Humana

Minutes

Kentucky Medicaid Plan Pharmacy and Therapeutics Meeting

Date: March 26, 2020
Time: 9:00 – 11:00am EST

Teleconferance Dial-In: 1-800-937-7000 (access code): 590507986 (posted to the web)

X: when in attendance

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

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:** • **December P&T**	
Presenter	**Policy Title**	**Policy Type**
	Review of Existing Clinical Policies – No Recommended Clinical Changes (58)	
Andrea Bloomfield	Lotronex (alosetron HCl)	Prior Authorization
	Soriatane (acitretin)	Prior Authorization
	Topical Antivirals	Prior Authorization
	Topical Retinoid Products	Prior Authorization
	Dupixent (dupilumab) injection	Prior Authorization
	Zortress (everolimus)	Prior Authorization
Brian Garcia	Corifact (Factor XIII Concentrate [Human])	Prior Authorization
	Factor IX Replacement Products (Hemophilia B)	Prior Authorization
	FEIBA NF (Anti-Inhibitor Coagulant Complex)	Prior Authorization
	NovoSeven RT (Coagulation Factor VIIa [Recombinant])	Prior Authorization
	Obizur [Antihemophilic (recombinant), porcine sequence]	Prior Authorization
	Orkambi (lumacaftor/ivacaftor)	Prior Authorization
	Drug Utilization Management and Clinical Edits Tools	Guidance
	Thrombate III [Antithrombin III (Human)]	Prior Authorization
	Tretten (Coagulation Factor XIII A-Subunit [Recombinant])	Prior Authorization
Brock Bizzell	Prialt (ziconotide intrathecal infusion)	Prior Authorization
	Yutiq (fluocinolone acetonide intravitreal implant)	Prior Authorization
	Opiod Day's Supply	Quantity Limit
	Qutenza (capsaicin)	Prior Authorization
Daniel Cornett	Rubraca (rucaparib)	Prior Authorization
Kenneth Kennedy	Beleodaq (belinostat)	Prior Authorization
	Defitelio (defibrotide sodium)	Prior Authorization
	Lupron (leuprolide acetate)	Prior Authorization
	Provenge (sipuleucel-T)	Prior Authorization
	Vitrakvi (larotrectinib)	Prior Authorization
	Xofigo (radium Ra 223 dichloride)	Prior Authorization
	Xospata (gilteritinib)	Prior Authorization
	Zoladex (goserelin)	Prior Authorization
	Arzerra (ofatumumab)	Prior Authorization

	Besponsa (inotuzumab ozogamicin)	Prior Authorization
	Elzonris (tagraxofusp-erzs)	Prior Authorization
	Mylotarg (gemtuzumab ozogamicin)	Prior Authorization
	Oncaspar (pegaspargase)	Prior Authorization
	Oral tretinoin (tretinoin capsule)	Prior Authorization
	Pomalyst (pomalidomide)	Prior Authorization
	Rydapt® (midostaurin)	Prior Authorization
	Unituxin (dinutuximab)	Prior Authorization
Mike Tindal	Briviact (brivaracetam)	Prior Authorization
	Elaprase (idursulfase)	Prior Authorization
	Exondys 51 (eteplirsen)	Prior Authorization
	Kanuma (sebelipase alfa)	Prior Authorization
	Kuvan (sapropterin)	Prior Authorization
	Lumizyme (alglucosidase alpha)	Prior Authorization
Sheetal Sheth	Erivedge (vismodegib)	Prior Authorization
	Bevacizumab products	Prior Authorization
	Caprelsa (vandetanib)	Prior Authorization
	Cometriq (cabozantinib)	Prior Authorization
	Medication Waste	Guidance
	Odomzo (sonidegib)	Prior Authorization
	Votrient (pazopanib)	Prior Authorization
	Cabometyx (cabozantinib)	Prior Authorization
	Levoleucovorin products (Fusilev, Khapzory)	Prior Authorization
	Stivarga (regorafenib)	Prior Authorization
	Tykerb (lapatinib)	Prior Authorization
Yunus Meah	Nuplazid (pimavanserin)	Prior Authorization
	Modafinil	Prior Authorization
	Xyrem (sodium oxybate)	Prior Authorization
	Review of Existing Clinical Policies – Recommended Clinical Changes (24)	
Devin Pence	Reasonable Quantity Edit	Guidance
Kenneth Kennedy	Calquence (acalabrutinib)	Prior Authorization
	Daurismo (glasdegib)	Prior Authorization
	Erleada (apalutamide)	Prior Authorization
	Imbruvica (ibrutinib)	Prior Authorization
	Nubeqa (darolutamide)	Prior Authorization
	Rituximab products	Prior Authorization
	Sylvant (siltuximab)	Prior Authorization
Daniel Cornett	IVIG (Immune Globulin)	Prior Authorization

	Lynparza (olaparib)	Prior Authorization
	Tecentriq (atezolizumab)	Prior Authorization
	Xgeva (denosumab)	Prior Authorization
Sheetal Sheth	Keytruda (pembrolizumab)	Prior Authorization
	Verzenio (abemaciclib)	Prior Authorization
Mike Tindal	Botox (botulinum toxin)	Prior Authorization
	Glatiramer Products	Prior Authorization
	Growth Hormones	Prior Authorization
	Ocrevus (ocrelizumab)	Prior Authorization
	Tysabri (natalizumab)	Prior Authorization
Brock Bizzell	Lidocaine 5% topical patch	Prior Authorization
	Zilretta (triamcinolone acetonide extended-release injectable suspensión)	Prior Authorization
Brian Garcia	Factor VIII Replacement Products (Hemophilia A)	Prior Authorization
Yunus Meah	Antipsychotic Utilization Program	Prior Authorization
	Pediatric Antipsychotic Utilization Program	Prior Authorization

	Therapeutic Class Review
Presenter	**Topic**
Brock Bizzell	AMD VEGF Inhibitors
Andrea Bloomfield	Anemia in CKD
Mike Tindal	Alzheimer's Disease

	New Drug Clinical Reviews
Presenter	**Topic**
Andrea Bloomfield	Givlaari (givosiran)
Brian Garcia	Reblozyl (luspatercept-aamt)
	Trikafta (elexacaftor-tezacaftor-ivacaftor)
	Esperoct (Antihemophilic factor [recombinant], glycopegylated-exei)
Brock Bizzell	Reyvow (lasmiditan)
	Beovu (brolucizumab)
	Ubrelvy (ubrogepant)
Daniel Cornett	Padcev (enfortumab vedotin-ejfv)
Kenneth Kennedy	Brukinsa (zanubrutinib)
Mike Tindal	Rybelsus (semaglutide)

Sheetal Sheth	Ayvakit (avapritinib)
	Enhertu (fam-trastuzumab deruxtecan-nxki)
Yunus Meah	Caplyta (lumateperone)

	New Clinical Policies (7)	
Presenter	**Policy Title**	**Policy Type**
Andrea Bloomfield	Givlaari (givosiran)	Prior Authorization
Brian Garcia	Trikafta (elexacaftor-tezacaftor-ivacaftor)	Prior Authorization
Brock Bizzell	Beovu (bolucizumab)	Prior Authorization
Daniel Cornett	Padcev (efortumab vedotin-ejfv)	Prior Authorization
Sheetal Sheth	Enhertu (fam-trastuzumab deruxtecan-nxki)	Prior Authorization
Mike Tindal	Spinraza (nuninersen)	Prior Authorization
	Zolgensma (onasemnogene abeparvovec-xlol)	Prior Authorization

	Formulary Updates
Presenter	
Andrea Bloomfield	

	Other Topics/Operational Policies
Presenter	**Topic**
Andrea Bloomfield	PT 20.001 KY Medicaid Pharmacy and Therapeutics Committee
	PT 20.002 Medicaid Periodic and Annual Review of New Drugs
	PT 20.003 Medicaid Physician Administered Drugs and Exceptions
	PT 20.004 Medical and Clinical Edits
	PT 20.005 Medicaid Formulary Change Notification

	Archived Clinical Policies	
Presenter	**Policy Title**	**Policy Type**
Mike Tindal	Copaxone (glatiramer)	Prior Authorization

	Questions/Discussion
Presenter	

Facilitator	Meeting Adjournment
Andrea Bloomfield	• **Follow up and action items** • **Closing Remarks**

Announcements:

- Humana is currently instituting state directives due to COVID-19. The various directives were described to the meeting participants.
- Current membership is 144,549.

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:

- All listed clinical policies with no recommended clinical 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 AMD VEGF inhibitors, Anemia in CKD agents, and Alzheimer's Disease drugs. No changes recommended. Approved by the committee.

New 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:

- None.

Other Topics/Operational Policies:

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

Archived Clinical Policies:

- Listed archived clinical policy was approved by the committee.

Questions/Discussion:

- None.

Follow up and action items:

- None.

Closing Remarks:

- Next meeting will be June 25, 2020.

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Humana Pharmacy Solutions

Clinical Review – Givlaari™ (givosiran)

***Company*:** Anylam Pharmaceuticals
Current Status: FDA Approved November 2020 and currently marketed
Therapeutic Category: acute hepatic porphyria treatment
Pharmacologic Category: aminolevulinate synthase 1-drected small interfering molecule
Similar Drugs: None
Route of Administration: subcutaneous injection
Dosage Forms: 189 mg/mL single-dose vial

Indications: Givlaari (givosiran) is indicated for the treatment of adults with acute hepatic porphyria (AHP).

Dosage and Administration:

- The recommended dose of Givlaari (givosiran) is 2.5 mg/kg administered via subcutaneous injection once monthly. In patients with severe or clinically significant transaminase elevations, who have dose interruption and subsequent improvement, reduce the dose to 1.25 mg/kg once monthly. In patients who resume dosing at 1.25 mg/kg once monthly without recurrence of severe or clinically significant transaminase elevations, the dose may be increased to the recommended dose of 2.5 mg/kg once monthly.
- Ensure that medical support is available to appropriately manage anaphylactic reactions.
- Givlaari is intended for subcutaneous use by a healthcare professional only.

Background:

Acute hepatic porphyrias are a group of four inherited disorders, each resulting from the deficient activity of a specific enzyme in the heme biosynthesis pathway and they present clinically with neurovisceral symptoms which may be sporadic or recurrent and potentially severe. The four disorders include acute intermittent porphyria (AIP), hereditary coproporphyria (HCP), variegate porphyria (VP) and 5-aminolevulinic acid dehydratase deficiency porphyria (ADP). All are characterized clinically by neurovisceral symptoms. These symptoms may include abdominal pain, nausea, and occasionally seizures.

The combined prevalence of the disorders is estimated to be 5 per 100,000. Greater than 90% of heterozygotes for the disease-causing mutations remain asymptomatic for life. About 3-5% of patients have recurrent attacks (greater than 4 attacks per year). Patients with acute hepatic porphyrias are predisposed to triggering factors such as certain drugs, stress, fasting, alcohol use, smoking, and female sex hormones. Symptomatic attacks occur primarily in females between 14 and 15 years of age.

Management of acute hepatic porphyria attacks consists of identification and avoidance of precipitating factors. Hemin is used to treat acute attacks and has been used prophylactically to prevent acute attacks if they still occur after identifiable precipitating factors are eliminated. Cyclic attacks that occur related to the menstrual cycle have been managed using a GnRH analog or low-dose oral contraceptives.

Pharmacology:

- Givlaari (givosiran) is an aminolevulinate synthase 1-directed small interfering molecule.
- Givosiran is a double-stranded small interfering RNA that causes degradation of aminolevulinate synthase 1 (ALAS1) mRNA in hepatocytes through RNA interference, reducing the elevated levels of liver ALAS1 mRNA. This leads to reduced circulating levels of neurotoxic intermediates aminolevulinic acid (ALA) and porphobilinogen (PBG), factors associated with attacks and other disease manifestations of AHP.

Pharmacokinetics:

		Givosiran	AS(N-1)3′ Givosiran
General Information			
Steady-State Exposure	**C_{max} [Mean (CV%)]**	321 ng/mL (51%)	123 ng/mL (64%)
	AUC_{24} [Mean (CV%)]	4130 ng·h/mL (43%)	1930 ng·h/mL (63%)
Dose Proportionality		• Steady-state maximum plasma concentration (C_{max}) and area under the curve (AUC) for givosiran and AS(N-1)3′ givosiran increase proportionally over the 0.35 mg/kg to 2.5 mg/kg once monthly dose range (0.14 to 1-fold the approved recommended dosage). • C_{max} and AUC for givosiran and AS(N-1)3′ givosiran increase slightly greater than proportionally at doses greater than 2.5 mg/kg once monthly.	
Accumulation		• No accumulation of givosiran or AS(N-1)3′ givosiran was observed following multiple dosing.	
Absorption			
T_{max} [Median (range)]		3 (0.5-8) hours	7 (1.5-12) hours
Distribution			
Apparent Central Volume of Distribution (Vz/F) [Mean (RSE%)][a]		10.4 L (2.3%)	
Protein Binding		90%[b]	Not evaluated
Organ Distribution		Givosiran and AS(N-1)3′ givosiran distribute primarily to the liver after subcutaneous dosing.	
Elimination			
Half-Life [Mean (CV%)]		6 hours (46%)	6 hours (41%)
Apparent Clearance [Mean (CV%)][a]		35.1 L/hr (18%)	64.7 L/hr (33%)
Metabolism			
Primary Pathway		Givosiran is metabolized by nucleases to oligonucleotides of shorter lengths. Givosiran is not a substrate of CYP enzymes[c].	
Active Metabolite		The active metabolite, AS(N-1)3′ givosiran, is equipotent to givosiran in plasma and the AUC_{0-24} represents 45% of givosiran AUC, at the approved recommended givosiran dosage.	
Excretion			
Primary Pathway		The dose recovered in urine was 5%-14% as givosiran and 4%-13% as AS(N-1)3′ givosiran[d].	

[a] Based on population PK model estimation.
[b] Givosiran plasma protein binding was concentration-dependent and decreased with increasing givosiran concentrations (from 92% at 1 µg/mL to 21% at 50 µg/mL).
[c] Based on in vitro study result.
[d] After single and multiple subcutaneous doses of givosiran 2.5 mg/kg and 5 mg/kg.

Drug Interactions:

- Increases the concentration of CYP1A2 and CYP2D6 substrates which may increase the adverse reactions of these substrates. Avoid with substrates for which minimal concentration changes may lead to serious toxicities. May also decrease dosage of those substrates.

Contraindications:

- Patients with known severe hypersensitivity to givosiran. Anaphylaxis has occurred with givosiran.

Warnings and Precautions:

- Anaphylaxis has occurred with GIVLAARI treatment (<1% of patients in clinical trials). Ensure that medical support is available to appropriately manage anaphylactic reactions when administering. If anaphylaxis occurs, immediately discontinue administration of GIVLAARI and institute appropriate medical treatment.
- Transaminase elevations (ALT) of at least 3 times the upper limit of normal (ULN) were observed in 15% of patients treated with GIVLAARI in the placebo-controlled trial. Transaminase elevations primarily occurred between 3 to 5 months following initiation of treatment. Measure liver function tests prior to initiating treatment with GIVLAARI, repeat every month during the first 6 months of treatment, and as clinically indicated thereafter. Interrupt or discontinue treatment for severe or clinically significant transaminase elevations. Follow dosing guidelines for resumption of treatment.
- Increases in serum creatinine levels and decreases in estimated glomerular filtration rate (eGFR) have been reported during treatment. In the placebo-controlled study, 15% of the patients in the givosiran arm experienced a renally-related adverse reaction. The median increase in creatinine at Month 3 was 0.07 mg/dL. Monitor renal function during treatment as clinically indicated.

Adverse Reactions:

- Anaphylactic reactions (<1% of patients in clinical trials)
- Transaminase Elevations (ALT of at least 3 times the ULN in 15% patients in placebo controlled trial)
- Serum Creatinine Increase (15% of patients in placebo controlled trial)
- Injection site reactions (25% of patients in placebo controlled trial)

Special Populations:

- Pregnancy and lactation: No data on the effects of givosiran on lactation or pregnancy in women.
- Hepatic Impairment: Dose should be interrupted for severe or clinically significant transaminase elevations.
- Renal Impairment: No specific recommendations.

- Pediatric use: Safety and efficacy has not been established.
- Geriatric use: Clinical trials did not include a sufficient number of patients over 65 to determine differences.

Evidence Table of Clinical Studies:

Table 1. Clinical data for Givlaari (givosiran).

	ENVISION [NCT03338816]
Study Type*	Phase III, DB, PC, Multicenter, multinational
Interventions and Sample Size	Randomized 1:1 to receive Givlaari or placebo qmonth for 6 months (N=94)
Populations	Inclusion criteria: • Greater than or equal to 2 documented porphyria attacks in past 6 months ○ Composite porphyria attack defined as those requiring hospitalization, an urgent healthcare visit, or intravenous hemin administration at home. • Greater than or equal to 12 years of age • Elevated urinary or plasma ALA or PBG values in last year • Discontinue hemin prophylaxis or not use hemin prophylaxis • Negative pregnancy test and use of contraceptive Exclusion criteria: • Anticipated liver transplant • Pancreatitis • Active HIV, HCV or HBV Population Characteristics: Givlaari vs Placebo. Table 10. ENVISION key demographic and baseline characteristics Parameter / Placebo (n=46) / GIVLAARI (n=48) Age, y, median (range) 36 (20, 60) 42 (19, 65) Female, n (%) 41 (89) 43 (90) Race, n (%) White/Caucasian 34 (74) 39 (81) Asian 7 (15) 8 (17) Other 5 (11) 1 (2) Age at diagnosis, y, median (range) 29 (17, 51) 30 (5, 58) Region, n (%) North America 18 (39) 16 (33) Europe 19 (41) 23 (48) Other 9 (20) 9 (19) AHP type, n (%) AIP 43 (94) 46 (96) HCP 0 1 (2) VP 1 (2) 1 (2) AHP without identified mutation 2 (4) 0 Porphyria attacks* in past 6 mo, median (range) 3 (0, 25) 4 (2, 24) Prior hemin prophylaxis therapy, n (%) 18 (39) 20 (42) Used opioids daily or most days in between attacks, n (%) 13 (28) 14 (29) Daily chronic symptoms between attacks, n (%) 26 (57) 23 (48) Current or prior central venous catheter, n (%) 32 (70) 35 (73) Ever diagnosed with neuropathy, n (%) 16 (35) 20 (42) Ever diagnosed with iron overload, n (%) 15 (33) 16 (33) Liver transaminase elevation (>ULN), n (%)† 3 (7) 13 (27) eGFR <60 mL/min/1.73 m², n (%) 11 (24) 16 (33)

	ENVISION [NCT03338816]

General Summary: Efficacy	**Primary endpoint**:
	• Reduction in mean annualized rate of composite porphyria attacks compared to placebo (Measured in AIP which is the most common type)
	  ○ 74% reduction (P<0.001); 3.2 vs 12.5 attacks.
	  ○ Similar reduction across all pre-specified subgroups (age, race, region, bmi, prior hemin prophylaxis status, attack rate, prior opioid use, and presence of prior chronic symptoms when not having attacks.
	
	Secondary endpoints of interest: Givlaari vs. Placebo.
	• Hemin use
	  ○ 6.77 vs 29.71 annualized days on hemin in AIP
	• ALA and PBG levels
	  ○ ALA: 1.8 vs 20 at 6 months
	  ○ PBG: 13 vs 49
	• Composite attack rate in all AHP patients
	  ○ 3.35 vs 12.26
	
	Secondary endpoints that did not achieve statistical significance are: Change in daily worst pain, change in daily worst fatigue, change in daily worst nausea, improvement in short form 12 health survey.

General Summary: Safety	• Safety report from ENVISION trial plus extension study.
	• Frequency of adverse events was comparable in treatment arms.
	• No deaths reported.
	• 20.8% of patients reported serious adverse events verses 8.7% in placebo arm
	  ○ ALT levels higher than 3x the ULN were reported in 14.6% of patients while only 2.2% on placebo. One patient permanently discontinued due to elevations higher than 8x ULN. Most stabilized by month 6.
	  ○ Increases in serum creatinine and decreases in eGFR occurred in 15% of patients. The increases resolved by month 6. No discontinuations occurred.
	• AE's occurring in in greater than or equal to 5% difference in treatment groups

Category, n (%)	Placebo (n=46)	GIVLAARI (n=48)
AEs with higher frequency in the GIVLAARI group		
Injection site reaction	0	8 (16.7)
Nausea	5 (10.9)	13 (27.1)
Chronic kidney disease	0	5 (10.4)
Glomerular filtration rate decreased	0	3 (6.3)
Rash	0	3 (6.3)
Alanine aminotransferase increased	1 (2.2)	4 (8.3)
Fatigue	2 (4.3)	5 (10.4)
AEs with higher frequency in the placebo group		
Pyrexia	6 (13.0)	1 (2.1)
Hypoaesthesia	4 (8.7)	0
Dyspepsia	4 (8.7)	0
Vomiting	5 (10.9)	2 (4.2)
Urinary tract infection	6 (13.0)	3 (6.3)
Back pain	4 (8.7)	1 (2.1)

	ENVISION [NCT03338816]
Comments	• Study did not compare to hemin prophylaxis, hormone regulation, dietary management, trigger avoidance. Little information on how the participant triggers were controlled during the trial. • Did not reach statistical significance demonstrating improvement in several secondary clinical endpoints. • Several significant safety concerns such as renal and hepatic adverse events as well as potential anaphylaxis.
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]

Cost and/or Utilization Data of Similar Treatment Options:

Table 2: Pricing

Drug	Strength	Package size	WAC/Package	WAC/Year
Givlaari	189/ml	1 ml	$39,000	~$575,000
Panhematin	350mg/vial	1 vial	$7,902	~410,904
Luprelide	1mg/0.2mL	14 syringes/1 kit	$705	~16,000
Amethia (numerous Oral contraceptives are covered)	0.15-0.03-.01mg	91	$214	~856

Table 3: Humana Tiering for Similar Treatment Options

	Panhematin	Leuprolide
KYMD	NF	T1W/PA

Place in Therapy:

Table 4. Comparison of Givlaari (givosiran) current treatments

	Givlaari (givosiran)
Meet an Unmet Medical Need[1]	No **Comment:** • Acute hepatic porphyria disorders are very rare and even symptomatic disease is even uncommon. Only 10% of patients with the disorder are symptomatic and only about 5% have frequent attacks. Around 80-90% of the patients who have acute attacks are pre-menopausal females. The condition does not generally occur in post-menopausal women. There were no patients in the phase III trial that were over 65. • Because attacks occur due to triggers, the Porphyrias Consortium of the Rare Diseases Clinical Research Network's 2017 treatment recommendations include avoiding triggers (e.g. adequate diet and hydration, avoiding certain medications that are known triggers).

