P&T Committee Meeting Minutes
Commercial, Exchange, CHIP
January 14, 2025

Present (via Teams):	**Absent:**
Bret Yarczower, MD, MBA – Chair	Michael Evans, RPh
Amir Antonious, Pharm.D.	Nichole Hossler, MD
Leslie Astleford, Pharm.D.	Jason Howay, Pharm.D.
Emily Bednarz, Pharm.D.	Jamie Miller, RPh
Kristen Bender, Pharm.D.	Andrei Nemoianu, MD
Jeremy Bennett, MD	Jonas Pearson, RPh
Angela Bolesta, Pharm.D.	
Kim Castelnovo, RPh	
Kimberly Clark, Pharm.D.	
Bhargavi Degapudi, MD	
Keri Donaldson, MD, MSCE	
Michael Dubartell, MD	
Kelly Faust, Pharm.D.	
Tricia Heitzman, Pharm.D.	
Keith Hunsicker, Pharm.D.	
Kelli Hunsicker, Pharm.D.	
Emily Jacobson, Pharm.D.	
Dennis Janosczyk, Pharm.D.	
Alexandra Kempf-Malys, MSW, BSc	
Kerry Ann Kilkenny, MD	
Philip Krebs, R.EEG T	
Briana LeBeau, Pharm.D.	
Ted Marines, Pharm.D.	
Lisa Mazonkey, RPh	
Tyreese McCrea, Pharm.D.	
Perry Meadows, MD	
Mark Mowery, Pharm.D.	
Austin Paisley, Pharm.D.	
Lauren Pheasant, Pharm.D.	
Kimberly Reichard, Pharm.D.	
Melissa Sartori, Pharm.D.	
Kristen Scheib, Pharm.D.	
Michael Shepherd, MD	
Kirsten Smith, Pharm.D.	
Aubrielle Smith-Masri, Pharm.D.	
Michael Spishock, RPh	
Todd Sponenberg, Pharm.D.	
Jill Stone, Pharm.D.	
Luke Sullivan, DO	
Kevin Szczecina, RPh	
Amanda Taylor, MD	
Ariana Wendoloski, Pharm.D.	
Brandon Whiteash, Pharm.D.	
Margaret Whiteash, Pharm.D.	
Jeremy Garris, Pharm.D. (non-voting participant)	
Abigail Chua, MD (non-voting participant)	
Scott Friedenberg, MD (non-voting participant)	
Jonathan Spahr, MD (non-voting participant)	
Abigail Perriello, PharmD. (pharmacy resident)	

Call to Order:
Dr. Bret Yarczower called the meeting to order at 1:02 p.m., Tuesday, January 14, 2025.

Review and Approval of Minutes:
Dr. Bret Yarczower asked for a motion or approval to accept the October 2024 e-vote and November 19, 2024 minutes as written. Minutes approved unanimously. None were opposed.

DRUG REVIEWS

ITOVEBI (inavolisib)

Review: Itovebi is indicated in combination with palbociclib and fulvestrant for the treatment of adults with endocrine-resistant, PIK3CA-mutated, hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer, as detected by an FDA-approved test, following recurrence on or after completing adjuvant endocrine therapy. Itovebi + palbociclib + fulvestrant is the only PI3Kα inhibitor-based first-line treatment regimen for patients with HR+,HER2- breast cancer with PIK3CA mutations. Piqray and Truqap also target PIK-3CA but are considered for second-line therapies and beyond. Itovebi is also being evaluated in the INAVO121 trial, and ongoing clinical trial comparing it to Piqray for second-line treatment.

The recommended dosage of Itovebi is 9 mg orally once daily, with or without food, until disease progression or unacceptable toxicity. Itovebi is administered in combination with palbociclib and fulvestrant. The recommended dosage of palbociclib is 125 mg orally once daily for 21 consecutive days followed by 7 days off treatment for a 28-day cycle. In the event of adverse reactions the dosage can be reduced to 6 mg daily for the first reduction and to 3 mg daily for the second reduction. For patients with moderate renal impairment, the recommended starting dose is 6 mg orally once daily. Itovebi is supplied as 3 mg and 9 mg tablets.

The safety and efficacy of Itovebi in combination with palbociclib and fulvestrant was evaluated in INAVO120, a randomized, double-blind, placebo-controlled trial in adult patients with endocrine-resistant, PIK3CA-mutated, HR-positive, HER2-negative (defined as IHC 0 or 1+, or IHC 2+/ISH-), locally advanced or metastatic breast cancer whose disease progressed during or within 12 months of completing adjuvant endocrine therapy and who have not received prior systemic therapy for locally advanced or metastatic disease.

Primary endocrine resistance was defined as relapse while on the first 2 years of adjuvant endocrine therapy (ET) and secondary endocrine resistance was defined as relapse while on adjuvant ET after at least 2 years or relapse within 12 months of completing adjuvant ET. Tamoxifen (57%) and aromatase inhibitors (50%) were the most commonly used adjuvant endocrine therapies. Sixty-four percent of patients were considered to have secondary endocrine resistance. Eighty-three percent of patients had received prior chemotherapy (in the neo/adjuvant setting) and 1.2% of patients had been treated with a CDK4/6 inhibitor.

Patients were treated with Itovebi 9 mg (n=161) or placebo (n=164) orally once daily, in combination with palbociclib and fulvestrant. Treated was continued until disease progression or unacceptable toxicity.

The major efficacy outcome measure was investigator (INV)-assessed progression-free survival (PFS) per RECIST v.1.1. Additional outcome measures included overall survival (OS), INV-assessed objective response rate (ORR), and INV-assessed duration of response (DOR). Results are shown in Table 5. At the time of PFS analysis, OS data was not mature with 30% deaths in the overall population.

Table 5. Efficacy Results in Patients with Locally Advanced or Metastatic Breast Cancer in INAVO120[1]

Efficacy Endpoint	ITOVEBI + Palbociclib + Fulvestrant N=161	Placebo + Palbociclib + Fulvestrant N=164
Progression-Free Survival[a,b]		
Patients with event, n (%)	82 (51)	113 (69)
Median, months (95% CI)	15.0 (11.3, 20.5)	7.3 (5.6, 9.3)
Hazard ratio (95% CI)	0.43 (0.32, 0.59)	
p-value	< 0.0001	
Objective Response Rate[a,b,c]		
Patients with CR or PR, n (%)	94 (58)	41 (25)
95% CI	(50, 66)	(19, 32)
Duration of Response[b]		
Median DOR, months (95% CI)	18.4 (10.4, 22.2)	9.6 (7.4, 16.6)

CI = confidence interval; CR = complete response; DOR = duration of response; PR = partial response
[a] Per RECIST version 1.1.
[b] Based on investigator assessment.
[c] Based on confirmed ORR.

There are no black box warnings for Itovebi. Warnings include risk of severe hyperglycemia with increased fasting glucose occurring in 85% of patients. Clinical trials required patients to have HbA1C < 6% and fasting blood glucose < 126 mg/dL. Itovebi is not contraindicated but has not been studied in patients with Type 1 diabetes mellitus, or Type 2 diabetes mellitus requiring ongoing anti-hyperglycemic treatment as these patients were excluded from clinical trials. Other warnings include risk of severe stomatitis, severe diarrhea (including dehydration and acute kidney injury), and risk of embryo-fetal toxicity based on the mechanism of action.

During the INAVO120 trial, serious adverse reactions occurred in 24% of patients treated with Itovebi, most commonly anemia, diarrhea, and urinary tract infection. Fatal adverse reactions were reported in 3.7% of patients, including acute coronary syndrome, cerebral hemorrhage, cerebrovascular accident, COVID-19 infection, and gastrointestinal hemorrhage. Permanent discontinuation occurred in 6% of patients. Dosage interruptions occurred in 69% of patients and dose reductions occurred in 14% of patients. The most common adverse reactions were decreased neutrophils, decreased hemoglobin, increased fasting glucose, decreased platelets, decreased lymphocytes, stomatitis, diarrhea, decreased calcium, fatigue, decreased potassium, increased creatinine, increased ALT, nausea, decreased sodium, decreased magnesium, rash, decreased appetite, COVID-19 infection, and headache.

The safety and efficacy of Itovebi has not been evaluated in pediatric patients. Of the 162 patients treated with Itovebi in INAVO120, 15% were ≥ 65 years and 3% were ≥ 75 years. Dose modifications or interruptions due to adverse reactions occurred at a higher incidence for older patients compared to younger patients (79% vs. 68% respectively). Clinical studies did not include sufficient numbers of patients ≥ 65 years of age to determine if they respond differently from younger patients.

For patients with moderate renal impairment, a dosage reduction is recommended. No dosage adjustment is recommended for patients with mild renal impairment. Itovebi has not been evaluated in patients with severe renal 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: If you fail Itovebi, does it predict response to other PIK3 specific drugs such as Piqray? Kim will investigate further, it's possible they may target different mutations and are unrelated. There is nothing currently noted in NCCN. We will reach out for additional input. No comments or questions. The committee unanimously voted to accept the recommendations as presented. None were opposed (32 approved, 0 rejected).

Financial Discussion: No comments or questions. The committee unanimously voted to accept the recommendations as presented. None were opposed (32 approved, 0 rejected).

