Humana

Agenda

Kentucky Medicaid Plan Pharmacy and Therapeutics Meeting

Date: September 24, 2020
Time: 9:00 – 11:00am EST

Teleconferance Dial-In: 1-800-937-7000 (access code): 592826246

X: when in attendance

	Invited Voting P&T Members		Invited Guests				
X	Daniel Cornett, PharmD	X	Andrea Bloomfield, PharmD				
	Gerlinda Lowrey, MD	X	Brian Garcia, PharmD				
	Jay Mcknight, PharmD	X	Brock Bizzell, PharmD				
X	Jarrett Greer, MD	X	Daniel Cornett, PharmD				
X	Joseph Vennari, PharmD	X	Keli Abraham, PharmD				
X	Lisa Galloway, MD		Kenneth Kennedy, PharmD				
X	Lisa Musolin, D.O.	X	Michael Tindal, PharmD				
X	Valary Evans, MD	X	Yunus Meah, PharmD				
		X	Brandon Piazza, PharmD				
			Ellen Eiler, PharmD				
			Mark Malone				
							Residents
						X	Caroline Sanders, PharmD
							Katie Batliner, PharmD
							Students
							Meeting Facilitator
							Andrea Bloomfield, PharmD

HUMM03391

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Agenda

Facilitator	Meeting Call to Order	
Andrea Bloomfield	**Introduction:**	
Andrea Bloomfield	• **Announcements** • **Review of P&T Agenda** • **Conflict of Interest Disclosures**	
Andrea Bloomfield	**Review of Previous Meeting Minutes:** • **Sept 24, 2020 (Doc 2 Pg. 14)**	
Owner	**Policy Title**	**Policy Type**
Doc 3 Pg. 27	**Review of Existing Clinical Policies – No Recommended Clinical Changes (68) (Will not be presented but will require a vote)**	
Andrea Bloomfield	Entyvio (vedolizumab)	Prior Authorization
	Ilumya (tildrakizumab)	Prior Authorization
	Parsabiv (etelcalcetide)	Prior Authorization
	Stelara (ustekinumab) IV	Prior Authorization
Brian Garcia	Hemlibra (emicizumab-kxwh)	Prior Authorization
	Shingrix (zoster vaccine recombinant, adjuvanted)	Guidance
	Von Willebrand Factor Replacement Products	Prior Authorization
	Vyndaqel/Vyndamax (tafamidis)	Prior Authorization
	Zostavax (zoster vaccine live)	Guidance
Brock Bizzell	Opioid Utilization Program - Morphine Milligram Equivalent (MME) edits	Quantity Limit
	Previous Treatment/Prior Therapy/Trial	Guidance
Daniel Cornett	Akynzeo (fosnetupitant/netupitant-palonosetron)	Prior Authorization
	Cinvanti (aprepitant)	Prior Authorization
	Enbrel (etanercept)	Prior Authorization
	Soliris (eculizumab)	Prior Authorization
	Varubi (rolapitant)	Prior Authorization
Keli Abraham	Cytogam (cytomegalovirus immune globulin, human)	Prior Authorization
	Intron A (interferon alfa-2b)	Prior Authorization
	Mavyret (glecaprevir/pibrentasvir)	Prior Authorization
	Sofosbuvir-velpatasvir tablet	Prior Authorization
	VFEND (voriconazole)	Prior Authorization
Kenneth Kennedy	Aliqopa (copanlisib)	Prior Authorization
	Bendamustine products (Treanda, Bendeka, Belrapzo)	Prior Authorization
	Blincyto (blinatumomab)	Prior Authorization
	Bortezomib products (Velcade, bortezomib for injection)	Prior Authorization
	Bosulif (bosutinib)	Prior Authorization
	Copiktra (duvelisib)	Prior Authorization

	Darzalex (daratumumab)	Prior Authorization
	Gazyva (obinutuzumab)	Prior Authorization
	Gleevec (imatinib mesylate)	Prior Authorization
	Iclusig (ponatinib)	Prior Authorization
	Inrebic (fedratinib)	Prior Authorization
	Kyprolis (carfilzomib)	Prior Authorization
	Marqibo (vincristine sulfate liposome injection)	Prior Authorization
	Mozobil (plerixafor)	Prior Authorization
	Ninlaro (ixazomib)	Prior Authorization
	Polivy (polatuzumab vedotin-piiq)	Prior Authorization
	Poteligeo (mogamulizumab-kpkc)	Prior Authorization
	Revlimid (lenalidomide)	Prior Authorization
	Sprycel (dasatinib)	Prior Authorization
	Sylatron (peginterferon alfa-2b)	Prior Authorization
	Tasigna (nilotinib)	Prior Authorization
	Thalomid (thalidomide)	Prior Authorization
	Vyxeos (daunorubicin and cytarabine) liposome	Prior Authorization
Mike Tindal	Austedo (deutetrabenazine)	Prior Authorization
	Firdapse (amifampridine)	Prior Authorization
	Fycompa (perampanel)	Prior Authorization
	Korlym (mifepristone)	Prior Authorization
	Krystexxa (pegloticase)	Prior Authorization
	Macrilen (macimorelin)	Prior Authorization
	Onfi (clobazam)	Prior Authorization
	Ruzurgi (amifampridine)	Prior Authorization
	Serostim (somatropin)	Prior Authorization
	Signifor LAR (pasireotide)	Prior Authorization
	Testopel (testosterone)	Prior Authorization
	Zorbtive (somatropin)	Prior Authorization
Sheetal Sheth	Cyramza (ramucirumab)	Prior Authorization
	Keytruda (pembrolizumab)	Prior Authorization
	Lenvima (lenvatinib)	Prior Authorization
	Xeloda (capecitabine)	Prior Authorization
Yunus Meah	Berinert (C1 esterase inhibitor, human)	Prior Authorization
	Cinryze (C1 esterase inhibitor, human)	Prior Authorization
	Clinical Trials Pharmacy Policy	Prior Authorization
	Firazyr (icatibant)	Prior Authorization

	Haegarda (C1 esterase inhibitor, human)	Prior Authorization
	Kalbitor (ecallantide)	Prior Authorization
	Ruconest (C1 esterase inhibitor, recombinant)	Prior Authorization
	Takhzyro (lanadelumab-flyo)	Prior Authorization
Doc 4 Pg. 420	**Review of Existing Clinical Policies – Recommended Clinical Changes (32) (Will not be presented but will require a vote)**	
Andrea Bloomfield	Cosentyx® (secukinumab)	Prior Authorization
Brian Garcia	Gardasil® (human papillomavirus vaccine)	Prior Authorization
	Ofev® (nintedanib) & Esbriet® (pirfenidone)	Prior Authorization
Brock Bizzell	Beovu (brolucizumab)	Prior Authorization
	Tepezza (teprotumumab)	Prior Authorization
Daniel Cornett	Lutathera (lutetium Lu 177 dotatate)	Prior Authorization
	Lynparza (olaparib)	Prior Authorization
	Mircera (methoxy polyethylene glycol-epoetin beta)	Prior Authorization
	Rubraca (rucaparib)	Prior Authorization
	Tecentriq (atezolizumab)	Prior Authorization
	Zejula (niraparib)	Prior Authorization
Keli Abraham	COVID-19 Emergency Declaration Clinical Policy	Guidance
	Cresemba (isavuconazonium sulfate)	Prior Authorization
	Noxafil (posaconazole)	Prior Authorization
Kenneth Kennedy	Bavencio (avelumab)	Prior Authorization
	Kyprolis (carfilzomib)	Prior Authorization
	Ninlaro (ixazomib)	Prior Authorization
	Opdivo (nivolumab)	Prior Authorization
	Pomalyst (pomalidomide)	Prior Authorization
	Xpovio (selinexor)	Prior Authorization
	Yervoy (ipilimumab)	Prior Authorization
Mike Tindal	Duopa (carbidopa and levodopa) enteral suspension	Prior Authorization
	Epidiolex (cannabidiol) Oral Solution	Prior Authorization
	H. P. Acthar (repository corticotropin) Injection	Prior Authorization
	Radicava (edaravone)	Prior Authorization
	Xeomin (Botulinum Toxin)	Prior Authorization
Sheetal Sheth	Erbitux (cetuximab)	Prior Authorization
	Herceptin Hylecta (trastuzumab and hyaluronidase-oysk) – 3 revisions	Prior Authorization
	Nerlynx (neratinib)	Prior Authorization
	Trastuzumab products	Prior Authorization
	Xeloda (capecitabine)	Prior Authorization
Heather Wind	Non-Formulary Exceptions	Guidance

Doc 5 Pg. 651	Therapeutic Class Review
Presenter	**Topic**
Brian Garcia	Hemophilia and Gene Therapy
Andrea Bloomfield	Atopic Dermatitis
Sheetal Sheth	Small Cell Lung Cancer

Doc 6 Pg. 688	New Drug Clinical Reviews
Presenter	**Topic**
Brian Garcia	Breztri Aerosphere (budesonide/glycopyrrolate/formoterol fumarate)
Brock Bizzell	Durysta (bimatoprost implant)
Keli Abraham	Rukobia (fostemsavir)
	Oriahnn (elagolix-estradiol-norethindrone)
Kenneth Kennedy	Inqovi (decitabine and cedazuridine)
	Tecartus (brexucabtagene autoleucel)
Mike Tindal	Dojolvi (triheptanoin)
	Fintepla (fenfluramine)
	Isturisa (osilodrostat)
Sheetal Sheth	Quinlock (ripretinib)
	Retevmo (selpercatinib)
	Tabrecta (capmatinib)
	Zepzelca (lurbinectedin)
Yunus	Dayvigo (lemborexant)

Doc 7 Pg. 769	New Clinical Policies (11)	
Presenter	**Policy Title**	**Policy Type**
Brock Bizzell	Durysta (bimatoprost implant)	Prior Authorization
Daniel Cornett	Jelmyto (mitomycin)	Prior Authorization
Kenneth Kennedy	Darzalex Faspro (daratumumab and hyaluronidase-fihj)	Prior Authorization
	Tecartus (brexucabtagene autoleucel)	Prior Authorization
Mike Tindal	Dojolvi (triheptanoin) Oral Liquid	Prior Authorization
	Fensolvi (leuprolide acetate) subcutaneous syringe	Prior Authorization
	Octreotide Products	Prior Authorization
Sheetal Sheth	Phesgo (pertuzumab, trastuzumab, and hyaluronidase-zzxf)	Prior Authorization
	Qinlock (ripretinib)	Prior Authorization
	Retevmo (selpercatinib)	Prior Authorization
	Tabrecta (capmatinib)	Prior Authorization
	Zepzelca (lurbinectedin)	Prior Authorization

Doc. 1 Pg. 8	Formulary Updates
Presenter	
Andrea Bloomfield	Quarterly Formulary Changes

	Other Topics/Operational Policies (Will not be presented but will require a vote)
Presenter	**Topic**
	None

Doc 8 Pg. 828	Archived Clinical Policies (Will not be presented but will require a vote)	
Owner	**Policy Title**	**Policy Type**
Mike Tindal	Sandostatin® S.C., Sandostatin LAR® Depot (octreotide acetate for injection)	Prior Authorization

	Questions/Discussion
Presenter	

Facilitator	Meeting Adjournment
Mike Tindal	• **Follow up and action items** • **Closing Remarks**

Announcements:

- None

Review of P&T Agenda:

- Approved by the committee.

Conflict of Interest Disclosures:

- No conflicts of interest to disclose.

Review of Previous P&T Meeting Minutes

- Approved by the committee.

Review of Existing Clinical Policies with no revisions

- All listed clinical policies with no recommended changes were approved by the committee.

Review of Existing Clinical Policy with Revisions:

- All listed clinical policies with recommended revisions were approved by the committee.

Therapeutic Class Review

- Reviewed treatment recommendations, current formulary coverage and impactful pipeline agents for the treatment of hemophilia, atopic dermatitis, and small cell lung cancer. There were no recommended changes which was approved by the committee.

New Clinical Drug Clinical Reviews:

- All listed new drug clinical reviews were approved by the committee. See attached reviews.

New Clinical Policies:

- All listed new clinical policies were approved by the committee.

Formulary Updates:

- Formulary updates listed below were approved by the committee.

Drug	Chage Type	Previous Tier	New Tier
Children's Flonase Allergy Relief 50 mcg/actuation nasal spray,susp	Coverage Update	T2	NF
Flonase Allergy Relief 50 mcg/actuation nasal spray,suspension	Coverage Update	T2	NF
Lamisil AT 1 % topical cream	Coverage Update	T1	NF
Nicoderm CQ 14 mg/24 hr daily transdermal patch	Coverage Update	T2	NF
Nicoderm CQ 21 mg/24 hr daily transdermal patch	Coverage Update	T1	NF
Nicoderm CQ 7 mg/24 hr daily transdermal patch	Coverage Update	T2	NF
Nicorette 2 mg buccal lozenge	Coverage Update	T2	NF
Nicorette 2 mg buccal mini lozenge	Coverage Update	T2	NF
Nicorette 2 mg gum	Coverage Update	T2	NF
Nicorette 4 mg buccal lozenge	Coverage Update	T2	NF
Nicorette 4 mg buccal mini lozenge	Coverage Update	T2	NF
Nicorette 4 mg gum	Coverage Update	T2	NF
Prevacid 24Hr 15 mg capsule,delayed release	Coverage Update	T2	NF
Tums 200 mg calcium (500 mg) chewable tablet	Coverage Update	T2	NF
Tums 300 mg (750 mg) chewable tablet	Coverage Update	T2	NF
Tums E-X 300 mg (750 mg) chewable tablet	Coverage Update	T2	NF
Tums Extra Strength Smoothies 300 mg (750 mg) chewable tablet	Coverage Update	T2	NF
Tums Freshers 200 mg calcium (500 mg) chewable tablet	Coverage Update	T2	NF
Humira 40 mg/0.8 mL subcutaneous syringe kit	QL update	QL 31/365	QL 6/28
HUMIRA PEDI CROHN 40 MG/0.8 ML	QL update	QL 31/365	QL 6/28
Humira(CF) Pen 40 mg/0.4 mL subcutaneous kit	QL update	QL 31/365	QL 6/28
Epidiolex 100 mg/mL oral solution	Age Min update	Age Min 2	Age Min 1
Stelara 45 mg/0.5 mL	Age Min Update	Age Min 12	No age min
Stelara 90 mg/mL subcutaneous syringe	Age Min Update	Age Min 12	No age min

Other Topics/Operational Policies:

- None

Questions/Discussion:

- None

Archived Clinical Policies:

- Listed archived clinical policies were approved by the committee.

Follow up and action items:

- Next meeting is scheduled for December 17, 2020.

Closing Remarks:

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Deitsch (Pennsylvania Dutch) Wann du [Deitsch (Pennsylvania German / Dutch)] schwetzscht, kannscht du mitaus Koschte ebber gricke, ass dihr helft mit die englisch Schprooch. Ruf selli Nummer uff: Call 1-**800-444-9137** (TTY: 711).

ध्यान दिनुहोस्(Nepali): तपाईंले नेपाली बोल्नुहुन्छ भने तपाईंको निम्ति भाषा सहायता सेवाहरू निःशुल्क रूपमा उपलब्ध छ । फोन गर्नुहोस् 1-800-444-9137. (टिटिवाइ: 711) ।

Oroomiffa (Oromo) XIYYEEFFANNAA: Afaan dubbattu Oroomiffa, tajaajila gargaarsa afaanii, kanfaltiidhaan ala,

ni argama. Bilbilaa 1-**800-444-9137** (TTY: 711).

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Pharmacy Solutions

Clinical Review – Breztri Aerosphere™ (budesonide-glycopyrrolate-formoterol)

***Company*:** AstraZeneca
Current Status: FDA Approved July 23rd 2020
Launch: Expected Mid-September
Therapeutic Category: Chronic Obstructive Pulmonary Disorder (COPD)
Pharmacologic Category: Inhaled Corticosteroid, Long-Acting Beta$_2$ Agonist, Long-Acting Muscarinic Agonist
Similar Drugs: Trelegy Ellipta
Route of Administration: Oral Inhalation
Dosage Forms: Oral Inhaler

Indications: Indicated for the maintenance treatment of patients with chronic obstructive pulmonary disease (COPD).

Dosage and Administration: 2 Inhalations twice daily administered by oral inhalation

Background:
Chronic obstructive pulmonary disease (COPD) is a common respiratory condition characterized by airflow limitation. It affects more than 5 percent of the population and is associated with high morbidity and mortality. It is the fourth-ranked cause of death in the United States, killing more than 120,000 individuals each year. As a consequence of its high prevalence and chronicity, COPD causes high resource utilization with frequent clinician office visits, frequent hospitalizations due to acute exacerbations, and the need for chronic therapy (e.g., supplemental oxygen therapy, medication).

Pharmacology:
Breztri Aerosphere contains budesonide, glycopyrrolate, and formoterol fumarate. These drugs represent three different classes of medications (ICS, LAMA, LABA) that have different effects on clinical physiology and inflammatory indices of COPD. Budesonide is an anti-inflammatory corticosteroid that exhibits potent glucocorticoid activity and weak mineralocorticoid activity. Glycopyrrolate is a long-acting antimuscarinic agent, it has similar affinity to the subtypes of muscarinic receptors M1 to M5. In the airways, it exhibits pharmacological effects through inhibition of the M3 receptor at the smooth muscle leading to bronchodilation. Formoterol fumarate is a long-acting selective beta$_2$-adrenergic agonists with a rapid onset of action. Inhaled formoterol fumarate acts locally in the lung as a bronchodilator.

Pharmacokinetics:
All 3 components have linear pharmacokinetics. Steady state is achieved after 1 day of repeated dosing. Glycopyrrolate achieves steady state after 3 days of related dosing. Formoterol achieves steady state after 2 days of repeated dosing.

Drug Interactions:
- The main route of metabolism of corticosteroids, including budesonide is via CYP3A4. Concomitant administration of a CYP3A4 inhibitor may inhibit the metabolism of, and increase systemic exposure to budesonide.
- Diuretics, xanthine derivatives or steroids may potentiate hypokalemia or ECG changes

- Use with caution with beta-blockers; may block bronchodilatory effects of beta-agonists and produce severe bronchospasm.
- May interact additively with concomitantly used anticholinergic medications. Avoid administration with other anticholinergics.

***Adverse Effects*:**
Most common adverse reactions (incidence >2%) are upper respiratory tract infection, pneumonia, back pain, oral candidiasis, influenza, muscle spasm, urinary tract infection, cough, sinusitis, and diarrhea.

Contraindications:
Hypersensitivity to budesonide, glycopyrrolate, formoterol fumarate, or to any of the excipients.

Warnings and Precautions:
- Do not initiate in acutely deteriorating COPD. Do not use to relieve acute symptoms
- Risk of impaired adrenal function when transferring from systemic corticosteroids. Taper patients slowly from systemic corticosteroids if transferring to Breztri
- If paradoxical bronchospasm occurs, discontinue Breztri and institute alternative therapy

Monitoring:
None

Evidence Table of Clinical Studies:
Table 1. Clinical data for Oxbryta (voxelotor)

	ETHOS Trial New England Journal of Medicine / 2020
Study Type*	Phase III MC, DB, PG, RCT
Interventions and Sample Size	N=8,588 Subjects randomized 1:1:1 :1 Breztri 320/18/9.6mcg vs Breztri vs BGF 160/18/9.6mcg vs GF 18/9.6mcg vs BF (320/9.6mcg) Treatment duration: 52 weeks
Populations	*Inclusion Criteria* • Hx ≥1 moderate or severe exacerbation in year prior to screening • Post-bronchodilator FEV_1/FVC ratio <0.7 • Post-bronchodilator FEV_1 <65% predicted normal value *Exclusion Criteria* • Asthma Diagnosis • COPD due to Alpha-1 antitrypsin deficiency • Significant diseases or conditions other than COPD • Acute worsening of COPD ≤ 6 weeks prior to screening, resulting in tx with OCS or Abx *Baseline Characteristics* • Mean age: 65 y • Sex: 60% Male • Race: 85% Caucasian • Avg smoking history: 48 pack years • Current Smoker: 41% • Mean Post-bronchodilator ppFEV_1=43% (16-73) • 39% on ICS/LAMA/LABA at study start

	ETHOS Trial New England Journal of Medicine / 2020
	• 31% on ICS/LABA • 14% on LAMA/LABA
General Summary: Efficacy	Primary Endpoint: *Rate of moderate or severe COPD exacerbations of Breztri vs GF and BF*: Breztri vs GF (24% reduction) RR: 0.76 (CI: 0.69-0.83); Breztri vs BF (13% reduction) RR: 0.87 (CI: 0.79-0.95) Key Secondary Endpoints: *Rate of severe COPD Exacerbations*: Breztri vs GF (16% reduction) RR: 0.84 (CI: 0.69-1.03)-**not SS.** Breztri vs BF (20% reduction) RR: (CI: 0.66-0.97). *Time to first moderate or severe COPD exacerbation*: Breztri vs GF: HR 0.88 (CI:0.81 - 0.96); Breztri vs BF: HR 0.89 (CI: 0.81-0.97) *Time to death (all cause)*: Breztri vs GF: **not SS**; Breztri vs BF: 46% Reduction (HR: 0.54 (CI: 0.34-0.87)
General Summary: Safety	Rates of pneumonia and oral candidiasis were higher in both arms that included an ICS. The most common AEs (>5%) for Breztri were Nasopharyngitis, URTI, and COPD. There were no notable differences in pneumonia or MACE that is not in line with published literature for individual components.
Comments	• Breztri reduced the rate of moderate or severe COPD exacerbations compared to both ICS/LABA and LAMA/LABA dual therapies, but only reduced severe exacerbations versus ICS/LABA therapy and reduced mortality versus LAMA/LABA therapy • Breztri was also studied in KRONOS trial in patients that did NOT have a history of moderate or severe COPD exacerbations and resulted in an improvement in FEV1 AUC at week 24 versus BF, and increase. The comparison of Breztri with GF at week 24 was not SS • Results of the ETHOS and KRONOS trial have mixed results that show benefit of Breztri in individual endpoints
Grade^	▪ A. ETHOS Trial provided solid evidence in the appropriate COPD population to show benefit in some individual endpoints over both dual-therapy single-inhaler treatment options currently available based on individual components.

*Study type abbreviations: CC=Case-control study, COH=Cohort study, CS=Case study, DB=double blind, EPI=Epidemiologic study, META=Meta-analysis, NRCT=Nonrandomized clinical trial, OBS=Observational study, PC=placebo-controlled, PG=parallel-group, RCT=randomized trial, XO=crossover [if not listed, please type in under study type]
^A=Useful, B=Possibly useful, C=Possible to uncertain usefulness, U=Uncertain validity and/or usefulness, X=Not useful
(For further information, please refer to the document Grading of Clinical Evidence; NA=Not applicable. [Disclaimer: Grade the study if able to pull the literature]

Special Populations:

Geriatric Population: There are no recommendations for dosage adjustments for geriatric patients
Pediatric Population: Not indicated for use in pediatric patients
Hepatic Impairment: Budesonide and formoterol fumarate are predominantly cleared by hepatic metabolism. Patients with severe hepatic disease should be closely monitored
Renal Impairment: Patients with severe renal impairment (CrCL ≤30 ml/min/1.73m^2) or ESRD should only use Breztri if expected benefits outweigh the potential risk.
Pregnancy Considerations: No adequate and well-controlled studies with Breztri or with glycopyrrolate or formoterol in pregnant women to inform a drug-associated risk. Budesonide has been studied in animal

reproduction studies and causes structural abnormalities, was embryocidal, and reduced fetal weights. Studies of pregnant women receiving budesonide in isolation did not have increased risk of abnormalities.
Breastfeeding Considerations: Budesonide, like other ICS, is present in breast milk. There is not data available on the effects of Breztri, or it's individual components on the breastfed child or on milk production.