	Additionally for female patients with hormone related attacks GnRH agonists and low dose hormonal contraceptives are recommended options. Hemin prophylaxis is also recommended for those that continue to experience attacks. These medication treatments are off-label. • The condition is not common to Humana's population and treatments recommended by the Porphyria's Consortium are available. • Additionally, Givlaari should be medically administered and requires monitoring. It is not recommended to be self-administered.
Comparable Efficacy[2]	**Comment:** Trials did not compare givosiran to known recommended treatments such as avoidance of triggers, hormone regulation or hemin prophylaxis.
Comparable Safety[3]	**Comment:** Existing recommended treatments such as hemin prophylaxis or hormone regulation have potential side effects including iron overload for hemin and bone loss and menopausal symptoms with GnRH agonist (estradiol replacement would should be provided), however, givosiran also has the risk of serious renal and hepatic adverse effects. Avoidance of triggers would likely be safer than other options.
Comparable Cost-Effectiveness[4]	**Comment:** Givlaari would be more expensive than current recommended options but the true cost-effectiveness is due to lack of head to head trials.
Adherence[5]	**Comment:** Similar adherence to available options is likely.
Advantages	• Givlaari is the first drug to receive FDA approval for the treatment of acute hepatic porphyria. • Demonstrated a statistically significant reduction in attacks and showed a reduction in toxin levels.
Disadvantages	• Givlaari is associated with serious hepatic and renal adverse effects as well as anaphylaxis. • It's expensive. • Did not demonstrate a statistically significant improvement in daily worst pain, daily worst fatigue, daily worst nausea, or in short form 12 health survey. • Unclear how Givlaari compares to existing treatments.

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.

Formulary Recommendation:

- Medicaid: Non-formulary, MIT PAL

References:

1. IBM Micromedex® DRUGDEX® (electronic version). Truven Health Analytics, Greenwood Village, Colorado, USA. Available at: http://www.micromedexsolutions.com/(March 2020).
2. Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc.; URL: http://www.clinicalpharmacology.com. (March 2020).
3. GIivlaari (givosiran) [Package Insert]. Cambridge, MA: Alnylam Pharmaceuticals, Inc; 2019.
4. Gouya L, Ventura P, Balwani M, Bissell DM, Rees DC, et al. EXPLORE: A prospective, multinational, natural history study of patients with acute hepatic porphyria with recurrent attacks [published online ahead of print, September 12, 2019]. Hepatology. 2019; doi: 10.1002/hep.30936.
5. Balwani M, Wang B, Yazici C, Anderson KE, Bissell DM, et al. Acute Hepatic Porphyrias: Recommendations for Evaluation and Long Term Management. Heptatology 2017; 66(4): 1314-1322.
6. Wang B, Rudnick Sean, Cegia B, Bonkovsky HL. Acute Hepatic Porphyrias: Review and Recent Progress. Hepatology Communications 2019;3:193-206.

***Company*:** Celgene
Current Status: FDA Approved November 8th 2019
Launch: November 16th 2019
Therapeutic Category: Beta-thalassemia
Pharmacologic Category: Erythroid Maturation Agent (EMA)
Similar Drugs: None
Route of Administration: Subcutaneous injection
Dosage Forms: Lyophilized powder for reconstitution

Indications: Treatment of anemia in adult patients with beta thalassemia who require regular red blood cell (RBC) transfusions.

- Reblozyl is not indicated for use as a substitute for RBC transfusions in patients who require immediate correction of anemia.

Dosage and Administration:
Reblozyl is administered at 1mg/kg once every 3 weeks by subcutaneous injection.
Assess and review hemoglobin (Hgb) results prior to each administration.

- If an RBC transfusion occurred prior to dosing, the pretransfusion Hgb must be considered for dosing purposes.
- If the pre-dose Hgb is $\geq$ 11.5g/dL and the Hgb level is not influenced by recent transfusion, delay dosing until the Hgb is $\leq$ 11g/dL.

Background:
Beta-thalassemia is a hereditary hemoglobinopathy due to a globin chain synthesis production defect creating impaired production of beta globin chains and an excess of unstable alpha globin chains, leading to ineffective erythropoiesis and anemia. Currently the standard of care for management of Beta-thalassemia is life-long red blood cell transfusions and iron chelation. The incidence of Beta-thalassemia in the US is small, but the at-risk population has increased over the past 5 decades, likely due in part to the immigration of people from countries with a higher risk of thalassemia. As of April 2019, the international ITHANET hemoglobinopathy database lists only 716 known cases of Beta-thalassemia in the US, with 0.4% of the population estimated as carriers for the disease.

Pharmacology:
Luspatercept-aamt is a recombinant fusion protein that binds several endogenous TGF-Beta superfamily ligands, thereby diminishing Smad2/3 signaling. Luspatercept-aamt promoted erythroid maturation through differentiation of late-stage erythroid precursors (normoblasts), and decreased abnormally elevated Smad2/3 signaling and improved hematology parameters associated with ineffective erythropoiesis in nonclinical trials.

Pharmacokinetics:
Absorption/Distribution: The median time to maximum concentration of luspatercept-aamt was approximately 7 days post-dose in patients with beta thalassemia.

Metabolism/Elimination: Luspatercept-aamt is expected to be catabolized into amino acids by general protein degradation processes in multiple tissues and has a mean apparent total clearance of 0.44L/day in patients with beta thalassemia.
Plasma Half-Life (hrs): Mean half-life was approximately 11 days

Drug Interactions:

- No clinically significant differences in luspatercept-aamt PK were observed when used concomitantly with iron chelating agents

Adverse Effects:

Clinically significant adverse reactions included Thrombosis/Thromboembolism and Hypertension, discussed in the *Warnings and Precautions* section below.
The most common adverse reactions (at least 10% were headache, bone pain, arthralgia, fatigue, cough, abdominal pain, diarrhea, and dizziness. Of note, hyperuricemia occurred in 7% of patients, with 3% of these patients having a Grade 3 or higher adverse reaction.
Liver Function abnormalities also occurred, with 11-12% of patients having ALT and AST $\geq$ 3x ULN, and 64% of patients have total bilirubin $\geq$2x ULN.

Contraindications:

- None

Warnings and Precautions:

- *Thrombosis/Thromboembolism*: reported in 3.6% of treated patients, including DVT, PE, portal vein thrombosis, ischemic strokes. Patients with known risk factors at higher risk, consider thromboprophylaxis in patients with increased risk
- *Hypertension*: reported in 10.7% of treated patients. Grade 3-4 HTN ranged from 1.8%-8.6%. 6.2% of patients with normal baseline BP developed HTN.
- *Embryo-Fetal Toxicity*: Administration may result in adverse developmental outcomes including increased embryo-fetal mortality, alterations to growth, and structural abnormalities at the maximum recommended human dose.

Monitoring:

- Monitor patients for signs and symptoms of thromboembolic events and institute treatment promptly
- Monitor blood pressure prior to each administration, mange new-onset HTN/exacerbation using anti-hypertensive agents

Evidence Table of Clinical Studies:

Table 1. Clinical data for Reblozyl (luspatercept-aamt)

	BELIEVE Trial Cappellini MD, et al. /2018
Study Type*	Phase III Multicenter, DB, PC, RCT
Interventions and Sample Size	N=336

Humana
Pharmacy Solutions

	BELIEVE Trial Cappellini MD, et al. /2018
	Subjects randomized 2:1 Luspatercept+BSC* (n=224) vs placebo + BSC (n=112) every 21 days for 48 weeks. *BSC=Best Supportive Care: RBC Transfusions, iron chelation therapy, use of abx, antivirals, antifungals, and/or nutritional support
Populations	Inclusion Criteria • Age ≥ 18 years • Dx of Beta-thalassemia or HbE/Beta-thalassemia (Beta-thalassemia with mutations and/or multiplications of alpha-globin was allowed) • Requirement of regular RBCTs: 6 to 20 RBC units received within 24 weeks before randomization and no transfusion-free periods of ≥ 35 days within the same time period • ECOG score 0 or 1 Select Exclusion Criteria • Diagnosis of Hb S/Beta-thalassemia or alpha-thalassemia • Chronic anticoagulant therapy • Chronic systemic glucocorticoid use or major surgery ≤12 weeks before randomization • Proteinuria grade ≥ 3 Baseline Characteristics: 336 patients were randomized in 2:1 ratio with median age of 30 years, 58% female, 54% white, with median Hgb of 9 and median transfusion burden of 6 units/12 weeks. 58% had already undergone splenectomy
General Summary: Efficacy	Primary Endpoint: Greater or equal to 33% reduction from baseline in RBCT burden between weeks 13 and 24 21.5% (48 of 224) versus 4.5% (5 of 112) 17% Risk Difference; 95% CI [10.4,23.6]; p <0.0001 Key Secondary Endpoint: Greater or equal to 33% reduction from baseline in RBCT burden between weeks 37 and 48; greater or equal to 50% reduction from baseline in RBCT burden between weeks 13 and 24; and weeks 37 and 48 weeks 33% reduction wk 37 to 48 - 16% Risk Difference; 95% CI [9.8, 22.4]; p <0.0001 50% reductions were also SS different, with risk difference of 5.8% (P=0.0303) in 13-24 week and 9.4% (P=0.0017) in week 37 to 48.
General Summary: Safety	Serious adverse reactions occurred in 3.6% of patients on luspatercept. Serious adverse reactions reported in 1% of patients were cerebrovascular accident and DVT. A fatal adverse reaction occurred in one patient treated with luspatercept who died due to an unconfirmed case of AML. Dosage reductions due to an adverse reaction occurred in 2.7% of patients, mostly because of hypertension and headache Dosage interruptions due to adverse reaction occurred in 15.2% of patients, with most frequent causes being upper respiratory tract infection, ALT increase, and cough.
Comments	▪ Study is being continued in up to 5 year OLE with additional post-treatment follow-up of 3 years on top of original 48 week study. Luspatercept had durability of effect for both short term and long term treatment with continued SS reduction of RBC transfusions. ▪ Subanalysis showed that 45% of luspatercept-treated patients had clinical benefit, with median duration of 76 weeks ▪ Luspatercept seems well tolerated overall, but increases in blood uric acid and AST/ALT were noted, without changes in dosing required.
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, Geriatric Use, Renal Impairment, Hepatic Impairment-Use Only Pertinent Population]

There are no recommendations for dosage adjustments for geriatric, renally impaired, or hepatically impaired patients.

Pregnancy Considerations: Luspatercept may cause fetal harm – females of reproductive potential should use effective contraception during luspatercept therapy and for at least 3 months after last luspatercept dose

Breastfeeding considerations: Breastfeeding is not recommended during therapy and for 3 months after the last luspatercept dose.

Cost and/or Utilization Data of Similar Treatment Options:

Table 2: Pricing

Drug	Strength	WAC/unit	Package size	WAC/Package
Reblozyl® (luspatercept-aamt)	25mg/vial	$137.64/mg	25mg	$3,441.18/vial
Reblozyl® (luspatercept-aamt)	75mg/vial	$137.64/mg	75mg	$10323.53/vial

Place in Therapy:

Table 3. Reblozyl (luspatercept-aamt)

	Reblozyl (luspatercept-aamt)
Meet an Unmet Medical Need[1]	☒ **Yes.** Luspatercept provides the first medical treatment for Beta-thalassemia. Until the approval of this agent, patients had to be managed only through Red Blood Cell Transfusions (RBCTs) which carry multiple risks, and additional supportive care. Luspatercept has been shown to reduce the frequency of RBCTs and attributable consequences and risks associated with RBCTs.
Comparable Efficacy[2]	**Comment:** The results of the BELIEVE study show that luspatercept reduce the burden of RBCTs by ≥33% in 21% of patients treated with luspatercept.
Comparable Safety[3]	**Comment:** Luspatercept has a fairly benign safety profile but has warnings and precautions around thrombosis, hypertension, and embryo-fetal toxicity
Comparable Cost-Effectiveness[4]	**Comment:** Per the mfg dossier - luspatercept is expected to cost $170k for a million-member plan in 2020, risking to $380k in 2022.
Adherence[5]	**Comment:** Luspatercept has a unique dosing recommendation of 1mg/kg once every 3 weeks by subcutaneous injection with Hgb review before each administration. Luspatercept should be reconstituted and administered by a HCP, so although it has a unique dosing schedule, the requirement for HCP administration should maintain good adherence.
Advantages	▪ Only FDA-approved therapy for Beta-Thalassemia

	▪ Decreases amount of RBCTs
Disadvantages	▪ Must be Health-care administered ▪ Dosed every 3 weeks ▪ Lack of long-term data ▪ Cost
Comments	▪ Luspatercept provides a new treatment option for patients with the rare disease Beta-thalassemia. If patients do not respond to luspatercept within 9 weeks at the maximum dose level, it should be discontinued.

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]
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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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Recommendation:

Covered on Specialty Tier with a PA

References:

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3. Micromedex Healthcare Series: DRUGDEX. Thomson Micromedex, Greenwood Village, CO. 2019. Accessed December 2019.
4. Reblozyl [Package Insert]. Summit, NJ: Celgene Corporation ; Revised November 2019.
5. Reblozyl (luspatercept-aamt) [AMCP Dossier]. Summit, NJ: Celgene Corporation; Revised November 22, 2019

***Company*:** Vertex Pharmaceuticals
Current Status: FDA Approved October 22nd 2019
Launch: October 29th 2019
Therapeutic Category: Cystic Fibrosis
Pharmacologic Category: CFTR Potentiator/CFTR Corrector
Similar Drugs: Kalydeco, Symdeko, Orkambi
Route of Administration: Oral
Dosage Forms: Tablets

Indications: Indicated for the treatment of cystic fibrosis (CF) in patients aged 12 years and older who have at least one *F508del* mutation in the *CFTR* gene.

If the patient's genotype is unknown, an FDA-cleared CF mutation test should be used to confirm the presence of at least one *F508del* mutation.

Dosage and Administration:
Adults and pediatric patients aged 12 yars and older:

- Morning dose: two elexacaftor 100mg, tezacaftor, ivacaftor 75mg tablets
- Evening dose: one ivacaftor 150mg tablet
- Morning and Evening dose should be taken approximately 12 hours apart with fat-containing food.

Background: Cystic fibrosis is an orphan disease that leads to a multitude of diseases and short life expectancy. Overall, CF affects at least 30,000 people in the US with around 1,000 new diagnoses annuallyTrikafta is the 3rd combination agent, and first triple-therapy built on the ivacaftor backbone. Other medications indicated for the treatment of CF are Kalydeco (ivacaftor), Orkambi (lumacaftor/ivacaftor), and Symdeko (tezacaftor/ivacaftor + ivacaftor). Trikafta provides a new treatment option for ~5,700 patients with minimal function mutations (Het Min). CF is caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) protein, a complex chloride channel and regulatory protein. Deranged transport of chloride and/or other CFTR-affected ions leads to thick, viscous secretions in the lungs, pancreas, liver, intestine, and reproduce tract, and increased salt content in sweat gland secretions (a commonly used biomarker to determine efficacy of treatment options). Typical respiratory manifestations of CF include a persistent, productive cough, hyperinflation of the lung fields on chest radiograph, and pulmonary function tests that are consistent with obstructive airway disease.

Pharmacology: Elexacaftor and tezacaftor bind to different sites on the CFTR protein and have an additive effect in facilitating the cellular processing and trafficking of F508del-CFTR to increase the amount of CFTR protein delivered to the cell surface compared to either molecule alone. Ivacaftor potentiates the channel open probability (or gating) of the CFTR protein at the cell surface.
The combined effect of elexacaftor, tezacaftor and ivacaftor is increased quantity and function of F508del-CFTR at the cell surface, resulting in increased CFTR activity as measured by CFTR mediated chloride transport.

Pharmacokinetics:
Metabolism/Elimination: Elexacaftor, tezacaftor, and ivacaftor are all mainly metabolized by CYP3A4 and CYP3A5. Trikafta™ is is primarily excreted in the feces, with tezacaftor being the only component with >10%

excreted in the urine. M1, M2, and M5 are the major circulating metabolites of tezacaftor, with M1 being the only pharmacologically active metabolite. M1 and M6 are the major metabolites of ivacaftor.

*Effect of Food:*AUC of elexacaftor increases 1.9 to 2.5 fold with moderate-fat meal. Ivacaftor exposure increases 2.5 to 4 fold in the presence of food.

Plasma Half-life: Elexacaftor: 29.8 hours; tezacaftor 17.4 hours; ivacaftor 15.0 hours

Drug Interactions:

- Strong CYP3A inducers: rifampin, rifabutin, phenobarbital, carbamazepine, phenytoin, and St. John's Wort decrease Trikafta's efficacy. Coadministration with strong CYP3A inducers is not recommended.
- Strong CYP3A inhibitors: ketoconazole, itraconazole, posaconazole, voriconazole, telithromycin, and clarithromycin increase the AUC of Trikafta's individual compontents by 2.8 to 15.6 fold. The dosage of Trikafta should be decreased if co-administered with Strong CYP3A inhibitors
    - Avoid food containing grapefruit
- Digoxin and other P-gp substrates: Trikafta consistently increased P-gp substrate exposure by approximately 1.3-fold

***Adverse Effects*:** The most common adverse drug reactions to Trikafta (occuring in >5% of patients) were headache, upper respiratory tract infection, abdominal pain, diarrhea, rash, alanine aminotransferace increase, nasal congestion, blood creatine phophokinase increased, aspartate aminotransferase increased, rhinorrhea, rhinitis, influena, sinusitis, and blood bilirubin increased.

Contraindications: None

Warnings and Precautions: Transaminase elevations, concomitant use with CYP3A inhibitors, cataracts

Monitoring:

- Transaminase levels (ALT and AST) should be assessed for all patients prior to initiating Trikafta, every 3 months during the first year of treatment, and annually thereafter
- Co-administration with strong CYP3A inducers is not recommended due to its effects of decreasing Trikafta effectiveness
- Ophthalmological examinations are recommended for pediatric patients at baseline and during follow-up

Evidence Table of Clinical Studies:

Table 1. Clinical data for Trikafta

	Elexacaftor-Tezacaftor-Ivacaftor for Cystic Fibrosis with a Single Phe508del Allele Middleton P.G. et al 2019.	**Efficacy & Safety of the elexacaftor/tezacaftor/ivacaftor combination regimen in CF Patients homozygous for the *F508del* mutation Heijerman H., 2019.**
Study Type*	Phase III Multicenter RCT, DB, PC, PG	Phase III, Multicenter, RCT, DB, Active-controlled
Interventions	N=403	N=113

	Elexacaftor-Tezacaftor-Ivacaftor for Cystic Fibrosis with a Single Phe508del Allele Middleton P.G. et al 2019.	**Efficacy & Safety of the elexacaftor/tezacaftor/ivacaftor combination regimen in CF Patients homozygous for the *F508del* mutation Heijerman H., 2019.**
and Sample Size	4-week screening period + 24-week intervention. Randomized 1:1 triple therapy vs placebo	4-week tezacaftor + ivacaftor run-in + 4-week intervention Randomized 1:1 triple therapy vs tezacaftor+ivacaftor
Populations	*Inclusions*: • Patients 12 years and up • Diagnosis of CF & *Phe508del* minimal function genotype • FEV_1 40-90% • Stable disease in screening period *Exclusions*: No notable clinical exclusions	*Inclusions*: • Patients 12 years and up • Diagnosis of CF, homozygous for *F508del* mutation • FEV_1 40-90% • Stable disease *Exclusions:* No notable clinical exclusions
General Summary (ITT population): Efficacy	**Primary Endpoint**: Absolute Change in $ppFEV_1$ at wk 4 from baseline: • Tx: 13.6 (12.4,14.8) P: -0.2 (-1.3,1.0) • Dif (95% CI): 13.8 (12.1,15.4) **Select Key Secondary Endpoints**: Absolute change from baseline in sweat chloride through week 24: • Tx: 0-42.2 (-44,-40.4) P: -0.4 (-2.2,1.4) • Dif (95% CI): -41.8 (-44.4,-39.3) Absolute change from baseline in CF Questionnaire: • Tx: 17.5 (15.6,19.5) P: -2.7 (-4.6,-0.8) • Dif (95% CI): 20.2 (17.5 to 23.0) Pulmonary Exacerbations through Wk 24: • Tx:41(0.37), P:113 (0.98) • Dif (95% CI): 0.37 (0.25 to 0.55)	**Primary Endpoint:** Absolute change from baseline in ppFEV1 at week 4: • Trikafta: 10.4(8.6,12.2) Symdeko: 0.4(-1.4,2.3) • Dif (95% CI): 10.0 (7.4,12.6) **Key Secondary Endpoints:** Absolute change from baseline at week 4 in sweat chloride concentration: • Trikafta: -43.4 (-46.9,-40.0) Symdeko: 1.7(-1.9,5.3) • Dif (95% CI): -45.1(-50.1,-40.1) Absolute change from baseline in Cystic Fibrosis Questionnaire: • Trikafta: 16.0(12.1,19.9) Symdeko: -1.4(-5.4,2.6) • Dif (95% CI): 17.4 (11.8,23.0)
General Summary Safety:	Adverse events occurring in at least 10% were consistent with common manifestations and complications of cystic fibrosis. 33% of AEs were mild, 50.5% were moderate. 2 patients d/c'd (rash & portal hypertension in cirrhosis patient)	Adverse events were similar across both treatment arms (63% of Symdeko arm; 58% of Trikafta arm), with the vast majority of AEs resolving during the study. The only adverse events related to either study drug were pulmonary exacerbations of cystic fibrosis and are in line with available treatments.
Comments	Trikafta appears to be an efficacious (decreased FEV reduction, decreased pulmonary exacerbations) and fairly safe (AEs in line with expections for CF) treatment alternative for patients with a Het Min mutation where previous CFTR therpaies were not effective.	Trikafta provides improvement over Symdeko therapy in terms of FEV1, change in sweat chloride concentrations, and in the CF Questionnaire. Trikafta's additional benefit is not accompanied with additional adverse reactions. This study does only show 4 weeks of