Outcome: Itovebi is a pharmacy benefit and will be added to the Oral Oncology Brand NP tier ($0 copay) of the Commercial, Marketplace, & GHP Kids formularies. The following prior authorization criteria will apply:

- Medical record documentation that Itovebi is prescribed by a hematologist or oncologist **AND**
- Medical record documentation of an age greater than or equal to 18 years **AND**
- Medical record documentation of hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer **AND**
- Medical record documentation of one or more PIK3CA mutations, as detected by an FDA approved test* **AND**
- Medical record documentation that Itovebi will be used in combination with combination with palbociclib and fulvestrant **AND**
- Medical record documentation of recurrence on or after completing adjuvant endocrine therapy

***NOTE:** The FDA approved test for the detection of PIK3CA mutations is the FoundationOne Liquid CDx.

GPI LEVEL: GPI-12

QUANTITY LIMIT: Itovebi 3 mg tablets: 2 tablets per day, 30 day supply per fill
Itovebi 9 mg tablets: 1 tablet per day, 30 day supply per fill

AUTHORIZATION DURATION: Itovebi is configured as a prior authorization for new starts only. Itovebi 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

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.

VYLOY (zolbetuximab-clzb)

Review: Vyloy is indicated in combination with fluoropyrimidine- and platinum-containing chemotherapy for the first-line treatment of adults with locally advanced unresectable or metastatic human epidermal growth factor receptor 2 (HER2)-negative gastric or gastroesophageal junction adenocarcinoma whose tumors are claudin (CLDN) 18.2 positive as determined by an FDA approved test. Vyloy is a claudin 18.2 (CLDN18.2)-directed cytolytic antibody that depletes CLDN18.2-positive cells via antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC). Vyloy combined with chemotherapy had increased antitumor activity in CLDN18.2-expressing mouse tumor models compared to Vyloy or chemotherapy alone. Vyloy is the first and only approved CLDN18.2-directed therapy. CLDN18.2 is overexpressed in various digestive malignancies, such as GC, GEJ cancer, esophageal cancer, and pancreatic cancer to varying degrees. Approximately 30 to 40% of patients with gastric or gastroesophageal junction adenocarcinoma have CLDN18.2 positive tumors.

Vyloy is administered as an intravenous infusion at a recommended initial dose of 800 mg/m2 followed by 600 mg/m2 every 3 weeks or 400 mg/m2 every 2 weeks. Treatment is administered in combination with fluoropyrimidine- and platinum-containing chemotherapy and is continued until disease progression or unacceptable toxicity. When administered on the same day, Vyloy is administered first. No dosage

reduction is recommended for Vyloy. Adverse reactions are managed by reduction of the infusion rate, infusion interruption, withholding the dose, and/or permanent discontinuation of treatment. Vyloy is supplied as 100 mg single-dose vial for reconstitution.
The efficacy of Vyloy was evaluated in the SPOTLIGHT and GLOW clinical trials.

SPOTLIGHT, a double-blind, randomized clinical trial evaluated the efficacy of Vyloy in combination with mFOLFOX6 in 565 patients with locally advanced unresectable or metastatic HER2-negative gastric or GEJ adenocarcinoma whose tumors were CLDN18.2 positive. Patients were excluded from the clinical trial if they had complete or partial gastric outlet syndrome, or a history of central nervous system metastases. Patients were randomized 1:1 to receive Vyloy (n=283) or placebo (n=282) in combination with mFOLFOX6. Patients were treated with Vyloy every 3 weeks with up to 12 treatments (4 cycles) of mFOLFOX6. After 12 treatments, patients were allowed to continue Vyloy + 5-fluorouracil and folinic acid (leucovorin or local equivalent) treatment at the discretion of the investigator until disease progression or unacceptable toxicity. The major efficacy endpoint was progression-free survival (PFS) as assessed by RECIST v1.1. Additional efficacy outcome measures were overall survival (OS), objective response rate (ORR) and duration of response (DOR). Vyloy in combination with mFOLFOX6 demonstrated a statistically significant improvement in PFS and OS compared with placebo + mFOLFOX6 (Table 6).

Table 6. Efficacy Results for SPOTLIGHT

Endpoint	VYLOY with mFOLFOX6 n=283	Placebo with mFOLFOX6 n=282
Progression Free Survival		
Number (%) of patients with events	146 (51.6)	167 (59.2)
Median in months (95% CI)[1]	10.6 (8.9, 12.5)	8.7 (8.2, 10.3)
Hazard ratio (95% CI)[2,3]	0.751 (0.598, 0.942)	
1-sided p-value[2,4]	0.0066	
Overall survival		
Number (%) of patients with events	149 (52.7)	177 (62.8)

1. Based on Kaplan-Meier estimate. 2. Stratification factors were region, number of metastatic sites and prior gastrectomy from IRT. 3. Based on a stratified Cox proportional hazards model. 4. Based on a 1-sided stratified log-rank test. 5. Based on confirmed response. 6. Based on binomial distribution (Clopper-Pearson).

GLOW, a double-blind, randomized clinical trial evaluated the efficacy of Vyloy with CAPOX in 507 patients with locally advanced or metastatic HER2-negative gastric or GEJ adenocarcinoma whose tumors were CLDN18.2 positive. Patients were randomized 1:1 to receive Vyloy (n=254) or placebo (n=253) in combination with CAPOX. Patients were treated every 3 weeks with up to 8 treatments (8 cycles) of CAPOX. After 8 treatments, patients were allowed to continue Vyloy + capecitabine treatment at the discretion of the investigator until disease progression or unacceptable toxicity. The major efficacy endpoint was progression free survival (PFS) as assessed by RECIST v1.1 by IRC. Additional efficacy outcome measures were overall survival (OS), objective response rate (ORR), and duration of response (DOR) as assessed per RECIST v1.1.

Vyloy in combination with CAPOX demonstrated a statistically significant improvement in PFS and OS compared with placebo in combination with CAPOX (Table 7).

Table 7. Efficacy Results in GLOW

Endpoint	VYLOY with CAPOX n=254	Placebo with CAPOX n=253
Progression Free Survival		
Number (%) of patients with events	137 (53.9)	172 (68.0)
Median in months (95% CI)[1]	8.2 (7.5, 8.8)	6.8 (6.1, 8.1)
Hazard ratio (95% CI)[2,3]	0.687 (0.544, 0.866)	
1-sided p-value[2,4]	0.0007	
Overall survival		
Number (%) of patients with events	144 (56.7)	174 (68.8)
Median in months (95% CI)[1]	14.4 (12.3, 16.5)	12.2 (10.3, 13.7)
Hazard ratio (95% CI)[2,3]	0.771 (0.615, 0.965)	
1-sided p-value[2,4]	0.0118	
Objective Response Rate (CR + PR)[5]		
ORR (%) (95% CI)[6]	32.3 (26.6, 38.4)	31.2 (25.6, 37.3)
Complete response rate (%)	6 (2.4)	2 (0.8)
Partial response rate (%)	76 (29.9)	77 (30.4)
Duration of Response	N=82	N=79
Median in months (95% CI)	8.3 (6.3, 11.4)	6.2 (6.0, 7.6)

1. Based on Kaplan-Meier estimate. 2. Stratification factors were region, number of metastatic sites and prior gastrectomy from IRT. 3. Based on a stratified Cox proportional hazards model. 4. Based on a 1-sided stratified log-rank test. 5. Based on confirmed response. 6. Based on binomial distribution (Clopper-Pearson).

Vyloy carries a warning for hypersensitivity reactions, including anaphylaxis and serious and fatal infusion-related reactions, and severe nausea and vomiting. Nausea and vomiting occurred in 82% and 67% of patients respectively and occurred more often during the first cycle of treatment. The most common adverse reactions were nausea, vomiting, fatigue, decreased appetite, diarrhea, peripheral sensory neuropathy, abdominal pain, constipation, weight loss, hypersensitivity reactions, and pyrexia. The most common laboratory abnormalities were decreased neutrophils, leucocytes, albumin, hemoglobin, lymphocytes, platelets, sodium, potassium, and magnesium, and increased creatinine, glucose, alanine aminotransferase, and phosphate.

The safety and efficacy of Vyloy in pediatric patients have not been established. Of the 533 patients in clinical studies, of Vyloy in combination with mFOLFOX6 or CAPOX, 34% were over 65 years and 5% were over 75 years. No overall differences in safety and 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: No comments or questions. The committee unanimously voted to accept the recommendations as presented. None were opposed (30 approved, 0 rejected).

Financial Discussion: No comments or questions. The committee unanimously voted to accept the recommendations as presented. None were opposed (29 approved, 0 rejected).

Outcome: Vyloy is a medical benefit and will require a prior authorization for Commercial, Marketplace, and GHP Kids. Vyloy will be added to the medical benefit cost share list. When processed at a specialty pharmacy, Vyloy will process on the Specialty or Brand NP tier for members with a three-tier benefit. The following prior authorization criteria will apply:

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

- Medical record documentation of locally advanced unresectable or metastatic human epidermal growth factor receptor 2 (HER2)-negative gastric or gastroesophageal junction adenocarcinoma **AND**
- Medical record documentation that Vyloy will be used in combination with fluoropyrimidine- and platinum-containing chemotherapy for first-line treatment **AND**
- Medical record documentation of Claudin (CLDN) 18.2 positive tumors (defined as ≥75% of tumor cells demonstrating moderate to strong membranous CLDN18 immunohistochemical staining) as determined by an FDA approved test*

***NOTE:** The FDA approved test for detection of Claudin (CLDN) 18.2 protein expression is VENTANA CLDN18 (43-14A) RxDx Assay

AUTHORIZATION DURATION: Initial approval will be for 6 months or less if the reviewing provider feels it is medically appropriate. Subsequent approvals will be for an additional 6 months or less if the reviewing provider feels it is medically appropriate and will require medical record documentation of continued disease improvement or lack of disease progression. The medication will no longer be covered if the member experiences unacceptable toxicity or worsening of disease.