Cost and/or Utilization Data of Similar Treatment Options:

Table 2: Breztri Aerosphere™ versus other COPD Treatment Pricing

Drug	WAC/unit	WAC/Year
Breztri Aerosphere	$590.40	$7,084
Trelegy Ellipta	$573.20	$6,878
Breo Ellipta*	$361.81	$3,804
Stiolto Respimat*	$421.52	$5,058

- **Would need to be taken in addition to another inhaled product to have equal number of active ingredients as Breztri**

Place in Therapy:

Table 5. Comparison of Breztri Aerosphere with Trelegy Ellipta

	Breztri Aerosphere	Trelegy Ellipta
Meet an Unmet Medical Need[1]	☒ No – Breztri Aerosphere provides another treatment option for COPD, specifically for those who have moderate or severe COPD exacerbations and remain uncontrolled on dual therapy. Trelegy Ellipta provides these same treatment options	
Comparable Efficacy[2]	☒ Breztri Aerosphere is similarly efficacious relative to Trelegy Ellipta Comment: Breztri reduced exacerbations by 24% against glycopyrrolate/formoterol, and Trelegy reduced exacerbations by 15% against fluticasone/vilanterol. As these trials were not built equivalently and are against different active comparators, a direct numerical comparison cannot be made, but both agents trend towards improved efficacy over dual-therapy	
Comparable Safety[3]	☒ Breztri Aerosphere would likely have similar safety relative to Trelegy Ellipta. **Comment:** Both agents have a relatively clean safety profile, with increased risks of pneumonia and oral thrush similar for both agents, presumably because of their ICS component.	
Adherence[5]	☒ Breztri Aerosphere would likely have lower adherence to Trelegy Ellipta. **Comment:** Breztri requires 2 inhalations twice daily compared to Trelegy Ellipta's one inhalation once daily. This difference in dosing regimen may result in better adherence for Trelegy Ellipta	
Advantages	▪ Aerosphere inhaler may be easier for patients with poor inhalation capacity	▪ Has 3 years of RWE in COPD ▪ Dosing regimen (1 inhalation once daily)
Disadvantages	▪ Dosing regimen (2 inhalations BID)	▪ Dry powder inhaler can be difficult for patients to use
Comments	Breztri Aerosphere provides an additional treatment option for patients with advanced COPD. Triple therapy inhalers like Breztri and Trelegy are currently only recommended in the GOLD guidelines for patients who continue to have symptoms and exacerbations despite adequately administered dual therapy (ICS/LABA or LAMA/LABA). Although there are some differences in dosing and results from pivotal trial between Breztri and Trelegy, there are no notable differences in these agents to make one superior.	

Definitions

1. Unmet medical need - Medical need that is not addressed adequately by an existing therapy (examples: a) No available therapy for condition exists b) If available therapy for the condition exists i) New therapy has

improved effects on serious outcomes, ii) Similar benefits to alternative therapies while avoiding serious toxicity).[IV]

2. Efficacy – The extent to which an intervention produces a beneficial result under ideal conditions (i.e clinical trials). [III]
3. Safety – Substantive evidence of an absence of harm (examples: clinical adverse events (disease, signs, and symptoms).[II]
4. Cost-effectiveness – The cost and health benefits associated with the use of the drug therapies.[I]
5. Adherence - The consistence and accuracy with which a patient will follow a recommended medical regimen (examples of factors that may affect adherence: frequency of administration, adverse events, cost of drug).[I]

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I. Berger ML, Bigefors K, Hedblom EC, Pashos CL, Torrance GW. Health care cost, quality, and outcomes: ISPOR book of terms. Lawrenceville, NJ: International Society for Pharmacoeconomics and Outcomes Research; 2003.
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Recommendation:

KY Medicaid: NF w QL

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Humana Pharmacy Solutions

Clinical Review – Durysta™ (bimatoprost)

***Company*:** Allergan

Current Status: FDA Approved (March 2020)

Therapeutic Category: Antiglaucoma Agent

Pharmacologic Category: Prostaglandin analog

Similar Drugs:

- Latanoprost, Bimatoprost, Travoprost, Zioptan, Lumigan,

Dosage Forms: 10mcg intracameral implant

Indications:

- For the reduction of elevated or increased intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension

Dosage and Administration:

- Insert a single 10mcg biodegradable implant via intracameral injection. Durysta should not be readministered to an eye that received a prior implant.

Background:

Glaucoma is an optic neuropathy that is a leading cause of blindness in the US and worldwide. The prevalence of glaucoma in patients 40-80 years of age is estimated to be 3.5%. In the United States, roughly 3 million people have glaucoma, of that 1 million have functional vision loss and 120,000-130,000 are legally blind from glaucoma. Glaucoma occurs more often in the elderly, and can cause difficulties in performing normal daily activities. Because the number of patients most at risk for glaucoma will rise over the next decade, the prevalence of the disease is only expected to grow. One major risk factor for the progression of glaucoma is elevated intra-ocular pressure (IOP). IOP is the most important and the only modifiable risk factor.

There are 6 drug classes with multiple available therapeutic agents within them which can be used to treat elevated IOP. Those classes are; alpha-adrenergic agonists, beta-adrenergic antagonists, carbonic anhydrase inhibitors (CAIs), cholinergics, prostaglandin analogs (PGAs), and Rho Kinase inhibitors.

Pharmacology:

- Bimatoprost is a prostaglandin analog that has ocular hypotensive activity. It is believed to lower IOP by increasing the outflow of aqueous humor through both the trabecular meshwork and uveoscleral routes. Durysta is a biodegradable, sustained-release bimatoprost implant that is administered into the anterior chamber of the eye. The implant is designed to provide sustained release of bimatoprost with efficacy demonstrated of at least 15 weeks. No removal is needed of the implant. After administration, Durysta is hydrolyzed and metabolized to water and carbon dioxide.

Pharmacokinetics:

- Bimatoprost, once in the systemic circulation, distributes into tissues with a steady-state volume of distribution of 0.67 L/kg. Bimatoprost is metabolized via oxidation to form a variety of metabolites. The elimination half-life is approximately 45 minutes. Following the insertion of a single 10 mcg implant, bimatoprost concentrations were below the lower limit of quantitation in a majority of recipients.

Drug Interactions:

- None

***Adverse Effects*:**

- Corneal Adverse Reactions:
  - Durysta has been associated with an increased risk of corneal endothelial cell loss. Administration should be limited to a single implant per eye without retreatment. Caution in patients with limited corneal endothelial cell reserve.
- Macular Edema
- Intraocular Inflammation
- Increased pigmentation of the iris
- Endophthalmitis

Contraindications:

- Ocular or Periocular Infections
- Corneal Endothelial Cell Dystrophy
- Prior Corneal Transplantation
- Absent or Ruptured Posterior Lens Capsule

Evidence Table of Clinical Studies:

Table 1. Clinical data for Durysta (bimatoprost)

	ARTEMIS 1 and ARTEMIS 2 ***NCT02247804, NCT02250651***
Study Type*	Phase III, 20 month, PG, RCT
Interventions and Sample Size	Bimatoprost 10mcg every 16 weeks (Day 1, Week 16, Week 32) = 374 Timolol 0.5% comparator BID = 374
Populations	Inclusion criteria • Diagnosis of OAG or OHT in each eye and both eyes require IOP-lowering treatment. • Age ≥ 18 years Exclusion criteria • Eye surgery (including cataract surgery) and/or any eye laser surgery within the past 6 months in the study eye • Anticipated need for laser eye surgery in either eye within the first 52 weeks of the study duration • History of glaucoma surgery
General Summary: Efficacy	**Primary Endpoints:** 1) IOP at hours 0 and 2 in the study eye at weeks 2, 6, and 12 (noninferiority) • In both studies, Durysta 10mcg was considered to be noninferior to timolol based on the presspecified definition for noninferiority.

	ARTEMIS 1 and ARTEMIS 2 *NCT02247804, NCT02250651*

- ARTEMIS 1: upper limit of th e95% CI ≤ 1.5 mmHg for each of the six primary time points (weeks 2, 6 and 12).
- ARTEMIS 2: upper limit of the 95% CI ≤ 1 mmHg for three or more of the six primary time points.

- IOP Week 2
  - Hour 0:
    - Durysta 10mcg: 16.83
    - Timolol BID: 17.54
  - Hour 2:
    - Durysta 10mcg: 16.06
    - Timolol BID: 16.89
- Week 6
  - Hour 0
    - Durysta 10mcg: 16.9
    - Timolol BID: 17.62
  - Hour 2
    - Durysta 10mcg: 16.15
    - Timolol BID: 16.70
- Week 12
  - Hour 0
    - Durysta 10mcg: 17.45
    - Timolol BID: 17.71
  - Hour 2
    - Durysta 10mcg: 16.74
    - Timolol BID: 17.06

Secondary Endpoints

1) IOP at hours 0 and 2 in the study eye at weeks 2, 6, and 12. (Superiority)
   - Using the same model as the primary analysis, Durysta did not meet the criteria to claim superiority for IOP compared to timolol.

ARTEMIS 1: DURYSTA™ 10 µg vs. timolol BID

	Week 2	Week 6	Week 12	Week 15
Hour 0	−0.8 (−1.47 to −0.14)	−0.8 (−1.47 to −0.21)	−0.3 (−1.09 to 0.43)	1.1 (0.22-1.89)
Hour 2	−0.9 (−1.50 to −0.31)	−0.7 (−1.27 to −0.04)	−0.2 (−0.90 to 0.46)	0.9 (0.10-1.64)

ARTEMIS 2: DURYSTA™ 10 µg vs. timolol BID

	Week 2	Week 6	Week 12	Week 15
Hour 0	−0.6 (−1.30 to 0.13)	−0.6 (−1.35 to 0.17)	−0.1 (−0.88 to 0.72)	1.0 (0.15-1.94)
Hour 2	−0.7 (−1.38 to −0.05)	−0.6 (−1.36 to 0.06)	−0.3 (−1.11 to 0.42)	1.2 (0.35-2.06)

General Summary: Safety	▪ Most common ocular adverse reaction was conjunctival hyperemia (in 27% of patients) ▪ Other common reactions (5%-10%) were: foreign-body sensation, eye pain, photophobia, conjunctival hemorrhage, dry eye, eye irritation, increased IOP, corneal endothelial cell loss, blurred vision, iritis, and headache.
Comments	▪ Durysta demonstrated an IOP reduction of approximately 5 to 8 mmHg in patients with a mean baseline IOP of 24.5 mmHg ▪ Due to the adverse effect profile, retreatment with Durysta is not FDA-approved. Durysta is for single

	ARTEMIS 1 and ARTEMIS 2 *NCT02247804, NCT02250651*
	administration per eye and should not be readministered to an eye that received a prior Durysta implant.

*Study type abbreviations: CC=Case-control study, COH=Cohort study, CS=Case study, DB=double blind, EPI=Epidemiologic study, META=Meta-analysis, NRCT=Nonrandomized clinical trial, OBS=Observational study, PC=placebo-controlled, PG=parallel-group, RCT=randomized trial, XO=crossover [if not listed, please type in under study type]
^A=Useful, B=Possibly useful, C=Possible to uncertain usefulness, U=Uncertain validity and/or usefulness, X=Not useful
(For further information, please refer to the document Grading of Clinical Evidence; NA=Not applicable. [Disclaimer: Grade the study if able to pull the literature]

Special Populations:

- **Pediatric Use:** Safety and efficacy has not been established
- **Geriatric Use:** No overall significant differences in safety or effectiveness were seen between elderly and other adult subjects.

Cost and/or Utilization Data of Similar Treatment Options:

Table 2: Durysta (bimatoprost) pricing

Drug	Strength	WAC/implant
Durysta	10mcg implant	$1950.00

Table 3: Humana Tiering for Similar Treatment Options

	Latanoprost	Travoprost	Lumigan
KYMD	1	1	2

Place in Therapy:

Table 5. Comparison of Durysta (bimatoprost) and timolol drops

	Durysta (bimatoprost) implant	Timolol drops
Meet an Unmet Medical Need[1]	☒ **No.** **Comment: Many options exist for the treatment of open angle glaucoma or ocular hypertension.**	
Comparable Efficacy[2]	☒ Durysta has similar efficacy relative to Timolol drops. **Comment: Phase III trials showed noninferiority, but did not show superiority of Durysta versus Timolol.**	
Comparable Safety[3]	☒ Durysta would likely be less safe relative to Timolol drops. **Comment: With Durysta, risk of adverse events is such that the product is not indicated for retreatment.**	
Adherence[5]	☒ Members taking Durysta would likely achieve a greater adherence rate relative to Timolol drops. **Comment: With Durysta being a single implant administration and Timolol drops requiring twice a day dosing, Durysta is likely to achieve greater adherence.**	
Advantages	▪ Sustained release dose form ▪ Efficacy of a single implant demonstrated thru 15 weeks ▪	▪ Established safety and efficacy with extended use
Disadvantages	▪ Only approved for single use	▪ Twice daily dosing

	▪ Risk of ocular side effects (e.g. corneal endothelial cell loss)	▪ Potential cardiovascular side effects (e.g. bradycardia, hypotension)

Definitions

1. Unmet medical need - Medical need that is not addressed adequately by an existing therapy (examples: a) No available therapy for condition exists b) If available therapy for the condition exists i) New therapy has improved effects on serious outcomes, ii) Similar benefits to alternative therapies while avoiding serious toxicity).[IV]
2. Efficacy – The extent to which an intervention produces a beneficial result under ideal conditions (i.e clinical trials). [III]
3. Safety – Substantive evidence of an absence of harm (examples: clinical adverse events (disease, signs, and symptoms).[II]
4. Cost-effectiveness – The cost and health benefits associated with the use of the drug therapies.[I]
5. Adherence - The consistence and accuracy with which a patient will follow a recommended medical regimen (examples of factors that may affect adherence: frequency of administration, adverse events, cost of drug).[I]

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Recommendation:

- Ky Medicaid: NF with QL
- QL = 2 implants / 365 days

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Humana
Pharmacy Solutions

Clinical Review – Rukobia® (fostemsavir)

***Company*:** ViiV Healthcare
Current Status: FDA approved July 2020
Launch: July 2020
Therapeutic Category: HIV-1 antiretroviral treatment
Pharmacologic Category: HIV-1 gp120-directed attachment inhibitor prodrug
Similar Drugs: Fuzeon (enfuviritide), Trogarzo (ibalizumab)
Route of Administration: By mouth
Dosage Forms: 600mg extended-release tablet

Indications:
Rukobia, in combination with other antiretroviral(s), is indicated for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in heavily treatment-experienced adults with multidrug-resistant HIV-1 infection failing their current antiretroviral regimen due to resistance, intolerance, or safety considerations.

Dosage and Administration:
One tablet taken twice daily with or without food

Background:

While most patients living with HIV-1 benefit from effective antiretroviral therpy, but there is a small subset of patients who are resistent to multiple agents in this class. These patients are unable to achieve or maintain viral suppression ith currently available antiretrovirals which puts them at risk of AIDS-defining events and death. About 1% of patients with HIV-1 experience multi-drug resistant disease, and Rukobia is a first-in-class oral attachment inhibitor that showed sustained efficacy in these patients in urgent need of new treatment due to resistance, safety, or tolerability with their current regimens.

Pharmacology:
Rukobia is a first-in-class prodrug oral attachment inhibitor that targets the virus directly before it attaches to the host cell. The active moiety, temsavir, attaches directly to the gp120 viral envelope protein on the surface of HIV-1 virion located near the CD4 attachment sites. This attachment locks the protein into a closed formation that prevents the interaction between the virus and the host immune cells. Overall, this action prevents the first step of viral entry.

Pharmacokinetics:
Absorption: Fostemsavir was not detected in plasma after oral administration, but temsavir is readily absorbed with an absolute bioavailability of 26.9%. Meals have no significant effect on absorption.
Distribution: 88.4% plasma protein binding with a steady-state volume of distribution of 29.5 L
Elimination: Mean elimination half-life is 11 hrs
Metabolism: Primarily metabolized by esterases and CYP3A4
Excretion: 51% of dose excreted unchanged in urine, and 33% of dose excreted unchanged in feces

Drug Interactions:
-Avoid strong CYP3A4 inducers such as rifampin. They can decrease temsavir plasma concentrations.

-May increase the plasma concentrations of grazoprevir and voxilaprevir. Use an alternative hepatitis C regimen if possible.
-Use lowest possible starting dose for statins and monitor for statin-assiciated adverse events.
-Do not take doses of estrogen-based therapies, including oral contraceptives, that contain more than 30 mcg/day of ethinyl estradiol. This may increase your risk of thromboembolic events.

***Adverse Effects*:**
The most common adverse effects (≥2%) are nausea, diarrhea, headache, abdominal pain, dyspepsia, fatigue, rash, sleep disturbances, Immune Reconstitution Inflammatory Syndrome, somnolence, and vomiting.

Contraindications:
-Patients with previous hypersensitivity to fostemsavir or any of the components of Rukobia
-Patients coadministered strong CYP3A4 inducers such as enzalutamide, phenytoin, rifampin, mitotane, or St John's wort. This may decrease the plasma concentration of temsavir which may result in a loss of virologic response.

Warnings and Precautions:
-Immune Reconstitution Syndrome: During the initial phase of combination antiretroviral treatment, patients whose immune systems respond may develop an inflammatory response to residual opportunisitic infections which may require further evaluation and treatment.
-QTc Prolongation: With higher than recommended doses, QTc prolongation can occur. Monitor closely in those with a history of QTc interval prolongation or those at risk for Torsades de Pointes.
-Elevations in Hepatic Transaminases: Monitoring of liver chemistries is recommended in patients with hepatitis B or C coinfection.
-Risk of loss of virulogic response due to drug interactions: See *Drug Interactions*

Monitoring:
-CD4 count, HIV RNA plasma levels
-Hepatic transaminases in hepatitis B virus and/or hepatitis C virus coinfected patients

Evidence Table of Clinical Studies:
Table 1. Clinical data for Rukobia (fostemsavir)

	BRIGHTE Study
Study Type*	This was a multi-arm, Phase 3, randomized, PC, double-blind clinical trial that evaluated the safety and efficacy of Rukobia as functional monotherapy for heavily treatment-experienced people living with HIV.
Interventions and Sample Size	N=371 Those in the Randomized Cohort (N=272) were randomized 3:1 to treatment with doubleblinded Rukobia (600 mg twice daily) or placebo added to their current failing regimen. After day 8 it became open-label Rukobia in combination with OBT.

	BRIGHTE Study
	Individuals who had no remaining fully active antiretroviral agents at Baseline (N = 99) were assigned to the Non-randomized Cohort and received open-label Rukobia (600 mg twice daily) in addition to OBT for the duration of the study. Dosing modifications to patients' OBT by investigators were allowed per protocol.
Populations	*Select Inclusions*: • HIV-infected adults (≥18 years of age) who were heavily treatment-experienced • Failing current ART regimen with confirmed HIV-1 RNA ≥400 c/mL *Select Exclusions:* • HIV-2 infected • Chronic untreated HBV • ALT or AST >7 x ULN • Alkaline phosphatase >5 x ULN • Bilirubin ≥1.5 x ULN, unless subject is currently on atazanavir and has predominantly unconjugated hyperbilirubinemia *Baseline Characteristics:* • Baseline characteristics for the Rukobia Randomized Cohort group included 70% males and 30% females with 57% being under 50 years of age. • Basline characteristics for the Non-randomized Cohort group included 90% males and 10% females with 44% being under 50 years old. • 22% of the overall study population was Black/African American, and 86% of the study population had a history of AIDS, and 70% were treated for HIV infection for 16 years or more. The median viral load was 4.7 and 4.3 log10 copies/mL at baseline for the Randomized and Non-randomized Cohorts, respectively.
General Summary: Efficacy	**Primary Endpoint:** The primary endpoint was the adjusted mean log10 change in HIV-1 RNA from Day 1 to Day 8 in the Randomized Cohort. The difference in adjusted mean log10 change from Day 1 to Day 8 between the placebo and Rukobia groups was -0.625 (95% CI: -0.810 to 0.441; P < 0.0001). Thus, Rukobia demonstrated superior efficacy compared with placebo over the blinded period. **Key Secondary Endpoints:** Secondary endpoints included the durability of response through Weeks 24, 48, and 96 (with visits measured from the start of open-label Rukobia) and changes in CD4 counts at the same time points. • The proportion of patients in the Randomized Cohort who achieved virologic success increased from Week 24 to Week 96, while proportions of virologic success were maintained in the Non-randomized Cohort over the same time period. At Week 24, 53% of patients in the Randomized Cohort were considered virologic responders, while 40% were virologic non-responders and 7% of patients lacked virologic data. By Week 96, 60%

	BRIGHTE Study
	of patients in this cohort were considered virologic responders, 30% were virologic non-responders, and 10% lacked data. • At Week 24, the mean CD4 count increase was 90.2 cells/mm3 (SD: 111.91) for the Randomized Cohort and 41.0 cells/mm3 (SD: 78.63) for the Non-randomized Cohort. Notably, the patients with the lowest CD4 counts at Baseline (<20 cells/mm3) had the largest increase by Week 96 with a mean increase of 239.8 cells/ mm3, a clinically meaningful improvement.
General Summary: Safety	Nausea, headache, and diarrhea were the three most common AEs with rates of 7%, 4%, and 6%, respectively in the Rukobia group of the Randomized Cohort. Five participants in the Randomized Cohort withdrew from the study during the blinded period due to AEs (1 lost to follow up; 1 protocol deviation; 2 non-serious AEs; 1 SAE). The participant who withdrew due to an SAE was in the placebo group, while the four other participants received Rukobia. The majority of AEs leading to discontinuation were related to infections, and most SAEs were due to infections or complications associated with advanced AIDS. SAEs and deaths were more frequent in immunocompromised patients, particularly those with baseline CD4 counts <20 cells/mm3.
Comments	The BRIGHTE study inclusion criteria, which required that patients in the Randomized Cohort had exhausted all fully active agents across four antiretroviral classes, were more restrictive compared to other completed trials for PLHIV with MDR infections.
Grade	B

*Study type abbreviations: AC=Active-comparator, CC=Case-control study, COH=Cohort study, CS=Case study, DB=double blind, EPI=Epidemiologic study, META=Meta-analysis, NRCT=Nonrandomized clinical trial, OBS=Observational study, PC=placebo-controlled, PG=parallel-group, RCT=randomized trial, XO=crossover [if not listed, please type in under study type]
^A=Useful, B=Possibly useful, C=Possible to uncertain usefulness, U=Uncertain validity and/or usefulness, X=Not useful
(For further information, please refer to the document Grading of Clinical Evidence; NA=Not applicable. [Disclaimer: Grade the study if able to pull the literature] OBT=optimized background treatment

Special Populations:

- Pregnancy: There is a pregnancy exposure registry that monitors pregnancy outcomes in individuals exposed to Rukobia that healthcare providers are encouraged to register patients. Rukobia may cause fetal harm when administered to pregnant women based on findings from animal studies. There are no available data on the use of Rukobia in pregnant women to evaluate for a drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes.
- Lactation: The Centers for Disease Control and Prevention recommends that HIV-1–infected mothers in the United States not breastfeed their infants to avoid risking postnatal transmission of HIV-1 infection. It is not known whether RUKOBIA is present in human breast milk, affects human milk production, or has effects on the breastfed infant. When administered to lactating rats, fostemsavir-related drug was present in rat milk.

- Pediatric Use: The safety and effectiveness of RUKOBIA have not been established in pediatric patients.
- Geriatric Use: Clinical trials of RUKOBIA did not include sufficient numbers of subjects aged 65 and older to determine whether they respond differently from younger subjects. In general, caution should be exercised in administration of RUKOBIA in elderly patients reflecting greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy as they may be more susceptible to drug-induced side effects.
- Renal Inpairment: No dosage adjustment is required for patients with renal impairment or those on hemodialysis.
- Hepatic Impairment: No dosage adjustment is required in patients with mild to severe hepatic impairment (Child-Pugh Score A, B, or C).

