P&T Committee Meeting Minutes
Commercial/Exchange/CHIP
March 19, 2024

Present (via Teams):	**Absent:**
Bret Yarczower, MD, MBA – Chair Amir Antonius, Pharm.D. Emily Bednarz, Pharm.D. Kristen Bender, Pharm.D. Alyssa Cilia, RPh Kimberly Clark, Pharm.D. Bhargavi Degapudi, MD Michael Dubartell, MD Kelly Faust, Pharm.D. Tricia Heitzman, Pharm.D. Jason Howay, Pharm.D. Keith Hunsicker, Pharm.D. Kelli Hunsicker, Pharm.D. Derek Hunt, Pharm.D. Emily Jacobson, Pharm.D. Philip Krebs, R.EEG T Briana LeBeau, Pharm.D. Ted Marines, Pharm.D. Lisa Mazonkey, RPh Tyreese McCrea, Pharm.D. Perry Meadows, MD Jamie Miller, RPh Mark Mowery, Pharm.D. Austin Paisley, Pharm.D. Lauren Pheasant, Pharm.D. Kimberly Reichard, Pharm.D. Melissa Sartori, Pharm.D. Kristen Scheib, Pharm.D. Leslie Shumlas, Pharm.D. Aubrielle Smith-Masri, Pharm.D. Kirsten Smith, Pharm.D. Michael Spishock, RPh Todd Sponenberg, Pharm.D. Jill Stone, Pharm.D. Luke Sullivan, DO Kevin Szczecina, RPh Ariana Wendoloski, Pharm.D. Brandon Whiteash, Pharm.D. Margaret Whiteash, Pharm.D. Benjamin Andrick, Pharm.D. (non-voting participant) Birju Bhatt, MD (non-voting participant) Alfred Denio, MD (non-voting participant) Keri Jon Donaldson, MD (non-voting participant) Jeremy Garris, Pharm.D. (non-voting participant) Andrei Nemoianu, MD (non-voting participant) Ruth John, Pharmacy Student	Jeremy Bennett, MD Kim Castelnovo, RPh Michael Evans, RPh Nichole Hossler, MD Kerry Ann Kilkenny, MD Jonas Pearson, RPh William Seavey, Pharm.D. Michael Shepherd, MD Amanda Taylor, MD

Call to Order:

Dr. Bret Yarczower called the meeting to order at 1:03 p.m., Tuesday, March 19, 2024.

Review and Approval of Minutes:
Dr. Bret Yarczower asked for a motion or approval to accept the December 2023 e-vote and January 16, 2024 minutes as written. Minutes approved unanimously. None were opposed.

DRUG REVIEWS

BREYNA (budesonide/formoterol fumarate dihydrate)

Review: Breyna is a new combination product containing a corticosteroid and a long acting beta2-adrenergic agonist (LABA) which is indicated for the treatment of asthma in patients 6 years and older and as maintenance treatment of airflow obstruction and reducing exacerbations in patients with COPD including chronic bronchitis and emphysema. Breyna is available as a 10.3gm metered dose aerosol inhaler containing 120 actuations per canister of budesonide (80mcg or 160mcg) and formoterol fumarate dihydrate (4.5mcg). Breyna is not indicated for relief of acute bronchospasm and is for oral inhalation only.

The FDA approved dose of Breyna is as follows:
- Treatment of asthma in patients 12 years and older: 2 inhalations of BREYNA 80 mcg/4.5 mcg or 160 mcg/4.5 mcg twice daily. Starting dosage is based on asthma severity.
- Treatment of asthma in patients aged 6 to less than 12 years: 2 inhalations of BREYNA 80 mcg/4.5 mcg twice daily.
- Maintenance treatment in COPD: 2 inhalations of BREYNA 160 mcg/4.5 mcg twice daily.

Summary of clinical trials:
Patients with asthma 12 years of age and older:
Two clinical trials evaluated budesonide/formoterol fumarate dihydrate in a combination inhaler compared to budesonide and formoterol fumarate dihydrate given as separate inhalers, budesonide monotherapy, formoterol monotherapy, and placebo dosed as 2 inhalers twice daily in asthma patients 12 years of age and older. Patients receiving combination therapy had significantly greater mean improvements from baseline in pre-dose FEV1 at the end of treatment compared to individual components and placebo therapy. Patients on combination therapy had clinically meaningful improvement in overall asthma-specific quality of life, as defined by mean different between treatment groups of >0.5 points in change from baseline in overall Asthma Quality of Life Questionnaire (AQLQ) score. Two additional trials of combination therapy demonstrated clinically significant bronchodilation in 15 minutes and maximum improvement in 3 hours with clinically significant improvement maintained over 12 hours. Reduction in asthma symptoms, albuterol rescue use and morning & evening PEF occurred within 1 day of first dose and was maintained at 12 weeks of therapy. FEV1 improved markedly during the first 2 weeks of treatment and continued to show improvement at week 6.
Budesonide/formoterol fumarate dihydrate demonstrated safety and efficacy in patients 12 years and older with asthma, through a post marketing study demonstrating non-inferiority to budesonide in terms of time to first serious asthma-related event.

Patients with asthma 6 years to less than 12 years of age:
In patients with asthma 6 years to less than 12 years of age, three studies established safety and efficacy of budesonide/formoterol. Budesonide 80mcg dose was supported by a placebo-controlled study showing statistically significantly greater improvement compared to placebo in change from baseline to the treatment period average in pre-dose morning PEF and change in pre-dose morning FEV1. Formoterol 4.5mcg showed a dose response compared to placebo for FEV1 averaged over 12 hours post dose; the 9mcg dose showed numerically similar results compared to the active control. In patients receiving budesonide/formoterol fumarate dihydrate 80mcg/4.5mcg a statistically significant change in 1 hour post dose FEV1 was seen compared to budesonide 80mcg.

Lung Function in COPD:
The efficacy of budesonide/formoterol fumarate dihydrate in the maintenance treatment of airflow obstruction in COPD patients was demonstrated in two placebo-controlled clinical trials over 6 and 12 months. Budesonide/formoterol fumarate dihydrate 160mcg/4.5mcg as two inhalations twice daily, demonstrated significantly greater mean improvement from baseline in pre-dose FEV1 averaged over treatment period compared to formoterol 4.5mcg and placebo. This treatment group also had significantly greater mean improvement from baseline in 1- hour post dose FEV1 averaged over treatment period compared to budesonide 160mcg and placebo. Patients receiving 80mcg/4.5mcg as two inhalations twice daily did not show the same significantly greater improvement in pre-dose FEV1 compared to formoterol 4.5mcg.

Exacerbations of COPD:
Two studies were designed to evaluate the effect of budesonide/formoterol 160mcg/4.5mcg on COPD exacerbations. Patients treated with 160mcg/4.5mcg two inhalations twice daily had a significantly lower annual rate of moderate/severe COPD exacerbations compared to formoterol 4.5mcg in both the 12 month and 6 month active control studies.

Breyna is contraindicated for use as primary treatment of status asthmaticus or other acute episodes of asthma or COPD where intensive therapy is required, as well as in patients with hypersensitivity to any component. Warnings and precautions noted in the package labeling for Breyna are comparable to other inhaler corticosteroid/LABA combinations current used for the treatment of asthma and COPD. The most common adverse reactions include: nasopharyngitis, headache, upper respiratory tract infection, pharyngolarygneal pain, sinusitis, influenza, back pain, nasal congestion, stomach discomfort, vomiting, bronchitis, and oral candidiasis. Drug interactions, as with other budesonide/formoterol products may occur with inhibitors of CYP4503A4, MAOIs, TCAs, beta blockers, and diuretics.

Per Briggs Drugs in Pregnancy and Lactation, use of corticosteroids during the first trimester should be limited, however it is known that poorly controlled asthma may result in adverse maternal, fetal and neonatal outcomes. The benefits of treatment may outweigh the potential embryo fetal risk, therefore pregnant women who require an inhaled corticosteroid for control of their asthma should be counseled as to the risks and benefits of therapy, but treatment should not be withheld because of their pregnancy. A 2007 study showed the average plasma concentration of budesonide in breast fed infants was estimated to be 1/600th of the material concentration, leading to the conclusion that there is support for continued use of inhaled budesonide during breastfeeding.

The safety and effectiveness of budesonide/formoterol fumarate dihydrate inhaler in asthma patients less than 6 years of age has not been established. The growth of pediatric patients receiving daily orally inhaled corticosteroids should be monitored. If growth suppression is suspected, the potential growth effects of prolonged treatment should be weighed against the clinical benefit. To minimize risks, it is recommended to use the lowest strength that effectively controls the patient's asthma.

No overall differences in safety or efficacy were observed in patients over 65 years of age compared to younger patients, however, caution is recommended when using Breyna in geriatric patients with concomitant cardiovascular disease that could be adversely affected by beta2 agonists. No dose adjustments are currently recommended in patients with hepatic disease, however, they should be monitored closely since both ingredients are predominantly cleared by hepatic metabolism. No formal studies have been conducted in patients with renal impairment and therefore no dose adjustments are currently recommended.

A Clinical Review including Clinical Information, Efficacy Evidence, Safety Evidence, Other Considerations and a Financial Review Based on Cost Analysis were presented.

Clinical Discussion: No comments or questions. The committee unanimously voted to accept the recommendations as presented. None were opposed.

Financial Discussion: No comments or questions. The committee unanimously voted to accept the recommendations as presented. None were opposed.

Outcome: Breyna is a pharmacy benefit and will not be added to the Commercial, Exchange, or CHIP formularies at this time. The following prior authorization criteria will apply:

- Medical record documentation of age greater than or equal to 6 years **AND**
- Medical record documentation of a diagnosis of asthma **OR** chronic obstructive pulmonary disease (COPD) **AND**
- Medical record documentation of therapeutic failure on generic budesonide/formoterol **AND** generic fluticasone/salmeterol Diskus

QUANTITY LIMIT: 10.3gm per 30 days

GPI LEVEL: GPI-12

RPH SIGNOFF REQUIRED: No

FORMULARY ALTERNATIVES: budesonide/formoterol, fluticasone/salmeterol Diskus, Wixela, fluticasone/salmeterol HFA, Advair HFA, Breo Ellipta, Dulera

Additional evidence of the criteria used to make this decision can be found in the drug review presented to the committee.

XPHOZAH (tenapanor)

Review: Xphozah is a sodium hydrogen exchanger 3 (NHE3) inhibitor indicated to reduce serum phosphorus in adults with chronic kidney disease (CKD) on dialysis as add-on therapy in patients who have an inadequate response to phosphate binders or who are intolerant of any dose of phosphate binder therapy. Tenapanor was initially approved for the treatment of irritable bowel syndrome with constipation (IBS-C) (Ibsrela). It inhibits NHE3, an antiporter expressed on the apical surface of the epithelium of the small intestine and colon. Inhibition of NHE3 result in reduced sodium absorption and decreased phosphate absorption by reduction phosphate permeability through the paracellular pathway.

The recommended dosage of Xphozah is 30 mg orally twice daily before the morning and evening meals. Serum phosphorus should be monitored and the dosage should be adjusted as needed to manage gastrointestinal tolerability. Patients should take Xphozah just prior the first and last meals of the day. Xphozah should not be taken right before a hemodialysis session and instead take it right before the next meal following dialysis. Xphozah is supplied as 10 mg, 20 mg, and 30 mg tablets.

The efficacy of Xphozah in adults with CKD on dialysis was evaluated in 3 trials: TEN-02-201, TEN-02-301, and TEN-02-202. Both monotherapy trials (TEN-02-201 and TEN-02-301) enrolled patients who, following a 3-week washout period, had an increase in serum phosphorus of at least 1.5 mg/dL (compared to pre-wash out value) and a serum phosphorus level of at least 6.0 mg/dL and not more than 10.0 mg/dL.