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

TRYVIO (aprocitentan)

Review: Tryvio is an endothelin receptor antagonist (ERA) indicated for the treatment of hypertension in combination with other antihypertensive drugs, to lower blood pressure in adult patients who are not adequately controlled on other drugs. Tryvio is the first oral antihypertensive medication to be approved in more than 30 years and works on a new pathway that inhibits the binding of endothelin (ET)-1 to ET_A and ET_B receptors, in turn inhibiting ET-1 hypertensive effects such as endothelial dysfunction, vascular hypertrophy and remodeling, sympathetic activation, and increased aldosterone synthesis. Tryvio is available as a 12.5 mg oral tablet with a recommended dose of 12.5 mg once daily, with or without food.

Hypertension is the leading cause of death worldwide and affects approximately 32% of adults in the United States. Hypertension is defined as a systolic blood pressure (SBP) 140 mm Hg and higher or a diastolic blood pressure (DBP) 90 mm Hg and higher. Resistant hypertension (RH) is defined as a blood pressure greater than 140/90 mm Hg in a patient taking at least 3 antihypertensive medications at optimal doses (one being a diuretic) and after excluding pseudo resistance (i.e., white-coat effect, nonadherence, suboptimal antihypertensive medications, inaccurate blood pressure readings, etc.) and drug-induced hypertension/secondary hypertension. Patients with RH have a higher risk for cardiovascular events and are more likely to have a secondary cause of high blood pressure.

In patients with RH, first optimize non-pharmacologic management such as stopping medications that increase blood pressure, lifestyle modifications, and improving adherence. Management of RH also includes switching patients from thiazide diuretics to long-acting thiazide-like diuretics (i.e. chlorthalidone or indapamide). The use of mineralocorticoid receptor antagonists (MRA) (i.e. spironolactone or eplerenone) as 4^{th} line treatment may be appropriate in some patients. Additionally, stepwise addition of antihypertensive drugs with complementary mechanisms such as beta-blockers, hydralazine, and minoxidil can be considered in patients with blood pressure that remains elevated.

Tryvio was evaluated in a Phase 3, multicenter, multipart, blinded, randomized, parallel-group study called PRECISION that evaluated the safety and efficacy of Tryvio in 730 adults with SBP $\geq$ 140 mm Hg taking at least 3 antihypertensive medications, including a diuretic. The trial included a placebo run-in period followed by 3 parts, outlined below. Patients were switched to standard background antihypertensive therapy consisting of an ARB, calcium channel blocker, and a diuretic (all continued through the study) prior to the placebo run-in period. Patients taking concomitant beta-blockers continued

doing so throughout the study. At baseline, 63% of patients reported taking 4 or more antihypertensive medications.

Table 1. PRECISION Interventions

Part 1: Double-blind treatment period (4 weeks)	Part 2: Single-blind treatment period (32 weeks)	Part 3: Double-blind withdrawal period (12 weeks)
Patients randomized 1:1:1 to receive 1 of the following, once daily: • Tryvio 12.5 mg • Tryvio 25 mg • Placebo	Tryvio 25 mg once daily	Patients re-randomized 1:1 to receive 1 of the following, once daily: • Tryvio 25 mg • Placebo

The primary efficacy endpoint was change in sitting systolic blood pressure (SiSBP) from baseline to Week 4 during Part 1, measured as trough by unattended automated office blood pressure (uAOBP). The key secondary endpoint was change in SiSBP measured at trough by uAOBP from Week 36 (i.e. prior to randomized withdrawal to 25 mg Tryvio or placebo in Part 3) to Week 40. Table 2 shows the reductions in BP compared to placebo based on uAOBP measurements at trough.

Table 2. Reduction in Sitting Trough BP (mm Hg) at Week 4 of Double-Blind Treatment in PRECISION Trial

				Difference to Placebo	
Treatment Group	**N**	**Baseline Mean[a]**	**LS mean**	**LS mean**	***P*-value**
SiSBP (Primary Endpoint)			**LS Mean (97.5% CL)**	**LS Mean (97.5% CL)**	
12.5 mg	243	153.2	-15.4 (-17.5, -13.3)	-3.8 (-6.8, -0.8)	0.0043[b]
Placebo	244	153.3	-11.6 (-13.7, -9.5)	--	--
SiDBP			**LS Mean (97.5% CL)**	**LS Mean (97.5% CL)**	
12.5 mg	243	87.9	-10.4 (-11.7, -9.1)	-4.0 (-5.8, -2.1)	--
Placebo	244	87.1	-6.4 (-7.8, -5.1)	--	--

Abbreviations: LS mean, least squares mean; SiSBP, sitting systolic blood pressure; SiDBP, sitting diastolic blood pressure; CL, confidence limits

[a] Observed baseline value.

[b] Statistically significant at the 2.5% level as prespecified in the testing strategy.

Tryvio showed a statistically significant reduction in SiSBP at week 4 compared to placebo. Most of the BP-lowering effect of Tryvio occurred within the first 2 weeks of treatment. Tryvio is only approved at a 12.5 mg dose, not a 25 mg dose, because the efficacy for the 25 mg dose was similar to the 12.5 mg and had increased risk of edema and fluid retention. The BP-lowering effect was consistent amongst subgroups.

Tryvio has a black box warning for embryo-fetal toxicity. Tryvio can cause major birth defects if used by pregnant patients and is only available through a restricted program called the TRYVIO Risk Evaluation and Mitigation Strategy (REMS) program. In patients that can become pregnant, obtain a negative pregnancy test and use acceptable methods of contraception before the start of, during, and for 1 month after stopping Tryvio. Patients should be advised not to breastfeed during treatment with Tryvio. Tryvio may impair fertility in males of reproductive potential. Safety and efficacy of Tryvio in pediatric patients have not been established. In the PRECISION trial, 44% of patients were 65 years and older and 10% of patients were 75 years and older; no dose adjustment is required in patients over the age of 65, but edema/fluid retention was more common in these patients. Tryvio is not recommended in patients with kidney failure (eGFR < 15 mL/min) or on dialysis; no dose adjustment is required in mild to severe renal impairment (eGFR $\geq$ 15 mL/min). Tryvio is not recommended in patients with moderate to severe hepatic

impairment (Child-Pugh class B and C); no dose adjustment is required in mild hepatic impairment (Child-Pugh class A).

Contraindications	Pregnancy Hypersensitivity to aprocitentan or any of its excipients
Warnings and Precautions	Embryo-fetal toxicity Tryvio REMS (prescribers and pharmacies must be certified) Hepatotoxicity Fluid retention Hemoglobin decrease Decreased sperm counts
Adverse Reactions (more frequent than placebo and ≥ 2% in Tryvio-treated patients)	Edema/fluid retention Anemia

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 (40 approved, 0 rejected).

Financial Discussion: No comments or questions. The committee unanimously voted to accept the recommendations as presented. None were opposed (38 approved, 0 rejected).

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

- Medical record documentation of age 18 years or older **AND**
- Medical record documentation of diagnosis of resistant hypertension **AND**
- Medical record documentation of continued concurrent use of a medication from ALL the following antihypertensive classes at maximally tolerated doses:
    - Renin-angiotensin system [angiotensin-converting enzyme (ACE) inhibitor OR angiotensin II receptor blocker (ARB)]
    - Calcium channel blocker
    - Diuretic

  AND
- Medical record documentation of therapeutic failure on intolerance to, or contraindication to at least two (2) additional formulary alternatives of different classes (i.e. beta blockers, aldosterone receptor antagonists, alpha-blockers, vasodilators, etc.).

AUTHORIZATION DURATION: Initial authorization will be for 3 months. Subsequent approvals will be for an additional 12 months and will require:

- Medical record documentation of clinical improvement or lack of worsening in blood pressure shown through office visit blood pressure readings.

QUANTITY LIMIT: 1 tablet 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.

YORVIPATH (palopegteriparatide)

Review: Yorvipath (palopegteriparatide) is a parathyroid hormone analog (PTH(1-34)) indicated for the treatment of hypoparathyroidism in adults. Yorvipath is a prodrug that contains an inert carrier of teriparatide and mimics endogenous parathyroid hormone (PTH). PTH is one of three key hormones that regulates serum calcium and phosphate homeostasis by increasing serum calcium and decreasing serum phosphate. PTH is excreted by the parathyroid glands in response to low serum calcium levels. PTH exerts its effects primarily on the bones, kidneys, and intestines.

Hypoparathyroidism is an endocrine disorder characterized by the insufficient secretion or action of PTH, leading to hypocalcemia and hyperphosphatemia. Hypoparathyroidism can occur due to genetic disorders, surgery, autoimmune conditions, radiation-induced destruction of parathyroid glands, infiltration of parathyroid gland, hungry-bone syndrome, and HIV infection. Clinical manifestations of hypoparathyroidism range from none/few symptoms to life-threatening seizures, refractory heart failure, and laryngospasm. Clinical manifestations are determined by severity, rate of development of hypocalcemia, and chronicity. Acute manifestations of hypoparathyroidism include signs and symptoms of hypocalcemia (tetany, fatigue, hyperirritability, anxiety and depression, and cardiac findings). Chronic manifestations of hypoparathyroidism can present similarly to that of acute hypocalcemia, however, also include presence of basal ganglia calcifications, cataracts, dental abnormalities, and ectodermal manifestations.

Management of hypoparathyroidism primarily involves calcium and active vitamin D supplementation. PTH-based therapies are reserved for patients with chronic hypoparathyroidism who cannot maintain stable serum and urinary calcium levels with calcium and vitamin D supplementation. Goals of therapy for patients diagnosed with hypoparathyroidism are to relieve symptoms, raise and maintain the serum calcium concentration in the low-normal range, avoid hypercalciuria and iatrogenic development of nephrocalcinosis and kidney stones, and avoid hyperphosphatemia.