	Elexacaftor-Tezacaftor-Ivacaftor for Cystic Fibrosis with a Single Phe508del Allele Middleton P.G. et al 2019.	Efficacy & Safety of the elexacaftor/tezacaftor/ivacaftor combination regimen in CF Patients homozygous for the *F508del* mutation Heijerman H., 2019.
		therapy on Trikafta, with data from the OLE required to fully validate durability of effect.
Grade^	▪ A	▪ 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:

Hepatic Impairment:

- Mild Impairment (Child-Pugh Class A): No doing adjustments needed
- Moderate (Child-Pugh Class B): Patients should not take evening 150mg ivacaftor dose. Use with caution, drug has not been studied in this population
- Severe Impairment (Child-Pugh Class C): Do Not Use

Cost and/or Utilization Data of Similar Treatment Options:

Table 2: Cystic Fibrosis Treatment Pricing

Drug	WAC/28 days	Package size	WAC/year
Trikafta	$23,896	4 week pkg	$311,503
Kalydeco	$23,896	4 week pkg	$311,503
Orkambi	$20,919	4 week pkg	$272,697
Symdeko	$22,400	4 week pkg	$272,697

Table 3: Humana Tiering for Similar Treatment Options

	Kalydeco	Orkambi	Symdeko
KY Medicaid	T2wPA	T2wPA	NF

Place in Therapy:

Table 4. Comparison of Trikafta (elexacaftor, tezacaftor, ivacaftor) and Symdeko (tezacaftor, ivacaftor) product(s) and/or another similar drug in the pipeline]

	Trikafta (elexacaftor, tezacaftor, ivacaftor)	Symdeko (tezacaftor, ivacaftor)
Meet an Unmet Medical Need[1]	☒ Yes – Prior to Trikafta, approved medications only treated 50% of the CF population. The approval of Trikafta broadens eligibility to ~90% of CF Patients.	
Comparable Efficacy[2]	☒ Trikafta is more efficacious relative to Symdeko **Comment: Trikafta has an expanded indication over Symdeko, covering Het Min patients that**	

	previously had no treatment options. Additionally, Trikafta showed additional benefit in FEV1 improvement over stable Symdeko treatment.	
Comparable Safety[3]	☒ Trikafta would like have similar safety relative to Symdeko **Comment: comparison trial between Trikafta and Symdeko showed no appreciable differences in safety profiles.**	
Adherence[5]	☒ Members taking Trikafta would likely achieve a similar adherence rate relative to Symdeko **Comment: Although Trikafta does have an additional medication in it, the new medication is in the same tablet and dosing regimen as Symdeko. As patients will experience better efficacy with similar safety and the same dosing regimen, they should have a similar adherence rate.**	
Advantages	▪ New treatment option for CF patients that previously had no treatment options ▪ Improved efficacy over available treatment options	▪ Approved for patients 6 years and up ▪ Lower Cost
Disadvantages	▪ Approved for patients 12 years and up ▪ Must be taken with fat-containing food ▪ Higher Cost	▪ No efficacy in Het Min Patients
Comments	▪ Trikafta provides a new treatment option for the undertreated Cystic Fibrosis population. Although both clinical trials were short, they are in line with previous clinical trial durations and can be expected to have a similar durability of response.	

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.
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: T2 w PA/QL
QL: 84 tablets per 28 days

References:

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4. Trikafta [Package Insert]. Boston, MA: Vertex Pharmaceuticals; Revised October 2019
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Humana Pharmacy Solutions

Clinical Review – Esperoct® (Antihemophilic factor [recombinant], glycopegylated-exei))

***Company*:** Novo Nordisk
Current Status: FDA approved February 19, 2019
Potential Launch: January 18, 2020
Therapeutic Category: *Hemophilia A*
Pharmacologic Category: *Recombinant coagulation factor VIII*
Similar Drugs: Eloctate, Adynovate, Jivi
Route of Administration: Intravenous Infusion
Dosage Forms: Lyophilized powder for reconstitution

Indications:

- On-demand treatment and control of bleeding episodes in adults and children with hemophilia A
- Perioperative management of bleeding in adults and children with hemophilia A
- Routine prophylaxis to reduce the frequency of bleeding episodes in adults and children with hemophilia A

Dosage and Administration:

- On-demand treatment of bleeding episodes
  - Adolescents/adults:
    - Minor/moderate bleeds: 40 IU/kg body weight
    - Major bleeds: 50 IU/kg body weight
  - Children (<12 years):
    - Minor/moderate/major bleeds: 65 IU/kg body weight
- Perioperative management of minor/major surgery
  - Adolescents/adults:
    - Pre-operative dose of 50 IU/kg body weight
  - Children (<12):
    - Pre-operative dose of 65 IU/kg body weight
- Routine prophylaxis:
  - Adolescents/adults:
    - 50 IU/kg every 4 days
  - Children (<12 years):
    - 65 IU/kg twice weekly
- Esperoct can also be dosed to achieve a specific target Factor VIII activity level using the following formula:
  - Dosage (IU) = Body Weight (kg) × Desired Factor VIII Increase (IU/dL or % normal) × 0.5 (IU/kg per IU/dL).

Background:

Hemophilia is an inherited, lifelong bleeding disorder caused by a deficiency in endogenous coagulation factors. Lack of these factors can lead to failed clotting which can result in bleeding into soft tissue, joints, internal organs, and most severely, intracranial bleeding which is often fatal. Hemophilia is an X-linked recessive disease found predominantly in male children of female carriers. The two most common types are hemophilia A which is a deficiency in clotting factor VIII, and Hemophilia B which is a deficiency in clotting factor IX. Standard pharmacologic treatment is factor replacement with the deficient clotting factor either

during On-demand during bleeding events, or through continuous prophylaxis. The current hemophilia market has been estimated at nearly $11 billion and is likely to grow. Hemophilia A and B have a combined prevalence of 13 cases per 100,000 male lives in a typical commercial population and 25 cases per 100,000 male lives in a typical Medicaid population.

Pharmacology:
Esperoct is a recombinant, glycopegylated coagulation factor VIII analog that can be used to replace endogenous clotting factor VIII which is deficient in Hemophilia A.

Pharmacokinetics:
Plasma Half-Life (hrs): mean half-life is approximately 19 hours

Drug Interactions:
None

***Adverse Effects*:**
The most common adverse reactions were rash (5.2%), injection site reaction (2.6%), redness (1.9%), and itching (1.5%)

Contraindications:
- Do not use in patient who have known hypersensitivity to Esperoct or its components, including hamster proteins.

Warnings and Precautions:
- Hypersensitivity reactions: Esperoct contains traces of hamster proteins which in some patients can cause allergic reactions, including anaphylaxis. Discontinue Esperoct and administer appropriate treatment in the setting of hypersensitivity reactions
- Neutralizing antibodies: formation of neutralizing antibodies to Factor VIII has occurred following administration of Esperoct. If expected Factor VIII activity plasma levels are not attained, or if bleeding is not controlled after Esperoct administration, suspect the presence of a neutralizing antibody. A Bethesda assay can be performed to confirm the presence of Factor VIII inhibitors

Monitoring:
- IF Factor VIII monitoring is performed, use a chromogenic or one-stage clotting assay appropriate for use with Esperoct. Some silica based aPTT reagents may underestimate the activity of Esperoct by up to 60%, while other reagents may overestimate the activity by 20%. If an appropriate chromogenic or one-stage clotting assay is not available, use a reference laboratory.

Evidence Table of Clinical Studies:

Table 1. Clinical data for Esperoct®.

The safety and efficacy of Esperoct® have been evaluated in five multinational, open-label trials in male subjects with severe hemophilia A (<1% endogenous Factor VIII activity). Studies in Pediatric populations had similar safety and efficacy and are not reported in the comparison table below.

	On-Demand Treatment and Control of Bleeding Episodes	Routine prophylaxis in Adolescents/Adults	Perioperative Management
Study Type*	Open-label, multinational	Open-label, multinational	Open-label, multinational
Interventions and Sample Size	N=254 Evaluation of hemostatic response was assessed using a 4-point scale of excellent, good, moderate, or none. Doses used for treatment of bleeding episodes depended on age, treatment regimen an the severity of the bleed	N= 175 Evaluation of response was based on median annualized bleed rate (ABR) Patients <12 years received a dose of 65 IU/kg and patients >12 years received a dose of 50 IU/kg every 4 days (Q4D)	N=33 45 major surgical procedures Evaluation of hemostatic response during major surgery was assessed using a 4-point scale of excellent, good, moderate, or none. The number of doses and duration of treatment varied by procedure
Populations	Inclusion Criteria: • Male • Severe hemophilia A (<1% endogenous Factor VIII activity)* • Previously treated patients (PTPs) ○ Defined as having received other Factor VIII products for ≥150 exposure days for adolescents and adults, and ≥ 50 exposure days for pediatric subjects Key Exclusion criteria: • Known or suspected hypersensitivity to trial or related products • Known history of Factor VIII inhibitors or current inhibitor ≥ 0.6 Bethesda units (BU)		
General Summary: Efficacy	• Of the 1407 mild and moderate bleeding episodes in all subjects in the adolescent/adult study, the median dose used was 42 IU/KG	• In subjects receiving routine prophylaxis, the median initial dose was 52 IU/kg, and 76.4% of the bleeds were	• The hemostatic effect of Esperoct was rated as excellent or good in 43/45

	On-Demand Treatment and Control of Bleeding Episodes	Routine prophylaxis in Adolescents/Adults	Perioperative Management
	○ 87.3% had an excellent/good response and 11.1% had a moderate response to first treatment • For subjects on the on-demand arm the median initial dose was 28 IU/kg and 88.4% of the bleeds were treated successfully with a single dose	successfully treated with a single dose • Of the 15 severe bleeds, 12 (80%) required more than one dose with a total median dose of 111 IU/kg • The median annualized bleeding rate (ABR) for treated bleeds in adults and adolescents treated every 4 days was 1.2 and mean ABR was 3.0	surgeries (95.6%) and moderate in 2 surgeries (4.4%) • The median pre-operative dose for adults and adolescents was 52 IU/kg and the median total dose was 702 IU/kg.
General Summary: Safety	During the clinical trials in PTPs, adverse reactions occurred at a rate of 0.10 events per patient year of exposure. The most frequently reported adverse reactions were rash (5.2%), injection site reaction (2.6%), redness (1.9%), and itching (pruritus) (1.5%). This is in line with other Hemophilia Factor Replacement agents		
Comments	Concerns regarding the study: ▪ Study was open label, and non-controlled ▪ Lack of control and blinding means that the most meaningful way of assessing safety/efficacy is by comparison with similar drugs	▪ The definition of hemostatic response** is not standardized across drug trials ▪ The clinical trial data was not published by the manufacturer ▪ Study was open label and non-controlled ▪ An optional extension trial was also launched for the adolescent/adult arm which compared 75 IU/kg Q7D with 50 IU/kg Q4D. Treatment success of the Q7D arm was not established	▪ The definition of hemostatic response** is not standardized across drug trials ▪ The clinical trial data was not published by the manufacturer ▪ Study was open label and non-controlled ▪ The number of doses and duration of treatment varied by procedure

*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]
*Severe hemophilia A: < 1% endogenous Factor VIII activity
**Hemostatic Response Scale:

- Excellent response: abrupt relief and/or unequivocal improvement in objective signs of bleeding within approximately 8 hours after a single injection
- Good response: definite pain relief and/or improvement in signs of bleeding within approximately 8 hours after one injection, but possibly requiring more than one injection for complete resolution
- Moderate response: Probable or slight beneficial effect within approximately 8 hours after the first injection; usually requiring more than one injection
- None: no beneficial effect within approximately 8 hours after the first injection

Special Populations:
There are no recommendations for dosage adjustments for renal impairment and hepatic impairment

Pregnancy: there is no data regarding the use of Esperoct in pregnant women nor are there animal reproduction studies to assess fetal harm with use during pregnancy. It is unknown whether Esperoct can cause fetal harm when administered to a pregnant woman or can affect fertility.

Lactation: There is no information regarding the presence of Esperoct in human mil, the effect on the breastfed infant, and the effects on milk production.

Pediatric Use: no difference in the safety profile of Esperoct was observed between previously treated pediatric subjects and adult subjects. Children < 12 years of age demonstrated higher rates of clearance, sorter half-life, and lower incremental recovery of Factor VIII compared to adults. A higher dose and more frequent dosing may be needed in this population.

Geriatric Use: Clinical studies of Esperoct did not include sufficient numbers of subjects age 65 years and over to determine whether or not they respond differently than younger subjects. It is recommend that dose selection should be cautious, starting on the lower end reflecting decreased, hepatic, renal, or cardiac function and increased likelihood of concomitant disease and other drug therapy.

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

Drug	Strength	WAC/unit	Package size	WAC/Package
Esperoct	1,000 IU vial	$2.23/IU	1,000	$2,230
Advate	800-1,200 IU vial	$1.52/IU	1,000	$1,152

Adynovate	801-1,250 IU vial	$2.10/IU	1,000	$2,100

Table 3: Key Metrics for Medicare and Employer Group* (Advate & Adynovate used for comparison across LOBs)

Place in Therapy:

Table 3. Comparison of Esperoct and Adynovate

	Esperoct	Adynovate
Meet an Unmet Medical Need[1]	☒ **No** There are several other antihemophilic agents already on the market use to treat hemophilia A with similar safety and efficacy	
Comparable Efficacy[2]	☒ Esperoct has similar efficacy relative to Adynovate **Comment:** Both agents provided similar response to first treatment for on-demand treatment, similar overall ABR for routine prophylaxis, and similar response ratings in perioperative management.	
Comparable Safety[3]	☒ Esperoct would likely have similar safety relative to Adynovate **Comment:** Both agents showed similar incidences of adverse events. While Adynovate had slightly lower rates of comparable adverse events, two cases of acute pancreatitis, with no precipitating cause were reported in adults during an extension study of Adynovate. In both cases, Adynovate was continued and both cases resolved.	
Comparable Cost-Effectiveness[4]	☒ Esperoct has similar cost-effectiveness relative to Adynovate **Comment:** Both agents are priced very similarly with similar clinical effects	
Adherence[5]	☒ Members taking Esperoct would likely achieve a similar adherence rate relative to Adynovate **Comment:** Dosing for routine prophylaxis is similar at roughly twice weekly for both Adynovate and Esperoct	
Advantages	▪ Has a fixed standard dose for routine prophylaxis, with no adjustment needed ▪ Vials contain consistent levels of Factor VIII ▪ Simpler On-demand and Perioperative dosing; no need to account for estimated/desired Factor VIII level	▪ Provider experience ▪ More data available

Disadvantages	▪ Higher cost, $2,230 per package of 1000 IU (Esperoct) vs $2,100 per package of 801-1250 IU (Adynovate) ▪ Cutaneous and injection site ADRs	▪ Levels of Factor VIII per vial varies ▪ Headache and nausea ADRs
Comments	▪ Fixed dosing and consistent Factor VIII levels per vial allow for Esperoct allow for monitoring against a target and better cost monitoring. Simpler dosing may also mean less errors for administering HCPs	

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. 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]

Recommendation:

- KY Medicaid – non formulary for pharmacy (medical benefit)
- Add to MIT-PAL

References:

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   Tiede A, Brand B, Fischer R, et al. Enhancing the pharmacokinetic properties of recombinant factor VIII: first-in-human trial of glycoPEGylated recombinant factor VIII in patients with hemophilia A. *J Thromb Haemost*. 2013;11(4):670-678.
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***Company*:** Eli Lilly

Current Status: FDA approved (October 2019)

Potential Launch: February 2020

Therapeutic Category: Antimigraine – acute treatment

Pharmacologic Category: Serotonin (5-HT_{1F}) receptor agonist

Similar Drugs: sumatriptan, rizatriptan, naratriptan

Dosage Forms: 50mg and 100mg oral tablets

Indications:

- For the acute treatment of migraine with or without aura in adults. Limitations of use: Reyvow is not indicated for the preventive treatment of migraine.

Dosage and Administration:

- The recommended dose of Reyvow is 50mg, 100mg, or 200mg taken orally as needed with or without food. No more than one dose should be taken in 24 hours. A patient should wait at least 8 hours between dosing and driving or operating machinery. If treating the same migraine attack, a second dose of Reyvow has not shown to be effective. The safety of treating more than 4 migraines in a 30 day period has not been established.

Background:

- Migraines affect approximately 1 in 7 individuals globally. In the U.S., migraines affect ~15% of the population. Prevalence peaks between 25 and 55 years of age. Studies have shown that migraines affect women more than men, with rates being almost 3 times higher. The annual total cost for migraines is estimated to be $27 Billion in the U.S. Oral triptans (e.g. sumatriptan) are the most commonly prescribed medication for the acute management of migraines. The triptans are considered the current standard of care. However, there is a proportion of individuals that have suboptimal response to triptans or have tolerability issues that require the use of other acute medications.

Pharmacology:

- Serotonin, with its direct action upon the cranial vasculature and its role in central pain control pathways, has been suggested to play a role in migraine pathogenesis. This is supported by the fact that serotonin reuptake inhibitors (i.e. tricyclic antidepressants) have shown to be effective

antimigraine prophylactic agents and serotonin (5-HT_{1B-1D}) agonists (i.e. sumatriptan) have shown to be effective for acute treatment. Reyvow is a serotonin (5-HT_{1F}) agonist that acts on the trigeminal system without causing vasoconstriction, in part due to its low affinity for the 5-HT_{1B} receptor.

Pharmacokinetics:

- Absorption: Administration of Reyvow with a high-fat meal increased the mean C_{max} and AUC values by 22% and 19% respectively. The difference is not expected to be significant.
- Metabolism/Elimination: Reyvow is eliminated by ketone reduction. Reyvow inhibits P-gp and Breast Cancer Resistant Protein (BCRP) in vitro.
- Plasma Half-Life: 5.7 hours

Drug Interactions:

- Reyvow can cause sedation and should be used with caution in combination with alcohol or other CNS depressants.
- Reyvow has been associated with lowering the heart rate and should be used with caution in combination with other medications that lower the heart rate.
- Concomitant use of Reyvow and drugs that are P-gp or BCRP substrates should be avoided.

***Adverse Effects*:**

- Dizziness
- Sedation
- Fatigue
- Paresthesia

Contraindications:

- None

Warnings and Precautions:

- Driving Impairment: Patients should not drive or operate machinery until at least 8 hours after taking each dose.
- CNS depression: Use with caution with alcohol or other CNS depressants.
- Serotonin Syndrome: Serotonin syndrome reactions were reported in patients who were treated with Reyvow.
- Medication Overuse Headache: Acute migraine drugs used for 10 or more days per month may lead to an increase in frequency or worsening of headaches.

Evidence Table of Clinical Studies:

Table 1. Clinical data for Reyvow (lasmiditan).