Study TEN-02-301 included a 26-week, randomized, active-controlled, open-label treatment period followed by a 12-week, blinded placebo-controlled randomized withdrawal period. A total of 564 patients were randomized in the 26-week treatment period to received Xphozah (n=423) or control (n=141). Two hundred fifty five patients randomized to Xphozah completed the 26-week treatment period and were rerandomized 1:1 to remain on Xphozah (n=128) or placebo (n=127). During the randomized withdrawal phase, the phosphorus concentration rose in the placebo group by 0.7 mg/dL relative to patients who remained on Xphozah.

Study TEN-02-201 included an 8-week randomized, double-blind period evaluating three dosing regimens of Xphozah (3 mg twice daily, 10 mg twice daily, or a titration regimen). This period was followed by a 4-

week placebo-controlled randomized withdrawal phase, during which patients were rerandomized to continue Xphozah or switch to placebo. Of the 219 patients included in the trial, 164 patients completed the 8-week randomized period and were rerandomized 1:1 to receive Xphozah (n=82) or placebo (n=82). During the randomized withdrawal phase, the phosphorus concentration rose in the placebo group by 0.7 mg/dL compared to patients who remained on Xphozah.

Study TEN-02-202 was a randomized, parallel-group, double-blind, placebo-controlled study that evaluated the effect of Xphozah on the change in serum phosphorus when used as add-on therapy in patients on stable phosphate-binder therapy with serum phosphorus greater than or equal to 5.5 mg/dL. A total of 236 patients were randomized to receive Xphozah (n=117) or placebo BID (n=119) for 4 weeks. During the 4-week period, the serum phosphorus decreased by 0.7 mg/dL in the add-on Xphozah group compared to add-on placebo group.

Xphozah is contraindicated in patients under 6 years of age because of the risk of diarrhea and serious dehydration and in patients with known or suspected mechanical gastrointestinal obstruction. Warnings and precautions for Xphozah include diarrhea, which was reported in up to 53% of patients, reported as severe in 5%, and associated with dehydration and hyponatremia in less than 1% of patients.
During clinical trials, the most common adverse reaction was diarrhea, which occurred in 43-53% of patients. Diarrhea was the only adverse reaction reported in at least 5% of patients with CKD on dialysis treated with Xphozah. The majority of events were mild-to-moderate in severity and resolved over time or with a dose reduction. Diarrhea was typically reported soon after initiation but could occur at any time during treatment with Xphozah. Severe diarrhea was reported in 5% of patients. Tenapanor inhibits intestinal uptake transporter, OATP2B1. Drugs that are substrates of OATP2B1 may have reduced exposures when concomitantly taken with Xphozah. Patients should be monitored for signs related to loss of efficacy and the dosage should be adjusted as needed when administered concomitantly.
Xphozah also potentially interreacts with Sodium Polystyrene sulfonate (SPS) and administration should be separated by at least 3 hours. SPS binds to many commonly prescribed oral medications.
Xphozah is contraindicated in patients less than 6 years of age. In nonclinical studies, deaths occurred in young juvenile rats (approximate human age equivalent of less than 2 years of age) and in older juvenile rats (approximate human age-equivalent of 2 years of age). The safety and efficacy of Xphozah in pediatric patients has not been established. Of 1010 adult patients with CKD on dialysis, 282 (28%) were 65 years and older. Clinical studies did not include sufficient numbers of patients aged 65 years and older to determine whether they respond differently from younger patients.

A Clinical Review including Clinical Information, Efficacy Evidence, Safety Evidence, Other Considerations and a Financial Review Based on Cost Analysis were presented.

Clinical Discussion: No comments or questions. The committee unanimously voted to accept the recommendations as presented. None were opposed.

Financial Discussion: No comments or questions. The committee unanimously voted to accept the recommendations as presented. None were opposed.

Outcome: Xphozah is a pharmacy benefit and will be added to the Specialty tier or Brand non-preferred tier for members with a three tier benefit of the Commercial, Marketplace, and GHP Kids formularies. The following prior authorization criteria will apply:

- Medical record documentation of age greater than or equal to 18 years **AND**
- Medical record documentation that Xphozah is prescribed by a nephrologist **AND**
- Medical record documentation of a diagnosis of chronic kidney disease (CKD) on dialysis **AND**
- Medical record documentation that Xphozah is being used as add-on therapy to control serum phosphorus levels **AND**
- Medical record documentation of therapeutic failure on, intolerance to, or contraindication to calcium acetate **AND** sevelamer carbonate **AND** lanthanum carbonate

QUANTITY LIMIT: 2 tablets per day

GPI LEVEL: GPI-12

RPH SIGNOFF REQUIRED: No

Additional evidence of the criteria used to make this decision can be found in the drug review presented to the committee.

IWILFIN (eflornithine)

Review: Iwilfin is an ornithine decarboxylase inhibitor indicated to reduce the risk of relapse in adult and pediatric patients aged greater than or equal to 1 year with high-risk neuroblastoma (HRNB) who have demonstrated at least a partial response to prior multiagent, multimodality therapy including anti-GD2 immunotherapy.

Iwilfin is an irreversible inhibitor of the enzyme ornithine decarboxylase, the first and rate-limiting enzyme in the biosynthesis of polyamines and a transcriptional target of MYCN, an oncogene that plays an important role in regulating cell growth and division and the self-destruction of cells. Polyamines are involved in differentiation and proliferation of mammalian cells and are important for neoplastic transformation. Inhibition of polyamine synthesis by Iwilfin restored the balance of the LIN28/Let-7 metabolic pathway, which is involved in regulation of cancer stem cells and glycolytic metabolism, by decreasing the expression of the oncogenic drivers MYCN and LIN28B in MYCN-amplified neuroblastoma. In vitro, Iwilfin induced senescence and suppressed neurosphere formation in MYCN-amplified and MYCN non-amplified neuroblastoma cells, indicating a cytostatic effect. Treatment with Iwilfin prevented or delayed tumor formation in mice injected with limiting dilutions of MYCN-amplified neuroblastoma cells.

Iwilfin is supplied only as 192 mg oral tablets. Tablets may be swallowed whole, chewed, or crushed and mixed with soft food or liquid.
Prior to initiation of Iwilfin, perform baseline audiogram, complete blood count, and liver function tests. See Warnings and Precautions section for additional information.

Iwilfin dosage is based on body surface area (BSA). Recalculate BSA every 3 months during treatment with Iwilfin. The recommended dosing is provided in Table 1. The recommended dose reductions for adverse reactions are provided in Table 2. If subsequent adverse reactions occur with dose reduction, continue reducing the dose until reaching the minimum dose of 192 mg once per day. Permanently discontinue Iwilfin if the patient is unable to tolerate the minimum dose of 192 mg once daily.

The efficacy of Iwilfin is based on an externally controlled trial comparison of Study 3b (investigational arm) and Study ANBL0032 (clinical trial-derived external control arm).

Study 3b (NCT02395666) was a multi-center, open label, non-randomized trial with two cohorts. Eligible patients in one cohort (Stratum 1) were pediatric patients with high-risk neuroblastoma (HRNB) who demonstrated at least a partial response to prior multiagent, multimodality therapy, including induction, consolidation, and anti-GD2 immunotherapy. A total of 105 eligible patients received Iwilfin orally twice daily, dosage based on body surface area until disease progression, unacceptable toxicity, or for a maximum of 2 years. Tumor assessments were performed at 3, 6, 9, 12, 18 months, completion of treatment, and as clinically indicated. Following completion of Iwilfin therapy, patients were followed for a total duration of 7 years. The major efficacy outcome measure was event free survival (EFS), defined as disease progression, relapse, secondary cancer, or death due to any cause. An additional efficacy outcome measure was overall survival (OS), defined as death due to any cause. Study 3b was prospectively designed to compare outcomes to the historical EFS rate from Study ANBL0032 reported in published literature.

The external control arm was derived from 1,241 patients on the experimental arm of Study ANBL0032, a multi-center, open-label, randomized trial of dinutuximab, granulocyte-macrophage colony stimulating factor, interlukin-2, and cis-retinoic acid compared to cis-retinoic acid alone in pediatric patients with HRNB previously treated with induction and consolidation therapy who demonstrated at least a partial response. Tumor assessments were performed post-immunotherapy at 3, 6, 9, 12, 18, 24, 30, and 36 months, then per standard of care for a total of 10 years.

Iwilfin was studied as continuation therapy in a multi-center, single arm Phase 2 trial (Study 3B) in 105 children with high-risk neuroblastoma that had responded to frontline therapy that included induction, consolidation, and anti-GD2 directed immunotherapy. Patients who had a partial response or better following standard frontline therapy were eligible to enroll in Study 3b following completion of immunotherapy and received Iwilfin at the recommended dose for up to 2 years. Data from 92 patients on Study 3b were compared to an external control arm consisting of 852 patients treated with anti-GD2 immunotherapy, cytokines, and isotretinoin on COG ANBL0032 who did not go on to receive Iwilfin continuation therapy. Patients on Study 3b had superior outcomes compared to the external compare group. Further analyses using propensity score matching and sensitivity analyses also demonstrated higher event free survival and overall survival for patients on Study 3b.

A Clinical Review including Clinical Information, Efficacy Evidence, Safety Evidence, Other Considerations and a Financial Review Based on Cost Analysis were presented.

Clinical Discussion: There are different genes that have amplification in neuroblastoma. When they studied this did they look at the efficacy of Iwilfin based on what genes were amplified? NYCN was the specific gene that was included in clinical trials. Should Iwilfin be restricted to members with this amplification or was the FDA approval non-specific? Mark will review clinical trials in more depth, but package insert does not specifically require amplification of NYCN. No additional comments or questions. The committee unanimously voted to accept the recommendations as presented. None were opposed.

Financial Discussion: No comments or questions. The committee unanimously voted to accept the recommendations as presented. None were opposed.

Outcome: Iwilfin is a pharmacy benefit and will be added to the Oral Oncology Brand Non-Preferred tier ($0 copay) for Commercial, Marketplace, and GHP Kids formulary. Iwilfin will require a prior authorization for new starts only. The following prior authorization criteria will apply:

- Medical record documentation that Iwilfin is prescribed by a hematologist or oncologist **AND**
- Medical record documentation of age greater than or equal to 1 year **AND**
- Medical record documentation that Iwilfin is being used to reduce the risk of relapse in patients with high-risk neuroblastoma (HRNB) **AND**
- Medical record documentation that the patient demonstrated at least a partial response to prior multiagent, multimodality therapy including anti-GD2 immunotherapy

RE-AUTHORIZATION CRITERIA: Iwilfin is configured as a prior authorization for new starts only. Iwilfin will no longer be covered if it is identified that the member is not receiving appropriate follow-up care from the prescribing specialist or if the member has greater than or equal to a 90 day break in therapy.

- Medical record documentation that the member is receiving appropriate follow-up care from the prescribing specialist

QUANTITY LIMIT: 8 tablets per day, 240 tablets per 30 days

GPI LEVEL: GPI-12

RPH SIGNOFF REQUIRED: Yes

Additional evidence of the criteria used to make this decision can be found in the drug review presented to the committee.

ZEPBOUND (tirzepatide)

Review: Zepbound is a glucose-dependent insulinotropic polypeptide (GIP) receptor and glucagon-like peptide-1 (GLP-1) receptor agonist indicated as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adults with an initial body mass index (BMI) of:

- 30 kg/m^2 or greater (obesity) or
- 27 kg/m^2 or greater (overweight) in the presence of at least one weight-related comorbid condition (e.g. hypertension, dyslipidemia, type 2 diabetes mellitus, obstructive sleep apnea, or cardiovascular disease).

Zepbound contains tirzepatide. Coadministration with other tirzepatide-containing products or with any glucagon-like peptide-1 (GLP-1) receptor agonist is not recommended. The safety and efficacy of Zepbound in combination with other products intended for weight management, including prescription drugs, over-the-counter drugs, and herbal preparations, have not been established. Zepbound has not been studied in patients with a history of pancreatitis.