PTH-based therapies are not considered first-line for hypoparathyroidism due to high cost and subcutaneous administration. PTH-based therapies are an option for patients with chronic hypoparathyroidism who cannot maintain stable serum and urinary calcium levels with calcium and vitamin D treatment alone. PTH-based therapies include Natpara (parathyroid hormone), Forteo (teriparatide), and Yorvipath (palopegteriparatide). Natpara will no longer be manufactured as of 2025, and Forteo is only indicated for osteoporosis at this time, therefore leaving Yorvipath as the only currently approved PTH analog for the treatment of hypoparathyroidism. Yorvipath does have limitations of use as it was not studied for acute post-surgical hypoparathyroidism and its titration method was only evaluated in adults who first achieved an albumin-corrected serum calcium of at least 7.8 mg/dL using calcium and active vitamin D treatment.

Yorvipath is a once daily subcutaneous injection. Dosage is individualized with a goal of maintaining serum calcium within the normal range without the need for active vitamin D or therapeutic calcium doses. Close monitoring of albumin-corrected serum calcium and active vitamin D are essential to assess efficacy of Yorvipath and correctly dose Yorvipath, calcium, and vitamin D supplements. The recommended starting dosage of Yorvipath is 18 mcg once daily and is titrated in 3 mcg increments or decrements. The maximum recommended dosage of Yorvipath is 30 mcg once daily. Yorvipath is supplied in a prefilled, disposable, 14-dose pen-injector. No more than one injection to achieve the once daily recommended dosage should be used as using two injections increases the risk of hypo- or hypercalcemia.

Yorvipath is contraindicated in patients with severe hypersensitivity to palopegteriparatide or to any of its excipients. Warnings and precautions include risk of unintended changes in serum calcium levels related to number of daily injections, serious hypercalcemia/hypocalcemia, potential risk of osteosarcoma, orthostatic hypotension, and risk of digoxin toxicity with concomitant use of digitalis compounds. The most common adverse reactions include injection site reactions, vasodilatory signs and symptoms, headache, diarrhea, back pain, hypercalcemia, and oropharyngeal pain. The safety and effectiveness of Yorvipath

have not been established in pediatric patients. It is unclear whether geriatric patients respond differently than younger adult patients to Yorvipath therapy. No renal or hepatic dosage adjustments are required.

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 (38 approved, 0 rejected).

Financial Discussion: No comments or questions. The committee unanimously voted to accept the recommendations as presented. None were opposed (41 approved, 0 rejected).

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

- Medical record documentation of a diagnosis of hypoparathyroidism **AND**
- Medical record documentation of age ≥ 18 years **AND**
- Medical record documentation that Yorvipath is being prescribed by an endocrinologist **AND**
- Medical record documentation of no increased baseline risk for osteosarcoma **AND**
- Medical record documentation of serum 25(OH) vitamin D within normal range within 2 weeks prior to the first dose **AND**
- Medical record documentation of albumin-corrected serum calcium ≥ 7.8 mg/dL within 2 weeks prior to the first dose **AND**
- Medical record documentation of one of the following:
    - Medical record documentation of therapeutic failure on, intolerance to, or contraindication to calcitriol **OR**
    - Medical record documentation that member will use Yorvipath in addition to calcitriol and/or elemental calcium.

NOTE:

- The safety and effectiveness of Yorvipath was not studied in patients diagnosed with postsurgical acute hypoparathyroidism.
- Increased risks of osteosarcoma:
    - Open epiphyses
    - Metabolic bone diseases other than hypoparathyroidism, including Paget's disease of bone
    - Unexplained elevations of alkaline phosphatase
    - Bone metastases or a history of skeletal malignancies
    - History of external beam or implant radiation therapy involving the skeleton
    - Hereditary disorders predisposing to osteosarcoma
- The normal range for albumin-corrected serum calcium is 8.3 to 10.6 mg/dL.
- The normal range for serum 25(OH) vitamin D is ≥ 20 ng/mL

QUANTITY LIMIT:

- Yorvipath INJ 168mcg/0.56mL (GPI 3090516000D220): 1.12mL per 28 days
- Yorvipath INJ 294mcg/0.98mL (GPI 3090516000D230): 1.96mL per 28 days
- Yorvipath INJ 420mcg/1.4mL (GPI 3090516000D240): 2.8mL per 28 days

AUTHORIZATION DURATION: Initial approval will be for 12 months. S Subsequent approvals will be for an additional 12 months and will require:

- Medical record documentation of albumin-corrected serum calcium within the lower-half of the normal reference range **AND**
- Medical record documentation of prescriber attestation that member is responding to Yorvipath therapy

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.

NEMLUVIO (nemolizumab-ilto)

Review: Nemluvio is indicated for the treatment of adults with prurigo nodularis. Nemluvio is a humanized IgG3 monoclonal antibody that selectively binds IL-31 RA and inhibits IL-31 signaling and IL-31-induced responses including release of proinflammatory cytokines and chemokines. PN is a rare, chronic skin condition characterized by raised, hyperkeratotic, intensely itchy bumps which are symmetrically distributed on the arms, legs, and trunk. Nemluvio is the second treatment approved for PN after Dupixent which was approved for PN in 2022. Prior to approval of Dupixent, topical, oral, or intralesional corticosteroids, topical calcineurin inhibitors (TCIs), topical vitamin D analogs, topical capsaicin, oral antihistamines, gabapentin, and methotrexate were used off label to treat PN with limited efficacy.

The recommended dosage of Nemluvio for adults weighing less than 90 kg is an initial dose of 60 mg (two 30 mg injections) subcutaneously, followed by 30 mg every 4 weeks. For adults weighing 90 kg or more the recommended dose is an initial dose of 60 mg (two 30 kg injections) subcutaneously, followed by 60 mg every 4 weeks. Patients may self-inject Nemluvio after receiving training on subcutaneous injections.

The efficacy and safety of Nemluvio was evaluated in OLYMPIA 1 and OLYMPIA 2, two randomized, double-blind, placebo-controlled trials in 560 adult patients with prurigo nodularis (PN). Disease severity was defined using Investigator's Global Assessment (IGA) in overall assessed of PN nodules on a severity scale of 0 to 4. Patients included in the trial had an IGA score ≥ 3, severe pruritis as defined by a weekly average of the peak pruritic numeric rating scale (PP-NRS) score of ≥ 7 on a scale of 0 to 10, and greater than or equal to 20 nodular lesions. IGA is a 5-category scale indicating the investigator's assessment of the pruriginous nodules. PP-NRS is a weekly average of daily PP-NRS scores on an 11 point scale from 0-10 assessing intensity of pruritic in the last 24 hours. OLYMPIA 1 and OLYMPIA 2 assessed the effect of Nemluvio on signs and symptoms of PN, targeting improvement in skin lesions and pruritic over 16 weeks. In OLYMPIA 1, subjects were extended up to 24 weeks of treatment.

The baseline weekly average PP-NRS score was a mean of 8.5. Fifty-eight (58)% of subjects had a baseline IGA score of 3 (moderate PN), and 42% of subjects had a baseline IGA of 4 (severe PN). Efficacy was based on the proportion of patients with an improvement of at least 4 from baseline in PP-NRS, the proportion of patients with an IGA score of 0 or 1 and a ≥ 2 point improvement from baseline, the proportion of patients who achieved a response in both PP-NRS and IGA, and the proportion of patients with PP-NRS <2. Efficacy results are shown in Table 5.

Table 5. Efficacy Results at Week 16 in Adult Subjects with PN in OLYMPIA 1 and OLYMPIA 21

	OLYMPIA 1			OLYMPIA 2		
	NEMLUVIO (N=190)	Placebo (N=96)	Difference from Placebo (95% CI)	NEMLUVIO (N=183)	Placebo (N=91)	Difference from Placebo (95% CI)
Proportion of subjects with both an improvement (reduction) of ≥4 from baseline in PP-NRS and IGA 0 or 1[a,b]	22%[a]	2%[a]	15% (8%, 21%)[a]	25%[a]	4%[a]	22% (14%, 30%)[a]
Proportion of subjects with IGA 0 or 1[b]	26%	7%	15% (7%, 23%)	38%	11%	29% (19%, 38%)
Proportion of subjects with an improvement (reduction) of ≥4 from baseline in PP-NRS[b]	56%	16%	38% (27%, 48%)	49%	16%	34% (23%, 45%)
Proportion of subjects with PP-NRS <2[b]	32%	4%	28% (20%, 36%)	31%	7%	26% (18%, 34%)

Warnings for Nemluvio include hypersensitivity reactions, including facial angioedema. Nemluvio also contains warnings for potential impact on the safety or effectiveness of live vaccines. All age-appropriate vaccinations should be completed prior to treatment with Nemluvio. The most common adverse reactions that occurred with Nemluvio were headache, dermatitis atopic, eczema, and eczema nummular.
The safety and efficacy of Nemluvio has not been established in pediatric patients. Of the 370 subjects with prurigo nodularis in OLYMPIA 1 and OLYMPIA 2, 99 subjects were 65 years or older. The long term safety was assessed in 508 subjects, of which 133 (26.2%) were 65 years of age or older. Clinical trials of Nemluvio did not include sufficient number of patients 65 years of age or older to determine if 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 (37 approved, 0 rejected).

Financial Discussion: No comments or questions. The committee unanimously voted to accept the recommendations as presented. None were opposed (38 approved, 0 rejected).

