5]

Clinical Pharmacology: exact mechanism unknown[1,3]

- Proposed mechanism[3]
  - Free radical and peroxynitrite scavenger
  - Prevents oxidative damage to cell membranes
  - Inhibits progression of ALS

Notable Pharmacokinetics[3]:

- *Absorption:*
  - Maximum plasma concentration (Cmax) is reached by the end of infusion

- *Distribution:*
  - Binds to serum proteins, mainly albumin, with no concentration dependence between 0.1-50 micromol/L.
- *Metabolism:*
  - Metabolized to a sulfate conjugate and a glucuronide conjugate, which are inactive metabolites
  - In human plasma, is mainly detected as the sulfate conjugate, which is thought to be formed by sulfotransferases
  - Glucuronide conjugation involves many iridine diphosphate glucuronosyltransferase (UGT) isoforms including UGT1A6, UGT1A9, UGT2B7, and UGT2B17 in the liver and kidney
- *Elimination:*
  - Mean terminal half-life is 4.5-6 hours
  - Metabolite half-lives are 2-2.8 hours
  - 70-90% of the dose is excreted in the urine as its glucuronide conjugate, 5-10% of the dose is excreted in the urine as the sulfate conjugate, and 1% or less of the dose is excreted in the urine as the unchanged form

Efficacy: *Lancet Neurol.* 2017:16:505-12[7].

Trial Design/Population	- Phase III, randomized, double-blind, placebo-controlled study - Inclusion criteria: age 20-75 years; ALS of grade 1 or 2 in the Japan ALS Severity Classification; scores of 2 or more on all 12 items of ALS Functional Rating Scale (ALSFRS-R); forced vital capacity of 80% or more; definite or probable ALS according to the revised El Escorial criteria; disease duration of 2 years or less; decrease in the ALSFRS-R score of at least 1-4 points during the 12 week observation process before randomization
Groups	137 completed observation period and randomly assigned - 69 assigned to edaravone 60 mg - 68 assigned to placebo
Outcomes	Primary - Change in ALSFRS-R score from baseline to end of cycle 6 or at discontinuation Secondary - Change in forced vital capacity (FVC), Modified Norris Scale scores, ALS Assessment Questionnaire (ALSA Q-40) score, and grip and pinch strength - Time to death or time to a specified state of disease progression occurring during the 6 cycles Safety - Edaravone group: two of 69 patients in the treatment group had adverse drug reactions (three events: abdominal discomfort, eczema, and abnormal liver function test) - Placebo group: five of 68 patients in the placebo group had adverse drug reactions (seven events: dizziness, constipation, rash, chondrocalcinosis pyrophosphate, increased blood bilirubin, increased blood creatine phosphokinase, and abnormal liver function test)
Results	Mean ALSFRS-R scores - Edaravone least-squares mean change: -5.01 - Placebo least-squares mean change: -7.50 - Least-squares mean difference: 2.49 - P-value: 0.0013 Modified Norris Scale scores (total) - Edaravone least-squares mean change: -15.91 - Placebo least-squares mean change: -20.80 - Least-squares mean difference: 4.89 - P-value: 0.0393 ALSA Q-40 showing deterioration of quality of life - Edaravone least-squares mean change: 17.25 - Placebo least-squares mean change: 26.04 - Least-squares mean difference: -8.79 - P-value: 0.0309 FVC - No difference (p-value = 0.0942) Modified Norris Scale scores (limb and bulbar) - No difference (p-value = 0.0757, 0.1092, respectively) Grip and pinch strength - No difference (p-value = 0.8583, 0.5478, respectively) Safety - No significant differences in safety outcomes
Conclusion	- Findings support that edaravone 60 mg resulted in significantly:

	o Less progression in mean ALSFRS-R score o Less progression in total Modified Norris Scale o Less progression in deterioration of life using the ALSA Q-40 - Edaravone is considered a promising new treatment of slowing the progression of ALS in patients of the early stages of definite or probable ALS

Ongoing Clinical Trials[8]:

Completed, no results available: Expanded Controlled Study of Safety and Efficacy of MCI-186 in Patients With Amyotrophic Lateral Sclerosis (ALS)

Completed, limited results available: Efficacy and Safety Study of MCI-186 for Treatment of Amyotrophic Lateral Sclerosis (ALS)

Completed, no results available: Efficacy and Safety Study of MCI-186 for Treatment of Amyotrophic Lateral Sclerosis (ALS) Who Met Severity Classification III.

Completed, no results available: Phase 3 Study of MCI-186 for Treatment of Amyotrophic Lateral Sclerosis

Active, not yet recruiting: Treatment Effect of Edaravone in Patients With Amyotrophic Lateral Sclerosis (ALS)

Contraindications[3]:

- Patients with a history of hypersensitivity to edaravone or any of the inactive ingredients of the product

Warnings/Precautions[2]:

- *Hypersensitivity Reactions:*
  - Hypersensitivity reactions including redness, wheals, and erythema multiforme have been reported
  - Cases of anaphylaxis including urticarial, decreased blood pressure, and dyspnea have been reported
  - Patients should be monitored for hypersensitivity reactions and discontinued upon development of reaction
- *Sulfite Allergic Reactions:*
  - Edaravone contains sodium bisulfite, which may cause allergic type reactions, including anaphylactic symptoms and asthmatic episodes that could be life-threatening
  - Sulfite sensitivity occurs more frequently in asthmatic patients

Drug Interactions[3]:

- Not expected to be affected by inhibitors of CYP enzymes, UGTs, or major transporters
- At clinical doses, edaravone and its metabolites did not significantly inhibit cytochrome P450 enzymes, UGT1A1, UGT2B7, or transporters *in vitro.*

Common Adverse Effects[3]: Adverse effects that occurred in ≥2% of edaravone-treated patients occurred ≥2% more frequently than in placebo patients

- Most common (≥10%):
  - Contusion (15%)
  - Gait disturbance (13%)
  - Headache (10%)
- Common (≥2%):
  - Dermatitis (8%)
  - Eczema (7%)
  - Respiratory failure, respiratory disorder, hypoxia (6%)
  - Glycosuria (4%)
  - Tinea infection (4%)
- Less Common (<2%):
  - Anaphylaxis
  - Hypersensitivity reaction

Safety:

- No major safety issues identified by ISMP[8-9]
- No REMS requirement[10]

Dosage/Administration[3]:

- Recommended adult dose is 60 mg as an intravenous infusion over 60 minutes

- Initial treatment cycle: daily dosing for 14 days followed by 14 days of no drug therapy
- Subsequent treatment cycles: daily dosing for 10 days out of 14 days followed by 14 days of no drug therapy

Special Drug Monitoring[3]:

- Monitor for hypersensitivity reactions

Handling and Preparation[3]:

- Supplied as a 30 mg/100 mL clear, colorless, sterile solution in a single-dose bag or 2 bags per carton[2]
- Administer two consecutive bags for a total of 60 mg/200 mL over 60 minutes for an infusion rate of 1 mg/min or 3.33 mL/min
- Packaging contains an oxygen absorber and oxygen indicator, which should be pink to ensure appropriate oxygen levels
  - Do not use Radicava® if oxygen indicator has turned blue/purple before opening
- Use Radicava® within 24 hours of opening overwrap package
- Intravenous solution should be visually inspected for particulate matter or discoloration prior to use
- Should be stored at up to 25°C (77°F) with excursions permitted from 15 to 30°C (59 to 86°F)
- Protect from light

Financial Impact:

- *Commonality of disease drug is used to treat*[5]*:*
  - ALS effects 2 of 100,000 people and approximately 6,000 people in the U.S. are diagnosed each year
  - Patients with ALS are expected to live two to five years from the time of diagnosis, with some patients living more than 5 years
  - ALS can affect any race or gender, while military veterans are twice as likely to develop ALS
- *Cost of illness*[11]:
  - Estimated to be $63,692 annually
  - Medical costs alone are estimated to be $31,121 annually

The following details the breakdown of direct monthly and yearly drug costs for potential therapies for ALS:

Drug	Radicava® (edaravone)[13]	Riluzole (generic of Rilutek®)[14]
AWP	Cycle 1 (28 days): $36,489.60 Ongoing cycles (28 days each): $26,064.00	$1,961.82 (30 day supply)
Maintenance cost	$349,257.60/yr	$23,868.81/yr

Place in Therapy:

- Edaravone is one of two drugs available to slow the progression of ALS
- Edaravone has mostly been studied in patients who are also taking riluzole concomitantly
- Riluzole acts to counter elevated levels of glutamate in the brain, while edaravone is believed to reduce free radicals in the brain
  - Together, target two pathways that may slow the progression of ALS

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Pharmacy &Therapeutics Committee Summary Review
Rydapt (midostaurin) – Novartis

Prepared by: CVS Health / Irina Yaroshenko

Presentation Date: 1/14/18

Therapeutic Class: Tyrosine kinase inhibitor

FDA Approval Date: 04/28/17

FDA Indication: Indicated for the treatment of adult patients with newly diagnosed acute myeloid leukemia (AML) that is FLT3 mutationpositive as detected by an FDA-approved test, in combination with standard cytarabine and daunorubicin induction and cytarabine consolidation. Also, indicated for treatment of aggressive systemic mastocytosis (ASM), systemic mastocytosis with associated hematological neoplasm (SM-AHN), or mast cell leukemia (MCL).

Comparable Products: None

Proposed Designation & Rationale

Recommendation: Non-Preferred, approved via e-vote on 08/30/17

- Criteria for use / Approval duration: See policy for criteria for use and approval durations.
  - For reference, Ohio Medicaid version of policy can be found at: Rydapt.
  - All other state specific policies can be found under Pharmacy Policies by clicking on the appropriate state.

Clinical Implications/ Place in Therapy:
The first agent to treat members with FLT3 mutation-positive AML in combination with standard chemotherapy and the first to treat Aggressive Systemic Mastocytosis (ASM), Systemic Mastocytosis With Associated Hematological Neoplasm (SM-AHN), and Mast Cell Leukemia (MCL). Criteria were written based on package insert of the drug and three studies listed in it. Drug considered safe and effective for targeted indications and would improve clinical outcomes by extending overall survival and event free survival.

Ongoing Clinical Trials:

- There are 15 clinical trials (recruiting; enrolling by invitation; active, not recruiting): https://clinicaltrials.gov/ct2/results?cond=&term=midostaurin&cntry1=&state1=&Search=Search&recrs=a&recrs=d&recrs=f

References:

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CVSHealth

CVS Caremark Pharmacy & Therapeutics Drug Monograph

Rydapt® (midostaurin) capsules
Novartis Pharmaceuticals Corporation

INDICATION

Rydapt (midostaurin) is indicated for the treatment of adult patients with newly diagnosed acute myeloid leukemia (AML) that is *FLT3* mutation-positive in combination with standard cytarabine and daunorubicin induction and cytarabine consolidation (Rydapt prescribing information, 2017). Rydapt (midostaurin) is not indicated as a single-agent induction therapy for the treatment of patients with AML.

Rydapt (midostaurin) is also indicated to treat aggressive systemic mastocytosis (ASM), systemic mastocytosis with associated hematological neoplasm (SM-AHN), or mast cell leukemia (MCL) (Rydapt prescribing information, 2017).

U.S. FOOD AND DRUG ADMINISTRATION (FDA)-REVIEW DESIGNATION

Rydapt (midostaurin) was approved by the FDA on April 28, 2017 with a review designation of 1P and was granted fast track designation for the mastocytosis indication and breakthrough therapy designation for the AML indication (FDA, 2017a; FDA, 2017b). An agent may qualify as a 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 endpoints compared with available therapies (FDA, 2017c).

DRUG SUMMARY

Rydapt (midostaurin)	
Place in Therapy	• Rydapt is the first FDA-approved targeted therapy to treat adult patients with *FLT3*+ AML and was also approved to treat SM, SM-AHN, and MCL. • NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) recommends standard induction with cytarabine plus an anthracycline (daunorubicin or idarubicin) and 3-4 cycles of HiDAC for consolidation in patients with AML < 60 years of age and when clinical trials are not practical. For patients > 60 years of age, choice of therapy depends on tolerability, and the NCCN Guidelines® recommends enrollment in a clinical trial or therapy with standard cytarabine plus an anthracycline for induction and consolidation if complete response is achieved in the induction phase. • The American Society of Hematology recommends interferon-α or cladribine for the treatment of slow progressing ASM. In patients with rapid progression of ASM or MCL, cladribine with or without polychemotherapy or HCT are recommended to obtain stable remission if possible. Gleevec (imatinib) is also indicated for adult patients with ASM without any *KIT* D816V mutation or with KIT mutation status unknown.
Efficacy	• FDA approval of Rydapt for newly diagnosed *FLT3*+ AML was based on a randomized, double-blind, placebo-controlled, phase III trial (N = 717) demonstrating the addition of Rydapt to standard chemotherapy for induction and consolidation followed by up to one year of maintenance therapy significantly improved event free and overall survival in newly diagnosed adult patients with *FLT3*+ AML. • FDA approval of Rydapt for ASM, SM-AHN, and MCL was based on two phase II trials (N = 112; N = 26) which demonstrated and observed response and patient tolerability to Rydapt in patients with ASM, SM-AHN, or MCL, including patients with *KIT* D816V mutation.
Safety	• Warnings and precautions: embryo-fetal toxicity and pulmonary toxicity • Common adverse events (≥ 20%) in patients with AML: febrile neutropenia, nausea, mucositis, vomiting, headache, petechiae, musculoskeletal pain, epistaxis, device-related infection, hyperglycemia, and upper respiratory tract infections. • Common adverse events (≥ 20%) in patients with ASM, SM-AHN, or MCL: nausea, vomiting, diarrhea, edema, musculoskeletal pain, abdominal pain, fatigue, upper respiratory tract infections, constipation, pyrexia, headache, and dyspnea.

AML = acute myeloid leukemia
ASM = aggressive systemic mastocytosis
FDA = Food and Drug Administration
HCT = hematopoietic stem cell transplant
HiDAC = high dose cytarabine
MCL = mast cell leukemia
SM = systemic mastocytosis
SM-AHN = systemic mastocytosis with associated hematologic neoplasm

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CLINICAL PHARMACOLOGY

Mechanism of Action

Midostaurin is an inhibitor of multiple receptor tyrosine kinases (Rydapt prescribing information, 2017). Midostaurin or its major metabolites inhibit the activity of wild type *FLT3*, internal tandem duplication (ITD) and tyrosine kinase domain (TKD) *FLT3* mutant kinases, *KIT* (wild type and D816V mutant), *PDGFR*α/β, *VEGFR2*, and members of the serine/threonine kinase protein kinase C (PKC) family.

Midostaurin also inhibits *FLT3* receptor signaling and cell proliferation, and it can induce apoptosis in leukemic cells expressing ITD and TKD mutant *FLT3* receptors or over expressing wild type *FLT3* and *PDGF* receptors (Rydapt prescribing information, 2017). In addition, midostaurin demonstrated the capability to inhibit *KIT* signaling, cell proliferation, and histamine release and induce apoptosis in mast cells.

Pharmacokinetics

Table 1: Selected Pharmacokinetics of Midostaurin

Route of Administration	T_{max}	Volume of Distribution	Protein Binding	Metabolism	Route of Elimination	$T_{1/2}$
oral	1 to 3 hours*	95.2 L	> 99.8%	Primarily via CYP3A4	95% via fecal route; 5% via renal route	21 hours

* Delayed to 2.5 to 3 hours when midostaurin is administered with a standard or high-fat meal
CYP = cytochrome P450 isoenzyme
$T_{1/2}$ = elimination half-life
T_{max} = time to maximum plasma concentration

(Rydapt prescribing information, 2017)

Pharmacogenomics

No pharmacogenomics data are available at this time for midostaurin.

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CLINICAL EFFICACY

Table 2: Efficacy of Rydapt (midostaurin) in Combination with Daunorubicin and Cytarabine in Newly Diagnosed *FLT3*+ AML Patients

Study, Treatments, and Groups	Study Design and Endpoints	Study Criteria	Results
Stone, 2015 Evidence Level Ib **Rydapt*** 50 mg orally twice daily with food (n = 360) vs. **Placebo*** orally twice daily with food (n = 357)	N = 717 **Study Design:** Phase III, randomized, double-blind, placebo-controlled trial **Objective:** To analyze the efficacy of adding Rydapt to induction and consolidation therapy followed by one year of maintenance therapy in comparison to standard chemotherapy in younger adult patients with newly-diagnosed *FLT3*-mutated AML **Primary Endpoint:** OS **Secondary Endpoints:** • EFS† • CR rate	**Inclusion Criteria:** • Patients 18 to 60 years of age newly diagnosed with AML (median age of 47 years; 44% male) • *FLT3* mutated AML status: TKD, ITD with allelic ratio < 0.7, or ITD with allelic ratio > 7.0 **Exclusion Criteria:** • Concurrent promyelocytic leukemia or therapy-related AML	See below

Endpoint	Rydapt (n = 360)	Placebo (n = 357)	Hazard Ratio	p-value
Median OS months (95% CI)	74.7 (31.5 to not estimable)	26.0 (18.5 to 46.5)	0.77 (0.63 to 0.95)	0.007
Median EFS months (95% CI)	8.0 (5.3 to 10.6)	3.0 (1.9 to 5.8)	0.80 (0.67 to 0.95)	0.0044
CR Rate	59%	54%	Not reported	0.18

- 402 out of 717 patients received allogeneic SCT (58% in the Rydapt treatment arm and 54% in the placebo group).
- Median time to allogeneic SCT was 5 months in the Rydapt group and 4.6 months in the placebo group (p = 0.23).
- Median follow-up was 57 months for surviving patients.
- Hazard ratios were similar for OS and EFS after censoring patients who received SCT

Safety

- There were no statistically significant differences in overall rate of grade 3 or higher hematologic or non-hematologic adverse events between Rydapt and placebo groups.
- A total of 37 grade 5 adverse events were reported with no statistical difference in treatment-related grade 5 adverse events observed between patients receiving Rydapt and those receiving placebo (p = 0.82).

Comments/Study Limitations: The trial is not yet published, therefore information is limited.

Conclusions: Overall, the trial demonstrated that the addition of Rydapt to standard chemotherapy for induction and consolidation followed by up to one year of maintenance therapy significantly improved EFS and OS in newly diagnosed patients with *FLT3*+ AML.

* Administered on days 8 to 21 for induction and consolidation in combination with standard chemotherapy for induction and consolidation: daunorubicin 60 mg/m² intravenous days 1 to 3 and cytarabine 200 mg/m² intravenous days 1 to 7 for up to two cycles of induction and up to four cycles of consolidation with cytarabine 3 g/m² over 3 hours every 12 hours on days 1, 3, and 5 followed by continuous Rydapt or placebo maintenance for up to 12 additional 28-day cycles

† Defined as a failure to obtain a complete remission within 60 days of initiation of protocol therapy, or relapse, or death from any cause

AML = acute myeloid leukemia
CI = confidence interval
CR = complete remission
EFS = event free survival
ITD = internal tandem duplication
OS = overall survival
SCT = stem cell transplant
TKD = tyrosine kinase domain

(Rydapt prescribing information, 2017; Stone, 2015)

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Data as of June 16, 2017
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Table 3: Efficacy of Rydapt (midostaurin) in the Treatment of Advanced Systemic Mastocytosis

Study	Gotlib, 2016 Evidence level IIa (N = 116)		Gotlib, 2010 Evidence level IIa (N = 26)	
Study Design	Multicenter, single-group, open-label, phase II trial			
Treatment	Rydapt 100 mg orally twice daily continuously until disease progression or intolerable toxicity			
Inclusion Criteria	Age ≥ 18 years with advanced SM, including ASM, SM-AHN, or MCL, according to WHO Criteria for mastocytosis staging • Median age of 64 years in the primary efficacy population (64% male; 97% Caucasian) • ECOG score of 0-3, Patients with ≥ 1 measurable C-finding related to mastocytosis were included in primary efficacy population		• Median age of 62 years (58% male; 81% Caucasian) • Specific criteria are not described but are similar to the trial by Gotlib, 2016 according to the prescribing information	
Exclusion Criteria	Three or more previous treatments for mastocytosis, cardiac ejection fraction < 50%, serum creatinine > 2.0 mg/dL, hepatic transaminases > 1.5 x ULN or > 5 x ULN if disease related, total bilirubin > 1.5 x ULN or > 3 x ULN if disease related, QTc > 450 msec, or any pulmonary infiltrates		None reported	
Treatment	**Rydapt (N = 89)**	**95% CI (p-value)**	**Treatment**	**Rydapt (N = 26)**
Results ORR	60%	49% to 70% (< 0.001*)	**Results** ORR	69%
Results MR rate	45%	Not reported	**Results** MR rate	38%
Results PR rate	15%	Not reported	**Results** PR rate	31%
Results Median OS	28.7 months	18.1 months to not estimated	**Results** GPR rate	19%
Results Median PFS	14.1 months	10.2 months to 24.8 months	**Results** MPR rate	12%
Efficacy Comments	• ORR in the ITT population was 46% (53 out of 116) with a median duration of treatment of 11.4 months (range: 0.3 to 51.5) • Median DOR was 24.1 months (95% CI 10.8 to not estimated) among 53 patients who had a response • *KIT* D816 mutation present in 98 (84%) out of 116 patients • ORR in the *KIT* D816V mutation positive population was 63% and 44% in the patient population without the mutation • Response rate was 75% in ASM, 58% in SM-AHN, and 50% in MCL		• Rydapt was administered for a median of 19.5 cycles (1.5 years) for MR patients and 15 cycles (1.2 years) for patients with PR • Of 17 patients with SM-AHN, 10 patients achieved a response (9 MR and 1 PR) • Of 6 patients with MCL, 1 patient achieved a MR and 1 patient achieved a PR • Subtype of advanced SM was unconfirmed in 3 patients • *KIT* D816V mutation present in 69% of patients	
Safety	The most common adverse events were nausea, vomiting, and diarrhea Most common grade 3 or 4 nonhematologic adverse events were fatigue and diarrhea		Grade 3 hematologic toxicities included worsening of pre-existing anemia and thrombocytopenia	
Comments	The study was single-arm with a small sample size. Out of the 116 patients, the efficacy data were based on the primary efficacy population (89 patients who had mastocytosis related organ damage). The ITT analysis included all 116 patients. Eighty-four (72%) out of 116 patients discontinued treatment, mostly due to disease progression. The study was funded by the manufacturer.		At the time of study cutoff, Rydapt was discontinued in 18 patients (69%). The trial is not published, and data are limited and extracted from the abstract and PI. Data were not analyzed for statistical significance.	
Conclusions	Rydapt demonstrated durable response and tolerability in patients with advanced SM regardless of *KIT* D816V mutation status, or exposure to previous therapy.			

* Based on a pre-specified 30% threshold for rejection of the null hypothesis. The null hypothesis was the overall response rate among enrolled patients would be no more than 30%.

ASM = aggressive systemic mastocytosis
C-finding = clinical findings that are related to organ damage from infiltrating mast cells
CI = confidence interval
DOR = duration of response
ECOG = Eastern Cooperative Oncology Group
GPR = good partial response; Defined as > 50% improvement in ≥ 1 C-finding
ITT = intent to treat
MCL = mast cell leukemia
MPR = minor partial response; Defined as > 20% to ≤ 50% improvement in ≥ 1 C-finding
MR = major response; Defined as complete resolution of ≥ 1 C-finding
ORR = overall response rate; includes MR and PR
OS = overall survival
PFS = progression-free survival
PR = partial response; includes GPR and MPR
SM = systemic mastocytosis
SM-AHN = systemic mastocytosis with associated hematologic neoplasm
ULN = upper limit of normal
WHO = World Health Organization

(Gotlib, 2016; Gotlib 2010; Rydapt prescribing information, 2017)

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SAFETY

Contraindications

Use of Rydapt (midostaurin) is contraindicated in patients with hypersensitivity to midostaurin or any of the excipients (Rydapt prescribing information, 2017).

Warnings and Precautions

Embryo-Fetal Toxicity

Based on its mechanism of action, Rydapt (midostaurin) may cause fetal harm when administered to pregnant women (Rydapt prescribing information, 2017). There are no data available on Rydapt (midostaurin) use in pregnant women to inform a drug-associated risk of major birth defects and miscarriage and pregnant women should be advised of the potential risk to a fetus. It should be noted that Rydapt (midostaurin) administration in animal studies resulted in embryo-fetal toxicities, including reduced fetal birth weight and embryo-fetal death. Due to the potential risk of embryo-fetal harm, pregnancy testing is recommended within seven days prior to initiating Rydapt (midostaurin) in females of reproductive potential. Female of reproductive potential should use effective contraception during treatment with Rydapt (midostaurin) and for four months after the last dose. Males with female sexual partners of reproductive potential should use effective contraception during Rydapt (midostaurin) therapy and for at least four months after stopping Rydapt (midostaurin) treatment. Rydapt (midostaurin) may impair fertility in males and females of reproductive potential, and it is not known if these effects on fertility are reversible.

Pulmonary Toxicity

Interstitial lung disease and fatal pneumonitis have occurred in patients treated with Rydapt (midostaurin) (Rydapt prescribing information, 2017). Patients should be monitored for pulmonary symptoms and Rydapt (midostaurin) should be discontinued in patients who present with signs or symptoms of interstitial lung disease or pneumonitis without an infectious etiology.

Nursing Mothers

There are no data on the presence of midostaurin or its active metabolites in human milk, the effect on the breastfed infant, or the effect on milk production (Rydapt prescribing information, 2017). It has been found that orally administered midostaurin and its active metabolites pass into the milk of lactating rats with approximately five times more in the milk of lactating rats compared to plasma. Due to the risk of serious adverse reactions in breastfed infants from Rydapt (midostaurin), women should not breastfeed during treatment with Rydapt (midostaurin) and for at least 4 months after the last dose.

Pediatric Use

The safety and effectiveness of Rydapt (midostaurin) have not been established in pediatric patients (Rydapt prescribing information, 2017).

Geriatric Use

In clinical studies for systemic mastocytosis, 64 of 142 patients (45%) were 65 years of age or older and 16 (11%) were 75 years of age or older. No overall differences were observed between subjects aged 65 years and older with younger subjects (Rydapt prescribing information, 2017). Clinical studies for AML did not meet sufficient numbers of subjects aged 65 years and older to determine differences in response compared to younger subjects. It should be noted that administration of Rydapt (midostaurin) in the elderly should be exercised with caution based on the patient's eligibility for concomitant chemotherapy and reflecting the greater frequency of concomitant disease or other drug therapy.

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Drug Interactions

Table 4: Potential Drug Interactions with Midostaurin

Interacting Agent	Outcome	Recommendation
Strong CYP3A Inhibitors	May inhibit midostaurin metabolism and ↑ midostaurin plasma concentrations and risk of toxicity	• Consider alternative therapy that does not strongly inhibit CYP3A activity • Alternatively, may monitor patients for increased risk of adverse events with coadministration
Strong CYP3A Inducers	May induce midostaurin metabolism and ↓ midostaurin plasma concentrations and efficacy	• Avoid coadministration

CYP = cytochrome P450 isoenzyme

(Rydapt prescribing information, 2017)

Adverse Events

AML

A study of 345 patients with newly diagnosed *FLT3* mutated AML who received Rydapt (midostaurin) with chemotherapy for a median duration of 42 days (range: 2 days to 576 days) found Rydapt (midostaurin) was permanently discontinued in 9% of patients due to adverse events, including renal insufficiency (1%) (Rydapt prescribing information, 2017). Conversely, out of 335 patients from the same study treated with placebo and chemotherapy found that 6% of patients discontinued treatment due to adverse events with a median treatment duration of 34 days (range 1 day to 465 days). The most common adverse events occurring with Rydapt (midostaurin) are described in Table 5, while the most common laboratory abnormalities are shown in Table 6.

Table 5: Adverse Events for Rydapt (midostaurin) with an incidence ≥ 10% of Patients and ≥ 2% More Common than with Placebo in Patients with AML

Adverse Event	All Grades		Grades ≤ 3	
	Rydapt with chemotherapy (n = 229)	Placebo with chemotherapy (n = 226)	Rydapt with chemotherapy (n = 345)	Placebo with chemotherapy (n = 335)
Febrile neutropenia	83%	81%	84%	83%
Nausea	83%	70%	6%	10%
Mucositis	66%	62%	11%	13%
Vomiting	61%	53%	3%	5%
Petechiae	36%	27%	1%	1%
Musculoskeletal pain	33%	31%	5%	2%
Epistaxis	28%	24%	3%	1%
Device-related infection	24%	17%	16%	10%
Upper respiratory tract infection	20%	15%	4%	3%
Hyperglycemia	20%	17%	7%	6%
Hemorrhoids	15%	11%	1%	0%
Hyperhidrosis	17%	8%	0%	0%
Arthralgia	14%	8%	< 1%	< 1%
Activated partial thromboplastin time prolonged	13%	8%	3%	2%
Renal insufficiency	12%	9%	5%	3%
Insomnia	12%	8%	0%	< 1%

AML = acute myeloid leukemia

(Rydapt prescribing information, 2017)

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Table 6: New or Worsening Laboratory Abnormalities for Rydapt (midostaurin) with an Incidence ≥ 10% of Patients and ≥ 2% More Common than with Placebo in Patients with AML

Adverse Event	Rydapt 50 mg twice daily (n = 345)		Placebo (n = 335)	
	All Grades	Grade 3 or 4	All Grades	Grade 3-4
Hypocalcemia	74	7	70	8
Alanine aminotransferase ↑	71	20	69	16
Hypernatremia	21	1	15	2

AML = acute myeloid leukemia

(Rydapt prescribing information, 2017)

Advanced SM

An analysis of 142 patients with ASM, SM-AHN, or MCL who received Rydapt (midostaurin) for a median duration of 11.4 months (range: 0 months to 81 months) found Rydapt (midostaurin) was permanently discontinued in 21% of patients due to adverse events, including infection, nausea, vomiting, QT prolongation, and gastrointestinal hemorrhage (Rydapt prescribing information, 2017). Dose modifications occurred in 56% of patients due to adverse events, including gastrointestinal symptoms, QT prolongation, neutropenia, pyrexia, thrombocytopenia, gastrointestinal hemorrhage, lipase increase, and fatigue. The most common adverse events occurring with Rydapt (midostaurin) in treating SM, SM-AHN, and MCL are described in Table 7, while the most common laboratory abnormalities are shown in Table 8.

Table 7: Adverse Events for Rydapt (midostaurin) with an Incidence ≥ 10% of Patients and ≥ 2% More Common than with Placebo in Patients with Advanced SM

Adverse Event	Rydapt 100 mg twice daily (n = 142)	
	All Grades	Grade ≥ 3
Nausea	82%	6%
Vomiting	68%	6%
Diarrhea	54%	8%
Edema	40%	7%
Musculoskeletal pain	35%	4%
Abdominal pain	34%	6%
Fatigue	34%	9%
Upper respiratory tract infection	30%	1%
Constipation	29%	< 1%
Pyrexia	27%	4%
Headache	26%	1%
Dyspnea	23%	7%
Arthralgia	19%	2%
Urinary tract infection	16%	3%
Gastrointestinal hemorrhage	14%	9%
Rash	14%	3%
Dizziness	13%	0%
Pleural effusion	13%	4%
Epistaxis	12%	3%
QT Prolongation	11%	< 1%
Insomnia	11%	0%
Renal insufficiency	11%	5%
Herpesvirus infection	10%	1%
Pneumonia	10%	8%

SM = systemic mastocytosis

(Rydapt prescribing information, 2017)

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Table 8: New or Worsening Laboratory Abnormalities* for Rydapt (midostaurin) with an Incidence ≥ 10% of Patients and ≥ 2% More Common than with Placebo in Patients with SM

Adverse Event	Rydapt 100mg twice daily (n = 142)	
	All Grades	Grade ≥ 3
Hyperglycemia (non-fasting)	80%	18%
Lymphopenia	66%	42%
Leukopenia	61%	19%
Anemia	60%	38%
Thrombocytopenia	50%	27%
Neutropenia	49%	22%
Alkaline phosphatase (ALP) ↑	39%	9%
Hypocalcemia	39%	2%
Lipase increase	37%	18%
Hyperuricemia	37%	11%
Gamma-glutamyl transferase (GGT) ↑	35%	9%
Hyponatremia	34%	5%
Aspartate aminotransferase (AST) ↑	32%	3%
Alanine aminotransferase (ALT) ↑	31%	4%
Hyperbilirubinemia	29%	4%
Hypoalbuminemia	27%	1%
Hypokalemia	25%	6%
Creatinine increase	25%	< 1%
Hyperkalemia	23%	4%
Hypophosphatemia	22%	1%
Amylase increase	20%	7%
Hypomagnesemia	20%	0%

* Includes abnormalities occurring up to 28 days after last dose of midostaurin, if new or worsened from baseline or if baseline was unknown
SM = systemic mastocytosis

(Rydapt prescribing information, 2017)

PRODUCT AVAILABILITY

Rydapt (midostaurin) is supplied as 25 mg capsules in cartons containing 56 capsules or 112 capsules (Rydapt prescribing information, 2017). Capsules should be stored in original package to protect from moisture.