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	SAMURAI [NCT02439320]	SPARTAN [NCT02605174]
Study Type*	Phase 3, DB, PC	Phase 3, DB, PC
Interventions and Sample Size	N = 2231 Lasmiditan 100mg / Lasmiditan 100mg = 496 Lasmiditan 100mg / Placebo = 248 Lasmiditan 200mg / Lasmiditan 200mg = 496 Lasmiditan 200mg / Placebo = 249 Placebo / Placebo = 742	N = 3005 Lasmiditan 50mg / Lasmiditan 50mg = 501 Lasmiditan 50mg / Placebo = 249 Lasmiditan 100mg / Lasmiditan 100mg = 502 Lasmiditan 100mg / Placebo = 252 Lasmiditan 200mg / Lasmiditan 200mg = 501 Lasmiditan 200mg / Placebo = 249 Placebo / Placebo = 751
Populations	Inclusion criteria ▪ Age ≥ 18 years ▪ Diagnosis of migraine (IHS diagnostic criteria 1.1 or 1.2.1) ▪ History of migraine for at least 1 year ▪ MIDAS total score ≥ 11 ▪ Migraine onset before age of 50 ▪ History of 3 to 8 migraine attacks per month (< 15 headache days per month) Exclusion criteria ▪ History of Chronic migraine or medication overuse headache where headache frequency was >15 headache days per month ▪ Initiation, or change in migraine preventative medication prior to screening Known coronary artery disease, arrhythmia, or uncontrolled hypertension	
Endpoints:	**Primary Endpoint:** ▪ Migraine pain freedom at 2 hours following initial dose. Patients assessed their pain severity using the IHS 4-point pain severity rating scale (no pain, mild pain, moderate pain and severe pain). Pain freedom was defined as a reduction in pain severity from mild, moderate, or severe at baseline to none. **Secondary Endpoint** ▪ The key secondary endpoint was Most Bothersome Symptom (MBS) freedom at 2 hours following initial dose. At baseline, patients indicated whether they were experiencing nausea, phonophobia, or photophobia. Patients were to then report which symptom was most bothersome to them. The presence or absence of each symptom was collected at all-time points. Freedom from MBS was defined as absence of the symptom at 2 hours following the first dose.	
General Summary: Efficacy	**Primary Endpoint: Pain Freedom at 2 hr** ▪ Lasmiditan 100mg: 28.2% (p<0.001) ▪ Lasmiditan 200mg: 32.2% (p<0.001) ▪ Placebo: 15.3% **Secondary Endpoint: MBS Freedom at 2 hr** ▪ Lasmiditan 100mg: 40.9% (p<0.001) ▪ Lasmiditan 200mg: 40.7% (p<0.001)	**Primary Endpoint: Pain Freedom at 2 hr** ▪ Lasmiditan 50mg: 28.6% (p=0.003) ▪ Lasmiditan 100mg: 31.4% (p<0.001) ▪ Lasmiditan 200mg: 38.8% (p<0.001) ▪ Placebo: 21.3% **Secondary Endpoint: MBS Freedom at 2 hr** ▪ Lasmiditan 50mg: 40.8% (p=0.009)

	SAMURAI [NCT02439320]	SPARTAN [NCT02605174]
	▪ Placebo: 29.5%	▪ Lasmiditan 100mg: 44.2% (p<0.001) ▪ Lasmiditan 200mg: 48.7% (p<0.001) ▪ Placebo: 33.5%
General Summary: Safety	Most Common Treatment Adverse Events: ▪ Dizziness (14.7%) ▪ Paraesthesia (5.7%) ▪ Somnolence (5.5%) ▪ Fatigue (3.8%) ▪ Nausea (3.4%) Driving Impairment: ▪ Per the FDA label, patients are not to drive or operate machinery until at least 8 hours after taking each dose of Reyvow. In a double-blinded, randomized, placebo-controlled simulated driving study, subjects given lasmiditan were observed to have a similar effect that has been previously identified to occur in subjects with a blood alcohol concentration of 0.05%.	
Comments	▪ Significantly more patients who took lasmiditan (200mg and 100mg) were headache pain-free and free from MBS at 2 hours compared to placebo. ▪ The placebo response rate for headache pain-freedom (15.3%) was higher in comparative studies of the oral triptans (generally <10%). This is thought to be attributed to the increased patient contact by investigators. ▪ Patients who took lasmiditan were less likely to need a second dose for rescue. ▪ The most common adverse event was dizziness and it was reported to be mild to moderate in intensity	▪ Study findings were limited to primarily a single dose. Evaluation of long term safety / efficacy was not evaluated in this study. ▪ Three doses were studied (50mg, 100mg, 200mg) and all showed a significantly greater proportion of patients were headache pain-free at 2 hours and free from MBS compared with placebo after a single lasmiditan dose. ▪ Safety and tolerability was consistent with previous studies and the most frequent adverse events were dizziness, fatigue, and nausea.

*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]

Special Populations:

- **Pediatric Use:** Safety and efficacy has not been established
- **Geriatric Use:** Dizziness occurred more frequently in patients 65 years of age or older. Dose selection should be cautious and start at the low end of the range.
- **Hepatic Impairment:** Reyvow is not recommended in severe hepatic impairment (Child-Pugh C).

Cost and/or Utilization Data of Similar Treatment Options:

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Table 2: Reyvow (lasmiditan) Pricing

Drug	Strength	WAC/tablet
Reyvow	50mg	$80
Reyvow	100mg	$80

Table 3: Humana Tiering for Similar Treatment Options

	Sumatriptan	Rizatriptan	Naratriptan
Medicaid			
KYMD	1	1	1

Place in Therapy:

Table 3. Comparison of Reyvow and Sumatriptan

	Reyvow (lasmiditan)	Sumatriptan tablets
Meet an Unmet Medical Need[1]	☒ **No.** **Comment: Many options exist for the treatment of acute migraines with or without aura.**	
Comparable Efficacy[2]	☒ Sumatriptan is as efficacious relative to Reyvow **Comment: A network meta-analysis performed by ICER found that lasmiditan compared to the triptans, is less efficacious. However, compared to sumatriptan, the analysis doesn't exclude comparable efficacy. The evidence for lasmiditan compared to the triptans was considered "comparable or inferior C-".**	
Comparable Safety[3]	☒ Sumatriptan would like have similar safety relative to Reyvow **Comment: The meta-analysis performed by ICER suggested that lasmiditan has a higher incidence of adverse events. Lasmiditan does have a FDA label restriction with regard to driving and operating machinery. However, lasmiditan is not contraindicated in patients with coronary artery disease.**	
Comparable Cost-Effectiveness[4]	☒ Sumatriptan is more cost-effective relative to Reyvow. **Comment: The network met-analysis ICER rates Reyvow as C-, demonstrating the net health benefit is either comparable or inferior compared to the triptans.**	
Adherence[5]	☒ Members taking Sumatriptan would likely achieve a similar adherence rate relative to Reyvow. **Comment: Both sumatriptan and Reyvow are oral tablets and are taken at the first sign of a headache. Adherence is expected to be similar between the two therapies.**	
Advantages	▪ Novel mechanism of action for the acute treatment of migraines ▪ Reduced safety concern related to vasoconstrictive effects compared to the triptans	▪ Established consistency of safety and efficacy with extended use ▪ Available in multiple dosage forms (i.e. tablet, injection, nasal spray).

Disadvantages	▪ Long term consistency of efficacy hasn't been determined ▪ Cost vs other options for acute migraines ▪ Only available in tablets, which may limit its use in patients with severe nausea/vomiting associated with their migraines. ▪ CNS Depression / Dizziness warning which requires a patient to not drive or operate machinery within 8 hours of taking a dose.	▪ Limitation of use in patients with cardiovascular disease

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.

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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: NF with QL

QL: 50mg – 4 tablets / 30 days, 100mg- 8 tablets / 30 days.

References:

1. Ashinia M, Vasudeva R, Jin L, et al. Onset of Efficacy Following Oral Treatment With Lasmiditan for the Acute Treatment of Migraine: Integrated Results From 2 Randomized Double-Blind Placebo-Controlled Phase 3 Clinical Studies. Headache. 2019;0:2-14.

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***Company*:** Novartis Pharmaceuticals Corporation
Current Status: FDA approved
Therapeutic Category: vascular endothelial growth factor (VEGF) inhibitor
Pharmacologic Category: Ophthalmic agents
Similar Drugs: Eylea, Lucentis, Avastin, Macugen
Route of Administration: intravitreal injection
Dosage Forms: 6 mg/0.05 mL single-dose vial

Indications: Beovu (brolucizumab) is indicated for the treatment of neovascular (wet) age-related macular degeneration (AMD).

Dosage and Administration: 6 mg monthly (approx. every 25-31 days) for the first three doses, then 6mg once every 8 to 12 weeks thereafter.

Background:
VEGF is a naturally occurring substance in the body responsible for the growth of new blood vessels (neovascularization). In the retina however, VEGF may stimulate growth of abnormally fragile vessels prone to leakage. This leakage causes scarring in the macula and eventually leads to loss of central vision.

Age-related macular degeneration (AMD) is a major cause of painless central vision loss and is a leading cause of blindness in people over 60.

AMD occurs in two forms: dry and wet. Dry AMD is associated with atrophic cell death of the central retina or macula, which is required for fine vision used for activities such as reading, driving or recognizing faces. Approximately 10-20% of patients with dry AMD eventually progress to wet AMD. Wet AMD is associated with growth of abnormal blood vessels under the macula. These new blood vessels tend to be very fragile and often leak blood and fluid and cause scar tissue that destroys the central retina. The blood and fluid raise the macula from its normal place at the back of the eye. Damage to the macula occurs rapidly and results in a deterioration of sight over a period of months to years. Between 80% to 90% of AMD is dry, yet more than 80% of the visual loss attributable to AMD is caused by the wet form. The natural history of AMD is variable, with clinical manifestations dependent on disease type, extent, and whether one or both eyes are affected. Principle risk factors include age, smoking, family history, Caucasian ethnicity, contralateral eye disease, diabetes, and cataract surgery. Genetics play a particularly strong role, with a single polymorphism estimated responsible for as much as 43% of disease occurrence.

Pharmacology:
Beovu (brolucizumab) is a human VEGF inhibitor that binds to the three major isoforms of VEGF-A. By inhibiting VEGF-A, brolucizumab reduces endothelial cell proliferation, neovascularization, and vascular permeability.

Pharmacokinetics:

The estimated systemic half-life after a single brolucizumab dose is 4.4 days. The metabolism and elimination has not been fully characterized, however it is expected to undergo metabolism via proteolysis and passive renal excretion.

Drug Interactions:

- There are no drug interactions with brolucizumab.

Contraindications:

- Ocular or Periocular Infections
- Active Intraocular Inflammation

Warnings and Precautions:

- Endophthalmitis and Retinal Detachments
- Increase in intraocular pressure
- Thomboembolic Events

Monitoring:

- Intraocular pressure

Evidence Table of Clinical Studies:

Table 1. Clinical data for Beovu® (brolucizumab).

	HAWK NCT02307682 (Dugel et al)	**HARRIER NCT02434328 (Dugel et al)**
Study Type*	Phase III, RCT, DB	Phase III,RCT, DB
Interventions and Sample Size	▪ Brolucizumab 3mg (loading dose 3mg monthly x 3 doses, then Q8-12 weeks thereafter), n=358 ▪ Brolucizumab 6mg (loading dose 6mg monthly x 3 doses, then Q8-12 weeks thereafter), n=360 ▪ Aflibercept 2mg (loading dose 2mg monthly x 3 doses, then Q8 weeks thereafter), n=360	▪ Brolucizumab 6mg (loading dose 6mg monthly x 3 doses, then Q8-12 weeks thereafter), n=370 ▪ Aflibercept 2mg (loading dose 2mg monthly x 3 doses, then Q8 weeks thereafter), n=369
Populations	Inclusion criteria: ▪ Patients aged ≥ 50 years ▪ active CNV lesions secondary to AMD ▪ Intraretinal and/or subretinal fluid affecting the central subfield of the study eye at screening ▪ BCVA between 78 and 23 letters Exclusion criteria: ▪ Intraocular or periocular infection ▪ Central subfield of the study eye affected by fibrosis or geographic atrophy or total area of fibrosis >50% of the total lesion in the study eye at screening. ▪ Subretinal blood affecting the foveal center point and/or >50% of the lesion of the study eye at screening.	

	HAWK NCT02307682 (Dugel et al)	HARRIER NCT02434328 (Dugel et al)
	▪ Any approved or investigational nAMD treatment in the study eye at any time ▪ Retinal pigment epithelial rip/tear or vitreous hemorrhage in the study eye within 4 weeks prior to baseline ▪ Pregnant or nursing women of child-bearing potential ▪ Stroke or myocardial infarction in the 6 month period prior to baseline	
General Summary: Efficacy	**<u>Primary endpoint</u>**: noniferiority in BCVA change from baseline to week 48 vs aflibercept ▪ Brolucizumab 3mg: 6.1 ▪ Brolucizumab 6mg: 6.6 ▪ Aflibercept 2mg: 6.8 ○ Brolucizumab 3mg vs Aflibercept -0.6, p<0.001 ○ Brolucizumab 6mg vs Aflibercept -0.2, p<0.001 **At week 48, Beovu demonstrated noninferiority in relation to BCVA compared to aflibercept for both strengths.** **<u>Secondary endpoints</u>**: % Patients with ≥ 15 letter gain from baseline to week 48: ▪ Beovu 3mg: 25.2% ▪ Beovu 6mg: 33.6% ▪ Aflibercept 2mg: 25.4% % of patients maintained q12week dosing through week 48: ▪ Beovu 3mg: 49.4% ▪ Beovu 6mg: 55.6% % of patients that had disease activity at week 16 ▪ Beovu 3mg: 28.1% ▪ Beovu 6mg: 24.0% ▪ Aflibercept 2mg: 34.5% CST reductions from baseline to week 16 ▪ Beovu 6mg -161.4 vs afibercept 2mg -133.6 um; p<0.001	**<u>Primary endpoint</u>**: noniferiority in BCVA change from baseline to week 48 vs aflibercept ▪ Brolucizumab 6mg: 6.9 ▪ Aflibercept 2mg: 7.6 ○ Brolucizumab 6mg vs Aflibercept -0.7, p<0.001 **At week 48, Beovu demonstrated noninferiority in relation to BCVA compared to aflibercept.** **<u>Secondary endpoints:</u>** % Patients with ≥ 15 letter gain from baseline to week 48: ▪ Beovu 6mg: 29.3% ▪ Aflibercept 2mg: 29.9% % of patients maintained q12week dosing through week 48: ▪ Beovu 6mg: 51.0% % of patients that had disease activity at week 16 ▪ Beovu 6mg: 22.7% ▪ Aflibercept 2mg: 32.2% CST reductions from baseline to week 16 ▪ Beovu 6mg -174.4 vs aflibercept 2mg -134.2 um, p<0.001 % of patients with presence of IRF and/or SRF at week 16 ▪ Beovu 6mg: 29.4% ▪ Aflibercept 2mg: 45.1%d **Over 50% of patients on Beovu can be treated q12 weeks following the loading dose. Beovu demonstrated less disease activity and better anatomical outcomes compared with aflibercept.**

	HAWK NCT02307682 (Dugel et al)	HARRIER NCT02434328 (Dugel et al)
	% of patients with presence of IRF and/or SRF at week 16 ▪ Beovu 3mg: 41.8% ▪ Beovu 6mg: 33.9% ▪ Aflibercept 2mg: 52% **Over 50% of patients on Beovu can be treated q12 weeks following the loading dose. Beovu demonstrated less disease activity and better anatomical outcomes compared with aflibercept.**	
General Summary: Safety	Overall safety profile of Beovu with both 3mg and 6mg was comparable to aflibercept. Most common adverse events ▪ conjunctival hemorrhage (3mg: 8.4%, 6mg: 6.4%) ▪ reduced visual acuity (3mg: 6.4%, 6mg: 5.3%) ▪ vitreous floaters (3mg: 5.9%, 6mg: 5.0%)	Overall safety profile of Beovu with both 3mg and 6mg was comparable to aflibercept. Most common adverse events ▪ conjunctival hemorrhage (6mg: 5.4%) ▪ vitreous floaters (6mg: 3.0%)
Comments	▪ In HAWK and HARRIER, Beovu q12 or q8 weeks met the primary endpoint of noninferiority in BCVA versus aflibercept q8 weeks. ▪ Greater than 50% of Beovu 6mg patients were maintained on the q12 week dosing interval ▪ Disease activity and retinal fluid outcomes favored Beovu over aflibercept. ▪ Overall Safety and adverse events were similar between Beovu and aflibercept.	
Grade^	A	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: The safety and efficacy of Beovu® (brolucizumab) in pediatric patients has not been estabilished
Geriatric Use: No significant differences in efficacy and safety were seen with increasing age.

Cost and/or Utilization Data of Similar Treatment Options:

Table 2: Beovu® (brolucizumab) Pricing

Drug	Strength	Package size	WAC/Package

Beovu	6 mg/0.05 mL	0.05 mL vial	$1,850

Table 3: Humana Tiering for Similar Treatment Options

Medicaid – 2020			
KYMD	NF (medical)	NF (medical)	NF (medical)
LAMD	NF (medical)	NF (medical)	NF (medical)

Place in Therapy:

Table 4. Comparison of Beovu® (brolucizumab) and Eylea® (aflibercept)

	Beovu® (brolucizumab)	**Eylea® (aflibercept)**
Meet an Unmet Medical Need[1]	No. **Comment: Four VEGF inhibitors (Eylea, Lucentis, Avastin, Macugen) are available and have support for use in nAMD.**	
Comparable Efficacy[2]	Beovu® (brolucizumab) has similar efficacy relative to Eylea® (aflibercept) **Comment: In the HAWK and HARRIER trials, Beovu was shown to be noninferior to aflibercept with regard to BCVA change from baseline at week 48. 50% of Beovu patients were able to be maintained on the q12 week dosing interval. Secondary endpoints showed that Beovu had less disease activity and retinal fluid outcomes.**	
Comparable Safety[3]	Beovu® (brolucizumab) would likely have similar safety relative to Eylea® (aflibercept) **Comment: In the HAWK and HARRIER trials, adverse event rates between Beovu and aflibercept were comparable.**	
Comparable Cost-Effectiveness[4]	Beovu® (brolucizumab) would likely be similar or slightly more cost-effective relative to Eylea® (aflibercept) **Comment: A cost-effectiveness model was developed to evaluate Beovu in comparisoin to aflibercept and ranibizumab. Beovu was less expensive compared to aflibercept and ranibizumab, with total cost of $63,665 vs $72,247 for aflibercept and $128,261 for ranibizumab. Beovu yielded slightly more QALYs than both aflibercept and ranibizumab; 4.577 for Beovu, 4.569 for aflibercept, and 4.566 ranibizumab.**	
Adherence[5]	Members taking Beovu® (brolucizumab) would likely achieve a similar adherence rate relative to Eylea® (aflibercept) **Comment: Both Beovu and Eylea are intravitreal injections with q8 week and q12 week dosing and would be expected to have similar adherence rates.**	
Advantages	▪ Q8 week and q12 week dosing intervals appear to provide similar BCVA efficacy as q8 week Eylea. ▪ Measurements of disease activity and anatomic outcomes at week 16 favor Beovu over Eylea	▪ Brand market share leader ▪ FDA approved in multiple dosing intervals up to q12 weeks ▪ Available in a prefilled syringe as well as a vial

Disadvantages	▪ Intravitreal injection requiring multiple provider visits throughout the year.	▪ Intravitreal injections requiring multiple provider visits throughout the year.

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:

- Medicaid: NF with QL, MIT PAL
- QL = 0.8 (16 doses) / 365 days

References:

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2. Beovu [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; October 2019.
3. Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc.; 2019. URL:http://www.clinicalpharmacology.com. Accessed December 2019.
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Humana Pharmacy Solutions

Clinical Review – Ubrelvy™ (ubrogepant)

***Company*:** Allergan
Current Status: FDA Approved December 2019
Therapeutic Category: Antimigraine
Pharmacologic Category: Calcitonin gene-related peptide (CGRP) receptor antagonist
Similar Drugs:

- CGRP inhibitors: Aimovig, Emgality, Ajovy
- Acute migraine treatments: sumatriptan, naratriptan, rizatriptan

Dosage Forms: 50mg and 100mg oral tablets

Indications:

- For the acute treatment of migraine with or without aura in adults. Limitations of use: Ubrelvy™ is not indicated for the preventive treatment of migraine.

Dosage and Administration:

- The recommended dose of Ubrelvy™ is 50mg or 100mg orally with or without food. If needed a second dose can be taken 2 hours after the initial dose. The maximum dose in 24 hours is 200mg. The safety of treating more than 8 migraines in a 30 day period has not been established.

Background:

- Migraines affect approximately 1 in 7 individuals globally. In the U.S., migraines affect ~15% of the population. Prevalence peaks between 25 and 55 years of age. Studies have shown that migraines affect women more than men, with rates being almost 3 times higher. The annual total cost for migraines is estimated to be $27 Billion in the U.S. Oral triptans (e.g. sumatriptan) are the most commonly prescribed medication for the acute management of migraines. The triptans are considered the current standard of care. However, there is a proportion of individuals that have suboptimal response to triptans or have tolerability issues that require the use of other acute medications. The CGRP antagonists will have a role in those types of situations. CGRP antagonists, up until now, have been primarily used for the prevention of episodic and chronic migraines. Now with the approval of Ubrelvy™, a CGRP antagonist is available in the acute management space.

Pharmacology:

- Ubrelvy™ is a calcitonin gene-related peptide (CGRP) receptor antagonist. CGRP is distributed throughout the central nervous system and plays a role in the pathophysiology of migraines. CGRP concentrations are elevated during acute migraine attacks and may be chronically elevated in patients who suffer from chronic migraines.

Pharmacokinetics:

- Absorption: When given with a high-fat meal, the time to Cmax was delayed by 2 hours with no change in AUC. In the clinical efficacy studies, Ubrelvy™ was administered without regard to food.
- Metabolism/Elimination: Ubrelvy™ is primary metabolized by CYP3A4. The elimination half-life is approximately 5-7 hours.

Drug Interactions:

- CYP3A4 /P-gp inhibitors or inducers can interact with ubrogepant. Inhibitors can increase the exposure of ubrogepant but it is not expected to be more than two-fold.

***Adverse Effects*:**

- Nausea
- Somnolence

Contraindications:

- Concomitant use with strong CYP3A4 inhibitors

Evidence Table of Clinical Studies:

Table 1. Clinical data for Ubrelvy™ (ubrogepant).