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

- Medical record documentation that Nemluvio is prescribed by or in consultation with an allergist, immunologist, or dermatologist **AND**
- Medical record documentation of age greater than or equal to 18 years **AND**
- Medical record documentation of a diagnosis of prurigo nodularis **AND**
- Medical record documentation that the member is receiving an appropriate dose based on patient's weight **AND**
- Medical record documentation of therapeutic failure on, intolerance to, or contraindication to Dupixent **AND**
- Medical record documentation of one of the following:
    - Medical record documentation of a failure on a very-high potency topical corticosteroid (for example, clobetasol dipropionate 0.05% ointment) **OR** calcineurin inhibitor (i.e. tacrolimus) if topical corticosteroids are not advisable **OR**
    - Medical record documentation of widespread or recalcitrant disease **AND** contraindication to, intolerance to, or therapeutic failure on an adequate trial of phototherapy (UVA/UVB treatment) **AND** systemic therapy (including methotrexate and/or cyclosporine)

***NOTE:** The recommended dosage for adult patients weighing ≥ 90 kg is 60 mg (two 30-mg injections) initially, followed by 60 mg every 4 weeks. The recommended dosage for adult patients weighing < 90 kg is 60 mg (two 30-mg injections) initially, followed by 30 mg every 4 weeks.

AUTHORIZATION DURATION: Initial approval will be for 6 months or less if the reviewing provider feels it is medically appropriate. Subsequent approvals will be for an additional 12 months or less if the reviewing provider feels it is medically appropriate. The medication will no longer be covered if the member experiences unacceptable toxicity or worsening of disease.

- Medical record documentation of continued disease improvement or lack of disease progression **AND**
- Medical record documentation that the member is receiving an appropriate dose based on patient's weight

QUANTITY LIMIT: 2 auto-injectors per 28 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.

LIVDELZI (seladelpar)

Review: Livdelzi is the second peroxisome proliferator-activated receptor (PPAR) agonist indicated for the treatment of primary biliary cholangitis (PBC) in combination with ursodeoxycholic acid (UDCA) in adults who have had an inadequate response to UDCA, or as monotherapy in patients unable to tolerate UDCA. PBC is a rare liver disease characterized by destruction and inflammation of the small bile ducts. It is a chronic and progressive disease varying among patients. More recently patients have been diagnosed with the disease in earlier stages and have responded well to treatment, which has led to a decrease in liver transplantation caused by the disease. If left untreated, patients can progress to liver cirrhosis or end-stage liver disease resulting in the need for a liver transplant. The prevalence of the disease is exceedingly rare and there are about 131,000 individuals with PBC in the United States affecting mainly women aged 45-65 years old. The goal of treatment for PBC is to prevent disease progression and manage symptoms related to chronic cholestasis. The most common symptoms of the disease are pruritus and fatigue. Livdelzi works by inhibiting bile acid synthesis through activation of PPAR-delta, which subsequently downregulates fibroblast growth factor 21 (FGF21). This growth factor is a key enzyme in the synthesis of bile acids from cholesterol.

Livdelzi is supplied as a 10mg tablet taken once daily with or without food. Currently, on the market there are two other FDA approved second-line treatment options, Ocaliva (Obeticholic acid) also abbreviated as OCA and Iqirvo (Elafibranor). Ocaliva is a farnesoid X receptor (FXR) agonist, which received accelerated approval from the FDA in 2016 for the treatment of adult patients with PBC without cirrhosis or with compensated cirrhosis who do not have evidence of portal hypertension, either in combination with UDCA for patients with an inadequate response to UDCA, or as monotherapy in patients unable to tolerate UDCA. Recently in November 2024, Ocaliva was denied by the FDA for full approval due to safety concerns and the company plans to continue to work to submit safety data to the FDA.

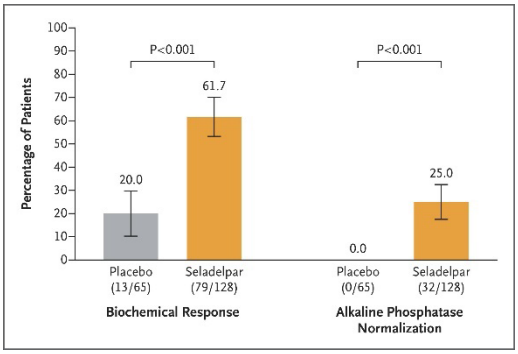
Iqirvo is the other second line agent that just received approval in June 2024. It is also a peroxisome proliferator–activated receptor (PPAR) agonist, but it activates both the PPAR-alpha and delta. Iqirvo has differentiated itself from Ocaliva in that it may not worsen pruritus and dyslipidemia, which are both side effects of Ocaliva. Iqirvo also does not have any current safety concerns in compensated cirrhosis, whereas Ocaliva has a boxed warning for hepatic decompensations and failure in patients with PBC and cirrhosis. The drugs have not been studied head-to-head at this time to compare efficacy, but the treatments are similarly effective based upon reduction of ALP. In the clinical trials, Iqirvo did show a significant difference in its primary endpoint of a biochemical response and secondary outcome of reduction of ALP. For its secondary outcome on reduction of pruritus, it did not show a significant difference between placebo.

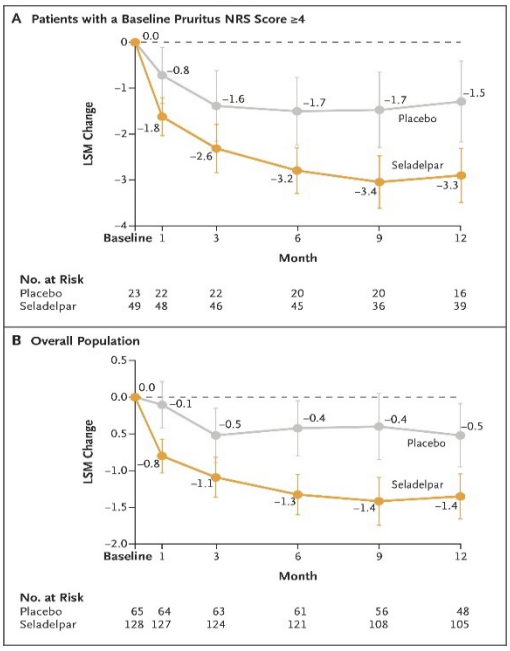
Livdelzi is the third drug to receive approval for PBC and has differentiated itself by showing a significant difference in its reduction of pruritus in its efficacy trials. Iqirvo did not achieve significance on this key secondary outcome measure, and data on pruritus are not included in the Iqirvo label. Ocaliva' s label carries the risk of worsening pruritus. In addition, Ocaliva is contraindicated in patients with PBC who have decompensated cirrhosis, a prior decompensation event, or with compensated cirrhosis who have evidence of portal hypertension. The AASLD guidelines recommend careful monitoring of any patient on Ocaliva with cirrhosis, even if it is not advanced. In contrast, Livdelzi and Iqirvo do not have these safety signals in compensated cirrhosis. Livdelzi was also shown to have similar safety among patients with compensated cirrhosis. However, the use of Iqirvo and Livdelzi is not recommended in patients who have or develop decompensated cirrhosis. Livdelzi' s label includes a warning for liver test abnormalities and Iqirvo' s label has warnings for myalgia, myopathy, and rhabdomyolysis, along with drug induced liver injury. Overall, all three agents appear to have similar efficacy for PBC.

The Primary Biliary Cholangitis: 2018 Practice Guidance from the American Association for the Study of Liver Diseases recommends UDCA at a dose of 13 to 15 mg/kg/day for first-line therapy. For second-line treatment, the guidelines also mention that OCA was approved by the Food and Drug Administration in May 2016 to be used in combination with UDCA in patients with PBC who have inadequate response to at least 1 year of treatment with UDCA, or as monotherapy for those patients who are intolerant to UDCA. Patients who are inadequate responders to UDCA should be considered for treatment with OCA, starting at 5 mg/day. The guidelines were updated in 2021 with a few additional recommendations stating fibrates can be considered as off-label alternatives for patients with inadequate response to UDCA and the guidelines also added that they discouraged use of OCA patients with decompensated liver and the medication is contraindicated in patients with advanced cirrhosis and even those without advanced cirrhosis careful monitoring should be completed. Iqirvo and Livdelzi were both not on the market at the time of the current guideline publications.

The safety and efficacy of Livdelzi was studied in the RESPONSE Trial. This was a phase 3, randomized, double-blind, placebo-controlled study to evaluate the safety and efficacy of Livdelzi 10mg in adult patients with PBC who had an inadequate response or intolerance to UDCA. This trial included 193 patients who were randomized and 128 patients received Livdelzi 10mg daily and 65 patients received placebo. The key inclusion criteria for the trial were patients 18 to 75 years old with PBC who received treatment with UDCA for at least 12 months or had an unacceptable side effect to UDCA at least 3 months prior to screening. Patients also had to have alkaline phosphatase level (APL) of at least 1.67 times the upper limit of the normal range (ULN) and a total bilirubin level (TBL) of no more than 2 times the ULN. Patients AST and ALT also had to be no more than 3 times or less the ULN. Patients eGFR also had to be greater than 45 mL/min/1.73 m2 and their INR had to be less than 1.1 times the ULN. The key exclusion criteria were advanced PBC as defined by the Rotterdam criteria, presence hepatic decompensation, history of liver transplantation, complications of portal hypertension, cirrhosis with complications, or other chronic liver diseases. Patients were also excluded with any clinically important alcohol consumption or treatment with Ocaliva or fibrates 6 weeks prior to screening.