DOSAGE AND ADMINISTRATION

The recommended dosage of Rydapt (midostaurin) in *FLT3*-mutated AML is 50 mg orally twice daily with food on days 8 to 21 of each cycle of induction with cytarabine and daunorubicin and on days 8 to 21 of each cycle of consolidation with high-dose cytarabine (Rydapt prescribing information, 2017).

The recommended dose of Rydapt (midostaurin) in ASM, SM-AHN, and MCL is 100 mg orally twice daily with food (Rydapt prescribing information, 2017). Patients are to be monitored at least weekly for the first four weeks, every other week for the next 8 weeks, and monthly thereafter while on treatment. Dose modifications of Rydapt (midostaurin) are recommended based on adverse events.

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APPROACHES TO TREATMENT

AML

AML is the most common acute leukemia in adults with the highest incidence reported in the United States, Australia, and Western Europe (Deschler, 2006). The disease pathophysiology is characterized by the infiltration of bone marrow, blood, and other tissues by proliferative and abnormal hematopoietic cells (Dohner, 2015). It is estimated that there will be 21,380 new cases and 10,590 deaths due to AML in 2017 (National Cancer Institute [NCI], 2017). AML presents with a wide variety of non-specific symptoms that generally include weight loss, fatigue, night sweats, fevers or infections, bleeding and clotting problems, confusion, slurred speech, and swelling in the abdomen (American Cancer Society [ACS], 2016a). Despite strong initial response to induction therapy, the disease has a poor prognosis with cure rates of approximately 35% to 40% in adults aged 60 years or younger and only 5% to 15% in adults older than 60 years of age (Dohner, 2015).

Negative prognostic factors in AML include high white blood cell count at the time of diagnosis, previous history of blood disorders such as myelodysplastic syndrome, active blood infections, metastasis into the central nervous system, and poor response to treatment (ACS, 2016b). In addition, expression of the cluster of differentiation 34 (CD34) protein and/or the p-glycoprotein MDR1 gene product on the surface of leukemia cells generally results in worse outcomes. Other risk factors include older age (> 60 years), cigarette smoking, exposure to chemicals such as benzene, previous radiation treatment, and familial history with AML (ACS, 2016c). It has also been noted that previous chemotherapy treatment with alkylating agents, anthracyclines, topoisomerase-II inhibitors and taxanes can increase the risk of AML (Deschler, 2006). Gene mutations can improve or negatively affect prognosis. One in three patients with AML have the *FLT3* mutation, which is associated with poorer outcomes (ACS, 2016b). Conversely, patients with AML associated with changes in the *NPM1* gene and the *CEBPA* gene tend to have better outcomes. Lastly, chromosome abnormalities can also affect disease outlook as translocation, deletion, inversion and other changes of various chromosomes can have a positive or negative impact on disease prognosis.

AML has been classified by the World Health Organization (WHO) into several groups: AML with certain genetic abnormalities, AML with myelodysplasia-related changes, AML related to previous chemotherapy or radiation, AML not otherwise specified, myeloid sarcoma, myeloid proliferations related to Down syndrome, and undifferentiated and biphenotypic acute leukemias (ACS, 2016b). The WHO classification builds off of the older French-American-British (FAB) classification of AML while incorporating new discoveries in the genetics and clinical features of AML (ACS, 2016b; NCI, 2017).

Treatment

According to the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®), AML treatment can be divided into induction and consolidation therapy segments (National Comprehensive Cancer Network® [NCCN®], 2017). When enrollment into clinical trials is not feasible, the use of cytarabine with an anthracycline remains the standard induction regimen for initiating AML treatment in patients younger than 60 years of age. Standard-dose cytarabine combined with daunorubicin or idarubicin remains as a category 1 recommendation. Daunorubicin is the most common anthracycline of choice (Dohner, 2015). Other options include, cytarabine in conjunction with daunorubicin and cladribine, high-dose cytarabine (HiDAC) with an anthracycline, and idarubicin with fludarabine with subsequent fludarabine and cytarabine (NCCN, 2017).

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For consolidation therapy in patients with favorable cytogenetics (those with core binding factor AML, without *KIT* mutations) the NCCN Guidelines® recommend three to four cycles of HiDAC therapy if participation in a clinical trial is not practical. For intermediate-risk patients (those with normal karyotype AML without gross structural changes and those with structural changes that are neither poor-risk or favorable), allogeneic hematopoietic cell transplant (HCT) or three to four cycles of HiDAC are recommended to lower the risk of relapse. For patients with poor prognostic factors such as the presence of the *FLT3* mutation, the guidelines recommend enrollment into clinical trials or allogeneic HCT from a matched sibling or alternative donor. Hypomethylating agents such as decitabine with sorafenib (Nexavar) may be considered for patients with *FLT3*+ AML who have relapsed or refractory disease.

For patients older than 60 years of age and who are able to undergo intensive anthracycline and cytarabine remission induction, the NCCN Guidelines recommend enrollment into clinical trials, standard infusion cytarabine with an anthracycline, or lower-intensity therapy (e.g. low-dose cytarabine) (NCCN, 2017). Generally, patients who achieve CR (complete response) with standard induction chemotherapy can receive further consolidation with the same agents. Other options for consolidation can include intermediate-dose cytarabine, hypomethylating agents, or observation. Reduced intensity conditioning allogeneic HCT is also an additional option for patients experiencing CR to induction therapy and also for those who fail induction therapy with low-volume disease.

Rydapt (midostaurin) is the first targeted therapy in combination with chemotherapy that is FDA-approved for use in patients the AML (FDA, 2017b). The use of Rydapt (midostaurin) in the setting of AML has not yet been incorporated into the NCCN Guidelines.

Mastocytosis

Mastocytosis is a group of disorders characterized by abnormal clonal mast cell growth and expansion in at least one organ system (Georgin-Lavialle, 2013). According to WHO, there are seven categories of mastocytosis: cutaneous mastocytosis, indolent systemic mastocytosis (ISM), SM, ASM, SM-AHN , MCL, mast cell sarcoma, and extracutaneous mastocytoma. Mastocytosis is a rare disorder and the true incidence and prevalence rates of the disease remain unknown; however, recent population-based studies estimate that mastocytosis occurs in 1 case per 10,000 people (Theoharides, 2015). Worldwide prevalence of systemic mastocytosis is estimated to be 1 case per 20,000 to 40,000 people (Orphanet, 2017). MCL is the least common form of the disease, accounting for approximately less than 1% of all cases of mastocytosis (Georgin-Lavialle, 2013). Cutaneous mastocytosis most often occurs in children and is usually limited to the layers of the skin. This condition is generally resolved by puberty. Systemic forms of mastocytosis are characterized by mast cell infiltration of visceral organs. The bone marrow is affected in nearly all cases while other commonly affected tissues include the liver, gastrointestinal tract, and cortical bone (Valent, 2010; Theoharides, 2015). The *KIT* D816V mutation is detected in nearly all patients with ISM and approximately 80% of patients with SM (Theoharides, 2015). The *KIT* D8V16V mutation may be limited to only mast cells or may be present in other cells of hematologic lineage, in which case it is a risk factor for disease progression. Although rare, ISM has progressed to more aggressive forms of SM. Advanced SM is associated with poor outcomes, with a median overall survival of 3.5 years in patients with ASM, two years in patients with SM-AHN, and six months in patients with MCL.

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Symptoms of advanced SM are caused by the release of vasoactive mediators and by organ damage as a result of abnormal mast cell infiltration (Gotlib, 2016). Common symptoms include headache, diarrhea, flushing of the skin, fever, and tachycardia (Georgin-Lavialle, 2013). The diagnosis of SM is based on the presence of one major and one minor criterion or the presence of three minor criteria (Theoharides, 2015). The major criterion is the presence of multifocal and dense clusters of mast cells (> 15 mast cells per aggregate) identified by tryptase immunohistochemical analysis, KIT immunohistochemical analysis, or both in a non-cutaneous organ. Minor criteria include the presence of mast cells with atypical morphology, the presence of the *KIT* D816V mutation, expression of CD2 or CD25 on mast cells, and an increased basal serum tryptase level (≥ 20 ng/mL). Common C-findings related to organ damage from infiltrating mast cells include cytopenias, hypoalbuminemia, liver-function changes, weight loss, ascites, and bone lesions (Georgin-Lavialle, 2013). ASM is described by the presence of at least one clinical finding, while the discovery of at least 20% atypical mast cells in the bone marrow indicates a diagnosis of MCL (Gotlib, 2016). MCL usually presents with hepatosplenomegaly, anemia, and thrombocytopenia with an elevated serum tryptase level. It is recommended to consider a bone marrow biopsy in patients with skin lesions, unexplained hypotension, or syncope, especially when serum tryptase levels are significantly elevated to determine a diagnosis of SM (Theoharides, 2015).

Treatment

There are no therapy guidelines in place for the treatment of SM. According the American Society of Hematology, treatment of SM can be divided into two categories: (1) treatment to control MC mediator-related symptoms and (2) treatment to limit MC burden in aggressive forms and increase survival (Georgin-Lavialle, 2013). In treating ASM with slow progression, interferon-α (IFN- α) is recommended as first-line treatment (Valent, 2010). Prednisolone or other steroids are also administered at the onset of the disease to induce a reduction in MC burden and provide relief of disease associated symptoms including flushing, pain, ascites, and cytopenia (Georgin-Lavialle, 2013; Valent, 2010). The effect of steroids is usually temporary, and proton pump inhibitors are often added to control the risk of gastrointestinal bleeding from steroid use (Georgin-Lavialle, 2013). In patients who fail first-line therapy with IFN-α, cladribine or enrollment in clinical trials are second-line therapy options (Valent, 2010). In patients with rapid progression, more intensive therapy is required.

For the treatment of ASM with rapid progression and MCL, therapy with either IFN-α and cladribine are either short-lived or non-responsive (Valent, 2010). Nonetheless, cladribine is often administered in an attempt to obtain control over the disease and reduce MC burden and symptoms (Theoharides, 2015; Valent, 2010). Hematopoietic stem cell transplantation (SCT) has shown potential for inducing remission in patients with ASM and MCL but lacks the ability to completely eradicate the disease (Valent, 2010). Prior to attempting SCT, debulking should be performed with cladribine and polychemotherapy (regimens containing high-dose cytosine arabinoside and a nucleoside such as fludarabine) or repeated cycles of cladribine (Valent, 2010). If the patient is appropriately fit and responsive to treatment, SCT may be considered. If a patient relapses or fails cladribine and polychemotherapy, experimental drugs can be administered if available or palliative cytoreduction with hydroxyurea should be initiated. The treatment of MCL is similar to that of ASM with rapid progression. However, in the setting of MCL, cladribine should not be considered as monotherapy. It remains unknown if patients with MCL may benefit from the combination of polychemotherapy and cladribine. Cytoreduction is recommended in the setting of ASM and MCL and may also be achieved through the use of imatinib (Theoharides, 2015). Gleevec (imatinib) has also obtained FDA-approval for the treatment of ASM lacking the *KIT* D816V mutation or with an unknown *KIT* mutational status in adult patients (Gleevec prescribing information, 2017). Sprycel (dasatinib) also has activity against mast cells expressing the *KIT* D816V mutation, however, clinical studies have failed to demonstrate the efficacy of Sprycel (dasatinib) in this setting (Georgin-Lavialle, 2013; Theoharides, 2015).

Rydapt (midostaurin) is the first and only FDA-approved drug therapy indicated for the treatment of multiple forms of advanced SM: ASM, SM-AHN, and MCL (Novartis, 2017)

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National Institute for Health and Care Excellence (NICE)

NICE currently only recognizes Vidaza (azacitidine) as first-line treatment for AML as a replacement of supportive care and low-dose and standard-dose chemotherapy (NICE, 2011). Vidaza (azacitidine) is recommended in AML with 20-30% blasts and multilineage dysplasia, according to WHO. Vidaza (azacitidine) is not recommended for AML treatment in patients with more than 30% bone marrow blasts who are older than 65 years of age and are not eligible for hematopoietic SCT (NICE, 2016). Guidance for the use of Rydapt (midostaurin) in the setting of AML or mastocytosis has not yet been reviewed by NICE but is expected to be released in November 2017 (NICE, 2017). NICE does not provide guidance for the treatment of mastocytosis.

Table 10: Advantages and Disadvantages of Agents for Aggressive Systemic Mastocytosis

Drug	Advantages	Disadvantages
Rydapt (midostaurin)	• Also indicated in the treatment of SM-AHN, MCL, and *FLT3*+ AML • Demonstrated efficacy in patients with *KIT* D816V mutation	• Risk of pulmonary toxicity
Gleevec (imatinib)	• Multiple additional indications, including Philadelphia chromosome + CML, myelodysplastic or myeloproliferative disease, HES and/or CEL, metastatic dermatofibrosarcoma protuberans, *KIT*+ metastatic malignant GIST, and adjuvant treatment of *KIT*+ GIST • Once daily dosing	• Only indicated in ASM in patients without the *KIT* D816V mutation or mutational status unknown • Multiple warnings and precautions including severe hepatotoxicity, cytopenia, and cardiogenic shock • Drug interactions with CYP2D6 substrates

* Clinical trials were conducted in different patient populations and cannot be directly compared; limited efficacy data available for all agents (pivotal trials were single armed, and no effect on survival has been demonstrated)
AML = acute myeloid leukemia
ASM = aggressive mastocytosis
CEL = chronic eosinophilic leukemia
CML = chronic myeloid leukemia
CYP = cytochrome P450 isoenzyme
GIST = gastrointestinal stromal tumors
HES = hypereosinophilic syndrome
MCL = mast cell leukemia
SM-AHN = systemic mastocytosis with associated hematologic neoplasm

(Gotlib, 2016; Prescribing Information: Gleevec 2017; Rydapt, 2017)

PRODUCT COMPARISON

Table 11: Market Share Comparison of Agents for Systemic Mastocytosis

Product	Cost (AWP)	CVS Caremark Data	
		Mail and Retail Rxs	Market Share (Combined Mail/Retail)
Rydapt (midostaurin) capsules*	$160.61 per capsule	—	—
imatinib tablets†	$102.53 per 100 mg tablet $371.97 per 400 mg tablet	10,418	79.8%
Gleevec (imatinib) tablets†	$112.36 per 100 mg tablet $404.89 per 400 mg tablet	2,636	20.2%

Boldface indicates generic availability
* Rydapt launched on May 3, 2017
† May include utilization for other indications
AWP = average wholesale price

(CVS Administrative Claims Data, February 2017 to April 2017; *Medi-Span® Master Drug Data Base v2.5 (MDDB®)*, 05 May 2017, Clinical Drug Information, LLC)

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FORMULARY AND DRUG LIST AVAILABILITY

Table 12: Formulary/Drug List Availability of Agents for Systemic Mastocytosis

Product	National Formulary	Prescribing Guide*	Performance Drug List*	Advanced Control Formulary	Value Formulary*
Gleevec (imatinib) tablets	✓	Excluded†	Excluded†	Excluded	—
imatinib tablets	✓	✓	✓	✓	✓‡
Rydapt (midostaurin) capsules	—	—	—	—	—

Boldface indicates generic availability
* Advanced Control Specialty Formulary may be applied to Prescribing Guide, Performance Drug List, or Value Formulary
† Excluded for some clients
‡ Prior authorization

Table 13: 2017/2018 Health Exchanges Formularies Availability of Agents for Systemic Mastocytosis with UM Tools

Product	Managed Medicaid Drug List	2017/2018 5-Tier Health Exchanges Template Formulary	2017/2018 6-Tier Health Exchanges Template Formulary	2017/2018 3-Tier Health Exchanges Formulary New York	2017/2018 4-Tier Health Exchanges Formulary California	2017/2018 6-Tier Health Exchanges Formulary South Carolina
Gleevec (imatinib) tablets	—	—	—	—	—	—
imatinib tablets	✓*	tier 4*	tier 5*	tier 3*	tier 1*	tier 5*
Rydapt (midostaurin) capsules	—	—	—	—	—	—

Boldface indicates generic availability
* Prior authorization
UM = utilization management

Table 14: 2017 Medicare Part D Drug List Availability of Agents for Systemic Mastocytosis with Optional UM Tools*

Product	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
Gleevec (imatinib) tablets	—	—	—	—	—	—	tier 5§‖	—	—	—
imatinib tablets	tier 5§‖	tier 5§‖	tier 5§‖	tier 5§‖	tier 2§‖	tier 5§‖	tier 5§‖	tier 5§‖	tier 4§‖	tier 5§‖
Rydapt (midostaurin) capsules	—	—	—	—	—	—	—	—	—	—

Boldface indicates generic availability
* 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
§ Prior Authorization
‖ Quantity limit
EGWP = Employer Group Waiver Plan
MMP = Medicare-Medicaid Plan
PDP = Prescription Drug Plan
UM = utilization management

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Table 15: 2018 Medicare Part D Drug List Availability of Agents for Systemic Mastocytosis with Optional UM Tools*

Product	PDP Choice/ PDP Plus Drug List	Client Drug Lists									
		Select†	Generic Strategy Standard†	Generic Strategy Essential	MMP	Standard‡	Expanded	Performance	Core	EGWP	
	5-Tier	5-Tier			2-Tier	5-Tier	5-Tier			4-Tier	5-Tier
Gleevec (imatinib) tablets	—	—	—	—	—	—	tier 5	—	—	—	—
imatinib capsules	**tier 5§‖**	**tier 5§‖**	**tier 5§‖**	**tier 5§‖**	**tier 2§‖**	**tier 4§‖**	**tier 5§‖**	**tier 5§‖**	**tier 5§‖**	**tier 4§‖**	**tier 5§‖**
Rydapt (midostaurin) capsules	—	—	—	—	—	—	—	—	—	—	—

Boldface indicates generic availability
* 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
§ Prior authorization
‖ Quantity limit
EGWP = Employer Group Waiver Plan
MMP = Medicare-Medicaid Plan
PDP = Prescription Drug Plan
UM = utilization management

FORMULARY CONSIDERATIONS

Rydapt (midostaurin) is the first FDA-approved targeted drug therapy to treat adults with *FLT3*+ AML. Results from a randomized, double blind, phase III, placebo-controlled trial demonstrated that the addition of Rydapt (midostaurin) to standard chemotherapy for induction and consolidation and followed by one year of maintenance therapy considerably improved clinical outcomes by significantly extending overall survival and event free survival when compared to standard chemotherapy alone in newly diagnosed patients with *FLT3*+ AML. Rydapt (midostaurin) was also approved by the FDA to treat SM, SM-AHN, and MCL. Based on two phase II studies, Rydapt (midostaurin) demonstrated a durable response and tolerability in patients with ASM, SM-AHN, and MCL regardless of *KIT* D816V mutation status, or exposure to previous therapy. Warnings and precautions associated with Rydapt (midostaurin) include embryo-fetal toxicity and pulmonary toxicity. Overall, Rydapt (midostaurin) was shown to be safe and efficacious as the first targeted-agent approved by the FDA to treat patients with *FLT3*+ AML in combination with standard chemotherapy and as the first drug to treat multiple forms of advanced SM: ASM, SM-AHN, or MCL, including those with *KIT* D816V mutation.

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Data as of June 16, 2017
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DRUG MONOGRAPH PREPARED BY:

Elias Pittos, Pharm.D.
June 16, 2017

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Pharmacy &Therapeutics Committee Summary Review
Brineura (cerliponase) – BioMarin Pharmaceutical Inc.

Prepared by: AMCP eDossier / Irina Yaroshenko

Presentation Date: 1/4/18

Therapeutic Class: Hydrolytic lysosomal N-terminal tripeptidyl peptidase

FDA Approval Date: 04/27/17

FDA Indication: Indicated to slow the loss of ambulation in symptomatic pediatric patients 3 years of age and older with late infantile neuronal ceroid lipofuscinosis type 2 (CLN2), also known as tripeptidyl peptidase 1 (TPP1) deficiency.

Comparable Products: None

Proposed Designation & Rationale

Recommendation: Non-Preferred, approved via e-vote on 05/31/17

- Criteria for use / Approval duration: See policy for criteria for use and approval durations.
  - For reference, Ohio Medicaid version of policy can be found at: Brineura.
  - All other state specific policies can be found under Pharmacy Policies by clicking on the appropriate state.

Clinical Implications/ Place in Therapy:

New drug Brineura for treatment of a specific form of Batten disease was reviewed. It is the first FDA-approved treatment to slow loss of walking ability (ambulation) in symptomatic pediatric patients (3 years of age and older) with late infantile neuronal ceroid lipofuscinosis type 2 (CLN2), also known as tripeptidyl peptidase-1 (TPP1) deficiency. Based on available literature, packed insert, and clinical trials date, criteria were written for Brineura policy. Brineura-treated patients were compared to untreated patients from a natural history cohort in clinical trials and demonstrated fewer declines in the Motor domain for Brineura-treated patients.

Ongoing Clinical Trials:

- There are 2 clinical trials (recruiting; enrolling by invitation; active, not recruiting): https://clinicaltrials.gov/ct2/results?cond=&term=cerliponase&cntry1=&state1=&Search=Search&recrs=a&recrs=d&recrs=f

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FormularyDecisions.com®
eMonograph

Brineura

(cerliponase)

BioMarin Pharmaceutical Inc.

Prepared by:

Date: November 29, 2017

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Brineura

(cerliponase)

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Indication	**Brineura is a hydrolytic lysosomal N-terminal tripeptidyl peptidase indicated to slow the loss of ambulation in symptomatic pediatric patients 3 years of age and older with late infantile neuronal ceroid lipofuscinosis type 2 (CLN2), also known as tripeptidyl peptidase 1 (TPP1) deficiency. (1)** **FDA Approval Date: Apr 27, 2017**
Treatment Comparisons for Indications	
Place in Therapy	
Pharmacology	
Dosage and Administration	**Strengths Available:** Injection: Brineura 150 mg/5 mL (30 mg/mL) solution, two single-dose vials per carton co-packaged with Intraventricular Electrolytes Injection 5 mL in a single-dose vial. (3) **Dosage Frequency:** • Aseptic technique must be strictly observed during preparation and administration. Brineura should be administered by, or under the direction of a physician knowledgeable in intraventricular administration. Brineura is administered to the cerebrospinal fluid (CSF) by infusion via a surgically implanted reservoir and catheter. (2.1) • Pre-treatment of patients with antihistamines with or without antipyretics or corticosteroids is recommended 30 to 60 minutes prior to the start of infusion. (2.2) • The recommended dosage is 300 mg administered once every other week as an intraventricular infusion followed by infusion of Intraventricular Electrolytes over approximately 4.5 hours. (2.2)

	• For complete information on preparation, specific intraventricular access device for use, and administration, see the full prescribing information. (2.1,2.3,2.4,2.5)
Safety	Most common adverse reactions (≥8%) are: pyrexia, ECG abnormalities, decreased CSF protein, vomiting, seizures, hypersensitivity, increased CSF protein, hematoma, headache, irritability, pleocytosis, device-related infection, bradycardia, feeling jittery, and hypotension. (6.1) To report SUSPECTED ADVERSE REACTIONS, contact BioMarin at 1-866-906-6100 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch. **Contraindications:** • Acute intraventricular access device-related complications (e.g., leakage, device failure, or device-related infection). (4) • Patients with ventriculoperitoneal shunts. (4)
Use in Specific Populations	8.1 Pregnancy Risk Summary There are no available data on Brineura use in pregnant women to inform a drug-associated risk of pregnancy-related outcomes. Animal reproduction studies have not been conducted using cerliponase alfa. The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively. 8.2 Lactation Risk Summary There are no data on the presence of cerliponase alfa in human milk, the effects on the breastfed child, or the effects on milk production. The lack of clinical data during lactation precludes a clear determination of the risk of

	Brineura to an infant during lactation; therefore, the development and health benefits of breastfeeding should be considered along with the mother's clinical need for Brineura and any potential adverse effects on the breastfed infant from Brineura or from the underlying maternal condition. 8.4 Pediatric Use Safety and effectiveness of Brineura have been established in pediatric patients 3 years of age and older. Pediatric use of Brineura to slow the loss of ambulation in symptomatic pediatric patients 3 years of age and older with late infantile neuronal ceroid lipofuscinosis type 2 (CLN2), also known as tripeptidyl peptidase 1 (TPP1) deficiency, is supported by a non-randomized single-arm dose escalation clinical study with extension in patients with CLN2 disease and compared to untreated patients with CLN2 disease from an independent natural history cohort [see Clinical Studies (14)]. Safety and effectiveness in patients less than 3 years of age have not been established.
Clinical Highlights	
Availability and Pricing	
Economic Value Proposition	
Formulary Considerations	

Appendix: PI Highlights

For the complete Product Insert click here.

Product Description

Cerliponase alfa is a purified human enzyme produced by recombinant DNA technology in a Chinese hamster ovary cell line. The active substance is a recombinant human tripeptidyl peptidase-1 (rhTPP1), a lysosomal exopeptidase. The primary activity of the mature enzyme is the cleavage of N-terminal tripeptides from a broad range of protein substrates.

Cerliponase alfa contains 544 amino acids with an average molecular mass of 59 kDa. The mature enzyme is 368 amino acids in length. There are 5 consensus N-glycosylation sites on rhTPP1 that contain high mannose, phosphorylated high mannose and complex glycosylation structures.

Brineura (cerliponase alfa) Injection and Intraventricular Electrolytes Injection are administered by intraventricular infusion. The solutions are sterile, nonpyrogenic, and free of foreign particulates. Brineura is a clear to slightly opalescent and colorless to pale yellow solution. Intraventricular Electrolytes is a clear to colorless solution.

Brineura and Intraventricular Electrolytes Injection are packaged in 10 mL clear Type 1 single-dose glass vials[see How Supplied/Storage and Handling (16)]. Each vial of Brineura provides 5 mL of solution containing 150 mg cerliponase alfa. Each vial of Intraventricular Electrolytes Injection provides 5 mL of solution. Both Brineura and Intraventricular Electrolytes Injection are formulated with the following excipients: calcium chloride dihydrate (1.05 mg); magnesium chloride hexahydrate (0.8 mg); potassium chloride (1.1 mg); sodium chloride (43.85 mg); sodium phosphate, dibasic, heptahydrate (0.55 mg); sodium phosphate, monobasic, monohydrate (0.4 mg); and Water for Injection, USP. The pH of the solution is between 6.2 to 6.8 for Brineura, and between 6.0 to 7.0 for Intraventricular Electrolytes Injection.

Each vial contains: sodium: 0.76 mEq, and potassium: 0.015 mEq.

Indications and Usage

Brineura is indicated to slow the loss of ambulation in symptomatic pediatric patients 3 years of age and older with late infantile neuronal ceroid lipofuscinosis type 2 (CLN2), also known as tripeptidyl peptidase 1 (TPP1) deficiency.

Dosage and Administration

Injection: Brineura 150 mg/5 mL (30 mg/mL) solution, two single-dose vials per carton co-packaged with Intraventricular Electrolytes Injection 5 mL in a single-dose vial. Brineura is a

clear to slightly opalescent and colorless to pale yellow solution. Intraventricular Electrolytes is a clear to colorless solution[see How Supplied/Storage and Handling (16)].

2.1 Important Preparation and Administration Information

- Aseptic technique must be strictly observed during preparation and administration.
- Brineura should be administered by, or under the direction of a physician knowledgeable in intraventricular administration.
- Brineura is administered into the cerebrospinal fluid (CSF) by infusion via a surgically implanted reservoir and catheter (intraventricular access device). Brineura is intended to be administered via the Codman®HOLTER RICKHAM Reservoirs (Part Numbers: 82-1625, 82-1621, 82-1616) with the Codman®Ventricular Catheter (Part Number: 82-1650). The intraventricular access device must be implanted prior to the first infusion. It is recommended that the first dose be administered at least 5 to 7 days after device implantation.
- Brineura is intended to be administered with the B Braun Perfusor®Space Infusion Pump System. The essential performance requirements for this syringe pump used to deliver Brineura are as follows:
    - Delivery rate of 2.5 mL/hr with delivery accuracy of +/- 1 mL/hr
    - Compatible with 20 mL syringes provided in the Administration Kit for use with Brineura
    - Occlusion alarm setting to ≤ 281 mm Hg
- Administer Brineura and the Intraventricular Electrolytes using the provided Administration Kit for use with Brineura components[see How Supplied/Storage and Handling (16)].

2.2 Dosage

The recommended dosage of Brineura in pediatric patients 3 years of age and older is 300 mg administered once every other week by intraventricular infusion. Administer Brineura first followed by infusion of the Intraventricular Electrolytes each at an infusion rate of 2.5 mL/hr. The complete Brineura infusion, including the required infusion of Intraventricular Electrolytes, is approximately 4.5 hours.

Pre-treatment of patients with antihistamines with or without antipyretics or corticosteroids is recommended 30 to 60 minutes prior to the start of infusion.

2.3 Method of Administration

Brineura and the Intraventricular Electrolytes must only be administered by the intraventricular route, using the provided Administration Kit for use with Brineura. Each vial of Brineura and Intraventricular Electrolytes is intended for a single dose only.

Each infusion consists of 10 mL of Brineura followed by 2 mL of Intraventricular Electrolytes. The complete infusion must be administered using an infusion set with a 0.2 micron inline filter. The Intraventricular Electrolytes are used to flush the infusion line, port needle, and intraventricular access device in order to fully administer Brineura and to maintain patency of the intraventricular access device.

2.4 Preparation for Infusion

Gather supplies:

- Brineura and Intraventricular Electrolytes Injection vials (package 1 of 2)[see How Supplied/Storage and Handling (16)]
- Administration Kit for use with Brineura (package 2 of 2) [see How Supplied/Storage and Handling (16)]
- Syringe pump (not supplied)

Inspect the Administration Kit infusion components to ensure the components are in the individual packages and have not been compromised.

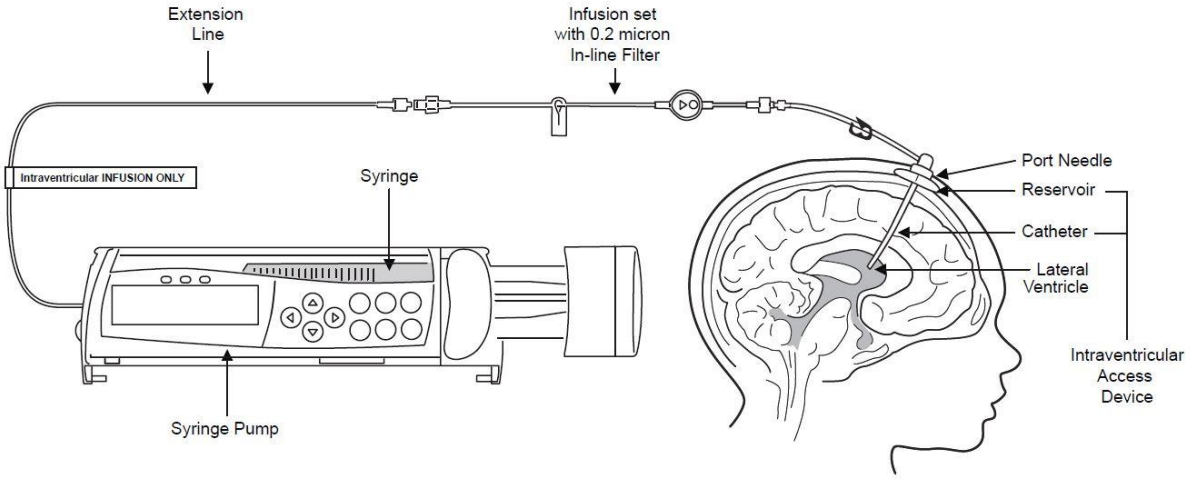
Thaw Brineura and Intraventricular Electrolytes Injection vials at room temperature for approximately 60 minutes.Do notthaw or warm vials any other way.Do notshake vials. Condensation will occur during thawing period.Do notre-freeze vials or freeze syringes containing Brineura or Intraventricular Electrolytes.