Cost and/or Utilization Data of Similar Treatment Options:

Table 2:

Drug	Strength	WAC/unit	Package size	WAC/month
Rukobia	600mg/ tablet	$127.50/tablet	60 tablets	$7,650
Fuzeon	90mg/ vial	$62.55/vial	60 vials	$3,753

Place in Therapy:

Table 5. Comparison of Rukobia with Fuzeon

	Rukobia (fostemsavir)	Fuzeon (enfuviritide)
Meet an Unmet Medical Need[1]	☒ No – Rukobia reaches a subgroup of patients that have failed all other treatment options for heavily treatment-experienced HIV-1, but there are other treatment options available for this indication	
Comparable Efficacy[2]	☒ Rukobia is similarly efficacious relative to Fuzeon **Comment**: The difference in adjusted mean log10 change from Day 1 to Day 8 between the placebo and Rukobia groups was -0.625 and for Fuzeon versus placebo it was about -0.79. Also, the changes in CD4 cell counts between the different medications versus placebos were relatively similar.	
Comparable Safety[3]	☒ Rukobia would likely have similar safety relative to Fuzeon **Comment:** Neither medication currently carries a black box warning. Rukobia has several drug interactions as it is metabolized by CYP3A4. It also has warnings for QTc prolongation, immune reconstitution syndrome, elevations in hepatic transaminases in patients with Hepatitis B. Fuzeon has several warnings including injection site reactions, bruising/hematomas, post-injection bleeding, pneumonia, and immune reconstitution.	
Adherence[5]	☒ Members taking Rukobia would likely achieve increased adherence rate relative to Fuzeon **Comment:** Rukobia is taken by mouth twice daily whereas Fuzeon is a subcutaneous injection twice daily. The most common adverse reactions for Fuzeon and Rukobia are local injection site reactions and nausea, respectively. Injections are typically less tolerated than oral tablets.	
Advantages	• Oral medications require less extensive counseling • Offers new class of antiretrovirals in multi- drug resistant HIV-1 • No warnings for injection site reactions, bruising/hematomas, post-injection bleeding, or pneumonia.	• Approved in pediatric patients weighing at least 11 kg • No drug interactions • No dosage adjustments required

Disadvantages	• High potential for drug-drug interactions due to its CYP3A4 metabolism • Dosage adjustments are necessary for those taking ethinyl estradiol • Only approved in adult patients	• Injectable medications require more extensive counseling. • Carries risk of injection site reactions, bruising/hematomas, post-injection bleeding, and pneumonia.
Comments	• Rukobia has not yet been incorporated in the NIH treatment guidelines	

Definitions

1. Unmet medical need - Medical need that is not addressed adequately by an existing therapy (examples: a) No available therapy for condition exists b) If available therapy for the condition exists i) New therapy has improved effects on serious outcomes, ii) Similar benefits to alternative therapies while avoiding serious toxicity).[IV]
2. Efficacy – The extent to which an intervention produces a beneficial result under ideal conditions (i.e clinical trials). [III]
3. Safety – Substantive evidence of an absence of harm (examples: clinical adverse events (disease, signs, and symptoms).[II]
4. Cost-effectiveness – The cost and health benefits associated with the use of the drug therapies.[I]
5. Adherence - The consistence and accuracy with which a patient will follow a recommended medical regimen (examples of factors that may affect adherence: frequency of administration, adverse events, cost of drug).[I]

References

I. Berger ML, Bigefors K, Hedblom EC, Pashos CL, Torrance GW. Health care cost, quality, and outcomes: ISPOR book of terms. Lawrenceville, NJ: International Society for Pharmacoeconomics and Outcomes Research; 2003.
II. Chou R, Aronson N, Atkins D. Chapter 7. Assessing harms when comparing medical interventions. In: methods guide for effectiveness and comparative effectiveness reviews. AHRP Publication No. 10(11)-EHC063-EF. March 2011; http://www.effectivehealthcare.ahrq.gov. Accessed May 2012.
III. Glossary of terms in the Cochrane Collaboration. Version 4.2.5. Updated May 2005. http://www.cochrane.org/glossary. Accessed May 2012.
IV. U.S. Food and Drug Administration. FDA guidance for industry on Fast Track Drug Development Programs: Designation, Development, and Application Review. January 2006. http://www.fda.gov/downloads/ Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079736.pdf. Accessed May 2012.

Recommendation:

KY Medicaid: Tier 2 with QL

QL: 60/30 tablets

References:

1. Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc.; 2020. URL: http://www.clinicalpharmacology.com. Aug 2020.
2. Fuzeon® (enfuviritide) [package insert]. Genentech USA, Inc. Aug 2020.
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5. Micromedex Healthcare Series: DRUGDEX. Thomson Micromedex, Greenwood Village, CO. 2020. Aug 2020.
6. Rukobia® (fostemsavir) [package insert]. ViiV Healthcare US. Aug 2020.
7. Rukobia® (fostemsavir) [product dossier]. ViiV Healthcare US. Aug 2020.

***Company*:** AbbVie
Current Status: FDA Approved June 1st, 2020
Launch: FDB June 6th, 2020
Therapeutic Category: women's health
Pharmacologic Category: gonadotropin-releasing hormone (GnRH) receptor antagonist + hormonal ABT
Similar Drugs: Orilissa, leuprolide, hormonal contraceptives
Route of Administration: Oral
Dosage Forms: 300 mg elagolix/1 mg estradiol/0.5 mg norethindrone capsules; 300 mg elagolix capsules

Indications:
Indicated for the management of heavy menstrual bleeding associated with uterine leiomyomas (fibroids) in premenopausal women.

Dosage and Administration:
- Administer one capsule (elagolix 300 mg, estradiol 1 mg, norethindrone acetate 0.5 mg) in the morning and one capsule (elagolix 300 mg) in the evening for up to 24 months.

Background:

Uterine fibroids (UF) are hormone dependent benign tumors which may cause serious symptoms such as heavy menstrual bleeding (HMB). Also known as leiomyomas, UF are the most common benign pelvic tumors in women of reproductive age. Fibroids arise from the uterine smooth muscle and consist primarily of extracellular matrix that contains collagen, fibronectin, and proteoglycan. Development and growth of fibroids is primarily dependent on estrogen and progesterone and they are usually slow growing. Development of fibroids may also be attributed to growth factors and disordered wound healing as well as genetic factors. Most women (~60%) with UF are asymptomatic; however, for those women exhibiting symptoms, there can be a substantial decrease in health and quality of life. Symptoms vary depending on the size, number, and locations of the fibroids and most commonly includes abnormal uterine bleeding, in particular, HMB as well as dysmenorrhea. However, it has been noted that HMB severity in UF is not related to fibroid size or location. Other potential symptoms include abdominal swelling, prolonged bleeding, irregular periods, infertility, dyspareunia, increased urinary frequency, constipation and anemia. In addition, 30% to 50% (~400,000) of all hysterectomies in the US are due to UF.

Pharmacology:
Elagolix is a GnRH receptor antagonist that inhibits endogenous GnRH signaling by binding competitively to GnRH receptors in the pituitary gland. Administration of elagolix results in dose-dependent suppression of luteinizing hormone (LH) and follicle-stimulating hormone (FSH), leading to decreased blood concentrations of estradiol and progesterone and reduces bleeding associated with uterine fibroids. Estradiol acts by binding to nuclear receptors that are expressed in estrogen-responsive tissues. The addition of exogenous estradiol may reduce the increase in bone resorption and resultant bone loss that can occur due to a decrease in circulating estrogen from elagolix alone. Progestins such as norethindrone act by binding to nuclear receptors that are expressed in progesterone responsive tissues. Norethindrone may protect the uterus from the potential adverse endometrial effects of unopposed estrogen.

Pharmacokinetics:

Metabolism/Elimination: Hepatic metabolism. Prodominantly CYP3A, with minor involvement of CYP2D6, CYP2C8, and uridine glucuronosyl transferases (UGTs). Other pathways include sulfation and glucoronidation.

Plasma Half-life: 6 hours (elagolix), 15 hours (estradiol), and 9 hours (norethindrone).

Drug Interactions:

- A weak to moderate inducer of cytochrome P450 (CYP3A).
- A weak inhibitor of CYP2C19.
- An inhibitor of efflux transporter P-glycoprotein (P-gp).
- Strong CYP3A inducers may decrease elagolix, estradiol, and norethindrone plasma concentrations and may result in a decrease of the therapeutic effects of Oriahnn.
- Rifampin is not recommended. The concomitant use of rifampin increased plasma concentrations of elagolix.
- Strong CYP3A inhibitors are not recommended. Concomitant use of Oriahnn with strong CYP3A inhibitors may increase elagolix, estradiol, and norethindrone plasma concentrations and increase the risk of adverse reactions.
- OATP1B1 inhibitors that are known or expected to significantly increase elagolix plasma concentrations is contraindicated due to increased risk of elagolix-associated adverse reactions.

Table 3. Drug Interactions: Effects of ORIAHNN on Other Drugs

Concomitant Drug Class: Drug Name	Effect on Plasma Exposure of Concomitant Drug	Clinical Recommendations
Cardiac glycosides: digoxin	↑ digoxin	Increase monitoring of digoxin concentrations and potential signs and symptoms of clinical toxicity when initiating ORIAHNN in patients who are taking digoxin. If ORIAHNN is discontinued, increase monitoring of digoxin concentrations.
Benzodiazepines: oral midazolam	↓ midazolam	Consider increasing the dose of midazolam by no more than 2-fold and individualize midazolam therapy based on the patient's response.
Statins: rosuvastatin	↓ rosuvastatin	Monitor lipid levels and adjust the dose of rosuvastatin, if necessary.
Proton pump inhibitors: omeprazole	↑ omeprazole	No dose adjustment needed for omeprazole 40 mg once daily when co-administered with ORIAHNN. When ORIAHNN is used concomitantly with higher doses of omeprazole, consider dosage reduction of omeprazole.

See Tables 6 and 7 *[see Clinical Pharmacology (12.3)]*.
The direction of the arrow indicates the direction of the change in the area under the curve (AUC) (↑= increase, ↓ = decrease).

***Adverse Effects*:** Oriahnn has a black box warning for thromboembolic disorders and vascular events. Most common ADEs (incidence ≥ 5% and greater than placebo) include hot flashes, headache, fatigue, and metrorrhagia.

Contraindications:

- High risk of arterial, venous thrombotic, or thromboembolic disorder
- Pregnancy
- Known osteoporosis
- Current or history of breast cancer or other hormonally-sensitive malignancies
- Known liver impairment or disease
- Undiagnosed abnormal uterine bleeding
- Organic anion transporting polypeptide (OATP)1B1 inhibitors that are known or expected to significantly increase elagolix plasma concentrations

Warnings and Precautions:

- Black Box Warning - Thromboembolic Disorders and Vascular Events: Discontinue Oriahnn if an arterial or venous thrombotic, cardiovascular, or cerebrovascular event occurs. Stop Oriahnn if there is sudden unexplained partial or complete loss of vision, proptosis, diplopia, papilledema, or retinal vascular lesions and evaluate for retinal vein thrombosis immediately.
- Bone Loss: Duration-dependent decreases in bone mineral density (BMD) that may not be completely reversible. Baseline and periodic BMD assessments are recommended. Assess risk-benefit for women with additional risk factors for bone loss.
- Suicidal Ideation and Mood Disorders: Advise patients to seek medical attention for suicidal ideation, suicidal behavior, new onset or worsening depression, anxiety, or other mood changes.
- Hepatic Impairment and Transaminase Elevations: Counsel patients on signs and symptoms of liver injury.
- Elevated Blood Pressure: Do not use in women with uncontrolled hypertension. For women with well-controlled hypertension, continue to monitor blood pressure and stop Oriahnn if blood pressure rises significantly.
- Change in Menstrual Bleeding Pattern and Reduced Ability to Recognize Pregnancy: Advise women to use non-hormonal contraception during treatment and for one week after discontinuing Oriahnn. Oriahnn may delay the ability to recognize the occurrence of a pregnancy because it alters menstrual bleeding. Perform pregnancy testing if pregnancy is suspected and discontinue Oriahnn if pregnancy is confirmed.
- Risk of Allergic Reactions Due to the Inactive Ingredient (FD&C Yellow No 5): This product contains FD&C Yellow No. 5 (tartrazine), which may cause allergic-type reactions (including bronchial asthma) in certain susceptible persons.

Monitoring:

- Blood pressure
- Bone mineral density
- Pelvic exam
- Pregnancy testing
- Serum cholesterol profile

Evidence Table of Clinical Studies:

Table 1. Clinical data for Oriahnn (elagolix + estradiol/norethindrone)

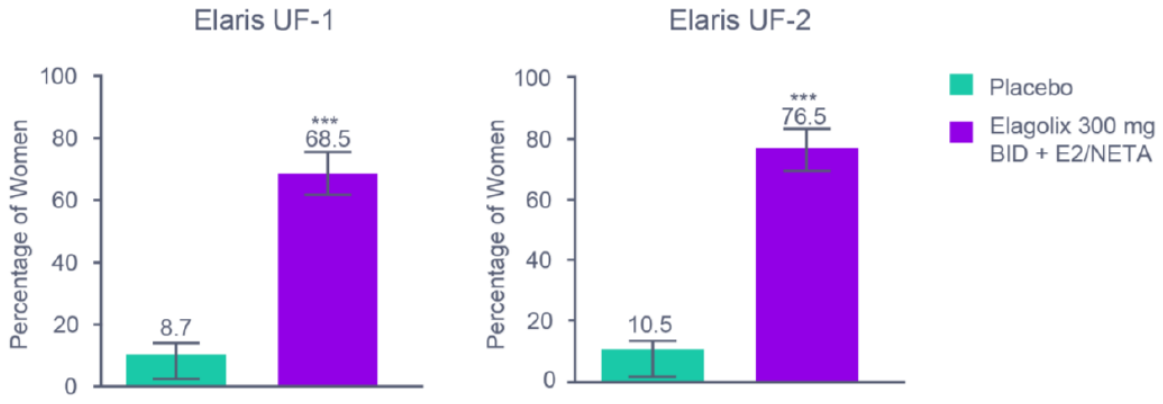
The approval was based on two randomized Phase 3 clinical trials, ELARIS UF-I and ELARIS UF-II, in which Oriahnn achieved the primary endpoint of clinically meaningful reduction in bleeding (defined as the proportion of women

who achieved both at least a 50% reduction in menstrual blood loss at final month of treatment and a total menstrual blood loss amount of less than 80 mL), compared with placebo in final month of study for patients, with seven out of 10 women no longer experiencing heavy menstrual bleeding versus one out of 10 women on placebo (P<0.001 for both trials). Oriahnn also reduced heavy menstrual bleeding due to uterine fibroids by 50% within the first month of use.

	ELARIS UF-I and UF-II NCT02654054/ NCT02691494 Schlaff, 2020
Study Type*	Phase III, Multicenter, RCT, DB, PC
Interventions and Sample Size	N= 790 Patients were randomly assigned in a 1:1:2 ratio to receive placebo. 300 mg BID Elagolix; 300 mg BID Elagolix + 1 mg estradiol/0.5 mg norethindrone QQ (E2/NETA); or placebo.
Populations	*Inclusions*: ▪ Premenopausal women age 18-51 years ▪ HMB >80 mL of menstrual blood loss (MBL) per cycle ▪ Ultrasound-confirmed diagnosis of uterine fibroids o fibroid of ≥2 cm diameter if intramural, submucosal non-pedunculated or of ≥4 cm if solitary subserosal o Or multiple small fibroids with total uterine volume of ≥200 cm3 to ≤2,500 cm3 *Exclusions:* ▪ Pregnancy ▪ Persisent or complex ovarian cysts ▪ Malignancy ▪ Pelvic inflammatory disease ▪ History of osteoporosis ▪ BMD T-score ≤ -1.5 at lumbar spine, total hip, or femoral neck
General Summary: Efficacy	**<u>Primary Endpoint:</u>** ▪ The percentage of women who had MBL volume <80 mL during the final month and ≥50% reduction in MBL volume from baseline to the final month o Result: Elagolix + E2/NETA demonstrated statistically significant greater reductions of HMB compared with placebo at the final month in both studies

	ELARIS UF-I and UF-II NCT02654054/ NCT02691494 Schlaff, 2020

Figure 3-3. Primary Endpoint of Reduced HMB at Final Month[a]



[a]MBL volume <80 mL during the final month and ≥50% reduction in MBL volume from baseline to the final month
BID = twice daily; E2 = estradiol; HMB = heavy menstrual bleeding; NETA = norethindrone acetate.
UF-1, placebo (N = 102), elagolix + E2/NETA (N = 206); UF-2, placebo (N = 94), elagolix + E2/NETA (N = 189)
*** *P*<0.001. Error bars = 95% CI

Key Secondary Endpoints:

- Mean change from baseline to final month in MBL volume
  - Elagolix + E2/NETA demonstrated statistically significant reductions in MBL from baseline to final month in both studies vs placebo.
    - UF-1: -176.7 mL vs 0.8 mL (placebo)
    - UF-2: -168.8mL vs -4.3mL (placebo)
- Percent of women with low baseline hemoglobin (≤ 10.5 g/dL) who had an increase in hemoglobin by >2 g/dL from baseline to month 6
  - Compared with patients taking placebo, a significantly greater percentage of patients receiving elagolix + E2/NETA had hemoglobin increase by >2 g/dL from baseline to 6 months in women who had low hemoglobin (≤10.5 g/dL) at baseline in both studies. 62% and 50% (vs 16% and 21% in placebo).
- Health related quality of life (HRQoL) measured using Uterine Fibroids Symptom of Quality of Life (UFS-QoL) instrument.
  - Symptom Severity
    - Elagolix + E2/NETA demonstrated significantly greater mean improvement from baseline to 6 months vs placebo. UF-1 saw a 33.2 decrease in score vs 10.3 for placebo. UF-2 had a 41.4 decrease in score vs 7.9 for placebo.
  - HRQoL total score and 6 subscale scores of Concern, Activities, Energy/Mood, Control, Self-conscious, and Sexual Function
    - Elagolix + E2/NETA demonstrated significantly greater mean improvement from baseline to 6 months vs placebo. UF-1 had a 38 point increase in score and UF-2 had a 42 point increase (vs 10.9 and 6.5 for placebo respectively)

	ELARIS UF-I and UF-II NCT02654054/ NCT02691494 Schlaff, 2020
General Summary: Safety	▪ ADE similar betweek elagolix + E2/NETA and placebo in UF-1, however ADEs were significantly greater with elagolix + E2/NETA in UF-2. ▪ Compared to placebo, the mean percent decrease in lumbar spine BMD from baseline to month 6 did not significantly differ for elagolix + E2/NETA but was significantly decreased for elagolix alone in both trials. ▪ The most common ADEs (≥5% in UF-1 or UF-2) with elagolix + E2/NETA included hot flushes, nausea, headache, fatigue and night sweats. Those ADEs which were significantly higher with elagolix + E2/NETA versus placebo were hot flushes (UF-1 and UF-2), and metrorrhagia (UF-1). Patients experiencing hot flush of moderate or severe intensity was 6.8% and 0.5% with elagolix + E2/NETA in UF-1 and 5.3% and 1.1% in UF-2 compared with 31.7% and 1.9% with elagolix alone in UF-1 and 16.8% and 5.3% in UF-2.
Comments	▪ In Studies UF-1 and UF-2, the median age of enrolled women was 43 years (ranging from 25 to 53 years); 68% of the women were Black or African American, 29% were White, and 3% were other races. ▪ Efficacy analyses were conducted on the intent-to-treat population (all randomized patients). ▪ MBL was assessed by the alkaline hematin method and the primary endpoint was analyzed via a logistic regression model including treatment as the main effect and baseline MBL volume as a covariate ▪ Studies placebo controlled vs comparing to hormonal contraceptives
Grade^	▪ B

*Study type abbreviations: AC=Active-comparator, CC=Case-control study, COH=Cohort study, CS=Case study, DB=double blind, EPI=Epidemiologic study, META=Meta-analysis, NRCT=Nonrandomized clinical trial, OBS=Observational study, PC=placebo-controlled, PG=parallel-group, RCT=randomized trial, XO=crossover [if not listed, please type in under study type]
^A=Useful, B=Possibly useful, C=Possible to uncertain usefulness, U=Uncertain validity and/or usefulness, X=Not useful
(For further information, please refer to the document Grading of Clinical Evidence; NA=Not applicable. [Disclaimer: Grade the study if able to pull the literature]

Special Populations:

- Contraindicated in pregnancy – women must use non hormonal birthcontrol during treatment and for one week after discontinuing
- Contraindicated in women with any hepatic impairment or disease
- Safety and efficacy not established in pediatric patients

Cost and/or Utilization Data of Similar Treatment Options:

Table 2: Pricing

Drug	Strength	WAC/unit	Package size	WAC/month
Oriahnn	300 mg & 300 mg/1 mg/0.5 mg	$16.20/cap	56 caps/28 DS	$907.39

ethinyl estradiol/ norgestimate	35 mcg-0.25 mg	$0.85/tablet	28 tablets per blister pack	$23.68/28 days
ethinyl estradiol/ drospirenone	0.02 mg-3 mg	$0.61/tablet	28 tablets per blister pack	$17.11/28 days

Place in Therapy:

Table 5. Comparison of Oriahnn with hormonal contraceptives.

	Oriahnn (elagolix + estradiol/norethindrone)	Hormonal contraceptives
Meet an Unmet Medical Need[1]	☒ No – hormonal contraceptives can provide the same relief from heavy menstrual bleeding while also having the capability of being used longer term.	
Comparable Efficacy[2]	☒ Oriahnn is similarly efficacious relative to Hormonal contraceptives **Comment:** Hormonal contraceptives are effective for many women, while some women are unable to adequately control bleeding. It is highly individualized. In those women, Oriahnn may be a viable option.	
Comparable Safety[3]	☒ Oriahnn would likely have compromised safety relative to Hormonal contraceptives. **Comment:** Oriahnn's safety profile includes greater risk for more serious ADEs, including thromboembolic disorders, vascular events, and changes to BMD that may or may not be reversible.	
Comparable Cost-Effectiveness[4]	☒ Oriahnn would likely have a less cost effectiveness relative to Hormonal contraceptives. **Comment:** Hormonal contraceptive drugs are plentiful at very inexpensise	
Adherence[5]	☒ Members taking Oriahnn would likely achieve a lower adherence rate relative to Hormonal contraceptives **Comment:** Oriahnn is twice daily dosing while hormonal contraceptives are typically day dosing. Patches and rings provide even less adherence concerns.	
Advantages	▪ Addition of E2/NETA add-back therapy helps to control side effects related to hormone suppression ▪ Potentially more potent therapy for some women	▪ Contraceptives can be taken for long periods of time, and are easily discontinued ▪ Multiple formulations of contraceptives and combinations of hormones to choose from to find a good fit ▪ Intrauterine devices may also decrease size of fibroids
Disadvantages	▪ Limited duration of therapy (24 months) ▪ Potential for irreversible BMD loss ▪ Black box warning for thromboembolic and vascular events ▪ No evidence of changes to size of fibroids	▪ May not be efficacious enough for certain women ▪ Could also cause intolerable side effects for some women
Comments	▪ Ultimately, the only cure for fibroids and associated side effects is hysterectomy or menopause ▪ Surgeries, such as myomectomies, are available to help remove fibroids and ease symptoms however the fibroids do recur more often than not	

Definitions

1. Unmet medical need - Medical need that is not addressed adequately by an existing therapy (examples: a) No available therapy for condition exists b) If available therapy for the condition exists i) New therapy has improved effects on serious outcomes, ii) Similar benefits to alternative therapies while avoiding serious toxicity).[IV]

2. Efficacy – The extent to which an intervention produces a beneficial result under ideal conditions (i.e clinical trials). [III]
3. Safety – Substantive evidence of an absence of harm (examples: clinical adverse events (disease, signs, and symptoms).[II]
4. Cost-effectiveness – The cost and health benefits associated with the use of the drug therapies.[I]
5. Adherence - The consistence and accuracy with which a patient will follow a recommended medical regimen (examples of factors that may affect adherence: frequency of administration, adverse events, cost of drug).[I]

References

I. Berger ML, Bigefors K, Hedblom EC, Pashos CL, Torrance GW. Health care cost, quality, and outcomes: ISPOR book of terms. Lawrenceville, NJ: International Society for Pharmacoeconomics and Outcomes Research; 2003.
II. Chou R, Aronson N, Atkins D. Chapter 7. Assessing harms when comparing medical interventions. In: methods guide for effectiveness and comparative effectiveness reviews. AHRP Publication No. 10(11)-EHC063-EF. March 2011; http://www.effectivehealthcare.ahrq.gov. Accessed May 2012.
III. Glossary of terms in the Cochrane Collaboration. Version 4.2.5. Updated May 2005. http://www.cochrane.org/glossary. Accessed May 2012.
IV. U.S. Food and Drug Administration. FDA guidance for industry on Fast Track Drug Development Programs: Designation, Development, and Application Review. January 2006. http://www.fda.gov/downloads/ Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079736.pdf. Accessed May 2012.

Recommendation:

KY Medicaid: NF with QL

QL: 56/28/2.6

References:

1. Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc.; 2020. URL: http://www.clinicalpharmacology.com Accessed August 2020.
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5. Oriahnn [package insert] Chicago, IL: AbbVie Inc. May 2020.
6. Orihann [AMCP dossier] Chicago, IL: AbbVie Inc. May 2020.