The primary endpoint was the biochemical response at month 12, defined as ALP <1.67 × ULN, ≥15% reduction in ALP, and TB ≤1.0 × ULN. The key secondary endpoints were normalization of ALP level at month 12 and change in pruritus Numerical rating score (NRS) from baseline to month 6 among patients with a baseline score of at least 4.The results showed a greater percentage of the patients in the Livdelzi group than in the placebo group had a biochemical response (61.7% vs. 20.0%; difference, 41.7%, p<0.001). For the secondary outcomes, normalization of the APL also occurred in a greater percentage of patients who received Livdelzi than of those who received placebo (25.0% vs. 0%; difference, 25.0%; p<0.001). Additionally, Livdelzi resulted in a greater reduction in the score on the pruritus NRS than placebo (least-squares mean change from baseline, −3.2 vs. −1.7; least-squares mean difference, −1.5; p=0.005).





There are no contraindications to Livdelzi, or black box warnings associated with it. There are warnings for the medication for fractures occurring. Per package labeling, it is recommended to consider the risk of fractures in patients treated with Livdelzi and monitor bone health according to typical standards of care. Another warning for the medication is for liver test abnormalities, which has been seen with the medication. Livdelzi is associate with increases in AST and ALT in patients who received at least 5 times higher than the recommended daily dose. When the medication was discontinued, the AST and ALT levels then returned to normal. It is recommended to obtain baseline liver function tests prior to starting Livdelzi and thereafter as accordance with standards of care. If liver function tests worsen while on the medications or patients develop clinical symptoms associated with acute hepatitis, then it is recommended to consider interrupting therapy and possible permanently discontinue it. The last warning is for any patient with a complete biliary obstruction or a suspected obstruction then the medication should be stopped. The most common adverse events patients experienced in the Livdelzi group compared to placebo were that's >5% patients experienced: COVID-19 disease (18% vs. 15.4%), headache (7.8% vs. 3.1%), nasopharyngitis (5.5% vs.7.7%), abdominal pain (7% vs. 1.5%), arthralgia (6.2% vs. 6.2%), fatigue (6.2% vs. 6.2%), AST or ALT elevations (7% vs. 10.8%). Adverse events that resulted in discontinuation of the regimen were uncommon in both groups (4.6% of the patients in the placebo group and 3.1% in the Livdelzi group).

Livdelzi does not have enough data to demonstrate if drug-associated risk of major birth defects, miscarriage, or other adverse maternal or fetal outcomes are present with the medication. In animal reproduction studies, no malformations or effects on embryo-fetal survival occurred in pregnant rats or rabbits after Livdelzi treatment at exposures of up to 176-times and 49-times the recommended dose based on AUC. There is no data on the presence of Livdelzi or its metabolite in either human or animal milk, the effects on the breastfed infant, or the effects on milk production. The safety and effectiveness of Livdelzi have not been established in pediatric patients. 23% patients in the trial were 65 years of age and older and 2% were 75 years of age and older. No overall differences in safety or effectiveness were observed between patients 65 to 75 years of age and younger adult patients. No dosage adjustment for patients 65 years of age and older is necessary. There are no renal dose adjustments. The safety and efficacy of Livdelzi in patients with decompensated cirrhosis have not been established so the use of Livdelzi is not recommended in patients who have or develop decompensated cirrhosis.

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 (36 approved, 0 rejected).

Financial Discussion: No comments or questions. The committee unanimously voted to accept the recommendations as presented. None were opposed (38 approved, 0 rejected).

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

- Medical record documentation of a diagnosis of primary biliary cholangitis (primary biliary cirrhosis) **AND**
- Medical record documentation of age greater than or equal to 18 years **AND**
- Medical record documentation that Livdelzi is prescribed by a board-certified gastroenterologist, hepatologist, or liver transplant specialist **AND**
- Medical record documentation that Livdelzi is not being used in members with complete biliary obstruction **AND**
- Medical record documentation that Livdelzi is not being used in members with decompensated cirrhosis **AND**
- Medical record documentation that Livdelzi is not being used in combination with Ocaliva or Iqirvo **AND**
- Medical record documentation of contraindication or intolerance to UDCA (ursodiol tablets, Urso Forte, or Reltone) **OR**

- Medical record documentation of inadequate biochemical response to an appropriate dose of UDCA (ursodiol tablets, Urso Forte, or Reltone) for at least 12 months **AND** that UDCA product will be continued in combination with Iqirvo

AUTHORIZATION DURATION: Initial approval will be for 12 months. Subsequent approvals will be for an additional 12 months. The medication will no longer be covered if medial record documentation does not show:

- Medical record documentation of a positive clinical response based on biochemical response (defined as: ALP <1.67 × ULN and ALP decrease ≥15% from baseline, and TB ≤1.0 xULN from baseline) OR clinical symptom improvement (ex: reduction of itch, fatigue) **AND**
- Medial record documentation that the patient does NOT have a complete biliary obstruction **OR** decompensated cirrhosis

GPI LEVEL: GPI-12

QUANTITY LIMIT: 1 tablet per day, 30-day supply per fill

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

VAFSEO (vadadustat)

Review: Vafseo is indicated for the treatment of anemia due to chronic kidney disease (CKD) in adults who have been receiving dialysis for at least three months. Vafseo has limitations of use that it has not been shown to improve quality of life, fatigue, or patient well-being, is not indicated for use as a substitute for transfusion in patients requiring immediate correction of anemia, and not indicated in patients with anemia due to CKD not on dialysis. Vafseo is the second oral HIF-PH inhibitor approved for the treatment of anemia due to CKD in adult patients on dialysis. Jesduvroq was approved for the same indication in patients who have been on dialysis for at least four months.

Vafseo dosage should be individualized to the lowest sufficient dose to reduce the need for red blood cell transfusions and a hemoglobin level higher than 11 g/dL should not be targeted. Prior to the initiation of Vafseo, other causes of anemia should be corrected and excluded. Iron stores should also be evaluated before and during treatment. Patients should receive supplemental iron therapy when serum ferritin is less than 100 mcg/L or when serum transferring saturation is less than 20%. The majority of patients with CKD will require supplemental iron during the course of therapy. The recommended starting dose of Vafseo in adults not being treated with an ESA is 300 mg orally once daily. For patients converting from an ESA to Vafseo, the recommended starting dose is 300 mg once daily. Red blood cell (RBC) transfusions or ESA treatment may be considered during the transition phase if Hb values fall below 9 g/dL or Hb response is considered not acceptable. Patients receiving RBC transfusions should continue VAFSEO treatment during the transfusion period. VAFSEO should be paused for those patients receiving temporary ESA rescue treatment and may be resumed when Hb levels are greater than or equal to 10 g/dL. Following ESA rescue, VAFSEO should be resumed at the prior dose or with a dose that is 150 mg greater than the prior dose. Following initiation of therapy, Hb levels should be monitored every two weeks until stable, then at least monthly. The dose should be increased no more frequently than once every 4 weeks (decreases in dose can occur more frequently). The dose should be adjusted in increments of 150 mg to achieve or maintain Hb levels within 10 g/dL to 11 g/dL. Doses may range from 150 mg to a maximum of 600 mg. If Hb rises too rapidly (more than 1 g/dL in any 2-week period or more than 2 g/dL in 4 weeks), the dose should be interrupted or reduced. If Hb level exceeds 11 g/dL, the dose should be interrupted until Hb is less than or equal to 11 g/dL, then resumed with a dose that is 150 mg less than the dose prior to interruption. Treatment should not continue beyond 24 weeks of therapy if a clinically meaningful increase in Hb level is not achieved. Vafseo is supplied as 150 mg, 300 mg, and 450 mg tablets.

The efficacy of Vafseo was evaluated in the INNO2VATE-1 and INNO2VATE-2 trials, two randomized,

active, controlled, non-inferiority, open-label trials in 3,932 adult patients for the treatment of anemia with CKD on dialysis. Patients were randomized 1:1 to received Vafseo with a starting dose of 300 mg once daily or darbepoetin alfa administered subcutaneously or intravenously for 52 weeks. Vafseo was titrated in increments of 150 mg up to 600 mg to achieve target Hb. After 52 weeks, patients continued to assess long-term safety until the event-driven major adverse cardiovascular event (MACE) endpoints were reached. Efficacy in each study was based on the difference in mean change of Hb from baseline to the primary evaluation period (Weeks 24 to 36). An additional efficacy endpoint was the difference in mean change of Hb from baseline to the secondary evaluation period (Weeks 40 to 52). MACE was defined as all-cause mortality, non-fatal MI and non-fatal stroke and was evaluated in both trials. INNO2VATE-1 included patients with incident DD-CKD who initiated dialysis within 16 weeks prior to the beginning their trial participation and who were ESA-naive, had limited prior ESA use or were maintained on ESAs. INNO2VATE-2 included patients on chronic maintenance dialysis for more than 12 weeks who had converted from prior ESA therapy.

In both trials, VAFSEO was non-inferior to darbepoetin alfa in correcting and maintaining Hb levels across geographic-specific target Hb ranges [10 to 11 g/dL in the US and 10 to 12 g/dL outside the US] in adults with DD-CKD at weeks 24 to 36 and weeks 40 to 52. Results are shown in Table 5.