Inspect fully thawed Brineura and Intraventricular Electrolytes Injection vials. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Brineura is a clear to slightly opalescent and colorless to pale yellow solution. Intraventricular Electrolytes is a clear to colorless solution.Do not useif the solutions are discolored or if there is other foreign particulate matter in the solutions. Brineura vials may occasionally contain thin translucent fibers or opaque particles. These naturally occurring particles are cerliponase alfa. These particles are removed via the 0.2 micron inline filter without having a detectable effect on the purity or strength of Brineura. Intraventricular Electrolytes may contain particles, which appear during the thaw period; however, these dissolve when the solution reaches room temperature.

2.5 Intraventricular Infusion Procedure

Intraventricular Infusion of Brineura

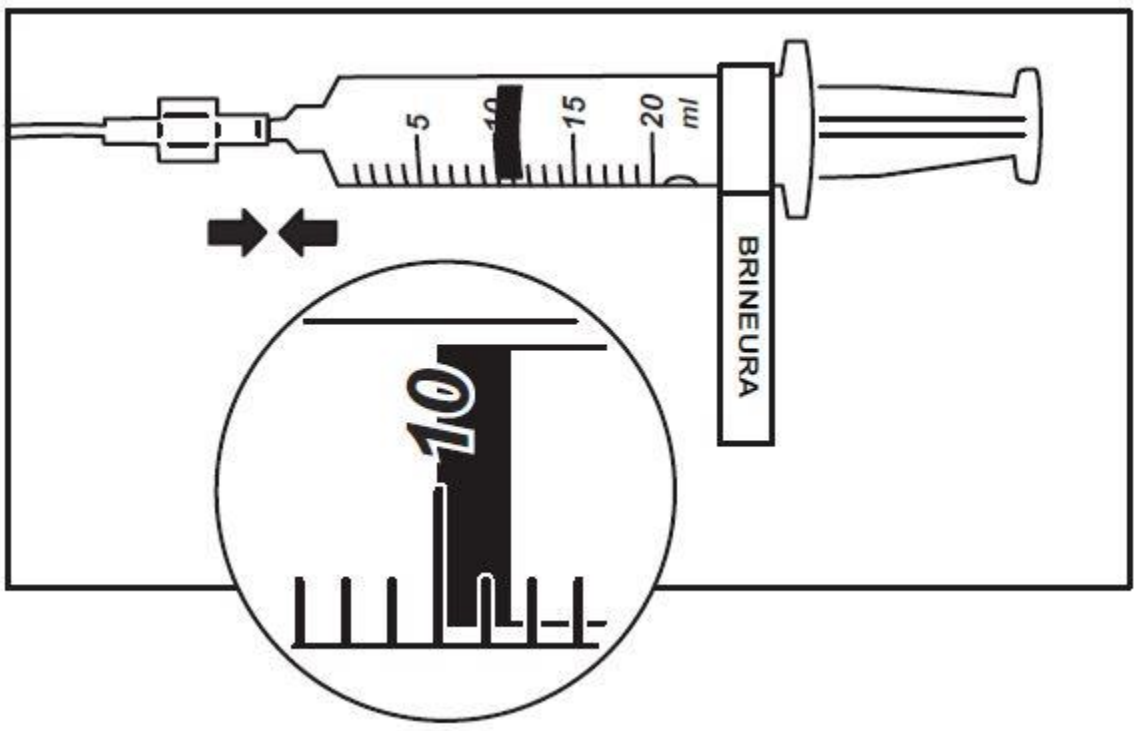
Figure 1 represents the intraventricular infusion system set up. Use aseptic technique during the infusion. Follow the steps below to proceed with the intraventricular infusion.



1. Use aseptic technique when preparing the Brineura syringe for infusion. Label one sterile syringe “Brineura” and attach the syringe needle. Remove the green flip-off caps from the two Brineura vials. Use the “Brineura” labeled syringe to withdraw a total of 10 mL from the Brineura vials.Do notdilute Brineura.Do notmix Brineura with any other drug.

2. Label the infusion line “intraventricular infusion only” (see Figure 1).

3. Attach the syringe containing Brineura to the extension line (see Figure 2). Then connect the extension line to the infusion set with a 0.2 micron inline filter (see Figure 1).

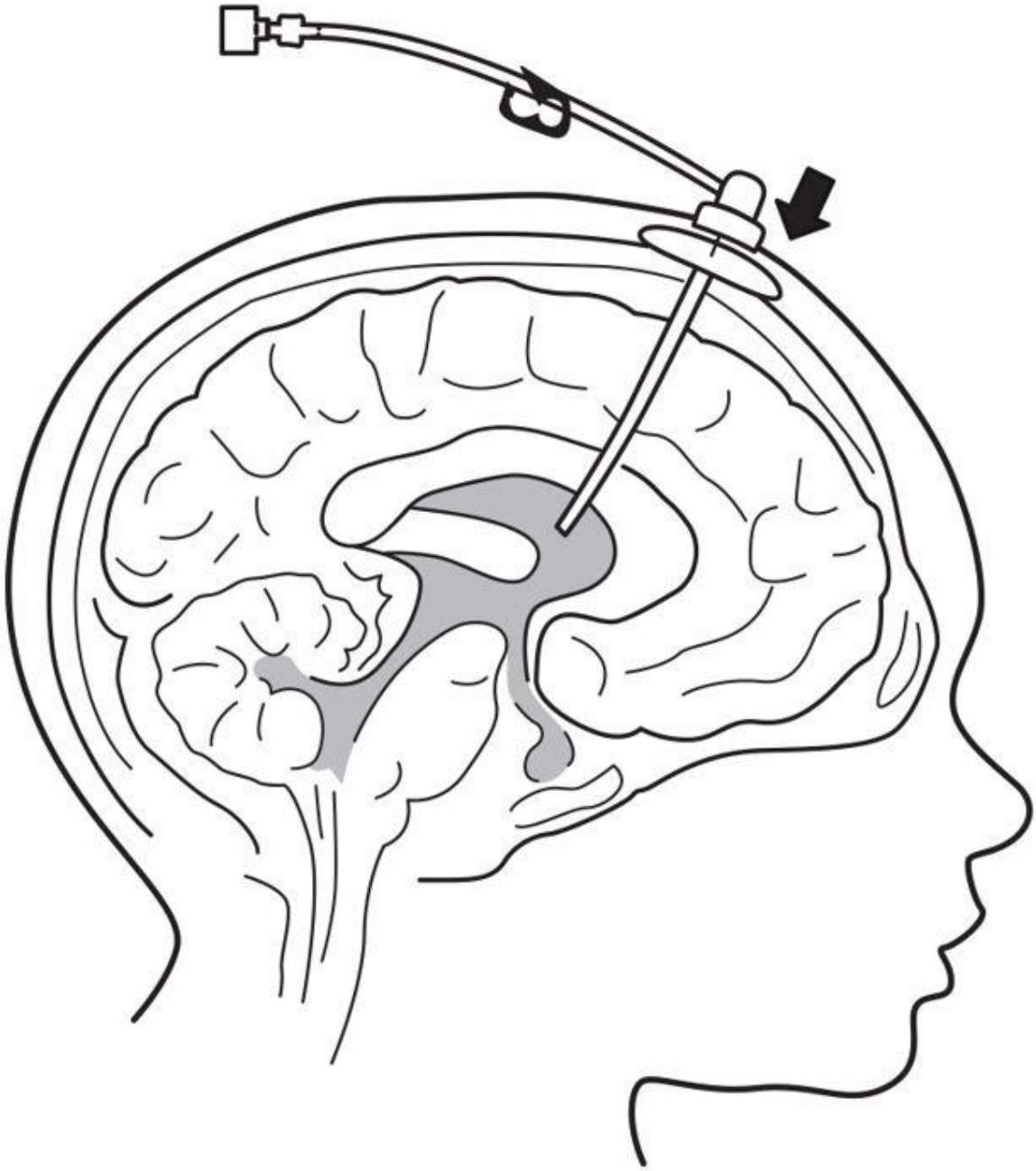


4. Prime the infusion components with Brineura.

5. Inspect scalp for signs of intraventricular access device leakage or failure and for potential infections[see Warnings and Precautions (5.1)].

6. Prepare the scalp for intraventricular infusion per institution standard of care.

7. Insert port needle into intraventricular access device (see Figure 3).



8. Connect a separate empty sterile single-use luer lock syringe, no larger than 3 mL (not provided) to the port needle. Withdraw 0.5 mL to 1 mL of CSF to check patency of intraventricular access device (see Figure 4) and send specimen for culture.

- Do not return CSF to intraventricular access device.
- Routinely send CSF samples for infection monitoring[see Warnings and Precautions (5.1)].

Figure 4

9. Attach the infusion set with 0.2 micron inline filter to the port needle (see Figure 1).

- Secure the components per institution standard of care.

10. Place the syringe containing Brineura into the syringe pump and program pump to deliver at an infusion rate of 2.5 mL per hour. Set the occlusion alarm setting to alert at pressure ≤ 281 mm Hg. See syringe pump operating manual for details.Do notdeliver as a bolus or manually.

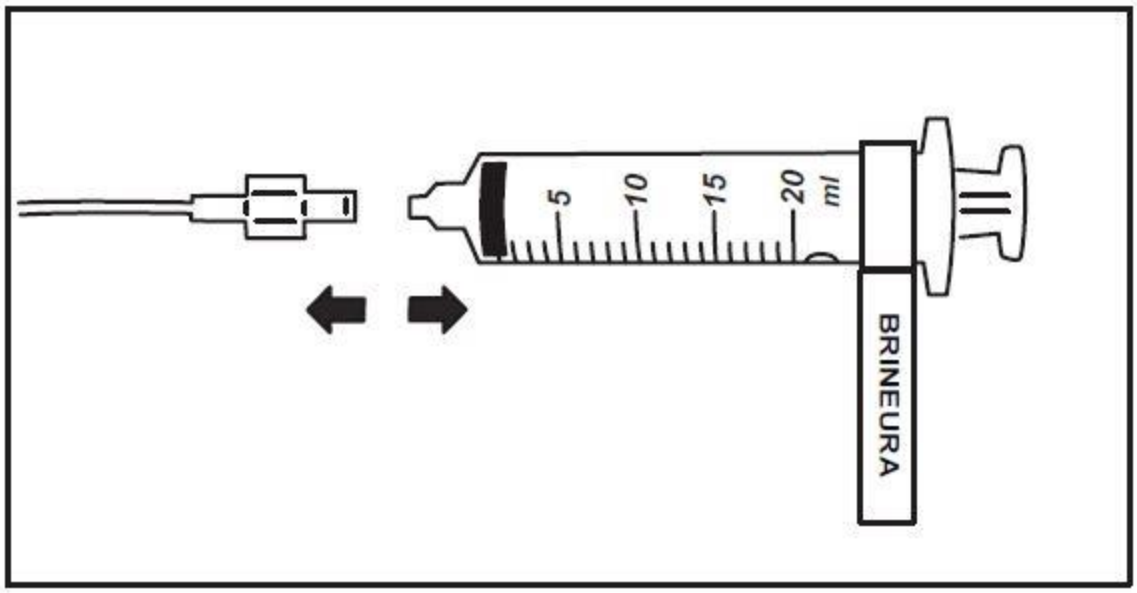
11. Administer pre-medication 30 to 60 minutes prior to the start of infusion[see Dosage and Administration (2.2)].

12. Monitor vital signs (blood pressure, heart rate) prior to the start of infusion, periodically during infusion, and post-infusion[see Warnings and Precautions (5.2)].

13. Initiate infusion of Brineura at a rate of 2.5 mL per hour.

14. Periodically inspect the infusion system during the infusion for signs of leakage or delivery failure[see Warnings and Precautions (5.1)].

15. When the Brineura infusion is complete, detach and remove the empty syringe from the pump and disconnect from the tubing (see Figure 5). Proceed to Step 16 for Intraventricular Electrolytes infusion.

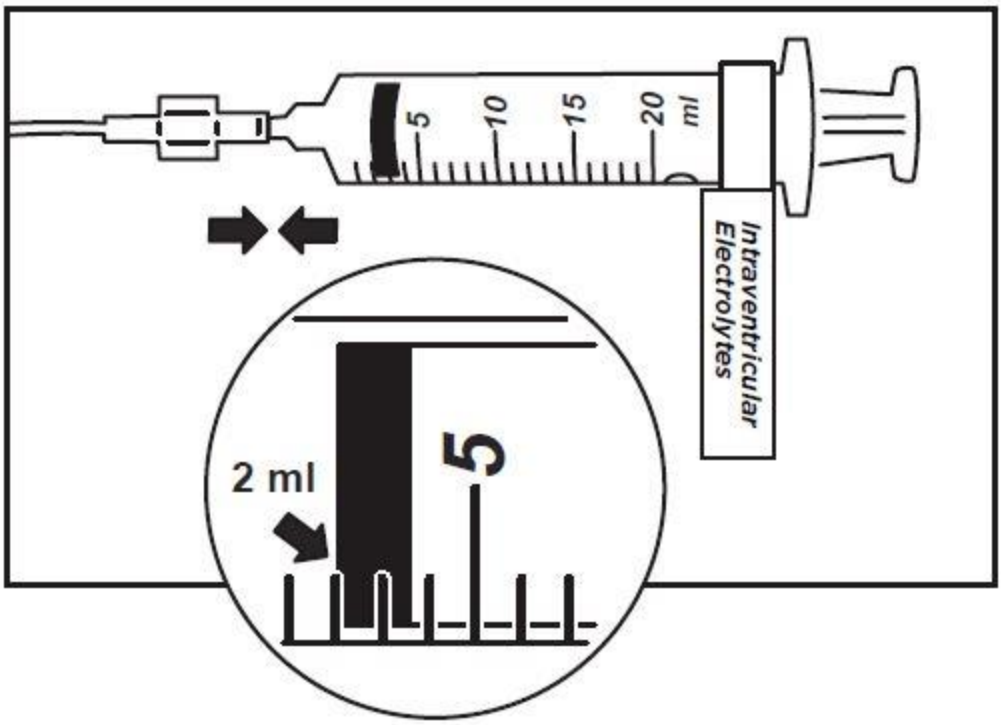


Intraventricular Infusion of Intraventricular Electrolytes

Administer the Intraventricular Electrolytes providedafter Brineura infusion is complete.

16. Use aseptic technique when preparing the Intraventricular Electrolytes syringe for infusion. Label one sterile syringe “Intraventricular Electrolytes” and attach the syringe needle. Remove the yellow flip-off cap from the Intraventricular Electrolytes Injection vial. Withdraw 2 mL of Intraventricular Electrolytes. Discard the remaining unused portion.

17. Attach the syringe to the extension line (see Figure 6).



18. Place the syringe containing Intraventricular Electrolytes into the syringe pump and program pump to deliver at an infusion rate of 2.5 mL per hour. Set the occlusion alarm setting to alert at pressure ≤ 281 mm Hg. See syringe pump operating manual for details.Do notdeliver as a bolus or manually.

19. Initiate infusion of Intraventricular Electrolytes at a rate of 2.5 mL per hour.

20. Periodically inspect the infusion system during the infusion for signs of leakage or delivery failure.

21. When the Intraventricular Electrolytes infusion is complete, detach and remove the empty syringe from the pump and disconnect from the infusion line.

22. Remove the port needle. Apply gentle pressure and bandage the infusion site per institution standard of care.

Dispose of the infusion components, needles, unused solutions and other waste materials in accordance with local requirements.

Storage of Thawed Product

Use thawed Brineura and Intraventricular Electrolytes immediately. If not used immediately, store unopened vials in the refrigerator at 2°C to 8°C and use within 24 hours.

Storage of Product in Syringes

Use product held in labeled syringes immediately. If not used immediately, store product held in labeled syringes in the refrigerator at 2°C to 8°C up to 4 hours prior to infusion.

Adverse Reactions

The following adverse reactions are described below and elsewhere in the labeling:

- Intraventricular Access Device-Related Complications[see Warnings and Precautions (5.1)]
- Cardiovascular Adverse Reactions[see Warnings and Precautions (5.2)]
- Hypersensitivity Reactions[see Warnings and Precautions (5.3)]

6.1 Clinical Trials Experience

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

The safety of Brineura was evaluated in 24 patients with CLN2 disease who received at least one dose of Brineura in a clinical study with extension of up to 161 weeks[see Clinical Studies (14)]. Table 1 summarizes the most common adverse reactions that occurred in Brineura-treated patients through 96 weeks.

Table 1: Adverse Reactions Reported in ≥ 8% of Symptomatic Pediatric Patients with CLN2 Disease in the Brineura Single-Arm Clinical Study with Extension at Week 96

Adverse Reaction	Patients Treated with Brineura n=24 (%)
Pyrexia*	17 (71)
ECG abnormalities†	17 (71)
Decreased CSF protein	17 (71)
Vomiting	15 (63)
Seizures‡	12 (50)
Hypersensitvity§	11 (46)
Increased CSF protein	5 (21)
Hematoma	5 (21)
Headache	4 (17)

Irritability	4 (17)
Pleocytosis	4 (17)
Device-related infection¶	2 (8)
Bradycardia	2 (8)
Feeling jittery	2 (8)
Hypotension	2 (8)

*Pyrexia includes: pyrexia and increased body temperature

†ECG abnormalities include: non-specific repolarization abnormality, notched QRS, ST segment elevation, biphasic T wave abnormality, supraventricular extrasystoles, bradycardia, sinus tachycardia, and intraventricular conduction delay

‡Seizures include: atonic, generalized tonic-clonic, focal, and absence.

§Hypersensitivity includes: immune reactions and signs and symptoms observed concomitantly with hypersensitivity reactions including pyrexia, vomiting, pleocytosis or irritability

¶Device-related infections include:Propionibacterium acnesandStaphylococcus epidermidis

Description of Selected Adverse Reactions

Seizures

Seizures were reported in 12 of 24 (50%) patients. The seizure types reported include atonic, generalized tonic-clonic, focal, and absence. Seizures were managed with standard anti-convulsive therapies and did not result in discontinuation of Brineura treatment.

Device-Related Complications

Adverse reactions related to the device were observed in 12 of 24 (50%) of patients. Device-related adverse reactions include infection, delivery system-related complications, and pleocytosis. Nine of these patients (38%) experienced adverse reactions, which involved complications of the non-implanted delivery system components. Four patients (16%) had device-related adverse reactions, which required medical intervention, including two patients (8%) with intraventricular access device-related CNS infections, and one patient (4%) each with leakage of the intraventricular access device and pleocytosis. Device-related infections were diagnosed by increased CSF pleocytosis and microbiology culture and organism identification, without accompanying signs and symptoms of meningitis. Intraventricular access devices were replaced and infections were treated with antibiotics. Device-related complications did not result in discontinuation of Brineura treatment[see Warnings and Precautions (5.1)].

Hematoma

Hematoma adverse reactions were reported in 5 (21%) patients treated with Brineura and presented as hematoma, post procedural hematoma, traumatic hematoma and subdural hematoma. Hematomas did not require treatment and did not interfere with Brineura infusion.

Hypersensitivity

Hypersensitivity reactions were reported in 11 out of 24 patients (46%) treated with Brineura during or within 24 hours after completion of the Brineura infusion, despite pre-medication with antihistamines with or without antipyretics or corticosteroids[see Warnings and Precautions (5.1)]. The most common manifestations observed concomitantly with hypersensitivity included pyrexia with vomiting, pleocytosis, or irritability, which are not consistent with classic immune mediated hypersensitivity. Symptoms resolved over time or with administration of antipyretics, antihistamines and/or corticosteroids and no patient discontinued treatment with Brineura.

One patient experienced hypoxia (decreased oxygen saturation less than 88% by pulse oximeter), 8 hours after Brineura infusion, followed by a low mean arterial pressure at 15 hours post infusion. Symptoms resolved after oxygen administration, airway repositioning and normal saline infusion. One patient reported decreased oxygen saturation (90% by pulse oximeter), 45 minutes after starting Brineura with associated low diastolic blood pressures. Hypoxia resolved after oxygen administration. No treatment was administered for the low diastolic blood pressure, which returned to normal while the patient continued to receive Brineura infusion without change to the infusion rate or dose.

6.2 Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to cerliponase alfa in the studies described below with the incidence of antibodies in other studies or to other products may be misleading.

Anti-drug antibodies (ADAs) to cerliponase alfa were detected in both serum and CSF in 79% and 33%, respectively, of patients treated with Brineura for up to 161 weeks. Patients who experienced hypersensitivity adverse reactions were tested for drug-specific IgE and found to be negative, including three patients for whom grade 3 (severe) hypersensitivity adverse reactions were reported. No association was found between serum or CSF ADA titers and incidence or severity of hypersensitivity. Drug-specific neutralizing antibodies (NAb) have not been evaluated.

Clinical Trials Results

The efficacy of Brineura was assessed over 96 weeks in a non-randomized single-arm dose escalation clinical study with extension in symptomatic pediatric patients with late infantile

neuronal ceroid lipofuscinosis type 2 (CLN2) disease, confirmed by TPP1 deficiency. Brineura-treated patients were compared to untreated patients from a natural history cohort. The Motor domain of a CLN2 Clinical Rating Scale was used to assess disease progression. Scores ranged from 3 (grossly normal) to 0 (profoundly impaired) with unit decrements representing milestone events in the loss of motor function (ability to walk or crawl). Due to the inability to establish comparability for the CLN2 Language domain ratings between the clinical study with extension and the natural history cohort, efficacy of Brineura for the Language domain cannot be established.

Twenty-four patients, aged 3 to 8 years were enrolled in the Brineura single-arm clinical study. Sixty-three percent of patients were female and 37% were male. Ninety-six percent of patients were Caucasian and 4% were Asian. One patient withdrew after week 1 due to inability to continue with study procedures; 23 patients were treated with Brineura 300 mg every other week for 48 weeks, and continued treatment during the extension period.

In the clinical study with extension, patients were assessed for decline in the Motor domain of the CLN2 Clinical Rating Scale at 48, 72 and 96 weeks. Decline was defined as having an unreversed (sustained) 2-category decline or an unreversed score of 0 in the Motor domain of the CLN2 Clinical Rating Scale. Patients' responses to Brineura treatment were evaluated if at screening a combined Motor plus Language CLN2 score of less than 6 was recorded. Two patients with a combined Motor plus Language CLN2 score of 6 were excluded from the analyses; they maintained that score throughout the study period. The patient who terminated early was analyzed as having a decline at the time of termination. Data used in the analyses from the natural history cohort began at 36 months of age or greater and at the first time a Motor plus Language CLN2 score less than 6 was recorded.

Motor scores of the 22 Brineura-treated patients in the clinical study with extension were compared to scores of the independent natural history cohort that included 42 untreated patients who satisfied inclusion criteria for the clinical study. The results of logistic modeling with covariates (screening age, screening motor score, genotype: 0 key mutations (yes/no)), demonstrated the odds of Brineura-treated patients not having a decline by 96 weeks were 13 times the odds of natural history cohort patients not having a decline (Odds Ratio (95% CI): 13.1 (1.2, 146.9)).

Descriptive non-randomized comparison

In an unadjusted non-randomized comparison, of the 22 patients treated with Brineura and evaluated for efficacy at week 96, 21 (95%) did not decline, and only the patient who terminated early was deemed to have a decline in the Motor domain of the CLN2 Clinical Rating Scale. Results from the natural history cohort demonstrated progressive decline in motor function; of the 42 patients in the natural history cohort, 21 (50%) experienced an unreversed (sustained) 2-category decline or unreversed score of 0 in the Motor domain of the CLN2 Clinical Rating Scale over 96 weeks.

Given the non-randomized study design, a Cox Proportional Hazards Model adjusted for age, initial motor score, and genotype was used to evaluate time to unreversed 2-category decline or unreversed score of 0 in the Motor domain. This model showed a lesser decrease in motor

function in the Brineura-treated patients when compared to the natural history cohort (see Figure 7).

Figure 7. Estimated Time to Unreversed (Sustained) 2-Category Decline or Unreversed Score of Zero in Motor Domain for Symptomatic Pediatric Patients in the Brineura Single-Arm Clinical Study with Extension and for Patients in a Natural History Cohort (Based on the Cox Proportional Hazards Model Adjusting for Covariates)

Shading represents 95% confidence intervals.

Follow-up for the natural history cohort begins at 36 months of age or greater and at the first time a Motor plus Language CLN2 score less than 6 was recorded.

The Brineura-treated population is the full population (N=24) minus two patients with baseline Motor plus Language CLN2 score = 6.

Covariates: screening age, screening Motor score, genotype: 0 key mutations (yes/no). "Screening age" was defined in the natural history cohort as the age at the first time a Motor plus Language CLN2 score less than 6 was recorded, and no earlier than 36 months of age. The "screening Motor score" of the natural history cohort was defined as the Motor score at the screening age.

Decline is defined as an unreversed (sustained) 2-category decline or unreversed score of 0 in the Motor domain of the CLN2 Clinical Rating Scale.

Motor Domain Scores: Matched Patients Only

To further assess efficacy, the 22 patients from the Brineura clinical study with a baseline combined Motor plus Language CLN2 score less than 6 were matched to 42 patients in the natural history cohort. Patients were matched based on the following covariates: baseline age at time of screening within 3 months, genotype (0, 1, or 2 key mutations), and baseline Motor domain CLN2 score at time of screening.

Using the Motor domain of the CLN2 Clinical Rating Scale, decline was defined as having an unreversed 2-category decline or an unreversed score of 0. At 96 weeks, the matched analysis based on 17 pairs demonstrated fewer declines in the Motor domain for Brineura-treated patients compared to untreated patients in the natural history cohort (see Table 3).

Table 3: Proportion of Matched Symptomatic Pediatric Patients with CLN2 Disease without Decline* in the Brineura Single-Arm Clinical Study with Extension and in the Natural History Cohort assessed at Weeks 48, 72, and 96

Time Point/Period	Natural History Cohort (N=17)	Brineura-Treated (N=17)	Difference	Odds Ratio***
	n (%)	n (%)	% (95% CI**)	OR (95% CI)

Follow-up through Week 48	13 (76)	16 (94)	18% (-19, 51)	4 (0.4, 200)
Follow-up through Week 72	11 (65)	16 (94)	29% (-7, 61)	5.9 (0.7, 250)
Follow-up through Week 96	6 (35)	16 (94)	59% (24, 83)	11 (1.6, 500)

*Decline is defined as an unreversed (sustained) 2-category decline or unreversed score of 0 in the Motor domain of the CLN2 Clinical Rating Scale.

** Exact confidence interval for risk difference (Santner and Snell)

***Based on McNemar's Exact test

Matched on baseline age at time of screening within 3 months, genotype (0, 1, or 2 key mutations), and baseline Motor domain CLN2 score at time of screening.

The Brineura-treated population is based on the full population minus two patients with baseline Motor plus Language CLN2 score = 6.

Clinical Pharmacology

Mechanism of Action

CLN2 disease is a neurodegenerative disease caused by deficiency of the lysosomal enzyme tripeptidyl peptidase-1 (TPP1), which catabolizes polypeptides in the CNS. TPP1 has no known substrate specificity. Deficiency in TPP1 activity results in the accumulation of lysosomal storage materials normally metabolized by this enzyme in the central nervous system (CNS), leading to progressive decline in motor function.

Cerliponase alfa (rhTTP1), a proenzyme, is taken up by target cells in the CNS and is translocated to the lysosomes through the Cation Independent Mannose-6-Phosphate Receptor (CI-MPR, also known as M6P/IGF2 receptor). Cerliponase alfa is activated in the lysosome and the activated proteolytic form of rhTPP1 cleaves tripeptides from the N-terminus of proteins.

Pharmacokinetics

Drug Interactions

Contraindications

Brineura is contraindicated in patients with:

- acute intraventricular access device-related complications (e.g., leakage, device failure, or device-related infection)[see Warnings and Precautions (5.1)].
- ventriculoperitoneal shunts.

Use in Specific Populations

8.1 Pregnancy

Risk Summary

There are no available data on Brineura use in pregnant women to inform a drug-associated risk of pregnancy-related outcomes. Animal reproduction studies have not been conducted using cerliponase alfa.

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

8.2 Lactation

Risk Summary

There are no data on the presence of cerliponase alfa in human milk, the effects on the breastfed child, or the effects on milk production. The lack of clinical data during lactation precludes a clear determination of the risk of Brineura to an infant during lactation; therefore, the development and health benefits of breastfeeding should be considered along with the mother's clinical need for Brineura and any potential adverse effects on the breastfed infant from Brineura or from the underlying maternal condition.

8.4 Pediatric Use

Safety and effectiveness of Brineura have been established in pediatric patients 3 years of age and older. Pediatric use of Brineura to slow the loss of ambulation in symptomatic pediatric patients 3 years of age and older with late infantile neuronal ceroid lipofuscinosis type 2 (CLN2), also known as tripeptidyl peptidase 1 (TPP1) deficiency, is supported by a non-randomized

single-arm dose escalation clinical study with extension in patients with CLN2 disease and compared to untreated patients with CLN2 disease from an independent natural history cohort [see Clinical Studies (14)]. Safety and effectiveness in patients less than 3 years of age have not been established.

Pharmacy &Therapeutics Committee Summary Review
Zejula (niraparib)– TESARO

Prepared by: CVS Health / Irina Yaroshenko

Presentation Date: 1/4/18

Therapeutic Class: PARP Inhibitor

FDA Approval Date: 06/30/17

FDA Indication: ZEJULA is a poly (ADP-ribose) polymerase (PARP) inhibitor indicated for the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy.

Comparable Products: Rubraca (non-preferred), Lynpraza (non-preferred)

Proposed Designation & Rationale

Recommendation: Non-Preferred, approved via e-vote on 08/30/17

- Criteria for use and approval duration: See policy for criteria for use and approval durations.
  - For reference, Ohio Medicaid version of policy can be found at: Zejula.
  - All other state specific policies can be found under Pharmacy Policies by clicking on the appropriate state.

Clinical Implications/ Place in Therapy:
New drug for recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer was reviewed. Criteria for Zejula are written based on drug's package insert and Trial 1 (NOVA) that was included in package insert.

Ongoing Clinical Trials:

- There are 13 clinical trials (recruiting; enrolling by invitation; active, not recruiting): https://clinicaltrials.gov/ct2/results?term=niraparib&Search=Apply&recrs=a&recrs=f&recrs=d&age_v=&gndr=&type=&rslt

References:

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CVSHealth

CVS Caremark Pharmacy & Therapeutics
Condensed Drug Monograph

Zejula™ (niraparib) capsules
Tesaro, Inc.

INDICATION

Zejula (niraparib) is indicated for maintenance treatment for adults with recurrent epithelial ovarian, fallopian tube, and primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy.

KEY POINTS

Ovarian cancer is the fifth leading cause of cancer deaths among women, causing more deaths than any other cancer of the female reproductive system (American Cancer Society [ACS], 2017). In 2017, it is estimated approximately 22,000 women will be newly diagnosed, and 14,000 women will die from ovarian cancer in the United States. A family history, including inherited gene mutations such as breast cancer susceptibility gene (BRCA) 1 and BRCA2, is associated with early-onset disease and accounts for about 15% of ovarian cancer disease (National Comprehensive Cancer Network® [NCCN®], 2017). Women with BRCA1 or BRCA2 mutations have an increased risk of developing ovarian cancer (ACS, 2016).