Humana Pharmacy Solutions

Clinical Review – Inqovi® (decitabine and cedazuridine)

***Company*:** Taiho Oncology
Current Status: FDA approved on 7-7-20
Potential Launch: on FDB report 8-15-20
Therapeutic Category: Antineoplastic
Pharmacologic Category: Hypomethylators
Similar Drugs: decitabine IV, azacitidine IV
Route of Administration: Oral
Dosage Forms: Tablet (35 mg decitabine and 100 mg cedazuridine)

Indications: for treatment of adult patients with myelodysplastic syndromes (MDS), including previously treated and untreated, de novo and secondary MDS with the following French-AmericanBritish subtypes (refractory anemia, refractory anemia with ringed sideroblasts, refractory anemia with excess blasts, and chronic myelomonocytic leukemia [CMML]) and intermediate-1, intermediate-2, and high-risk International Prognostic Scoring System groups.

Dosage and Administration: One tablet (containing 35 mg decitabine and 100 mg cedazuridine) orally once daily on Days 1 through 5 of each 28-day cycle for a minimum of 4 cycles until disease progression or unacceptable toxicity. A complete or partial response may take longer than 4 cycles.

- Do not substitute Inqovi for an intravenous decitabine product within a cycle.

Background:
Myelodysplastic syndrome (MDS) and chronic myelomonocytic leukemia (CMML) are disorders of the bone marrow. MDS, is diagnosed in approximately 10,000 people in the US every year and manifests as one or more cyteopenias. CMML is a clonal disorder of bone marrow stem cells, with a heterogeneous presentation. Hypomethylators, like azacitidine and decitabine, are used in these disorders.

Pharmacology:
Decitabine is a nucleoside metabolic inhibitor that inhibition of DNA methyltransferase, causing hypomethylation of DNA and cellular differentiation and/or apoptosis.

Cytidine deaminase (CDA) is an enzyme that catalyzes the degradation of cytidine, including the cytidine analog decitabine. High levels of CDA in the gastrointestinal tract and liver degrade decitabine and limit its oral bioavailability. Cedazuridine is a CDA inhibitor. Administration of cedazuridine with decitabine increases systemic exposure of decitabine.

Pharmacokinetics:
Metabolism/Elimination:

- Decitabine - Primarily by cytidine deaminase (CDA) and by physicochemical degradation
- Cedazuridine - Conversion to epimer by physicochemical degradation

Plasma Half-Life (hrs):

- Decitabine – 1.5 hours
- Cedazuridine – 6.7 hours

Drug Interactions:

- Decitabine had no clinically meaningful effect on the pharmacokinetics of cedazuridine. Cedazuridine increased the exposure of decitabine.

- Cedazuridine is an inhibitor of the cytidine deaminase (CDA) enzyme. Coadministration of Inqovi with drugs that are metabolized by CDA may result in increased systemic exposure with potential for increased toxicity of these drugs. Per prescribing information (section 12.3) cedazuridine was not reported to be substrate, inducer, or inhibitor for major CYP pathways. Cedazuridine also not reported as substrate or inhibitor of major transporter systems.

***Adverse Effects*:**
Some common side effects of Inqovi included fatigue, constipation, hemorrhage, muscle pain, mucositis (mouth sores), arthralgia (joint pain), nausea, and fever with low white blood cell count. Serious adverse reactions in > 5% of patients included febrile neutropenia (30%), pneumonia (14%), and sepsis (13%). Fatal adverse reactions occurred in 6% of patients. These included sepsis (1%), septic shock (1%), pneumonia (1%), respiratory failure (1%), and one case each of cerebral hemorrhage and sudden death

Contraindications: None

Warnings and Precautions:
- Myelosuppression – Myelosuppression (thrombocytopenia, neutropenia, anemia, and febrile neutropenia) is the most frequent cause of Inqovi dose reduction or interruption, occurring in 36% of patients. Permanent discontinuation due to myelosuppression (febrile neutropenia) occurred in 1% of patients. Myelosuppression and worsening neutropenia may occur more frequently in the first or second treatment cycles and may not necessarily indicate progression of underlying MDS.
    - Based on laboratory values, new or worsening thrombocytopenia occurred in 82% of patients, with Grade 3 or 4 occurring in 76%. Neutropenia occurred in 73% of patients, with Grade 3 or 4 occurring in 71%. Anemia occurred in 71% of patients, with Grade 3 or 4 occurring in 55%. Febrile neutropenia occurred in 33% of patients, with Grade 3 or 4 occurring in 32%.

Monitoring:
- Obtain complete blood cell counts prior to initiation of Inqovi, prior to each cycle, and as clinically indicated to monitor response and toxicity.
- Monitor complete blood cell counts until return of absolute neutrophil count and platelets are meet or exceed recommended thresholds for treatment.
- Due to the potential for increased adverse reactions, monitor patients with moderate renal impairment (CLcr 30 to 59 mL/min) frequently for adverse reactions.

Evidence Table of Clinical Studies:
Table 1. Clinical data for [drug name].

	ASCERTAIN **Garcia-Manero G, et al. Blood (2019) 134 (Supplement_1): 846.**
Study Type*	Phase 3, randomized, open-label, crossover study
Interventions and Sample Size	1:1 randomization to received decitabine/cedazuridine tablets (DEC-C) or IV decitabine in cycle 1 and then crossed over to other therapy in cycle 2 N=133 Endpoints: • Primary: total 5-day AUC exposure of decitabine • Secondary: ORR, transfusion independence, duration of response, leukemia-free survival, OS, maximum long interspersed nucleotide elements-1 (LINE-1) demethylation, and incidence and severity of AEs. (LINE-1s are heavily methylated areas of repetitive genomic elements, so LINE-1 demethylation is

	ASCERTAIN Garcia-Manero G, et al. Blood (2019) 134 (Supplement_1): 846.
	a pharmacodynamic surrogate marker for global DNA methylation. While not routinely monitored in the clinical management of patients with MDS, the measurement of LINE-1 demethylation provides a proxy for measuring pharmacodynamic equivalence between IV and oral decitabine.)
Populations	▪ Key Inclusion criteria: Adults with previously treated or untreated de novo or secondary MDS, including all French-American-British subtypes (refractory anemia, refractory anemia with ringed sideroblasts, refractory anemia with excess blasts, refractory anemia with excess blasts in transformation, and CMML), and subjects with MDS IPSS int-1, -2, or high-risk MDS ▪ Key Exclusion criteria: ○ Previous treatment with ≥2 cycles of decitabine or azacitidine ○ Hospitalization for febrile neutropenia, pneumonia, sepsis, or systemic infection lasting >2 days in the 30 days prior to screening ○ Cytotoxic chemotherapy or prior azacitidine or decitabine within 4 weeks of the first dose of study treatment ○ Rapidly progressing disease or highly proliferative disease (total white blood cell count of >15 × 10^9/L) or other criteria that may require cytotoxic therapy in the next 3 months ○ Concurrent MDS therapies within 1 week before the first dose of study treatment ○ Poor medical risk, active uncontrolled infections, or comorbidities that put the patient at risk of not completing at least 2 cycles of treatment ○ Known significant mental illness or other condition that puts the patient at risk of non-compliance ○ Life-threatening illness or organ dysfunction that may compromise patient safety, DEC-C absorption or metabolism, or completion of the study or integrity of study outcomes ○ Prior malignancy
General Summary: Efficacy	• Primary: Total 5-day AUC of decitabine. The oral:IV GMR of the 5-day decitabine AUC was 98.9% (90% CI: 93, 106). • Secondary ○ Maximum %LINE-1 demethylation: No significant differences in the maximum %LINE-1 DNA demethylation were seen between DEC-C and IV decitabine in cycles 1 and 2. ○ ORR = 64.4%; CR = 11.9% (by independent review committee) ○ Transfusion dependence: 53% became independent of RBC and platelet transfusions during any 56-day post-baseline period. ○ In the overall population, 27 (20%) of the 133 patients went on to stem cell transplantation following DEC-C treatment
General Summary: Safety	• No significant differences in AEs observed between DEC-C vs IV decitabine. Of note, gastrointestinal (GI) AEs of grade ≥3 occurred in <1% of patients who received DEC-C and IV decitabine in cycles 1 or 2. • Common ADES for DEC-C: thrombocytopenia (44%), neutropenia (35%), anemia (37%), fatigue (34%), constipation(16%), nausea (18%), leukopenia (19%), diarrhea (15%), febrile neutropenia (14%), and headache (15%).
Comments	▪ Baseline: Median age 71 years, male 65%, median weight 83 kg, median BSA 1.99 m^2, CMML in 12%, high risk MDS 16%, int-1 and int-2 62%, and low risk 8%, transfusion dependent – 39% RBC and 7.5% platelets

	ASCERTAIN Garcia-Manero G, et al. Blood (2019) 134 (Supplement_1): 846.
	▪ Median follow up was 5 months. Could have received either DEC-C or IV dec as cycle 1, then cross over. From cycle 3 onward everyone received DEC-C. ▪ Primary endpoint was PK-PD. Secondary endpoint did report ORR and CR.
Grade^	▪ C

*Study type abbreviations: CC=Case-control study, COH=Cohort study, CS=Case study, DB=double blind, EPI=Epidemiologic study, META=Meta-analysis, NRCT=Nonrandomized clinical trial, OBS=Observational study, PC=placebo-controlled, PG=parallel-group, RCT=randomized trial, XO=crossover [if not listed, please type in under study type]
^A=Useful, B=Possibly useful, C=Possible to uncertain usefulness, U=Uncertain validity and/or usefulness, X=Not useful
(For further information, please refer to the document Grading of Clinical Evidence; NA=Not applicable. [Disclaimer: Grade the study if able to pull the literature]

Special Populations:

- **Geriatric Use –** Of the 208 patients in clinical studies who received Inqovi, 75% were age 65 years and older, while 36% were age 75 years and older. No overall differences in safety or effectiveness were observed between patients age 65 years and older, 75 years and older, and younger patients.
- **Renal Impairment** – No dosage modification of Inqovi is recommended for patients with mild or moderate renal impairment (creatinine clearance [CLcr] of 30 to 89 mL/min based on Cockcroft-Gault). Due to the potential for increased adverse reactions, monitor patients with moderate renal impairment (CLcr 30 to 59 mL/min) frequently for adverse reactions. Inqovi has not been studied in patients with severe renal impairment (CLcr 15 to 29 mL/min) or end-stage renal disease (ESRD: CLcr <15 mL/min).

Cost and/or Utilization Data of Similar Treatment Options:

Table 2: Inqovi (decitabine and cedazuridine) Pricing

Drug	Strength	WAC/unit	Package size	WAC/Package
Inqovi	35-100mg tablet	$1,499	5	$7,495
Decitabine	50 mg vial	$654	1	$654
Azacitidine	100 mg vial	$246	1	$246

Table 4: Humana Tiering for Similar Treatment Options

	Decitabine IV	Azacitidine IV	n/a
KY Medicaid	NF	NF	n/a

Place in Therapy:

Table 5. Comparison of Inqovi and IV decitabine

	Inqovi (decitabine and cedazuridine)	IV decitabine
Meet an Unmet Medical Need[1]	☒ No, Inqovi does not meet an unmet medical need. Intravenous decitabine is a standard of care in treatment of MDS. While Inqovi does present an oral option, no available data suggests improved outcomes. Inqovi demonstrated similar ADEs, with no improvements.	
Comparable Efficacy[2]	☒ Inqovi likely has similar efficacy relative to IV decitabine. **Comment:** The phase 3 crossover study, ASCERTAIN, demonstrated no significant differences in PK	

	between IV decitabine and oral Inqovi. Patients were treated with either formulation during cycle 1, then crossed over during cycle 2 to the other formulation. Beyond cycle 3 all patients were on oral Inqovi. There is no head to head study evaluating outcomes between IV decitabine and Inqovi..	
Comparable Safety[3]	☒ Inqovi would likely have similar safety relative to IV decitabine. **Comment:** In phase 3 study, ASCERTAIN, no significant differences in ADEs during first 2 cycles. Of note, no increased GI toxicities with Inqovi, which exerts its effects in the GI tract and the liver.	
Adherence[5]	☒ Members taking IV decitabine would likely achieve a greater adherence rate relative to Inqovi. **Comment:** Intravenous decitabine is given in a provider's office or infusion center, which ensures compliance. However, this does require 5 days of return visits for administration. Five days of Inqovi taken as an oral therapy can be administered at home, but unknown if administered.	
Advantages	▪ First oral decitabine formulation ▪ Self-administration	▪ A standard of care ▪ Ensures compliance ▪
Disadvantages	▪ Current data does not show improved outcomes.	▪ Requires IV administration ▪
Comments	▪ Same administration schedule as IV ▪ Similar ADE profile (no increased ADEs, but also no advantages) ▪ NCCN lists as "could be considered as a substitution for intravenous decitabine" ▪ Onureg (oral azacitidine) recently approved for AML. Recommend evaluating this space and new oral entrants for 2022 build.	

Definitions

1. Unmet medical need - Medical need that is not addressed adequately by an existing therapy (examples: a) No available therapy for condition exists b) If available therapy for the condition exists i) New therapy has improved effects on serious outcomes, ii) Similar benefits to alternative therapies while avoiding serious toxicity).[IV]
2. Efficacy – The extent to which an intervention produces a beneficial result under ideal conditions (i.e clinical trials). [III]
3. Safety – Substantive evidence of an absence of harm (examples: clinical adverse events (disease, signs, and symptoms).[II]
4. Cost-effectiveness – The cost and health benefits associated with the use of the drug therapies.[I]
5. Adherence - The consistence and accuracy with which a patient will follow a recommended medical regimen (examples of factors that may affect adherence: frequency of administration, adverse events, cost of drug).[I]

References

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II. Chou R, Aronson N, Atkins D. Chapter 7. Assessing harms when comparing medical interventions. In: methods guide for effectiveness and comparative effectiveness reviews. AHRP Publication No. 10(11)-EHC063-EF. March 2011; http://www.effectivehealthcare.ahrq.gov. Accessed May 2012.
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Recommendation:

- KY Medicaid: NF
- QL: 5 / 28

References:

1. Inqovi [AMCP Dossier Chapter 3, containing summaries of key clinical data and supporting references]. Princeton, NJ; Taiho Oncology. 2020.
2. Inqovi [package insert]. Princeton, NJ; Taiho Oncology. 2020.

***Company*:** Kite Pharma, Inc. (a Gilead company)
Current Status: FDA approved July 24,2020
Launch:
Therapeutic Category: Oncology
Pharmacologic Category: CD19-targeted chimeric antigen receptor T-cell (CAR-T) therapy
Similar Drugs: Calquence (acalabrutinib), Kymriah (tisagenlecleucel)
Route of Administration: Intravenous
Dosage Forms: Genetically modified autologous T cells in one infusion bag labeled for the specific patient

Indications:
Tecartus is indicated for the treatment of adult patients with relapsed or refractory mantle cell lymphoma (MCL).

Dosage and Administration:

- For autologous use only. The patient's identity must match the patient identifiers on the Tecartus cassette and infusion bag. Do not infuse Tecartus if the information on the patient-specific label does not match the intended patient.
- T-cells are collected from the patient and sent to Kite Pharma's manufacturing facility. After cellular expansion and purification, the cells are cryopreserved and shipped back to the facility for the patient.
- One treatment consists of pretreatment with a lymphodepleting chemotherapy regimen of cyclophosphamide and fludarabine intravenously on each of the fifth, fourth, and third days before infusion of Tecartus and premedication with acetaminophen and diphenhydramine or another H1-antihistamine approximately 30 to 60 minutes prior to Tecartus infusion.
- A single dose of Tecartus is administered
    - Suspension of 2×10^6 CAR-positive viable T cells per kg of body weight, with a maximum of 2×10^8 CAR-positive viable T cells in approximately 68 mL

Background:
Mantle Cell Lymphoma comprises roughly 6% of non-Hodgkin lymphomas and is an aggressive malignancy arising from antigen-naïve pre-germinal center B cells found in the lymph node's mantle zone. The annual incidence of MCL is about one to two cases per 100,000 Americans, and it is more likely to affect older adults, males, and Caucasians. The disease is considered incurable and the median overall survival is between 3 and 5 years. The prognosis for the blastoid variant, which accounts for an estimated 10–15% of MCL cases, is poor. It has frequent extranodal involvement and often responds poorly to commonly used treatments. A majority of cases of MCL becomes relapsed or refractory disease. Current treatments available for relapsed or refractory MCL include first line chemotherapy options or the Bruton's tyrosine kinase (BTK) inhibitors. Tecartus is the first CAR-T cell therapy approved for the treatment of relapsed or refractory MCL.

Pharmacology:
Tecartus is a CD19-directed genetically modified autologous T cell immunotherapy that binds to CD10-expressing cancer cells and normal B cells. Following anti-CD19 CAR T cell engagement with CD19-expressing target cells, the CD28 and CD-zeta co-stimulatory domains activate downstream signaling cascades that lead

to T cell activation, proliferation, acquisition of effector functions, and secretion of inflammatory cytokines and chemokines. This leads to killing of CD19-expressing cells.

Pharmacokinetics:

- Metabolism/Elimination:
  - Hepatic and renal impairment studies were not conducted
- Onset: Median time to initial response: 1 month (range: 0.8 to 3.1 months); median time to complete response: 3 months (range: 0.9 to 9.3 months) (Wang 2020).
- Duration: Anti-CD19 CAR T cells displayed an initial rapid expansion followed by a decline to near baseline levels by 3 months post-brexucabtagene autoleucel infusion.
- Time to peak: Peak levels of anti-CD19 CAR T cells occurred within the first 7 to 14 days after infusion.

Drug Interactions:

- HIV and the lentivirus used to make Tecartus have limited, short spans of identical genetic material (RNA). Therefore, some commercial HIV nucleic acid test (NAT) tests may yield false-positive results in patients who have received Tecartus.
- Avoid other immunosuppressants

***Adverse Effects*:**

The most common adverse reactions (incidence ≥ 20%) were pyrexia, CRS, hypotension, encephalopathy, fatigue, tachycardia, arrhythmia, infection–pathogen unspecified, chills, hypoxia, cough, tremor, musculoskeletal pain, headache, nausea, edema, motor dysfunction, constipation, diarrhea, decreased appetite, dyspnea, rash, insomnia, pleural effusion, and aphasia. Serious adverse reactions occurred in 66% of patients. The most common serious adverse reactions (> 2%) were encephalopathy, pyrexia, infection – pathogen unspecified, CRS, hypoxia, aphasia, renal insufficiency, pleural effusion, respiratory failure, bacterial infections, dyspnea, fatigue, arrhythmia, tachycardia, and viral infections.

Contraindications:

- None

Warnings and Precautions:

- Black Box Warnings:
  - Cytokine Release Syndrome, including fatal or life-threatening reactions, occurred in patients receiving Tecartus. Do not administer Tecartus to patients with active infection or inflammatory disorders. Treat severe or life-threatening CRS with tocilizumab.
  - Neurologic toxicities, which may be severe or life-threatening, can occur following treatment with Tecartus, including concurrently with CRS. Monitor for neurological events after treatment with Tecartus. Provide supportive care as needed.
  - Tecartus is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the Yescarta and Tecartus REMS Program.
- Hypersensitivity reactions
- Severe infections
- Prolonged cytopenias

- Hypogammaglobulinemia
- Secondary malignancies
- Effects on ability to drive and use machines

Monitoring:

- Monitor patients for signs or symptoms of CRS for at least 4 weeks after treatment with Tecartus
- Monitor for neurological events after treatment with Tecartus
- Monitor for hypersensitivity reactions during infusion
- Monitor patients for signs and symptoms of infection; treat appropriately
- Monitor immunoglobulin levels after treatment with Tecartus and provide replacement therapy until resolution
- Monitor life-long for secondary malignancies

Evidence Table of Clinical Studies:

Table 1. Clinical data for Tecartus (brexucabtagene autoleucel)

	ZUMA-2
Study Type*	This was a single-group, multicenter, open-label, Phase 2 trial that evaluated the efficacy and safety of a single infusion of TECARTUS in adult patients with relapsed or refractory mantle cell lymphoma (MCL) who had previously received anthracycline- or bendamustine-containing chemotherapy, an anti-CD20 antibody, and a Bruton tyrosine kinase inhibitor (BTKi; ibrutinib or acalabrutinib).
Interventions and Sample Size	N=60 All patients underwent leukapheresis to obtain cells for Tecartus manufacturing They received fludarabine at a dose of 30 mg per square meter of body-surface area per day and cyclophosphamide at a dose of 500 mg per square meter per day on days 5, 4, and 3 before a single intravenous infusion of Tecartus was administered at a dose of 2×10^6 CAR T cells per kilogram of body weight on day 0.
Populations	*Select Inclusions*: • Patients with relapsed or refractory MCL who were previously treated with anthracycline- or bendamustine-containing chemotherapy, anti-CD20 antibody therapy, and a BTKi (ibrutinib or acalabrutinib). • Eligible patients also had disease progression after their last regimen or refractory disease to their most recent therapy. • Adequate renal, hepatic, pulmonary, and cardiac function • Absolute neutrophil count ≥ 1 000/uL • Platelet count ≥ 75 000/uL *Select Exclusions:* • Patients with active or serious infections • Patients with prior allogeneic hematopoietic stem cell transplant (HSCT) • Patients with detectable cerebrospinal fluid malignant cells or brain metastases • Patients with any history of central nervous system (CNS) lymphoma or CNS disorders

	ZUMA-2
	Baseline Characteristics: • The median age was 65 years (range 38 to 79 years) • 85% were male • 93% were white • 83% had stage IV disease
General Summary: Efficacy	**Primary Endpoint:** The primary endpoint was the percentage of patients with an objective response (complete or partial) as assessed by the independent radiology review committee according to the Lugano classification. Bone marrow evaluation in addition to PET-CT was necessary to confirm a complete response. • 93% of the 60 patients had objective response • 67% had complete response **Key Secondary Endpoints:** Key secondary endpoints included the duration of response, progression-free survival, overall survival, and several others. • At the median follow-up of 12.3 months, 57% were in remission • At 12 months, the estimated progression-free survival and overall survival were 60% and 83%, respectively
General Summary: Safety	• All patients had at least one adverse event of any grade • Adverse events of grade 3 or higher were cytopenias (in 94% of patients) and infections (in 32%) ○ Cytopenias included neutropenia (in 85%), thrombocytopenia (51%), and anemia (50%) • Cytokine release syndrome occurred in 91% of patients, but no patient died • 63% of patients had neurologic events, but no patients died • 68% of patients had serious adverse events • 16 patients died primarily from progressive disease
Comments	A recent study of ibrutinib plus rituximab therapy in patients with relapsed or refractory mantle-cell lymphoma showed that those with a Ki-67 proliferation index of 50% or higher, 50% of patients had an objective response and 17% had a complete response, and the 3-year progression-free survival was 1%. In ZUMA-2, 94% of patients with Ki-67 indexes of 50% or higher had an objective response. A high percentage of patients with blastoid or pleomorphic morphologic features or TP53 mutation had objective responses as well. This suggests that Tecartus may benefit patients who typically have a poorer prognosis than patients without these characteristics.
Grade	B

*Study type abbreviations: AC=Active-comparator, CC=Case-control study, COH=Cohort study, CS=Case study, DB=double blind, EPI=Epidemiologic study, META=Meta-analysis, NRCT=Nonrandomized clinical trial, OBS=Observational study, PC=placebo-controlled, PG=parallel-group, RCT=randomized trial, XO=crossover [if not listed, please type in under study type]
^A=Useful, B=Possibly useful, C=Possible to uncertain usefulness, U=Uncertain validity and/or usefulness, X=Not useful
(For further information, please refer to the document Grading of Clinical Evidence; NA=Not applicable. [Disclaimer: Grade the study if able to pull the literature] OBT=optimized background treatment

Special Populations:

- Pregnancy: There is no available data with Tecartus use in pregnant women and no animal reproductive and developmental toxicity studies have been conducted. Tecartus is not recommended for women who are pregnant, and pregnancy after Tecartus infusion should be discussed with the treating physician.
- Lactation: There is no information regarding the presence of Tecartus in human milk, the effect on the breastfed infant, and the effects on milk production. The developmental health benefits of breastfeeding should be considered along with the mother's clinical need for Tecartus and any potential adverse effects on the breastfed infant from Tecartus or the underlying maternal condition.
- Pediatric Use: The safety and efficacy of Tecartus have not been established in pediatric patients.
- Geriatric Use: No overall differences in safety or effectiveness were observed between patients ≥ 65 years of age and younger patients.
- Renal Impairment: Renal impairment studies of Tecartus were not conducted.
- Hepatic Impairment: Hepatic impairment studies of Tecartus were not conducted.