Table 5. Vafseo Efficacy Results (INNO$_2$VATE Trials)

	INNO$_2$VATE-1		**INNO$_2$VATE- 2**	
Hemoglobin (g/dL)	**VAFSEO N = 181**	**Darbepoetin Alfa N = 188**	**VAFSEO N = 1777**	**Darbepoetin Alfa N = 1777**
Baseline Mean (SD)	9.4 (1.1)	9.2 (1.1)	10.3 (0.9)	10.2 (0.8)
Week 24 to 36 Mean (SD)	10.4 (1.1)	10.6 (0.9)	10.4 (1.0)	10.5 (1.0)
Adjusted LSM change from baseline [95% CI]	1.3 [1.1, 1.5]	1.6 [1.4, 1.8]	0.2 [0.1, 0.3]	0.4 [0.3, 0.4]
Treatment Difference [95% CI] VAFSEO – Darbepoetin Alfa	-0.3 [-0.5, -0.1]		-0.2 [-0.2, -0.1]	
Week 40 to 52 Mean (SD)	10.5 (1.2)	10.6 (1.1)	10.4 (1.0)	10.6 (1.0)
Adjusted LSM Change from Baseline [95% CI]	1.4 [1.2, 1.7]	1.5 [1.2, 1.8]	0.2 [0.2, 0.3]	0.4 [0.3, 0.5]
Treatment Difference [95% CI] VAFSEO – Darbepoetin Alfa	-0.1 [-0.3, 0.2]		-0.2 [-0.3, -0.1]	

CI: confidence interval; LSM: least squares mean; SD: standard deviation
A pre-specified non-inferiority margin of -0.75 g/dL was used to determine efficacy of VAFSEO.
The estimated treatment difference (VAFSEO – Darbepoetin Alfa) is obtained from an analysis of covariance (ANCOVA) model (treatment group, baseline Hb level, stratification factors [region and NYHA-CHF] as predictor variables) with multiple imputation.

MACE was assessed in pooled analysis from INNO2VATE-1 and -2 and Vafseo was found to be non-inferior to darbepoetin alfa in time to first occurrence of MACE (Table 6).

Table 6. Major Adverse Cardiovascular Events in the INNO2VATE Trials (ITT Analyses[a])

	VAFSEO N = 1947 PY=3134.4	**Darbepoetin Alfa N = 1955 PY=3164.0**
First occurrence of MACE	355	377
All-cause Mortality, n	253	253
Non-fatal Myocardial Infarction, n	76	87
Non-fatal Stroke, n	26	37
MACE Hazard Ratio[b] (95% CI)	0.96 (0.83, 1.11)	
MACE Incidence Rate per 100 PY	11.3	11.9

CI = Confidence interval; ITT = Intent to treat; MACE = Major adverse cardiovascular events; PY = Person Years
[a] ITT analyses included events on and off treatment after randomization in patients who received at least one dose of study medication.
[b] Adjusted for baseline covariates

Vafseo has a black box warning for increased risk of death, myocardial infarction, stroke, venous thromboembolism, and thrombosis of vascular access. Vafseo increased the risk of thrombotic vascular events, including major adverse cardiovascular events (MACE). Targeting a hemoglobin level greater than 11 g/dL is expected to further increase the risk of death and arterial and venous thrombotic events, as occurs with erythropoietin stimulating agents (ESAs), which also increase erythropoietin levels.

Other warnings include hepatotoxicity, hypertension, seizures, gastrointestinal erosion, serious adverse reactions in patients with anemia due to CKD and not on dialysis, and risk of malignancies. In clinical trials, permanent discontinuation due to an adverse reaction was reported in 4.9% of patients treated with Vafseo and 1.1% of patients treated with darbopoetin alfa. Gastrointestinal symptoms (nausea, vomiting, and diarrhea) resulted in permanent treatment discontinuation in 1.8% of patients treated with Vafseo. The most common adverse reactions were hypertension and diarrhea.

The safety and efficacy of Vafseo has not been established in pediatric patients. In the pooled clinical trials, there were 1330 patients aged 65 years and older. Of the total number of Vafseo treated patients, 449 were 64-74 years of age, 194 were 75 to 84 years of age, and 24 were 85 years of age and older. No overall differences were observed between older and younger adult patients. Vafseo is not recommended in patients with cirrhosis or active, acute liver disease.

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 (36 approved, 0 rejected).

Financial Discussion: Have we received much interest in using this product to date? Not at this time, it is very similar to other products already available. No additional comments or questions. The committee unanimously voted to accept the recommendations as presented. None were opposed (41 approved, 0 rejected).

Outcome: Vafseo 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 three 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

NOTE:

- 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 11 g/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.

QUANTITY LIMIT: 150 mg: 1 tablet per day
300 mg: 2 tablets per day

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

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.

CREXONT (carbidopa and levodopa)

Review: Crexont ER capsules contain carbidopa (an aromatic amino acid decarboxylation inhibitor) and levodopa (an aromatic amino acid) indicated by the FDA for the treatment of Parkinson's disease, post-encephalitic parkinsonism, and parkinsonism that may follow carbon monoxide intoxication or manganese intoxication in adults.

Crexont is supplied as extended-release capsules that contain white to off-white granules and pellets available in the following strengths: carbidopa 35mg/levodopa 140mg, carbidopa 52.5mg/levodopa 210mg, carbidopa 70mg/levodopa 280mg, and carbidopa 87.5mg/levodopa 350mg. Each available capsule has specific imprints and opaque colored caps to correspond to the strength. Dose should be swallowed whole. Do not chew, divide or crush capsules. It may be taken with or without food; however, a high-fat, high calorie meal may delay the absorption of levodopa to reach peak plasma concentration by 2 hours. Do not take it with alcohol.

Dosing for Crexont will vary depending on situation. If patient is naïve to levodopa therapy, it is recommended to start the patient on Crexont 35mg/140mg twice daily for the first three day. Then, increase the dose gradually as needed to a maximum dose of Crexont 525mg/2100mg daily dose divided up to four times daily. If patient is converting from immediate-release carbidopa/levodopa to Crexont, it is important to note that the IR products cannot be substituted on a 1:1 basis with ER products. To convert, first determine the patient's total daily dose of IR levodopa. Then, determine the patient's most frequent single dose of IR levodopa. (If more than 1 dose corresponds to most frequent, use the highest of the doses.) Then, find the 2 determined values in the table to determine where to start the Crexont dose.

After 1 to 3 days, the dose and/or frequency may be adjusted as needed based on tolerability and response. To note, if the patient converting from IR product to Crexont and is taking a catechol-O-methyl transferase inhibitor (COMT, e.g. entacapone, opicapone), the initial dose of Crexont may need to be increased if the COMT inhibitor is discontinued. If patient is converting from ER carbidopa/levodopa (Rytary) to Crexont, you may convert on a 1:1 basis for dose. If discontinuing Crexont, it should be tapered slowly.

Most patients diagnosed with Parkinson's disease (PD) are started on a levodopa regimen as initial treatment, and titrated and evaluated to be sure the dose is correct for symptom/disease management. Controlled-release tablet formulations of levodopa are most useful in early PD when patients have limited or no motor complications and want 2 times a day dosing regimen rather than 3 times daily. There is no clinical advantage; there is only improvement in patient preference and regimen if desired. Extended-release capsules may be helpful for patients experiencing motor fluctuations despite optimized dosing of standard tablet forms of levodopa and adjunctive dopaminergic medications. If levodopa adjustments for "wearing off" are not adequate or tolerated, the addition of an adjunctive therapy is considered to reduce "off time". Adjunct options include monoamine oxidase type B (MAO B) inhibitors (selegiline, rasagiline), dopamine agonists (amantadine, pramipexole, ropinirole, bromocriptine), catechol-O-methyl transferase (COMT) inhibitors (entacapone), and istradefylline.

The effectiveness of Crexont was established in an active-controlled, multicenter, 20-week clinical trial. This study consisted of a 3-week dose adjustment period of immediate-release carbidopa-levodopa treatment prior to a 4-week conversion period to Crexont, which was then followed by a 13-week, double blind, double-dummy, randomized, parallel group period comparing Crexont to immediate-release carbidopa-levodopa. This study enrolled 630 patients who had been maintained on a stable regimen of at

least 400mg per day of levodopa prior to start of trial and who experienced a minimum of 2.5 hours of "off" time per day while awake. At baseline, 73% of patients on Crexont and 63% of oral IR carbidopa-levodopa group were taking at least 1 or more classes of PD medications other than carbidopa-levodopa. 74% of patients were continued on concomitant medication use [52% dopamine agonists, 33% MAO-B inhibitors, 19% amantadine, 4% anticholinergics] provided they were stable on these doses for at least 4 weeks prior to screening. Patients were not allowed to receive supplemental products [containing carbidopa-levodopa, COMT inhibitors, MAO inhibitors, selective MAO-A inhibitors, apomorphine, or antidopaminergic agents] during the trial. The primary efficacy measure was the mean change from baseline in "on" time without troublesome dyskinesia in hours per day at the end of the study, as assessed but the patient's PD diary. "On" time without troublesome dyskinesia was defined as the sum of "on" time without dyskinesia and "on" time with non-troublesome dyskinesia. Patients reported an improvement in "on" time without troublesome dyskinesia with Crexont compared to IR carbidopa-levodopa, which was statistically significant (p=0.019). Crexont-treated patients also reported less "off" time compared to IR carbidopa-levodopa, which was statistically significant (p=0.025).