Zejula (niraparib) was approved by the Food and Drug Administration (FDA) on March 27, 2017 and is the third FDA-approved poly (adenosine diphosphate [ADP]-ribose) polymerase (PARP) inhibitor indicated for ovarian cancer (FDA, 2017a). In contrast to Lynparza (olaparib) and Rubraca (rucaparib), Zejula (niraparib) is the only PARP inhibitor that is indicated for maintenance treatment for ovarian cancer, in patients with or without BRCA mutations, and does not require failing prior chemotherapies (Prescribing information: Lynparza, 2017; Rubraca, 2016; Zejula, 2017).

CLINICAL EFFICACY

The clinical efficacy and safety of Zejula (niraparib) was evaluated in a randomized, multicenter, placebo-controlled, double-blind, phase 3 trial in patients with platinum-sensitive, recurrent ovarian cancer with or without BRCA mutations (Evidence level Ib) (Mirza, 2016). The trial included 553 adults (median age 57 years to 63 years) with histologically diagnosed ovarian, fallopian tube, or primary peritoneal cancer with predominantly high-grade serous histologic feature. Of these, 203 patients were identified for inclusion in the germline BRCA mutation cohort and 350 patients in the non-germline BRCA cohort. Additional inclusion criteria included patients who received two or more platinum-based treatments and demonstrated sensitivity to platinum-based treatment. For penultimate platinum-based chemotherapy prior to study enrollment, patients must have had complete or partial response and disease progression more than six months after completion of last round of platinum therapy. Patients were randomized to receive either Zejula (niraparib) 300 mg (n = 234) or placebo (n = 116) once daily no later than eight weeks after completing their last dose of platinum-based therapy. The primary endpoint for the trial was progression-free survival (PFS). Treatment with Zejula (niraparib) compared with placebo significantly increased median PFS in both patients with deleterious germline BRCA mutations (21 months vs. 5.5 months; $p < 0.001$) and without deleterious germline BRCA mutations (9.3 months vs. 3.9 months; $p < 0.001$). Overall survival data were not yet mature.

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SAFETY

Warnings and precautions for Zejula (niraparib) include myelodysplastic syndrome (MDS)/acute myeloid leukemia (AML), bone marrow suppression, and cardiovascular adverse events. Patients should be monitored for hematological toxicity, and therapy should be discontinued if not resolved ≤ 28 days following interruption or if MDS/AML is confirmed. Grade 3 or higher hematologic adverse events including thrombocytopenia (29%), anemia (25%), and neutropenia (20%) have been reported in Zejula (niraparib)-treated patients. Zejula (niraparib) should not be initiated until patients recover from hematological toxicity caused by previous chemotherapy. Grade 3 to 4 hypertension occurred in 9% of Zejula (niraparib)-treated patients compared to 2% of placebo-treated patients. Blood pressure and heart rate should be monitored in patients receiving Zejula (niraparib), especially in patients with cardiovascular disorders. Medically manage hypertension with antihypertensives and adjust Zejula (niraparib) dose if necessary.

The most commonly reported adverse events with an incidence ≥ 10% include nausea (74%), thrombocytopenia (61%), fatigue/asthenia (57%), anemia (50%), constipation (40%), vomiting (34%), abdominal pain/distention (33%), neutropenia (30%), insomnia (27%), headache (26%), decreased appetite (25%), nasopharyngitis (23%), rash (21%), hypertension (20%), mucositis/stomatitis (20%), dyspnea (20%), diarrhea (20%), myalgia (19%), dyspepsia (18%), back pain (18%), dizziness (18%), leukopenia (17%), cough (16%), urinary tract infection (13%), arthralgia (13%), anxiety (11%), palpitations (10%), dry mouth (10%), aspartate aminotransferase or alanine aminotransferase elevation (10%), and dysgeusia (10%).

PRODUCT AVAILABILITY

Zejula (niraparib) is available as 100 mg capsules. Zejula (niraparib) launched on April 19, 2017 (RxPipeline, 2017). The average wholesale price (AWP) of Zejula (niraparib) is $196.67 per capsule (*Medi-Span® Master Drug Data Base v2.5 [MDDB®]*, 27 April 2017, Clinical Drug Information, LLC).

DOSAGE AND ADMINSTRATION

The recommended dosage of Zejula (niraparib) is three 100 mg oral capsules administered once daily with or without food. Treatment should be started no later than 8 weeks following the most recent platinum-containing regimen. Treatment should be continued until disease progression or unacceptable toxicity. For adverse events, treatment should be interrupted and/or the dosages should be decreased by 100 mg for up to two dose reductions.

PLACE IN THERAPY

- Zejula (niraparib) is the third FDA-approved PARP inhibitor indicated as monotherapy for the treatment of ovarian cancer but is the only PARP indicated for maintenance therapy (FDA, 2017a).
- In contrast to Rubraca (rucaparib) and Lynparza (olaparib), treatment with Zejula (niraparib) does not require failing previous lines of chemotherapy prior to use, is indicated in patients with or without BRCA mutations, is indicated only in platinum-sensitive patients, and is administered once daily.
- The NCCN Clinical Practice Guidelines In Oncology (NCCN Guidelines®) recommend three preferred targeted therapies indicated for recurrent epithelial ovarian cancer: bevacizumab, olaparib, and rucaparib in platinum-resistant patients (NCCN, 2017). The NCCN Guidelines® also recommend niraparib as an option for maintenance therapy for patients with platinum-sensitive ovarian cancer.
- Zejula (niraparib) significantly increased PFS compared with placebo in patients with platinum-sensitive, recurrent ovarian cancer with or without germline BRCA mutations or homologous recombinant deficiency status, with the greatest benefit demonstrated in patients with BRCA mutations (Mirza, 2016).
- Zejula (niraparib) is associated with the highest incidence of thrombocytopenia, anemia, neutropenia, leukopenia, and grade 3 or 4 hypertension when indirectly compared with other PARP inhibitors for ovarian cancer (Prescribing information: Lynparza, 2017; Rubraca, 2016; Zejula, 2017)
- No effect on overall survival has been demonstrated with any of the PARP inhibitors (Domcheck, 2016, FDA, 2017b; Kaufman, 2015; Mirza, 2016; Oaknin, 2017).

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CONDENSED DRUG MONOGRAPH PREPARED BY:

Angela S. Kang, Pharm.D.

May 17, 2017

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CareSource

Androgens

Current PDL	Recommended	Rationale	P&T Decision
<u>Preferred</u> Esterified estrogens and methyltestosterone (estratest, covaryx) Estrogens and methyltestosterone H.S. (Estratest H.S., Covaryx H.S.) Testosterone (Androgel) Gel Packet 1% (25 mg/2.5g) - *Diagnosis of Hypogonadism* - *Total Testosterone Lab Value = ≤ 300 ng/dL Before Treatment (For New Starts Only)* - *Quantity Limit: 75G/30 Days* Testosterone (Androgel, Testim, Vogelxo) Gel Packet 1% (50 mg/5 g) - *Diagnosis of Hypogonadism* - *Total Testosterone Lab Value = ≤ 300 ng/dL Before Treatment (For New Starts Only)* - *Quantity Limit: 150G/30 Days* Testosterone Cypionate (Depotestosterone) Injection Oil - *Diagnosis of Hypogonadism* - *Total Testosterone Lab Value = ≤ 300 ng/dL Before Treatment (For New Starts Only)* - *Quantity Limit: 50 to 400 mg every 2 to 4 weeks (FDA-approved dose range)* Testosterone Enanthate Vial - *Diagnosis of Hypogonadism* o *Total Testosterone Lab Value = ≤ 300 ng/dL Before Treatment (For New Starts Only)* o *Quantity Limit: 50 to 400 mg every 2 to 4 weeks (FDA-approved dose range) OR* - *Diagnosis of breast cancer (female)* o *Quantity Limit: 200 to 400 mg every 2 to 4 weeks OR* - *Diagnosis of delayed puberty (male)* o *Quantity Limit: 50 to 200 mg every 2 to 4 weeks for a limited duration (example: 4-6 months)* Testosterone TD (Fortesta) Gel Pump - *For new KY MCD members, requesting CC:* o *Must have been on this medication for at least the last 60 days per pharmacy claims or provider information* - *If previously approved for and currently using: Testim, Striant, Androxy, Methitest, Android (Testred), Androgel or Androderm OR* - *Diagnosis of hypogonadism* - *Total Testosterone lab value = ≤ 300ng/dL before treatment (for new starts only)* - *Quantity Limit: 60GMs per 30 days*	No changes at this time	- No new drugs - No new data or evidence to alter therapy	Approved

CareSource

Androgens			
Non-Preferred First-Testosterone cream - *Diagnosis of hypogonadism* - *Total Testosterone lab value = ≤ 300ng/dL before treatment (for new starts only) OR a Total Testosterone lab value within the normal range during treatment (for continuation of care)* - *Clinical reason (OH MCD ONLY) supported by chart notes why (after a 90 day trial of) the below cannot be used* - *Trial of: Testosterone TD (Fortesta) or Testosterone (Androgel, Testim, Vogelxo) 1% (50 mg/5G) Gel Packet (both still require a PA also)* First-Testosterone ointment - *Diagnosis of hypogonadism* - *Total Testosterone lab value = ≤ 300ng/dL before treatment (for new starts only) OR a Total Testosterone lab value within the normal range during treatment (for continuation of care)* - *Clinical reason (OH MCD ONLY) supported by chart notes why (after a 90 day trial of) the below cannot be used* - *Trial of: Testosterone TD (Fortesta) or Testosterone (Androgel, Testim, Vogelxo) 1% (50 mg/5G) Gel Packet (both still require a PA also)* Methitest tablet - *Diagnosis of hypogonadism* - *Total Testosterone lab value = ≤ 300ng/dL before treatment (for new starts only) OR a Total Testosterone lab value within the normal range during treatment (for continuation of care)* - *Clinical reason (OH MCD ONLY) supported by chart notes why (after a 90 day trial of) the below cannot be used* - *Trial of: Testosterone TD (Fortesta) or Testosterone (Androgel, Testim, Vogelxo) 1% (50 mg/5G) Gel Packet (both still require a PA also)* Methyltestosterone (Android, Testred) Capsule - *Diagnosis of hypogonadism* - *Total Testosterone lab value = ≤ 300ng/dL before treatment (for new starts only)* - *Clinical reason (OH MCD ONLY) supported by chart notes why (after a 90 day trial of) the below cannot be used* - *Trial of: Testosterone TD (Fortesta) or Testosterone (Androgel, Testim, Vogelxo) 1% (50 mg/5G) Gel Packet (both still require a PA also)* Natesto Testosterone Nasal Gel - *Total Testosterone lab value = ≤ 300ng/dL before treatment (for new starts only)*			

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Androgens			
- *Clinical reason (OH MCD ONLY) supported by chart notes why (after a 90 day trial of) the below cannot be used: Testosterone TD (Fortesta) or Testosterone (Androgel, Testim, Vogelxo) 1% (50 mg/5G) Gel Packet (both still require a PA also)* Striant Buccal Mucoadhesive - *Diagnosis of hypogonadism* - *Total Testosterone lab value = ≤ 300ng/dL before treatment (for new starts only)* - *Clinical reason (OH MCD ONLY) supported by chart notes why (after a 90 day trial of) the below cannot be used* - *Trial of: Testosterone TD (Fortesta) or Testosterone (Androgel, Testim, Vogelxo) 1% (50 mg/5G) Gel Packet (both still require a PA also)* Testone CIK IM Solution - *Diagnosis of hypogonadisim* - *Total testosterone lab value = ≤ 300 ng/dl before treatment for new starts, morning levels on different days (must submit lab documentation)* - *Baseline PSA less than 4 ng/mL (must submit lab documentation)* - *Hematocrit < 54% (must submit lab documentation)* - *Clinical reason (OH MCD only) supported by chart notes why after a 90-day trial (30-days KY) of each of the following cannot be used (must trial both, both require prior authorization): testosterone cypionate, testosterone ethanate* - Quantity Limit: 1 kit / 26 Days Testopel Pellet Implant - *Diagnosis of hypogonadism* - *Total Testosterone lab value = ≤ 300ng/dL before treatment (for new starts only)* - *Clinical reason (OH MCD ONLY) supported by chart notes why (after a 90 day trial of) the below cannot be used: Testosterone TD (Fortesta) or Testosterone (Androgel, Testim, Vogelxo) 1% (50 mg/5G) Gel Packet (both still require a PA also)* Testosterone TD (Androgel, Vogelxo) Gel Pump - *Diagnosis of Hypogonadism* - *Total Testosterone Lab Value = ≤ 300ng/dL Before Treatment (For New Starts Only)* - *Clinical Reason (OH MCD Only) Supported By Chart Notes Why (After A 90 Day Trial Of) The Below Cannot Be Used:* - *Testosterone TD (Fortesta) Or Testosterone (Androgel, Testim, Vogelxo) 1% (50 mg/5G) Gel Packet (Both Still Require A PA Also)* - *Quantity Limit: 100G/30 Days* Androderm Patch - *Diagnosis of Hypogonadism* - *Total Testosterone Lab Value = ≤ 300ng/dL Before Treatment (For New Starts Only)*			

Androgens			
- *Clinical Reason (OH MCD Only) Supported By Chart Notes Why (After A 90 Day Trial Of) The Below Cannot Be Used:* - *Testosterone TD (Fortesta) Or Testosterone (Androgel, Testim, Vogelxo) 1% (50 mg/5G) Gel Packet (Both Still Require A PA Also)* Androgel packet - *Diagnosis of Hypogonadism* - *Total Testosterone Lab Value = ≤ 300ng/dL Before Treatment (For New Starts Only) OR a Total Testosterone lab value within the normal range during treatment (for continuation of care)* - *Clinical Reason (OH MCD Only) Supported By Chart Notes Why (After A 90 Day Trial Of) The Below Cannot Be Used:* - *Testosterone TD (Fortesta) Or Testosterone (Androgel, Testim, Vogelxo) 1% (50 mg/5G) Gel Packet (Both Still Require A PA Also)* Androgel pump - *Diagnosis of Hypogonadism* - *Total Testosterone Lab Value = ≤ 300ng/dL Before Treatment (For New Starts Only) OR a Total Testosterone lab value within the normal range during treatment (for continuation of care)* - *Clinical Reason (OH MCD Only) Supported By Chart Notes Why (After A 90 Day Trial Of) The Below Cannot Be Used:* - *Testosterone TD (Fortesta) Or Testosterone (Androgel, Testim, Vogelxo) 1% (50 mg/5G) Gel Packet (Both Still Require A PA Also)* Androxy tablet - *Diagnosis of Hypogonadism* - *Total Testosterone Lab Value = ≤ 300ng/dL Before Treatment (For New Starts Only) OR a Total Testosterone lab value within the normal range during treatment (for continuation of care)* - *Clinical Reason (OH MCD Only) Supported By Chart Notes Why (After A 90 Day Trial Of) The Below Cannot Be Used:* - *Testosterone TD (Fortesta) Or Testosterone (Androgel, Testim, Vogelxo) Gel 1% (50 mg/5G) Packet (Both Still Require A PA Also)*			

CareSource

Anti-Viral: Hepatitis C

Current PDL	Recommended	Rationale	P&T Decision
<u>Preferred</u> Pibrentasvir/Glecaprevir (Mavyret®) - *IN:* o *Excluded Benefit* - *OH & KY:* o *Member not currently participating in alcohol abuse or illicit substance abuse* ▪ *One confirmed negative urine drug and alcohol screen within the last 60 days* ▪ *Previous abusers: confirm current monthly negative urine drug and alcohol screen for 3 consecutive months* o *Zepatier preferred for genotypes 1a, 1b, 4* o *Epclusa preferred for genotypes 2, 3, 5, 6* o *Failed trial of Epclusa or Zepatier due to allergy, side effects, or if viral load is present after completed course of therapy* o *Diagnosis of HCV genotypes 1, 2, 3, 4, 5, or 6 with or without cirrhosis* o *Diagnosis of Peg/Riba-experienced HCV genotypes 1, 2, 3, 4, 5, or 6 with or without cirrhosis* o *Diagnosis of Peg/Riba + sofosbuvir-experienced HCV genotype 2* o *Diagnosis of NS3 Protease Inhibitor and Peg/Riba-experienced HepC genotype 1* o *Diagnosis of non-NS5A inhibitor + sofosbuvir-containing regimen-experienced HCV genotype 1 with or without cirrhosis* o *Diagnosis of NS5A inhibitor DAA-experienced HCV genotype 1* Ribavirin (Rebetol®, Ribasphere®) - *IN:* o *Excluded Benefit* - *OH & KY:* o *Member not currently participating in alcohol abuse or illicit substance abuse* ▪ *One confirmed negative urine drug and alcohol screen within the last 60 days* ▪ *Previous abusers: confirm current monthly negative urine drug and alcohol screen for 3 consecutive months*	No changes at this time *Addition of Mavyret as preferred agent approved via e-vote on 11/22/2017. Policy currently being updated to reflect new criteria as preferred agent.	- No new drugs - No new data or evidence to alter therapy	Approved

CareSource

Anti-Viral: Hepatitis C

Non-Preferred Velpatasvir/Sofosbuvir (Epclusa®) - *Preferred treatment in types 1, 3, 4, 5, and 6* - *IN:* o *Excluded Benefit* - *OH & KY:* o *Hepatitis C without cirrhosis or with compensated cirrhosis* ▪ *Member is treatment-naïve without cirrhosis or treatment-naïve with compensated cirrhosis (Child-Turcotte-Pugh Class A); AND* ▪ *Member must be 18 years of age or older; AND* ▪ *Member has Genotype 2, 3, 5 or 6 (laboratory documentation required). Note: For genotypes 1 and 4 must use Zepatier (prior authorization required); AND* ▪ *Medication must be prescribed by a board certified hepatologist, gastroenterologist, infectious disease specialist or a nurse practitioner working with the above specialists; AND* ▪ *Member's documented viral load taken within 6 months of beginning therapy and submitted with chart notes; AND* ▪ *Member's life expectancy is not less than one year due to non-liver related comorbidities; AND* ▪ *Member has been tested for Hepatitis B; AND* ▪ *Member is not currently participating in alcohol abuse or illicit substance abuse program and has documented current monthly negative urine drug and alcohol screens for 3 consecutive months (laboratory documentation required); AND* ▪ *Member must have evidence of liver fibrosis stage 2, 3 or 4 confirmed by liver biopsy, or elastography only (lab chart notes required) unless one of the following (fibrosis stage F0-4 covered):* • *Hepatocellular carcinoma meeting Milan criteria (awaiting liver transplantation);*			

Anti-Viral: Hepatitis C

• *Post liver transplantation;* • *Extrahepatic disease (i.e. kidney disease: proteinuria, nephrotic syndrome or membranoproliferative glomerulonephritis; cryoglobulinemia with end- organ manifestations (e.g. vasculitis));* • *HIV or HBV coinfection.* ▪ *Dosage allowed: One tablet once daily for 12 weeks.* o *Hepatitis C for decompensated cirrhosis* ▪ *Member has decompensated cirrhosis (Child-Turcotte-Pugh Class B or C) who may or may not be a candidate for liver transplantation, including those with hepatocellular carcinoma; AND* ▪ *Member must be 18 years of age or older; AND* ▪ *Member has Genotype 1, 2, 3, 4, or 6 (laboratory documentation required); AND* ▪ *Member will be prescribed Epclusa (sofosbuvir/velpatasvir) in combination with ribavirin (if ribavirin ineligible must submit documentation of one of the following results obtained within the past month: neutrophils <750 cells/mm3; hemoglobin < 10 g/dL; platelets <50 000 cells/ mm3; OR documented hypersensitivity to drugs used to treat HCV); AND* ▪ *Medication must be prescribed by a board certified hepatologist, gastroenterologist, infectious disease specialist or a nurse practitioner working with the above specialists; AND* ▪ *Member's documented viral load taken within 6 months of beginning therapy and submitted with chart notes; AND* ▪ *Member's life expectancy is not less than one year due to non-liver related comorbidities; AND* ▪ *Member has been tested for Hepatitis B; AND* ▪ *Member is not currently participating in alcohol abuse or illicit substance abuse program and has documented current monthly negative urine drug and alcohol screens for 3 consecutive months (laboratory documentation required); AND*			

Anti-Viral: Hepatitis C

▪ *Evidence of stage 4 liver fibrosis confirmed by liver biopsy, or elastography only (lab chart notes required).* ▪ *Dosage allowed: One tablet once daily for 12 weeks. If member is ribavirin ineligible and request is for genotype 1, 3, 4 or 6 Epclusa may be approved for an additional 12 weeks, not to exceed the total of 24 weeks treatment duration.* Elbasvir/Grazoprevir (Zepatier®) - *Preferred treatment in types 1 and 4* - *IN:* o *Excluded Benefit* - *OH:* o *Retail Lock List* - *OH & KY:* o *Hepatitis C without cirrhosis or with compensated cirrhosis* ▪ *Member is treatment-naïve without cirrhosis or treatment-naïve with compensated cirrhosis (Child-Turcotte-Pugh Class A); AND* ▪ *Member must be 18 years of age or older; AND* ▪ *Member has Genotype 1a, 1b or 4 (laboratory documentation required). Note: For Genotypes 2, 3, 5, and 6 must use Epclusa (prior authorization required); AND* ▪ *Member has been tested for NS5A resistance-associated polymorphisms if Genotype is 1a; AND* ▪ *Medication must be prescribed by a board certified hepatologist, gastroenterologist, infectious disease specialist or a nurse practitioner working with the above specialists; AND* ▪ *Member's documented viral load taken within 6 months of beginning therapy and submitted with chart notes; AND* ▪ *Member's life expectancy is not less than one year due to non-liver related comorbidities; AND* ▪ *Member has been tested for Hepatitis B; AND* ▪ *Member is not currently participating in alcohol abuse or illicit substance abuse program and has documented current monthly negative urine drug and alcohol*			

screens for 3 consecutive months (laboratory documentation required); AND ▪ *Member has not been diagnosis with decompensated cirrhosis.* ▪ *Dosage allowed: One tablet once daily for 12 weeks OR one tablet once daily with ribavirin for 16 weeks if member has NS5A resistance-associated polymorphisms.* o *OH only:* ▪ *Member has evidence of stage 2, 3 or 4 liver fibrosis confirmed by liver biopsy, or elastography only (lab chart notes required) unless one of the following (fibrosis stage F0-4 covered):* • *Hepatocellular carcinoma meeting Milan criteria (awaiting liver transplantation);* • *Post liver transplantation;* • *Extrahepatic disease (i.e., kidney disease: proteinuria, nephrotic syndrome or* • *membranoproliferative glomerulonephritis; cryoglobulinemia with end- organ manifestations (e.g.* • *vasculitis));* • *HIV or HBV coinfection.* o *KY only:* ▪ *Member has evidence of stage 3 or 4 liver fibrosis confirmed by liver biopsy, or elastography only (lab chart notes required) unless one of the following (fibrosis stage F0-4 covered):* • *Hepatocellular carcinoma meeting Milan criteria (awaiting liver transplantation);* • *Post liver transplantation;* • *Extrahepatic disease (i.e., kidney disease: proteinuria, nephrotic syndrome or membranoproliferative glomerulonephritis; cryoglobulinemia with end- organ manifestations (e.g. vasculitis));* • *HIV or HBV coinfection.*			

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Anti-Viral: Hepatitis C			
Sofosbuvir (Sovaldi®) - *IN:* o *Excluded Benefit* - *OH & KY:* o *Lower Cost* o *Member not currently participating in alcohol abuse of illicit substance abuse* ▪ *One confirmed negative urine drug and alcohol screen within the last 60 days* ▪ *Previous abusers: confirmed current monthly negative urine drug and alcohol screen for 3 consecutive months* o *Zepatier preferred for genotypes 1a, 1b, 4* o *Epclusa preferred for genotypes 1, 2, 3, 5, 6* o *Failed trial of Epclusa or Zepatier due to allergy, side effects, or if viral load is present after completed course of therapy* o *Diagnosis of treatment naïve HepC genotypes 1a, 1b, 2, 3 without cirrhosis or 2 or 3 with cirrhosis* ▪ *In combination with Olysio or Daklinza* o *Diagnosis of Peg/Riba-experienced HepC genotypes 1a, 1b, 2, or 3 without cirrhosis or genotype 2 or 3 with cirrohosis* ▪ *In combination with Olysio or Daklinza* Daclatasvir (Daklinza®) - *IN:* o *Excluded Benefit* - *OH & KY:* o *Lower Cost Alternative* o *Member not currently participating in alcohol abuse or illicit substance abuse* ▪ *One confirmed negative urine drug and alcohol screen within the last 60 days* ▪ *Previous abusers: confirm current monthly negative urine drug and alcohol screen for 3 consecutive months* o *Zepatier preferred for genotypes 1a, 1b, 4* o *Epclusa preferred for genotypes 1, 2, 3, 5, 6* o *Failed trial of Epclusa or Zepatier due to allergy, side effects, or if viral load is present after completed course of therapy* o *Diagnosis of treatment naïve HepC genotypes 1a, 1b, 2, or 3 without cirrhosis or genotypes 2 or 3 with compensated cirrhosis*			

Anti-Viral: Hepatitis C

▪ *In combination with Sovaldi for 12 weeks* ▪ *Clinical reason why unable to take ribavirin* o *Diagnosis of Peg/Riba-experienced HepC genotypes 1a, 1b, 2, or 3 without cirrhosis or genotype 2 with cirrhosis* ▪ *In combination with Sovaldi for 12 weeks* Ledipasvir/Sofosbuvir (Harvoni®) - *IN:* o *Excluded Benefit* - *OH & KY:* o *Lower Cost Alternative* o *Member not currently participating in alcohol abuse or illicit substance abuse* ▪ *One confirmed negative urine drug and alcohol screen within the last 60 days* ▪ *Previous abusers: confirm current monthly negative urine drug and alcohol screen for 3 consecutive months* o *Zepatier preferred for genotypes 1a, 1b, 4* o *Epclusa preferred for genotypes 1, 2, 3, 5, 6* o *Failed trial of Epclusa or Zepatier due to allergy, side effects, or if viral load is present after completed course of therapy* o *Diagnosis of treatment naïve HepC genotypes 1a, 1b, or 4 without cirrhosis or genotypes 1a, 1b, 4, 5, or 6 with cirrhosis* o *Diagnosis of Peg/Riba-experienced HepC genotypes 1a, 1b, 4, 5, or 6 with or without cirrhosis* o *Diagnosis of NS3 Protease Inhibitor and Peg/Riba-experienced HepC genotype 1* o *Diagnosis of non-NS5A inhibitor + sofosbuvir-containing regimen-experienced HCV genotype 1 without cirrhosis* Paritaprevir/Ombitasvir/Ritonavir (Technivie®) - *IN:* o *Excluded Benefit* - *OH & KY:* o *Lower Cost Alternative* o *Member not currently participating in alcohol abuse or illicit substance abuse* ▪ *One confirmed negative urine drug and alcohol screen within the last 60 days*			

Anti-Viral: Hepatitis C

▪ *Previous abusers: confirm current monthly negative urine drug and alcohol screen for 3 consecutive months* o *Zepatier preferred for genotype 1a, 1b, and 4* o *Failed trial of Zepatier due to allergy, side effects, or if viral load is present after completed course of therapy* o *Diagnosis of HCV genotypes 1a or 1b without cirrhosis or genotypes 1b or 4 with cirrhosis* o *Diagnosis of Peg/Riba-experienced HCV genotypes 1a, 1b, or 4 without cirrhosis or 1b or 4 with cirrhosis* Sofosbuvir/Velpatasvir/Voxilaprevir (Vosevi®) - *IN:* o *Excluded Benefit* - *OH & KY:* o *Lower Cost Alternative* o *Member not currently participating in alcohol abuse or illicit substance abuse* ▪ *One confirmed negative urine drug and alcohol screen within the last 60 days* ▪ *Previous abusers: confirm current monthly negative urine drug and alcohol screen for 3 consecutive months* o *Zepatier preferred for genotypes 1a, 1b, 4* o *Epclusa preferred for genotypes 2, 3, 5, 6* o *Failed trial of Epclusa or Zepatier due to allergy, side effects, or if viral load is present after completed course of therapy* o *Diagnosis of treatment-naïve HCV genotype 3 with cirrhosis* o *Diagnosis of Peg/Riba-experienced HCV genotype 3 with or without cirrhosis* o *Diagnosis of non-NS5A inhibitor + sofosbuvir-containing regimen-experienced HCV genotype 1 with or without cirrhosis* o *Diagnosis of NS5A inhibitor DAA-experienced HCV genotype 1, 3, 4, 5, or 6 with or without cirrhosis* Ombitasvir/Dasabuvir/Paritaprevir/Ritonavir (Viekira Pak®, Viekira XR®) - *IN:* o *Excluded Benefit* - *OH & KY:* o *Lower Cost Alternative*			

Anti-Viral: Hepatitis C			
o *Member not currently participating in alcohol abuse or illicit substance abuse* ▪ *One confirmed negative urine drug and alcohol screen within the last 60 days* ▪ *Previous abusers: confirm current monthly negative urine drug and alcohol screen for 3 consecutive months* o *Zepatier preferred for genotype 1* o *Failed trial of Zepatier due to allergy, side effects, or if viral load is present after completed course of therapy* o *Diagnosis of treatment-naïve HCV genotypes 1a or 1b without cirrhosis or genotype 1b with cirrhosis* o *Diagnosis of Peg/Riba-experienced HCV genotypes 1a or 1b without cirrhosis or 1b with cirrhosis* Simeprevir (Olysio®) - *IN:* o *Excluded Benefit* - *OH & KY:* o *Lower Cost Alternative* o *Member not currently participating in alcohol abuse or illicit substance abuse* ▪ *One confirmed negative urine drug and alcohol screen within the last 60 days* ▪ *Previous abusers: confirm current monthly negative urine drug and alcohol screen for 3 consecutive months* o *Zepatier preferred for genotype 1* o *Failed trial of Zepatier due to allergy, side effects, or if viral load is present after completed course of therapy* o *Diagnosis of treatment-naïve HCV genotypes 1a or 1b without cirrhosis* ▪ *In combination with Sovaldi for 12 weeks* o *Diagnosis of Peg/Riba-experienced HCV genotypes 1a or 1b without cirrhosis* ▪ *In combination with Sovaldi for 12 weeks*			

CareSource

Antiviral: Influenza Agents

Current PDL	Recommended	Rationale	P&T Decision
<u>Preferred</u> **Oseltamivir** (Tamiflu) gelcaps - *30 mg: 20 caps/180 days* - *45 mg: 10 caps/180 days* - *75 mg: 10 caps/180 days* **Oseltamivir** (Tamiflu) suspension - *180 mL/180 days* **Zanamivir** (Relenza) diskhaler - *Diskhaler: 1 inhaler/180 days* <u>Non-preferred</u> **Paramivir** (Rapivab) intravenous solution - *Disease: treatment of acute, uncomplicated influenza in adults who have been symptomatic for 2 days or less*	None	- No new data or evidence to alter preferred agents or criteria	Approved

Anti-Infectives: Oral Fluoroquinolones

Current PDL	Recommended	Rationale	P&T Decision
<u>Preferred</u> **Ciprofloxacin** (Cipro) tablet, ER tablet, oral suspension **Levofloxacin** (Levaquin) tablets **Ofloxacin** tablets - *No PA required for: 2 tabs/day* <u>Non-Preferred</u> **Moxifloxacin** (Avelox) tablets - *One time Trial of: ciprofloxacin or levofloxacin* **Gemifloxacin** (Factive) tablets - *One time Trial of: ciprofloxacin or levofloxacin*	No changes at this time	- No new drugs - No new data or evidence to alter therapy	Approved