	ACHIEVE I **Dodick DW/2019**	**ACHIEVE II** **Lipton RB/2019**
Study Type*	Phase III, DB, PC, RCT	Phase III, DB, PC, RCT
Interventions and Sample Size	ubrogepant 50mg = 556 ubrogepant 100mg = 557 placebo = 559	ubrogepant 25mg = 561 ubrogepant 50mg = 562 placebo = 563
Populations	• 1 year history of migraine with or without aura • Migraine onset before age 50 • History of migraines lasting 4 to 72 hours • History of 2 to 8 migraine attacks per month in each of the previous 3 months	
General Summary: Efficacy	Endpoints: 1) % of participants with pain freedom at 2 hours vs placebo • 50mg: 19% vs 12%, p=0.002 • 100mg: 21% vs 12%, p<0.001 2) % of participants with absence of the most bothersome symptom at 2 hours vs placebo • 50mg: 39% vs 28%, p<0.001 • 100mg: 38% vs 28%, p<0.001	Endpoints: 1) % of participants with pain freedom at 2 hours vs placebo • 25mg: 20.7% vs 14.3%, p=0.028 • 50mg: 21.8% vs 14.3%, p=0.012 2) % of participants with absence of the most bothersome symptom at 2 hours vs placebo • 25mg: 34.1% vs 27.4% ***P=0.07*** • 50mg: 38.9% vs 27.4%, p=0.013
General Summary: Safety	Nausea, dizziness, dry mouth, and somnolence was most common side effect in the trials. Overall ubrogepant was well tolerated and no safety concerns were identified.	
Comments	▪ Both doses (50mg and 100mg) met both the primary endpoints. ▪ Limitations to this study: 1) there was no active comparator and no evaluation of consistency of effect as this was a single attack trial 2) safety and side-effect data was based on a single attach and therefore repeated use cannot be inferred.	▪ The 25mg and 50mg doses led to significant greater rates of pain freedom at 2 hours. However only the 50mg strength showed significant difference for the absence of the most bothersome migraine associated symptom at 2 hours. ▪ Limitations to this study: 1) participants treated their migraine when headache pain was moderate or severe which differs from the guideline recommendation to treat at the first sign of headache. 2) The consistency with which ubrogepant relieves recurrent attack pain cannot be determined since this was a single attack trial.

*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:** For elderly patients, dose selection should be cautious starting at the low end of the dosing range.
- **Renal Impairment:** Dose adjustment is recommended for patients with severe renal impairment (CrCl 15-29 mL/min), with the initial and second dose being 50mg. Ubrogepant should be avoided in patients with end-stage renal disease (CrCl <15 mL/min).
- **Hepatic Impairment:** No dose adjustments are recommended for mild to moderate hepatic impairment. For severe hepatic impairment (Child-Pugh Class C), the initial and second dose should be 50mg.

Cost and/or Utilization Data of Similar Treatment Options:

Table 2: Ubrelvy™ (ubrogepant) Pricing

Drug	Strength	WAC/tablet
Ubrelvy (ubrogepant)	50mg	$85
Ubrelvy (ubrogepant)	100mg	$85

Table 3: Humana Tiering for Similar Treatment Options

	Sumatriptan	Rizatriptan	Naratriptan
Medicaid – 2020			
KYMD	1	1	1

Place in Therapy:

Table 4. Comparison of Ubrelvy and Sumatriptan

	Ubrelvy™ (ubrogepant)	Sumatriptan tablets
Meet an Unmet Medical Need[1]	☒ **No.** **Comment: Many options exist for the treatment of acute migraines with or without aura.**	
Comparable Efficacy[2]	☒ Sumatriptan is more efficacious relative to Ubrelvy **Comment: A network meta-analysis performed by ICER found that when ubrogepant is compared to the triptans, a lesser proportion of patients achieved freedom from pain and relief from pain at two hours post dose.**	
Comparable Safety[3]	☒ Sumatriptan would like have similar safety relative to Ubrelvy **Comment: Side effect profiles for both sumatriptan and Ubrelvy appear to be similar**	
Comparable Cost-Effectiveness[4]	☒ Sumatriptan is more cost-effective relative to Ubrelvy. **Comment: The network met-analysis ICER rates ubrogepant as C-, demonstrating the net health benefit is either comparable or inferior compared to the triptans.**	

Adherence[5]	☒ Members taking Sumatriptan would likely achieve a similar adherence rate relative to Ubrelvy. **Comment: Both sumatriptan and Ubrelvy are oral tablets and are taken at the first sign of a headache. Adherence is expected to be similar between the two therapies.**	
Advantages	▪ Novel mechanism of action for the acute treatment of migraines ▪ Is not contraindicated in patients with coronary artery disease.	▪ Established consistency of safety and efficacy with extended use ▪ Available in multiple dosage forms (i.e. tablet, injection, nasal spray).
Disadvantages	▪ Long term consistency of efficacy hasn't been determined ▪ Cost vs other options for acute migraines ▪ Only available in tablets, which may limit its use in patients with severe nausea/vomiting associated with their migraines.	▪ Limitation of use in patients with cardiovascular disease

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]
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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.

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

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Recommendation:

- Ky Medicaid: NF with QL
- QL = 8 tablets / 30 days

References:

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2. Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc.; 2020 URL: http://www.clinicalpharmacology.com. February 2020.
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Humana Pharmacy Solutions

Clinical Review – Padcev (enfortumab vedotin-ejfv)

***Company*:** Co-development between Astellas Pharma and Seattle Genetics
Current Status: FDA approval 12/18/2019
Potential Launch: Hit FDB 12/27/2019
Therapeutic Category: Anti-Nectin-4
Pharmacologic Category: Antibody-Drug Conjugates
Similar Drugs: Adcetris, Besponsa, Enhertu, Kadcyla, Mylotarg
Route of Administration: Intravenous
Dosage Forms: Lyophilizied powder single-dose vials for injection (20 mg and 30 mg)

Indications: for the treatment of adult patients with locally advanced or metastatic urothelial cancer who have previously received a programmed death receptor-1 (PD-1) or programmed death-ligand 1 (PD-L1) inhibitor, and a platinum-containing chemotherapy in the neoadjuvant/adjuvant, locally advanced or metastatic setting.

Dosage and Administration:

- Given only as an intravenous infusion, and should not be given in IV push or bolus routes
- Medication should not be mixed with any other medications
- Recommended dose is 1.25 mg/kg with a maximum dose of up to 125 mg, which is administered through IV route over a 30 minute period on days 1, 8, and 15 of a complete 28 day cycle.
- Should be avoided in patients that have moderate or severe hepatic impairment

Background: Bladder cancer is the ninth most common cancer worldwide with an estimated 80,000 new cases and 18,000 deaths each year in the United States. It forms in the urothelial cells of the bladder, and develops through abnormal growth of these cells. The urothelial cells begin to mutate, which leads to rapid proliferation and eventual tumor formation. Urothelial carcinoma is the most common histologic type in the United States and Europe,where it makes up to 90% of bladder cancer cases. Risk factors for the disease include smoking, environmental exposures. Locally advanced or metastatic urothelial carcinoma of the renal pelvis, ureters, bladder, or urethra is an incurable disease with poor long-term survival. Platinum-based therapies are the first-line treatment for most patients, with objective response rates of 41% to 50% and median progression-free survival of 7.6 months. In the post-platinum setting, phase III studies of anti–programmed death 1 or anti–programmed death ligand 1 (PD-1/L1) therapy demonstrated objective response rates of 21% and 13%, respectively, with an overall survival advantage compared with second-line chemotherapy demonstrated in one of two studies conducted to date. For patients who have experienced progression after platinum-based therapy and anti–PD-1/L1 therapy, treatment options are limited to chemotherapies that have modest activity.

Pharmacology: Padcev (enfortumab vedotin-ejfv) is an antibody-drug conjugate (ADC). This particular antibody is a human IgG1 that targets Nectin-4, which is an adhesion protein found on the cell surface. A small molecule, known as a microtubule-disrupting agent (MMAE) attaches to the antibody through a protease-cleavable linker. The anticancer activity of this particular drug is thought to occur due to the binding of the antibody-drug conjugate to nectin-4 expressed cells. This results in the internalization of the ADC-Nectin-4 complex and the release of MMAE through proteolytic cleavage. Once MMAE is released, a disruption occurs within the cell, which leads to apoptosis of the cells.

Pharmacokinetics:

- Metabolism/Elimination:
  - Metabolism: Has not been studied on humans, but metabolism is expected to catabolize to smaller peptides, amino acids, unconjugated MMAE, and unconjugated MMAE.
  - Elimination: Not completely classified
- Plasma Half-Life:
  - ADC: 3.4 days

- MMAE: 2.4 days

Drug Interactions:

- Concomittant use with CYP3A4 inhibitors may result in an increase of free MMAE exposure that can lead to increase toxicity effects of PADCEV.

***Adverse Effects*:**

- The most common adverse effects consist of peripheral neuropathy, fatigue, reduced appetite, nausea, dysgeusia, diarrhea, alopecia, pruritis, and dry skin.
- Severe adverse effects: Urinary tract infection, cellulitis, febrile neutropenia, sepsis, acute kidney injury, dyspnea, and rash.

Contraindications:

- None

Warnings and Precautions:

- Hyperglycemia can occur in patients regardless of prior diabetes diagnosis, and can result in diabetic ketoacidosis and death
  - Grade 3-4 hyperglycemia had an increased presence in patients that had higher body mass indexes or higher baseline A1C
- Peripheral Neuropathy
  - Sensory was seen in 49% of the 310 patients in clinical trials
  - Important to monitor for increased signs and symptoms of peripheral neuropathy
  - Average onset time of greater than Grade 2 was 3.8 months, and resulted in the discontinuation of treatment in 6% of patients
- Ocular Disorders
  - Present in 46% of 310 patients given
  - Primarily present within the cornea and effects consisted of blurred vision, symptoms related to dry eyes, keratitis, and limbal stem cell deficiency
  - 36% of patients experienced dry eye related symptoms and 14% reported blurred vision
- Skin Reactions
  - 54% of patients developed skin reactions
  - 26% presented with maculopapular rash while 30% of patients had pruritis
  - 10% of patients had Grade 3-4 reactions

Monitoring:

- Blood glucose
- LFT's
- Pregnancy status
- New or worsening symptoms of peripheral neuropathy, ocular disorder, skin reactions and potential extravasation
- CBC

Evidence Table of Clinical Studies:

Table 1. Clinical data for Padcev (enfortumab vedotin-ejfv)

	EV-201
Study Type*	• Two-cohort, single-arm, phase II multicenter trial evaluating efficacy and safety Padcev in patients that presented with locally advanced or metastatic UC • Reporting results of only Cohort 1
Interventions and Sample Size	• 128 patients enrolled in Cohort 1 that had a diagnosis of locally advanced or metastatic urothelial cancer - 51 study centers throughout the United States and Japan - 3 patients withdrew before treatment initiation • Cohort 1: - Enrolled patients that previously were treated with both platinum chemotherapy and anti-PD1/L1 therapy. • Cohort 2: Continued enrollment - Patients that had been treated prior with anti-PD-1/L1 therapy • Padcev was given intravenously at 1.25 mg/kg based on body weight (max dose of 125 mg). - Given over 30 minutes on days 1, 8, and 15 of a 28 day cycle
Populations	Inclusion Criteria: • Patients that present with locally advanced or metastatic urothelial carcinoma. • Were previously treated with anti-PD-1/L1 therapy • 18 years or older • ECOG score of 1 or less • Adequate baseline organ function Exclusion Criteria: • Patients with current motor or sensory neuropathy that was grade 2 or higher. • Active CNS metastases • Uncontrolled diabetes (A1C of 8% or more) Baseline demographics: • 70% of patients were male • Median age: 69 years old • 73% of patients were less than 75 years old, while 27% were 75 years or older • 94% of patients were located in North America, and 6% in Asia • ECOG score of 0: 32% • ECOG score of 1: 68% • 65% had tumor in the bladder • 67% of patients had urothelial carcinoma only • Median number of 3 previous systemic therapies in locally advanced or metastatic setting
Primary Endpoints	• Objective response rate based on blinded independent central review
Secondary Endpoints	• Duration of response • Progression-free survival based on BICR • Overall survival • Safety • Tolerability
General Summary: Efficacy	Summary: • Objective response rate: 44% • Complete response rate: 12%

	EV-201
	• Median time to response: 1.84 months • Median duration of response: 7.6 months • Partial response: 32% • Ongoing responses in 44% of all responders • 47% response in patients <75 years old, and 35% in patients >75 years old. • Target lesions decreased in 84% of evaluated patients. • Median PFS: 5.8 months • Median OS: 11.7 months
General Summary: Safety	Safety Assessments: • Physical and ocular exams • Routine chemistry • Hematologic lab exams • Pre-specified adverse events - Peripheral neuropathy - Rash - Infusion site reactions - Hyperglycemia Summary: • All 125 patients experienced at least one adverse event. • 117 (94%) of patients experienced a treatment related adverse event. • 54% of patients experienced a treatment related adverse event of Grade ≥3**.** • Serious treatment-related adverse events were reported in 19% of patients. • 32% of patients had a dose reduction, while 12% discontinued treatment as a result of treatment-related adverse events. • Most commonly reported treatment-related adverse events consisted of fatigue (50%), alopecia (49%), decreased appetite (44%), dysgeusia (40%), and peripheral sensory neuropathy (40%). - Treatment related peripheral neuropathy was observed in 50% of patients. - 94% of those patients were Grade 2 or lower. - 48% of the patients that developed peripheral neuropathy did not experience a worsening of effects. - 76% of peripheral neuropathy was resolved or an ongoing Grade 1. • Most commonly reported Grade ≥3 treatment-related adverse event included anemia (7%), fatigue (6%), and neutropenia (8%). • Most reported serious treatment-related adverse event was febrile neutropenia (4%). • 48% of patients developed treatment related rash, and 75% of those patients were Grade 2 or lower. - 73% of these patients were completely resolved and 20% had improved by follow-up. • Hyperglycemia present in 11% of patients regardless of their hyperglycemia baseline. - 57% were completely resolved and 14% experienced improvement. - 1 patient experienced Grade 4 hyperglycemia and was discontinued from treatment (later recovered). - 68% of the 19 patients that had hyperglycemia at baseline did not experience a hyperglycemic treatment related event. • No-treatment related deaths, but one patient died due to interstitial lung disease.
Comments	• Preliminary and ongoing trial • No active comparator • Potential hangover benefit from prior PD-1/L1 reflected in reported ORR • Safety appears manageable

	EV-201
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**
  - Can result in fetal harm when given to a pregnant patient
  - In animal reproduction studies, administration of PADCEV led to maternal toxicity, embryo-fetal lethality, and structure malformations (dose of 1.25 mg/kg)
- **Pediatric Use**
  - Efficacy and safety in pediatric patients has not been established
- **Geriatric Use**
  - 60% of the 310 patients treated with PADCEV in clinical trials were 65 years or older
  - 26% of the patients tested were 75 years or older.
  - Between the two groups, there was no overall difference with regard to efficacy or safety in comparison with younger patients
- **Hepatic Impairment**
  - Avoid use of PADCEV in patients with moderate to severe hepatic impairment
  - Incidence of Grade 3 or higher adverse effects were seen in patients that had moderate to severe hepatic impairment
  - No dose adjustments indicated for patients that present with mild hepatic impairment.
- **Renal Impairment**
  - Dose adjustment not required for patients with renal impairment.

Cost and/or Utilization Data of Similar Treatment Options:

Table 2: Padcev Pricing

Drug	WAC/Package

Padcev	• WAC per mg vial = $105.5
	  ○ 20 mg – $2,110 per vial
	  ○ 30 mg – $3,165 per vial
	• Estimated cost for course of therapy = $110K – 120K

Place in Therapy:

Table 3. Comparison of Padcev and Single Agent Chemotherapy (docetaxel, paclitaxel)

	Padcev	Single Agent Chemotherapy
Meet an Unmet Medical Need[1]	☒ **No** – While efficacy appears promising and the adverse event profile seem manageable. Continued approval is pending based upon the clinical benefit of the indication in confirmatory trials. Specifically, EV-301 (NCT03474107) is an ongoing phase 3 trial initiated in June 2018 with completion expected by September 2021. This global, open-label, randomized phase 3 trial is designed to evaluate Padcev monotherapy (1.25 mg/kg IV) versus investigator's choice of chemotherapy (docetaxel, paclitaxel, or vinflunine) in approximately 600 adult patients who were	

	previously treated with PD-1/L1 inhibitor therapies and platinum-based therapies.
Comparable Efficacy[2]	**Comparable efficacy is questionable and unknown at this time.** Potential hangover benefit from prior PD-1/L1 has been suggested. There is an ongoing phase EV-301 is comparing Padcev vs versus investigator's choice of chemotherapy (docetaxel, paclitaxel, or vinflunine). Results of EV-301 should directly answer the comparable efficacy question.
Comparable Safety[3]	☒ **Padcev would likely be more safe relative to single agent chemotherapy.** Due to the improved tumor-to-normal tissue selectivity and specificity associated with antibody-drug conjugates, systemic exposure and therefore toxicity is expected to be less with Padcev than with single agent chemotherapy. Padcev is associated with a more manageable profile (i.e., neuropathy and rash, slight anemia and neutropenia)
Advantages (Padcev vs Single Agent Chemotherapy)	▪ Rapid onset of action associated with Padcev ▪ Bone marrow suppression not as severe with Padcev
Disadvantages (Padcev vs Single Agent Chemotherapy)	▪ Physicians have less world experience with Padcev ▪ Peripheral neuropathy more common with Padcev
Comments	▪ Padcev demonstrated efficacy in a heavily treated population ▪ Continued approval is pending based upon the clinical benefit of the indication in confirmatory trials ▪ Phase 3 trial comparing Padcev vs single agent chemotherapy is ongoing (completion expected September 2021) ▪ Evaluations ongoing for Padcev in the first-line setting, in combination with anti–PD-1 and/or platinum-based therapies

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.

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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:

- Medicaid:NF (Medical)

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3. Micromedex® Healthcare Series: Thomson Micromedex, Greenwood Village, CO (2020).
4. National Comprehensive Cancer Network. Cancer Guidelines and Drugs and Biologics Compendium 2020.
5. Padcev (enfortumab vedotin-ejfv) [prescribing information]. Astellas Pharma US, Inc., Northbrook, Illinois. December 2019.
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Humana Pharmacy Solutions

Clinical Review – Brukinsa® (zanubrutinib)

***Company*:** BeiGene, Ltd.
Current Status: FDA approved 11/14/2019
Potential Launch: on FDB report 11/23/2019
Therapeutic Category: Oncology
Pharmacologic Category: BTK inhibitor
Similar Drugs: Calquence, Imbruvica
Route of Administration: Oral
Dosage Forms: 80 mg Capsules

Indications: Indicated for the treatment of adult patients with mantle cell lymphoma (MCL) who have received at least one prior therapy.

Dosage and Administration:
Recommended Dosage: 160 mg orally twice daily or 320 mg orally once daily

- Swallow whole with water and with or without food

Background:

- Lymphoma is a group of cancers that originate from B, T, or NK cells. Mantle Cell Lymphoma (MCL) is often an aggressive form of non-Hodgkin's lymphoma that comes from the B-cells originating in the "mantle zone". About 74,200 people in the United States will be diagnosed with non-Hodgkin's lymphoma (NHL) in 2019 with Mantle Cell Lymphoma representing about 6% of all new cases of non-Hodgkin's lymphoma. MCL often carries a poor prognosis with a median survival of 3 to 4 years as the disease is often diagnosed at a later stage.

Pharmacology:

- Brukinsa (zanubrutinib) is a small-molecule inhibitor of BTK. Brukisna forms a covalent bond with a cysteine residue in the BTK active site, leading to inhibition of BTK activity. BTK is a signaling molecule of the B-cell antigen receptor (BCR) and cytokine receptor pathways. In B-cells, BTK signaling results in activation of pathways necessary for B-cell proliferation, trafficking, chemotaxis, and adhesion. In nonclinical studies, Brukinsa inhibited malignant B-cell proliferation and reduced tumor growth.

Pharmacokinetics:

- Metabolism/Elimination: Zanubrutinib is primarily metabolized by cytochrome P450(CYP)3A. Following a single radiolabeled zanubrutinib dose of 320 mg to healthy subjects, 87% of the dose was recovered in the feces (38% unchanged) and 8% in the urine (<1% unchanged).
- Plasma Half-Life (hrs): The mean half-life is approximately 2-4 hours following a single oral dose of 160 mg or 320 mg.

Drug Interactions:

- CYP3A Inhibitors: Modify Brukinsa dose with moderate or strong CYP3A inhibitors.
  - Moderate- 80 mg once daily, interrupt dose as recommended for adverse reactions
  - Strong- 80 mg twice daily, interrupt dose as recommended for adverse reactions
- CYP3A Inducers: Avoid co-administration with moderate or strong CYP3A inducers.

***Adverse Effects*:**

- The most common adverse reactions (>20%) seen were neutrophil count decrease platelet count decrease, upper respiratory tract infection, white blood cell count decrease, hemoglobin decrease, rash, bruising, diarrhea, and cough.

Contraindications:

- None

Warnings and Precautions:

- Hemorrhage: Monitor for bleeding and manage appropriately.
- Infections: Monitor patients for signs and symptoms of infection, including opportunistic infections, and treat as needed.
- Cytopenias: Monitor complete blood counts during treatment.
- Secondary primary malignancies: Other malignancies have occurred in patients including skin cancers. Advise patients to use sun protection.
- Cardiac Arrhythmias: Monitor for atrial fibrillation and atrial flutter and manage appropriately.
- Embryo-Fetal Toxicity: Can cause fetal harm. Advise women of the potential risk to a fetus and to avoid pregnancy.
- Lactation: Advise not to breastfeed.

Monitoring:

- Monitor complete blood counts and for atrial fibrillation and atrial flutter.

Evidence Table of Clinical Studies:

Table 1. Clinical data for Brukinsa (zanubrutinib).

	NCT03206970	NCT02343120
Study Type*	Ph2, Single-Arm, Open-Label, Multicenter	Ph1/2, Open-Label, Safety/Efficacy Study, Dose-Escalation
Interventions and Sample Size	• N=86 • Patients received Brukinsa at a dose of 160 mg orally twice daily until disease progression or unacceptable toxicity.	• N=32 • Brukinsa was given orally at 160 mg twice daily or 320 mg daily.
Populations	Key Inclusion Criteria: • 18-75 years of age. • Diagnostic report had to include evidence for morphological and cyclin D1 or t (11;14). • ECOG performance status of 0-2. • Received prior regimens for MCL. • Life expectancy > 4 months. • Measurable disease by computed tomography/magnetic resonance imaging. (CT/MRI). • Documented failure to achieve any response, or documented progressive disease after response to the most recent treatment regimen. • AST and ALT ≤ 2.5 x ULN.	Key Inclusion Criteria: • ≥ 18 years of age and voluntary consent to the study. • Disease that has relapsed, or is refractory, following at least one line of therapy, with no therapy of higher priority available. • ECOG performance status of 0-2. • Adequate hematologic, renal, and liver function. • Those of childbearing potential must practice birth control.