The recommended dosage of Zepbound is 2.5 mg injected subcutaneously once weekly. The 2.5 mg dosage is for treatment initiation and is not intended for chronic weight management. After 4 weeks, the dosage is increased to 5 mg subcutaneously once weekly. The dosage may be increased in 2.5 mg increments after at least 4 weeks on the current dose. The recommended maintenance dosages of Zepbound in adults are 5 mg, 10 mg, or 15 mg injected once weekly. The maximum dosage of Zepbound is 15 mg once weekly. Zepbound is available as prefilled single dose pens in 2.5 mg/0.5 mL, 5 mg/0.5 mL, 7.5 mg/0.5 mL, 10 mg/0.5 mL, 12.5 mg/0.5 mL, and 15 mg/0.5 mL. It is supplied in cartons containing 4 single-dose pens.

The efficacy of Zepbound for chronic weight management (weight reduction and maintenance) in conjunction with a reduced-calorie diet and increased physical activity was studied in two randomized, double-blind, placebo-controlled trials (Study 1 and 2), which assessed weight reduction after 72 weeks of treatment. In Study 1, Zepbound or matching placebo was titrated to 5 mg, 10 mg, or 15 mg once weekly during a 20-week titration period followed by a maintenance period. In Study 2, the dose of Zepbound or matching placebo was escalated to 10 mg or 15 mg subcutaneously once weekly during a 20-week titration period followed by a maintenance period.
Study 1 enrolled 2,539 adult patients with obesity, or overweight with at least one weight-related comorbid condition such as dyslipidemia, hypertension, obstructive sleep apnea, or cardiovascular disease. Patients with type 2 diabetes mellitus were excluded. Patients were randomized 1:1:1:1 to Zepbound 5 mg, Zepbound 10 mg, or Zepbound 15 mg, or placebo once weekly.

Study 2 enrolled 938 adult patients with a BMI ≥ 27 kg/m^2 and type 2 diabetes mellitus. Patients included in the trial had HbA1c 7-10% and were treated with either diet and exercise alone or any oral anti-hyperglycemic agent except dipeptidyl peptidase-4 (DPP-4) inhibitors or GLP-1 receptor agonists. Patients who were taking insulin or injectable GLP-1 receptor agonists for type 2 diabetes mellitus were excluded. Patients were randomized 1:1:1 to Zepbound 10 mg, Zepbound 15 mg, or placebo once weekly.

The primary efficacy parameters for both studies were mean percent change in body weight and the percentage of patients achieving ≥ 5% weight reduction from baseline to Week 72. After 72 weeks of treatment, Zepbound resulted in statistically significant reduction in body weight compared with placebo, and greater proportion of patients treated with Zepbound 5 mg, 10mg, and 15 mg achieved at least 5% weight reduction compared to placebo (Table 12). Among patients treated with Zepbound 10 mg and 15 mg, greater proportions of patients achieved at least 10%, 15%, and 20% weight reduction compared to placebo. A reduction in body weight was observed with Zepbound irrespective of age, sex, race, ethnicity, baseline BMI, and glycemic status.

Table 12. Changes in Body Weight at Week 72 in Studies 1 and 2

Intention-to-Treat (ITT) Population[a]	Study 1				Study 2		
	Placebo N = 643	**ZEPBOUND 5 mg** N = 630	**ZEPBOUND 10 mg** N = 636	**ZEPBOUND 15 mg** N = 630	**Placebo** N = 315	**ZEPBOUND 10 mg** N = 312	**ZEPBOUND 15 mg** N = 311
Body Weight							
Baseline mean (kg)	104.8	102.9	105.8	105.6	101.7	100.9	99.6
% Change from baseline[b]	-3.1	-15.0	-19.5	-20.9	-3.2	-12.8	-14.7
% Difference from placebo[b] (95% CI)		-11.9 (-13.4, -10.4)[d]	-16.4 (-17.9, -14.8)[d]	-17.8 (-19.3, -16.3)[d]		-9.6 (-11.1, -8.1)[d]	-11.6 (-13.0, -10.1)[d]
% of Patients losing ≥5% body weight	34.5	85.1	88.9	90.9	32.5	79.2	82.8
% Difference from placebo (95% CI)		50.3 (44.3, 56.2)[c,d]	54.6 (49.1, 60.0)[c,d]	56.4 (50.9, 62.0)[c,d]		46.8 (39.5, 54.1)[c,d]	50.4 (43.1, 57.8)[c,d]
% of Patients losing ≥10% body weight	18.8	68.5	78.1	83.5	9.5	60.5	64.8
% Difference from placebo (95% CI)		49.3 (43.6, 54.9)[c,e]	59.5 (54.2, 64.9)[c,d]	64.8 (59.6, 70.1)[c,d]		51.0 (44.4, 57.7)[c,d]	55.3 (48.6, 62.0)[c,d]
% of Patients losing ≥15% body weight	8.8	48.0	66.6	70.6	2.7	39.7	48.0
% Difference from placebo (95% CI)		38.7 (33.6, 43.7)[c,e]	58.1 (53.2, 63.0)[c,d]	62.0 (57.2, 66.8)[c,d]		37.0 (31.1, 42.9)[c,d]	45.4 (39.4, 51.4)[c,d]
% of Patients losing ≥20% body weight	3.1	30.0	50.1	56.7	1.0	21.5	30.8
% Difference from placebo (95% CI)		26.6 (22.4, 30.7)[c,e]	47.3 (42.7, 51.9)[c,d]	53.8 (49.3, 58.3)[c,d]		20.5 (15.7, 25.4)[c,d]	29.7 (24.3, 35.0)[c,d]

Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; N = number of patients randomly assigned to study drug. a The intention-to-treat population includes all randomly assigned patients. For Study 1 at Week 72, body weight was missing for 21.6%, 10.2%, 10.5%, and 9.4% of patients randomly assigned to placebo, ZEPBOUND 5 mg, 10 mg, and 15 mg, respectively. For Study 2 at Week 72, body weight was missing for 11.1%, 4.8%, and 8.4% of patients randomly assigned to placebo, ZEPBOUND 10 mg, and 15 mg, respectively. The missing values were imputed by a hybrid approach using retrieved dropouts from the same treatment group (if missing not due to COVID-19) or using all non-missing data assuming missing at random (for missing solely due to COVID-19). b Least-squares mean from ANCOVA adjusted for baseline value and other stratification factors. Analyzed using logistic regression adjusted for baseline value. d p-value

Changes in waist circumference and cardiometabolic parameters with Zepbound are shown in Table 13.

Table 13. Changes in Anthropometry and Cardiometabolic Parameters at Week 72 in Studies 1 and 2

Intention-to-Treat (ITT) Population[a]	Study 1				Study 2		
	Placebo N = 643	**ZEPBOUND 5 mg** N = 630	**ZEPBOUND 10 mg** N = 636	**ZEPBOUND 15 mg** N = 630	**Placebo** N = 315	**ZEPBOUND 10 mg** N = 312	**ZEPBOUND 15 mg** N = 311
Waist Circumference (cm)							
Baseline mean	114.0	113.2	114.8	114.4	116.0	114.2	114.6
Change from baseline[b]	-4.0	-14.0	-17.7	-18.5	-3.3	-10.8	-13.1
Difference from placebo[b] (95% CI)		-10.1 (-11.6, -8.6)[e]	-13.8 (-15.2, -12.3)[d]	-14.5 (-15.9, -13.0)[d]		-7.4 (-9.0, -5.9)[d]	-9.8 (-11.2, -8.3)[d]
Systolic Blood Pressure (mmHg)							
Baseline mean	122.9	123.6	123.8	123.0	131.0	130.6	130.0
Change from baseline[b]	-1.0	-6.6	-7.7	-7.4	-1.2	-5.6	-7.1
Difference from placebo[b] (95% CI)		-5.6 (-7.2, -3.9)[e]	-6.7 (-8.4, -5.0)[e]	-6.4 (-8.0, -4.8)[e]		-4.4 (-6.7, -2.1)[e]	-5.9 (-8.3, -3.6)[e]

Diastolic Blood Pressure (mmHg)							
Baseline mean	79.6	79.3	79.9	79.3	79.4	80.2	79.7
Change from baseline[b]	-0.8	-4.9	-5.0	-4.5	-0.3	-2.1	-2.9
Difference from placebo[b] (95% CI)		-4.1 (-5.2, -3.0)[e]	-4.2 (-5.3, -3.0)[e]	-3.7 (-4.8, -2.7)[e]		-1.8 (-3.3, -0.4)[e]	-2.7 (-4.2, -1.2)[e]
Pulse Rate (beats per minute)							
Baseline mean	72.9	72.4	71.8	72.4	74.8	75.9	75.6
Change from baseline[f]	0.1	0.6	2.3	2.6	-0.5	0.6	1.0
Difference from placebo[f] (95% CI)		0.5 (-0.5, 1.5)[e]	2.2 (1.2, 3.2)[e]	2.5 (1.5, 3.4)[e]		1.2 (-0.1, 2.5)[e]	1.5 (0.2, 2.8)[e]
Total Cholesterol (mg/dL)							
Baseline mean[g]	187.5	187.1	190.6	187.5	174.9	173.9	167.0
% change from baseline[b]	-1.8	-3.8	-4.4	-6.3	2.8	-2.8	-1.0
Relative difference from placebo[b] (95% CI)		-2.1 (-4.5, 0.4)[c,e]	-2.7 (-5.1, -0.2)[c,e]	-4.6 (-6.8, -2.2)[c,e]		-5.5 (-8.7, -2.2)[c,e]	-3.8 (-7.1, -0.3)[c,e]
LDL Cholesterol (mg/dL)							
Baseline mean[g]	109.4	108.7	112.3	109.3	92.4	90.5	85.7
% change from baseline[b]	-1.7	-4.6	-5.6	-7.1	7.4	1.8	4.1
Relative difference from placebo[b] (95% CI)		-2.9 (-6.6, 0.9)[c,e]	-4.0 (-7.5, -0.5)[c,e]	-5.5 (-8.9, -2.0)[c,e]		-5.2 (-10.1, 0.1)[c,e]	-3.0 (-8.4, 2.6)[c,e]
HDL (mg/dL)							
Baseline mean[g]	46.6	47.6	47.6	47.6	42.7	43.8	42.2
% change from baseline[b]	-0.7	6.9	9.2	8.0	0.2	8.2	9.7
Relative difference from placebo[b] (95% CI)		7.7 (4.6, 10.8)[c,e]	9.9 (6.7, 13.2)[c,e]	8.7 (5.7, 11.8)[c,e]		8.0 (4.2, 11.8)[c,e]	9.5 (5.6, 13.5)[c,e]
Non-HDL (mg/dL)							
Baseline mean[g]	138.3	137.0	140.4	137.5	129.6	127.2	121.9
% change from baseline[b]	-2.3	-8.0	-9.4	-11.7	3.7	-6.6	-5.2
Relative difference from placebo[b] (95% CI)		-5.8 (-8.9, -2.6)[c,e]	-7.2 (-10.3, -4.1)[c,e]	-9.6 (-12.4, -6.6)[c,e]		-9.9 (-14.1, -5.6)[c,e]	-8.5 (-12.9, -4.0)[c,e]
Triglycerides (mg/dL)							
Baseline mean[g]	130.8	128.7	125.7	128.1	165.0	158.8	158.5
% change from baseline[b]	-5.6	-21.2	-23.8	-29.1	-3.3	-27.1	-27.3
Relative difference from placebo[b] (95% CI)		-16.5 (-21.2, -11.4)[c,e]	-19.3 (-23.9, -14.4)[c,e]	-24.9 (-29.1, -20.4)[c,e]		-24.6 (-30.0, -18.7)[c,e]	-24.8 (-30.3, -18.9)[c,e]
HbA1c (%)							
Baseline mean	5.6	5.6	5.5	5.6	8.0	8.0	8.1
Change from baseline[b]	-0.1	-0.4	-0.4	-0.4	-0.5	-2.1	-2.1
Difference from placebo[b] (95% CI)		-0.3 (-0.3, -0.2)[e]	-0.4 (-0.4, -0.3)[e]	-0.4 (-0.4, -0.3)[e]		-1.6 (-1.7, -1.4)[d]	-1.6 (-1.8, -1.4)[d]

Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; N = number of patients randomly assigned to study drug. a The intention-to-treat population includes all randomly assigned patients. The missing values were imputed by a hybrid approach using retrieved dropouts from the same treatment group (if missing not due to COVID-19) or using all non-missing data assuming missing at random (for missing solely due to COVID-19). b Least-squares mean from ANCOVA adjusted for baseline value and other stratification factors. Analyzed using log-transformed data. d p-value e Not controlled for type I error rate. f Least-squares mean from mixed model for repeated measures adjusted for baseline value and other stratification factors. g Baseline value is the geometric mean.