CareSource

Bisphosphonates

Current PDL	Recommended	Rationale	P&T Decision
<u>Preferred</u> Alendronate tablet Ibandronate tablet <u>Non-Preferred</u> Alendronate (Fosamax) solution - *Clinical reason (OH MCD ONLY) supported by chart notes why (after a trial of) the alendronate (Fosamax) tablets cannot be used* Risedronate (Actonel) tablets - *Approve for 1 Year: Will be added to formulary* Risedronate sodium (Atelvia) DR tablets - *Allergy, side effects or intolerance to: alendronate (Fosamax) OR Trials of: alendronate* Ibandronate (Boniva) syringe, vial; Zoledronic acid (Reclast, Zometa) vial - *Hypercalcemia of malignancy when ALL of the following are met:* o *Albumin-corrected serum calcium of 12 mg/dL (3 mmol/L) or greater* o *Hypercalcemia due to malignancy* - *Skeletal metastases from cancer, as indicated by ALL of the following:* o *Standard antineoplastic therapy continues* o *Osteolytic bone lesions, bone pain, or metastases from 1 or more of the* o *following:* ▪ *Breast cancer* ▪ *Multiple myeloma* - *Moderate to severe Paget's disease, as indicated by 1 or more of the following:* o *Asymptomatic, but likely progression in high-risk areas, as indicated by 1 or more of the following:* ▪ *Potential compression would cause neurologic syndrome* ▪ *Potential fracture in weight-bearing long bone* o *Symptoms from active bone lesions, including 1 or more of the following:* ▪ *Back pain due to Pagetic radiculopathy or arthropathy* ▪ *Bone pain* ▪ *Fissure fractures* ▪ *Headache with skull involvement*	No changes at this time	- No new drugs - No new data or evidence to alter therapy	Approved

CareSource

Bisphosphonates

▪ *Other neurologic syndromes* o *Elective surgery planned for Pagetic site* o *Hypercalcemia from immobilization* o *Serum alkaline phosphatase elevated to 2 or more times upper limit of normal age-specific reference range* - *Osteoporosis, as indicated by ALL of the following:* o *Oral bisphosphonate medications are not therapeutic option, as indicated by 1 or more of the following:* ▪ *Esophageal dysmotility or varices* ▪ *Intolerance or failure to trials of 2 or more different oral* ▪ *bisphosphonate drugs* ▪ *Patient not adherent to oral bisphosphonate medications* ▪ *Patient unable to stand or sit upright for 30 to 60 minutes* o *Osteoporosis, and need for treatment, as indicated by 1 or more of the following:* ▪ *Documented postmenopausal osteoporosis, as indicated by 1 or* ▪ *more of the following* • *Femoral neck, spine, or total hip bone mineral density Tscore minus 2.5 or less* • *Hip or vertebral fragility (ie, low-trauma) fracture in female older than 50 years* ▪ *For zoledronic acid use only, osteoporosis in male, as indicated by 1 or more of the following:* • *Femoral neck, spine, or total hip bone mineral density Tscore minus 2.5 or less* • *Hip or vertebral fragility fracture in patient older than 50 years* • *Osteoporosis secondary to hypogonadism and failure of or intolerance to testosterone* ▪ *For zoledronic acid use only, prevention or treatment of glucocorticoid-induced osteoporosis in male or female, as indicated by ALL of the following:* • *Duration of glucocorticoid therapy expected to be 1 or more of the following:* o *Three months or more for male 50 years or older*			

Bisphosphonates

o *Three months or more for any patient with history of fragility (ie, low-trauma fracture)* o *Three months or more for postmenopausal female* o *Twelve months or more for any patient without history of fragility fracture* • *Daily dose of glucocorticoid, as indicated by 1 or more of the following:* o *Glucocorticoid daily dose equivalent to 7.5 mg or more of prednisone* o *Glucocorticoid daily dose equivalent to 5 mg or more of prednisone and 1 or more of the following risk factors for fracture:* ▪ *Alcohol intake of 3 or more drinks per day* ▪ *BMI less than 20* ▪ *Current or past history of cigarette smoking* ▪ *Osteoporosis (ie, femoral neck, spine, or total hip bone mineral density T-score minus 2.5 or less)* ▪ *Parental hip fracture* ▪ *Previous or current fracture* ▪ *Rheumatoid arthritis* Pamidronate vial - *OH & KY* o *Included in parenteral calcium channel regulators policy* - *IN* o *Diagnosis of hypercalcemia of malignancy, pagets, or osteolytic bone metastases of breast cancer or bone lesions of multiple myeloma* Etidronate tablet - *If fax states allergy, side effects or intolerance to: alendronate (Fosamax) OR* - *Trials of: alendronate*			

Calcium Regulators

Current PDL	Recommended	Rationale	P&T Decision
<u>Preferred</u> Alendronate tablet Ibandronate tablet Calcitonin (Miacalcin) nasal spray Fortical nasal spray <u>Non-Preferred</u> Alendronate (Fosamax) solution - *Clinical reason (OH MCD ONLY) supported by chart notes why (after a trial of) the alendronate (Fosamax) tablets cannot be used* Risedronate (Actonel) tablets - *Approve for 1 Year: Will be added to formulary* Risedronate sodium (Atelvia) DR tablets - *Allergy, side effects or intolerance to: alendronate (Fosamax) OR Trials of: alendronate* Ibandronate (Boniva) syringe, vial; Zoledronic acid (Reclast, Zometa) vial - *Hypercalcemia of malignancy when ALL of the following are met:* o *Albumin-corrected serum calcium of 12 mg/dL (3 mmol/L) or greater* o *Hypercalcemia due to malignancy* - *Skeletal metastases from cancer, as indicated by ALL of the following:* o *Standard antineoplastic therapy continues* o *Osteolytic bone lesions, bone pain, or metastases from 1 or more of the* o *following:* ▪ *Breast cancer* ▪ *Multiple myeloma* - *Moderate to severe Paget's disease, as indicated by 1 or more of the following:* o *Asymptomatic, but likely progression in high-risk areas, as indicated by 1 or more of the following:*	No changes at this time	- No new drugs - No new data or evidence to alter therapy	Approved

Calcium Regulators

▪ *Potential compression would cause neurologic syndrome* ▪ *Potential fracture in weight-bearing long bone* o *Symptoms from active bone lesions, including 1 or more of the following:* ▪ *Back pain due to Pagetic radiculopathy or arthropathy* ▪ *Bone pain* ▪ *Fissure fractures* ▪ *Headache with skull involvement* ▪ *Other neurologic syndromes* o *Elective surgery planned for Pagetic site* o *Hypercalcemia from immobilization* o *Serum alkaline phosphatase elevated to 2 or more times upper limit of normal age-specific reference range* - *Osteoporosis, as indicated by ALL of the following:* o *Oral bisphosphonate medications are not therapeutic option, as indicated by 1 or more of the following:* ▪ *Esophageal dysmotility or varices* ▪ *Intolerance or failure to trials of 2 or more different oral* ▪ *bisphosphonate drugs* ▪ *Patient not adherent to oral bisphosphonate medications* ▪ *Patient unable to stand or sit upright for 30 to 60 minutes* o *Osteoporosis, and need for treatment, as indicated by 1 or more of the following:* ▪ *Documented postmenopausal osteoporosis, as indicated by 1 or* ▪ *more of the following* • *Femoral neck, spine, or total hip bone mineral density Tscore minus 2.5 or less* • *Hip or vertebral fragility (ie, low-trauma) fracture in female older than 50 years* ▪ *For zoledronic acid use only, osteoporosis in male, as indicated by 1 or more of the following:* • *Femoral neck, spine, or total hip bone mineral density Tscore minus 2.5 or less*			

Calcium Regulators

• *Hip or vertebral fragility fracture in patient older than 50 years* • *Osteoporosis secondary to hypogonadism and failure of or intolerance to testosterone* ▪ *For zoledronic acid use only, prevention or treatment of glucocorticoid-induced osteoporosis in male or female, as indicated by ALL of the following:* • *Duration of glucocorticoid therapy expected to be 1 or more of the following:* o *Three months or more for male 50 years or older* o *Three months or more for any patient with history of fragility (ie, low-trauma fracture)* o *Three months or more for postmenopausal female* o *Twelve months or more for any patient without history of fragility fracture* • *Daily dose of glucocorticoid, as indicated by 1 or more of the following:* o *Glucocorticoid daily dose equivalent to 7.5 mg or more of prednisone* o *Glucocorticoid daily dose equivalent to 5 mg or more of prednisone and 1 or more of the following risk factors for fracture:* ▪ *Alcohol intake of 3 or more drinks per day* ▪ *BMI less than 20* ▪ *Current or past history of cigarette smoking* ▪ *Osteoporosis (ie, femoral neck, spine, or total hip bone mineral density T-score minus 2.5 or less)*			

Calcium Regulators

▪ *Parental hip fracture* ▪ *Previous or current fracture* ▪ *Rheumatoid arthritis* Pamidronate vial - *OH & KY* o *Included in parenteral calcium channel regulators policy* - *IN* o *Diagnosis of hypercalcemia of malignancy, pagets, or osteolytic bone metastases of breast cancer or bone lesions of multiple myeloma* Etidronate tablet - *If fax states allergy, side effects or intolerance to: alendronate (Fosamax) OR* - *Trials of: alendronate*			

Contraceptives

Current PDL	Recommended	Rationale	P&T Decision
<u>Preferred</u> Estrogen/progesterone: altavera tab alyacen tab 1/35, 7/7/7 amethia tab aranelle tab ashlyna tab aviane tab azurette tab 28 day caziant pak cesia pak chateal tab 0.15/30 cryselle-28 tab 28 tabs	No changes at this time	- No new drugs - No new data or evidence to alter therapy	Approved

CareSource

Contraceptives			
cyclafem tab 1/35 cyclafem tab 7/7/7 dasetta tab 1/3, 7/7/7 elinest tab emoquette tab enpresse-28 tab falmina tab gianvi tab 3-0.02mg gildess fe tab 1.5/30, 1/20, 1.5/30, 1/20 introvale tab junel 1.5/30 tab junel 1/20 tab junel fe tab 1.5/30, 1/20 kariva tab 28 day kelnor tab 1/35 kurvelo tab 0.15/30 larin tab 1.5/30 leena tab lessina tab levonest tab levonorg-eth est tab 0.1-0.02mg(84) & ethest tab 0.01mg(7) levora-28 tab 0.15/30 LO LOESTRIN TAB lomedia 24 tab fe loryna tab 3-0.02mg low-ogestrel tab lutera tab marlissa tab 0.15/30 "mibelas 24 chw fe (RECALLED)" mono-linyah tab 0.25-35 mononessa tab myzilra tab necon tab 0.5/35 necon tab 1/35 necon tab 1/50-28 necon tab 7/7/7 NECON TAB 10/11-28			

CareSource

Contraceptives			
nikki tab 3-0.02mg norethindrone & ethinyl estradiol-fe chew tab 0.8 mg-25 mcg nortrel tab 0.5/35 nortrel tab 1/35 nortrel tab 7/7/7 ocella tab 3-0.03mg ogestrel tab orsythia tab pirmella tab 1/35 portia-28 tab previfem tab reclipsen tab solia tab sprintec 28 tab 28 day sronyx tab syeda tab 3-0.03mg tilia fe tab tri-linyah tab tri-previfem tab tri-sprintec tab trinessa tab trivora-28 tab velivet pak vestura tab 3-0.02mg viorele tab wera tab 0.5/35 zarah tab 3-0.03mg zovia 1/35e tab zovia 1/50e tab Progesterone Only: Camila Deblitane Errin Heather Jolivette Nora-BE			

CareSource

Contraceptives

Emergency Contraceptives: Levonorgestrel, Next Choice One-Step, My Way, Take Action, Fallback Solo (Plan B One-Step) Ulipristal 30 mg Non-Oral Contraceptives: Depo-provera (medroxyprogesterone) 150 mg/mL Depo-provera (medroxyprogesterone) 400 mg/mL Medroxyprogesterone acetate 150 mg/mL Medroxyprogesterone acetate 2.5 mg, 5 mg, 10 mg Implanon Mirena Liletta IUD Skyla IUD Xulane Nuva-Ring <u>Non-Preferred</u> amethyst tab 90-20mcg, levonorgestrel & ethinyl estradiol (91-day)tab 0.15-0.03 mg, levonorgestrel & ethinyl estradiol tab 0.15mg-30 mcg - *Continuity of Care OR* - *Trial of any formulary birth control* fayosim tab - *Continuity of care OR* - *Trial of any formulary birth control* Lo Loestrin Fe Tablet - *Continuity of care OR* - *Trial of any formulary birth control* NATAZIA TAB - *Continuity of care OR* - *Trial of any formulary birth control* norgestimate & ethinyl estradiol tab 0.25mg-35 mcg, 0.18-25/0.215-25/0.25-25 mg-mcg, 0.18-35/0.215-35/0.25-35 mg-mcg - *Continuity of care OR* - *Trial of any formulary birth control* SAFYRAL TAB - *Continuity of care OR* - *Trial of any formulary birth control*			

CareSource

Contraceptives			
TAYTULLA CAP - *Continuity of care OR* - *Trial of any formulary birth control* zenchent fe chw 0.4mg-35 , zenchent tab - *Continuity of care OR* - *Trial of any formulary birth control* Depo-Provera SubQ 104 mg - *Diagnosis of Endometriosis-associated pain or contraception AND* - *Clinical Reason (OH MCD ONLY) supported by chart notes why (after a 90 day trial of) the below cannot be used: Medroxyprogesterone acetate (Depo-provera) IM 150 mg/mL* ParaGard - *Diagnosis of contraception* - *No PA required if billed on medical benefit* Kyleena IUD - *Diagnosis of prevention of pregnancy* - *No PA required on medical benefit*			

Dermatology: Acne			
Current PDL	Recommended	Rationale	P&T Decision
<u>Preferred</u> Differin OTC Benzoyl peroxide cleanser (Panoxyl-4) Benzoyl peroxide cleanser (Panoxyl-8) - *[Dose: 6- grams/26 days]* Benzoyl peroxide lotion Benzoyl peroxide wash (Panoxyl) - *[Dose: 227ml/26 days]* BENZOYL PEROXIDE, CLEARPLEX V, PERSA-GEL XS, BP GEL (BENZAC AC) GEL - *[Dose: 60 Grams / 26 Days]*	No changes at this time	- No new drugs - No new data or evidence to alter therapy	Approved

BENZOYL PEROXIDE, DESQUAM-X, BP WASH, BPO-5 WASH (BENZAC AC, BENZAC W) WASH LIQUID - *[Dose: 227 mL / 26 Days]* BENZOYL PEROXIDE, OSCION (TRIAZ) CLEANSER BENZOYL PEROXIDE-ERYTHROMYCIN (BENZAMYCIN) GEL - *[Dose: 46.6 Grams (1 jar) / 26 Days]* Erythromycin gel/pledgets - *[Dose: 60 Grams / 26 Days]* Eryhthromycin solution - *[Dose: 60 mL / 26 Days]* SALICYLIC ACID SHAMPOO (Salex) Tretinoin capsules <u>Non-Preferred</u> Adapalene (Differin) gel pump 0.3% - *Clinical reason (OH MCD ONLY) supported by chart notes why (after a trial of) the below cannot be used: Adapalene (Differin) 0.1% cream or gel* - *[Dose: 45 Grams (1 Tube) / 26 Days]* Adapalene (Differin) lotion - *Clinical reason (OH MCD ONLY) supported by chart notes why (after a trial of) the below cannot be used;* ▪ *Adapalene (Differin) 0.1% cream or gel* ▪ *[Dose: 59 ML (1 bottle) / 26 Days]* Adapalene (Differin) cream - *OH & KY* o *30 day trial of Differin OTC OR* o *Claims history of 1 day use in the past 120 days* - *IN* o *Clinical Reason Supported By Chart Notes Why (After A Trial Of) The Below Cannot Be Used: Differin OTC* Adapalene (Differin) gel - *OH & KY* o *30 day trial of Differin OTC OR* o *Claims history of 1 day use in the past 120 days* - *IN* o *Clinical Reason Supported By Chart Notes Why (After A Trial Of) The Below Cannot Be Used: Differin OTC* Adapalene-benzoyl peroxide (Epiduo) gel			

- *Clinical reason (OH MCD ONLY) supported by chart notes why (after a trial of) the below cannot be used:*
  ▪ *benzoyl peroxide gel 2.5% and adapalene gel 0.1%*
  ▪ *[Dose: 45 Grams / 26 Days]*
Acanya gel pump
- *Clinical Reason (OH MCD Only) Supported By Chart Notes Why (After A 90 Day Trial Of) The Below Cannot Be Used:*
  ▪ *Benzoyl Peroxide 2.5% Gel AND Cindamycin, ClindaMax (Cleocin T) 1% Lotion, Clindamycin Swab (Cleocin T) 1% Pledgets, Or Clindamycin Phosphate 1% Solution Separately Used Together At The Same Time*
  ▪ *[Dose: 50 grams / 26 Days]*
Benzaclin gel pump
- *Clinical reason (OH MCD ONLY) supported by chart notes why (after a trial of) the below cannot be used*
- *BENZOYL PEROXIDE 5% GEL (Panoxyl) WITH CLINDAMYCIN, CLINDAMAX (CLEOCIN T)*
- *1% LOTION, CLINDAMYCIN SWAB (CLEOCIN T) 1% PLEDGETS, CLINDAMYCIN PHOSPHATE 1% SOLUTION separately used together*
- *[Dose: 50 Grams (1 Tube) / 26 Days]*
Benzamycin pak gel
- *Clinical reason (OH MCD ONLY) supported by chart notes why (after a trial of) the below cannot be used*
  ▪ *BENZOYL PEROXIDE-ERYTHROMYCIN (BENZAMYCIN) 5-3% GEL*
Benzepro, benzoyl peroxide (Benzefoam) emollient foam
- *Clinical reason (OH MCD ONLY) supported by chart notes why (after a 90 day trial of) the below cannot be used*
- *BENZOYL PEROXIDE 2.5% WASH or GEL (PANOXYL), BENZOYL PEROXIDE 4% CLEANSER (PANOXYL), BENZOYL PEROXIDE 5% GEL (PANOXYL), BENZOYL PEROXIDE 5% LOTION, BENZOYL PEROXIDE 3%, 6%, 9% CLEANSER (TRIZ), BENZOYL PEROXIDE 10% Wash (DESQUAM-X/PANOXYL), BENZOYL PEROXIDE 10% GEL (PANOXYL), BENZOYL PEROXIDE 10% LOTION or BENZOYL PEROXIDE-ERYTHROMYCIN (BENZAMYCIN) 5-3% GEL*
- *[Dose: 60 Grams / 26 Days]*
Benziq gel			

- *Clinical reason (OH MCD ONLY) supported by chart notes why (after a 90 day trial of) the below cannot be used* ▪ *BENZOYL PEROXIDE 2.5% WASH or GEL (PANOXYL), BENZOYL PEROXIDE 4% CLEANSER (PANOXYL), BENZOYL PEROXIDE 5% GEL (PANOXYL), BENZOYL PEROXIDE 5% LOTION, BENZOYL PEROXIDE 3%, 6%, 9% CLEANSER (TRIZ), BENZOYL PEROXIDE 10% Wash (DESQUAM-X/PANOXYL), BENZOYL PEROXIDE 10% GEL (PANOXYL), BENZOYL PEROXIDE 10% LOTION or BENZOYL PEROXIDE-ERYTHROMYCIN (BENZAMYCIN) 5-3% GEL* Benziq wash - *Clinical reason (OH MCD ONLY) supported by chart notes why (after a 90 day trial of) the below cannot be used* ▪ *BENZOYL PEROXIDE 2.5% WASH or GEL (PANOXYL), BENZOYL PEROXIDE 4% CLEANSER (PANOXYL), BENZOYL PEROXIDE 5% GEL (PANOXYL), BENZOYL PEROXIDE 5% LOTION, BENZOYL PEROXIDE 3%, 6%, 9% CLEANSER (TRIZ), BENZOYL PEROXIDE 10% Wash (DESQUAM-X/PANOXYL), BENZOYL PEROXIDE 10% GEL (PANOXYL), BENZOYL PEROXIDE 10% LOTION or BENZOYL PEROXIDE-ERYTHROMYCIN (BENZAMYCIN) 5-3% GEL* Clindamycin-Tretinoin (Veltin, Ziana) Gel - *Clinical Reason (OH MCD Only) Supported By Chart Notes Why (After A 30 Day Trial Of) The Below Cannot Be Used:* ▪ *Clindamycin Pledgets Or Clindamycin Topical Solution AND Tretinoin Gel Or Cream* ▪ *[Dose: 60 Grams (1 Tube) / 26 Days]* Absorica/Claravis/Myorisan/ Zenatane capsule - *Continuity of Care OR* - *Diagnosis of Non-Hodgkin's Lymphoma Or Prophylaxis Of Non-Melanoma Skin Cancers OR* - *Diagnosis of Acne* - *Trials Of 90 Days Total Of Each Group Below Either At The Same Time, Separately, Or Overlapping* - *Topicals: Benzoyl Peroxide 5% Or 10%; Benzoyl Peroxide 4% Or 8% Liquid (Panoxyl), Erythromycin/Benzoyl (Benzamycin), Sulfacetamide (Klaron), Clindamycin Topical (Cleocin T), Erythromycin Topical, Tretinoin Cream Or Gel Or Adapalene 0.1%*			

Gel Or Cream [Or Previously Approved For And Currently Using: Tazorac, Benzamycin, Acanya, Akne-Mycin, Or Tretinoin Microsphere] AND - *Orals: Minocycline, Doxycycline, Tetracycline, Or Erythromycin* - *[Dose: 60 Capsules/26 Days]* Salicylic acid (Salvax) foam - *Clinical reason (OH MCD ONLY) supported by chart notes why (after a trial of) the below cannot be used* ▪ *OTC SALICYLIC ACID 6% CREAM, GEL, OR LOTION* Salicylic acid cream kit - *Clinical reason (OH MCD ONLY) supported by chart notes why (after a trial of) the below cannot be used* ▪ *OTC SALICYLIC ACID 6% CREAM* Salicylic acid lotion kit - Clinical reason (OH MCD ONLY) supported by chart notes why (after a trial of) the below cannot be used ▪ OTC SALICYLIC ACID 6% LOTION - [Dose: 592 mL (1 kit) / 26 Days] SODIUM SULFACETAMIDE (OVACE PLUS WASH) LIQUID WASH - Clinical Reason Supported By Chart Notes Why (After A Trial Of) The Below Cannot Be Used: ▪ sulfacetamide sodium (Klarion) 10% lotion - [Dose: 340 Grams (1 Tube) / 26 Days] SODIUM SULFACETAMIDE (OVACE PLUS) SHAMPOO - Clinical Reason Supported By Chart Notes Why (After A Trial Of) The Below Cannot Be Used: ▪ sulfacetamide sodium (Klarion) 10% lotion - [Dose: 237 mL (1 bottle) / 26 Days] SODIUM SULFACETAMIDE WITH SULFUR (PLEXION) CLEANSER - CONTINUITY OF CARE OR - 90 Day Trial Of: Avar-E LS 10-2% cream, Sulfacetamide Sodium w/ Sulfur Suspension 10-5%, Sulfacetamide Sodium w/ Sulfur lotion 10-5%, Or Sulfacetamide Sodium w/ Sulfur emulsion, Avar cleanser, Rosanil, Prascion 10-5% SODIUM SULFACETAMIDE WITH SULFUR (PLEXION) CREAM - CONTINUITY OF CARE OR - 90 Day Trial Of: Avar-E LS 10-2% cream, Sulfacetamide Sodium w/ Sulfur Suspension 10-5%, Sulfacetamide Sodium w/ Sulfur lotion 10-5%, Or Sulfacetamide Sodium w/ Sulfur emulsion, Avar cleanser, Rosanil, Prascion 10-5%			

SODIUM SULFACETAMIDE WITH SULFUR (PLEXION) LOTION - CONTINUITY OF CARE OR - 90 Day Trial Of: Avar-E LS 10-2% cream, Sulfacetamide Sodium w/ Sulfur Suspension 10-5%, Sulfacetamide Sodium w/ Sulfur lotion 10-5%, Or Sulfacetamide Sodium w/ Sulfur emulsion, Avar cleanser, Rosanil, Prascion 10-5% SODIUM SULFACETAMIDE, SEB-PREV, RE 10 WASH, MEXAR (OVACE) WASH - Clinical Reason Supported By Chart Notes Why (After A Trial Of) The Below Cannot Be Used: ▪ sulfacetamide sodium (Klarion) 10% lotion - [Dose: 340 mL (1 bottle) / 26 Days] BP CLEANSING (SULFACETAMIDE SODIUM-SULFUR IN UREA) WASH - *CONTINUITY OF CARE (ages 12 and up) OR* - *DX: Acne rosacea, acne vulgaris, seborrheic dermatitis (ages 12 and up)* - *Trial of one of the following agents for 90 days: Avar-E Ls 10-2% Cream, Sulfacetamide Sodium W/ Sulfur Suspension 10-5%, Sulfacetamide Sodium W/ Sulfur Lotion 10-5%, Or Sulfacetamide Sodium W/ Sulfur Emulsion, Avar Cleanser , Rosanil, Prascion 10-5%* - *[Dose: 473 mL / 26 Days]* PLEXION CLEANSING CLOTHS - *CONTINUITY OF CARE OR* - *90 Day Trial Of: Avar-E LS 10-2% cream, Sulfacetamide Sodium w/ Sulfur Suspension 10-5%, Sulfacetamide Sodium w/ Sulfur lotion 10-5%, Or Sulfacetamide Sodium w/ Sulfur emulsion, Avar cleanser, Rosanil, Prascion 10-5%* Avage (Tazarotene) cream - *Cosmetic: Excluded Benefit* FABIOR AEROSOL FOAM - *Diagnosis of Acne* - *Clinical reason (OH MCD ONLY) supported by chart notes why (after a 90 day trial of) the below cannot be used* - *TAZORAC 0.1% CREAM or GEL (Which requires a 90 day Trial of: tretinoin* Tazorac (Tazarotene) cream - *CONTINUITY OF CARE OR* - *Diagnosis of Psoriasis* - *Trial Of: Calcipotriene (Dovonex) OR*			

- *Diagnosis of Acne* - *Trial Of: Tretinoin Cream Or Gel OR Adapalene 0.1% Gel Or Cream* - *[Dose: 30 Grams (1 Tube) / 26 Days]* Tretinoin (Atralin) Gel - *Diagnosis of Acne, Molluscum Contagiosum (Warts), Verruca Plana (Plantar Warts), Verruca Vulgaris (Vaginal Warts), Or Rosacea AND* - *Clinical Reason (OH MCD Only) Supported By Chart Notes Why (After A 30 Day Trial Of) The Below Cannot Be Used:* ▪ *Tretinoin (Retin-A) 0.05% Cream* ▪ *[Dose: 45 Grams (1 Tube) / 26 Days]* Tretinoin (Avita) Cream - *CONTINUITY OF CARE OR* - *If Age Below 12 Or Over 26, Diagnosis Below Is Required:* - *Diagnosis of Acne, Molluscum Contagiosum (Warts), Verruca Plana (Plantar Warts), Verruca Vulgaris (Vaginal Warts), OR Rosacea* Tretinoin (Avita) Gel - *CONTINUITY OF CARE OR* - *If Age Below 12 Or Over 26, Diagnosis Below Is Required:* - *Diagnosis of Acne, Molluscum Contagiosum (Warts), Verruca Plana (Plantar Warts), Verruca Vulgaris (Vaginal Warts), OR Rosacea* Tretinoin (Retin-A) Cream and Gel - *CONTINUITY OF CARE OR* - *If Age Below 12 Or Over 26, Diagnosis Below Is Required:* - *Diagnosis of Acne, Molluscum Contagiosum (Warts), Verruca Plana (Plantar Warts), Verruca Vulgaris (Vaginal Warts), OR Rosacea* - *[Dose: 45 Grams (1 Tube) / 26 Days]* Tretinoin Microsphere (Retin-A Micro) Gel - *Diagnosis of Acne, Molluscum Contagiosum (Warts), Verruca Plana (Plantar Warts), Verruca Vulgaris (Vaginal Warts), Or Rosacea AND* - *Clinical Reason (OH MCD Only) Supported By Chart Notes Why (After A 30 Day Trial Of) The Below Cannot Be Used:* - *Tretinoin (Retin-A) Gel Or Cream* - *[Dose: 45 Grams (1 Tube) / 26 Days* Tretin-X cream - *Diagnosis of Acne, Molluscum Contagiosum (Warts), Verruca Plana (Plantar Warts), Verruca Vulgaris (Vaginal Warts), Or Rosacea* - *AND* - *Clinical Reason (OH MCD Only) Supported By Chart Notes Why (After A 30 Day Trial Of) The Below Cannot Be Used:* ▪ *Tretinoin (Retin-A) Gel Or Cream*			

Tretin-X Cream W/ Cleanser & Moisturizer Kit - *Diagnosis of Acne, Molluscum Contagiosum (Warts), Verruca Plana (Plantar Warts), Verruca Vulgaris (Vaginal Warts), Or Rosacea AND* - *Clinical Reason (OH MCD Only) Supported By Chart Notes Why (After A 30 Day Trial Of) The Below Cannot Be Used:* ▪ *Tretinoin (Retin-A) Gel Or Cream*			

Dermatology: Antipsoriatics

Current PDL	Recommended	Rationale	P&T Decision
<u>Preferred</u> Calcipotriene (Dovonex) cream - *0.005%: 1 tube (60 grams) per 30 days* Calcipotriene (Dovonex) ointment - *0.005%: 1 tube (60 grams) per 30 days* Calcipotriene (Dovonex) solution - *0.005%: 1 bottle (60 mL) per 30 days* <u>Non-preferred</u> 8-Mop capsule - *Dx: psoriasis* - *30-day trial of calcipotriene (Dovonex)* Acitretin (Soriatane) capsule - *Continuity of Care OR* - *Previously approval for Enbrel, Humira, Stelara OR* - *Trial of calcipotriene (Dovonex) (90-day for OH, 30-day for other MCD LOBs)* Calcipotriene – betamethasone diproprionate (Taclonex) ointment - *Continuity of Care OR* - *Trial of calcipotriene (Dovonex) (90-day for OH, 30-day for other MCD LOBs)* Calcitriol (Vectical) ointment - *Continuity of Care OR* - *Trial of calcipotriene (Dovonex) (90-day for OH, 30-day for other MCD LOBs)* Dritho-Crème HP cream - *Continuity of Care OR*	No changes at this time	- No new drugs - No new data or evidence to alter therapy	Approved

CareSource

Dermatology: Antipsoriatics			
- *Trial of calcipotriene (Dovonex) 0.005% cream (90-day for OH, 30-day for other MCD LOBs)* Enstilar aerosol foam - *Continuity of Care OR* - *Dx: plaque psoriasis* - *Age = 18 years or older* - *7 day Trial of calcipotriene (Dovonex)* Oxsoralen lotion - *Excluded benefit - cosmetics* Oxsoralen-ultra (Methoxsalen) capsule - *Dx: Psoriasis* - *Trial of calcipotriene (Dovonex) (90-day for OH, 30-day for other MCD LOBs)* Sorilux foam - *Continuity of Care OR* - *Trial of calcipotriene (Dovonex) (90-day for OH, 30-day for other MCD LOBs)* Taclonex scalp suspension - *Continuity of Care OR* - *Trial of calcipotriene (Dovonex) (90-day for OH, 30-day for other MCD LOBs)* Tazarotene (Tazorac) cream - *Dx: psoriasis* - *Trial of calcipotriene (Dovonex) (90-day for OH, 30-day for other MCD LOBs)* Tazorac cream - *Continuity of Care OR* - *Dx: psoriasis* - *Trial of calcipotriene (Dovonex) (90-day for OH, 30-day for other MCD LOBs)* Tazorac gel - *0.05% and 0.1%* - *Continuity of Care OR* - *Dx: psoriasis* - *Trial of calcipotriene (Dovonex) (90-day for OH, 30-day for other MCD LOBs)* Zithranol shampoo - *Continuity of Care OR*			

CareSource

Dermatology: Antipsoriatics

- *30-day trial of calcipotriene (Dovonex) 0.005% solution* Zithranol RR cream - *Continuity of Care OR* - *30-day trial of calcipotriene (Dovonex) 0.005% cream*			