Cost and/or Utilization Data of Similar Treatment Options:

Table 2:

Drug	Strength	WAC/unit	Package size	WAC/month
Tecartus	-	$373,000/infusion	1 time infusion	-
Calquence	100 mg cap	$234	60	$14,064

Table 4: Humana Tiering for Similar Treatment Options

	Calquence 100 mg cap		
KY Medicaid	T2 / PA		

Place in Therapy:

Table 5. Comparison of Tecartus (brexucabtagene autoleucel) with Calquence (acalabrutinib)

	Tecartus (brexucabtagene autoleucel) – review drug	Calquence (acalabrutinib)– comparator
Meet an Unmet Medical Need[1]	☒ Yes- Based on improved complete remission rate and potential improvements in survival. Currently there are limited alternatives for patients who have failed first line chemotherapy agents or BTKis other than hematopoietic cell transplant. No head-to-head comparisons exist between Tecartus and conventional chemotherapy regimens.	

Comparable Efficacy[2]	☒ Tecartus is potentially more efficacious relative to Calquence **Comment**: In patients treated with Tecartus in the ZUMA-2 trial, 93% had an objective response. In a Phase 2 clinical trial with Calquence, the overall response rate was 80%. IN the ZUMA-2 trial 67% of patients had a complete response while only 40% of patients in the Calquence trial experienced a complete response. The two trials are difficult to compare due to prior treatment with a BTKi being an exclusion for the Calquence trial and an inclusion for the ZUMA-2 trial.	
Comparable Safety[3]	☒ Tecartus would likely be less safe relative to Calquence **Comment:** Tecartus has black box warnings for Cytokine Release Syndrome as well as neurologic toxicities while Calquence does not have any. Tecartus also requires enrollment into a REMS program in order to receive the infusion. Calquence and Tecartus both possess risks of infection, cytopenias, and secondary malignancies.	
Adherence[5]	☒ Members taking Tecartus would likely achieve increased adherence rate relative to Calquence **Comment:** Calquence is an oral tablet taken twice daily until disease progression or unacceptable toxicity. Tecartus treatment consists of pretreatment with a lymphodepleting chemotherapy regimen of cyclophosphamide and fludarabine intravenously on each of the fifth, fourth, and third days before Tecartus infusion and premedication with acetaminophen and diphenhydramine or another H1-antihistamine approximately 30 to 60 minutes prior to Tecartus infusion. Tecartus is a one-time infusion.	
Advantages	• Single-dose • Improved remission rates •	• No Black Box Warnings • Oral medication
Disadvantages	• Logistically challenging (e.g. cell collection, processing, administration) • REMS program and Black Box Warnings	• Therapy continues until disease progression or toxicity • Avoid in patients with severe hepatic impairment • High potential for drug-drug interactions (dosage adjustments necessary)
Comments	• NCCN Category 2A (only given after chemoimmunotherapy and BTK inhibitor)	• NCCN Category 2A

Definitions

1. Unmet medical need - Medical need that is not addressed adequately by an existing therapy (examples: a) No available therapy for condition exists b) If available therapy for the condition exists i) New therapy has improved effects on serious outcomes, ii) Similar benefits to alternative therapies while avoiding serious toxicity).[IV]
2. Efficacy – The extent to which an intervention produces a beneficial result under ideal conditions (i.e clinical trials). [III]
3. Safety – Substantive evidence of an absence of harm (examples: clinical adverse events (disease, signs, and symptoms).[II]
4. Cost-effectiveness – The cost and health benefits associated with the use of the drug therapies.[I]
5. Adherence - The consistence and accuracy with which a patient will follow a recommended medical regimen (examples of factors that may affect adherence: frequency of administration, adverse events, cost of drug).[I]

References

I. Berger ML, Bigefors K, Hedblom EC, Pashos CL, Torrance GW. Health care cost, quality, and outcomes: ISPOR book of terms. Lawrenceville, NJ: International Society for Pharmacoeconomics and Outcomes Research; 2003.
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Recommendation:

- KY Medicaid: NF (medical)
- Add to MIT-PAL: Yes (transfer to Humana Transplant team)

References:

1. Calquence® (acalabrutinib) [package insert]. AstraZeneca. Sept 2020.
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Humana Pharmacy Solutions

Clinical Review – Dojolvi™ (triheptanoin)

***Company*:** Ultragenyx
Current Status: FDA approved July 16th, 2020
Potential Launch: July 20th, 2020 launch
Therapeutic Category: General Nutrient
Pharmacologic Category: Fatty acid supplement
Similar Drugs: N/A (MCT Oil – OTC supplement)
Route of Administration: Oral
Dosage Forms: Solution 100% triheptanoin w/w

Indications: a source of calories and fatty acids for the treatment of pediatric and adult patients with molecularly confirmed long-chain fatty acid oxidation disorders (LC-FAOD)

Dosage and Administration: Initiate triheptanoin at a total daily dosage of approximately 10% daily caloric intake (DCI) and increase to the recommended total daily dosage of up to 35% DCI over a period of 2 to 3 weeks.

Background:
LC-FAODs are a group of rare, inborn errors of metabolism in which the body is unable to convert long-chain fatty acids into energy. Patients with LC-FAOD can present with a wide range of symptoms varying from severe neonatal hypoglycemia to cardiomyopathy, sometimes leading to sudden death. Milder adolescent and adult phenotypes can present with recurrent rhabdomyolysis and exercise intolerance. Although newborn screenings and early intervention have reduced mortality, many patients continue to experience frequent hospitalizations and significant morbidity despite dietary treatment.

Pharmacology:
It is a highly purified, synthetic, medium odd-chain fatty acid consisting of three 7-carbon fatty acids on a glycerol backbone that bypasses the deficient long-chain fatty acid oxidation enzymes. Once metabolized, it increases intermediate substrates in the Krebs cycle, a key energy-generating process

Pharmacokinetics:
Metabolism/Elimination: Heptanoate, formed by hydrolysis of triheptanoin, can be metabolized to beta-hydroxypentanoate (BHP) and beta-hydroxybutyrate (BHB) in the liver.
Plasma Half-Life (hrs): Could not be determined per package insert

Drug Interactions:
Heptanoate is not an inhibitor of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A4. Heptanoate and BHP are not CYP substrates nor UGT substrates. Heptanoate increases the unbound fraction of valproic acid by approximately 2-fold.

***Adverse Effects*:**
The most common adverse reactions to DOJOLVI reported in the pooled safety population of Study 1 and Study 2 were gastrointestinal (GI)-related, and included abdominal pain (abdominal discomfort, abdominal pain, abdominal distension, abdominal pain upper, GI pain) [60%], diarrhea [44%], vomiting [44%], and nausea [14%].

Contraindications:

- None

Warnings and Precautions:

- Feeding Tube Dysfunction: Regularly monitor the tube to ensure proper functioning and integrity.

- Intestinal Malabsorption in Patients with Pancreatic Insufficiency: Low or absent pancreatic enzymes may reduce absorption of DOJOLVI. Avoid administration of DOJOLVI in patients with pancreatic insufficiency

Monitoring:

- Monitor patients' total caloric intake during dosage titration, especially in patients with gastrointestinal adverse reactions, and adjust all components of the diet as needed.

Evidence Table of Clinical Studies:

Table 1. Clinical data for Dojolvi

	Clinical Study #3 (NCT01379625): Gillingham et al, 2017
Study Type*	A double blinded, randomized controlled trial
Interventions and Sample Size	32 patients were randomized to receive either of the following for 4 months: • Triheptanoin (n= 16) • Trioctanoin (n = 16)
Populations	▪ Confirmed diagnosis of VLCAD, CPT II, TFP, or LCHAD deficiency ▪ Evidence of at least one significant episode of rhabdomyolysis ▪ 7 years of age or older (range: 7−64 years of age) ▪ 62.5% female; 37.5% male ▪ Exclusion criteria: Hgb < 10 g/dL, peripheral neuropathy that limits ability to complete treadmill studies, inclusion in another research study that alters macronutrient intake, pregnant females, and history of myocardial infarction or cardiovascular disease ▪ Subjects consumed approximately 16% and 14% of total caloric intake from triheptanoin and trioctanoin, respectively ▪ Baseline resting left ventricular ejection fraction was normal for both treatment groups
General Summary: Efficacy	Primary outcomes: Changes in total energy expenditure (TEE), cardiac function by echocardiogram, exercise tolerance, and phosphocreatine recovery following acute exercise Secondary outcomes: Body composition, blood biomarkers, and adverse events, including incidence of rhabdomyolysis Patients in the triheptanoin group increased left ventricular ejection fraction by 7.4% (P = .046) compared with patients taking trioctanoin. • Patients had similar mean changes from baseline in wall mass on resting echocardiogram and similar maximal heart rates on treadmill ergometry. • Five patients experienced 7 events of rhabdomyolysis in the triheptanoin group, and 4 patients experienced 7 events of rhabdomyolysis in the trioctanoin group. • No differences were observed between triheptanoin and trioctanoin groups in blood markers of metabolism including glucose, insulin, lactate, total serum, ketones, acylcarnitines, and serum-free fatty acid concentrations

	Clinical Study #3 (NCT01379625): Gillingham et al, 2017
General Summary: Safety	The most common adverse reactions (>10%) include abdominal pain, diarrhea, vomiting, and nausea. In Study 3, there were no differences in adverse reactions reported in patients receiving triheptanoin and trioctanoin, and the adverse reactions were similar to those reported in Study 1 and Study 2.
Comments	▪ Showed efficacy in LVEF vs active comparator ▪ No major difference in other endpoints ▪ No new safety issues identified ▪ Showed meaningful improvement in clinical events at week 78 vs pretreatment baseline in a phase 2 trial
Grade^	▪ B

*Study type abbreviations: CC=Case-control study, COH=Cohort study, CS=Case study, DB=double blind, EPI=Epidemiologic study, META=Meta-analysis, NRCT=Nonrandomized clinical trial, OBS=Observational study, PC=placebo-controlled, PG=parallel-group, RCT=randomized trial, XO=crossover [if not listed, please type in under study type]
^A=Useful, B=Possibly useful, C=Possible to uncertain usefulness, U=Uncertain validity and/or usefulness, X=Not useful
(For further information, please refer to the document Grading of Clinical Evidence; NA=Not applicable. [Disclaimer: Grade the study if able to pull the literature]

Special Populations:

Pregnancy/breastfeeding/geriatric: no data available

Cost and/or Utilization Data of Similar Treatment Options:

Table 2: _Dojolvi___® Pricing

Drug	Strength	WAC/unit	Package size	WAC/Package
Dojolvi	8.3kcal/ml	$9.75/ml	500ml	$4,875/package

Place in Therapy:

[Comparison Table: *If comparing new product to existing products as well as similar product in the pipeline;*

- Advantages vs disadvantages (consider including if able-not all inclusive): efficacy, indications, dosage frequency, route of administration, pharmacology, metabolism, drug-interactions, adverse effects, monitoring parameters, and/or storage
- Delete non-pertinent items under the comparison table]

Table 5. Comparison of [new product] and [Existing product(s) and/or another similar drug in the pipeline]

	Dojolvi	N/A
Meet an Unmet Medical Need[1]	☒ Yes There are no other FDA approved drugs for the treatment of LC-FAOD	

Definitions

1. Unmet medical need - Medical need that is not addressed adequately by an existing therapy (examples: a) No available therapy for condition exists b) If available therapy for the condition exists i) New therapy has improved effects on serious outcomes, ii) Similar benefits to alternative therapies while avoiding serious toxicity).[IV]
2. Efficacy – The extent to which an intervention produces a beneficial result under ideal conditions (i.e clinical trials). [III]

3. Safety – Substantive evidence of an absence of harm (examples: clinical adverse events (disease, signs, and symptoms).[II]
4. Cost-effectiveness – The cost and health benefits associated with the use of the drug therapies.[I]
5. Adherence - The consistence and accuracy with which a patient will follow a recommended medical regimen (examples of factors that may affect adherence: frequency of administration, adverse events, cost of drug).[I]

References

I. Berger ML, Bigefors K, Hedblom EC, Pashos CL, Torrance GW. Health care cost, quality, and outcomes: ISPOR book of terms. Lawrenceville, NJ: International Society for Pharmacoeconomics and Outcomes Research; 2003.
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Recommendation:

KY MCD: T2 w/ PA

References:

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2. Dojolvi [prescribing information]. Novato, CA; Ultragenyx Pharmaceuticals Inc. June 2020.
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4. Gillingham MB, Heitner SB, Martin J, et al. Triheptanoin versus trioctanoin for long- chain fatty acid oxidation disorders: a double blinded, randomized controlled trial. J
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Humana Pharmacy Solutions

Clinical Review – Fintepla® (fenfluramine)

***Company*:** Zogenix, Inc.
Current Status: FDA Approved June 26, 2020,
Potential Launch: Launched July 11, 2020
Therapeutic Category: Anticonvulsant
Pharmacologic Category: Anticonvulsant, Miscellaneous; Serotonin 5HT-2 Receptor Agonist
Similar Drugs: N/A
Route of Administration: Oral
Dosage Forms: Oral solution

Indications: Dravet Syndrome-associated Seizures

Dosage and Administration:
- Initial: 0.1 mg/kg twice daily; may increase based on response and tolerability after 7 days to 0.2 mg/kg twice daily; may further increase based on response and tolerability after 7 days to 0.35 mg/kg twice daily
- Maximum dose: 26 mg/day
- Dose can be administered with or without food using a calibrated oral syringe

Background:
Dravet Syndrome (DS), previously known as severe myoclonic epilepsy of infancy (SMEI), is a life-threatening, rare and chronic form of genetic epilepsy. DS is a rare disorder affecting 1 in 15,700 to 1 in 40,000 live births and is commonly caused by gene mutations. The most common cause of DS is due to a mutation in the voltage-gated sodium channel alpha-1 subunit (*SCN1A*). However, a mutation at this site is not required for diagnosis. Other genes have been linked to DS (*PCDH19, SCN1B, GABRA1, STXBP1, CHD2, SCN2A, HCN1, KCNA2, and GABRG2)* as well as dysfunction of inhibitory interneurons. DS is described by severe and unrelenting seizures despite medical treatment. Clinical manifestations of this disease include refractory epilepsy characterized by multiple different seizure types, neurodevelopmental delay and neurological disability that begin after seizure onset, and cognitive and motor system dysfunction persisting into adulthood.

Pharmacology:
- Mechanism of Action: Unknown; Fenfluramine and norfenfluramine (metabolite) increase extracellular levels of serotonin through interaction with serotonin transporter proteins and exhibit activity at serotonin 5HT-2 receptors.
- Pharmacodynamics: Cardiac Electrophysiology; at a dose 4 times the maximum recommended dose, FINTEPLA did not prolong the QT interval when tested in an adult population.

Pharmacokinetics:
- Absorption: Tmax of 4 to 5 hours at steady state; bioavailability of 68-74% with no effect of food on the pharmacokinetics of fenfluramine or its metabolites.
- Distribution: The geometric mean (CV%) apparent volume of distribution (Vz/F) of fenfluramine is 11.9 (16.5%) L/kg following oral administration of FINTEPLA in healthy subjects. Fenfluramine is 50% bound to human plasma proteins in vitro and binding is independent of drug concentrations.
- Elimination:
    - Metabolism: 75% is metabolized primarily by CYP1A2, CYP2B6, and CYP2D6 to active metabolite norfenfluramine; CYP2C9, CYP2C19, and CYP2D6 are involved to a minor extent. Norfenfluramine is deaminated and oxidized to inactive metabolites.

  - Excretion: >90% of fenfluramine is excreted in the urine as fenfluramine, norfenfluramine, or other metabolites with fenfluramine and norfenfluramine accounting for less than 25% of the total; less than 5% is found in feces.
- Plasma Half-Life (hrs): 20 hours
- Cmax: 68.0 (41%) ng/mL
- $AUC_{0\text{-}24h}$: 1390 (44%) ng*h/mL

Drug Interactions:
- Stiripentol plus clobazam; coadministraton increases fenfluramine plasma concentrations and decreases its metabolite, norfenfluramine.
- Strong CYP1A2 and CYP2B6 inducers; coadministration with rifampin or a strong CYP1A2 and CYP2B6 inducer will decrease fenfluramine plasma concentrations.
- Serotonin receptor antagonists; cyproheptadine and potent 5-HT1A, %-HT1D, 5-HT2A, and 5-HT2C serotonin receptor antagonists may decrease the efficacy of fenfluramine.
- Serotonergic drugs; concomitant administration of FINTEPLA and drugs (e.g., SSRIs, SNRIs, TCAs, MAOIs, trazodone, etc.), over the counter medications (e.g., dextromethorphan), or herbal supplements (e.g., St. John's Wort) that increase serotonin may increase the risk of serotonin syndrome.

***Adverse Effects*:**
- Decreased appetite
- Somnolence
- Sedation
- Lethargy
- Diarrhea
- Constipation
- Abnormal echocardiogram
- Fatigue
- Malaise
- Asthenia
- Ataxia
- Balance disorder
- Gait disturbance
- Blood pressure increased
- Drooling
- Salivary hypersecretion
- Pyrexia
- Upper respiratory tract infection
- Vomiting
- Decreased weight
- Fall
- Status epilepticus

Contraindications:
- Hypersensitivity to fenfluramine or any component of the formulation
- Concomitant use with or within 14 days of monoamine oxidase inhibitors

Warnings and Precautions:
- <u>Pulmonary arterial hypertension [Black Boxed Warning]:</u> There is an association between serotonergic drugs with 5-HT2B receptor agonist activity, including fenfluramine, and pulmonary arterial hypertension. Echocardiogram assessments are required before, during, and after treatment with fenfluramine. The benefits vs the risks of initiating or continuing fenfluramine must be considered, based on echocardiogram findings. Because of the risks of pulmonary arterial hypertension, fenfluramine is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the FINTEPLA REMS.
- <u>Valvular heart disease [Black Boxed Warning]:</u> There is an association between serotonergic drugs with 5-HT2B receptor agonist activity, including fenfluramine, and valvular heart disease. Echocardiogram assessments are required before, during, and after treatment with fenfluramine. The benefits vs the risks of initiating or continuing fenfluramine must be considered, based on echocardiogram findings. Because of the risks of valvular heart disease, fenfluramine is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the FINTEPLA REMS.
- Fenfluramine may result in decreases in appetite and weight. In clinical trials in patients ≥2 years and <18 years with Dravet syndrome, decreased appetite was reported in 37% of patients receiving fenfluramine vs 8% receiving placebo. By the end of a 14- to 15-week clinical trial treatment period, measured weight had

decreased by ≥7% from baseline in 19% of patients; weight decrease appeared to be dose-related, and most patients resumed expected growth-associated weight gain by the end of the 3-year open-label extension study. Monitor growth and weight regularly during treatment with fenfluramine; consider dose reduction if weight decreases.

Monitoring:

- Valvular heart disease; prior to starting treatment, patients must undergo an echocardiogram to evaluate for valvular heart disease. Echocardiograms should be repeated every 6 months, and once 3-6 months post-treatment with FINTEPLA.
- Pulmonary Arterial Hypertension; prior to starting treatment, patients must undergo an echocardiogram to evaluate for pulmonary arterial hypertension. Echocardiograms should be repeated every 6 months, and once 3-6 months post-treatment with FINTEPLA.
- Suicidal thoughts or behaviors: prior to initiation evaluate balance of risk for development with risk of untreated illness; monitor for the emergence or worsening of depression, suicidal thoughts or behavior, or any unusual changes in mood or behavior during treatment
- Signs and symptoms of serotonin syndrome including mental status changes, autonomic instability, neuromuscular signs, and gastrointestinal symptoms

Evidence Table of Clinical Studies:

Table 1. Clinical data for Fintepla.

	[Clinical Study #1] Lagae L, et al. 2019	**[Clinical Study #2] Nabbout MD, et al. 2019**
Study Type*	DB, PC, RCT	DB, PC, RCT
Interventions and Sample Size	N=119; ▪ 0.7 mg/kg/day; 34 ▪ 0.2 mg/kg/day; 39 ▪ Placebo; 37	N=85; ▪ 0.4 mg/kg/day; 36 ▪ Placebo; 41
Populations	▪ 2 to 18 years of age ▪ Clinical diagnosis of Dravet syndrome ▪ Inadequately controlled on at least 1 AED or another antiseizure treatment including: ○ Vagal nerve stimulation ○ Ketogenic diet ▪ Patients must have had at least 4 convulsive seizures in a 4-week period during the 12 weeks before entering the screening period ▪ Exclusion: ○ PAH ○ History of cardiovascular or cerebrovascular disease ○ Current treatment with centrally acting anorectic agents, monoamine oxidase inhibitors, or any centrally acting agent with serotonin agonist or antagonist properties, or cannabinoid products	▪ 2 to 18 years of age ▪ Clinical diagnosis of Dravet syndrome ▪ Inadequately controlled on at least 1 AED or another antiseizure treatment including: ○ Vagal nerve stimulation ○ Ketogenic diet ▪ Patients who were receiving stiripentol and either clobazam, valproate, or both ▪ Free of cardiovascular disease ▪ Exclusion: ○ PAH ○ Current condition or history of cardiovascular or cerebrovascular disease ○ Concomitant treatment with modulators of serotonergic activity AEDs with sodium channel antagonist activity, or cannabinoid products

	[Clinical Study #1] Lagae L, et al. 2019	[Clinical Study #2] Nabbout MD, et al. 2019
	○ Treatment with stiripentol within 21 days before screening	
General Summary: Efficacy	▪ Reduction in mean convulsive seizure frequency (MCSF) compared with placebo: ○ Fenfluramine 0.7 mg/kg/day 62.3% greater reduction compared with placebo (95% CI 47.7–72.8, p<0.0001) ○ Fenfluramine 0.2 mg/kg/day 32.4% reduction in mean MCSF compared with placebo (95% CI 6.2–52.3, p=0.0209)	▪ Reduction in MCSF compared with placebo: ○ Oral fenfluramine provided a 54.0% (95% CI, 35.6%-67.2%; P < .001) greater reduction in mean monthly convulsive seizure frequency than placebo ▪ 54% of patients demonstrated a clinically meaningful (≥50%) reduction in monthly convulsive seizure frequency vs 5% with placebo (*P* < .001) ▪ The median (range) longest seizure-free interval was 22 (3.0-105.0) days with fenfluramine and 13 (1.0-40.0) days with placebo (*P* = .004)
General Summary: Safety	Most common adverse effects included: ▪ Decreased appetite (38% vs 20% vs 5%) ▪ Diarrhea (18% vs 31% vs 8%) ▪ Nasopharyngitis (18% vs 10% vs 12%) ▪ Lethargy (18% vs 10% vs 5%) ▪ Somnolence (10% vs 15% vs 8%) ▪ Pyrexia (5% vs 18% vs 20%)	Most common adverse effects included: ▪ Decreased appetite (44% vs 11%) ▪ Pyrexia (26% vs 9%) ▪ Fatigue (26% vs 5%) ▪ Diarrhea (23% vs 7%)
Comments	▪ Fenfluramine demonstrated efficacy in a 3rd/4th line setting ▪ Label indicates can be used as monotherapy but no evidence of efficacy in 1st line setting ▪ Each trial had small treatment numbers ▪ Trial durations were very short – long-term safety and efficacy has yet to be established	
Grade^	▪ B	▪ B

*Study type abbreviations: CC=Case-control study, COH=Cohort study, CS=Case study, DB=double blind, EPI=Epidemiologic study, META=Meta-analysis, NRCT=Nonrandomized clinical trial, OBS=Observational study, PC=placebo-controlled, PG=parallel-group, RCT=randomized trial, XO=crossover [if not listed, please type in under study type]
^A=Useful, B=Possibly useful, C=Possible to uncertain usefulness, U=Uncertain validity and/or usefulness, X=Not useful
(For further information, please refer to the document Grading of Clinical Evidence; NA=Not applicable. [Disclaimer: Grade the study if able to pull the literature]

Special Populations:

[Pediatric Use, Geriatric Use, Renal Impairment, Hepatic Impairment-Use Only Pertinent Population]

Cost and/or Utilization Data of Similar Treatment Options:

Table 2: Dravet Syndrome Pricing

Drug	Strength	WAC/unit	Package size	WAC/Package
Fintepla	2.2mg/ml	$42.6/ml		$15,336/package

Table 4: Humana Tiering for Similar Treatment Options

	Epidiolex 100mg/ml oral solution
KY Medicaid	T2 w/ PA

Place in Therapy:

Table 5. Comparison of Fintepla and Epidiolex

	Fintepla	Epidiolex
Meet an Unmet Medical Need[1]	☒ No, there are multiple supported agents in a 3rd/4th line setting with comparable efficacy	
Comparable Efficacy[2]	☒ Fintepla has similar efficacy relative to Epidiolex **Comment:** Median convulsive seizure reduction and those reaching 50% reduction in convulsive seizures was similar in trials	
Comparable Safety[3]	☒ Epidiolex would like have similar safety relative to Epidiolex **Comment:** Both agents have safety concerns. Fintepla has cardiovascular black box warning due to past safety issues in a previous formulation. These were not evident in the clinical trials for DS. Epidiolex has hepatic enzyme elevation concerns upon initiation of therapy.	
Comparable Cost-Effectiveness[4]	☒ Epidiolex is more cost-effective relative to Fintepla **Comment:** Epidiolex is estimated to cost less annually than Fintepla therapy	
Adherence[5]	☒ Members taking Fintepla would likely achieve a similar adherence rate relative to Epidiolex **Comment:** Both are taken twice daily and would be anticipated to have similar adherence	
Advantages	▪ No hepatic concerns	▪ Cost
Disadvantages	▪ Cost ▪ Past significant safety issues ▪ Extensive REMS	▪ Elevated liver transaminases upon initiation
Comments	▪ Both newer agents show efficacy in 3rd/4th line settings ▪ Efficacy is comparable between agents ▪ Fintepla uptake will likely be limited due to extensive REMS/Monitoring requirement	

Definitions

1. Unmet medical need - Medical need that is not addressed adequately by an existing therapy (examples: a) No available therapy for condition exists b) If available therapy for the condition exists i) New therapy has improved effects on serious outcomes, ii) Similar benefits to alternative therapies while avoiding serious toxicity).[IV]
2. Efficacy – The extent to which an intervention produces a beneficial result under ideal conditions (i.e clinical trials). [III]
3. Safety – Substantive evidence of an absence of harm (examples: clinical adverse events (disease, signs, and symptoms).[II]
4. Cost-effectiveness – The cost and health benefits associated with the use of the drug therapies.[I]
5. Adherence - The consistence and accuracy with which a patient will follow a recommended medical regimen (examples of factors that may affect adherence: frequency of administration, adverse events, cost of drug).[I]

References

I. Berger ML, Bigefors K, Hedblom EC, Pashos CL, Torrance GW. Health care cost, quality, and outcomes: ISPOR book of terms. Lawrenceville, NJ: International Society for Pharmacoeconomics and Outcomes Research; 2003.