Zepbound carries a black box warning for an increased risk of thyroid c-cell tumors. In rats, tirzepatide causes dose-dependent and treatment duration dependent thyroid C-cell tumors at clinically relevant exposures. It is unknown whether Zepbound will cause thyroid c-cell tumors in humans. It is contraindicated in patients with a personal or family history of medullary thyroid cancer (MTC) or in patients with multiple endocrine neoplasia syndrome type 2 (MEN 2).

Other warnings include severe gastrointestinal adverse reactions, acute kidney injury (resulting from dehydration due to GI adverse reactions), acute gallbladder disease, acute pancreatitis, hypersensitivity reactions, hypoglycemia, diabetic retinopathy complications in patients with Type 2 diabetes mellitus, and suicidal behavior and ideation.

Permanent discontinuation occurred in 4.8%, 6.3%, and 6.7% of patients treated with Zepbound 5 mg, 10 mg, and 15 mg across both Study 1 and 2. The majority of patients who discontinued treatment due to adverse reactions did so during the first few months of treatment due to gastrointestinal adverse reactions. The most common adverse reactions reported in clinical trials were nausea, diarrhea, vomiting, constipation, abdominal pain, dyspepsia, injection site reactions, fatigue, hypersensitivity reactions, eructation, hair loss, gastroesophageal reflux disease.

When Zepbound is initiation, the dose of concomitantly administered insulin secretagogues or insulin may need to be reduced to reduce the dosage of hypoglycemia. Zepbound delays gastric emptying and has the potential to impacted the absorption of concomitantly administered oral medications. Caution should be used when Zepbound is used with oral medications dependent on threshold concentrations for efficacy and those with a narrow therapeutic index. Patients using oral hormonal contraceptives should be switched to non-oral contraceptive methods or a barrier method for 4 weeks after initiation of Zepbound and for 4 weeks after each dose escalation.

The safety and efficacy of Zepbound have not been established in pediatric patients less than 18 years of age. In clinical trials, 226 (9%) of patients were 65 years or older and 13 (0.5%) of patients were 75 years or older. No overall differences in safety or efficacy were observed between older and younger patients.

A Clinical Review including Clinical Information, Efficacy Evidence, Safety Evidence, Other Considerations and a Financial Review Based on Cost Analysis were presented.

Clinical Discussion: If someone gets bariatric surgery do you continue on Zepbound or Wegovy? Has seen this happen and we are not aware of anything in the labeling that says it can not be used with bariatric surgery. Will confirm. Consider looking at claims to determine impact on other utilization? Will continue this discussion offline. Dr. Sullivan asked to clarify if they should stay on Zepbound following surgery? Bret clarified his question was whether someone would need to continue Zepbound after bariatric surgery. We have seen members start it ahead of surgery. No comments or questions. The committee majority voted to accept the recommendations as presented.

Financial Discussion: No comments or questions. The committee unanimously voted to accept the recommendations as presented. None were opposed.

Outcome: Zepbound is a pharmacy benefit and will be excluded from the Commercial, Exchange, and GHP Kids pharmacy formulary except for certain TPA clients that request this benefit (weight loss). For certain TPA clients that request this benefit (weight loss), Zepbound will be added to the Brand Non-Preferred tier for members with a three-tier benefit. Zepbound will be added to Commercial Policy 686.0 for Wegovy with the following updates to the prior authorization criteria:

Commercial Policy 686.0 Wegovy and Zepbound

- Medical record documentation that member has participated in comprehensive lifestyle modifications including reduced-calorie diet, physical activity, and behavioral health for at least 3 months prior to beginning Wegovy or Zepbound **AND**
- Medical record documentation of use as adjunct therapy to reduced calorie diet and increased physical activity for chronic weight management **AND**
- Medical record documentation of one of the following:
    - Medical record documentation of age greater than or equal to 18 years with one of the following:
        - Medical record documentation of body mass index (BMI) greater than or equal to 30 kg/m^2 OR
        - Medical record documentation of body mass index (BMI) greater than or equal to 27 kg/m^2 and at least one weight-related comorbid condition (e.g., hypertension, type 2 diabetes mellitus, or dyslipidemia) **AND**

- For Wegovy Only: Medical record documentation of age greater than or equal to 12 years and less than 18 years with an initial body mass index (BMI) in the 95th percentile or higher for age and sex

NOTE: Wegovy and Zepbound are not indicated for treatment of chronic weight management:

- In combination with semaglutide or tirzepatide containing products or any other GLP-1 receptor agonist
- In combination with other products for weight loss, as safety and efficacy or coadministration has not been established
- In patients with acute pancreatitis. Use in caution in patients with history of pancreatitis.
- In patients with personal or family history of medullary thyroid C-cell carcinoma or Multiple Endocrine Neoplasia syndrome type 2
- In known hypersensitivity to semaglutide or tirzepatide or any of the excipients
- In pregnancy

GPI LEVEL: GPI-12

QUANTITY LIMIT: 2 mL per 28 days

AUTHORIZATION DURATION: Initial approval will be for 6 months. Subsequent approvals will be for an additional 6 months and will require:

- Medical record documentation that the member continues to experience clinical benefit from Wegovy or Zepbound based on the prescriber's assessment **AND**
- Medical record documentation that member has experienced at least a 5% reduction in weight from baseline

RPH SIGNOFF REQUIRED: yes

Additional evidence of the criteria used to make this decision can be found in the drug review presented to the committee.

RYKINDO EXTENDED-RELEASE INJECTABLE SUSPENSION (risperidone)

Review: Rykindo is an atypical antipsychotic indicated for the treatment of schizophrenia in adults and as monotherapy or as adjunctive therapy to lithium or valproate for the maintenance treatment of bipolar 1 disorder in adults. It is available in extended-release injectable suspension: 12.5 mg, 25 mg, 37.5 mg, and 50 mg. Oral tolerability must be established prior to initiating Rykindo. It should be administered by a health care professional, by gluteal injection. For Schizophrenia, recommended dosage is 25 mg every two weeks with the first dose of Rykindo administered with 7 days of oral risperidone. 37.5 mg or 50 mg may be used if patients do not respond to 25 mg. no additional benefit was observed over 50 mg in this population, but more adverse effects were observed. Dose titration should not be made more frequently than every 4 weeks. For maintenance treatment of Bipolar 1 disorder, recommended dose is 25 mg every 4 weeks, dosages above 50 mg have not been studied in this population. If switching from Risperdal Consta, the dose for Rykindo should be the same, administered 4 weeks after last injection of Risperdal Consta and oral risperidone is not recommended.

According to PK studies of Rykindo, there is no dose-dumping or abnormal drug concentration spikes in any clinical studies conducted in the EU or China. Frequent blood sampling at 3 hours, 8 hours, 1 day, 3 days, 5 days, 7 days, 10 days, 12 days, and 14 days after injection were conducted throughout the studies. 242 patients were included for PK assessment. Most of the analysis of Rykindo was compared in PK studies to Risperdal Consta. Overall, there were more "PK alerts" (defined as plasma concentrations of total active drug above 120 ng/mL after a 50-mg dose), compared to Rykindo. Based on this PK data with evidence of similar safety findings (i.e. similar adverse events, vital signs, ECGs), it was determined the risk assessment for Rykindo was favorable.

The most common adverse reactions with risperidone (≥5% and greater than placebo) were headache, parkinsonism, dizziness, akathisia, fatigue, constipation, dyspepsia, sedation, weight increase, pain in extremity, and dry mouth. Neonates exposed to antipsychotic drugs during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms following delivery. There is a risk to the mother from untreated schizophrenia and schizophrenia is associated with increased adverse perinatal outcomes including preterm birth. The clinical significance of Rykindo administered before or during pregnancy is unknown. Extrapyramidal and/or withdrawal symptoms (including agitation, hyper and hypotonia, tremor, respiratory distress, and feeding disorder) have been reported in neonates who were exposed to antipsychotic drugs during the third trimester of pregnancy. With renal and hepatic impairment, patients should be treated with titrated oral risperidone prior to initiating treatment with Rykindo. Starting dose is 0.5 mg twice daily for one week, which can be increased to 1 mg twice daily or 2 mg once daily during the second week. If total daily dose of at least 2 mg is well tolerated, Rykindo 25 mg can be administered every two weeks with oral supplementation for 7 days following the first injection. Patients with Parkinson's Disease or Dementia with Lewy Bodies can experience increased sensitivity to Rykindo.

A Clinical Review including Clinical Information, Efficacy Evidence, Safety Evidence, Other Considerations and a Financial Review Based on Cost Analysis were presented.

Clinical Discussion: No comments or questions. The committee unanimously voted to accept the recommendations as presented. None were opposed.

Financial Discussion: No comments or questions. The committee unanimously voted to accept the recommendations as presented. None were opposed.

Outcome: Rykindo will be a medical benefit. Rykindo will be added to the medical benefit cost share list. If processed at a specialty pharmacy, Rykindo will process at the Specialty tier or Brand Non-Preferred tier for those with a three-tier benefit. Rykindo will require a prior authorization and be added to MBP 106.0 as outlined below:

- Medical record documentation that the patient is 18 years of age or older **AND**
- Medical record documentation of a history of poor adherence to oral medications and documentation that education to improve adherence has been attempted **AND**
- Medical record documentation of use for an FDA approved indication:
    - Abilify Maintena – Schizophrenia or maintenance monotherapy treatment of Bipolar I Disorder
    - Aristada – Schizophrenia
    - Aristada Initio – Initiation of Aristada (in combination with oral aripiprazole) to treat schizophrenia
    - Invega Hafyera - Schizophrenia
    - Invega Sustenna – Schizophrenia or Schizoaffective disorders as monotherapy and as an adjunct to mood stabilizers or antidepressants
    - Invega Trinza – Schizophrenia
    - Perseris- Schizophrenia
    - Risperdal Consta – Schizophrenia or Bipolar I Disorder as monotherapy or as adjunctive therapy to lithium or valproate
    - Rykindo– Schizophrenia or Bipolar I Disorder as monotherapy or as adjunctive therapy to lithium or valproate
    - Zyprexa Relprevv – Schizophrenia
    - Uzedy- Schizophrenia
- In addition: The following criteria should apply to Invega Trinza:
    - Medical record documentation that the patient has been adequately treated with Invega Sustenna for at least 4 months
- In addition: The following criteria should apply to Invega Hafyera:
    - Medical record documentation that the patient has been adequately treated with Invega Sustenna for at least 4 months **OR** Invega Trinza for at least 3 months

QUANTITY LIMIT: One syringe per 14 days

GPI LEVEL: GPI-12

RPH SIGNOFF REQUIRED: no

Additional evidence of the criteria used to make this decision can be found in the drug review presented to the committee.

VELSIPITY (etrasimod)

Review: Velsipity is a sphingosine 1-phosphate receptor modulator indicated for the treatment of moderately to severely active ulcerative colitis in adults. Velsipity binds to S1P receptors 1, 4, and 5. The mechanism by which Velsipity exerts therapeutic effects in UC is unknown but may involve the reduction of lymphocyte migration into the intestines. Velsipity is the second S1P receptor modulator indicated for UC, following Zeposia, which is also indicated in multiple sclerosis (MS).

The recommended dosage of Velsipity is 2 mg orally once daily. Velsipity is supplied as 2 mg tablets. Before initiation of treatment with Velsipity, patients should be assessed with a complete blood count, cardiac evaluation, liver function tests, ophthalmic assessment, and assessment for current or prior mediations, vaccinations, and skin examinations.