Dermatology: Rosacea Agents

Current PDL	Recommended	Rationale	P&T Decision
<u>Preferred</u> Metronidazole (Metrocream) cream - *0.75%: 1 tube (45 grams) per 26 days* Metronidazole (Rosadan) gel - *0.75%: 1 tube (45 grams) per 26 days* Metronidazole (Rosadan, Vitazol, Metrolotion) lotion - *0.75%: 1 bottle (59 mL) per 26 days* Sulfacetamide sodium/sulfur (Avar-E LS) cream Sulfacetamide sodium/sulfur (Avar cleanser, Rosanil, Prascion foam wash) emulsion - *10-5%: 1 bottle (355 mL) per 26 days* Sulfacetamide sodium/sulfur lotion - *10-5%: 1 bottle (30 mL) per 26 days* Sulfacetamide sodium/sulfur suspension - *10-5%: 1 bottle (30 mL) per 26 days* Sulfacetamide sodium/sulfur in urea gel <u>Non-preferred</u> Rhofade cream - *Dx: rosacea* - *Member Is 18 Years Of Age Or Older; AND* - *Medication Prescribed By Dermatologist, Allergist, Or Immunologist; AND* - *30 Day Trial And Failure Of 2 Of The Following Lower Cost Agents: Doxycycline Oral Capsules Or Tablets, Metronidazole 75% Topical And Finacea 15% Gel/Foam; AND* - *Baseline Erythema Assessment (Clinician Erythema Assessment (CEA) And Subject Self-Assessment For Rosacea Facial Redness (SSA) With Scores Of ≥3 On Both (5-point Scales)); AND*	No changes at this time	- No new drugs - No new data or evidence to alter therapy	Approved

CareSource

Dermatology: Rosacea Agents			
- *Cannot Be Used In Combination With Another Topical Alpha Adrenergic Agonist (i.e., RhoFade)* Mirvaso gel - *Dx: rosacea* - *Member Is 18 Years Of Age Or Older; AND* - *Medication Prescribed By Dermatologist, Allergist, Or Immunologist; AND* - *30 Day Trial And Failure Of 2 Of The Following Lower Cost Agents: Doxycycline Oral Capsules Or Tablets, Metronidazole 75% Topical And Finacea 15% Gel/Foam; AND* - *Baseline Erythema Assessment (Clinician Erythema Assessment (CEA) And Subject Self-Assessment For Rosacea Facial Redness (SSA) With Scores Of ≥3 On Both (5-point Scales)); AND* - *Cannot Be Used In Combination With Another Topical Alpha Adrenergic Agonist (i.e., RhoFade)* Soolantra cream - *Dx: rosacea* - *Trial of metronidazole 0.75% or Tretinoin (Retin-A)* Sulfacetamide sodium/sulfur in urea wash - *Continuity of Care OR* - *Dx: acne rosasea* - *Trial of one of the following agents for 90 days (30 days KY): Avar-E Ls 10-2% Cream, Sulfacetamide Sodium W/ Sulfur Suspension 10-5%, Sulfacetamide Sodium W/ Sulfur Lotion 10-5%, Or Sulfacetamide Sodium W/ Sulfur Emulsion, Avar Cleanser , Rosanil, Prascion 10-5%* Sulfacetamide sodium with sulfur (Plexion) cleanser - *Continuity of Care OR* - *90 Day Trial Of: Avar-E LS 10-2% cream, Sulfacetamide Sodium w/ Sulfur Suspension 10-5%, Sulfacetamide Sodium w/ Sulfur lotion 10-5%, Or Sulfacetamide Sodium w/ Sulfur emulsion, Avar cleanser, Rosanil, Prascion 10-5%* Sulfacetamide sodium with sulfur (Plexion) cream - *Continuity of Care OR* - *90 Day Trial Of: Avar-E LS 10-2% cream, Sulfacetamide Sodium w/ Sulfur Suspension 10-5%, Sulfacetamide Sodium w/ Sulfur lotion 10-5%, Or Sulfacetamide Sodium w/ Sulfur emulsion, Avar cleanser, Rosanil, Prascion 10-5%*			

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Dermatology: Rosacea Agents			
Sulfacetamide sodium with sulfur (Plexion) lotion - *Continuity of Care OR* - *90 Day Trial Of: Avar-E LS 10-2% cream, Sulfacetamide Sodium w/ Sulfur Suspension 10-5%, Sulfacetamide Sodium w/ Sulfur lotion 10-5%, Or Sulfacetamide Sodium w/ Sulfur emulsion, Avar cleanser, Rosanil, Prascion 10-5%* Sulfacetamide sodium with sulfur (Avar LS) cleanser - *Clinical reason (OH MCD ONLY) supported by chart notes why (after a 90 day trial of) the below cannot be used: Sulfacetamide sodium with sulfur (Avar-E LS) 10-2% cream* Sulfacetamide sodium with sulfur (Clarifoam EF) emollient foam - *Clinical reason (OH MCD ONLY) supported by chart notes why (after a 90 day trial of) the below cannot be used: Sulfacetamide Sodium w/ Sulfur Suspension 10-5%, Sulfacetamide Sodium w/ Sulfur lotion 10-5%, Or Sulfacetamide Sodium w/ Sulfur emulsion, Avar cleanser, Rosanil, Prascion 10-5%* Sulfacetamide sodium with sulfur (Sumadan) cleanser - *Continuity of Care OR* - *Trial Of: Avar-E LS 10-2% cream, Sulfacetamide Sodium w/ Sulfur Suspension 10-5%, Sulfacetamide Sodium w/ Sulfur lotion 10-5%, Or Sulfacetamide Sodium w/ Sulfur emulsion, Avar cleanser, Rosanil, Prascion 10-5%* Sulfacetamide sodium with sulfur (Sumaxin) cleansing pads - *Continuity of Care OR* - *Trial Of: Avar-E LS 10-2% cream, Sulfacetamide Sodium w/ Sulfur Suspension 10-5%, Sulfacetamide Sodium w/ Sulfur lotion 10-5%, Or Sulfacetamide Sodium w/ Sulfur emulsion, Avar cleanser, Rosanil, Prascion 10-5%* Sulfacetamide sodium with sulfur (Sumadan Kit) wash plus skin cleanser - *Clinical reason (OH MCD ONLY) supported by chart notes why (after a trial of) the below cannot be used: *SULFACETAMIDE SODIUM W/ SULFUR (SUMADAN) 9% - 4.5% (which requires a prior authorization) WITH a formulary skin cleanser used separately at the same time* Sulfacetamide sodium with sulfur (Avar-E Green, SE 10-5 SS, SSS, Virti-Sulf) cream - *Clinical reason (OH MCD ONLY) supported by chart notes why (after a 90 day trial of) the below cannot be used: Sulfacetamide*			

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Dermatology: Rosacea Agents

Sodium w/ Sulfur Suspension 10-5%, Sulfacetamide Sodium w/ Sulfur lotion 10-5%, Or Sulfacetamide Sodium w/ Sulfur emulsion, Avar cleanser, Rosanil, Prascion 10-5% Sulfacetamide sodium with sulfur (Sumaxin TS) topical suspension - *Continuity of Care OR* - *Trial Of: Avar-E LS 10-2% cream, Sulfacetamide Sodium w/ Sulfur Suspension 10-5%, Sulfacetamide Sodium w/ Sulfur lotion 10-5%, Or Sulfacetamide Sodium w/ Sulfur emulsion, Avar cleanser, Rosanil, Prascion 10-5%* Sulfacetamide sodium with sulfur (Sumaxin, Zencia) wash - *Continuity of Care OR* - *Trial Of: Avar-E LS 10-2% cream, Sulfacetamide Sodium w/ Sulfur Suspension 10-5%, Sulfacetamide Sodium w/ Sulfur lotion 10-5%, Or Sulfacetamide Sodium w/ Sulfur emulsion, Avar cleanser, Rosanil, Prascion 10-5%*			

Diabetes: Injectables

Current PDL	Recommended	Rationale	P&T Decision
Preferred Dulaglutide (Trulicity) pen - *0.75 mg/0.5 mL: max 2 mL (4 pens) per 24 days* - *1.5 mg/0.5 mL: max 2 mL (4 pens) per 24 days* - *Step Therapy: 30-day trial of Metformin or Metformin ER (Glucophage or Glucophage ER); OR* - *(Not required if: allergy, intolerance, or side effects to Metformin, renal/kidney disease/elevated creatinine (Cr), or HbA1C greater than 7.5%)* Liraglutide (Victoza) pen - *2-pack: max 3 pens per 26 days* - *3-pack: max 3 pens per 26 days* - *Continuity of Care OR* - *Step Therapy: 30-day trial of Metformin or Metformin ER (Glucophage or Glucophage ER); OR* - *(Not required if: allergy, intolerance, or side effects to Metformin, renal/kidney disease/elevated creatinine (Cr), or HbA1C greater than 7.5%)*	No changes at this time	- No new drugs - No new data or evidence to alter therapy	Approved

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Diabetes: Injectables			
Insulin human regular (Humulin R) vial - *100 units/mL: max 40 mL (4 vials)/25 days* - *500 units/mL: max 40 mL (20,000 units)/25 days* Insulin human regular (Humulin R) Kwikpen - *500 units/mL: max 40 mL (2 vials)/25 days* Insulin human regular (Novolin R Relion) vial - *100 units/mL: max 40 mL (4 vials)/25 days* Insulin human regular (Novolin R) vial - *100 units/mL: max 40 mL (4 vials)/25 days* Insulin isophane human (Humulin N) insulin pen - *100 units/mL: max 45 mL (3 boxes)/25 days* Insulin isophane human (Humulin N) kwikpen - *100 units/mL: max 45 mL (3 boxes)/25 days* Insulin isophane human (Humulin N) vial - *100 units/mL: max 40 mL (4 vials)/25 days* Insulin isophane human (Novolin N Relion) vial - *100 units/mL: max 40 mL (4 vials)/25 days* Insulin isophane human (Novolin N) vial - *100 units/mL: max 40 mL (4 vials)/25 days* Insulin isophane human 70%/regular 30% (Humulin 70/30) insulin pen - *70-30 units/mL: max 45 mL (3 boxes)/25 days* Insulin isophane human 70%/regular 30% (Humulin 70/30) kwikpen - *70-30 units/mL: max 45 mL (3 boxes)/25 days* Insulin isophane human 70%/regular 30% (Humulin 70/30) vial - *70-30 units/mL: max 40 mL (4 vials)/25 days* Insulin isophane human 70%/regular 30% (Novolin 70/30 Relion) vial - *70-30 units/mL: max 40 mL (4 vials)/25 days* Insulin isophane human 70%/regular 30% (Novolin 70/30) vial - *70-30 units/mL: max 40 mL (4 vials)/25 days* Insulin aspart (Novolog) cartridge - *100 units/mL: max 40 mL (4 vials)/25 days* Insulin aspart (Novolog) flexpen - *100 units/mL: max 45 mL (3 boxes)/25 days* Insulin aspart (Novolog) vial - *100 units/mL: max 40 mL (4 vials)/25 days* Insulin aspart protamine 70%/insulin aspart 30% (Novolog mix 70/30) flexpen - *100 units/mL: max 45 mL (3 boxes)/25 days*			

CareSource

Diabetes: Injectables

Insulin aspart protamine 70%/insulin aspart 30% (Novolog mix 70/30) vial - *100 units/mL: max 40 mL (4 vials)/25 days* Insulin degludec (Tresiba) flextouch pen - *100 units/mL: max 45 mL (3 boxes)/25 days* - *200 units/mL: max 27 mL/25 days* Insulin glargine (Basaglar kwikpen) solution - *100 units/mL: max 45 mL (3 boxes)/25 days* Insulin glulisine (Apidra) vial - *100 units/mL: max 40 mL (4 vials)/25 days* Insulin glulisine (Apidra) solostar - *100 units/mL: max 45 mL (3 boxes)/25 days* Insulin lispro (Humalog) cartridge - *100 units/mL: max 45 mL (3 boxes)/25 days* Insulin lispro (Humalog) kwikpen - *100 units/mL: max 45 mL (3 boxes)/25 days* - *200 units/mL: max 24 mL (4 boxes)/25 days* Insulin lispro protamine/insulin lispro (Humalog mix) - *50-50 units/mL: max 45 mL (3 boxes)/25 days* <u>Non-preferred</u> Adlyxin pen injector - *30 Day Trial of Victoza or Trulicity (which require a 30-day trial of Metformin or Metformin ER)* - *Dose limit 2 prefilled pens (6 mL total) per 28 days* Bydureon pen injector - *Continuity of Care if approved by CareSource on or after 01/01/17 OR* - *60 Day Trial of Victoza or Trulicity (which require a 30-day trial of Metformin or Metformin ER)* Bydureon vial - *Continuity of Care if approved by CareSource on or after 01/01/17 OR* - *60 Day Trial of Victoza or Trulicity (which require a 30-day trial of Metformin or Metformin ER)* Byetta dose pen - *Continuity of Care if approved by CareSource on or after 01/01/17 OR*			

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Diabetes: Injectables			
- *60 Day Trial of Victoza or Trulicity (which require a 30-day trial of Metformin or Metformin ER)* Lantus solostar pen injector - *100 units/mL* - *If member has a paid claim within the last 120 days, approve for 1 year; OR* - *30 Day Trial of Basaglar or Tresiba.* - *Dose limit 45 mL/30 days* Lantus vial - *100 units/mL* - *If member has a paid claim within the last 120 days, approve for 1 year; OR* - *30 Day Trial of Basaglar or Tresiba.unless fax notes member is using ½ unit dosing (which cannot be obtained from a pen)* - *Dose limit 40 mL/30 days* Levemir flexpen or flextouch - *100 units/mL* - *Continuity of care if approved by CareSource on or after 01/01/17 OR* - *If fax states member is pregnant OR* - *Allergy, adverse effects, or intolerance to Basaglar or Tresiba.OR* - *30 day trial of Basaglar or Tresiba* - *Dose limit 45 mL/30 days* Levemir vial - *100 units/mL* - *Continuity of care if approved by CareSource on or after 01/01/17 OR* - *If fax states member is pregnant OR* - *Allergy, adverse effects, or intolerance to Basaglar or Tresiba.OR* - *30 day trial of Basaglar or Tresiba* - *Dose limit 45 mL/30 days* Ryzodeg IV solution - *100 units/mL* - *30 day trial of Basaglar or Tresiba AND 30 day trial of Novolog separately but at the same time (same 30 consecutive day period)* Soliqua pen - *100/33 units-mcg/mL*			

CareSource

Diabetes: Injectables

- **Clinical reason (OH MCD ONLY) supported by chart notes why (after a 30 day trial of) the below cannot be used: Insulin Glargine (Lantus or Basaglar) AND a GLP 1 agonist (Victoza, Trulicity, Bydureon, Byettta, or Tanzeum) separately taken together at the same time* - *Dose limit: 60 Units/Day* Tanzeum pen injector - *60 Day Trial of Victoza or Trulicity (which require a 30-day trial of Metformin or Metformin ER)* Toujeo solostar pen injector - *300 IU/mL* - **Clinical reason (OH MCD ONLY) supported by chart notes why (after a 30 day trial of) the below cannot be used: Basaglar or Tresiba.* Xultophy pen - *100 units/3.6 mg per mL* - **Clinical reason (OH MCD ONLY) supported by chart notes why (after a 30 day trial of) the below cannot be used: A long acting insulin: Basaglar (preferred agent), Lantus (requires PA), Levemir (requires PA), Tresiba (preferred agent), or Toujeo (requires PA) AND A GLP 1 agonist: Victoza (preferred agent), Trulicity (preferred agent), Bydureon (requires PA), Byettta (requires PA), or Tanzeum (requires PA)* - *separately taken together at the same time* - *Dose limit: 60 Units* Symlinpen pen injector - *2,700 mcg/2.7 mL* - *1,500 mcg/1.5 mL* - *Continuity of care OR* - *60 day trial of Humalog, Novolog, or Apidra*			

CareSource

Oral Antidiabetics

Current PDL	Recommended	Rationale	P&T Decision
<u>Preferred</u> Miglitol (Glyset) - *Continuity of Care OR* - *30 Day Trial Of: Metformin IR Or Metformin ER (Glucophage Or Glucophage ER) - [Not Required If: Allergy, Intolerance, Or Side Effect To Metformin, Renal/Kidney Disease/Elevated Creatine (CR), Or HbA1C Greater Than 7.5%]* Acarbose (Precose) Metformin (Glucophage) Metformin ER (Glucophage XR) Glyburide/metformin (Glucovance) - *No PA required for 300 tab per 30 days* Canagliflozin/metformin (Invokamet) - *Continuity of Care OR* - *30 Day Trial Of: Metformin IR Or Metformin ER (Glucophage Or Glucophage ER) - [Not Required If: Allergy, Intolerance, Or Side Effect To Metformin, Renal/Kidney Disease/Elevated Creatine (CR), Or HbA1C Greater Than 7.5%]* Canagliflozin/metformin (Invokamet XR) - *Continuity of Care OR* - *30 Day Trial Of: Metformin IR Or Metformin ER (Glucophage Or Glucophage ER) - [Not Required If: Allergy, Intolerance, Or Side Effect To Metformin, Renal/Kidney Disease/Elevated Creatine (CR), Or HbA1C Greater Than 7.5%]* Glipizide/metformin (Metaglip) Alogliptin (Nesina) Alogliptin/pioglitazone (Oseni) Repaglinide (Prandin) Nateglinide (Starlix) Canagliflozin (Invokana) - *Continuity of Care OR* - *30 Day Trial Of: Metformin IR Or Metformin ER (Glucophage Or Glucophage ER) - [Not Required If: Allergy, Intolerance, Or Side Effect To Metformin, Renal/Kidney Disease/Elevated Creatine (CR), Or HbA1C Greater Than 7.5%]* Glimepiride (Amaryl)	No changes at this time	- No new drugs - No new data or evidence to alter therapy	Approved

CareSource

Oral Antidiabetics			
Glipizide (Glucotrol) Glipizide XL (Glucotrol XL) Glyburide - *No PA required for 20 mg per day* Glyburide micronized (Glynase Pres tab) - *No PA required for 12 mg per day* Glipizide/metformin (Metagip) - *No PA required for 300 tabs per 30 days* Tolbutamide - *No PA required for: 3 grams (6 tablet) per day (180 tablet per Month)* Pioglitazone (Actos) Alogliptin/metformin (Kazano) Metformin/pioglitazone (Actoplus Met) Metformin/pioglitazone XR (Actoplus Met XR) - *Continuity of Care OR* - *30 Day Trial Of: Metformin IR Or Metformin ER (Glucophage Or Glucophage ER) - [Not Required If: Allergy, Intolerance, Or Side Effect To Metformin, Renal/Kidney Disease/Elevated Creatine (CR), Or HbA1C Greater Than 7.5%]* Pioglitazone/glimepiride (Duetact) - *Continuity of Care OR* - **30 Day Trial Of: Metformin IR Or Metformin ER (Glucophage Or Glucophage ER) - [Not Required If: Allergy, Intolerance, Or Side Effect To Metformin, Renal/Kidney Disease/Elevated Creatine (CR), Or HbA1C Greater Than 7.5%]* <u>Non-Preferred</u> Bromocriptine (Cycloset) - *Continuity of Care OR* - *Diagnosis of Type 2 Diabetes* - *30 day trial of 2 different agents:* o *Metformin or Metformin ER (Glucophage IR or ER)* o *Januvia, Tradjenta, Onglyza* o *Invokana, Farxiga* o *JanuMet, Jentadueto, Kombiglyze* o *Pioglitazone (Actos) or Avandia* o *Glipizide or Glimepiride* o *Lantus or Levemir*			

Oral Antidiabetics			
o *Humalog or Novolog* o *Byetta, Bydureon, Victoza* o *Symlin* Colesevelam (Welchol) packet - *Diagnosis of Hyperlipidemia* o *30 Day Trial Of: Simvastatin Or Atorvastatin Or Rosuvastatin AND* o *Allergy, Adverse Effects, Side Effects Or Intolerance To: Cholestyramine Or Colestipol OR* o *30 Day Trial Of: Cholestyramine Or Colestipol* - *Diagnosis of Liver Disease* o *Allergy, Adverse Effects, Side Effects Or Intolerance To: Cholestyramine OR* o *30 Day Trial Of: Cholestyramine* - *Diagnosis of Diabetes* o *30 Day Trial Of: Metformin IR Or Metformin ER (Glucophage Or Glucophage ER) - [Not Required If: Allergy, Intolerance, Or Side Effect To Metformin, Renal/Kidney Disease/Elevated Creatine (CR), Or HbA1C Greater Than 7.5%]* Colesevelam (Welchol) tablet - *Diagnosis of Hyperlipidemia* o *30 Day Trial Of: Simvastatin Or Atorvastatin Or Rosuvastatin AND* o *Allergy, Adverse Effects, Side Effects Or Intolerance To: Cholestyramine Or Colestipol OR* o *30 Day Trial Of: Cholestyramine Or Colestipol* - *Diagnosis of Liver Disease* o *Allergy, Adverse Effects, Side Effects Or Intolerance To: Cholestyramine OR* o *30 Day Trial Of: Cholestyramine* - *Diagnosis of Diabetes* o *30 Day Trial Of: Metformin IR Or Metformin ER (Glucophage Or Glucophage ER) - [Not Required If: Allergy, Intolerance, Or Side Effect To Metformin, Renal/Kidney Disease/Elevated Creatine (CR), Or HbA1C Greater Than 7.5%]* Chlorpropamide - *30 Day trial of Each of the following: glimepiride, glipizide, and glyburide* - *[Dose: 750mg (7 tablets) per day (210 tablets per Month)]*			

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Oral Antidiabetics			
Metformin ER (Fortamet) - *Clinical reason (OH MCD ONLY) supported by chart notes or provider call (after trial listed below) why the below cannot be used: 30 day trial of metformin ER (Glucophage ER)* Empagliflozin/metformin (Synjardy) - *30 Day Trial Of: Metformin IR Or ER THEN* - *60 Day Trial Of: Invokana With Metformin Separately Taken Together At The Same Time* Metformin ER (Glumetza ER) - *Clinical Reason (OH MCD Only) Supported By Chart Notes Why Metformin HCL (Glumetza) ER (Which Is A Modified ER Tablet) Is Required AND* - *30 Day Trial Of: Metformin ER (Glucophage ER)* Empagliflozin/linagliptin (Glyxambi) - *30 day trial of: Invokana AND* - *30 day trial of: Alogliptin (Nesina), Alogliptin-Metformin (Kazano), or Alogliptin-Pioglitazone (Oseni)* Sitagliptin (Januvia) - *30 day Trial of: Alogliptin (Nesina), Alogliptin-Metformin (Kazano), or Alogliptin-Pioglitazone (Oseni)* Saxagliptin (Onglyza) - *30 day Trial of: Alogliptin (Nesina), Alogliptin-Metformin (Kazano), or Alogliptin-Pioglitazone (Oseni)* Dapagliflozin (Farxiga) - *30 day trial of: Metformin IR or Metformin ER (Glucophage or Glucophage ER) - [Not required if: Allergy, intolerance, or Side effect to Metformin, Renal/Kidney disease/Elevated Creatine (CR), or HbA1C greater than 7.5%] THEN* - *60 day trial of: Invokana* Empagliflozin (Jardiance) - *30 day trial of: Metformin IR or Metformin ER (Glucophage or Glucophage ER) - [Not required if: Allergy, intolerance, or Side effect to Metformin, Renal/Kidney disease/Elevated Creatine (CR), or HbA1C greater than 7.5%] THEN* - *60 day trial of: Invokana* Dapagliflozin/metformin (Xigduo XR) - *30 Day Trial Of: Metformin IR Or ER THEN*			

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Oral Antidiabetics			
- *30 Day Trial Of: Invokana With Metformin Separately Taken Together At The Same Time* Rosiglitazone (Avandia) - *30 day trial of: metformin IR or metformin ER (Glucophage or Glucophage ER) - [Not required if: Allergy, intolerance, or Side effect to metformin, Renal/Kidney disease/Elevated Creatine (CR), or HbA1C greater than 7.5%] AND* - *60 day Trial of: pioglitazone (Actos)* Metformin/sitagliptin (Janumet) - *30 day Trial of: Alogliptin (Nesina), Alogliptin-Metformin (Kazano), or Alogliptin-Pioglitazone (Oseni)* Metformin sitagliptin XR (Janumet XR) - *30 day Trial of: Alogliptin (Nesina), Alogliptin-Metformin (Kazano), or Alogliptin-Pioglitazone (Oseni)* Metformin/saxagliptin (Kombiglyze XR) - *30 day Trial of: Alogliptin (Nesina), Alogliptin-Metformin (Kazano), or Alogliptin-Pioglitazone (Oseni)* Metformin/repaglinide (Prandimet) - *Continuity of Care OR* - *30 Day Trial Of: Metformin IR Or Metformin ER (Glucophage Or Glucophage ER) [Not Required If: Allergy, Intolerance, Or Side Effect To Metformin, Renal/Kidney Disease/Elevated Creatine (CR), Or HbA1C Greater Than 7.5%]* Metformin/rosiglitazone (Avadamet) - *30 day trial of: metformin IR or metformin ER (Glucophage or Glucophage ER) - [Not required if: Allergy, intolerance, or Side effect to metformin, Renal/Kidney disease/Elevated Creatine (CR), or HbA1C greater than 7.5%] AND* - *60 day Trial of: pioglitazone-metformin (Actoplus Met)* Tolazamide - *30 Day trial of Each of the following: glimepiride, glipizide, and glyburide* - *[Dose: 1000 mg / Day]* Linagliptin (Tradjenta) - *30 day Trial of: Alogliptin (Nesina), Alogliptin-Metformin (Kazano), or Alogliptin-Pioglitazone (Oseni)* Linagliptin/metformin (Jentadueto) - *30 day Trial of: Alogliptin (Nesina), Alogliptin-Metformin (Kazano), or Alogliptin-Pioglitazone (Oseni)*			

CareSource

Oral Antidiabetics

Diabetes Supplies

Current PDL	Recommended	Rationale	P&T Decision
<u>Preferred</u> Alcohol swabs - *No PA required for 400/30 days* - *Cost limit = $8.63 per fill* Freestyle Freedom Lite Meter - *No PA required for 1 meter/year* Freestyle Freedom Lite Test Strips - *No PA required for 200 strips/26 days* Freestyle Insulinx - *No PA required for 1 meter/year* Freestyle Insulinx Test Strips - *No PA required for 200 strips/26 days* Freestyle Lite Meter - *No PA required for 1 meter/year* Freestyle Lite Test Strips - *No PA required for 200 strips/26 days* Precision Xtra Meter - *No PA required for 1 meter/year* Precision Xtra Test Strips - *No PA required for 102 strips/month* - *Approve for quantity greater than 102 if SIG on PA form match quantity requested* Freestyle Libre Continuous Glucose Monitor Glucose Meter Control Solution – Freestyle and Precision Lancets - *No PA required for 204/30 days* Lancing Device - *No PA required for 2 per 365 days* - *Cost limit = $27 per fill* Accu-Chek Lancets - *No PA required for 204 lancets/30 days* - *Cost limit = $20 per fill*	No changes at this time	- No new drugs - No new data or evidence to alter therapy	Approved

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Diabetes Supplies			
Precision Xtra Beta Ketone Test Strips - *No PA required for 20 strips/30 days* Insulin Syringe 29 Gauge BD U-500 Insulin Syringe 31G X 15/64” Pen needles - *No PA required for 400/26 days* Glucose Chewable tablet Keto-Diastix V-Go insulin delivery device <u>Non-Preferred</u> Freestyle Libre Pro - *Must use a formulary meter* Freestyle Precision Neo Meter - *Must use a formulary meter* Freestyle Precision Neo Test Strips - *Must use a formulary test strips* Accu-Chek Test Strips/Meter - *Approve if fax states being used with an insulin pump OR* - *Clinical reason (OH MCD ONLY) supported by chart notes (After a trial of the below) why the requested non-formulary meter/test strips are required* Agamatrix Amp Blood Glucose Strips/Meter - *Approve if fax states being used with an insulin pump OR* - *Clinical reason (OH MCD ONLY) supported by chart notes (After a trial of the below) why the requested non-formulary meter/test strips are required* Ascensia Contour Test Strips/Meter - *Approve if fax states being used with an insulin pump OR* - *Clinical reason (OH MCD ONLY) supported by chart notes (After a trial of the below) why the requested non-formulary meter/test strips are required* Embrace Blood Glucose Test Strips/Meter - *Approve if fax states being used with an insulin pump OR* - *Clinical reason (OH MCD ONLY) supported by chart notes (After a trial of the below) why the requested non-formulary meter/test strips are required* Onetouch and Onetouch Ultra Test Strips/Meter			

Diabetes Supplies			
- *Approve If Fax States Being Used With An Insulin Pump (for quantity greater than 200, SIG on PA form must match quantity requested) OR* - *Clinical Reason (OH MCD ONLY) Supported By Chart Notes (After A Trial Of The Below) Why The Requested Non-Formulary Meter/Test Strips Are Required AND* - *90 Day Trial Of: Abbott Freestyle Or Precision Xtra Test Strips Or Glucometers* Prodigy Test Strips and Meter - *Approve If Fax States Being Used With An Insulin Pump OR* - *Clinical Reason (OH MCD ONLY) Supported By Chart Notes (After A Trial Of The Below) Why The Requested Non-Formulary Meter/Test Strips Are Required AND* - *90 Day Trial Of: Abbott Freestyle Or Precision Xtra Test Strips Or Glucometers* Truetrack or Truetest Test Strips/Meter - *Approve If Fax States Being Used With An Insulin Pump (for quantity greater than 102, SIG on PA form must match quantity requested) OR* - *Clinical Reason (OH MCD ONLY) Supported By Chart Notes (After A Trial Of The Below) Why The Requested Non-Formulary Meter/Test Strips Are Required AND* - *90 Day Trial Of: Abbott Freestyle Or Precision Xtra Test Strips Or Glucometers* *Glucose Meter Control – All Non-Formulary* - *If fax states being used with an insulin pump OR* - *Clinical reason (OH MCD ONLY) supported by chart notes (after a trial of the below) why the REQUESTED NON-FORMULARY GLUCOSE METER CONTROL SOLUTION are required AND* - *90 day trial of Abbott Freestyle or Precision PRODUCTS*			

Estrogens

Current PDL	Recommended	Rationale	P&T Decision
<u>Preferred</u> Estradiol (Estrace) tablets Estradiol (Minivelle) patch Estrace vaginal cream Estradiol (Climara) patch Premarin vaginal cream, tablets Menest tablets Estradiol Acetate vaginal ring Estradiol valerate (Delestrogen) vial 20mg/ml <u>Non-Preferred</u> *Duavee tablet* - *Clinical Reason (OH MCD Only) Supported By Chart Notes Why (After A Trial Of) The Below Cannot Be Used* - *CombiPatch, Prempro, Premarin, Or Norethindrone Acetate-Ethinyl (FemHRT)* Femring (estradiol acetate) vaginal cream - *Clinical Reason Supported By Chart Notes Why (After A Trial Of) The Below Cannot Be Used::* - *Norethindrone Acetate-Ethinyl (Femhrt) or Prempro* Depo-estradiol (Estradiol cypionate) injection - *OH & KY* o *Clinical Reason (OH MCD ONLY) Supported By Chart Notes Why (After A 90 Day Trial Of) The Below Cannot Be Used:* o *Estradiol Tablets, Estradiol Patches (Climara) Or Alora* - *IN* o *Preferred* Estradiol (Vivelle—dot) patch - *Approve for 1 Year: Will be added to formulary* Estradiol (Minivelle) patch - *Approve for 1 Year: Will be added to formulary* Estradiol valerate (Delestrogen) vial 10mg/ml, 40mg/ml - *Clinical reason supported by chart notes why (after a 90 day trial of) the below cannot be used:* - *Estradiol Tablets, Estradiol Patches (Climara) Or Alora* Evamist (estradiol transdermal patch)	No changes at this time	- No new drugs - No new data or evidence to alter therapy	Approved