II. Chou R, Aronson N, Atkins D. Chapter 7. Assessing harms when comparing medical interventions. In: methods guide for effectiveness and comparative effectiveness reviews. AHRP Publication No. 10(11)-EHC063-EF. March 2011; http://www.effectivehealthcare.ahrq.gov. Accessed May 2012.

III. Glossary of terms in the Cochrane Collaboration. Version 4.2.5. Updated May 2005. http://www.cochrane.org/glossary. Accessed May 2012.

IV. U.S. Food and Drug Administration. FDA guidance for industry on Fast Track Drug Development Programs: Designation, Development, and Application Review. January 2006. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079736.pdf. Accessed May 2012.

Recommendation:

KY MCd: non-par (recommend NF when par)
QL: 360 ml per 30 days
Age min: 2 years

References:

1. Andrade DM, Nascimento FA. UptoDate. Dravet syndrome: Gentetics, clinical features, and diagnosis. Accessed August 10, 2020. Available at: https://www.uptodate.com/contents/dravet-syndrome-genetics-clinical-features-and-diagnosis?search=dravet%20syndrome&source=search_result&selectedTitle=2~34&usage_type=default&display_rank=2
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Humana Pharmacy Solutions

Clinical Review – Isturisa® (osilodrostat)

***Company*:** Recordati Rare Disease, Inc.
Current Status: FDA Approved March 6, 2020
Potential Launch: FDB Launch April 15, 2020
Therapeutic Category: Cushing's disease
Pharmacologic Category: Cortisol Synthesis Inhibitor
Similar Drugs: Lysodren (mitotane), ketoconazole
Route of Administration: Oral
Dosage Forms: 1 mg, 5 mg, and 10 mg tablets

Indications: Treatment of adult patients with Cushing's disease for whom pituitary surgery is not an option or has not been curative

Dosage and Administration:
- Correct hypokalemia and hypomagnesemia, and obtain baseline ECG prior to starting
- Initiate dosage at 2 mg orally twice daily
- Titrate dosage by 1 to 2 mg twice daily, no more frequently than every 2 weeks based on rate of cortisol changes, individual tolerability and improvement in signs and symptoms
- If a patient tolerates Isturisa dosage of 10 mg twice daily and continues to have elevated 24-hour urine free cortisol (UFC) levels above upper normal limit, the dosage can be titrated further by 5 mg twice daily every 2 weeks
- Maximum recommended daily dosage is 30 mg twice daily

Background:
Cushing's disease is a rare disease that occurs when an adenoma forms in the pituitary gland, causing excessive release of ACTH and, subsequently, elevated production of cortisol. Prolonged exposure and increased cortisol levels results in the signs and symptoms of Cushing's disease which include weight gain, hirsutism, hyperglycemia, hypertension, and a round face or "moon face." The Endocrine Society Guidelines for the Treatment of Cushing's Syndrome recommend first-line treatment for endogenous Cushing's syndrome to be the removal of the tumor unless surgery is not possible or is unlikely to address excess cortisol. Medical treatment is typically used as second-line therapy in patients for whom surgery is not possible or was non-curative. The Endocrine Society Guidelines recommend the use of steroidogenesis inhibitors as second-line treatment after transsphenoidal selective adenomectomy in patients with Cushing's disease, either with or without radiation therapy or radiation surgery.

Pharmacology:
Osilodrostat is a cortisol synthesis inhibitor. It inhibits 11beta-hydroxylase (CYP11B1), the enzyme responsible for the final step of cortisol biosynthesis in the adrenal gland.

Pharmacokinetics:
Metabolism/Elimination: Multiple CYP enzymes (CYP3A4, CYP2B6, and CYP2D6) and UDP-glucuronosyltransferases contribute to osilodrostat metabolism and no single enzyme contributes greater than 25% to the total clearance. Eliminated in the urine (90.6%), with only a minor amount eliminated in the feces (1.58%).
Plasma Half-Life (hrs): 4 hrs

Drug Interactions:

- CYP3A4 Inhibitor: Reduce the dose by half with concomitant use of a strong CYP3A4 inhibitor
- CYP3A4 and CYP2B6 Inducers: A dosage increase may be needed if used concomitantly with strong CYP3A4 and CYP2B6 inducers. A reduction in dosage may be needed if strong CYP3A4 and CYP2B6 inducers are discontinued while using Isturisa (osilodrostat).

***Adverse Effects*:**

- Most common adverse reactions (incidence >20%) are adrenal insufficiency, fatigue, nausea, headache, and edema.

Contraindications:

- None

Warnings and Precautions:

- Hypocortisolism: Isturisa (osilodrostat) lowers cortisol levels and can lead to hypocortisolism and sometimes life-threatening adrenal insufficiency. Lowering of cortisol can cause nausea, vomiting, fatigue, abdominal pain, loss of appetite, dizziness. Significant lowering of serum cortisol may result in hypotension, abnormal electrolyte levels, and hypoglycemia
- QTc Prolongation: Isturisa (osilodrostat) is associated with a dose-dependent QT interval prolongation (maximum mean estimated QTcF increase of up to 5.3 ms at 30 mg), which may cause cardiac arrhythmias
- Elevations in Adrenal Hormone Precursors and Androgens: Isturisa (osilodrostat) blocks cortisol synthesis and may increase circulating levels of cortisol and aldosterone precursors (11-deoxy cortisol and 11-deoxycorticosterone) and androgens. Elevated 11-deoxycorticosterone levels may activate mineralocorticoid receptors and cause hypokalemia, edema and hypertension. Accumulation of androgens may lead to hirsutism, hypertrichosis and acne (in females).

Monitoring:

- Monitor patients closely for hypocortisolism and potentially life-threatening adrenal insufficiency
- Monitor for hypokalemia, worsening of hypertension, edema, and hirsutism
- Perform baseline electrocardiogram in all patients

Evidence Table of Clinical Studies:

Table 1. Clinical data for Isturisa®

	Efficacy and Safety of Osilodrostat in Patients with Cushing's Disease (LINC 3): A Multicentre Phase III Study with a Double Blind, Randomised Withdrawal Phase [Pivonello/2020]
Study Type*	Multicenter, open-label, four-period, phase III trial ▪ Period 1: 12-week open-label, single-arm, dose escalation period ▪ Period 2: 12-week open-label, single-arm, stable treatment period ▪ Period 3: 8 week randomized, double-blind, placebo controlled withdrawal period ▪ Period 4: 12-week open-label, single-arm treatment period
Interventions and Sample Size	▪ Period 1 (12 weeks): ○ N= 137

	Efficacy and Safety of Osilodrostat in Patients with Cushing's Disease (LINC 3): A Multicentre Phase III Study with a Double Blind, Randomised Withdrawal Phase [Pivonello/2020]
	○ Arm 1: All patients initiated osilodrostat 2 mg PO BID with dose adjustments every two weeks up to week 12 based on efficacy and tolerability (range 1-30 mg BID). The dose was increased if mUFC was >ULN and throughout the study the dose was decreased if mUFC was below ULN or was low normal in patients with symptoms of hypocortisolism or adrenal insufficiency. ▪ Period 2 (12 weeks): ○ N= 130 ○ Arm 1: Patients continued their individual therapeutic dose established during period 1. Patients were considered to be responders and eligible to enter the Randomization Withdrawal phase (Period 3) if they did not require further dose increase, tolerated the drug, and had a mUFC ≤ ULN at the end of Period 2. ▪ Period 3 (8 weeks): ○ N= 71 ○ Arm 1: 36 patients randomized 1:1 to remain on their assigned treatment dose (osilodrostat 1-30 mg PO BID) ○ Arm 2: 35 patients randomized 1:1 to placebo ○ Patients were stratified at randomization according to dose received at Week 24 (≤ 5 mg twice daily vs 5 mg twice daily) and history of pituitary irradiation (yes/no) ▪ Period 4 (12 weeks): ○ N= 117 ○ Arm 1: Patients who were not eligible for randomization (n=47), patients who were considered responders during period 3 (n=41), and patients considered non-responders (n=29) during period 3 received open-label osilodrostat at their therapeutic dose until week 48.
Populations	▪ **Key Inclusion Criteria:** 18-75 years of age, confirmed active persistent/recurrent Cushing's disease following pituitary surgery and/or irradiation or de novo patients who were not surgical candidates, and evidence of pituitary origin for the excess ACTH ▪ **Key Exclusion Criteria:** Stereotactic radiosurgery in prior 2 years, conventional radiotherapy in the prior 3 years, pituitary surgery in the previous 29 days, treatment with another investigational agent within 30 days or 5 half-lives (whichever was longer), history of hypersensitivity to osilodrostat or therapies of a similar chemical class, and presence or high-risk of compression of optic chiasm. ▪ **Baseline Characteristics:** The median age was 40.0 years and 106 (77%) participants were female. Baseline characteristics were generally well balanced between the treatment groups during period 3, although the median of the mUFC

	Efficacy and Safety of Osilodrostat in Patients with Cushing's Disease (LINC 3): A Multicentre Phase III Study with a Double Blind, Randomised Withdrawal Phase [Pivonello/2020]
	was higher in patients in the osilodrostat group compared to placebo. However, mUFC was similar between the two groups at the start of period 3.
General Summary: Efficacy	▪ **Key Primary Endpoint:** The proportion of patients maintaining complete response (mUFC≤ULN) without a dose increase during the randomized withdrawal period at end of period 3. ○ **Results:** At the end of period 3, statistically significantly more patients continuing to receive osilodrostat than those receiving placebo achieved complete response by maintaining mUFC ≤ULN without a dose increase (31/36 [86.1%] vs. 10/34 [29.4%]; OR 13.7 [95% CI 3.7-53.4], P<0.001). ▪ **Key Secondary Endpoint:** The proportion of patients with mUFC≤ULN at end of period 2 without dose-up titration during weeks 13-24. ○ **Results:** At the end of period 2, 72/137 (52.6% [95% CI 43.9-61.1]) of all patients achieved complete response by maintaining mUFC≤ULN without a dose increase after week 12.
General Summary: Safety	▪ Most frequently reported adverse events in the study included nausea (42%), headache (34%), fatigue (28%), and adrenal insufficiency (28%) ▪ The most frequently reported grade 3-4 adverse events included hypokalemia (n=7), adrenal insufficiency (n=6), glucocorticoid deficiency (n=5), headache (n=4), vomiting (n=4) ▪ No male patients experienced signs or symptoms related to increased testosterone or estrogen. In female patients, hirsutism (8.8%), acne (8.8%), and hypertrichosis (0.7%) were reported; all were grade 1 or 2 and none led to study discontinuation ▪ QTc prolongation was reported in 5 patients with all events being non-serious, and one leading to discontinuation ▪ 19 patients discontinued treatment by data cut-off due to an adverse event, most commonly because of adrenal insufficiency or change in pituitary tumor
Comments	▪ No enrolled patients were >70 years of age ▪ During the randomized, double-blind withdrawal phase, mean (SD) osilodrostat dose was 10.0 (9.6) mg/day
Grade^	▪ B

*Study type abbreviations: CC=Case-control study, COH=Cohort study, CS=Case study, DB=double blind, EPI=Epidemiologic study, META=Meta-analysis, NRCT=Nonrandomized clinical trial, OBS=Observational study, PC=placebo-controlled, PG=parallel-group, RCT=randomized trial, XO=crossover [if not listed, please type in under study type]

^A=Useful, B=Possibly useful, C=Possible to uncertain usefulness, U=Uncertain validity and/or usefulness, X=Not useful

(For further information, please refer to the document Grading of Clinical Evidence; NA=Not applicable. [Disclaimer: Grade the study if able to pull the literature]

Special Populations:

- **Pediatric Use**: The safety and effectiveness of Isturisa (osilodrostat) in pediatric patients have not been established.
- **Geriatric Use**: Of the 167 patients in clinical trials, 10 (6%) were 65 years and older. There were no patients above 70 years of age. Based on available data, no dose adjustment is required.
- **Renal Impairment**: No dose adjustment is needed in patients with impaired renal function. Osilodrostat exposure was similar in three renal functional groups: normal, severe, and ESRD. In patients with moderate to severe renal impairment, UFC levels should be interpreted with caution due to reduced UFC excretion.
- **Hepatic Impairment**: Dose adjustment is not required in patients with mild hepatic impairment (Child-Pugh A) but is required for patients with moderate or severe hepatic impairment (Child-Pugh B or C). There was a trend of increasing AUC in moderate and severe hepatic impaired subjects compared to normal subjects. Exposures of osilodrostat in the mild hepatic impairment group were similar to those in the normal group. More frequent monitoring of adrenal function may be required during dose titration in all patients with hepatic impairment.
- **Lactation**: There are no available data on the presence of osilodrostat in human or animal milk, the effects on the breastfed infant, or the effects on milk production. Because of the potential for serious adverse reactions (such as adrenal insufficiency) in the breastfed infant, advise patients that breastfeeding is not recommended during treatment with Isturisa (osilodrostat) and for one week after the final dose.

Cost and/or Utilization Data of Similar Treatment Options:

Table 2: Isturisa® Pricing

Drug	Strength	WAC/unit	Package size	WAC/Package
Isturisa	1 mg	110.00000	20 tablets	2200.00000
Isturisa	1 mg	110.00000	60 tablets	6600.00000
Isturisa	2 mg	400.00000	20 tablets	8000.00000
Isturisa	2 mg	400.00000	60 tablets	24000.0000
Isturisa	10 mg	475.00000	20 tablets	9500.00000
Isturisa	10 mg	475.00000	60 tablets	28500.0000

Table 4: Humana Tiering for Similar Treatment Options

	Ketoconazole 200 mg	Lysodren (mitotane)
KY Medicaid	T1	T2

Place in Therapy:

Table 5. Comparison of Isturisa (osilodrostat) and Lysodrine (mitotane)

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Clinical Review – Isturisa® (osilodrostat)

	Isturisa (osilodrostat)	Lysodren (mitotane)
Meet an Unmet Medical Need[1]	☒ No, Isturisa (osilodrostat) does not meet an unmet medical need. While Isturisa (osilodrostat) offers a novel mechanism of action for the treatment of Cushing's Disease in patients for whom pituitary surgery is not an option or has not been curative, several steroidogenesis inhibitors are already available and recommended by current guidelines.	
Comparable Efficacy[2]	☒ Isturisa (osilodrostat) has similar efficacy relative to Lysodren (mitotane) **Comment: Limited evidence for Lysodren (mitotane) use in CD. In a retrospective study of 76 CD patients, 72% achieved 24 hr-UFC normalization.**	
Comparable Safety[3]	☒ Isturisa (osilodrostat) would likely be more safe relative to Lysodren (mitotane) **Comment: Lysodren (mitotane) can cause fetal harm and has a black box warning for adrenal crisis in the setting of shock or severe trauma with impaired response to shock. There are no available data on osilodrostat use in pregnant women.**	
Adherence[5]	☒ Members taking Isturisa (osilodrostat) would likely achieve a greater adherence rate relative to Lysodren (mitotane) **Comment: Twice daily dosing with Isturisa (osilodrostat) compared to three to four times daily dosing with Lysodren (mitotane)**	
Advantages	▪ Oral ▪ Twice daily dosing ▪ Lack of black box warnings	▪ Oral
Disadvantages	▪ Long-term efficacy and safety has not been established ▪ Potential for clinically significant drug interactions ▪ Risk of QTc prolongation	▪ Three to four times daily dosing ▪ Potential for clinically significant drug interactions ▪ Evidence of fetal harm ▪ Black box warning
Comments	▪ The safety and efficacy of Isturisa (osilodrostat) are currently being confirmed in a second phase III trial (LINC-4) with an estimated completion date of January 2021	

Definitions

1. Unmet medical need - Medical need that is not addressed adequately by an existing therapy (examples: a) No available therapy for condition exists b) If available therapy for the condition exists i) New therapy has improved effects on serious outcomes, ii) Similar benefits to alternative therapies while avoiding serious toxicity).[IV]
2. Efficacy – The extent to which an intervention produces a beneficial result under ideal conditions (i.e clinical trials). [III]
3. Safety – Substantive evidence of an absence of harm (examples: clinical adverse events (disease, signs, and symptoms).[II]
4. Cost-effectiveness – The cost and health benefits associated with the use of the drug therapies.[I]
5. Adherence - The consistence and accuracy with which a patient will follow a recommended medical regimen (examples of factors that may affect adherence: frequency of administration, adverse events, cost of drug).[I]

References

I. Berger ML, Bigefors K, Hedblom EC, Pashos CL, Torrance GW. Health care cost, quality, and outcomes: ISPOR book of terms. Lawrenceville, NJ: International Society for Pharmacoeconomics and Outcomes Research; 2003.

II. Chou R, Aronson N, Atkins D. Chapter 7. Assessing harms when comparing medical interventions. In: methods guide for effectiveness and comparative effectiveness reviews. AHRP Publication No. 10(11)-EHC063-EF. March 2011; http://www.effectivehealthcare.ahrq.gov. Accessed May 2012.
III. Glossary of terms in the Cochrane Collaboration. Version 4.2.5. Updated May 2005. http://www.cochrane.org/glossary. Accessed May 2012.
IV. U.S. Food and Drug Administration. FDA guidance for industry on Fast Track Drug Development Programs: Designation, Development, and Application Review. January 2006. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079736.pdf. Accessed May 2012.

Recommendation:

KY Medicaid: NF
QL: 1 mg: 240/30, 5 mg: 60/30, 10 mg: 180/30

References:

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Clinical Review – Qinlock® (ripretinib)

***Company*:** Deciphera Pharmaceuticals
Current Status: Approved 5/15/2020
Potential Launch: Week of 5/23/2020
Therapeutic Category: Oncology - Antineoplastic Agent
Pharmacologic Category: Tyrosine Kinase Inhibitor (TKI)
Similar Drugs: Ayvakit (avapritinib), Gleevec (imatinib), Stivarga (regorafenib), Sutent (sunitinib)
Route of Administration: Oral
Dosage Forms: 50mg oral tablet

Indications: Adult patients with advanced gastrointestinal stromal tumors (GIST) who have received prior treatment with 3 or more TKIs, including imatinib.

Dosage and Administration: 150mg by mouth daily until disease progression or unacceptable toxicity.

Background:
Gastrointestinal stromal tumors (GIST) are a rare type of sarcoma with 4,000 – 6,000 cases per year in the United States. Approximately 50% of patients present with advanced disease, which has a 5-year survival rate of 52%. The TKI imatinib is used in initial management of GIST. However, over time mutations can arise that cause disease resistance to imatinib, necessitating therapy escalation. Currently, three lines of TKI therapy exist (imatinib -> sunitinib -> regorafenib), however once progression occurs on 3rd line therapy, there is no agent with a 4th line indication.

Pharmacology:
Switch-control tyrosine kinase inhibitor. Locks kinase in inactive state (preventing cell proliferation) through a dual mechanism of action that binds to both the switch pocket and activation loop of the kinase. This inhibits both KIT and PDGFRa activity and blocks common primary and secondary resistance mutations.

Pharmacokinetics:
Has an active metabolite (DP-5439)
Metabolism/Elimination: Primarily hepatic via CYP3A4. CYP2C8, CYP2D6, and CYP2E1 (DP-5439 only) are minor metabolizers.
Plasma Half-Life (hrs): Ripretinib – 14.8h; DP-5439 – 17.8h

Drug Interactions:
- Strong CYP3A inhibitors – may increase exposure of ripretinib - aprepitant, clofazimine, conivaptan, duvelisib, fosaprepitant, fosnetupitant, fusidic acid, idelalisib, larotrectinib, netupitant, palbociclib, simeprevir, stiripentol
- Strong CYP3A inducers – may decrease anti-tumor activity - dabrafenib, deferasirox, erdafitinib, ivosidenib, sarilumab, siltuximab, tocilizumab

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Clinical Review – Qinlock® (ripretinib)

***Adverse Effects*:**
Abdominal pain
Alopecia
Arthralgia
Cardiac dysfunction
Constipation
Decreased appetite
Diarrhea
Decreased labs (Calcium, phosphate, sodium)
Dyspnea
Fatigue
Hypertension
Headache
Increased ALT, amylase, bilirubin, creatininie phosphokinase INR, lipase, PT, triglycerides
Muscle spasm
Myalgia
Nausea
New primary cutaneous malignancies
Palmar-plantar erythrodysesthesia syndrome
Peripheral edema
Pruritus
Stomatitis
Vomiting
Weight loss
Xeroderma
*all adverse effects >10% incidence. **Bold indicates >20% in INVICTUS phase III study**

Contraindications:
- None

Warnings and Precautions:
- Palmar-Plantar Erythrodysethesia Syndrome
    - In INVICTUS, 21% (18 out of 85 patients) incidence rate in treatment group (all grade 1-2), 0% control incidence
    - Managed by withholding dose until recovery, then resume at same (grade 2) or reduced dose (grade 3)
    - Led to dose discontinuation in 1.2% (1), dose interruption in 2.4% (2), and dose reduction in 1.2% (1) in treatment group
- New Primary Cutaneous Malignancies
    - In INVICTUS, 4.7% (4) incidence in treatment group of squamous cell carcinoma and 2.4% (2) incidence of melanoma
    - In pooled safety population (n=351), melanoma occurred in 0.9% (3) of patients

Clinical Review – Qinlock® (ripretinib)

  - Perform dematologic exams when initiating Qinlock & routinely during treatment.
  - Continue Qinlock at same dose
- Hypertension
  - In INVICTUS, 8.2% (7) incidence rate in treatment group (Grade 1-3) compared to 2.3% (1) in placebo group
  - Adequately control blood pressure before initiating Qinlock and monitor throughout therapy
  - Based on severity, withhold Qinlock and reinitiate at same (grade 3) or reduced dose (recurrent grade 3) or discontinue (grade 4)
- Cardiac Dysfunction
  - In INVICTUS, 1.2% (1) incidence rate in treatment group (grade 3) compared to 0% in placebo
  - In pooled safety population (n=351), 1.7% (6) patients experienced cardiac dysfunction, and 1.1% (4) experienced grade 3 adverse reactions
  - Decreased ejection fraction occurred in 2.6% (2) of 77 patients with ECG data
  - Cardiac failure led to dose discontinuation in 1.2% (1) of treatment group
  - Assess ejection fraction before and during treatment as clinically indicated. Discontinue Qinlock for grade 3-4 left ventricular systolic dysfunction
- Risk of Impaired Wound Healing
  - Theoretical potential to adversely effect wound healing through inhibition of vascular endothelial growth factor (VEGF) signaling pathway
  - Withhold Qinlock for one week before and two weeks after major surgery or until adequate wound healing
- Embryo-Fetal Toxicity
  - Animal studies found notable malformations and increased post-implantation loss
  - Advise pregnant women of risk to fetus.
  - Advise women of reproductive potential or male partners of women of reproductive potential to use contraception during and one week after last dose of Qinlock
- Reduced dosing
  - Reduce dose to 100mg/day, then 50mg/day if issues persist, then discontinue.