	NCT03206970	NCT02343120
	• Total bilirubin ≤ 2 x ULN (unless documented Gilbert's syndrome). • Females of childbearing age must agree to use highly effective forms of birth control. Key Exclusion Criteria: • Current or history of central nervous system (CNS) lymphoma. • Prior exposure to a BTK inhibitor before enrollment. • Prior corticosteroids with anti-neoplastic intent within 7 days. • Major surgery within 4 weeks of screening. • Currently clinically significant cardiovascular disease. • Known HIV, active hepatitis B or hepatitis C infection (detected by positive PCR). • Uncontrolled systemic infection, long QTC (>450 msecs) or other significant ECG abnormalities, any life-threatening illness or condition in which the investigators opinion could compromise the subject's safety, or put the study at risk. • Pregnant or lactating women.	Key Exclusion Criteria: • Current CNS involvement by disease. • Current histologically transformed disease. • Prior BTK inhibitor treatment. • Significant impairment to an organ system that would adversely impact their participating in the study. • On CYP3A inhibitors. • Allogeneic stem cell transplantation within 6 months, or has active GVHD requiring ongoing immunosuppression.
General Summary: Efficacy	• The Overall Response Rate was 84% with a mediation duration of response of 19.5 months. 59% had a complete response and 24 % had a partial response. 74.6% had 12 months progression free survival and 72.1% had 15 months of progression free survival.	• The Overall Response Rate was 84% with a mediation duration of response of 18.5 months. 22% had a complete response and 62% had a partial response.
General Summary: Safety	• The most common adverse events seen were decrease neutrophil count, decreased platelet count, upper respiratory tract infection, decreased white blood cell count, decreased hemoglobin, rash, bruising, diarrhea, cough, musculoskeletal pain, pneumonia, urinary tract infection, hematuria, constipation, and hemorrhage. Most frequent serious AE's were pneumonia and hemorrhage. Most frequent AE that led to treatment discontinuation was pneumonia and 1 patient experienced hepatitis B that led to dose reduction.	
Comments:	• Most frequent AE that led to treatment discontinuation was pneumonia and 1 patient experienced hepatitis B that led to dose reduction	
Grade^	▪ C	▪ 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:

- Pregnancy: Based on findings in animals, Brukinsa can cause fetal harm when administered to pregnant women. There is no available data on Brukinsa use in pregnant women.

- Lactation: There are no data on the presence of Brukinsa or its metabolites in human milk. Due to the potential for serious adverse reactions from Brukinsa in a breastfed child, advise lactating women not to breastfeed during treatment with Brukinsa and for at least two weeks following the last dose.

Cost and/or Utilization Data of Similar Treatment Options:

Table 2: Brukinsa® Pricing

Drug	Strength	WAC/unit	Package size	WAC/Package	30 day cost for MCL
Brukinsa	80 mg	$107.79/capsule	120	$12,935	$12,935
Calquence	100 mg	234.40/capsule	60	$14,064	$14,064
Imbruvica	560 mg	$463/tablet	28	$12,966	$13,892

Place in Therapy:

Table 3. Comparison of Brukinsa

	Brukinsa	Acalabrutinib	Ibrutinib
Meet an Unmet Medical Need[1]	• No, Brukinsa does not meet an unmet need. There are other FDA approved agents for mantle cell lymphoma.		
Comparable Efficacy[2]	• ORR at 84%. 59% complete response rate. • Most favorable efficacy data in class.	• ORR at 81%. 43% complete response rate.	• ORR at 61%. 17% complete response. • Least favorable efficacy data in class.
Comparable Safety[3]	• Brukinsa showed a higher rate of Neutropenia at 15% versus 10% (Acalabrutinib) and 13% (Ibrutinib) • Brukinsa also showed higher rates of pneumonia	• Similar side effects as seen in Brukinsa and Ibrutinib.	• Favorable pneumonia data (0% versus 5% Acalabrutinib and 10% Brukinsa).
Adherence[5]	• Similar adherence. Ibrutinib is dosed once daily and Brukinsa can be dosed once daily. Acalabrutinib is dosed twice daily.		
Advantages	• Better overall response rate in similar patient population	• Provider experience	• Provider experience
Disadvantages	• Provider inexperience		• Weakest ORR in class • Data suggests ibrutinib increases risk of hypertension and other major adverse cardiovascular events.
Comments	• Currently also being studied in chronic lymphocytic leukemia, Waldenstrom macroglobulinemia, follicular	• NCCN recommended for Second-Line Treatment of MCL.	• Risk of hypertension and MACE.

	lymphoma, and marginal zone lymphoma		• NCCN recommended for Second-Line Treatment of MCL with or without rituximab.

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]
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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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Recommendation:

- KY Medicaid: NF, non-participating
- QL: 120/30/4.6

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3. IMBRUVICA® (ibrutinib) Prescribing Information. Pharmacyclics LLC. 2019
4. Wang M, Rule S, Zinzani PL, et al. Long-Term Follow-Up of Acalabrutinib Monotherapy in Patients With Relapsed/Refractory Mantle Cell Lymphoma. Poster presentation at: American Society of Hematology 2018 Annual Meeting; December 2018; San Diego, CA. Abstract #2876.

Humana Pharmacy Solutions

Clinical Review – Brukinsa® (zanubrutinib)

Humana Pharmacy Solutions

Clinical Review – Rybelsus® (semaglutide)

***Company*:** Novo Nordisk
Current Status: FDA approved September 20th, 2019
Potential Launch: FDB September 28, 2019
Therapeutic Category: Anti-hyperglycemic
Pharmacologic Category: Glucagon-like Peptide-1 Receptor Agonist
Similar Drugs: Ozempic, Trulicity, Victoza
Route of Administration: Oral
Dosage Forms: 3mg, 7mg, 14mg tablets

Indications: indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus

Limitations of Use

- Not recommended as first-line therapy for patients inadequately controlled on diet and exercise
- Has not been studied in patients with a history of pancreatitis
- Not indicated for use in patients with type 1 diabetes mellitus or treatment of diabetic ketoacidosis

Dosage and Administration:

- Start with 3 mg once daily for 30 days. The 3 mg dose is intended for treatment initiation and is not effective for glycemic control.
- After 30 days on the 3 mg dose, increase the dose to 7 mg once daily.
- Dose may be increased to 14 mg once daily if additional glycemic control is needed after at least 30 days on the 7 mg dose.
- Taking two 7 mg tablets to achieve a 14 mg dose is not recommended.
- If a dose is missed, the missed dose should be skipped, and the next dose should be taken the following day.

Background: Type 2 diabetes is the most common form of diabetes. Current treatment options include oral medications (e.g. metformin, SGLT2-inhibitors, and DPP-IV inhibitors) as well as injectable medications (e.g. GLP-1 agonists, insulins). GLP-1 agonists exhibit their effects in lowering blood glucose by slowing digestion, promoting insulin production, and limiting inappropriate glucagon secretion. Rybelsus was studied in an extensive clinical trial series, consisting of 10 clinical trials, referred to as PIONEER.

Pharmacology: Semaglutide binds to the GLP-1 receptor. This activates the receptor and stimulates the release for GLP-1 peptide in response to an oral glucose load. Semaglutide reduces blood glucose through a mechanism where it stimulates insulin secretion and lowers glucagon secretion, both in a glucose-dependent manner. Thus, when blood glucose is high, insulin secretion is stimulated and glucagon secretion is inhibited. The mechanism of blood glucose lowering also involves a minor delay in gastric emptying in the early postprandial phase

Pharmacokinetics:

Metabolism/Elimination: The primary route of elimination for semaglutide is metabolism following proteolytic cleavage of the peptide backbone and sequential beta-oxidation of the fatty acid side chain.

Plasma Half-Life: Approximately 1 week

Drug Interactions:

- Semaglutide delays gastric emptying. When coadministering oral medications instruct patients to closely follow Semaglutide administration instructions. Consider increased clinical or laboratory monitoring for medications that have a narrow therapeutic index or that require clinical monitoring

***Adverse Effects*:**

The most common adverse reactions (≥5%), excluding hypoglycemia, that are associated with Rybelsus in the pool of the placebo-controlled trials are nausea, abdominal pain, diarrhea, decreased appetite, vomiting, and constipation.

Contraindications:

- Personal or family history of medullary thyroid carcinoma or in patients with Multiple Endocrine Neoplasia syndrome type
- Known hypersensitivity to semaglutide or any of the components in Rybelsus

Warnings and Precautions:

- Pancreatitis: Has been reported in clinical trials. Discontinue promptly if pancreatitis is suspected. Do not restart if pancreatitis is confirmed
- Diabetic Retinopathy Complications: Has been reported in a cardiovascular outcomes trial with semaglutide injection. Patients with a history of diabetic retinopathy should be monitored
- Hypoglycemia: When Rybelsus is used with an insulin secretagogue or insulin, consider lowering the dose of the secretagogue or insulin to reduce the risk of hypoglycemia
- Acute Kidney Injury: Monitor renal function in patients with renal impairment reporting severe adverse gastrointestinal reactions
- Hypersensitivity Reactions: Discontinue Rybelsus if suspected and promptly seek medical advice

Monitoring:

- Pancreatitis
- Diabetic Retinopathy
- Hypoglycemia with concomitant use of insulin secretagogues or insulin

Evidence Table of Clinical Studies:

Table 1. Clinical data for Rybelsus

	PIONEER 2	PIONEER 3	PIONEER 4
Study Type*	RCT, parallel-assignment, open label	RCT, DB, parallel-assignment	RCT, DB, parallel-assignment
Interventions and Sample Size	• Rybelsus 14mg vs Empagliflozin 25mg • N=816 • 52 weeks	• Rybelsus 3, 7, 14mg • Sitagliptin 100mg • Placebo • 26 weeks	• Semaglutide 14mg • Liraglutide 1.8mg • 52 weeks
Populations	Inclusions: ▪ T2DM	Inclusions: ▪ T2DM	Inclusions: ▪ T2DM

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Clinical Review – Rybelsus® (semaglutide)

	PIONEER 2	PIONEER 3	PIONEER 4
	▪ Concurrent metformin ▪ A1C: 7-10.5% ▪ eGFR: greater than 60ml/min Exclusions: ▪ Pancreatitis, proliferative retinopathy, Major CV event past 6 months, NYHA IV	▪ A1C: 7-10.5% ▪ eGFR: greater than 60ml/min ▪ Established on metformin +/- sulfonylurea Exclusions: ▪ Pancreatitis, proliferative retinopathy, Major CV event past 6 months, NYHA IV	▪ A1C: 7-9.5% ▪ +/- metformin ▪ eGFR: greater than 60ml/min Exclusions: ▪ Pancreatitis, proliferative retinopathy, Major CV event past 6 months, NYHA IV
General Summary (ITT population): Efficacy	<u>Change in A1C (vs empagliflozin):</u> ▪ @ 26 weeks: -0.4 (-0.6 to -0.3); p<0.001 ▪ @52 weeks: -0.4 (-0.5 to -0.3); p<0.001 <u>Weight Change (vs empagliflozin)</u> ▪ @26 weeks: -0.1 (-0.7, 0.5) ▪ @52 weeks: -0.2 (-0.9, 0.5)	<u>Change in A1C (vs sitagliptin)</u> ▪ @26 weeks: ○ 7mg: -0.3 (-0.4, -0.1); p<0.001 ○ 14mg: -0.5 (-0.6, -0.4); p<0.001 ▪ @52 weeks: ○ 7mg: -0.3 (-0.4, -0.1); p<0.001 ○ 14mg: -0.5 (-0.6, -0.4); p<0.001 <u>Weight Change (vs sitagliptin)</u> ▪ @ 26 weeks ○ 7mg: -1.6 (-2, -1.1) ○ 14mg: -2.5 (-3, -2) ▪ @52 weeks ○ 7mg: -1.7 (-2.3, -1.1) ○ 14mg: -2.7 (-3.3, -2.1)	<u>Change in A1C (vs liraglutide)</u> ▪ @26 weeks: vs liraglutide: -0.1 (-0.3, 0); vs PBO: -1.1 (-1.2, -0.9) ▪ @52 weeks: -0.3 (-0.5, -0.1) vs lira; p<0.001; Vs PBO: -1 (-1.2, -0.8); p<0.001 <u>Weight Change:</u> ▪ @26 weeks (p<0.001): vs lir: -1.2 (-1.9, -0.6); vs PBO: -3.8 (-4.7, -3) ▪ @52 weeks (p<0.001):vs lir: -1.3 (-2.1, -0.5); Vs PBO: -3.3 (-4.3, -2.4)
General Summary: Safety	Most adverse events were mild to moderate, with GI effects the most common. Overall treatment group experienced AE with 14mg at a rate of 70.5 to 80% vs 69.2 to 83.3% vs comparators In head to head trials, Nausea incidence was 15.1% to 20% (similar to liraglutide, higher vs empa and sitagliptin). Diarrhea was 9.3% and 15% and vomiting was 7.3 to 9% and was higher vs comparators. D/c rate for Rybelsus was 11% vs 4.4 to 9% of comparators. Serious AEs were similar. There was a nominally increased rate of diabetic retinopathy vs placebo; 89% was non-proliferative and 76% did not require further treatment. This rate was similar to injectable semaglutide		
Comments	• Efficacy is consistent with currently available GLP-1's • The greatest benefit is derived from the highest dose • Higher doses increase TEAEs (especially GI effects) • Oral semaglutide effects in the CVOTs were inferior to that of Ozempic and Victoza • ICER concluded this was not as cost-effective as empagliflozin		

	PIONEER 2	PIONEER 3	PIONEER 4
Grade^	▪ A	▪ A	▪ 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, Geriatric Use, Renal Impairment, Hepatic Impairment-Use Only Pertinent Population]

Cost and/or Utilization Data of Similar Treatment Options:

Table 2: _Rybelsus_® Pricing

Drug	Strength	WAC/unit	Package size	WAC/Package
Rybelsus	3, 7, 14mg tab	$25.75/tab	30	$772.50/package
Victoza	18mg/3ml Pen	$102.42/ml	3ml (per pen)	$307.26/pen
Ozempic	1.34mg/1ml	$257.47/0.75ml	1ml (per pen)	$386.22/pen
Trulicity	0.75, 1.5mg	$379.70/ml	0.5ml (per pen)	$189.85/pen

Table 3: Humana Tiering for Similar Treatment Options

	Victoza	Ozempic	Trulicity
KY Medicaid	NF	T2	T2

Place in Therapy:

Table 5. Comparison of Rybelsus (semaglutide) and Ozempic (semaglutide) product(s) and/or another similar drug in the pipeline]

	Rybelsus (semaglutide) tablet	Ozempic (semaglutide) injection
Meet an Unmet Medical Need[1]	☒ No, this does not meet an unmet need. This is the first oral GLP agonist but there are many available alternative agents	
Comparable Efficacy[2]	☒ Ozempic has similar efficacy relative to Rybelsus **Comment:** Both agents have produced similar A1C and weight loss reductions in a clinical trial setting	
Comparable Safety[3]	☒ Ozempic would like have similar safety relative to Rybelsus **Comment:** Both agents showed similar incidences of common adverse events. Both showed increases in retinopathy in clinical trials and have a high incidence of GI adverse events	
Comparable Cost-Effectiveness[4]	☒ Ozempic has similar cost-effectiveness relative to Rybelsus **Comment:** Both agents are priced very similar with similar clinical effects	
Adherence[5]	☒ Members taking Ozempic would likely achieve a greater adherence rate relative to Rybelsus **Comment:** Rybelsus has a very specific administration protocol that can affect its efficacy when not taken correctly. Ozempic is a once weekly SQ injection	
Advantages	▪ Oral	▪ Provider experience ▪ Once weekly

		▪ Showed benefit in CV outcomes in clinical trial
Disadvantages	▪ Strict administration protocol ▪ Uncertain CV benefit ▪ GI effects	▪ GI effects ▪ Injection
Comments	▪ Rybelsus doesn't offer any clinical benefit over existing GLP-1s ▪ The oral route may be attractive to newly diagnosed diabetics ▪ ICER concluded Rybelsus was not as cost effective as Jardiance as add-on therapy ▪ The CV effects on Rybelsus are uncertain based on clinical trial experience	

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

QL: 30 tablets per 30 days

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Clinical Review – Ayvakit® (Avapritinib)

***Company*:** Blueprint Medicines Corporation
Current Status: FDA approval on January 9th, 2020
Potential Launch: January 16th, 2020 (within 1 week of FDA approval)
Therapeutic Category: Tyrosine kinase inhibitor
Pharmacologic Category: Antineoplastic agent, tyrosine kinase inhibitor
Similar Drugs: Gleevec (Imatinib Mesylate), Stivarga (Regorafenib), Sutent (Sunitinib Malate)
Route of Administration: Oral
Dosage Forms: Tablet

Indications: Indicated for treatment in patients with advanced metastatic or unresectable gastrointestinal stromal tumors (GIST). This medication specficially targets the platelet derived growth factor (PDGFRA) exon 18 mutation in addition to PDGFRA D842V mutations.

Dosage and Administration:

- Administration:
  - Medication must be taken on an empty stomach, and can be given either one hour prior or two hours following a meal.
- Patient Eligibility:
  - Patient eligibility based on the identification of the specific PDGFRA exon 18 mutation.
- Dosage:
  - Available in doses of 100 mg, 200 mg, and 300 mg tablets
  - Per package insert, it is recommended to take 300 mg orally each day.

Background:

- GIST occurs as a result of specialized nerve cells that are present in the GI tract. Typically, GIST begins in the stomach or small intestines, but has often been found in other parts of the GI tract. Diagnosis of the disease is rare with 4000-6000 patients diagnosed each year in the United States, which is roughly 7-20 cases per million people. Of the reported cases, it is estimated that 6-10% have the PDGFRA exon 18 mutation.

Pharmacology:

- Ayvakit functions as a tyrosine kinase inhibitor, which works by targeting mutations at PDGFRA, PDGFRA D842, KIT exon 11 and 11/17. Mutations at these targets can lead to activation of the receptors, and result in tumor cell growth.

Pharmacokinetics:
Metabolism/Elimination: Metabolized through CYP3A4 and in lower amounts by CYP2C9.
Plasma Half-Life (hrs): 32-57 hours

Drug Interactions:

- Strong and Moderate CYP3A Inducers (Carbamazepine, Rifampin, Rifabutin, Ritonavir, St. John's wort)
  - Decrease Ayvakit plasma concentration, which may decrease Ayvakit efficacy.
- Strong and Moderate CYP3A Inhibitors (Clarithromycin, Ketoconazole, Diltiazem)
  - Increase Ayvakit plasma concentration, which can result in an increase in the incidence and severity of adverse reactions.

***Adverse Effects*:**

Clinical Review – Ayvakit® (Avapritinib)

- Common:, Fatigue, edema, diarrhea, change in hair color, stomach pain, constipation, rash, and a decrease in appetite.
- Serious: Confusion, drowsiness, dizziness, change in mood/behavior, hallucinations, difficulty thinking, word finding problems, brain bleed.

Contraindications:
- None

Warnings and Precautions:
- Intracranial Hemorrhage (severe headache, severe weakness on one side of the body, vision problems, severe sleepiness):
    - If a Grade 1 or 2 reaction occurs, Ayvakit should be stopped until the hemorrhage resolves. Once resolved, a decreased dose can then be resumed.
    - Ayvakit should be permanently discontuned following a recurrent Grade 1 or 2 reaction.
    - Ayvakit should be permanently discontinued following initial occurrence of Grade 3 or 4 reactions.
- CNS effects
- Embryo-fetal toxicity

Monitoring:
- PDGFRA exon 18 mutation presence
- CNS effects (dizziness, sleep/mood/speech disorders, cognitive impairment, hallucinations)
- Signs and symptoms for intracranial hemorrhage
- Monitor patient adherence
- Pregnancy status

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

	[NAVIGATOR] [Blueprint Medicines Corporation, 2015]
Study Type*	• Current phase 1, first-in-human, open-label, multicenter study of Ayvakit in adult patients with GIST. • Part 1 of the study: Dose escalation • Part 2 of the study: Expansion focusing on clinical efficiacy, safety and tolerability
Interventions and Sample Size	• 237 patients given 1 dose of Ayvakit. • 46 patients in Part 1 for dose escalation. • 191 patients in Part 2 for expansion • Part 1: - Followed a standard 3+3 dose escalation design through which the first cohort of patients were given a dose of Ayvakit at 30 mg. Subsequent increased doses would be given until it reached a maximum of 600 mg. • Part 2: - Three groups of patients were started on Ayvakit 400 mg, which was then followed by 300 mg daily for the remainder of the study.