CareSource

Estrogens

- *Clinical reason supported by chart notes why (after a 90 day trial of) the below cannot be used:* - *Estradiol Tablets, Estradiol Patches (Climara) Or Alora* Divigel gel packet - *Clinical Reason (OH MCD ONLY) Supported By Chart Notes Why (After A 90 Day Trial Of) The Below Cannot Be Used:* - *Estradiol Tablets, Estradiol Patches (Climara) Or Alora* Estring vaginal ring (Estradiol) - *Clinical Reason (OH MCD ONLY) Supported By Chart Notes Why (After A 90 Day Trial Of) The Below Cannot Be Used:* - *Estradiol Tablets, Estradiol Patches (Climara) Or Alora* Estrogel gel - *Clinical Reason (OH MCD ONLY) Supported By Chart Notes Why (After A 90 Day Trial Of) The Below Cannot Be Used:* - *Estradiol Tablets, Estradiol Patches (Climara) Or Alora* ESTRADIOL, YUVAFEM VAGINAL (VAGIFEM) TABLET - *OH & KY* o *Diagnosis of Atrophic Vaginitis AND* o *Clinical Reason (OH MCD ONLY) Supported By Chart Notes Why (After A 30 Day Trial Of) The Below Cannot Be Used:* o *Estradiol Tablets, Estradiol Patches (Climara) Or Alora* - *IN* o *Preferred*			

Fertility Regulators

Current PDL	Recommended	Rationale	P&T Decision
<u>Preferred</u> N/A <u>Non-Preferred</u> Clomiphene (Clomid) tablet - *Infertility:Send to RPH-Excluded Benefit OR* o *Diagnosis of Hypogonadism* o *Total Testosterone Lab Value = ≤ 300ng/dL Before Treatment (For New Starts Only)* Gonal-F Rff (Follitropin Alfa) pen injector/ vial	No changes at this time	- No new drugs - No new data or evidence to alter therapy	Approved

CareSource

Fertility Regulators

- *Infertility: Send To RPh-Excluded Benefit* Chorionic Gonadotropin/Novarel/Pregnyl - *Diagnosis of hypogonadotropic hypogonadism (hypogonadism secondary to a pituitary deficiency) in males prepubertal OR* - *Diagnosis of cryptorchidism not caused by anatomic obstruction* - *Excluded benefit for:* ▪ *Induction of ovulation and pregnancy in the anovulatory, infertile woman OR* ▪ *Preservation of fertility in chemo patients* - *For re-auths* ▪ *Hypogonadotropic hypogonadism (hypogonadism secondary to a pituitary deficiency) in males prepubertal OR* ▪ *Cryptorchidism not caused by anatomic obstruction* Ovidrel (recombinant gonadotropin)HCG - *Infertility: Excluded Benefit* Follistim AQ (Follitropin Beta) cartridge - *Infertility: Excluded Benefit* Menopur vial (Menotropin) - *Infertility: Excluded Benefit* Bravelle vial (Urofollitropin) - *Infertility: Excluded Benefit*			

Gaucher Disease

Current PDL	Recommended	Rationale	P&T Decision
<u>Preferred</u> Zavesca (miglustat) - *Member is 18 years of age or older; AND* - *Member has mild or moderate type 1 Gaucher disease (Glucocerebrosidase deficiency confirmed in chart notes); AND* - *Member is unable to receive enzyme replacement therapy (chart notes confirming that enzyme replacement therapy is not a therapeutic option required) AND member did not take enzyme replacement therapy in the preceding 6 months; AND* - *Baseline of liver volume, spleen volume, hemoglobin concentration, and platelet count submitted with chart notes.*	No changes at this time	- No new drugs - No new data or evidence to alter therapy	Approved

CareSource

Gaucher Disease

- *Dosage allowed: Recommended dosage is 100 mg administered orally three times a day at regular intervals* <u>Non-preferred</u> Cerdelga Capsule - *Diagnosis: Treatment Of Adult Patients With Gaucher Disease Type 1 (GD1) Who Are CYP2D6 Extensive Metabolizers, Intermediate Metabolizers, Or Poor Metabolizers* Cerezyme (imiglucerase), Elelyso (taliglucerase alfa), Vpriv (velaglucerase alfa) - *Diagnosis of non-neuropathic type 1 Gaucher disease documented and confirmed by* - *enzyme assay identifying reduced glucocerebrosidase activity or DNA testing. Include lab results and/or documentation.* - *Prescribed by or under the recommendation of a geneticist or hematologist, or under care of physician with expertise in Gaucher disease.* - *Patient must be:* o *2 years of age and older for use of imiglucerase (Cerezyme)* o *4 years of age and older for use of taliglucerase alfa (Elelyso)* o *4 years of age and older for use of velaglucerase (Vpriv)* - *Symptomatic disease defined by presence of:* o *One or more of the following in children documented in chart notes: malnutrition,* o *growth retardation, impaired psychomotor development and/or fatigue.* o *One or more of the following in adults: Anemia (hemoglobin <8 g/dL),* o *thrombocytopenia (platelet count <120,000/mm3), hepatomegaly (liver > 2.5 times* o *normal size), splenomegaly (spleen > 15 times normal size), or bone disease (chronic* o *bone pain, acute bone crises, bone fractures, osteopenia, osteonecrosis, osteolysis,* o *osteosclerosis, kyphosis).*			

CareSource

Genitourinary: BPH			
Current PDL	Recommended	Rationale	P&T Decision
<u>Preferred</u> Tamsulosin (Flomax) capsules Alfuzosin ER(Uroxatral) tablets Doxazosin (Cardura) tablets Prazosin capsule - *No PA for 20mg* Terazosin capsules <u>Non-Preferred</u> Dutasteride/Tamsulosin (Jalyn) capsules - Clinical Reason Supported By Chart Notes Why (After A 90 Day Trial Of) The Below Cannot Be Used: ▪ Tamsulosin AND Dutasteride (Avodart) Separately Taken Together At The Same Time Phenoxybenzamine (Dibenzyline) capsules - *Diagnosis of Pheochromocytoma* Prazosin capsule - OH & KY o *No PA required for 20mg per day* - *IN* o *Preferred* Silodosin - A 90 day trial of doxazosin, terazosin, tamsulosin, or prazosin	No changes at this time	- No new drugs - No new data or evidence to alter therapy	Approved

Genitourinary: Erectile Dysfunction

Current PDL	Recommended	Rationale	P&T Decision
<u>Preferred</u> N/A <u>Non-Preferred</u> Viagra tablets - Erectile dysfunction: Excluded benefit Stendra tablets - *Erectile dysfunction: Excluded benefit* Cialis tablets - *Erectile dysfunction: Excluded benefit* - *Diagnosis of Benign Prostatic Hypertrophy (BPH)* o *30-day trial and failure or clinically significant adverse effects with one of the following doxazosin, terazosin, tamsulosin, or prazosin AND* o *90-day trial (30-days for KY) and failure or clinically significant adverse effects with finasteride* Levitra tablets - *Erectile dysfunction: Excluded benefit* Caverject - *Erectile dysfunction: Excluded benefit* Edex - *Erectile dysfunction: Excluded benefit* Muse Urethral Pellet - *Erectile dysfunction: Excluded benefit* Osphena - *Erectile dysfunction: Ecluded benefit* Addyi - *Sexual dysfunction: Excluded benefit*	No changes at this time	- No new drugs - No new data or evidence to alter therapy	Approved

Genitourinary: Antispasmodics

Current PDL	Recommended	Rationale	P&T Decision
<u>Preferred</u> Bethanechol tablet Oxybutynin (Ditropan)tablet, syrup Oxybutynin ER (Ditropan XL) tablet Tolteridone (Detrol) tablet Trospium (Sanctura) tablet Flavoxate tablet <u>Non-Preferred</u> Darifenacin ER (Enablex) tablet - *30 days trial of oxybutynin, oxybutynin XL, Tolteridone, Trospium, or Trospium XR* Gelnique gel sachets - *90 day trial of oxybutynin, oxybutynin XL or oxybutynin syrup* Toviaz ER Tablets - *30 day of: oxybutynin, oxybutynin ER, Tolteridone, Trospium, or Trospium XR* Tolterodine ER (Detrol LA) capsule - *Set Up And Send To RPh* - *Clinical Reason Supported By Chart Notes Or Provider Call Why (After A 90 Day Trial Of) The Below Cannot Be Used:* ▪ *Tolterodine IR* Vesicare tablets - *30 days trial of: oxybutynin, oxybutynin XL, Tolterodine, Trospium, or Trospium XR* Myrbetriq ER tablets - *30 day trial of : Oxybutynin, Oxybutynin XL, Tolterodine, Trospium, or Trospium XR*	No changes at this time	- No new drugs - No new data or evidence to alter therapy	Approved

CareSource

Glucose Elevating Agents

Current PDL	Recommended	Rationale	P&T Decision
<u>Preferred</u> Dextrose (d-Glucose) injection - *Bill to medical benefit* Glucagen vial - *No PA required for: 2 vials per 30 days* Glucagon emergency kit - *No PA required for: 2 kits per 30 days* Glucagon chewable tablets <u>Non-Preferred</u> Proglycem oral suspension - *Continuity of Care OR* - *Diagnosis of hypoglycemia d/t extenuating circumstances*	No changes at this time	- No new drugs - No new data or evidence to alter therapy	Approved

Human Growth Hormone

Current PDL	Recommended	Rationale	P&T Decision
<u>Preferred</u> Omnitrope Vial - *Adult Growth Hormone Deficiency* o *Prescribed by an endocrinologist* o *Clinical findings consisting of one or more of the following:* ▪ *Acquired human growth hormone (HGH) deficiency due to pituitary disease or a condition affecting pituitary function.* ▪ *Childhood-onset HGH deficiency* o *Diagnosis of GHD confirmed by ONE of the following:* ▪ *a) Peak serum growth hormone concentration < 5 mcg/L by insulin tolerance testing* ▪ *b) Peak serum growth concentration < 3.1 mcg/L by glucagon stimulation testing* ▪ *c) Documented deficiency of at least 3 other pituitary hormones* ▪ *d) One pituitary hormone deficiency (other than growth hormone) and one of following:*	No changes at this time	- No new drugs - No new data or evidence to alter therapy	Approved

CareSource

Human Growth Hormone

• *Peak serum growth hormone concentration less than 5 mcg/L by insulin tolerance testing* • *Peak serum growth concentration < 3.1 mcg/L by glucagon stimulation testing* - *Pediatric chronic renal insufficiency* o *Prescribed by an endocrinologist* o *Chronic renal insufficiency or failure, with glomerular filtration rate less than 75 mL/min/1.73m2 (1.25 mL/sec/1.73m2)* o *Epiphyses not yet closed* - *Pediatric growth hormone deficiency* o *Prescribed by an endocrinologist* o *Epiphyses not yet closed* o *Growth rate of minus 2.5 SD below mean for age* o *GHD is confirmed by one of the following:* ▪ *Two growth hormone stimulation test below 10 mg/ml* ▪ *Documented presence of at least two other pituitary hormone deficiencies and Insulin-like growth factor 1 (IGF-1) measurement below age-appropriate level* ▪ *Neonate with hypoglycemia and growth hormone level of less than 10 ng/ml* ▪ *One growth hormone stimulation test below 10 mg/ml and a pituitary disease or a condition affecting pituitary function* - *Prader-Willi syndrome* o *Prescribed by an endocrinologist* o *Age 18 years or younger* o *Diagnosis of Prader-Willi syndrome confirmed by genetic testing* o *One growth hormone stimulation test below 10 mg/ml* - *Wasting or cachexia associated with AIDS* o *Age 18 years or older* o *Greater than 10% of baseline weight loss* o *Patient on concomitant antiretroviral therapy* <u>Non-Preferred</u>			

CareSource

Human Growth Hormone			
Genotropin, Humatrop, Norditropin, Nutropin AQ, Omnitrope Pen, Saizen, Serostim, Tev-Tropin - Adult growth hormone deficiency o *Prescribed by an endocrinologist* o *Clinical findings consisting of one or more of the following:* ▪ *Acquired human growth hormone (HGH) deficiency due to pituitary disease or a condition affecting pituitary function.* ▪ *Childhood-onset HGH deficiency* o *Diagnosis of GHD confirmed by ONE of the following:* ▪ *a) Peak serum growth hormone concentration <* ▪ *5 mcg/L by insulin tolerance testing* ▪ *b) Peak serum growth concentration < 3.1 mcg/L by glucagon stimulation testing* ▪ *c) Documented deficiency of at least 3 other pituitary hormones* ▪ *d) One pituitary hormone deficiency (other than growth hormone) and one of following:* • *Peak serum growth hormone concentration less than 5 mcg/L by insulin tolerance testing* • *Peak serum growth concentration < 3.1 mcg/L by glucagon stimulation testing* o *A minimum of a 30 day trial of Omnitrope Vial, and documented clinical reason why another agent must be used* - *Pediatric chronic renal insufficiency* o *Prescribed by an endocrinologist* o *Chronic renal insufficiency or failure, with glomerular filtration rate less than 75 mL/min/1.73m2 (1.25 mL/sec/1.73m2)* o *Epiphyses not yet closed* o *A minimum of a 30 day trial of Omnitrope Vial, and documented clinical reason why another agent must be used* - *Pediatric growth hormone deficiency* o *Prescribed by an endocrinologist* o *Epiphyses not yet closed* o *Growth rate of minus 2.5 SD below mean for age* o *GHD is confirmed by one of the following:*			

Human Growth Hormone			
▪ *Two growth hormone stimulation test below 10 mg/ml* ▪ *Documented presence of at least two other pituitary hormone deficiencies and Insulin-like growth factor 1 (IGF-1) measurement below age-appropriate level* ▪ *Neonate with hypoglycemia and growth hormone level of less than 10 ng/ml* ▪ *One growth hormone stimulation test below 10 mg/ml and a pituitary disease or a condition affecting pituitary function* o *A minimum of a 30 day trial of Omnitrope Vial, and documented clinical reason why another agent must be used* - *Prader-Willi syndrome* o *Prescribed by an endocrinologist* o *Age 18 years or younger* o *Diagnosis of Prader-Willi syndrome confirmed by genetic testing* o *One growth hormone stimulation test below 10 mg/ml* o *A minimum of a 30 day trial of Omnitrope Vial, and documented clinical reason why another agent must be used* - *Wasting or cachexia associated with AIDS* o *Age 18 years or older* o *Greater than 10% of baseline weight loss* o *Patient on concomitant antiretroviral therapy* o *A minimum of a 30 day trial of Omnitrope Vial, and documented clinical reason why another agent must be used*			

CareSource

Hyperparathyroidism Treatment: Calcimimetics

Current PDL	Recommended	Rationale	P&T Decision
Preferred Cinacalcet (Sensipar) tablet Non-Preferred N/A	No changes at this time	- No new drugs - No new data or evidence to alter therapy	Approved

Hyperparathyroidism Treatment: Vitamin D Analogs

Current PDL	Recommended	Rationale	P&T Decision
Preferred Calcitriol capsule 0.25 mcg, 0.5 mcg Calcitriol injection 1 mcg/mL Calcitriol solution 1 mcg/mL Paricalcitol (Zemplar) Capsule 1 mcg, 2 mcg, 4 mcg Doxercalciferol (Hectorol) capsule 0.5 mcg, 1 mcg, 2.5 mcg Non-Preferred N/A	Remove Paricalcitol (Zemplar) and Doxercalciferol (Hectorol)	Significant cost difference of paricalcitol and doxercalciferol vs calcitriol (average spend per rx for paricalcitol is $470.83 and $907.67 for doxercalciferol vs $63.29 for calcitriol). All are recommended as options in KDIGO guidelines, and all are indicated for secondary hyperparathyroidism in CKD.	Approved

Ophthalmic: Anti-allergics

Current PDL	Recommended	Rationale	P&T Decision
Preferred Zaditor (Ketotifen) eye drops Azelastine eye drops - No Pa required for 60ml (2 bottles) per 25 days Non-Preferred Pataday eye drops - OH & KY o *Continuity of care* OR	No changes at this time	- No new drugs - No new data or evidence to alter therapy	Approved

CareSource

Ophthalmic: Anti-allergics			
o *15 day trial of OTC Ketotifen (Refresh/Zyrtec Eye Drops/Wal-Zyr/Alaway/Claritin Eye Drops/RiteAid or CVS Eye Itch EYE DROPS (Zaditor) AND* o *15 day trial of azelastine (Optivar) OR* o *If child is age 2-3 Years old* - *IN* o *Continuity of Care (Age 3 & Up) OR* o *Member is Age 3 Or Older* o *15 Day Trial Of OTC Ketotifen (Refresh/Zyrtec Eye Drops/Wal-Zyr/Alaway/Claritin Eye Drops/RiteAid Or CVS Eye Itch Eye Drops (Zaditor)* o *AND* o *15 Day Trial Of Azelastine (Optivar)* Pazeo - *Continuity of care* OR - *Approve If Previously Approved For Alocril, Alrex, Bepreve, Or Epinastine (Elestat) OR* - *15 Day Trial Of: OTC Ketotifen (Alaway/Claritin Eye Drops/Refresh/RiteAid Or CVS Eye Itch Eye Drops (Zaditor)/Wal-Zyr/ Zyrtec Eye Drops) AND* - *15 Day Trial Of: Azelastine (Optivar) OR* - *If child is age 2-3 Years old* Olopatadine (Patanol) eye drops - *Continuity of care (Age 3 & Up) OR* - *Member is Age 3 Or Older* - *15 Day Trial Of OTC Ketotifen (Refresh/Zyrtec Eye Drops/Wal-Zyr/Alaway/Claritin Eye Drops/RiteAid Or CVS Eye Itch Eye Drops (Zaditor) AND* - *15 Day Trial Of Azelastine (Optivar)* Bepreve eye drops - *Continuity of care (Age 2 & Up OR* - *Approve If Previously Approved For Alocril, Alrex, Epinastine (Elestat), Or Pazeo OR* - *Age 2 Years Or Older* - *15 Day Trial Of: OTC Ketotifen (Alaway/Claritin Eye Drops/Refresh/RiteAid Or CVS Eye Itch Eye Drops (Zaditor)/Wal-Zyr/ Zyrtec Eye Drops) AND* - *15 Day Trial Of: Azelastine (Optivar)*			

CareSource

Ophthalmic: Anti-allergics			
Emadine eye drops - *Age 3 years or older* - *If fax states pt is pregnant OR* - *15 day trial of OTC Ketotifen (Refresh/Zyrtec Eye Drops/Wal-Zyr/Alaway/Claritin Eye Drops/RiteAid or CVS Eye Itch EYE DROPS (Zaditor) AND* - *15 day trial of azelastine (Optivar)* Lastacaft 0.25% eye drops - *If fax states pt is pregnant OR* - *If child is age 2-3 Years old OR* - *15 day trial of OTC Ketotifen (Refresh/Zyrtec Eye Drops/Wal-Zyr/Alaway/Claritin Eye Drops/RiteAid or CVS Eye Itch EYE DROPS (Zaditor) AND* - *15 day trial of azelastine (Optivar)* Epinastine (Elestat) eye drops - *Continuity of Care (Age 2 & Up) OR* - *Approve If Previously Approved For Alocril, Alrex, Bepreve, Or Pazeo OR* - *Age 2 Years Or Older* - *15 Day Trial Of: OTC Ketotifen (Alaway/Claritin Eye Drops/Refresh/RiteAid Or CVS Eye Itch Eye Drops (Zaditor)/Wal-Zyr/ Zyrtec Eye Drops) AND* - *15 Day Trial Of: Azelastine (Optivar)* Alocril eye drops - OH & KY o *Age 3 years or older: Continuity of Care OR* o *Approve If Previously Approved For Alrex, Bepreve, Epinastine (Elestat), Or Pazeo OR* o *15 Day Trial Of: OTC Ketotifen (Alaway/Claritin Eye Drops/Refresh/RiteAid Or CVS Eye Itch Eye Drops (Zaditor)/Wal-Zyr/ Zyrtec Eye Drops) AND* o *15 Day Trial Of: Azelastine (Optivar)* - IN o *Continuity of Care (Age 3 & Up) OR* o *Approve If Previously Approved For Alrex, Bepreve, Epinastine (Elestat), Or Pazeo OR* o *Age 3 Years Or Older*			

CareSource

Ophthalmic: Anti-allergics

o *15 Day Trial Of: OTC Ketotifen (Alaway/Claritin Eye Drops/Refresh/RiteAid Or CVS Eye Itch Eye Drops (Zaditor)/Wal-Zyr/ Zyrtec Eye Drops) AND* o *15 Day Trial Of: Azelastine (Optivar)* Elestat - *Age 2 years or older: Continuity of Care OR* - *Approve If Previously Approved For Alocril, Alrex, Bepreve, Or Pazeo OR* - *15 Day Trial Of: OTC Ketotifen (Alaway/Claritin Eye Drops/Refresh/RiteAid Or CVS Eye Itch Eye Drops (Zaditor)/Wal-Zyr/ Zyrtec Eye Drops) AND* - *15 Day Trial Of: Azelastine (Optivar)*			

Ophthalmic: Anti-Infectives/Combinations

Current PDL	Recommended	Rationale	P&T Decision
<u>Preferred</u> Bacitracin ointment - [Dose: 30 Grams / 26 Days] BACITRACIN-POLYMYXIN EYE OINTMENT NEOMYCIN-BACITRACIN-POLYMYXIN EYE OINTMENT NEOMYCIN-BACITRACIN-POLYMYXIN-HYDROCORTISONE EYE OINTMENT NEOMYCIN-POLY-HC EYE DROPS NEOMYCIN-POLYMYXIN B-GRAMICIDIN (NEOSPORIN) EYE DROPS Erythromycin ointment Erythromycin gel - [Dose: 60 Grams / 26 Days] Gentamicin eye drops, Gentamicin ointment - [Dose: 15 Grams (1 Tube) / 26 Days] Ofloxacin (Ocuflox) eye drops - No PA required for: 1 bottle per Month Blephamide eye ointment BLEPHAMIDE, SULFACETAMIDE SODIUM-PREDNISOLONE EYE DROP SUSPENSION SULFACETAMIDE SODIUM (BLEPH-10) EYE DROPS SULFACETAMIDE SODIUM OPHTHALMIC OINTMENT - Approve for 1 Year: Will be added to formulary	No changes at this time	- No new drugs - No new data or evidence to alter therapy	Approved

CareSource

Ophthalmic: Anti-Infectives/Combinations

Tobramycin eye drops
Moxifloxacin (Vigamox) eye drops
- IN Only: Step therapy
  o Continuity of care OR
  o Diagnosis of Cataract Surgery Or Corneal Ulcer/Keratitis OR
  o Diagnosis of Conjunctivitis
  o One Time Trial Of: Ciprofloxacin Or Ofloxacin Ophthalmic
Maxitrol 0.1% eye drops, ointment
 	
<u>Non-Preferred</u>
Ciloxan ointment
- *Clinical reason (OH MCD ONLY) supported by chart notes why (after a one time trial of) the below cannot be used: ciprofloxacin solution*
Azasite eye drops
- *One time Trial of: ciprofloxacin or ofloxacin ophthalmic*
Besivance suspension
- *Diagnosis of cataract surgery or Corneal ulcer/Keratitis OR*
- *Diagnosis of conjunctivitis*
- *One time trial of: ciprofloxacin or ofloxacin ophthalmic*
Gatifloxacin (Zymaxid) eye drops
- *Diagnosis of cataract surgery or Corneal ulcer/Keratitis OR*
- *Diagnosis of conjunctivitis*
- *One time trial of: ciprofloxacin or ofloxacin ophthalmic*
Levofloxacin eye drops
- *One time Trial of: ciprofloxacin or ofloxacin ophthalmic*
Moxifloxacin (Vigamox) eye drops
- *OH & KY*
  o *Continuity of care OR*
  o *Diagnosis of Cataract Surgery Or Corneal Ulcer/Keratitis OR*
  o *Diagnosis of Conjunctivitis*
  o *One Time Trial Of: Ciprofloxacin Or Ofloxacin Ophthalmic*			

CareSource

Ophthalmic: Anti-inflammatory

Current PDL	Recommended	Rationale	P&T Decision
<u>Preferred</u> Pred-G Ophthlamic suspension 0.3-1% Pred-G S.O.P. Ophthalmic ointment 0.3-0.6% Prednisolone (Pred Mild) 0.12% ophthalmic ointment Prednisolone acetate 1% (Pred forte, Omnipred) Prednisolone sodium phosphate ophthlamic suspension 1% Fluorometholone, Fluor-OP 0.1% (FML Liquifilm drops) Vexol 1% eye drops Diclofenac (voltaren) 0.1% eye drops Ketorolac (Acular) eye drops <u>Non-Preferred</u> Maxidex 0.1% eye drops - *One time trial of: dexamethasone 0.1% ophthalmic solution* Durezol 0.05% eye drops - *One time Trial of: DEXAMETHASONE 0.1% OPHTHALMIC SOLUTION, PREDNISOLONE ACETATE (PRED FORTE, OMNIPRED) 1%, or PREDNISOLONE SODIUM PHOSPHATE 1%* Flarex 0.1% ophthalmic suspension - *One time Trial of: FLUOROMETHOLONE, FLUOR-OP (Fml LIQUIFLM) 0.1% DROPS* FML Forte 0.25% eye drops - *One time Trial of: FLUOROMETHOLONE, FLUOR-OP (Fml LIQUIFLM) 0.1% DROPS* Alrex 0.2% Eye drops - *Continuity of Care (Age 18 & Up) OR* - *Approve If Previously Approved For Alocril, Bepreve, Epinastine (Elestat), Or Pazeo OR* - *Age 18 Years Or Older* o *15 Day Trial Of: OTC Ketotifen (Alaway/Claritin Eye Drops/Refresh/RiteAid Or CVS Eye Itch Eye Drops (Zaditor)/Wal-Zyr/ Zyrtec Eye Drops) AND* o *15 Day Trial Of: Azelastine (Optivar)* Lotemax 0.5% eye drops, gel, ointment - *One Time Trial Of: Pred Mild 0.12%, Prednisolone Acetate (Pred Forte, Omnipred) 1%, Prednisolone Sodium Phosphate 1%,*	No changes at this time	- No new drugs - No new data or evidence to alter therapy	Approved

CareSource

Ophthalmic: Anti-inflammatory			
Dexamethasone 0.1%, Or Fluorometholone, Fluor-Op (FML Liquifilm) 0.1% Ophthalmic Drops Bromfenac eye drops - *30 day Trial of: DICLOFENAC (VOLTAREN) 0.1% EYE DROPS* Flurbiprofen sodium (Ocufen) eye drops - Trial Of Diclofenac Sodium (Ophthalmic) AND Ketroloac (0.4% Or 0.5%) Nevanac droptainer - *30 day Trial of: DICLOFENAC (VOLTAREN) 0.1% EYE DROPS*			

Ophthalmic: Beta-blockers			
Current PDL	Recommended	Rationale	P&T Decision
<u>Preferred</u> Timolol (Timoptic) eye drops Timolol (Timoptc-XE) gel eye solution Metipranolol (Optipranolol) eye drops Levobunolol 0.5% (Betagan) eye drops Levobunolol 0.25% eye drops Betaxolol eye drops Carteolol eye drop solution <u>Non-Preferred</u> Betimol eye drops 0.25%, 0.5% - *Clinical reason (OH MCD ONLY) supported by chart notes why (after a trial of) the below cannot be used: BETAXOLOL 0.5% EYE DROP* *Betoptic-s eye drops* - *Clinical reason (OH MCD ONLY) supported by chart notes why (after a trial of) the below cannot be used: BETAXOLOL 0.5% EYE DROP* Timoptic Ocudose Drop 0.25%, 0.5% - *Clinical reason (OH MCD ONLY) supported by chart notes why (after a 30 day trial of) the below cannot be used: TIMOLOL (TIMOPTIC) 0.25% EYE DROPS or TIMOLOL (TIMOPTIC-XE) 0.25% GEL EYE SOLUTION, TIMOLOL (TIMOPTIC) 0.5% EYE DROPS or TIMOLOL (TIMOPTIC-XE) 0.5% GEL EYE SOLUTION*	No changes at this time	- No new drugs - No new data or evidence to alter therapy	Approved

CareSource

Ophthalmic: Carbonic Anhydrase Inhibitors/combinations

Current PDL	Recommended	Rationale	P&T Decision
<u>Preferred</u> Dorzolamide (Trusopt) eye drops Dorzolamide-timolol (Cosopt) eye drops <u>Non-Preferred</u> Azopt eye drops - Trial of: Dorzolamide (Trusopt) 2% eye drops Cosopt PF solution - *Clinical Reason Supported By Chart Notes Why (After A Trial Of) The Below Cannot Be Used:* ▪ *Dorzolamide HCl/Timolol Maleate (COSOPT)*	No changes at this time	- No new drugs - No new data or evidence to alter therapy	Approved

Ophthalmic: Prostaglandins

Current PDL	Recommended	Rationale	P&T Decision
<u>Preferred</u> *Latanoprost (Xalatan) eye drops* <u>Non-Preferred</u> Lumigan eye drops - *Continuity of Care OR* - *30 day Trial of: Latanoprost 0.005% EYE DROPS* Latisse solution - *Cosmetic: Send to RPH-Excluded Benefit* Zioptan - *Continuity of Care OR* - *30 Day Trial Of: Latanoprost 0.005% Eye Drops* Travatan Z (Travoprost) eye drops - *Continuity of Care OR* - *30 day Trial of: Latanoprost 0.005% EYE DROPS*	No changes at this time	- No new drugs - No new data or evidence to alter therapy	Approved

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Ophthalmic: Sympathomimetics

Current PDL	Recommended	Rationale	P&T Decision
<u>Preferred</u> Combigan (brimonidine and timolol) eye drops Alphagan P (Brimonidine) 0.2% eye drops <u>Non-Preferred</u> Apraclonidine (Iopidine) eye drops - *Continuity of Care OR* - *Trial of: brimonidine 0.2% ophthalmic* Brimonidine 0.15% (Alphagan P)/ Brimonidine eye drops - *Clinical reason (OH MCD ONLY) supported by chart notes why (after a trial of) the below cannot be used: BRIMONIDINE 0.2% EYE DROP* Simbrinza suspension eye drops - *Continuity of Care OR* - *30 day trial of BRIMONIDINE 0.2% EYE DROP WITH DORZOLAMIDE (TRUSOPT) 2% EYE DROPS*	No changes at this time	- No new drugs - No new data or evidence to alter therapy	Approved

Oral Corticosteroids

Current PDL	Recommended	Rationale	P&T Decision
<u>Preferred</u> Prednisone tablet, solution Pediapred solution Budesonide EC (ENTOCORT EC) capsules Cortisone tablet Dexamethasone tablet, solution Fludrocortisone tablet Hydrocortisone tablet Methylprednisolone tablet, dose pack <u>Non-Preferred</u> Prednisolone (Orapred ODT) tablet - *30 day trial of: prednisone tablet or liquid or methylprednisolone tablet* Dexpak tablet	No changes at this time	- No new drugs - No new data or evidence to alter therapy	Approved

CareSource

Oral Corticosteroids

- *Clinical Reason Supported By Chart Notes Why (After A 30 Day Trial Of) The Below Cannot Be Used: dexamethasone tablet* Celestone solution - *One time trial of prednisolone tablet* Uceris - *30 Day Trial Of: Apriso ER, Mesalamine (Asacol HD), Delzicol, Or Balsalazide (Colazal)* Medrol tablet - *Clinical reason (OH MCD ONLY) supported by chart notes why (after a 30 day trial of) the below cannot be used:* - **methylprednisolone 4mg tablet* Millipred DP Dose Pack - *One time trial of prednisolone tablet* Millipred solution - *One time trial of prednisolone liquid* Millipred tablet - *One time trial of prednisolone tablet* Emflaza (Deflazacort) tablet - *Member must be 5 years of age or older; AND* o *2. Member has documented onset of weakness before 5 years of age; AND* o *3. Member has documented serum creatinine kinase activity at least 10 times the upper limit of normal* o *(ULN) at some stage in their illness; AND* - *Medication is prescribed by or in consultation with a physician who specializes in the treatment of DMD and/or neuromuscular disorders; AND* - *Member has documented trial and failure of prednisone for at least 6 months; AND* - *Member has documented baseline of Medical Research Council (MRC) 11-point scale score for Muscle Strength.* - *Dosage allowed: 0.9 mg/kg/day once daily* Veripred 20 solution - *One time trial of prednisolone 15 mg/5 mL solution* Rayos tablet - *Clinical reason (OH MCD ONLY) supported by chart notes why (after A one time trial of) the below cannot be used: prednisone tablets*			