The efficacy of Velsipity was evaluated in 2 randomized, double-blind, placebo-controlled clinical studies [UC-1 (NCT03945188) and UC-2 (NCT03996369)] in adult patients with moderately to severely active ulcerative colitis who had an inadequate response, loss of response, or intolerance to one or more of the following treatment options: oral aminosalicylates, corticosteroids, thiopurines, Janus kinase (JAK) inhibitors, or biologic therapies (e.g., TNF blocker, anti-integrin, anti-IL12/23). UC-1 was a 52 week study and UC-2 was a 12-week study. In both studies, subjects were randomized to Velsipity or placebo and continued on treatment for the entire duration of the study.

Disease severity was assessed based on the modified Mayo score (mMS), a 3-component Mayo score (0 to 9) which consists of the following subscores (0-3 for each subscore): stool frequency (SF), rectal bleeding (RB) and findings on centrally read endoscopy score (ES). An ES of 2 was defined as marked erythema, lack of vascular pattern, any friability, and/or erosions, and a score of 3 was defined by spontaneous bleeding and ulceration. Subjects in these studies may have received other concomitant UC therapies including stable daily doses of oral aminosalicylates and/or oral corticosteroids (≤20 mg/day prednisone, ≤9 mg/day budesonide, or equivalent steroid). Concomitant treatment with immunomodulators (e.g., thiopurines, methotrexate), biologic therapies, JAK inhibitors, rectal 5-ASA, or rectal corticosteroids was not permitted.

In UC-1, efficacy was evaluated in 408 adults with a baseline mMS of 5 to 9 including a centrally read endoscopy subscore of 2 or 3. Subjects were randomized 2:1 to receive Velsipity 2 mg or placebo administered orally once daily. A total of 30% of subjects had prior exposure to biologic/JAK inhibitors and a total of 14% of subjects had exposure to >1 biologic/JAK inhibitor. At baseline, 68% of subjects were receiving oral aminosalicylates and 31% of subjects were receiving oral corticosteroids.
Coprimary endpoints were the proportion of subjects achieving clinical remission at week 12 and at week 52. The secondary endpoints included the proportion of subjects achieving endoscopic improvement, histologic-endoscopic mucosal improvement, corticosteroid-free clinical remission, and maintenance of clinical remission. The relationship of histologic-endoscopic mucosal improvement at Week 12 or Week 52 to disease progression and longer-term outcomes after Week 52 was not evaluated in Study UC-1. Results showed a greater proportion of patients treated with Velsipity compared to placebo achieved clinical response, defined as ≥ 2 point and ≥30% decrease from baseline in mMS, and a ≥ 1 point decrease from baseline in RB subscore or an absolute RB subscore ≥ 1 at Week 12 (62% vs 34%). Decreases in stool frequency subscores were observed as early as Week 2 and decreases in RB

subscores were observed as early as Week 4 in subjects treated with Velsipity compared to placebo. Normalization of endoscopic appearance of the mucosa (endoscopic remission, ES 0) was achieved in a greater proportion of patients treated with Velsipity compared to placebo by Week 12, Week 52, and both Week 12 and Week 52.

In UC-2, efficacy was evaluated in 333 adult patients with a baseline mMS of 5 to 9, including centrally read endoscopy subscore of 2 or 3. Patients were randomized 2:1 to receive Velsipity 2 mg or placebo once daily. A total of 34% of subjects had prior exposure to biologic/JAK inhibitors and a total of 17% of subjects had exposure to >1 biologic/JAK inhibitor. At baseline, 66% of subjects were receiving oral aminosalicylates and 28% of subjects were receiving oral corticosteroids.
The primary endpoint was the proportion of patients achieving clinical remission at Week 12. The secondary endpoints included the proportion of patients achieving endoscopic improvement and histologic-endoscopic mucosal improvement at Week 12. The relationship of histologic-endoscopic mucosal improvement at Week 12 to disease progression and longer-term outcomes after Week 12 was not evaluated in Study UC-2.

A greater proportion of patients treated with Velsipity compared to placebo achieved clinical response, defined as ≥ 2 point and ≥ 30% decrease from baseline in mMS, and a ≥ 1 point decrease from baseline in RB subscore or an absolute RB subscore ≤ 1 at week 12. Decreases in stool frequency subscores were observed as early as Week 2 and decreases in RB subscores were observed as early as Week 4 in patients treated with Velsipity compared to placebo. Normalization of endoscopic appearance of the mucosa (endoscopic remission, ES 0) was achieved in a greater proportion of patients treated with Velsipity compared to placebo by Week 12.

Warnings are consistent with other S1P receptor modulators and include risk of infections, bradyarrhythmia and atrioventricular conduction delays, liver injury, macular edema, increased blood pressure, fetal risk, malignancies, posterior reversible encephalopathy syndrome (PRES), respiratory effects, additive immune system effects from prior treatment with immunosuppressive or immune-modulating drugs, and immune system effects after stopping Velsipity. In UC-1, adverse reactions reported in more than 2% of patients included headache, elevated liver tests, dizziness, arthralgia, hypertensions, urinary tract infection, nausea, hypercholesterolemia, and herpes viral infection. In UC-2, the most common adverse reactions reported in at least 2% of patients included headache, elevated liver tests, nausea, bradycardia, and urinary tract infection. In UC-1, for subjects with a baseline and follow-up examination, a decrease in visual acuity was reported in 2.6% (4/156) of subjects who received Velsipity and no patients who received placebo.

Velsipity is primary metabolized by CYP2C8, CYP2C9, and CYP3A4. Clinically relevant drug interactions when administered concomitantly with Velsipity include anti-arrhythmic and QT prolonging drugs, beta-blockers or calcium channel blockers, anti-neoplastic, immune-modulating, or non-corticosteroid immunosuppressive therapies, moderate to strong inhibitors of CYP2C9 and CYP3A4, CYP2C9 poor metabolizers using moderate to strong inhibitors of CYP2C8 or CYP3A4, and rifampin.

The safety and efficacy of Velsipity has not been established in pediatric patients. Of the 577 Velsipity-treated subjects in the three clinical trials (UC-1, UC-2, and UC-3), 30 subjects (5%) were 65 years and older and 3 (<1%) were 75 years of age and older. Clinical studies did not include sufficient number of patients aged 65 years and older to determine whether they respond differently from younger adult subjects. The pharmacokinetics of Velsipity are similar in subjects 65 years of age and older compared to younger patients. Velsipity undergoes extensive hepatic metabolism. Velsipity exposure was similar in patients with mild and moderate hepatic impairment compared to patients with normal hepatic function. Velsipity exposure was increased in patients with severe hepatic impairment compared to patients with normal hepatic function. Use of Velsipity is not recommended in patients with severe hepatic impairment. No dosage adjustment is needed for patients with mild to moderate hepatic impairment. Velsipity exposure increases in patients with are poor CYP2C9 metabolizers with concomitant use of moderate or strong inhibitors of CYP2C8 or CYP3A4 and Velsipity is not recommended in these patients.

A Clinical Review including Clinical Information, Efficacy Evidence, Safety Evidence, Other Considerations and a Financial Review Based on Cost Analysis were presented.

Clinical Discussion: Since clinical trials didn't mention subtypes of S1P, can we assume that which subtype is impact doesn't impact the effectiveness? No comments or questions. The committee unanimously voted to accept the recommendations as presented. None were opposed.

Financial Discussion: No comments or questions. The committee unanimously voted to accept the recommendations as presented. None were opposed.

Outcome: Velsipity is a pharmacy benefit and will not be added to the Commercial, Marketplace, and GHP Kids formulary. The following prior authorization criteria will apply:

- Medical record documentation that Velsipity is prescribed by a gastroenterologist **AND**
- Medical record documentation of a diagnosis of moderate to severe ulcerative colitis **AND**
- Medical record documentation of age greater than or equal to 18 years **AND**
- Medical record documentation of therapeutic failure on, intolerance to, or contraindication to three (3) preferred formulary biologics for the treatment of ulcerative colitis **AND**
- Medical record documentation of therapeutic failure on, intolerance to, or contraindication to Entyvio AND infliximab **AND**
- Medical record documentation that Velsipity is not being used concurrently with a tumor necrosis factor (TNF) blocker or other biologic agent

AUTHORIZATION DURATION: Approval will be given for an initial duration of six (6) months. For continuation of coverage, medical record documentation of clinical improvement or lack of progression in the signs and symptoms of ulcerative colitis at six (6) months of Velsipity therapy is required.

After the initial six (6) month approval, subsequent approvals for coverage will be for a duration of one (1) year requiring medical record documentation of continued or sustained improvement in the signs and symptoms of ulcerative colitis while on Velsipity therapy.

QUANTITY LIMIT: 1 tablet per day

GPI LEVEL: GPI-12

Additional evidence of the criteria used to make this decision can be found in the drug review presented to the committee.

MOTPOLY XR (lacosamide extended-release)

Review: Motpoly XR (lacosamide extended-release) is an oral antiepileptic indicated for the treatment of partial-onset seizures in adults and in pediatric patients weighing at least 50kg. Lacosamide selectively enhances slow inactivation of voltage-gated sodium channels, resulting in stabilization of hyperexcitable neuronal membranes and inhibition of repetitive neuronal firing. Lacosamide also binds to the collapsin response mediator protein 2 (CRMP2), which may be involved in epileptogenesis.

New onset epilepsy is initially treated with antiseizure medication (ASM) monotherapy. Approximately half of this patient population will become seizure free with the first ASM prescribed. If treatment failure should occur, due to breakthrough seizures or drug intolerance, a second drug trial should be attempted. It is preferable to maintain a patient on a single ASM regimen, when possible, to decrease side effects and drug interactions, and increase compliance. If adjunctive therapy is warranted, lacosamide would be a

reasonable option in many cases given its lack of effect on steady-state concentrations of the following ASMs: levetiracetam, carbamazepine, carbamazepine epoxide, lamotrigine, topiramate, oxcarbazepine monohydroxy derivative (MHD), phenytoin, valproic acid, phenobarbital, gabapentin, clonazepam, and zonisamide. Lacosamide dose reduction may be needed in patients who are taking strong CYP3A4 or CYP2C9 inhibitors.

No single ASM is optimal for every patient and therefore selection of ASM must be individualized based on the following: drug effectiveness for seizure type, potential adverse effects, drug interactions, comorbid conditions, age, gender, childbearing plans, lifestyle and patient preferences, and cost. There have been a limited number of randomized controlled trials (RCT) comparing various antiseizure medications head-to-head as initial monotherapy. Those RCTs that have been conducted have shown similar effectiveness between the different medications. Based on these results as well as expert opinion, lacosamide is a reasonable choice in the following scenarios: for initial treatment of focal epilepsy, for older adults with focal epilepsy, for comorbid depression with focal epilepsy, and in those with hepatic failure* or after organ transplantation.

*The likelihood of lacosamide to induce liver injury is low. Less than 3 single cases have been reported in the literature. Lacosamide can only be said to be a possible hepatotoxin. Dose adjustment for mild or moderate hepatic impairment is recommended. Use in patients with severe hepatic impairment is not recommended per package labeling.

The efficacy of immediate-release lacosamide as adjunctive therapy in partial-onset seizures was established in three 12-week, randomized, double-blind, placebo-controlled, multicenter trials in adult patients. Patients diagnosed with partial-onset seizures with or without secondary generalization who were not adequately controlled with 1 to 3 concomitant ASMs were included. During an 8-week baseline period, patients were required to have an average of 4 or more partial-onset seizures per 28 days with no seizure-free period exceeding 21 days.

Study 2 compared doses of lacosamide 200, 400, and 600mg/day versus placebo. Study 3 compared doses of lacosamide 400 and 500mg/day versus placebo. Study 4 compared doses of lacosamide 200 and 400mg/day versus placebo. For those randomized to treatment, doses were initiated at 100mg/day (50mg twice daily) and increased weekly by 100mg/day to target dose. The titration period lasted 6 weeks in Studies 2 and 3, and 4 weeks in Study 4. The titration phase was followed by a maintenance phase that lasted 12 weeks during which patients were to remain on a stable dose of lacosamide.