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Clinical Review – Ayvakit® (Avapritinib)

	[NAVIGATOR] [Blueprint Medicines Corporation, 2015]
Populations	▪ **Inclusion Criteria (Part 1):** 1. Patients older than 18 years with confirmed diagnosis of GIST or other advanced solid tumor. 2. Patient with GIST that have progressed through Imatinib and at least one alternative: dasatinib, pazopanib, regorafenib, sorafenib, or sunitinib. 3. Present with PDGFRA D842V mutation or on experimental kinase inhibitor. 4. Tumor sample has been collected to determine mutation. ▪ **Inclusion Criteria (Part 2)** 1. Patients confirmed diagnosis of GIST. 2. Patients present with PDGFRA D842V mutation before Ayvakit treatment. 3. Tumor sample has been collected to determine mutation. ▪ 61% male (all doses), PDGFRA Exon 18 Mutation: 67% ▪ 73% Caucasian (all doses) ▪ 97% ECOG status of 0-1 ▪ Median age of 62 years (all doses) ▪ 61% of patients were less than 65 years old ▪ GIST mutational subtype: - KIT: 72% - PDGFRa D842V: 24% - PDGFRa non-D842V: 4% ▪ 89% had metastatic disease ▪ 37% of PDGFRa patients were on 1 previous TKI therapy ▪ 19% of PDGFRa patients were on 2 previous TKI therapies ▪ 30% of KIT patients were on 5 or more previous TKI therapies
Primary Endpoint	▪ Part 1: Maximum tolerated dose in addition to the recommended phase 2 dose of Ayvakit. - Time frame during the first cycle of MTD treatment: 28 days - Time frame during end of every cycle for RP2D for 24 months or earlier (dependent on if patient is terminated from study) ▪ Part 1 & 2: The number of patients that have severe adverse effects, abnormal vital signs, ECG findings, and physical findings. - Time frame will be every 28 days over a period of 24 months ▪ Part 2: - Overall response rate
Secondary Endpoint	▪ Maximum plasma concentration of Ayvakit up to the fourth cycle and end of treatment. ▪ Time to reach maximum plasma concentration of Ayvakit up to the fourth cycle and end of treatment. ▪ Duration of response ▪ Progression-free survival ▪ Clinical benefit rate

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Clinical Review – Ayvakit® (Avapritinib)

	[NAVIGATOR] [Blueprint Medicines Corporation, 2015]
General Summary: Efficacy	▪ Ayvakit was shown to be effacicous at 300 mg in recommended phase 2 dose reduction from 400 mg. Initial dose was decreased due to toxicity and lack of observable difference in overall response rate between both dosing regimens. ▪ Applied to both PDGFRA exon 18 mutant and D842V patient populations. ▪ Ayvakit had an overall response rate of 84% in patients that had the PDGFRA exon 18 mutation and 89% in patients with PDGFRA D842V mutation. ▪ 61% of the patients in the PDGFRA exon 18 group had a response that lasted 6 or more months.
General Summary: Safety	▪ Each patient experienced at least 1 adverse effect throughout the study. ▪ Increased incidence of Grade 3 neurologic adverse effects noted in Ayvakit 400 mg tablet. - Based on safety and efficacy of data collected, 300 mg once daily was determined to be a more appropriate maximum dose. ▪ Most frequent adverse effects (≥ 20%) for patients whose starting dose was 300mg/400mg consisted of edema, change in hair color, nausea, cognitive impairment, and fatigue. ▪ Most adverse effects were Grade 1 or 2. ▪ Decreased hemoglobin in all grades (81%) - Decreased hemoglobin Grade ≥ 3 (28%) ▪ 52% of patients receiving Ayvakit had serious adverse reactions, and 22% were treatment based. - Severe adverse reactions (most common): 1. Anemia (9%) 2. Abdominal pain (3%) 3. Pleural effusion (3%) 4. Acute kidney injury (2%) 5. GI hemorrhage (2%) 6. Pneumonia (1%) - All other severe adverse reactions were only seen in <5% of the patients studied. ▪ Fatal adverse reactions occurred in 3.4% of patients - Fatal adverse reactions present in more than one patient: sepsis (1%), tumor hemorrhage (1%) ▪ Permanent discontinuation of therapy as a result of adverse reactions (16%) - Encephalopathy - Acute kidney injury - Anemia - Sepsis - Vomiting - Abdominal pain ▪ 24 deaths reported (12%) - None of the fatal adverse reactions were assessed to being related to the study treatment.

Clinical Review – Ayvakit® (Avapritinib)

	[NAVIGATOR] [Blueprint Medicines Corporation, 2015]
Comments	▪ Length of study: October 2015- November 2018 ▪ Geriatric population: 40% of patients were 65 years or older ▪ Limitations: - Difficulty differentiating between the effect of the medication, the placebo effect, or the effect of natural history. - Median duration of response was not reached for each group.
Grade^	▪ A

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

- **Pregnancy**
  - Based on studies done on animals in addition to the mechanism of action, Ayvakit can cause fetal harm if given to a pregnant patient. However, no available data is present for use in pregnant women.
- **Pediatric Use**
  - No data is present to demonstrate safety and effectiveness of Ayvakit in the pediatric patient population.
- **Geriatric Use**
  - No differences were observed between these patients and younger patients with respect to safety and efficacy.
- **Renal Impairment**
  - Dose adjustments have not been established or recommended.
- **Hepatic Impairment**
  - Dose adjustments have not been established or recommended.

Place in Therapy:

Table 2. Comparison of [new product] and [Existing product(s) and/or another similar drug in the pipeline]

	[Ayvakit]	[Existing products: Supportive Care]
Meet an Unmet Medical Need[1]	☒ Yes [It is the first drug in its class that targets the PDGFRA exon 18 mutation, which is responsible for advanced GIST formation. There were no prior therapies indicated for this particular mutation.] ☐ No [Reason]	
Comparable Efficacy[2]	☒ Ayvakit would likely be more efficacious than supportive care based on clinical trial results. ▪ Produced high response rates focusing on overall response rate and duration of response (primary endpoints). - Overall response rate for patients with PDGFRA exon 18 and PDGFRA D842V mutations were 84% and 89% respectively.	

Clinical Review – Ayvakit® (Avapritinib)

	- Duration of response ≥ 6 months was present in 61% of patients with PDGFRA exon 18 mutation and 59% of patients with PDGFRA D842V mutation.	
Comparable Safety[3]	☒ Ayvakit would likely have similar safety relative to supportive care services. • Most adverse effects of Ayvakit reported in clinical trials were classified as Grade 1 or 2. • Supportive care services focus on symptomatic relief and reducing discomfort related to adverse effects. Combined with co-morbid conditions and therapy (chemotherapy, additional medications), there can be similar side effects observed for both.	
Standard dosing cost comparison (do not really need to talk about: more cliff notes)	▪ Gleevec, Sutent, and Stivarga are less costly compared to Ayvakit based on whole sale price. This is primarily due to Ayvakit's specific target mutation and not having any direct competitors within their particular indication. - Ayvakit 300 mg: $32,000/month - Gleevec 400 mg: $12,147/month - Imatinib Mesylate (generic of Gleevec) 400 mg: $2,130/month - Sunitinib (generic of Sutent) 50 mg: $14,308/month - Stivarga 40 mg: $17,419/month	
Advantages (Ayvakit)	• Targets PDGFRA exon 18 mutation in patients with GIST. • High response rates	• Median duration of response was not reached for each group.
Disadvantages (Ayvakit)	• NAVIGATOR trial was a single arm study. • Long term clinical benefit	▪ Intracranial hemorrhage (monitor for signs and symptoms) ▪ CNS effects (cognitive impairment; uncommon in TKI)
Advantages (supportive care)	• Provider Experience	
Disadvantages (supportive care)	• Disease progression	• Adverse Effects

Comments (Current trials)	**<u>VOYAGER Trial</u>** ▪ Phase 3, open-label, randomized trial for patients with GIST. ▪ Comparison of Ayvakit against Regorafenib for patients that were previously treated with Imatinib or 2-3 previous tyrosine kinase inhibitors.

Clinical Review – Ayvakit® (Avapritinib)

	▪ 460 patients are enrolled and will be randomized (1:1 ratio) into 1 of 2 possible treatment arms. ▪ Primary focus of Blueprint Medicines due to FDA accelerated review of Ayvakit indication as fourth line treatment option. **COMPASS 2-L TRIAL (delayed)** ▪ Ongoing trial for indication of Ayvakit as second line treatment option for GIST **FDA approval** ▪ Fast track and orphan drug designation ▪ Updated NCCN guidelines, which now includes Ayvakit in treatment algorithim ▪ FDA split Ayvakit indications into two different NDA's: - PDGFRA exon 18 mutant - Fourth line GIST treatment

Recommendation:

- Based on results from the NAVIGATOR trial, Ayvakit is efficacious and safe for use in this patient population. Prior to its FDA approval, supportive care was thought to be the only therapeutic option given for the PDGFRA exon 18 mutation. No other medication has FDA approval or is able to target the exon 18 and D842V mutations as effectively as Ayvakit. Though rare, it is important to monitor for signs/symptoms of intracranial hemorrhage and any change in cognition.
- Formulary recommendation: NF (Non-participating), QL 30/30

Clinical Review – Ayvakit® (Avapritinib)

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Clinical Review – Ayvakit® (Avapritinib)

Clinical Review – Enhertu® (fam-trastuzumab deruxtecan)

***Company*:** Daiichi Sankyo, Inc.
Current Status: FDA Approved December 20, 2019
Potential Launch: December 30, 2019
Therapeutic Category: Anti-Neoplastic Agent
Pharmacologic Category: Antibody Drug Conjugate
Similar Drugs: Herceptin (trastuzumab), Kadcyla (ado-trastuzumab emtansine), Perjeta (pertuzumab)
Route of Administration: Intravenous Infusion
Dosage Forms: IV solution

Indications: Enhertu® is indicated for the treatment of adult patients with unresectable or metastatic HER2-positive breast cancer who have received two or more prior anti-HER2-based regimens in the metastatic setting.

Dosage and Administration: 5.4 mg/kg given as an intravenous infusion once every 3 weeks (21-day cycle). Dose reduction is permitted to 4.4 mg/kg or 3.2 mg/kg to manage adverse reactions

Background:

Breast cancer is the most frequently diagnosed cancer and the leading cause of cancer-related death among females worldwide.1 In the United States, the average risk for a woman to develop breast cancer is approximately 13%, or a 1 in 8 chance. The American Cancer Society estimates that there will be approximately 276, 480 new cases of invasive breast cancer diagnosed in 2020 in women. In 2020, about 42, 170 people will die from breast cancer. 48, 530 new cases of carcinoma in situ(CIS) which is the earliest form of breast cancer will be diagnosed. The incidence rates for Breast cancer have been increasing by less than 1% (0.3%) per year. Since 2007 the breast cancer death rate in women 50 or younger has remained consistent. There has been a gradual decrease in the incidence of breast cancer in older women by 1.3% per year. The downtrend has been widely attributed to increase in awareness and screening.

Female gender and increased age are the greatest risk factors for developing breast cancer. There are varying types of breast cancers, most of which we do not understand the etiology of. Screening tools and recommendations are targeted based on known risk factors. Women with an increased risk for breast cancer may consider risk reduction strategies with agents such as tamoxifen, raloxxifene or aromatase inhibitors.

NCCN Guidelines recommend systemic therapy in addition to HER-2 targeted therapy with pertuzumab, trastuzumab and a taxane as the first-line option for treatment of HER-2 positive breast cancer. In the CLEOPATRA (Clinical Evaluation of Pertuzumab and Trastuzumab) trial, the combination of trastuzumab, pertuzumab, and docetaxel resulted in a median duration of progression-free survival of 18.7 months and overall survival of 56.5 monthsStandard second-line therapy is the antibody-drug conjugate trastuzumab emtansine, which was associated with an objective response of 43.6% and a median duration of progression-free survival of 9.6 months when the drug was administered after trastuzumab and a taxane. No uniformly accepted standard of care has been defined after the administration of trastuzumab emtansine, and the currently available options have limited benefit, with response rates of approximately 9 to 31% and a duration of progression-free survival of approximately 3 to 6 months for third-line therapy.

The incidence rate of HER2-positive/ hormone receptor negative breast cancer was 5.4 new cases per 100,000 women from data collected from 2012-2016. Approximately 15 to 20% of metastatic breast cancers are characterized by overexpression or amplification of human epidermal growth factor receptor 2 (HER2).

Clinical Review – Enhertu® (fam-trastuzumab deruxtecan)

Pharmacology: Enhertu®is an antibody-drug conjugate with a humanized monoclonal antibody specifically targeting HER-2 attached to a potent topoisomerase I inhibitor as the cytotoxic drug.

Pharmacokinetics:

- Distribution: Vd: 2.77 L.
- Protein binding: ~97% (to plasma proteins)
- Metabolism: Metabolized into small peptides and amino acids via CYP3A4
- Half-life elimination: ~5.7 days
- Excretion: Clearance: 0.42 L/day (via urine? Renal)

Drug Interactions:

- No known clinically meaningful drug interactions

***Adverse Effects*:**

The **most common** adverse reactions were nausea, fatigue, vomiting, alopecia, constipation, decreased appetite, anemia, neutropenia, diarrhea, leukopenia, cough, and thrombocytopenia.

<10%	**10-30%**	**31-59%**	**60-80%**
Cellulitis (>1%) Intestinal Obstruction (>1%) Febrile Neutropenia (2%) Pneumonia (>1%) Antibody Development(<1%) Decreased Left Ventricular Ejection Fraction(<1%) Infusion Related Reaction (3%) Dizziness (10%) Skin Rash (10%) Interstitial Pulmonary Disease (9%)	Headache (19%) Hypokalemia (12% To 26%) Diarrhea (29%) Abdominal Pain (19%) Stomatitis (14%; Grades 3/4: <1%) Dyspepsia (12%) Neutropenia (30%; Grades 3/4: 16%) Leukopenia (22%; Grades 3/4: 6%) Thrombocytopenia (20%; Grades 3/4: 3%) Cough (20%) Dry Eye Syndrome (11%) Upper Respiratory Tract Infection (15%) Dyspnea (13%) Epistaxis (13%)	Fatigue (59%) Alopecia (46%) Vomiting (47%) Constipation (35%) Decreased Appetite (32%) Anemia (31%; Grades 3/4: 7%) Increased Serum Aspartate Aminotransferase (14% To 41%) Increased Serum Alanine Aminotransferase (10% To 38%)	Nausea (79%)

Contraindications:

- None

Warnings and Precautions:

Black Box Warning: Interstitial Lung Disease and Embryo-Fetal Toxicity

- **Interstitial Lung Disease/Pneumonitis:** Severe, life-threatening, or fatal interstitial lung disease (ILD), including pneumonitis, can occur in patients treated with Enhertu®.

  - Incidence**:** ILD occurred in 9% of patients. Fatal outcomes due to ILD and/or pneumonitis occurred in 2.6% of patients treated with Enhertu®.
  - Time to onset**:** Median time to first onset was 4.1 months (range: 1.2 to 8.3).
  - Patient counseling: Patients she be advised to report cough, dyspnea, fever, and/or any new or worsening respiratory symptoms immediately.
  - Monitoring parameters**:** Monitor for signs/symptoms of interstitial lung disease/pneumonitis. Evaluate patients with suspected ILD by radiographic imaging.
  - Management:
    - Asymptomatic ILD (Grade 1) IL: corticosteroid treatment stop Enhertu® until recovery
    - Symptomatic ILD (Grade 2 or greater): immediately initiate corticosteroids and gradual taper down once patient's symptoms improve. Permanently discontinue Enhertu® in patients who are diagnosed with any symptomatic (Grade 2 or greater) ILD.
- **Neutropenia:** Severe neutropenia, including febrile neutropenia, can occur in patients treated with Enhertu®.
  - Incidence: 30% of patients reported decrease in neutrophil and 16% had Grade 3 or 4 events.
    - Febrile neutropenia was reported in 1.7% of patients.
  - Time to onset: Median time to first onset was 1.4 months (range: 0.3 to 18.2).
  - Monitoring parameters: Monitoring of complete blood counts prior to initiation of Enhertu® and each dose (if clinically indicated).
  - Management: Dosage reduction or treatment interruption.
- **Left Ventricular Dysfunction**: Patients treated with Enhertu® may be at increased risk of developing left ventricular dysfunction. Left ventricular ejection fraction (LVEF) decrease has been observed with anti-HER2 therapies, including Enhertu®. Treatment with Enhertu® has not been studied in patients with a history of clinically significant cardiac disease or LVEF less than 50% prior to initiation of treatment.
  - Incidence: Two cases (0.9%) of asymptomatic LVEF decrease were reported.
  - Time to onset: Unknown
  - Monitoring: Assess LVEF prior to initiation of Enhertu® and at regular intervals during treatment as clinically indicated.
  - Management: Manage LVEF decrease through treatment interruption. Permanently discontinue Enhertu® if LVEF of less than 40% or absolute decrease from baseline of greater than 20% is confirmed. Permanently discontinue Enhertu® in patients with symptomatic congestive heart failure (CHF).
- **Embryo-Fetal Toxicity:** Based on its mechanism of action, Enhertu® can cause fetal harm when administered to a pregnant woman.
  - Monitoring Parameter: Women with the potential to have children should receive a pregnancy test prior to starting Enhertu®.
  - Patient Counseling: Advise patients of the potential risks to a fetus.
  - Management: Advise females of reproductive potential to use effective contraception during treatment and for at least 7 months following the last dose of Enhertu®. Male patients should use effective contraception during treatment and for at least 4 months after the last dose of Enherti\u.

Monitoring:

- Human epidermal growth factor receptor 2 status.
- CBC (prior to treatment initiation, prior to each dose, and as clinically indicated)
- Assess left ventricular ejection fraction prior to fam-trastuzumab deruxtecan initiation and at regular intervals during treatment as clinically indicated.
- Evaluate pregnancy status prior to therapy.

Evidence Table of Clinical Studies:

Clinical Review – Enhertu® (fam-trastuzumab deruxtecan)

Table 1. Clinical data for fam-trastuzumab deruxtecan (Enhertu®)

	Trastuzumab deruxtecan in Previously Treated HER2-Positive Breast Cancer (DESTINY-BREAST01) **Shanu Modi, M.D., Cristina Saura, M.D., Ph.D., Toshinari Yamashita, M.D., et al** **2019**	
Study Type*	Two part, open-label, single-group, multicenter, international, Phase 2 study	
Interventions and Sample Size	**Part 1 (dose-finding):** 50 Patients were given trastuzumab deruxtecan at a dose of 5.4 mg/kg, 48 patients received 6.4 mg/kg, and 21 received 7.4 mg/kg administered by intravenous infusion every 3 weeks	**Part 2 (safety and efficacy evaluation):** 134 patients received 5.4 mg/kg of fam-trastuzumab deruxtecan (Enhertu®) who had tumor progression during or after the administration of trastuzumab emtansine and in those who had discontinued trastuzumab emtansine for reasons other than progressive disease to evaluate the safety and efficacy of fam-trastuzumab deruxtecan (Enhertu®)
Populations	**Inclusion criteria:** • ≥18 years of age in all country sites except for ≥20 years in Japan and South Korea • A performance status score of 0 or 1 on the Eastern Cooperative Oncology Group scale (ranging from 0 [no disability] to 5 [death]) **Exclusion Criteria:** • Untreated or symptomatic brain metastases • A history of noninfectious interstitial lung disease or pneumonitis resulting in the use of glucocorticoids • Current or suspected interstitial lung disease or pneumonitis	
General Summary: Efficacy	**Primary endpoint**: Overall response (complete plus partial response) to trastuzumab deruxtecan therapy in patients who had tumor progression during or after the administration of trastuzumab emtansine (Kadcyla®) and who had received the recommended dose of fam-trastuzumab deruxtecan (Enhertu®)) in both parts 1 and 2 of the study • **Overall response:** 112 patients had a response to therapy 60.9%; (95% confidence interval [CI], 53.4 to 68.0) **Secondary Endpoints:** • **The median duration of follow-up**: 11.1 months • **The median response duration**: 14.8 months (95% CI, 13.8 to 16.9) • **The median duration of progression-free survival**: 16.4 months (95% CI, 12.7 to not reached) among all patients and 18.1 months (95% CI, 6.7 to 18.1) among the 24 patients who were enrolled with treated and asymptomatic brain metastases. • **Estimated overall survival @ 6 months**: 93.9% (95% CI, 89.3 to 96.6) • **Estimated overall survival @ 12 months**: 86.2% (95% CI, 79.8 to 90.7) The median overall survival had not been reached at the time of the report Comment: The median number of prior cancer regimens in the locally advanced/metastatic setting was 5 (range: 2-17). All patients received prior trastuzumab, ado-trastuzumab emtansine, and 66% had prior pertuzumab. Overall, response to therapy looks promising for patients who have been previously treated.	

Clinical Review – Enhertu® (fam-trastuzumab deruxtecan)

	Trastuzumab deruxtecan in Previously Treated HER2-Positive Breast Cancer (DESTINY-BREAST01) **Shanu Modi, M.D., Cristina Saura, M.D., Ph.D., Toshinari Yamashita, M.D., et al** **2019**
General Summary: Safety	• 99.6% of participants had at least one adverse event during treatment with Enhertu® • 56.1% of the patients that experienced an adverse event had an adverse event of grade 3 or higher The most common treatment emergent adverse events in >10% of grade 3 or higher in all enrolled patients : • Decreased neutrophil count (in 23.7%) • Anemia (in 11%) • Nausea (in 7.9%) • Decreased white-cell count (in 8.6%) • Decreased lymphocyte count (in 6.3%) • Fatigue (in 9.8%)
Comments	▪ The response rate and overall efficacy appear to exceed those of the other HER-2 targeted therapy options currently available BUT there are no direct comparator trials to determine the significance of the difference between Enhertu® and current treatments, if any. ▪ Treatment is still going on so further study and follow up will need to be done to determine the long-term effects of Enhertu® and how long therapy would need to be continued in a clinical setting. ▪ There was a higher incidence of Grade 3-4 adverse reactions observed in patients aged 65 years or older (53%) as compared to younger patients (42%). ▪ Efficacy and safety need to continue to be evaluated ▪ Enhertu® was approved via an accelerated approval based on tumor response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory 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: Enhertu® can cause harm to the fetus if administered to a pregnant woman. Post marketing reports show use during pregnancy resulted in cases of oligohydramnios manifesting as fatal pulmonary hypoplasia, skeletal abnormalities, and neonatal death. The Topoisomerase I inhibitor portion of Enhertu® can cause fetal harm as it attacks actively dividing cells.