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Parathyroid Hormone Analogs

Current PDL	Recommended	Rationale	P&T Decision
<u>Preferred</u> N/A <u>Non-Preferred</u> Natpara cartridge - *Diagnosis of hypocalcemia with hypoparathyroidism (low PTH levels)* - *30 day trial of: calcium and vitamin D separately taken together at the same time* Teriparatide (Forteo) - *Considered medically necessary when the ALL following criteria are met:* o *Clinical findings include 1 or more of the following:* ▪ *Postmenopausal osteoporosis, as indicated by 1 or more of the following:* • *Femoral neck, spine, or total hip bone mineral density T-score minus 2.5 or less* • *Hip or vertebral fragility (ie, low-trauma) fracture in female older than 50 years* ▪ *Osteoporosis in males, as indicated by 1 or more of the following:* • *Femoral neck, spine, or total hip bone mineral density T-score minus 2.5 or less* • *Hip or vertebral fragility fracture in patient older than 50 years* • *Osteoporosis secondary to hypogonadism and failure of or intolerance to testosterone* ▪ *Glucocorticoid-induced osteoporosis in male or female, as indicated by ALL of the following* • *Daily dose equivalent to 7.5 mg or more of prednisone* • *Duration of glucocorticoid therapy expected to be 1 or more of the following:* o *Three months or more for male 50 years or older* o *Three months or more for any patient with history of fragility*	Tymlos (abaloparatide) approved on April 28, 2017 indicated for osteoporosis: non-formulary	Oral and IV bisphosphonates available as preferred agents and recommended first line by osteoporosis guidelines	Approved

Parathyroid Hormone Analogs

o *Three months or more for postmenopausal female* o *Twelve months or more* - *Failure of, inability to tolerate, or contraindication to oral or intravenous bisphosphonates* o *Risk factors for fracture, as indicated by 1 or more of the following:* ▪ *Alcohol intake of 3 or more drinks per day* ▪ *BMI less than 20* ▪ *Corticosteroid use of more than 6 months' duration* ▪ *Current or past history of cigarette smoking* ▪ *Parental hip fracture* ▪ *Personal history of fragility or osteoporotic fracture after age 50 years* Tymlos (abiloparatide) - *Diagnosis of Postmenopausal osteoporosis, as indicated by 1 or more of the following:* o *Femoral neck, spine, or total hip bone mineral density T-score minus 2.5 or less* o *Hip or vertebral fragility (ie, low-trauma) fracture in female older than 50 years* - *Risk factors for fracture, as indicated by 1 or more of the following:* o *Alcohol intake of 3 or more drinks per day* o *BMI less than 20* o *Corticosteroid use of more than 6 months' duration* o *Current or past history of cigarette smoking* o *Parental hip fracture* o *Personal history of fragility or osteoporotic fracture after age 50 years* - *Failure of oral or intravenous bisphosphonates (OH, IN, GA = 90 day trial, KY = 30 day trial) or inability to tolerate or contraindication*			

Phenylketonuria Treatment

Current PDL	Recommended	Rationale	P&T Decision
<u>Preferred</u> N/A <u>Non-Preferred</u>	No changes at this time	- No new drugs - No new data or evidence to alter therapy	Approved

CareSource

Phenylketonuria Treatment			
Kuvan tablets, powder pack - *Continuity of Care* - *Diagnosis of Hyperphenylalaninemia or PKU (phenylketonuria)*			

Phosphate-binders: Calcium-based/Non-calcium-based			
Current PDL	Recommended	Rationale	P&T Decision
<u>Preferred</u> Calcium acetate capsule Calcium carbonate tablet, suspension Calcium gluconate vial - *Medical benefit only* Calcium lactate Fosrenol chewable tablet Magonate tablet,liquid <u>Non-Preferred</u> Sevelamer Carbonate (Renvela) - *MD States CA-PHos Product Levels Are Elevated OR* - *Diagnosis of Reduction Or Control Of Serum Phosphorous In Patients With CKD On Dialysis AND* - *30 Day Trial Of Calcium Acetate (PhosLo)* Lanthanum Carbonate (Fosrenol) powder - *OH & KY* o *Clinical reason (OH MCD ONLY) supported by chart notes why (after a trial of) the below cannot be used* ▪ *FOSRENOL 750MG/1000MG CHEWABLE TABLET* - *IN* o *Clinical Reason Supported By Chart Notes Why (After A Trial Of) The Below Cannot Be Used:* ▪ *FOSRENOL 750MGMG/1000MG CHEWABLE TABLET* Auryxia tablet - *Diagnosis of control of serum phosphorus levels in patients with chronic kidney disease (CKD) receiving dialysis* - *90 day trial of: calcium acetate (PhosLo)*	No changes at this time	- No new drugs - No new data or evidence to alter therapy	Approved

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Phosphate-binders: Calcium-based/Non-calcium-based			
Velphoro Chewable Tablet - *Continuity of Care OR* - *Fax States Elevated Calcium, High Calcium, Hypercalcemia, etc OR* - *Has A Fluid Restriction Or Has Difficulty Swallowing Pills OR* - *30 Day Trial Of: Calcium Acetate (PhosLo) [Not Required If: Member Has The Inability To Swallow]*			

Prenatal Vitamins			
Current PDL	Recommended	Rationale	P&T Decision
<u>Preferred</u> CompleteNate Chewable Tablet MacNatal CN DHA Capsule One-A-Day Women's Prenatal Pack Prenaissance Plus Capsule PrenaPlus Tablet Prenatal 19 Chewable Tablet Prenate AM Tablet Prenate Chewable Tablet Prenate DHA Capsule Prenate Elite Tablet Prenate Enhance Capsule Prenate Essential Capsule Prenate Mini Capsule Prenate Pixie Capsule Prenate Restore Capsule Prenate Star Tablet Se-Natal 19 Chewable Tablet Taron-BC Tablet Vinate GT Tablet Vol-Plus Tablet VP-CH-PNV Capsule Zatean-CH Capsule <u>Non-Preferred</u> All non-formulary prenatal vitamins	No changes at this time	- No new drugs - No new data or evidence to alter therapy	Approved

CareSource

Prenatal Vitamins			
- 90 Day Trial Of: MacNatal CN DHA Capsule, One-A-Day Women's Prenatal Pack, Prenaissance Plus Capsule, Prenate DHA Capsule, Prenate Enhance Capsule, Prenate Essential Capsule, Prenate Mini Capsule, Prenate Pixie Capsule, Prenate Restore Capsule, VP-CH-PNV Capsule, Or Zatean-CH Capsule			

Progestins			
Current PDL	Recommended	Rationale	P&T Decision
<u>Preferred</u> Crinone Gel Endometrin Vaginal Suppository First-Progesterone VGS compounding kit Prometrium capsule Progesterone vaginal suppositories Megestrol tablet Megestrol acetate suspension Aygestin; Camila; Deblitane; Errin; Heather; Jencycla; Jolivette Nora-BE; Ortho Micronor Depo-provera (medroxyprogesterone) 150 mg/mL Depo-provera (medroxyprogesterone) 400 mg/mL Medroxyprogesterone acetate 150 mg/mL Medroxyprogesterone acetate 2.5 mg, 5 mg, 10 mg <u>Non-Preferred</u> Makena Intramuscular oil (Single use and multi-use) vial - *Medical Benefit Only* Progesterone vial - *Clinical reason (OH MCD ONLY) supported by chart notes why (After a 90 day trial of) the below cannot be used: Progesterone capsule or progesterone vaginal suppositories*	No changes at this time	- No new drugs - No new data or evidence to alter therapy	Approved

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Respiratory: Anaphylaxis Treatment Agents

Current PDL	Recommended	Rationale	P&T Decision
<u>Preferred</u> Epipen Auto-injector - *No PA required for: 8 pens (4 packs)/365 Days or up to 3 boxes (qty of 6) if requested for multiple locations school, daycare, home, etc* Epipen JR Auto-injector - *No PA required for: 8 pens (4 packs)/ 365 Days or up to 3 boxes (qty of 6) if requested for multiple locations school, daycare, home, etc* <u>Non-Preferred</u> Auvi-Q Auto Injector - *Clinical Reason (OH MCD ONLY) why Epi-Pen (brand) or Epinephrine 0.15 mg/0.15 mL Cannot be used after a 90 Day Trial* o *KY = 30 day trial of Epi-Pen (brand) or epinephrine 0.15 mg/0.15 mL* - *Clinical Reason why Epi-Pen (brand) or Epinephrine 0.15 mg/0.15 mL Cannot be used after a 90 Day Trial*	No changes at this time	- No new drugs - No new data or evidence to alter therapy	Approved

Respiratory: Anti-cholinergics

Current PDL	Recommended	Rationale	P&T Decision
<u>Preferred</u> Spiriva Respimat Inhaler (Tiotropium) 1.25mcg Stiolto Respimat Mist Inhaler Ipratropium bromide solution 0.025% - *No PA required for:300mls per 30 days* Ipratropium and Albuterol (Duoneb) solution - *No PA required for:540ml/30 days* <u>Non-Preferred</u> Spiriva Respimat Handihaler 2.5mcg - *Diagnosis of COPD (emphysema, chronic bronchitis) AND* - *Clinical reason (OH MCD Only) supported by chart notes why (after a 30 day trial of the below cannot be used: Spiriva respimat* Tudorza Pressair Inhaler - *No CC unless approved by caresource on or after 01/01/17*	No changes at this time	- No new drugs - No new data or evidence to alter therapy	Approved

CareSource

Respiratory: Anti-cholinergics

- *Diagnosis of COPD (Emphysema, Chronic Bronchitis)* - *30 day trial of : Spiriva Respimat* Seebri Neohaler - *OH & KY* o *Diagnosis of COPD* o *30 Day Trial of: Spiriva Respimat* - *IN* o *Diagnosis COPD* o *30 Day trial of: Spiriva Respimat or Tudorza* Bevespi Aerosol - *Diagnosis of COPD* - *30-day trial and failure (in the last 90 days), contraindication, or adverse reaction to at least ONE agent from each of the below:* ▪ *Long acting anticholinergic: Spiriva Respimat, or Incruse (which requires PA) AND* ▪ *Long acting beta-2 agonist: Arcapta, Serevent, Brovana (which requires PA), Perforomist (which requires PA), Striverdi Respimat* Utibron Neohaler - *Diagnosis of COPD* - *30 Day Trial of: Stiolto Respimat Mist Inhaler* Incruse Ellipta Inhaler - *OH & KY: 30 Day Trial of: Spiriva Respimat (Respimat is preferred)* - IN: *30 Day Trial of Tudorza or Spiriva Respimat* Anoro Ellipta Inhaler - *Diagnosis of COPD AND* - *30 Day Trial Of: Stiolto Respimat Mist Inhaler*			

Respiratory: Beta agonists

Current PDL	Recommended	Rationale	P&T Decision
<u>Preferred</u> Ventolin HFA Inhaler - *No PA Required For: 2 Inhalers (36g)/30 Days* Arcapta Neohaler - *No PA required for: 1 inhaler/30 days* Serevent Diskus - *No PA required for: 1 inhaler (60 doses)/30 days*	Add Levalbuterol (Xopenex) HFA as a preferred agent	70% of PAs for xopenex HFA approved; will lower administrative costs; cost of Xopenex HFA $73.65 vs cost of Ventolin (preferred) $62.64	Approved

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Respiratory: Beta agonists			
Metaproterenol syrup <u>Non-Preferred</u> Striverdi Respimat Inhaled Aerosol solution - *Approve for 1 year: will be added to formulary, Max 1 inhaler (4G)/26 Days* Proair HFA inhaler/ Proair Respiclick - *Clinical Reason Supported By Chart Notes Why (After A 30 Day Trial Of) The Below Cannot Be Used: Ventolin HFA* - *Max 2 Inhalers (17g)/30 Days* Perforomist solution - *30 day trial of: Arcapta Neohaler* Levabuterol (Xopenex) concentrated nebulizer solution - *Intolerance Or Side Effects To Albuterol (i.e., Tachycardia, Jitteriness, Shaking, Increased Heart Rate, Aggitation) OR* - *30 Day Trial Of: Ventolin (Accepted But Not Recommended: ProAir Or Proventil)* - *Max 360 mL (5 boxes)/30 Days* Levalbuterol (Xopenex) HFA - *Intolerance Or Side Effects To Albuterol (i.e., Tachycardia, Jitteriness, Shaking, Increased Heart Rate, Aggitation) OR* - *30 Day Trial Of: Ventolin (Accepted But Not Recommended: ProAir Or Proventil)* - *Max 2 Inhalers (30g)/30 Days*			

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Leukotriene receptor antagonists

Current PDL	Recommended	Rationale	P&T Decision
<u>Preferred</u> Montelukast chewable tablets, granules, tablets Zafirlukast (Accolate) tablets <u>Non-Preferred</u> Zyflo (zileuton) CR - *Continuity of CareOR* - *30 Day Trial Of: Montelukast (Singulair)* Zyflo Filmtab - *Continuity of Care OR* - *30 Day Trial Of: Montelukast (Singulair)*	No changes at this time	- No new drugs - No new data or evidence to alter therapy	Approved

Nasal Antihistamines

Current PDL	Recommended	Rationale	P&T Decision
<u>Preferred</u> Azelastine (Astelin) nasal spray - *No PA required for 60ml (2 bottles) per 25 days* <u>Non-Preferred</u> Olopatadine (Patanase) nasal spray 0.6% - *30 Day Trial Of: Azelastine (Astelin) OR* - *Allergy, Intolerance, Or Side Effects To: Azelastine (Astelin)*	No changes at this time	- No new drugs - No new data or evidence to alter therapy	Approved

Nasal steroids

Current PDL	Recommended	Rationale	P&T Decision
<u>Preferred</u> Fluticasone (Flonase) nasal spray OTC Flonase Sensimist spray OTC - *No PA required for 9.9 mL (1 bottle)/ 26 days* Rhinocort allergy (OTC) nasal suspension - *IN* o *No PA required for 10 mL/26 days*	No changes at this time	- No new drugs - No new data or evidence to alter therapy	Approved

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Nasal steroids			
Flunisolide spray - *No PA required for: 50ml/30 days* Nasacort nasal spray OTC - *No PA Required For: 1 Bottle (16.9 mL)/26 Days* Nasacort AQ nasal spray - *No PA required for 1 Bottle (16.5 g)/26 days* <u>Non-Preferred</u> Rhinocort Aqua nasal suspension - *Approve for 1 year: will be added to formulary* Beclomethasne (Qnasl) nasal spray - *Ages 2-3: 30 Day Trial Of Nasacort OTC Allergy 24HR Spray OR* - *Ages 4-5: 30 Day Trial Of Fluticasone (Flonase), Flonase OTC Allergy Relief Spray, Or Nasacort OTC Allergy 24HR Spray OR* - *Ages 6 And Older: 30 Day Trial Of 2 Of The Following 4 Drugs: Fluticasone (Flonase), Flonase OTC Allergy Relief Spray, Flunisolide, Or Nasacort OTC Allergy 24HR Spray* Beclomethasne (Qnasl Children's) nasal spray - *Ages 2-3: 30 Day Trial Of Nasacort OTC Allergy 24HR Spray OR* - *Ages 4-5: 30 Day Trial Of Fluticasone (Flonase), Flonase OTC Allergy Relief Spray, Or Nasacort OTC Allergy 24HR Spray OR* - *Ages 6 And Older: 30 Day Trial Of 2 Of The Following 4 Drugs: Fluticasone (Flonase), Flonase OTC Allergy Relief Spray, Flunisolide, Or Nasacort OTC Allergy 24HR Spray* Beconase AQ Spray - *Ages 2-3: 30 Day Trial Of Nasacort OTC Allergy 24HR Spray OR* - *Ages 4-5: 30 Day Trial Of Fluticasone (Flonase), Flonase OTC Allergy Relief Spray, Or Nasacort OTC Allergy 24HR Spray OR* - *Ages 6 And Older: 30 Day Trial Of 2 Of The Following 3 Drugs: Fluticasone (Flonase), Flunisolide, Flonase OTC Allergy Relief Spray, Or Nasacort OTC Allergy 24HR Spray* Omnaris (ciclesonide) nasal spray - *Ages 2-3: 30 Day Trial Of Nasacort OTC Allergy 24HR Spray OR* - *Ages 4-5: 30 Day Trial Of Fluticasone (Flonase), Flonase OTC Allergy Relief Spray, Or Nasacort OTC Allergy 24HR Spray OR* - *Ages 6 And Older: 30 Day Trial Of 2 Of The Following 4 Drugs: Fluticasone (Flonase), Flonase OTC Allergy Relief Spray, Flunisolide, Or Nasacort OTC Allergy 24HR Spray*			

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Nasal steroids

Mometasone furoate (Nasonex) nasal spray - *Diagnosis of Nasal Polyps OR* - *Ages 2-3: 7 Day Trial Within The Last 90 Days Of: Nasacort OTC Allergy 24HR Spray OR* - *Ages 4-5: 7 Day Trial Within The Last 90 Days Of: Fluticasone (Flonase), Flonase OTC Allergy Relief Spray, Or Nasacort OTC Allergy 24HR Spray OR* - *Ages 6 And Older: 7 Day Trial Within The Last 90 Days Of 2 Of The Following Drugs: Fluticasone (Flonase), Flonase OTC Allergy Relief Spray, Flunisolide, Or Nasacort OTC Allergy 24HR Spray* - *Will Pay With An Electronic Step If There Are 7 Days Of 2 Of The Following Drugs: Fluticasone (Flonase), Flonase OTC Allergy Relief Spray, Flunisolide, Or Nasacort OTC Allergy 24HR Spray Use In The Last 120 Days]* Zetonna - *Ages 2-3: 30 Day Trial Of Nasacort OTC Allergy 24HR Spray OR* - *Ages 4-5: 30 Day Trial Of Fluticasone (Flonase), Flonase OTC Allergy Relief Spray, Or Nasacort OTC Allergy 24HR Spray OR* - *Ages 6 And Older: 30 Day Trial Of 2 Of The Following 4 Drugs: Fluticasone (Flonase), Flonase OTC Allergy Relief Spray, Flunisolide, Or Nasacort OTC Allergy 24HR Spray*			

Respiratory: Phosphodiesterase-4 Inhibitors

Current PDL	Recommended	Rationale	P&T Decision
<u>Preferred</u> Daliresp tablet - *Step Therapy* o *Continuity of Care OR* o *Diagnosis of Severe COPD* o *Currently On Albuterol (i.e., Albuterol Inhalation, Ventolin, ProAir, Proventil, Or Combivent) WITH* o *30 Day Trial From Two Of The Following Four Groups:* ▪ *Breo/Dulera/Advair OR Asmanex/Aerospan/Qvar/Flovent/Pulmicort OR Spiriva Respimat (Respimat Is Preferred)/ OR Montelukast (Singulair)/Theophylline With Continued Exacerbations*	No changes at this time	- No new drugs - No new data or evidence to alter therapy	Approved

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Respiratory: Phosphodiesterase-4 Inhibitors

Non-Preferred *N/A*			

Steroid/beta-agonist combinations

Current PDL	Recommended	Rationale	P&T Decision
Preferred Dulera - *No PA Required For: 2 Inhalers (26g)/30 Days* Advair Diskus 100-50 mcg - *No PA Required For: 1 Inhaler/30 Days* Breo Ellipta AirDuo Respiclick Non-Preferred Symbicort - *For Age 4-5* o *Off label age: Advair Diskus 100/50 is a formulary option* - *For Age 6-11* o *Unable to use Advair Diskus* - *For Age 12-17* o *Diagnosis of Asthma or COPD (Emphysema, Chronic Bronchitis)* o *30 Day Trial Of: Dulera (Does Not Need To Be Within The Last 120 Days)* - *For Age 18 years and older* o *Diagnosis of Asthma or COPD (Emphysema, Chronic Bronchitis)* o *30 Day Trial Of: Dulera or Breo Ellipta (Does Not Need To Be Within The Last 120 Days)* Advair Diskus 250-50mcg/ 500mcg-50mcg - *For Ages 4-11* o *Off label age* o *Note: Advair Diskus 100/50 is formulary option* - *For Ages 12-17* o *Diagnosis of Asthma or COPD (Emphysema, Chronic Bronchitis)*	No changes at this time	- No new drugs - No new data or evidence to alter therapy	Approved

Steroid/beta-agonist combinations			
o *30 Day Trial Of: Dulera (Does Not Need To Be Within The Last 120 Days)* - *For Ages 18 years and older* o *Diagnosis of Asthma or COPD (Emphysema, Chronic Bronchitis)* o *30 Day Trial Of: Dulera or Breo Ellipta (Does Not Need To Be Within The Last 120 Days)* AirDuo Respiclick - *For Ages 4-11* o *Off label age* o *Note: Advair Diskus 100/50 is formulary option* - *For Ages 12-17* o *Diagnosis of Asthma or COPD (Emphysema, Chronic Bronchitis)* o *30 Day Trial Of: Dulera (Does Not Need To Be Within The Last 120 Days)* - *For Ages 18 years and older* o *Diagnosis of Asthma or COPD (Emphysema, Chronic Bronchitis)* o *30 Day Trial Of: Dulera or Breo Ellipta (Does Not Need To Be Within The Last 120 Days)*			

Steroid Inhalants			
Current PDL	Recommended	Rationale	P&T Decision
<u>Preferred</u> Budesonide (Pulmicort) Inhalation suspension - *No PA required for: 120ml/30 days* Aerospan Inhaler - *No PA Required For: 2 Inhalers (17.8g)/30 Days* Asmanex HFA Inhaler - *No PA Required For: 2 Inhalers (26g)/30 Days* Qvar Inhaler - *No PA required for members 8 years old and younger* Flovent HFA - *No PA required for members 8 years old and younger* Flovent Diskus	No changes at this time	- No new drugs - No new data or evidence to alter therapy	Approved

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Steroid Inhalants			
- *No PA required for members 8 years old and younger* <u>Non-Preferred</u> Flovent HFA - *Approve If Fax States Member Is Disabled OR* - *Diagnosis of Eosinophilic Esophagitis (EoE) OR* - *Diagnosis of Asthma* - *30 Day Trial Of: Aerospan Or Asmanex (Does Not Need To Be Within The Last 120 Days)* - *No PA Is Required For Members 8 Years Old And Younger* - *Max Dose: 2 Inhalers (120 Doses)/30 Days* Flovent Diskus - *Approve if fax states member is disabled OR* - *Diagnosis of Eosiniphilic Esophagitis OR* - *Diagnosis of Asthma and 30 day trial of Aerospan or Asmanex (Does not need to be within the last 120 days)* - *Max dose: 2 inhalers/30 days* Qvar Inhaler - *Member Is Disabled OR* - *Diagnosis of Asthma* - *30 Day Trial Of: Aerospan Or Asmanex (Does Not Need To Be Within The Last 120 Days)* - *No PA Is Required For Members 8 Years Old And Younger* - *Max Dose: 3 Inhalers (26.1g)/30 Days* Alvesco - *Age 12 Years and Older* - *Diagnosis of Asthma* - *30 Day Trial Of Either: Aerospan Or Asmanex (Does Not Need To Be Within The Last 120 Days)* Pulmicort Flexhaler - *Approve if member is pregnant OR* - *Ages 4-5: Trial of Asmanex (does not need to be within the last 120 days) OR* - *Ages 5 and older: 30 day trial of Aerospan or Asmanex (Does not need to be within the last 120 days)*			

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Selective Estrogen Receptor Modulators

Current PDL	Recommended	Rationale	P&T Decision
Preferred Raloxifene (Evista) tablet Tamoxifen tablet Toremifene (Fareston) Non-Preferred Clomiphene (clomid) tablet - *OH & KY* o *Inftertility: Excluded benefit* o *Diagnosis of hypogonadism, total Testosterone Lab Value = ≤ 300ng/dL Before Treatment (For New Starts Only) OR a Total Testosterone lab value within the normal range during treatment (for continuation of care)* - *IN* o *Inftertility: Excluded benefit* o *Diagnosis of hypogonadism, total Testosterone Lab Value = ≤ 300ng/dL Before Treatment (For New Starts Only)* Ospemefine (Osphena) - *Excluded benefit: Sexual dysfunction*	No changes at this time	- No new drugs - No new data or evidence to alter therapy	Approved

Thyroid products

Current PDL	Recommended	Rationale	P&T Decision
Preferred Levothyroxine (Synthroid) tablet - *May approve if PA request is for DAW* Liothyronine (Cytomel) tablet Thyrolar (Liotrix) tablet - *No PA required for: 30 for 30 days* Armour thyroid tablet Non-Preferred Tirosint capsule - *Continuity of Care OR* - *Trial of: levothyroxine, Synthroid, armour thyroid, or liothyronine*	No changes at this time	- No new drugs - No new data or evidence to alter therapy	Approved

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Vasopressin receptor antagonists			
Current PDL	Recommended	Rationale	P&T Decision
<u>Preferred</u> Samsca tablet - *Continuity of care OR* - *Diagnosis of Hypervolemic And Euvolemic Hyponatremia* <u>Non-Preferred</u> N/A	No changes at this time	- No new drugs - No new data or evidence to alter therapy	Approved

Vasopressins			
Current PDL	Recommended	Rationale	P&T Decision
<u>Preferred</u> Desmopressin (DDAVP) tablets Desmopressin (DDAVP) nasal spray 0.01% Desmopressin vial 4 mcg/mL Desmopressin (DDAVP) ampule - *Preferred in IN only* <u>Non-Preferred</u> Desmopressin (DDAVP) AMPULE - *OH* o *Diagnosis of Diabetes insipidus AND* o *Clinical reason why after a 90 day trial that desmopressin tablets cannot be used* o *Quantity Limit: Max 1 mL (4 mcg) per day* - *KY* o *Diagnosis of Diabetes insipidus AND* o *30 day trial of desmopressin tablets* o *Quantity Limit: Max 1 mL (4 mcg) per day*	No changes at this time	- No new drugs - No new data or evidence to alter therapy	Approved

Viscosupplements

Current PDL	Recommended	Rationale	P&T Decision
<u>Preferred</u> Hyaluronic Acid Derivative Injection: *Gel-One, Gelsyn-3, Supartz-FX* - *Medical Benefit Only* - *OH, KY, & IN: Osteoarthritis of the knee* o *Initial authorization: Approval for 6 months if member meets all of the following requirements* ▪ *Age: 40 years or older* ▪ *Diagnosis of osteoarthritis confirmed by radiological evidence (e.g. Kellgren-Lawrence Scale score ≥grade 2)* ▪ *Prescriber must be one of the following: orthopedic surgeon, interventional pain physicians, rheumatologists, physiatrists (PM&R) or a sports medicine subspecialty* ▪ *Documentation that member tried and failed all of the following:* • *Weight loss attempts or attempts at lifestyle modifications to promote weight loss (only for members with BMI ≥30)* • *Sufficient trial (e.g. 2 to 3 months) of non-pharmacologic therapies (bracing/orthotics, physical/occupational therapy)* • *At least 3 simple analgesic therapies (acetaminophen, NSAIDs, oral or topical salicylates)* • *Intra-articular corticosteroid injection(s) (efficacy was < 4 weeks duration)* ▪ *Member is not using medication for hip or shoulder related conditions* o *Reauthorization: Approval for additional 6 months if member meets all of the following requirements* ▪ *Member must have documented significant pain relief that was achieved with the initial course of treatment* ▪ *Initial course of treatment has been completed for 6 months or longer* ▪ *Member meets all of the criteria for the initial approval.* *Product specific parameters*	No changes at this time	- No new data or evidence to alter preferred agents or criteria	Approved

CareSource

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- Gel-One (Cross-linked hyaluronate intraarticular gel) o *QL: 1 injection (1 unit)* o *Dosage allowed: Inject 30 mg (3 mL) once.* - Gelsyn-3 (Sodium hyaluronate) o *QL: 3 injections (504 units) - 168 billing units per 2 mL injection* o *Dosage allowed: Inject 16.8 mg (2 mL) once weekly for 3 weeks (total of 3 injections)* - Supartz FX (Sodium hyaluronate) o *QL: 5 injections (5 units)* o *Member is not allergic to avian proteins, feathers, and egg products.* o *Dosage allowed: Inject 20 mg (2 mL) once weekly for up to 5 weeks (total of 5 injections)* <u>Non-preferred</u> Durolane, Monovisc, Hymovis, Orthovisc, Synvisc-One, Synvisc, Euflexxa, GenVisc 850, Hyalgan, Visco-3 - *Medical Benefit Only* - *OH. KY, & IN: Osteoarthritis of the knee* o *Initial authorization: Approval for 6 months if member meets all of the following requirements* ▪ *Age: 40 years or older* ▪ *Diagnosis of osteoarthritis confirmed by radiological evidence (e.g. Kellgren-Lawrence Scale score ≥grade 2)* ▪ *Prescriber must be one of the following: orthopedic surgeon, interventional pain physicians, rheumatologists, physiatrists (PM&R) or a sports medicine subspecialty* ▪ *Documentation that member tried and failed all of the following:* • *Weight loss attempts or attempts at lifestyle modifications to promote weight loss (only for members with BMI ≥30)* • *Sufficient trial (e.g. 2 to 3 months) of non-pharmacologic therapies (bracing/orthotics, physical/occupational therapy)*			

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- *At least 3 simple analgesic therapies (acetaminophen, NSAIDs, oral or topical salicylates)*
- *Intra-articular corticosteroid injection(s) (efficacy was < 4 weeks duration)*

▪ *Member is not using medication for hip or shoulder related conditions*
▪ *Member has tried and failed to respond to treatment with Supartz FX or Gel-One or Gelsyn-3 (documented in chart notes and confirmed by claims history)*

o *Reauthorization: Approval for additional 6 months if member meets all of the following requirements*
▪ *Member must have documented significant pain relief that was achieved with the initial course of treatment*
▪ *Initial course of treatment has been completed for 6 months or longer*
▪ *Member meets all of the criteria for the initial approval.*

Product specific parameters

- Monovisc (Hyaluronan intraarticular solution)
  - *QL: 1 injection (1 unit)*
  - *Dosage allowed: Inject 88 mg (4 mL) once.*
- Hymovis (Hyaluronan intraarticular solution)
  - *QL: 2 injections (48 units)*
  - *Dosage allowed: Inject 24 mg (3 mL) once weekly for 2 weeks (total of 2 injections).*
- Orthovisc (Hyaluronan intraarticular solution)
  - *QL: 4 injections (4 units)*
  - *Member is not allergic to avian proteins, feathers, and egg products*
  - *Dosage allowed: Inject 30 mg (2 mL) once weekly for 3 to 4 weeks (total of 3 to 4 injections).*
- Synvisc-One (Hylan polymers A and B)
  - *QL: 1 injection (48 unit)*
  - *Member is not allergic to avian proteins, feathers, and egg products*
  - *Dosage allowed: Inject 48 mg (6 mL) once.*
- Synvisc (Hylan polymers A and B)
  - *QL: 3 injections (16 units)*

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o *Member is not allergic to avian proteins, feathers, and egg products* o *Dosage allowed: Inject 16 mg (2 mL) once weekly for 3 weeks (total of 3 injections).* - Euflexxa (Sodium hyaluronate) o *QL: 3 injections (3 units)* o *Dosage allowed: Inject 20 mg (2 mL) once weekly for 3 weeks (total of 3 injections).* - GenVisc 850 (Sodium hyaluronate) o *QL: 5 injections (125 units) - 25 billing units per injection* o *Dosage allowed: Inject 25 mg (2.5 mL) once weekly for 5 weeks (total of 5 injections); some patients may benefit from a total of 3 injections.* - Hyalgan (Sodium hyaluronate) o *QL: 5 injections (5 units)* o *Member is not allergic to avian proteins, feathers, and egg products* o *Dosage allowed: Inject 20 mg (2 mL) once weekly for up to 5 weeks (total of 5 injections).*			