The primary outcome was a reduction in 28-day seizure frequency in lacosamide-treated patients versus placebo. A statistically significant outcome was observed with the following lacosamide doses: 200mg/day, 400mg/day, and 600mg/day.

Adverse reactions that occurred in ≥2% of adult patients in lacosamide group in Studies 2, 3, and 4 include but are not limited to: vertigo, blurred vision, nausea/vomiting/diarrhea, fatigue, dizziness, headache, ataxia, somnolence, tremor, nystagmus, balance disorder, depression, and pruritis. Adverse reactions reported in clinical studies of pediatric patients were similar to those seen in adult patients. Post marketing adverse reactions include: blood and lymphatic system disorders (agranulocytosis), psychiatric disorders (aggression, agitation, hallucination, insomnia, psychotic disorder), skin and subcutaneous tissue disorders (angioedema, rash, urticaria, Stevens-Johnson syndrome, toxic epidermal necrolysis), and neurologic disorders (dyskinesia, and new or worsening seizures).

A Clinical Review including Clinical Information, Efficacy Evidence, Safety Evidence, Other Considerations and a Financial Review Based on Cost Analysis were presented.

Clinical Discussion: No comments or questions. The committee unanimously voted to accept the recommendations as presented. None were opposed.

Financial Discussion: No comments or questions. The committee unanimously voted to accept the recommendations as presented. None were opposed.

Outcome: Motpoly XR is a pharmacy benefit and will not be added to the Commercial, Exchange, or CHIP formularies. The following prior authorization criteria will apply:

- Medical record documentation of a diagnosis of partial-onset seizures **AND**
- Medical record documentation of weight greater than or equal to 50 kilograms (kg) **AND**
- Medical record documentation of a therapeutic failure on, intolerance to, or contraindication to three (3) formulary alternatives, one of which must be oral lacosamide immediate-release

QUANTITY LIMIT:

- Motpoly XR 100mg capsule (GPI 72600036007020): 1 capsule daily
- Motpoly XR 150mg capsule (GPI 73289006402): 2 capsules daily
- Motpoly XR 200mg capsule (GPI 72600036007030): 2 capsules daily

GPI LEVEL: GPI-12

RPH SIGNOFF REQUIRED: yes

FORMULARY ALTERNATIVES:

- For patients aged ≥ 1 month of age: lacosamide IR, carbamazepine, levetiracetam IR, phenobarbital, phenytoin, pregabalin
- Additional formulary alternatives for patients over certain ages: lamotrigine IR (2+), topiramate IR (2+), topiramate ER (2+), gabapentin (3+), oxcarbazepine (4+), divalproex (10+), levetiracetam ER (12+), tiagabine (12+), lamotrigine ER (13+), felbamate (14+), and zonisamide (16+)

Additional evidence of the criteria used to make this decision can be found in the drug review presented to the committee.

JESDUVROQ (daprodustat)

Review: Jesduvroq is a hypoxia-inducible factor prolyl hydroxylase (HIF PH) inhibitor indicated for the treatment of anemia due to chronic kidney disease in adults who have been receiving dialysis for at least four months. Jesduvroq has not been shown to improve quality of life, fatigue, or patient well-being. It is not indicated for use as a substitute for transfusion in patients requiring immediate correction of anemia and in patients not on dialysis.

Prior to initiation of Jesduvroq, other causes of anemia should be corrected and excluded (e.g. vitamin deficiency, metabolic or chronic inflammatory conditions, bleeding). Iron status should be evaluated before and during Jesduvroq treatment and supplemental iron therapy should be used when serum ferritin is less than 100 mcg/mL or when serum transferrin saturation is less than 20%. The majority of patients with CKD will require supplemental iron during the course of therapy. Serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, and total bilirubin should be evaluated prior initiation of Jesduvroq.

Jesduvroq dosing is individualized and patients should use the lowest dose sufficient to reduce the need for red blood cell transfusions. Jesduvroq can be administered without regard to timing or type of dialysis. For adults not being treated with an ESA, the starting dose of Jesduvroq is based on the hemoglobin level (Table 3).

Table 3. Starting Dose of Jesduvroq for Adults on Dialysis not Receiving an Erythropoiesis-Stimulating Agent

Pre-Treatment Hemoglobin Level (g/dL)	Starting Dose of JESDUVROQ (Once Daily Dosing)[a]
<9	4 mg
≥9 to ≤10	2 mg
>10	1 mg

For adults being switched from an ESA to Jesduvroq, the starting dose is based on the dose regimen of the ESA at the time of substitution (Table 4).

Table 4. Starting Dose of Jesduvroq for Adults on Dialysis Switching from an Erythropoiesis-Stimulating Agent

Current Dose of ESA			Dose of JESDUVROQ[a]
Epoetin Alfa[b] Intravenous (units/week)	Darbepoetin Alfa Subcutaneous /Intravenous (mcg/4 weeks)	Methoxy PEG-Epoetin Beta Subcutaneous /Intravenous (mcg/month)	Once Daily Dosing
Less than or equal to 2,000	20 to 30	30 to 40	4 mg
Greater than 2,000 to less than 10,000	Greater than 30 to 150	Greater than 40 to 180	6 mg
Greater than or equal to 10,000 to less than 20,000	Greater than 150 to 300	Greater than 180 to 360	8 mg
Greater than or equal to 20,000	Greater than 300	Greater than 360	12 mg

ESA = Erythropoiesis stimulating agent.

Hemoglobin levels should be monitored every 2 weeks for the first month following initiation of therapy and after each dose adjustment, then every 4 weeks thereafter. The dosage of Jesduvroq should not be increased more frequently more than once every 4 weeks. When the dose is adjusted, it should be increased or decreased by one dose level at a time (Table 5).

Table 5. Dose Levels of Jesduvroq

Daily dose of JESDUVROQ	1 mg	2 mg	4 mg	6 mg	8 mg	12 mg	16 mg	24 mg[a]

[a] 24 mg is the maximum recommended once daily dose.

The dosage of Jesduvroq should be decreased if hemoglobin increases rapidly (greater than 1 g/dL over 2 weeks or greater than 2 g/dL over 4 weeks) or if hemoglobin exceeds 11 g/dL. If hemoglobin exceeds 12 g/dL, Jesduvroq treatment should be interrupted. When hemoglobin is within target range, treatment may be restarted at one dose level lower. Treatment should not be continued between 24 weeks of therapy if a clinically meaningful increase in hemoglobin level is not achieved.

The starting dose of Jesduvroq should be reduced by half in patients with moderate or hepatic impairment except in patients whose starting dose is 1 mg. Use of Jesduvroq in patients with severe hepatic impairment is not recommended. The starting dose of Jesduvroq should also be reduced by half in patients who are on clopidogrel or a moderate CYP2C8 inhibitor except in patients whose starting dose is already 1 mg.

Jesduvroq is supplied as 1 mg, 2 mg, 4 mg, 6 mg, and 8 mg tablets

The efficacy of Jesduvroq was evaluated in the ASCEND-D trial, a randomized, sponsor-blind, active-controlled, event-driving clinical trial in 2,964 adults with anemia due to CKD on dialysis and receiving an ESA at the time of study entry. Patients were stratified by dialysis type and were required to be on dialysis for at least 4 months prior to first dose of Jesduvroq. Patients on hemodialysis (HD) were randomized 1:1 to receive oral Jesduvroq (n=1316) or intravenous epoetin alfa (n=1308) while patients on peritoneal dialysis (PD) were randomized to receive oral Jesduvroq (n=171) or subcutaneous darbepoetin alfa (n=169). The trial excluded patients with ferritin ≤100 ng/ml (≤100 mcg/L), transferrin saturation ≤20% at screening; evidence of non-renal anemia; cardiovascular abnormalities (including myocardial infarction, acute coronary syndrome, stroke or transient ischemic attack within 4 weeks of screening, New York Heart Association (NYHA) Class IV heart failure, and uncontrolled hypertension); liver disease; history of malignancy within 2 years of screening; current treatment of cancer and complex kidney cyst.

Dosing in each treatment arm followed a protocol-specified adjustment algorithm to achieve and/or maintain a hemoglobin target of 10 to 11 g/dL. The starting dose was 4 mg, 6 mg, 8 mg, or 12 mg orally once daily based on prior ESA dose. Patients receiving other ESAs were switched to epoetin alfa or darbepoetin alfa equivalent starting dose. The median doses at week 52 were Jesduvroq 6 mg, epoetin alfa 8,000 units per week, and darbepoetin alfa 150 mcg every four weeks.

The two co-primary endpoints evaluating safety and efficacy were the mean change in hemoglobin from baseline to evaluation period (Weeks 28 to 52) and time to first adjudicated MACE (defined as all-cause mortality, non-fatal myocardial infarction, or non-fatal stroke), using a non-inferiority comparison to rhEPO (epoetin alfa and darbepoetin alfa) for both endpoints.

The lower limit of the 95% confidence interval (CI) for the overall hemoglobin treatment difference was greater than the pre-specified non-inferiority margin of -0.75 g/dL, demonstrating non-inferiority of Jesduvroq to rhEPO with respect to mean change in hemoglobin between baseline and over the Evaluation Period. Results were comparable between hemodialysis and peritoneal dialysis.

The hazard ratio for the time to first occurrence of MACE, a composite of all-cause mortality, non-fatal myocardial infarction, and non-fatal stroke, comparing Jesduvroq to rhEPO was 0.93 and non-inferiority was achieved for this endpoint.

Jesduvroq carries a black box warning for increased risk of death, myocardial infarction, stroke, venous thromboembolism, and thrombosis of vascular access. Jesduvroq increases the risk of arterial and venous thrombotic events, which may be fatal. It should be avoided in patients with a history of myocardial infarction, cerebrovascular event, or acute coronary syndrome within the 3 months prior to starting Jesduvroq. A rate of hemoglobin rise of greater than 1 g/dL over two weeks and targeting a hemoglobin level greater than 11 g/dL may further increase the risk of death and thrombotic events, as occurs with ESAs. No trial has identified a hemoglobin target level, dose of Jesduvroq, or dosing strategy that does not increase these risks. Other warnings include risk of hospitalization for heart failure, hypertension, gastrointestinal erosion, serious adverse events in patients with anemia due to chronic kidney disease and not on dialysis, and malignancy.

In the ASCEND-D trial, Jesduvroq was found to be non-inferior to rhEPO on the time to first occurrence of major adverse cardiovascular events (MACE) in adults with anemia due to CKD who were on dialysis. Permanent discontinuation due to adverse reaction was reported in 19% of patients treated with Jesduvroq compared to 18% of patients treated with rhEPO. The most common adverse reactions in Jesduvroq treated patients were hypertension, thrombotic vascular events, and abdominal pain. Adjudicated thrombotic vascular events (fatal and non-fatal) were observed in 9.8 per 100 PY of patients treated with Jesduvroq and in 11.7 per 100 PY of patients treated with rhEPO.

Drug interactions include CYP2C8 inhibitors and inducers. Concomitant administration of strong CYP2C8 inhibitors is contraindicated due to marked increase in Jesduvroq exposure. Concomitant administration of CYP2C8 inhibitors can increase Jesduvroq exposure and the starting dose of Jesduvroq should be reduced when initiation treatment. CYP2C8 inducers may decrease Jesduvroq exposure, which may

result in loss of efficacy. Hemoglobin should be monitored when initiating or stopping concomitant treatment with CYP2C8 inducers and the dosage of Jesduvroq should be adjusted as necessary.

The safety and efficacy of Jesduvroq has not been established in pediatric patients. Of the 2,964 patients treated with Jesduvroq in ASCEND-D, 480 (32%) patients were 65 years and older and 159 (11%) were 75 years and older. No overall differences in safety or efficacy were observed between older and younger patients. No other reported clinical experience has identified differences in responses between older and younger patients.
No hepatic adjustment is required in patients with mild hepatic impairment. The recommended starting dose of Jesduvroq should be reduced by half in patients with moderate hepatic impairment except in patients whose starting dose is already 1 mg. Jesduvroq has not been studied and is not recommended in patients with severe hepatic impairment.