- Special Considerations for Fetal/Neonatal Adverse Reactions Monitor women who received Enhertu® during pregnancy or within 7 months prior to conception for oligohydramnios. If oligohydramnios occurs, perform fetal testing that is appropriate for gestational age and consistent with community standards of care.

Lactation: There is no data regarding the presence of fam-trastuzumab deruxtecan in human milk, the effects on the breastfed child, or the effects on milk production. Because of the potential for serious adverse reactions in a breastfed child, advise women not to breastfeed **during treatment with Enhertu® and for 7 months after the last dose.**

Reproductive Potential:

- **Pregnancy Testing**: Verify a negative pregnancy test before starting Enhertu® in women.
- **Contraception in Females**: Advise females of reproductive potential to use effective contraception during treatment and for at least 7 months following the last dose of Enhertu®.
- **Contraception in Males:** Because of the potential for genotoxicity, male patients should be advised to use effective contraception during treatment and for at least 4 months following the last dose of Enhertu®.
- **Fertility:** Based on findings in animal models, Enhertu® may inpair male reproductive function and fertility.

Pediatric Use: Safety and effectiveness of Enhertu® have not been established in pediatric patients.

Geriatric Use: No overall differences in efficacy were observed for patients over 65 years of age. There was a higher incidence of Grade 3-4 adverse reactions observed in patients aged 65 years or older (53%) as compared to younger patients (42%).

Renal Impairment: No renal dose adjustment is required for patients with mild or moderate renal impairment. (CrCl ≥30)

Hepatic Impairment: No dose adjustment of Enhertu® is required in patients with mild or moderate (hepatic impairment. In patients with moderate hepatic impairment, due to potentially increased exposure, closely monitor for increased toxicities related to the topoisomerase inhibitor. No data are available in patients with severe hepatic impairment.

Cost and/or Utilization Data of Similar Treatment Options:

Table 2: Pricing

Drug	Strength	WAC/unit	Package size	WAC/Package
Enhertu®	100 mg	$2,755.16 (AWP)	1 vial (5mL)	
Kadcyla®	100 mg	$3,785.39 (AWP)	I vial (5 mL)	
Kadcyla®	160 mg	$6,056.62 (AWP)	I vial (8 mL)	

Place in Therapy: Overall, Enhertu® shows a lot of promise based on based on tumor response rate and duration of response displayed in early trials. However, the study population is limited and we do not have long term data regarding safety. There does seem to be a correlation between higher doses and increased incidence of adverse effects.

Clinical Review – Enhertu® (fam-trastuzumab deruxtecan)

Table 3. Comparison of [new product] and [Existing product(s) and/or another similar drug in the pipeline]

	Enhertu®	Kadcyla®
Meet an Unmet Medical Need[1]	☐ Yes Enhertu® has a better response rate than currently available treatments while offering a different AE profile	
Comparable Efficacy[2]	☐ Enhertu® is more efficacious relative to Kadcyla® **Comment: There is no direct comparison data to interpret but early data from the BREAST-DESTINY01 trial indicates that Enhertu® has a better response rate than other comparable drugs like Kadcyla®.**	
Comparable Safety[3]	☐ Enhertu® would likely be more safe relative to Kadcyla® **Comment: Kadcyla® has known cardiotoxic and hepatotoxic effects that Enhertu® has not demonstrated.**	
Adherence[5]	☐ Members taking Kadcyla® would likely achieve a similar adherence rate relative to Enhertu® **Comment: Enhertu® is medically administered to patients as an IV infusion once every three weeks which is the same as Kadcyla®. However, having a different adverse event profile and greater tolerability could potentially influence the adherence rates with Enhertu® compared to similar drugs.**	
Patent Expiration		
Advantages	▪ Response in heavily pre-treated population	▪ Phase 3 data available ▪ Provider recognition
Disadvantage	▪ ILD ▪ Limited data on long term outcomes and safety	▪ Hepatotoxicity and cardiotoxicity warnings ▪ Potential to developing resistant cancer cells
Comments	▪ Enhertu® has been approved under accelerated approval based the promising clinical outcomes demonstrated in Phase 2 trials. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.	

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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Recommendation:

- KY Medicaid: NF (IV infusion), MIT PAL
- QL: 120/30/4.6

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10. Swain SM, Miles D, Kim S-B, et al. End-of-study analysis from the phase III, randomized, double-blind, placebo (Pla)- controlled CLEOPATRA study of first-line (1L) pertuzumab (P), trastuzumab (H), and docetaxel (D) in patients (pts) with HER2-positive metastatic breast cancer (MBC). J Clin Oncol 2019;15:Suppl:1020. Abstract

Humana Pharmacy Solutions

Clinical Review – Caplyta® (lumateperone)

***Company*:** Intra-Cellular Therapies
Current Status: Approved
Potential Launch: Late Q1 2020
Therapeutic Category: Behavioral Health
Pharmacologic Category: Atypical Antipsychotics
Similar Drugs: Risperdal (risperidone), Clozaril (clozapine), Abilify (aripiprazole), Rexulti (brexpiprazole), , Zyprexa (olanzapine), Seroquel (quetiapine), Geodon (ziprasidone), Latuda (lurasidone), Invega (paliperidone), Fanapt (iloperidone), Saphris (asenapine), Vraylar (cariprazine)
Route of Administration: Oral
Dosage Forms: Tablet

Indications: Treatment of schizophrenia in adults

Dosage and Administration: 42 mg administered orally as tablets once daily

Background:
Schizophrenia is a mental illness characterized by disruptions in normal thought processes, perceptions, emotional responsiveness, and social interactions. Symptoms of schizophrenia can be classified into three groups: positive symptoms, negative symptoms, and cognitive symptoms. To qualify for a diagnosis of schizophrenia, patients must have at least one positive symptom, including hallucinations, delusions, disorganized speech, and agitated body movements. Positive symptoms typically relapse and remit; however, negative symptoms, such as flat affect and anhedonia, and cognitive impairments are generally chronic and have a major impact on social functioning over time. Symptom onset varies by individual, but schizophrenia is usually diagnosed in late adolescence or early adulthood and tends to emerge earlier in males than females.

The prevalence of schizophrenia and related psychotic disorders in the United States range from 0.25% to 0.64%. The pooled median incidence rate for schizophrenia is estimated at 18.3 per 10,000 person-years. Although the prevalence and incidence rates of schizophrenia are relatively low, the socioeconomic burden is high and the condition is one of the top 15 leading causes of disability worldwide. Schizophrenia patients have been found to have an overall mortality rate that is two to three times higher than the general population, with life expectancy reduced by 10-20 years.

There is currently no curative therapy for schizophrenia. Available treatment includes a combination of antipsychotic medications with behavioral therapies, rehabilitation, and social support. Antipsychotics are typically administered chronically and, as a result, their associated side effects can have a major impact on morbidity and adherence. In general, first-generation antipsychotic agents are associated with a higher rate of extrapyramidal motor effects and prolactin elevation. Second-generation antipsychotics, in contrast, cause more sedation and metabolic effects. Due to their unfavorable side effect profiles, non-adherence to antipsychotic medications is key barrier to improving patient outcomes.

Pharmacology:
The mechanism of action of lumateperone in the treatment of schizophrenia is unknown. The efficacy of lumateperone could be mediated through a combination of antagonist activity at central serotonin 5-HT_{2A} receptors and postsynaptic antagonist activity at central dopamine D_2 receptors.

Pharmacokinetics:

Metabolism/Elimination: Extensively metabolized by the liver with more than twenty metabolites identified in vivo. In a human mass-balance study, 58% and 29% of the radioactive dose was recovered in the urine and feces, respectively. Less than 1% of the dose was excreted as unchanged lumateperone in the urine.

Plasma Half-Life (hrs): 1-2 hours

Volume of distribution: 4.1 L/kg

Drug Interactions:

- CYP3A4 inducers: Avoid concomitant use.
- Moderate/strong CYP3A4 inhibitors: Avoid concomitant use.

***Adverse Effects*:**

The most common adverse reactions (incidence of at least 5% of patients exposed to lumateperone and greater than twice the rate of placebo) are somnolence/sedation and dry mouth.

Contraindications:

- Known hypersensitivity to lumateperone or any components of Caplyta

Warnings and Precautions:

- Cerebrovascular adverse reactions in elderly patients with dementia-related psychosis: increased incidence of cerebrovascular adverse reactions (e.g. stroke and transient ischemic attack).
- Neuroleptic Malignant Syndrome (NMS): manage with immediate discontinuation and close monitoring
- Tardive dyskinesia: risk of tardive dyskinesia and the likelihood that it will become irreversible increase with the duration of treatment and the cumulative dose.
- Metabolic changes: Antipsychotic drugs have caused metabolic changes, including hyperglycemia, diabetes mellitus, dyslipidemia, and weight gain.
- Leukopenia, neutropenia, and agranulocytosis: Leukopenia and neutropenia have been reported during treatment with antipsychotic agents, including lumateperone. Agranulocytosis (including fatal cases) has been reported with other agents in the class.
- Orthostatic hypotension and syncope: Atypical antipsychotics cause orthostatic hypotension and syncope. Generally, the risk is greatest during initial dose administration.
- Falls: antipsychotics, including lumateperone, may cause somnolence, postural hypotension, and motor and sensory instability, which may lead to falls, and consequently, fracture and other injuries.
- Seizures: Like other antipsychotic drugs, lumateperone may cause seizures. The risk is greatest in patients with a history of seizures or with conditions that lower the seizure threshold.
- Potential for cognitive and motor impairment: may cause somnolence and has the potential to impair judgment, thinking, and motor skills.
- Body temperature dysregulation: Atypical antipsychotics may disrupt the body's ability to reduce core body temperature. Strenuous exercise, exposure to extreme heat, dehydration, and anticholinergic medications may contribute to an elevation in core body temperature; use lumateperone with caution in patients who may experience these conditions.
- Dysphagia: Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Antipsychotic drugs, including lumateperone, should be used cautiously in patients at risk for aspiration

Monitoring:

- Monitor for clinical manifestations of NMS, including hyperpyrexia, muscle rigidity, delirium, autonomic instability, elevated creatinine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure.
- Assess fasting plasma glucose before or soone after initiation of antipsychotic medication and monitor periodically during long-term treatment.
- Obtain a fasting lipid profile at baseline before or soon after initiation of antipsychotic medications and monitor periodically during treatment.
- Monitor weight at baseline and frequently thereafter.
- Monitor patients with clinically significant neutropenia for fever or other symptoms or signs of infection and treat promptly if such symptoms or signs occur. Discontinue lumateperone in patients with absolute neutrophil count < 1000/mm3 and follow their WBC until recovery.
- Monitor orthostatic vital signs in patients who are vulnerable to hypotension (e.g. elderly patients, patients with dehydration, hypovolemia, and concomitant antihypertensive medication use), patients with known cardiovascular disease, and patients with cerebrovascular disease.
- Complete fall risk assessments when initiating antipsychotic treatment in patients at high risk for motor and sensory instability and periodically during long-term treatment

Evidence Table of Clinical Studies:

Table 1. Clinical data for Caplyta (lumateperone).

	Efficacy and Safety of Lumateperone for Treatment of Schizophrenia Correll et al., 2020
Study Type*	Randomized clinical trial
Interventions and Sample Size	1:1:1 randomization • Lumateperone tosylate 60 mg (42 mg active moiety lumateperone) daily (n=150) • Lumateperone tosylate 40 mg (28 mg active moiety lumateperone) daily (n=150) • Placebo daily (n=150)
Populations	**Inclusion Criteria:** ▪ Adults age 18-60 years ▪ Clinical diagnosis of schizophrenia according to the DSM-5, confirmed by the Structured Clinical Interview for DSM-IV-TR Axis I disorders ▪ Experiencing acute exacerbation of psychosis, defined as a total score on the Brief Psychiatric Rating Scale of 40 or higher and score of 4 or higher on 2 or more positive symptoms ▪ Shown previous treatment response to antipsychotic therapy **Exclusion Criteria** ▪ Diagnosis of dementia, delirium, mental retardation, epilepsy, drug-induced psychosis, or brain trauma ▪ Imminent danger to self or others ▪ Suicidal ideation or behavior ▪ Unstable living environment ▪ Use of depot antipsychotic within 1.5 treatment cycles before baseline ▪ Use of any antipsychotic within the screening period ▪ Use of specific agents with known interaction with 5-HT_{2A} receptors **Baseline Characteristics (PBO/Low-dose/High-dose)** ▪ Mean age 41.4/43.5/42.4 years ▪ 82.6%/75.3%/73.3% male ▪ 64.4%/62.7%/72.0% Black/African-American ▪ 17.4/17.0/16.5 years since initial schizophrenia diagnosis ▪ Mean PANSS total score 90.1/89.3/90.1

	Efficacy and Safety of Lumateperone for Treatment of Schizophrenia Correll et al., 2020
General Summary: Efficacy	**Primary endpoint**: mean change from baseline to day 28 on the PANSS total score vs. placebo ▪ Change from baseline to day 28 PANSS total score vs. placebo (least-square mean difference [LSMD]) observed with 42 mg lumateperone was -4.2 (95% CI -7.8 to -0.6; nominal P = 0.02; multiplicity-adjusted P = 0.05) ▪ LSMD observed with 28 mg lumateperone vs. placebo was -2.6 (95% CI -6.2 to 1.1; nominal P = 0.16; multiplicity-adjusted P = 0.18) ▪ Statistically significant differences from placebo in the PANSS total score observed at the day 8 assessment and continued through the day 28 assessment with 42 mg of lumateperone ▪ Responder analysis indicated that 36.5% of patients treated with 42 mg of lumateperone, 36.3% of patients treated with 28 mg of lumateperone, and 25.5% of placebo-treated patients had 30% or greater improvement in PANSS total score **Secondary endpoints:** ▪ Statistically significant change in CGI-S score from baseline to day 28 with 42 mg lumateperone vs placebo – LSMD -0.3; 95% CI, -0.5 to -0.1; nominal P = 0.003 ▪ Significant difference between the 28 mg lumateperone group and the placebo group for CGI-S (LSMD, -0.2; 95% CI, -0.5 to 0; nominal P = 0.02) ▪ Treatment with 42 and 28 mg of lumateperone significantly improved the PANSS positive subscale score from baseline to day 28 compared with placebo (42 mg: LSMD, -1.7; 95% CI, -2.9 to -0.5; nominal P = 0.006; and 28 mg: LSMD, -1.2; 95% CI, -2.4 to -0.1; nominal P = 0.04) ▪ Changes in the PANSS negative subscale score from baseline to day 28 compared with placebo were not significant ▪ Statistically significant improvements vs placebo were observed with 42 mg lumateperone in the general psychopathology subscale score and in psychosocial function (LSMD, -2.4; 95% CI, -4.3 to -0.5; effect size, -0.3; nominal P = 0.01) ▪ Change in Calgary Depression Scale for Schizophrenia score from baseline to day 28 was not significantly different from that in the placebo group after treatment with 42 mg of lumateperone (LSMD, 0.4; 95% CI, -0.24 to 0.96; nominal P = 0.24) or 28 mg of lumateperone (LSMD, 0.2; 95% CI, -0.43 to 0.79; nominal P = 0.57)
General Summary: Safety	▪ Treatment-emergent adverse events (TEAEs) occurring in either lumateperone group in 5% of more of patients and more than twice the rate in the placebo group: somnolence, sedation, fatigue, and constipation ▪ 2 patients experienced severe-intensity TEAEs and discontinued treatment: orthostatic hypotension and convulsions ▪ Most TEAEs were mild or moderate in intensity ▪ No increase in suicidal ideation or behavior with lumateperone at either dose ▪ No extrapyramidal symptoms (EPS)-related TEAEs occurred in 5% or more of patients in any treatment arm ▪ Treatment with 42 or 28 mg of lumateperone was not associated with increased EPS as measured by the Simpson-Angus Scale, Barnes Akathisia Rating Scale, or Abnormal Involuntary Movement Scale ▪ Mean change in weight from baseline to day 28 was similar in all treatment arms (42 mg: 0.9 kg [range, -36 to 11 kg]; 28 mg: 0.6 kg [range, -12 to 13 kg]; Placebo: 0.7 kg [range -12 to 16 kg]) ▪ Weight changes of 7% or greater and shifts in BMI from overweight to obese were infrequent and similar among groups ▪ No significant mean changes in metabolic parameters from baseline to day 28 compared with placebo ▪ No patients had QT_c great than 500 ms or a change greater than 60 ms from baseline

	Efficacy and Safety of Lumateperone for Treatment of Schizophrenia Correll et al., 2020
Comments	▪ Superiority as compared to placebo ▪ Short study duration (28 days) – may not demonstrate meaningful efficacy in a chronic condition ▪ No significant impact on PANSS negative subscale score from baseline compared with placebo – negative symptoms are the major area of unmet need in schizophrenia ▪ Potentially less adverse effects (both EPS and metabolic) with lumateperone than with other available antipsychotics
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:

- Females and Males of Reproductive Potential: lumateperone may impair male and female fertility
- Pediatric: safety and effectiveness of lumateperone have not been established in pediatric patients
- Geriatric: controlled clinical studies of lumateperone did not include any patients aged 65 or older to determine whether or not they respond differently from younger patients; lumateperone is not approved for the treatment of patients with dementia-related psychosis
- Hepatic Impairment: use of lumateperone is not recommended for patients with moderate (Child-Pugh class B) to severe (Child-Pugh class C) hepatic impairment**;** no dosage adjustment is recommended for patients with mild hepatic impairment

Cost and/or Utilization Data of Similar Treatment Options:

Table 2: Caplyta (lumateperone)® Pricing

Drug	Strength	WAC/unit	Package size	WAC/Package
Caplyta (lumateperone)	42 mg	$44/capsule	30 capsules	$1,320.00
risperidone	4 mg	$0.37/tablet	60 tablets	$22.43
risperidone	4 mg	$0.18/tablet	60 tablets	$10.77
risperidone	4 mg	$0.18/tablet	500 tablets	$87.92
risperidone	4 mg	$2.67/tablet	60 tablets	$160.01
Latuda (lurasidone)	120 mg	$63.86/tablet	30 tablets	$1,915.80

Table 3: Humana Tiering for Similar Treatment Options

	Risperidone 4 mg	Latuda (lurasidone) 120 mg
KY Medicaid	T1	NF

Place in Therapy:

Table 4. Comparison of [new product] and [Existing product(s) and/or another similar drug in the pipeline]

	Caplyta (lumateperone)	Risperidone
Meet an Unmet Medical Need[1]	☒ **No**: There are multiple other antipsychotic agents available on the market. In addition, Caplyta (lumateperone) was not shown to be more effective in managing negative symptoms of schizophrenia, which are generally chronic and have a major impact on morbidity.	
Comparable Efficacy[2]	☒ Caplyta (lumateperone) has similar efficacy relative to risperidone. **Comment: Both Caplyta (lumateperone) and risperidone are atypical antipsychotic agents. Responder analysis indicated that 36.5% of patients treated with 42 mg of Caplyta (lumateperone) and 36.3% of patients treated with 28 mg of Caplyta (lumateperone) had 30% or greater improvement in PANSS total score. In a 4-week dose comparison trial of risperidone, doses of 4 mg and 8 mg were shown to be superior to placebo on several PANSS measures, including a response measure of > 20% reduction in total PANSS score.**	
Comparable Safety[3]	☒ Caplyta (lumateperone) would likely be more safe relative to risperidone. **Comment: First-generation antipsychotic agents are associated with a higher rate of extrapyramidal motor effects and prolactin elevation. Second-generation antipsychotics, such as risperidone, cause more sedation and metabolic effects. Use of Caplyta (lumateperone) has not been shown to be associated with either increased incidence of EPS or significant mean changes in metabolic parameters. Note that long term safety is unknown and studies completed were of short duration (4 weeks).**	
Comparable Cost-Effectiveness[4]	☒ Caplyta (lumateperone) is less cost-effective relative to risperidone. **Comment: WAC per month of Caplyta (lumateperone) is $1,320, while a 30 day supply of generic risperidone can have a WAC as low as $5 per month (depending on manufacturer and required dosage).**	
Adherence[5]	☒ Members taking Caplyta (lumateperone) would likely achieve a greater adherence rate relative to risperidone **Comment: Both Caplyta (lumateperone) and risperidone are administered once daily as oral formulations. Available evidence suggests that the adverse effect profile for Caplyta (lumateperone) is milder than that of risperidone. Less adverse effects associated with use may result in improved patient adherence.**	
Patent Expiration	08/2033	2008
Advantages	▪ Mild adverse effect profile ▪ Potentially improved adherence rates as compared to existing antipsychotic agents	▪ Provider familiarity and market experience ▪ Long term safety and efficacy well-understood ▪ Multiple labeled indications ▪ Inexpensive
Disadvantages	▪ Long term safety and efficacy unknown ▪ Significantly more expensive than available generic antipsychotic medications	▪ Significant adverse effects
Comments	▪ Risperidone selected as comparator agent because it was used as an active comparator in certain trials evaluating efficacy of Caplyta (risperidone) ▪ Caplyta (lumateperone) is a first-in-class agent that acts on three neurotransmitter systems (dopamine, serotonin and glutamate)	

	▪ Intra-Cellular Therapies announced in a press release that unique MOA of Caplyta (lumateperone) meant it could potentially impact negative symptoms of schizophrenia, however, study results have not shown this to be the case ▪ Although difficult to compare efficacy across trials, efficacy of Caplyta (lumateperone) and risperidone appear similar ▪ Safety profile of Caplyta (lumateperone) shown to be without the weight gain, metabolic or cardiovascular disturbances, and motor disturbances seen with other antipsychotic medications ▪ WAC pricing similar to that of branded antipsychotic agent Latuda (lurasidone)

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:

- NF
- QL: 30/30/1.3

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