Evidence Table of Clinical Studies:

Table 1. Clinical data for Qinlock (ripretinib).

	INVICTUS **Von Mehren et al. 6/2020**
Study Type*	▪ Phase 3, placebo-controlled double-blind RCT with crossover and escalation
Interventions and Sample Size	▪ 129 patients ▪ Randomized to receive 2:1 either oral ripretinib 150mg daily(n=85) or placebo (n=44) ▪ Patients on placebo could cross over to ripretinib upon progression ▪ Patients who progressed on 150mg daily could choose to escalate to 150mg twice daily
Populations	▪ >= 18 years old (median age 60) ▪ ECOG 0-2 ▪ Advanced GIST with progression on imatinib, sunitinib, and regorafenib OR documented intolerance to those treatments

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Clinical Review – Qinlock® (ripretinib)

	INVICTUS Von Mehren et al. 6/2020
	▪ Patients enrolled between Feb 2018 and Nov 2018, data cutoff in May 2019 ▪ Median follow-up time of 6.3 months
General Summary: Efficacy	▪ Median progression-free survival - 6.3 months for ripretinib vs. 1 month for placebo ▪ Median overall survival – 15.1 months for ripretinib vs. 6.6 months for placebo ▪ RECIST objective response – 9.4% for ripretinib vs. 0% for placebo
General Summary: Safety	▪ >= 20% of patients in ripretinib group experienced alopecia, myalgia, nausea, fatigue, palmar-plantar erythrodysesthesia and diarrhea. ▪ Dose interruption in 12 treatment patients and 3 placebo patients, dose reduction in 5 treatment patients and 1 placebo patient ▪ Study discontinuation in 4 treatment patients (due to cardiac failure, death of unknown cause, general health deterioration, and palmar-plantar erythrodysesthesia) and 1 placebo patient (fatigue) ▪ One patient death in the ripretinib group (cause unknown) and one patient death in the placebo group (pulmonary edema, septic shock)
Comments	▪ Patients receiving ripretinib had 0.15 times the hazard of disease progression compared to placebo ▪ Concerns – placebo controlled, unable to test for statistical significance for QoL/overall survival
Grade^	▪ Grade A

*Study type abbreviations: CC=Case-control study, COH=Cohort study, CS=Case study, DB=double blind, EPI=Epidemiologic study, META=Meta-analysis, NRCT=Nonrandomized clinical trial, OBS=Observational study, PC=placebo-controlled, PG=parallel-group, RCT=randomized trial, XO=crossover [if not listed, please type in under study type]
^A=Useful, B=Possibly useful, C=Possible to uncertain usefulness, U=Uncertain validity and/or usefulness, X=Not useful
(For further information, please refer to the document Grading of Clinical Evidence; NA=Not applicable. [Disclaimer: Grade the study if able to pull the literature]

Special Populations:
Pediatric Use – Safety and efficacy has not been established
Geriatric Use – Has not been extensively studied. No dosing adjustment currently recommended
Use in Hepatic Impairment – No dose adjustment is recommended in mild impairment. Recommended dosage has not been established for moderate/severe impairment.
Use in Renal Impairment – No dose adjustment is recommended. CrCl between 30-90 had no clinically meaningful effect on pharmacokinetics.

Cost and/or Utilization Data of Similar Treatment Options: **Table 2: Similar Pricing**

Drug	Strength	WAC/unit	Monthly Supply	Monthly WAC
Qinlock	50 mg	$355.56	90 ct	$32,000.00
Stivarga	40 mg	$214.80	120 ct	$25,776.00
Gleevec	400 mg	$337.41	60 ct	$20,244.60
Sutent	50 mg	$670.13	30 ct	$20,103.90

Clinical Review – Qinlock® (ripretinib)

Ayvakit	300 mg	$1066.67	30 ct	$32,000.10

Table 4: Humana Tiering for Similar Treatment Options

	imatinib 400 mg	Stivarga (regorafinib) 40 mg	Sutent (sunitinib) 50 mg
KY Medicaid	T1wPA	T2wPA	T2wPA

Place in Therapy:

Table 5. Comparison of Qinlock (ripretinib) and Ayvakit (avapritinib)

	Qinlock (ripretinib)	Ayvakit (avapritinib)
Meet an Unmet Medical Need[1]	☒ Yes - Currently no standard of care or approved/effective 4th line treatment available for GIST ☐ No	
Comparable Efficacy[2]	☐ Ayvakit (avapritinib) is more efficacious relative to Qinlock (ripretinib) ☐ Ayvakit (avapritinib) has similar efficacy relative to Qinlock (ripretinib) ☒ Ayvakit (avapritinib) is less efficacious relative to Qinlock (ripretinib) **Comment:** No head to head comparison. However, avapritinib demonstrated a median PFS of 4.2 months in the VOYAGER trial, whereas ripretinib demonstrated a median PFS of 6.3 months in INVICTUS trial. VOYAGER trial also examined 3rd and 4th line GIST, whereas INVICTUS was 4th line.	
Comparable Safety[3]	☐ Ayvakit (avapritinib) would likely be more safe relative to Qinlock (ripretinib) ☒ Ayvakit (avapritinib) would likely have similar safety relative to Qinlock (ripretinib) ☐ Ayvakit (avapritinib) would likely be less safe relative to Qinlock (ripretinib) **Comment:** Similar AE profile between two drugs, largely grade 1-2 events. Ripretinib demonstrated significantly more palmar-plantar erythrodysesthesia/alopecia, whereas more edema and memory impairment was reported with avapritinib.	
Patent Expiration	10/2028	10/2034
Advantages	▪ PFS and OS benefit	▪ Demonstrated benefit in PDGFRA exon 18 mutation
Disadvantages	▪ Study design was placebo only comparison	▪ Data that shows inferiority to continuing regorafinib in the 4th line setting (VOYAGER)
Comments	▪ Protected drug class ▪ Only drug FDA approved for 4th line GIST	▪ Protected drug class ▪ Pursued and was rejected for 4th line indication by the FDA. ▪ Currently indicated only for GIST w/ PDGFRA exon 18 mutation

Definitions

1. Unmet medical need - Medical need that is not addressed adequately by an existing therapy (examples: a) No available therapy for condition exists b) If available therapy for the condition exists i) New therapy has improved effects on serious outcomes, ii) Similar benefits to alternative therapies while avoiding serious toxicity).[IV]
2. Efficacy – The extent to which an intervention produces a beneficial result under ideal conditions (i.e clinical trials). [III]
3. Safety – Substantive evidence of an absence of harm (examples: clinical adverse events (disease, signs, and symptoms).[II]

Clinical Review – Qinlock® (ripretinib)

4. Cost-effectiveness – The cost and health benefits associated with the use of the drug therapies.[I]
5. Adherence - The consistence and accuracy with which a patient will follow a recommended medical regimen (examples of factors that may affect adherence: frequency of administration, adverse events, cost of drug).[I]

References

I. Berger ML, Bigefors K, Hedblom EC, Pashos CL, Torrance GW. Health care cost, quality, and outcomes: ISPOR book of terms. Lawrenceville, NJ: International Society for Pharmacoeconomics and Outcomes Research; 2003.
II. Chou R, Aronson N, Atkins D. Chapter 7. Assessing harms when comparing medical interventions. In: methods guide for effectiveness and comparative effectiveness reviews. AHRP Publication No. 10(11)-EHC063-EF. March 2011; http://www.effectivehealthcare.ahrq.gov. Accessed May 2012.
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IV. U.S. Food and Drug Administration. FDA guidance for industry on Fast Track Drug Development Programs: Designation, Development, and Application Review. January 2006. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079736.pdf. Accessed May 2012.

Recommendation:

- **KY Medicaid— T2 wPA and QL**
- QL 90/30/3.6 (50 mg tab)

References:

1. Blay JY, Serrano C, Heinrich MC, et al. Ripretinib in patients with advanced gastrointestinal stromal tumours (INVICTUS): a double-blind, randomized, placebo-controlled, phase 3 trial. *Lancet Oncol*. 2020; June 5th, 2020.
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Clinical Review – Retevmo (selpercatinib)

Company: Eli Lilly and Company
Current Status: FDA approved and launched in May 2020
Therapeutic Category/Pharmacologic Class: Anti-neoplastic agent; tyrosine kinase inhibitor
Similar Drugs: Cabozantinib, Caprelsa, Nexavar, Lenvima
Route of Administration: oral
Dosage Forms: 40, 80 mg capsule

Indications:

1. Adult patients with metastatic RET fusion-positive non-small cell lung cancer (NSCLC)
2. Adult and pediatric patients 12 years of age and older with advanced or metastatic RET-mutant medullary thyroid cancer (MTC) who require systemic therapy
3. Adult and pediatric patients 12 years of age and older with advanced or metastatic RET fusion-positive thyroid cancer who require systemic therapy and who are radioactive iodine-refractory (if radioactive iodine is appropriate)

Dosage and Administration:

Recommended starting dose is weight based for either adult or pediatric

- Less than 50kg: 120 mg twice daily
- Greater than or equal to 50kg: 160 mg twice daily

Background:

In 2020 an estimated 228K new cases of lung cancer cases will be diagnosed, where about 85% of these cases are NSCLC. RET fusion occurs in a small subset (about 1-2%). Treatment of advanced disease may include targeted therapy (e.g., cabozantinib), immuno-oncology therapy, or chemotherapy.

Pharmacology:

Retevmo (selpercatinib) is a kinase inhibitor which blocks both wild-type and multiple mutated RET subtypes as well as VEGFR (types 1 and 3) and FGFR (types 1-3).

Pharmacokinetics:

Metabolism/Elimination: metabolized via CYP 3A4A in vitro; 84% of dose found in feces, 12.6% of dose found in urine
Plasma Half-Life (hrs): 15.4hrs

Drug Interactions:

- Avoid co-administration with:
    - Acid reducing agents
    - Moderate to strong CYP 3A4 inducers/inhibitors
    - CYP 2C8/3A substrate
    -

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Clinical Review – Retevmo (selpercatinib)

***Adverse Effects*:**
The most frequently occurring adverse effects includes (but not limited to): electrolyte disorders [hyperglycemia increased transaminases], gastrointestinal [diarrhea, constipation], hypertension, fatigue, edema, and dry mouth.

Contraindications:
None

Warnings and Precautions:
- Hepatotoxicity: monitor transaminases frequently on therapy.
- Hypertension: recommended not to initiate Retevmo in uncontrolled hypertension.
- QT Prolongation: monitor QT intervals in patients who are at risk to developing prolonged intervals
- Hemorrhagic events: discontinue Retevmo if severe, life-threatening hemorrhaging event occurs
- Risk of impaired wound healing: withhold Retevmo seven days prior to elective surgery
- Embryo-Fetal Toxicity
    - Caution patients of reproductive age of the potential risk

Evidence Table of Clinical Studies:
Table 1. Clinical data for Retevmo.

	LIBRETTO-001
Study Type*	• Phase I/II trial, dose escalation, multi-cohort (ongoing)
General Summary: Efficacy	• Treatment naïve • ORR was reported as 85% [95% CI: 70, 94] • Median duration of response: NE • Previously treated • ORR was reported as 64% [95% CI: 54, 73] • Median duration of response: 17.9 months • Treatment naïve (n=8) • ORR was reported as 100% [95% CI: 63, 100] • Median duration of response: NE • Previously treated (n=19) • ORR was reported as 79% [95% CI: 54, 94] • Median duration of response: 18.4 months
General Summary:	• **Dry mouth (39%), diarrhea (37%), hypertension (35%), fatigue (35%)**

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Clinical Review – Retevmo (selpercatinib)

	LIBRETTO-001
Safety	• Dry mouth (39%), diarrhea (37%), hypertension (35%), fatigue (35%) • Grade 3/4 hypertension (18%) leukopenia (1.6%), thrombocytopenia (2.7%) • Dose interruption: 21% (elevated AST/ ALT, hypertension, diarrhea, QT prolongation) • Dose reduction: 28% (elevated AST/ ALT, QT prolongation) • Dose discontinuation less than 2% (elevated AST/ ALT, QT prolongation, fatigue)
Comments	▪ Median age 61 years ▪ Majority were female ▪ Majority of patients were ECOG PS 0-1 ▪ Up to 1/3 of patients has brain mets ▪ Median age 54 years ▪ Majority were male ▪ Majority of patients were ECOG PS 0-1 ▪
Grade^	▪ B

*Study type abbreviations: CC=Case-control study, COH=Cohort study, CS=Case study, DB=double blind, EPI=Epidemiologic study, META=Meta-analysis, NRCT=Nonrandomized clinical trial, OBS=Observational study, PC=placebo-controlled, PG=parallel-group, RCT=randomized trial, XO=crossover [if not listed, please type in under study type]
^A=Useful, B=Possibly useful, C=Possible to uncertain usefulness, U=Uncertain validity and/or usefulness, X=Not useful
(For further information, please refer to the document Grading of Clinical Evidence; NA=Not applicable. [Disclaimer: Grade the study if able to pull the literature]

Special Populations:

- Pregnancy and Lactation: can cause fetal harm if given to a pregnant patient.
- Safety not established in pediatric patients, severe renal or hepatic impairment

Place in Therapy:

[Comparison Table: *If comparing new product to existing products as well as similar product in the pipeline;*

- Advantages vs disadvantages (consider including if able-not all inclusive): efficacy, indications, dosage frequency, route of administration, pharmacology, metabolism, drug-interactions, adverse effects, monitoring parameters, and/or storage
- Delete non-pertinent items under the comparison table]

Table 5. Comparison of Pemazyre and Chemotherapy

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Clinical Review – Retevmo (selpercatinib)

	Retevmo	Cabozantinib, Nexavar, Lenvima (TC)/ Keytruda based therapy (NSCLC)
Meet an Unmet Medical Need	May meet unmet medical need. Retevmo was granted accelerated approval for all indications. Confirmatory trials are underway.	
Advantages	• First FDA approved agent to treat RET gene alterations • Improved response rates	• Provider experience • Standard of care
Disadvantages	• Provider awareness to test for RET gene alterations	• Keytruda based regimens administered intravenously • Keytruda based regimens are not specific to RET rearrangement
Comments	• NCCN supports Retevmo in both NSCLC and thyroid cancer	

Definitions

1. Unmet medical need - Medical need that is not addressed adequately by an existing therapy (examples: a) No available therapy for condition exists b) If available therapy for the condition exists i) New therapy has improved effects on serious outcomes, ii) Similar benefits to alternative therapies while avoiding serious toxicity).[IV]
2. Efficacy – The extent to which an intervention produces a beneficial result under ideal conditions (i.e clinical trials). [III]
3. Safety – Substantive evidence of an absence of harm (examples: clinical adverse events (disease, signs, and symptoms).[II]
4. Cost-effectiveness – The cost and health benefits associated with the use of the drug therapies.[I]
5. Adherence - The consistence and accuracy with which a patient will follow a recommended medical regimen (examples of factors that may affect adherence: frequency of administration, adverse events, cost of drug).[I]

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I. Berger ML, Bigefors K, Hedblom EC, Pashos CL, Torrance GW. Health care cost, quality, and outcomes: ISPOR book of terms. Lawrenceville, NJ: International Society for Pharmacoeconomics and Outcomes Research; 2003.

II. Chou R, Aronson N, Atkins D. Chapter 7. Assessing harms when comparing medical interventions. In: methods guide for effectiveness and comparative effectiveness reviews. AHRP Publication No. 10(11)-EHC063-EF. March 2011; http://www.effectivehealthcare.ahrq.gov. Accessed May 2012.

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Clinical Review – Retevmo (selpercatinib)

IV. U.S. Food and Drug Administration. FDA guidance for industry on Fast Track Drug Development Programs: Designation, Development, and Application Review. January 2006. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079736.pdf. Accessed May 2012.

Recommendation:

- KY Medicaid— tier 2 with PA, QL

References:

[AMA Style 10th edition; Alphabetical order—Examples below]

1. [Book]
Baselt RC, Cravey RH. *Disposition of Toxic Drugs and Chemicals in Man.* 4th ed. Foster City, CA: Chemical Toxicology Institute; 1995.
2. *Clinical Pharmacology*
Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc.; insert current year of copyright. URL: http://www.clinicalpharmacology.com. Updated Month Year. [example below]
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3. *DrugDex—Keep [internet database] below]*
DRUGDEX® System [Internet database]. Greenwood Village, Colo: Thompson Reuters (Healthcare) Inc. Updated periodically.
4. *[Journal articles. Note : if journal does not have a volume or issue number, use the issue date]*
Smith J, Canton EM. Weight-based administration of dalteparin in obese patients. *Am J Health-Syst Pharm*. 2003;60(7):683-687.
5. [Journal articles with >6 authors. List first 3, then et al.]
Hunter DJ, Hankinson SE Jr, Laden F, et al. Plasma organochlorine levels and the risk of breast cancer. *N Engl J Med*. 1997;337(18):1253-1258.
6. *[Package Insert-Example below → Keep "[package insert]"]*
Amitiza [package insert]. Deerfield, IL: Sucampo Pharma Americas, Inc and Takeda Pharmaceuticals; 2009.
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Humana
Pharmacy Solutions

Clinical Review – Tabrecta™ (capmatinib)

- ***Company: Novartis Pharmaceuticals Corp***
- ***Current Status: FDA approved and launched May 2020***
- ***Therapeutic Category/Pharmacologic Class: Oncology***
- ***Similar Drugs: None***
- ***Route of Administration/Dosage Forms: Oral (tablets)***
- ***Indications: Treatment of adult patients with metastatic MET exon 14 skipping non-small cell lung cancer (NSCLC) as detected by an FDA-approved test***

Indications:
Adult patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have a mutation that leads to mesenchymal-epithelial transition (MET) exon 14 skipping as detected by an FDA-approved test (companion diagnostic test FoundationOne CDX assay).

Dosage and Administration:
The recommended dose of Tabrecta is 400mg orally twice a day.

Background:
In 2020 an estimated 228K new cases of lung cancer cases will be diagnosed, where 85% of these cases are NSCLC. MET exon 14 skipping occurs in a small subset (about 3-4%). Treatment of advanced disease may include immuno-oncology therapy, targeted therapy (e.g., crizotinib), or chemotherapy.

Pharmacology/MOA: *kinase inhibitor which blocks phosphorylation of mesenchymal-epithelial transition (MET)*

Drug Interactions:
- Avoid co-administration with:
  - Acid reducing agents
  - Moderate to strong CYP 3A4 inducers/inhibitors
  - CYP 2C8/3A substrate

***Adverse Effects*:**
The most frequently occurring adverse effects include: peripheral edema, nausea, vomiting, fatigue, decreased appetite, and dyspnea.

Contraindications:
None

Warnings and Precautions:
- Interstitial lung disease/Pneumonitis
- Hepatotoxicity
- Risk of Photosensitivity

Clinical Review – Tabrecta™ (capmatinib)

- Embryo-fetal toxicity

Evidence Table of Clinical Studies:

Table 1. Clinical data for Retevmo.

	GEOMETRY mono-1 trial (n= 97)
Study Type*	• Phase II, non-randomized, open label
General Summary: Efficacy	• Treatment naïve • ORR was reported as 68% [95% CI: 48, 84] • Median duration of response: 12.6 months [95% CI: 5.5, 25.3] • Previously treated • ORR was reported as 41% [95% CI: 29, 53] • Median duration of response: 9.7 months [95% CI: 5.5, 13.0]
General Summary: Safety	• Peripheral edema (52%), nausea (44%)/vomiting (28%), fatigue (32%) • Grade 3/4 peripheral edema (9%), fatigue (8%) • Dose interruption: 54%; dose reduction: 23% • Permanent discontinuation occurred in 16%
Comments	▪ Peripheral edema (52%), nausea (44%)/vomiting (28%), fatigue (32%) ▪ Grade 3/4 peripheral edema (9%), fatigue (8%) ▪ Dose interruption: 54%; dose reduction: 23% ▪ Permanent discontinuation occurred in 16% ▪
Grade^	▪ B

*Study type abbreviations: CC=Case-control study, COH=Cohort study, CS=Case study, DB=double blind, EPI=Epidemiologic study, META=Meta-analysis, NRCT=Nonrandomized clinical trial, OBS=Observational study, PC=placebo-controlled, PG=parallel-group, RCT=randomized trial, XO=crossover [if not listed, please type in under study type]
^A=Useful, B=Possibly useful, C=Possible to uncertain usefulness, U=Uncertain validity and/or usefulness, X=Not useful
(For further information, please refer to the document Grading of Clinical Evidence; NA=Not applicable. [Disclaimer: Grade the study if able to pull the literature]

Special Populations:

- Pregnancy and Lactation: can cause fetal harm if given to a pregnant patient.

Clinical Review – Tabrecta™ (capmatinib)

- Safety not established in pediatric patients, severe renal or hepatic impairment

Place in Therapy:

	Tabrecta	**Xalkori**
Meet an Unmet Medical Need	May meet unmet medical need. Tabrecta was granted accelerated approval; confirmatory trial is underway.	
Advantages	• First FDA approved agent for mutation leading to MET exon 14 skipping	• Provider experience
Disadvantages	• Provider awareness to test for MET exon 14 skipping	• Compendium support as subsequent therapy for certain circumstances
Comments	Tabrecta is being studied in other diseases (e.g., hepatocellular carcinoma, renal cell carcinoma)	

Definitions

1. Unmet medical need - Medical need that is not addressed adequately by an existing therapy (examples: a) No available therapy for condition exists b) If available therapy for the condition exists i) New therapy has improved effects on serious outcomes, ii) Similar benefits to alternative therapies while avoiding serious toxicity).[IV]
2. Efficacy – The extent to which an intervention produces a beneficial result under ideal conditions (i.e clinical trials). [III]
3. Safety – Substantive evidence of an absence of harm (examples: clinical adverse events (disease, signs, and symptoms).[II]
4. Cost-effectiveness – The cost and health benefits associated with the use of the drug therapies.[I]
5. Adherence - The consistence and accuracy with which a patient will follow a recommended medical regimen (examples of factors that may affect adherence: frequency of administration, adverse events, cost of drug).[I]

References

I. Berger ML, Bigefors K, Hedblom EC, Pashos CL, Torrance GW. Health care cost, quality, and outcomes: ISPOR book of terms. Lawrenceville, NJ: International Society for Pharmacoeconomics and Outcomes Research; 2003.

Clinical Review – Tabrecta™ (capmatinib)

II. Chou R, Aronson N, Atkins D. Chapter 7. Assessing harms when comparing medical interventions. In: methods guide for effectiveness and comparative effectiveness reviews. AHRP Publication No. 10(11)-EHC063-EF. March 2011; http://www.effectivehealthcare.ahrq.gov. Accessed May 2012.
III. Glossary of terms in the Cochrane Collaboration. Version 4.2.5. Updated May 2005. http://www.cochrane.org/glossary. Accessed May 2012.
IV. U.S. Food and Drug Administration. FDA guidance for industry on Fast Track Drug Development Programs: Designation, Development, and Application Review. January 2006. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079736.pdf. Accessed May 2012.

Recommendation:

- KY Medicaid— tier 2 with PA, QL

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7. [Websites]
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The key and critical objectives of *JAMA*. http://jama.ama-assn.org/misc/aboutjama.dtl. Accessed December 29, 2008.