A Clinical Review including Clinical Information, Efficacy Evidence, Safety Evidence, Other Considerations and a Financial Review Based on Cost Analysis were presented.

Clinical Discussion: Dr. Bret Yarczower asked if for prior authorization requests we still see instances where a patient has low iron levels, but provider requests ahead of time in the event they are still anemic after iron is restored. Keith Hunsicker, Pharm.D., said that in general he doesn't see that as much as he used to. But we do sometimes have trouble with providers obtaining and submitting up-to-date levels for initial and reauthorization. The committee unanimously voted to accept the recommendations as presented. None were opposed.

Financial Discussion: No comments or questions. The committee unanimously voted to accept the recommendations as presented. None were opposed.

Outcome: Jesduvroq is a pharmacy benefit and will not be added to the Commercial, Marketplace, and GHP Kids formulary. The following prior authorization criteria will apply:

- Medical record documentation of age greater than or equal to 18 years **AND**
- Medical record documentation of a diagnosis of anemia due to chronic kidney disease **AND**
- Medical record documentation that member has been receiving dialysis for at least four months **AND**
- Medical record documentation of a Hemoglobin less than or equal to 11 g/dL **AND**
- Medical record documentation of ferritin greater than or equal to 100 ng/mL or transferrin saturation level greater than or equal to 20% or history of chelation therapy for iron

GENERAL GUIDANCE:

- For continuation of therapy, a repeat Hgb should be submitted after 12 months of therapy.
- In individuals whose Hgb is greater than or equal to 12g/dL or rises by 1g/dL in any two-week period, additional doses should be withheld.
- For initiation or continuation of therapy, a ferritin level no greater than 3 months old and/ or transferrin saturation level no greater than 6 months old should be submitted.
- The member should receive supplemental iron if serum ferritin is less than 100ng/ml and transferrin saturation is less than 20 percent.

AUTHORIZATION DURATION: Approval of Jesduvroq will be given for an initial duration of 12 months. Subsequent authorization will be considered based on the stated criteria.

QUANTITY LIMIT:

- 1 mg, 2 mg, 4 mg tablets: 1 tablet per day
- 6 mg tablets: 2 tablets per day
- 8 mg tablets 3 tablets per day

GPI LEVEL: GPI-12

RPH SIGNOFF REQUIRED: yes

Additional evidence of the criteria used to make this decision can be found in the drug review presented to the committee.

LODOCO (colchicine 0.5 mg)

Review: Lodoco is an alkaloid indicated to reduce the risk of myocardial infarction (MI), stroke, coronary revascularization, and cardiovascular death in adult patients with established atherosclerotic disease or with multiple risk factors for cardiovascular disease. The recommended dosage is 0.5 mg tablet orally once daily, available as a blister pack of 30 tablets.

The efficacy was determined based on the LoDoCo2 trial, a randomized, double-blind, placebo controlled, investigator-initiated, event-driven study to assess the efficacy of Lodoco in patients with stable coronary artery disease (as evidenced by coronary angiography, CT coronary angiography or a Coronary Artery Calcium (CAC) Score >400). The primary end point was a composite of cardiovascular death, spontaneous (nonprocedural) myocardial infarction, ischemic stroke, or ischemia-driven coronary revascularization. A total of 5522 patients were randomized, 2762 assigned to receive Lodoco 0.5 mg once daily and 2760 to placebo. Pertinent exclusion criteria were eGFR <50mL/min/1.73m2, severe heart failure (NYHA Class 3 or 4), and severe valvular disease. The mean age was 66±8.6 years and only 15.3% of patients were female. 84.4% had a history of acute coronary syndrome. Most patients also received standard of care therapy for secondary ASCVD prevention (99.7% were taking an antiplatelet or an anticoagulant, 96.6% were taking a lipid-lowering agent, 62.1% a beta-blocker, and 71.7% a renin–angiotensin system inhibitor). The median time on study medication was 28.6 months. A primary endpoint event occurred in 6.8% of patients in Lodoco group vs. 9.6% of patients receiving placebo (HR: 0.69; 95% [CI] 0.57 to 0.83; p<0.001).

In terms of safety, non-cardiovascular deaths occurred more frequently among the patients who received Lodoco than among those who received placebo, with incidence rates of 0.7 and 0.5 events, respectively, per 100 person-years (hazard ratio, 1.51; 95% CI, 0.99 to 2.31). In addition, among patients from Netherlands, myalgia was reported in 384 (21.2%) in the Lodoco group and 334 (18.5%) in the placebo group (cumulative incidence ratio, 1.15; 95% CI, 1.01 to 1.31). The use of LODOCO in patients with renal failure (CrCl < 15 mL/minute), severe hepatic dysfunction, pre-existing blood dyscrasias, and concomitant use of strong CYP3A4 inhibitors or P-glycoprotein inhibitors is contraindicated.

2023 AHA/ACC guidelines for the management of patients with chronic coronary disease state that in patients with chronic coronary disease, the addition of colchicine for secondary prevention may be considered to reduce recurrent ASCVD events (Class of Recommendation: 2b [weak] {benefit ≥ risk}; Level of Evidence: B-randomized).

A Clinical Review including Clinical Information, Efficacy Evidence, Safety Evidence, Other Considerations and a Financial Review Based on Cost Analysis were presented.

Clinical Discussion: No comments or questions. The committee unanimously voted to accept the recommendations as presented. None were opposed.

Financial Discussion: Dr. Alfred Denio asked what would keep the providers from prescribing the more cost-effective 0.6 mg colchicine for this indication. Tricia Heitzman, Pharm.D., stated there is nothing stopping them from doing this and it's reasonable to assume that providers may do this even though it hasn't been studied in that strength for this indication. We did not feel it was reasonable to make members try the 0.6 mg before receiving the Lodoco since they do not share the same indication. The committee unanimously voted to accept the recommendations as presented. None were opposed.

Outcome: Lodoco will be a pharmacy benefit and will be added to the Brand Non-Preferred Tier of the Commercial, Exchange, and CHIP formularies. The following prior authorization criteria will apply:

- Medical record documentation that patient is 18 years of age or older **AND**
- Medical record documentation that Lodoco is being prescribed to reduce the risk of myocardial infarction (MI), stroke, coronary revascularization, and cardiovascular death **AND**
    - The patient has established atherosclerotic disease [Clinical ASCVD includes acute coronary syndromes, history of myocardial infarction (MI), angina, coronary or other arterial revascularization, stroke, transient ischemic attack (TIA), or peripheral arterial disease (PAD)] **OR**
    - The patient has 2 or more risk factors for cardiovascular disease (e.g., family history of premature ASCVD, primary hypercholesteremia, metabolic syndrome, chronic kidney disease (CKD), current smoker, congestive heart failure, coronary artery calcium (CAC) score > 400, etc.) **AND**
- The patient is currently receiving standard of care therapy for chronic coronary disease (e.g., antiplatelets, anticoagulants, lipid-lowering agents, beta-blockers, renin-angiotensin inhibitors) unless contraindicated or not tolerated **AND**
- Patient has a creatinine clearance ≥ 15 mL/min/1.73m^2

QUANTITY LIMIT: 30 tablets per 30 days

GPI LEVEL: GPI-12

RPH SIGNOFF REQUIRED: yes

Additional evidence of the criteria used to make this decision can be found in the drug review presented to the committee.

IYUZEH (latanoprost ophthalmic solution)

Review: Iyuzeh is a prostaglandin F2α analogue that is FDA approved for the reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma (OAG) or ocular hypertension. Iyuzeh is an opalescent, white to slightly yellow ophthalmic solution. It is the first and only formulation containing latanoprost 0.005% (50 mcg/mL) that is free of preservatives, including the commonly used benzalkonium chloride (BAK). Iyuzeh is supplied as a 30-count carton containing 6 foil packs, each with 5 single-dose containers.

Iyuzeh is dosed as one drop in the affected eye(s) once daily in the evening. For contact wearers, contacts should be removed prior to and not reinserted for at least 15 minutes after administration. If a dose is missed, treatment should just continue with the next regularly scheduled dose. Reduction in IOP will start to be seen around 3 to 4 hours after administration, and maximum IOP reduction after 8 to 12 hours. The dose is to be used immediately after opening to one or both eyes. Since there are no preservatives, the remaining contents should be discarded immediately after use. If one or more ophthalmic drugs are in use, they should be administered at least 5 minutes apart. It is not recommended to use more than one drop daily into each eye or to use two or more prostaglandins or prostaglandin analogs at a time. It has been shown the IOP lowering effects are decreased and/or cause paradoxical elevations in IOP.

Due to effectiveness of IOP lowering, good tolerability, and once-daily dosing schedule, topical ophthalmic prostaglandins are initial therapy in open-angle glaucoma. Latanoprost, followed by Travoprost, are have the highest effect with least side effect profile compared to Bimatoprost. Ophthalmic beta-blockers are good as an additional, secondary treatment or primary treatment who cannot afford prostaglandins. Other drug classes are an option, although that first-line due to tolerability issues, such as alpha-adrenergic agonists, topical carbonic anhydrase inhibitors, and cholinergic agonists. Non-pharmacologic treatment option is laser therapy.

No major clinical trials were conducted for Iyuzeh, except to compare its' safety profile to its' similar, non-preservative free option, Xalatan (latanoprost) 0.005%. Similar adverse reactions were reported with comparable frequency in both products. No statistically significant difference in their safety profile was found. No studies were conducted to compare efficacy.

A Clinical Review including Clinical Information, Efficacy Evidence, Safety Evidence, Other Considerations and a Financial Review Based on Cost Analysis were presented.

Clinical Discussion: No comments or questions. The committee unanimously voted to accept the recommendations as presented. None were opposed.

Financial Discussion: No comments or questions. The committee unanimously voted to accept the recommendations as presented. None were opposed.

Outcome: Iyuzeh is a pharmacy benefit and will not be added to Commercial, Exchange, or CHIP formularies. Iyuzeh will require a prior authorization with the following criteria:

- Medical record documentation of therapeutic failure on, intolerance to, or contraindication to latanoprost **AND** tafluprost **AND** travoprost

QUANTITY LIMIT: 30 single-dose container (6mL) per 30 days

GPI LEVEL: GPI-12

FORMULARY ALTERNATIVES: latanoprost, tafluprost*, travoprost, Xelpros*, Lumigan*, Vyzulta*

RPH SIGNOFF REQUIRED: yes

Additional evidence of the criteria used to make this decision can be found in the drug review presented to the committee.

APHEXDA (motixafortide)

Review: Aphexda is a hematopoietic stem cell mobilizer, indicated with filgrastim (G-CSF) to mobilize hematopoietic stem cells to the peripheral blood for collection and subsequent autologous transplantation in patients with multiple myeloma. Aphexda inhibits the C-X-C Motif Chemokine Receptor 4 (CXCR4) and blocks the binding of its cognate ligand, stromal-derived factor-1α (SDF-1α)/C-X-C Motif Chemokine Ligand 12 (CXCL12) which plays a role in trafficking human hematopoietic stem cells to the marrow compartment. Treatment with Aphexda results in leukocytosis and elevations in circulating hematopoietic stem and progenitor cells into peripheral circulation. In a rodent transplantation model, stem cells mobilized by Aphexda were capable of engraftment with long-term repopulating capacity.

Aphexda is the second FDA approved stem cell mobilizer. Mozobil is a stem cell mobilizer indicated in combination with filgrastim in patients with non-Hodgkin's lymphoma and multiple myeloma. Mozobil was approved in 2008 and is available generically. There have been no head to head trials comparing Aphexda and Mozobil and it is unclear if there is a clinical advantage to using one product over another.

The recommended dosage of Aphexda is 1.25 mg/kg administered via slow (approximately 2 minutes) subcutaneous injection 10 to 14 hours prior to the initiation of the first apheresis. A second dose can be administered 10 to 14 hours before a third apheresis if necessary. Prior to each dose of Aphexda, all patients should be premedicated to reduce the risk of hypersensitivity and injection site reactions. Patients should be received diphenhydramine, an H2 blocker, and a leukotriene inhibitor approximately 30 to 60 minutes before injection of Aphexda. The additional of an analgesic medication is also recommended. Filgrastim 10 mcg/kg should be administered subcutaneously once daily starting 4 days

prior to the first dose of Aphexda and on each day prior to each apheresis. Aphexda is supplied as 62 mg lyophilized powder in a single-dose vial for reconstitution.

The efficacy of Aphexda was evaluated in the GENESIS trial, a randomized, double-blind, placebo-controlled study in 122 patients with multiple myeloma. Patients were randomized 2:1 to receive Aphexda 1.25 mg/k subcutaneously (n=80) or placebo (n=42). Prior to receiving Aphexda or placebo, patients received daily morning dose of filgrastim 10-15 mcg/kg for 4 days. On day 5, patients received the 5th morning dose of filgrastim within 1 hour prior to their first apheresis (12 hours ± 2 hours from Aphexda/placebo administration). The apheresis cell collection goal for the study was ≥ 6 x 106 CD34+ cells/kg. The assessment of CD34+ cells was performed by central and local laboratories. Central laboratory assessments were used for the efficacy results. Local laboratory results were used for clinical treatment decisions.

In the event that the cell collection goal was not achieved with the first apheresis on Day 5, patients received another morning dose of filgrastim on Day 6 within 1 hour prior to their second apheresis. In the event that the cell collection goal was still not achieved, patients received a second administration of APHEXDA or placebo on the evening of Day 6 and a seventh dose of filgrastim in the morning of Day 7 within 1 hour prior to a third apheresis. If the collection goal was not achieved, patients received an eighth dose of filgrastim in the morning of Day 8 within 1 hour prior to a fourth apheresis.

The efficacy of Aphexda was based on the proportion of patients who achieved a cell collection goal of ≥ 6 x 106 CD34+ cells/kg in up to 2 apheresis after administration of filgrastim and a single administration of Aphexda or placebo. Efficacy results showed that 67.5% of patients treated with Aphexda achieved the cell collection goal in up to 2 apheresis after a single administration of Aphexda compared to 9.5% of patients treated with placebo.

The safety profile of Aphexda is similar to that of Mozobil. Warnings and precautions include anaphylactic shock and hypersensitivity reactions, injection site reactions, tumor cell mobilization in patients with leukemia, leukocytosis, potential for tumor cell mobilization, and embryo fetal toxicity. Serious adverse reactions occurred in 5.4% of patients receiving Aphexda in combination with filgrastim. Serious adverse reactions included vomiting, injection site reaction, hypersensitivity reaction, injection site cellulitis, hypokalemia, and hypoxia. One patient did not receive the 5th dose of filgrastim due to elevated white blood cell count following administration of Aphexda. The most common adverse reactions occurring in Genesis were injection site reactions, injection site pain, injection site erythema, injection site pruritis, pruritis, flushing, and back pain.

The safety and efficacy of Aphexda have not been established in pediatric patients. Of the total number of patients in the GENESIS study, 33.8% were ≥ 65 years old, and 1.25% were ≥ 75 years old in the Aphexda arm. No overall differences were observed between older and younger patients.

A Clinical Review including Clinical Information, Efficacy Evidence, Safety Evidence, Other Considerations and a Financial Review Based on Cost Analysis were presented.

Clinical Discussion: No comments or questions. The committee unanimously voted to accept the recommendations as presented. None were opposed.

Financial Discussion: No comments or questions. The committee unanimously voted to accept the recommendations as presented. None were opposed.

Outcome: Aphexda is a medical benefit and will require a prior authorization. It will be added to medical benefit cost share list. When processed at a Specialty Pharmacy, Aphexda will process on the Specialty tier or Brand Non-preferred tier for members with a three-tier benefit. The following prior authorization criteria will be required:

- Medical record documentation of age greater than or equal to 18 years **AND**
- Medical record documentation that Aphexda is prescribed by a hematologist or oncologist **AND**

- Medical record documentation that Aphexda will be used in combination with filgrastim for the mobilization and collection of hematopoietic stem cells for subsequent autologous stem cell transplantation **AND**
- Medical record documentation of therapeutic failure, intolerance, or contraindication to plerixafor

AUTHORIZATION DURATION: 1 month

QUANTITY LIMIT: 30 day supply per fill

RPH SIGNOFF REQUIRED: Yes

FORMULARY ALTERNATIVES: plerixafor

Additional evidence of the criteria used to make this decision can be found in the drug review presented to the committee.

DAXXIFY (daxibotulinumtoxinA-lanm)

Review: Daxxify (daxibotulinumtoxinA-lamn) is an acetylcholine release inhibitor and neuromuscular blocking agent approved by the FDA in 2022 for cosmetic use of temporary improvement in the appearance of moderate to severe glabellar lines associated with corrugator and/or procerus muscle activity in adult patients. Daxxify (daxibotulinumtoxinA-lamn) received an additional approval in Aug 2023 for use in the treatment of cervical dystonia in adult patients.

Cervical dystonia (CD), also called spasmodic torticollis or torticollis, is one of the most common adult-onset focal dystonias. CD causes involuntarily neck muscle contractions which presents as abnormal movements, postures and positioning of the neck and head. These abnormal spasms can cause pain and discomfort with varying levels of severity. The spasms can present as sustained, continuous; or can resemble a tremor. CD affects women about twice as often as men with an average onset of age at development of 40 and 60 years old.

First line treatment therapy for cervical dystonia are botulinum toxins. There are currently five products available, which includes Daxxify (daxibotulinumtoxinA-lamn), Botox(onabotulinumtoxinA), Dysport(abobotulinumA), Xeomin (incobotulinumtoxinA), and Myobloc (rimabotulimuntoxinB) all of which are currently being used to treat cervical dystonia and other spastic diseases. Similarly to Daxxify(daxibotulinumtoxinA-lamn), these agents are not to be administered more frequently than every 12 weeks, however, in some circumstances, the neuromuscular blocking effect tends to wear off prior to the next administration. During clinical trial, Daxxify(daxibotulinumtoxinA-lamn) effects lasted at least the duration or longer than the treatment interval, which can potentially provide an advantage to other botulinum toxin products currently available. Daxxify (daxibotulinumtoxinA-lamn) is formulated with a thirty-five amino acid peptide excipient (RTP004) that prevents surface adsorption and thermal stability. All other botulinum toxin products contain human serum albumin (HSA) as an excipient for stability. Preclinical research suggests that the RTP004 protein in Daxxify (daxibotulinumtoxinA-lamn) adheres the botulinum toxin to the nerves close to the injection site, potentially making its effect last longer. Daxxify (daxibotulinumtoxinA-lamn) is supplied as a sterile lyophilized powder single dose unit vial of either 50 units or 100 units. The recommended dose for cervical dystonia is 125 units to 250 units divided among the affected muscle administered not more frequently than every 12 weeks.
The efficacy and safety of Daxxify (daxibotulinumtoxinA-lamn) was evaluated in two trials ASPEN-1 and ASPEN-OLS. ASPEN-1 was a randomized, double-blind, placebo-controlled, multicenter trial with 301 patients (NCT03608397). The average age of the patients were 58 years with 65% being women, and 96% being of white race. At study baseline, 84% of patients had previously received a botulinum toxin as treatment for cervical dystonia with a wash out period of ≥14 weeks. Patients had a clinical diagnosis of cervical dystonia with a baseline Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) total score ≥ 20, TWSTRS severity score ≥15, TWSTRS disability score ≥3, and TWSTRS pain score ≥1. The

Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) assesses the character and severity of cervical dystonia with a range from 0 to 85.

Patients were randomized (3:3:1) to receive a single administration of 2.5 mL of either Daxxify (daxibotulinumtoxinA-lamn) 125 units (n=125), Daxxify (daxibotulinumtoxinA-lamn) 250 units (n=130), or placebo (n=46), divided amongst the affected muscles as selected by the investigator. The primary endpoint was the mean change in the TWSTRS total score from baseline averaged over weeks 4 and 6.

The mean change from baseline in the total TWSTRS score was significantly greater for both dosage groups of Daxxify (daxibotulinumtoxinA-lamn) compared to placebo. ASPEN-OLS was a safety study conducted over a 52-week, open-label, repeat-dose in CD that included 357 adult patients (271 from ASPEN-1 and 86 newly enrolled) who met diagnostic criteria for CD. These patients received up to four sequential doses of 125 units, 200 units, 250 units, or 300 units of Daxxify (daxibotulinumtoxinA-lamn) for up to 88 weeks. Participants showed improvements in TWSTRS at Weeks 4 and 6, with a median duration of effect of 19.9 to 26.0 weeks. Patients in ASPEN-OLS received up to four treatments with Daxxify. Adverse reactions were reported in 138 patients (20%). Common treatment-related adverse events (≥5%) were headache (9%), injection site pain (8%), injection site erythema (5%), muscular, weakness (5%), and upper respiratory tract infection (5%). Dysphagia rates were 2.7% and 4.2% in ASPEN-1 and ASPEN-OLS, respectively. A Black Box warning exists to acknowledge the risk of toxin spread from local injection site to other areas of the body unintended. Other warnings and precautions to consider include cardiovascular events, exacerbation of neuromuscular compromise in patients with pre-existing condition, breathing, and swallowing difficulties.

A Clinical Review including Clinical Information, Efficacy Evidence, Safety Evidence, Other Considerations and a Financial Review Based on Cost Analysis were presented.

Clinical Discussion: No comments or questions. The committee unanimously voted to accept the recommendations as presented. None were opposed.

Financial Discussion: No comments or questions. The committee unanimously voted to accept the recommendations as presented. None were opposed.

Outcome: Daxxify (daxibotulinumtoxinA-lamn) is a Medical Benefit on the Specialty Tier that will require a prior authorization and will be added to Medical Policy MBP 011 Botulinum Toxin and Derivatives with the applicable clinical criterial for its FDA approval:

- Medical record documentation of age > or = 18
- Medical record documentation of a diagnosis of **Cervical Dystonia (Spasmodic torticollis) AND**
- Medical record documentation that the proposed injection sites and dosage regimen are consistent with Food and Drug Administration (FDA)-approved package labeling, nationally recognized compendia, or peer-reviewed medical literature for the requested indication

AUTHORIZATION DURATION: 12 months

RE-AUTHORIZATION CRITERIA:

- Medical record documentation of continued disease improvement or lack of disease progression** **AND**
- Medical record documentation of one of the following:
    - Repeated administrations are not being given more frequently than once every 12 weeks **OR**
    - Peer-reviewed literature citing well-designed clinical trials to indicate that the member's healthcare outcome will be improved by dosing more frequently than every 12 weeks.

QUANTITY LIMIT: 300 units per 12 weeks

GPI LEVEL: GPI-12

RPH SIGNOFF REQUIRED: Yes

FORMULARY ALTERNATIVES: Botox, Dysport, Xeomin, Myobloc

Additional evidence of the criteria used to make this decision can be found in the drug review presented to the committee.

UPDATES

DAY SUPPLY UPDATE

Background: Medications considered specialty and/or on the specialty tier are limited to a 34 day supply.

Recommendations: In order to allow claims to process at the appropriate day supply we added Ajovy and Keytruda to the minimum/maximum day supply list for Commercial/Exchange/CHIP. The following updates were made:

- Ajovy- minimum day supply: 30; maximum day supply: 90
- Keytruda- minimum day supply: 21; maximum day supply: 42

Discussion: No comments or questions. The committee unanimously voted to accept the recommendations as presented. None were opposed.

Outcome: The committee unanimously voted to accept the recommendations as presented. None were opposed.

Additional evidence of the criteria used to make this decision can be found in the drug review presented to the committee.

Meeting adjourned at 3:10 pm.

The next bi-monthly scheduled meeting will be held on May 21st, 2024 at 1:00 p.m.

Meeting will be held virtually via phone/Microsoft Teams.