Humana Pharmacy Solutions

Clinical Review – Zepzelca® (lurbinectedin)

***Company*:** Jazz Pharmaceuticals, Inc.
Current Status: FDA Approved June 15, 2020 in accelerated approval
Launch: Currently Available on Market
Therapeutic Category: Antineoplastic agent
Pharmacologic Category: DNA minor groove binder
Similar Drugs: Topotecan
Route of Administration: Intravenous
Dosage Forms: Lyophilized powder in a single-dose vial

Indications: Small cell lung cancer (SCLC)

Dosage and Administration: 3.2 mg/m^2 intravenously every 21 days

Background:
Small cell lung cancer (SCLC) accounts for approximately 15% of the lung cancer cases in the US and occurs almost exclusively in smokers. SCLC is an aggressive cancer with a general 5-year survival rate of 6%. The 5-year survival rate is 27% for localized SCLC, 16% for regional SCLC, and 3% for metastatic SCLC. NCCN has determined that oral or intravenous topotecan is the preferred treatment following a relapse in less than 6 months after prior treatment with platinum chemotherapy. After FDA approval of Zepzelca, now oral or intravenous topotecan and Zepzelca are preferred treatments in patients with relapsed SCLC within 6 months. If the relapse is in greater than 6 months from original treatment, a second treatment of the original regimen is preferred; Zepzelca is an additional option but is not preferred. SCLC may also be treated with immunotherapy. Opdivo and Keytruda are non-preferred treatment options for relapsed SCLC within 6 months of primary treatment. Tecentriq and Imfinzi may be each used with platinum-based chemotherapy and etoposide for primary therapy of extensive-stage SCLC. Currently, NCCN does not recommend utilizing combination of immunotherapies for the primary or subsequent treatment of SCLC.

Pharmacology:
Zepzelca (lurbinectedin) is an alkylating agent that binds to the minor grooves of DNA via guanine residues. This creates a formation of adducts and causes the DNA helix to bend towards the major groove of the DNA. These adduct formations cause an alteration of DNA binding protein activity, including transcription factors and DNA repair pathways. This disruption results in the interruption of the cell cycle and eventual cell death.

Pharmacokinetics:
Metabolism/Elimination: Metabolized by CYP3A4 in vitro
Plasma Half-Life (hrs): 51 hours

Drug Interactions:
- Dedicated drug-drug interaction studies with CYP3A modulators have not been completed.
- In vitro:
    - Metabolized by CYP3A4
    - Substrate of MDR1

***Adverse Effects*:**
Leukopenia
Lymphoenia

Fatigue
Anemia
Neutropenia
Increased creatinine
Increased alanine aminotransferase
Increased glucose
Thrombocytopenia
Nausea
Decreased appetite
Musculoskeletal pain
Decreased albumin
Constipation
Dyspnea
Decreased sodium
Increased aspartate aminotransferase
Vomiting
Cough
Decreased magnesium
Diarrhea
*all adverse effects >20% incidence. **Bold indicates >30% incidence in Study B-005 phase III trial.**

Contraindications:
- None

Warnings and Precautions:
- Myelosuppression
    - Do not administer Zepzelca to patients unless baseline neutrophil is at least 1,500 cells/mm^3 and platelets at least 100,000/mm^3. Patients with neutrophils less than 500 cells/mm^3 may receive granulocyte colony-stimulating factor (G-CSF) prophylaxis or hold Zepzelca dose until grade is less than 1 (>1500 cells/mm^3).
- Hepatotoxicity
    - Monitor liver function tests (LFTs) prior to initiation and periodically during treatment; discontinue or make dosage adjustments as needed
- Embryo-Fetal Toxicity
    - Animal studies showed fetal harm. Advise female patients on effective contraceptive use.

Monitoring:
- Monitor blood counts including neutrophils and platelets prior to each administration of Zepzelca for myelosuppression and monitor liver function tests prior to initiation and periodically throughout treatment as indicated for hepatotoxicity.

Evidence Table of Clinical Studies:
Table 1. Clinical data for [Zepzelca].

	Study B-005 Trigo, et al. 05/2020
Study Type*	Phase II, NCRT, multicenter
Interventions	N = 105

	Study B-005 Trigo, et al. 05/2020
and Sample Size	Patients received Zepzelca 3.2mg/m^2 every 21 days until disease progression or unacceptable toxicity. The median number of cycles was 4 (range 1-24 cycles; IQR 2-8 cycles).
Populations	*Inclusion:* ▪ Age 18 years or older ▪ Diagnosed with SCLC ▪ Prior treatment with one antineoplastic line ▪ Performance status less than or equal to 2 ▪ Adequate major organ function ▪ At least 3 weeks after last chemotherapy dose *Exclusion:* ▪ Prior treatment with Zepzelca or trabectedin ▪ Current or prior malignancy (unless 5 years of remission) ▪ Known CNS involvement ▪ Pregnant or breastfeeding women or fertile adults not using effective contraception
General Summary: Efficacy	▪ Median overall survival was 9.3 months. 63% of patients died during the testing period (median follow up was 17.1 months). The 6-month overall survival was 67.1% and 12-month overall survival was 34.2%. ▪ The overall response rate was 35%. 0% of patients had a complete response and 35% of patients had a partial response. The median duration of response was 5.3 months and 35% of patients maintained a response for greater than 6 months. The median progression-free survival was 3.5 months. ▪ When an independent review committee assessed the response, there was a 30% overall response rate. 0% of patients had a complete response and 30% of patients had a partial response. The median duration of response was 5.1 months and 25% of patients maintained a response for greater than 6 months.
General Summary: Safety	▪ The most common adverse effects include fatigue, nausea, decreased appetite, vomiting, and diarrhea. ▪ Laboratory abnormalities included decreased leukocytes, lymphocytes, hemoglobin, neutrophils, platelets, albumin, sodium, and magnesium. Other laboratory abnormalities included increased creatinine, ALT, AST, and glucose. ▪ The most common grade 3-4 adverse events were anemia (9%), leukopenia (29%), neutropenia (46%), thrombocytopenia (7%), febrile neutropenia (5%), ALT (5%), and AST (2%). ▪ 22% of patients received G-CSF as treatment or prophylaxis for neutropenia. ▪ There were no deaths due to the drug or adverse events related to treatment. 2% of patients discontinued therapy due to adverse events. ▪ 10% of patients had serious adverse events due to treatment (5% neutropenia, 5% febrile neutropenia). ▪ Zepzelca administration was delayed in 22% of patients and reduced in 26% of patients; most of these were related to neutropenia (12% and 16% respectively).
Comments	▪ 65% of patients were aged 65 or older; 60% were male; 92% were former smokers; 70% of patients had extensive disease; 92% were former or current smokers ▪ 100% of patients had prior platinum-based chemotherapy; 99% tried etoposide; 8% had prior immunotherapy; 93% of patients had 1 prior treatment line ▪ 28% (n=28) of patients had disease progression with treatment with lurbinectedin ▪ No reports of liver injury in response to treatment with lurbinectedin ▪ 45% of patients received further SCLC treatment after the trial of lurbinectedin
Grade^	▪ B

*Study type abbreviations: CC=Case-control study, COH=Cohort study, CS=Case study, DB=double blind, EPI=Epidemiologic study, META=Meta-analysis, NRCT=Nonrandomized clinical trial, OBS=Observational study, PC=placebo-controlled, PG=parallel-group, RCT=randomized trial, XO=crossover [if not listed, please type in under study type]
^A=Useful, B=Possibly useful, C=Possible to uncertain usefulness, U=Uncertain validity and/or usefulness, X=Not useful
(For further information, please refer to the document Grading of Clinical Evidence; NA=Not applicable. [Disclaimer: Grade the study if able to pull the literature]

Special Populations:

Pregnancy: Animal studies showed fetal harm after administration of Zepzelca. The incidence of major birth defects or miscarriages due to Zepzelca is unknown.

Geriatric Use: There is no difference in effectiveness in patients aged 65 years and older than those aged less than 65 years. There was a higher incidence of adverse reactions in those aged 65 years and older (49% compared to 26%) and most of these were related to myelosuppression.

Hepatic Impairment: Dose adjustment is indicated for moderate to severe hepatic impairment; the effects of moderate to severe hepatic impairment on the pharmacokinetics of Zepzelca has not been studied. There is no dose adjustment for mild hepatic impairment.

Cost and/or Utilization Data of Similar Treatment Options:

Table 2: Zepzelca Pricing

Drug	Strength	WAC/unit	Package size	WAC/Package
Zepzelca	4mg	$6,663/vial	1 vial	$6,663/vial
Topotecan HCl	4mg	$106.88/vial	1 vial	$106.88/vial

Place in Therapy:

Table 5. Comparison of Zepzelca and Topotecan

	Zepzelca	Topotecan
Meet an Unmet Medical Need[1]	No it does not meet an unmet need. There are multiple medications approved for SCLC as well as Topotecan is one of the other preferred treatments for SCLC that relapsed in 6 or less months in patients with a functional status of 0-2. If the relapse is greater than 6 months, then the original regimen is preferred and Zepzelca is not preferred but is a treatment option.	
Comparable Efficacy[2]	☒ Topotecan is less efficacious relative to Zepzelca. **Comment:** Zepzelca had a median overall survival of 9.3 months compared to Topotecan's median overall survival of 25 weeks (6.25 months). The two drugs have not been studied in a head-to-head trial.	
Comparable Safety[3]	☒ Topotecan would likely achieve similar safety relative to Zepzelca **Comment:** Zepzelca showed less incidence of grade 3-4 hematologic adverse events than Topotecan (thrombocytopenia 7% vs. 29%, neutropenia 46% vs. 70%, and anemia 10% vs. 42%). While there was a higher rate of serious adverse events with Zepzelca (10%) over Topotecan (4%), there were less discontinuations and deaths with Zepzelca (2% & 0%) compared to Topotecan (4% & 4%). As Zepzelca was approved on Phase II trial results, long term safety still needs to be assessed.	
Adherence[5]	☒ Members taking Topotecan would likely achieve a similar adherence rate relative to Zepzelca. **Comment:** Only 2% of patients discontinued Zepzelca in the trials where Topotecan has shown that 12.5% of patients discontinued treatment due to adverse events. Topotecan is available orally for members that would be unable to travel to a provider's office to receive infusions every 3 weeks. As Zepzelca was approved on Phase II trial results, long term adherence and safety still need to be assessed.	
Patent Expiration	12/13/2029 or 11/11/2031	Generic available
Advantages	▪ Less incidence of grade 3-4 adverse events in clinical studies ▪ Better overall survival	▪ Can be given orally ▪ Provider experience; standard of care for SCLC ▪ Generic availability

Disadvantages	▪ Approved for phase II clinical trial in accelerated approval ▪ Limited data on long-term safety and efficacy of Zepzelca ▪ Efficacy is reduced and the severity of adverse events is increased with coadministration of moderate to severe CYP3A inhibitors	▪ FDA Boxed Warning for bone marrow suppression ▪ Warning for neutropenia colitis, ILD, and extravasation
Comments	▪ A phase III trial of Zepzelca in combination with doxorubicin vs cyclophosphamide, doxorubicin, and vincristine or topotecan in treating relapsed SCLC was completed in February 2020. The results not published yet ▪ Current clinical trial studying Zepzelca with Tecentriq in combination for SCLC ▪ Zepzelca is also being studied in malignant pleural mesothelioma and select advanced solid tumors	

Definitions

1. Unmet medical need - Medical need that is not addressed adequately by an existing therapy (examples: a) No available therapy for condition exists b) If available therapy for the condition exists i) New therapy has improved effects on serious outcomes, ii) Similar benefits to alternative therapies while avoiding serious toxicity).[IV]
2. Efficacy – The extent to which an intervention produces a beneficial result under ideal conditions (i.e clinical trials). [III]
3. Safety – Substantive evidence of an absence of harm (examples: clinical adverse events (disease, signs, and symptoms).[II]
4. Cost-effectiveness – The cost and health benefits associated with the use of the drug therapies.[I]
5. Adherence - The consistence and accuracy with which a patient will follow a recommended medical regimen (examples of factors that may affect adherence: frequency of administration, adverse events, cost of drug).[I]

References

I. Berger ML, Bigefors K, Hedblom EC, Pashos CL, Torrance GW. Health care cost, quality, and outcomes: ISPOR book of terms. Lawrenceville, NJ: International Society for Pharmacoeconomics and Outcomes Research; 2003.

II. Chou R, Aronson N, Atkins D. Chapter 7. Assessing harms when comparing medical interventions. In: methods guide for effectiveness and comparative effectiveness reviews. AHRP Publication No. 10(11)-EHC063-EF. March 2011; http://www.effectivehealthcare.ahrq.gov. Accessed May 2012.

III. Glossary of terms in the Cochrane Collaboration. Version 4.2.5. Updated May 2005. http://www.cochrane.org/glossary. Accessed May 2012.

IV. U.S. Food and Drug Administration. FDA guidance for industry on Fast Track Drug Development Programs: Designation, Development, and Application Review. January 2006. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079736.pdf. Accessed May 2012.

Recommendation:

NF (medical benefit) KY Medicaid, MIT PAL

References:

1. Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc.; insert current year of copyright. URL: http://www.clinicalpharmacology.com. Updated August 2020.
2. Eckardt JR, Pawel J, Pujol JL, et al. Phase III study of oral compared with intravenous topotecan as second-line therapy in small-cell lung cancer. *J Clin Oncol*. 2007 May 20;25(15):2086-92. doi: 10.1200/JCO.2006.08.3998.
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Humana Pharmacy Solutions

Clinical Review – Dayvigo (lemborexant)

***Company*:** Eisai Inc.
Current Status: FDA Approved December 20th 2019
Launch: Currently Available on Market
Therapeutic Category: Insomnia
Pharmacologic Category: Orexin receptor antagonist
Similar Drugs: Belsomra (suvorexant)
Route of Administration: Oral
Dosage Forms: Tablets

Indications: Indicated as a treatment of adult patients with insomnia, characterized by difficulties with sleep onset and/or sleep maintenance.

Dosage and Administration:

- Administer 5mg orally at bedtime. May increase to 10mg at bedtime based on clinical response and tolerability.

Background: Characterized as difficulty falling asleep or staying asleep, insomnia can be classified as either acute or chronic. Acute insomnia, which tends to resolve without treatment, is usually caused by life circumstances that may cause stress for the individual (night before an exam, receiving bad news, etc.). Chronic insomnia is described as disrupted sleep that occurs at least three nights per week and lasts at least three months. There are many possible causes for chronic insomnia, such as shift work, changes in the individual's environment, and other clinical disorders or treatments. Chronic insomnia generally requires some form of treatment to help the individual return to healthy sleep patterns. Treatments may include behavioral, psychological, or medication management or a combination of these treatment options. The disease prevalance is approximately 30% of the adult population.

Because insomnia may be caused by environmental factors such as stress, initial treatment with cognitive behavioral therapy for insomnia (CBT-I), including relaxation therapy and stimulus control therapy should be considered prior to drug therapy. Some patients my require a combination of both CBT-I and drug treatment. There are currently multiple branded and generic oral agents for the treatment of insomnia with different mechanisms of action.

Pharmacology: Orexin receptor antagonist binds to orexin receptors OX1R and OX2R. When activated, OX1R suppresses REM sleep and OX2R suppresses both non-REM and REM sleep. By binding to these receptors and preventing their activation by the wake-promoting neuropeptides orexin A and B, lemborexant suppresses wake drive.

Pharmacokinetics:
Metabolism/Elimination: Hepatic metabolism. Lemborexant is excreted in the urine and feces. 57.4% is recovered in the feces, 29.1% is recovered in the urine.

Plasma Half-life: 17 and 19 hours, for lemborexant 5mg and 10mg, respectively.

Drug Interactions:

- Consider therapy modification for CYP3A inhibitors
  - Avoid concomitant use of lemborexant with strong or moderate CYP3A inhibitors
  - Avoid concomitant use of lemborexant with strong or moderate CYP3A inducers
  - Avoid concomitant use of lemborexant with weak CYP3A inhibitors greater than 5mg

***Adverse Effects*:** Most common (incidence ≥ 5% and greater than placebo) was somnolence.

Contraindications: Patients with narcolepsy.

Warnings and Precautions:

- CNS depressant effects and daytime impairment
- Sleep paralysis, hypnagogic/hypnopompic hallucinations, and cataplexy-like symptoms
- Complex sleep behaviors
- Worsening of depression/suicidal ideation
- Consider effect of Dayvigo for patients with compromised respiratory function
- Evaluate for co-morbid diagnoses

Monitoring:

Monitor patients for signs and symptoms of depression/suicidal ideation as appropriate.

Evidence Table of Clinical Studies:

Table 1. Clinical data for Dayvigo (lemborexant)

The approval was based on the results of two Phase 3 studies (SUNRISE 1 and SUNRISE 2), in which Dayvigo was evaluated over a one-month time period and a six-month time period versus comparators or placebo. SUNRISE 1 was a 1,006 partipant study with a primary outcome of a change from baseline in mean latency to persistent sleep (LPS). SUNDRISE had a primary efficacy endpoint as the primary endpoint for the study and is evaluated below.

	SUNRISE 1
Study Type*	Phase III, Multicenter, RCT, DB, PC, AC, PG
Interventions and Sample Size	N=1006 2-week run-in period with baseline PSG, then 30 nights treatment followed by a follow-up period of 14-18 days. Patients were randomized (5:5:5:4 ratio) to receive Dayvigo 5mg, Dayvigo 10mg, zolpidem tartrate ER 6.25mg, or placebo.
Populations	*Inclusions*: • Patients 55 years of age or older • Patients who met DSM-5 criteria for insomnia disorder • History of sWASO ≥ 60 minutes on at least 3 nights per week in the previous 4 weeks • Regular time spent in bed (7-9 hours) • Evidency of sleep maintenance insomnia • Insomnia Severity Index (ISI) score ≥ 13 *Exclusions:* • Current diagnosis of sleep-related breathing disorder (e.g. obstructive sleep apnea, periodic limb movement disorder, restless legs syndrome, circadian rhythm sleep disorder, or narcolepsy)

	SUNRISE 1
	• On the Munich Parasomnia Scale (MUPS), history of sleep-eating or reports a history of sleep-related violent behavior, sleep-driving, or symptoms of another parasomnia • Apnea-Hypopnea Index > 15 or Periodic Limb Movement with Arousal Index >15 as measured on the PSG at the second screening visit • Beck Depression Inventory - II (BDI-II) score >19 at Screening • Beck Anxiety Index (BAI) score >15 at Screening • A prolonged QT/QTcF interval (QTcF >450 milliseconds [ms]) as demonstrated by a repeated electrocardiogram (ECG) at Screening (repeated only if initial ECG indicates a QTcF interval >450 ms) • Comorbid nocturia resulting in frequent need to get out of bed to use the bathroom during the night • Any suicidal ideation/behavior

General Summary: Efficacy	**<u>Primary Endpoint:</u>**
	• Sleep onset by polysomnograpy (PSG) assessed by latency to persistent sleep (LPS; defined as minutes from lights off to the first epoch of 20 consecutive 30-second epochs of nonwakefulness) after the last 2 nights (nights 29 and 30) of 1 month of treatment
	  ○ Dayvigo 5mg vs placebo, 0.85; 95%CI, 0.75-0.96; *P* = .009
	  ○ Dayvigo 10mg vs placebo, 0.80; 95%CI, 0.70-0.90; *P* < .001
	  ○ zolpidem therapy; LSGM ratio vs zolpidem for lemborexant 5mg, 0.87; 95%CI, 0.78-0.98; *P* = .02
	  ○ zolpidem therapy; LSGM ratio vs zolpidem for lemborexant 10mg, 0.82; 95%CI, 0.73-0.92; *P* < .001
	<u>Key Secondary Endpoints:</u>
	• Sleep efficiency (proportion of time spent asleep per time in bed, calculated as total sleep time/interval from lights off until lights on [standardized at 8 hours])
	• Minutes of wake from LPS until lights on (WASO)
	• WASO in the second half of the night (WASO2H; minutes of wake from 240 minutes after lights off until lights on)

General Summary: Safety	The most common adverse reaction (reported in ≥5% of patients treated with Dayvigo and at least twice the rate of placebo) was somnolence. Dayvigo is contraindicated in patients with narcolepsy.
Comments	The study was conducted in North America and Europe, therefore would be applicable in US patients. Although, there was a larger percentage of female participants (86.4%) vs male participants. 72.3% of the participants were white, 25.4% were black. The age range was at least 55 years old, which may conflict with American Academy of Sleep Medicine and American Geriatric Society guidelines for foregoing use of sedative-hypnotic drugs in older adults due to risk of falls, hip fractures and risk of unintentional injury. Also, the end points used in this study included subjective criteria; there could be memory/recall discrepancies provided by self-reported sleep

	SUNRISE 1
	diaries. Because the study period was 1 month, the effects of long-term use of lemborexant therapy are not yet known.
Grade^	▪ A1

*Study type abbreviations: AC=Active-comparator, CC=Case-control study, COH=Cohort study, CS=Case study, DB=double blind, EPI=Epidemiologic study, META=Meta-analysis, NRCT=Nonrandomized clinical trial, OBS=Observational study, PC=placebo-controlled, PG=parallel-group, RCT=randomized trial, XO=crossover [if not listed, please type in under study type]
^A=Useful, B=Possibly useful, C=Possible to uncertain usefulness, U=Uncertain validity and/or usefulness, X=Not useful
(For further information, please refer to the document Grading of Clinical Evidence; NA=Not applicable. [Disclaimer: Grade the study if able to pull the literature]

Special Populations:

There are no available data on Dayvigo use in pregnant women, breastfeeding, pediatric patients, or patients with severe hepatic impairment. Use in these populations is not recommended. No dose adjustment is required in patients with mild, moderate, or severe renal impairment.

Because Dayvigo can increase somnolence and drowsiness, patients, particularly the elderly, are at a higher risk of falls. Exercise caution when using doses higher than 5 mg in patients ≥ 65 years old.

Cost and/or Utilization Data of Similar Treatment Options:

Table 2: Insomnia Treatment Pricing

Drug	Strength	WAC/unit	Package size	WAC/month
Dayvigo	5mg, 10mg	$9.16	30	$274.80
Belsomra	10mg	$12.19	30	$365.70
Zolpidem tartrate	10mg	0.08	100	$2.40

Place in Therapy:

Table 5. Comparison of Dayvigo with Belsomra.

	Dayvigo (lemborexant)	Belsomra (suvorexant)
Meet an Unmet Medical Need[1]	☒ No – There are other non-benzodiazepine sleep agents on the formulary and no studies have been completed to show Dayvigo superior with respect to safety or efficacy to other non-benzodiazepine sleep agents.	
Comparable Efficacy[2]	☒ Dayvigo is similarly efficacious relative to Belsomra Comment: Both Dayvigo and Belsomra are currently indicated for the treatment of insomnia, characterized by difficulties with sleep onset and/or sleep maintenance	
Comparable Safety[3]	☒ Dayvigo would likely have similar safety relative to Belsomra. **Comment:** Dayvigo has a clear safety profile, similar to Belsomra. Both Dayvigo and Belsomra provide treatment options for patients with insomnia.	
Comparable Cost-Effectiveness[4]	☒ Dayvigo would likely have a similar cost effectiveness relative to Belsomra. **Comment:** Dayvigo is priced at ~$9.16tab allowed cost, whereas Belsomra is priced at 12.19/tab allowed cost.	
Adherence[5]	☒ Members taking Dayvigo would likely achieve a similar adherence rate relative to Belsomra	

	Comment: Dayvigo and Belsomra are both once daily oral agents with similar safety and efficacy, and no adverse events that may change adherence.	
Advantages	▪ New treatment option for insomnia for both sleep initiation and maintenance symptoms	▪ Longer history of provider experience ▪ Has expanded use for treatment of patients with mild-mod AD via clinical trials
Disadvantages	▪ Lack of provider experience ▪ No indication in mild-mod AD; despite lack of information in label (unlike Belsomra) about use in AD/dementia patients, the company is currently studying Dayvigo for that population for a future label expansion for indication	
Comments	▪ Dayvigo provides a similar benefit to patients as Belsomra. ▪ There may be underlying conditions causing the patient's insomnia, providers should address these possible causes prior to initiating therapy for insomnia. Once it is determined that treatment for insomnia is appropriate, the decision as to which product to use may center on the type of insomnia (difficulty falling asleep, difficulty staying asleep, middle-of-the-night awakening) as well as available drugs to treat each type.	

Definitions

1. Unmet medical need - Medical need that is not addressed adequately by an existing therapy (examples: a) No available therapy for condition exists b) If available therapy for the condition exists i) New therapy has improved effects on serious outcomes, ii) Similar benefits to alternative therapies while avoiding serious toxicity).[IV]
2. Efficacy – The extent to which an intervention produces a beneficial result under ideal conditions (i.e clinical trials). [III]
3. Safety – Substantive evidence of an absence of harm (examples: clinical adverse events (disease, signs, and symptoms).[II]
4. Cost-effectiveness – The cost and health benefits associated with the use of the drug therapies.[I]
5. Adherence - The consistence and accuracy with which a patient will follow a recommended medical regimen (examples of factors that may affect adherence: frequency of administration, adverse events, cost of drug).[I]

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Recommendation:
KY Medicaid: NF

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