Table 3. Efficacy Results in Patients with Parkinson's Disease:

	Week 0 Enrollment	Week 7 Baseline (Randomization)	Week 20 End of Study (or Early Termination)	p-value
Mean "On" time without troublesome dyskinesia (hours)				
CREXONT	9.46	11.67	11.35	
Immediate-release carbidopa-levodopa	9.61	11.72	10.77	0.019*
Mean "Off" time (hours)				
CREXONT	6.15	3.95	4.18	
Immediate-release carbidopa-levodopa	6.05	4.02	4.75	0.025*

* p-value based on change from Week 7 (Baseline) to Week 20 (End of Study or Early Termination)

Crexont use is contraindicated in patients currently taking a nonselective monoamine oxidase (MAO) inhibitor or have taken within last 2 weeks. Use can cause hypertension. Warnings and precautions for Crexont include falling asleep during activities of daily living, especially in those with pre-existing somnolence; withdrawal-emergent hyperpyrexia and confusion that resembles neuroleptic malignant syndrome (elevated temperature, muscle rigidity, altered consciousness) usually associated with rapid-dose reduction versus a slow taper; cardiovascular ischemic events, especially those with a previous history of heart disease or risk factors – cardiac function should be monitored in an intensive care facility during initial dose adjustment for those with a previous history if myocardial infarction who have residual atrial, nodal, or ventricular arrhythmias; hallucination/psychosis accompanied by confusion, insomnia, excessive dreaming, abnormal thinking behavior, paranoid ideation, delusions, disorientation, agitation and delirium – levodopa dose reduction and non-dopamine affecting medications for psychosis may help; impulse control and compulsive behavior such as the urge to gamble, increased sexual urges, need to spend money, and binge eating can occur, and may be helped with dose reduction or medication discontinuation; dyskinesia may require dose reduction; peptic ulcer disease history may increase chance of developing upper GI hemorrhage; glaucoma development or worsening may occur since intraocular pressure can be increased by medication – IOP should be monitored regularly. Other adverse reactions to be aware of for Crexont include nausea, anxiety, dizziness, constipation, headache, and insomnia.

Using Crexont in pregnant women has not been studied, but animal studies suggest Crexont is developmentally toxic at clinically relevant doses with an estimated risk of 2-4% of major birth defects and 15-20% of miscarriages. Use is not recommended. Crexont use in lactating women is not recommended as the medication was found in the lactating milk. It is also known to decrease milk production. There is no adequate data on the effects on the breastfed infant; as such, it is not recommended. Safety and effectiveness have not been established in pediatric patients, and use is not advised. There were no differences in safety outcomes between patients less than 65 years of age, 65 to less than 75 years of age, and 75 years and older.

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 (38 approved, 0 rejected).

Financial Discussion: No comments or questions. The committee unanimously voted to accept the recommendations as presented. None were opposed (41 approved, 0 rejected).

Outcome: Crexont is a pharmacy benefit. It is not recommended to be added to Commercial, Exchange, or CHIP formularies. Crexont will require a prior authorization and is recommended to be added to Rytary Policy 380.0 with following changes to the original criteria:

- Medical record documentation of a diagnosis of Parkinson's disease, post-encephalitic parkinsonism, or parkinsonism that may follow carbon monoxide intoxication or manganese intoxication in adults **AND**
- Medical record documentation of therapeutic failure on, intolerance to, or contraindication to two (2) formulary alternatives, one of which must be ~~immediate release carbidopa/levodopa~~ carbidopa/levodopa ER tablet

GPI LEVEL: GPI-14

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

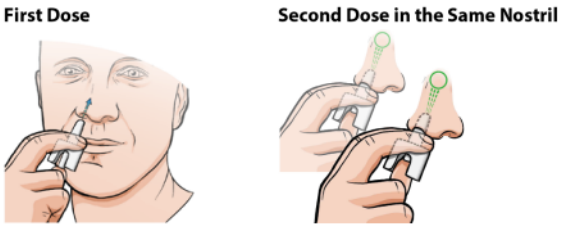
NEFFY (epinephrine nasal spray)

Review: Neffy is an alpha and beta-adrenergic receptor agonist indicated for emergency treatment of type I allergic reactions, including anaphylaxis, in adult and pediatric patients who weigh 30kg or greater.

The recommended dosage of neffy is one spray (2 mg of epinephrine) administered into one nostril. In absence of clinical improvement or if symptoms worsen after initial treatment, administer a second dose of neffy in the same nostril with a new nasal spray starting 5 minutes after the first dose.

- Patients should seek emergency medical assistance for close monitoring of the anaphylactic episode and in the event that further treatment is required.
- It is recommended that patients are prescribed and have immediate access to two neffy nasal sprays at all times.

Figure 1: Administration of Neffy



Neffy is supplied as a single use nasal spray that contains 2mg/0.1ml of epinephrine. Epinephrine is a first line treatment in anaphylaxis. Prior to Neffy, epinephrine was only able to be administered as an intramuscular or subcutaneous injection in an outpatient setting.

As far as clinical trials, studies were conducted to determine the pharmacokinetics and pharmacodynamics, as it is not ethical to test against life saving treatments when a patient is experiencing anaphylaxis. Neffy's FDA approval is based on studies of 175 healthy adults, without anaphylaxis. The concentration of epinephrine was measured in the blood following administration of

either neffy or an injectable epinephrine product. The results showed similar concentrations between these groups.

Study 1 & 2 compared PK data and PD data (pulse rate and systolic blood pressure) of epinephrine (1 – healthy subjects, 2 – adult patients with Type I allergy without anaphylaxis).

Study 3 &4: looked at adult subjects with Nasal Allergan Challenge Induced Rhinitis

Study 5: Pediatric patients with Type I Allergy without anaphylaxis –-(N = 21) children weighing at least 30kg. It showed that epinephrine concentrations in children were similar to those as adults who received neffy.

There are no contraindications to the use of epinephrine. There is a warning for neffy in those with certain nasal conditions, such as nasal polyps or nasal surgery, which may affect the drug absorption of neffy. These patients would be steered to use an injectable epinephrine product. There is also a warning about those with a sulfite allergy, however this should not limit the use of neffy. The most common adverse effects include throat irritation, headache, and other nasal discomfort. Caution should be taken with patients with coexisting conditions such as cardiac arrhythmias, coronary artery disease, hypertension, pulmonary edema, hyperthyroidism, renal impairment, Parkinson's disease, and diabetes. However, the benefit of epinephrine outweighs any risk associated with these conditions. Elderly patients may be more likely to experience adverse reactions.

There is a nasal epinephrine for those weighing 15kg to 30kg in the pipeline (1mg epinephrine) and waiting for FDA approval.

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 (39 approved, 0 rejected).

Financial Discussion: No comments or questions. The committee unanimously voted to accept the recommendations as presented. None were opposed (39 approved, 0 rejected).

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

- Medical record documentation of weight ≥ 30 kg **AND**
- Medical record documentation of being used for the treatment of type I allergic reactions, including anaphylaxis **AND**
- Medical record documentation that member does not have nasal polyps, or a history of nasal surgery, fracture, or injury **AND**
- Medical record documentation that the patient has shown the inability to properly use the generic epinephrine (EpiPen) device

QUANTITY LIMIT: 2 devices per fill

GPI LEVEL: GPI-14

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.

ERVEBO (Ebola Zaire Vaccine, Live)

Review: Ervebo, approved in the United States in 2019, is the first vaccine indicated for the prevention of disease caused by *Zaire ebolavirus* in individuals 12 months of age and older. The duration of protection conferred by Ervebo is unknown. Ervebo does not protect against other species of *Ebolavirus* or *Marburgvirus*. Effectiveness of the vaccine when administered concurrently with antiviral medication, IVIG, and/or blood or plasma transfusions is unknown.

Ervebo is a replication-competent, live, attenuated recombinant vesicular stomatitis virus vaccine. Ervebo is made by taking a small piece of the Ebola virus and adding it to the vesicular stomatitis virus, forming what is referred to as the "vaccine virus". Immunization with Ervebo results in an immune response and protection from disease caused by Zaire ebolavirus. The relative contributions of innate, humoral, and cell-mediated immunity to protection from Zaire ebolavirus are unknown.

Ervebo is not currently available to purchase in the United States. It is approved by the FDA, but the only supply is in the Federal Government stock for an emergency outbreak. Ervebo was used during a 2018 outbreak in Zaire and has since been used during other outbreaks with over 90,000 people vaccinated.

The ACIP recommends pre-exposure vaccination with Ervebo for adults 18 years of age and older who are at potential risk of exposure because they are responding to an outbreak of Zaire ebolavirus, work as healthcare personnel at a federally-designated Ebola Treatment Center, or work in a laboratory or are staff at biosafety-level 4 facilities.

The clinical development program for Ervebo included eight Phase 1 trials and four Phase 2/3 clinical studies conducted in North America, Europe, and Africa, in which a total of 15,399 adults received a dose of Ervebo. The total number of participants vaccinated with Ervebo in double-blind, placebo-controlled trials was 1,712 and in open label trials was 13,687. The duration of protection conferred by Ervebo is unknown.

The FDA stated that approval of Ervebo is supported by several trials, Including Study 3 conducted in Guinea during the 2014-2016 outbreak in individuals 18 years of age and older. The study was designed as a cluster vaccination study in which 3,537 contacts and contacts of contacts of individuals with laboratory-confirmed Ebolavirus received either "immediate" or 21-day "delayed" vaccination with Ervebo. The cluster design captures a social network of individuals and locations that might include dwellings or workplaces where a patient spent time while symptomatic, or the households of individuals who had contact with the patient during that person's illness or death. In both the individuals in the "immediate" vaccination arm and individuals in the "delayed" vaccination arm, Ervebo was determined to be 100% effective in preventing Ebola cases with symptom onset greater than 10 days after vaccination. No cases of Ebolavirus with symptom onset greater than 10 days after vaccination were observed in the "immediate" cluster group, compared with 10 cases of Ebolavirus in the 21-day "delayed" cluster group.

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 (34 approved, 0 rejected).

Financial Discussion: No comments or questions. The committee unanimously voted to accept the recommendations as presented. None were opposed (39 approved, 0 rejected).

Outcome: Ervebo is not currently available to purchase in the United States and will only be distributed by the Federal Government if needed for an outbreak. If Ervebo becomes commercially available, it will be a medical benefit if the member's specific plan allows for coverage of travel vaccines. Ervebo will be excluded from the Commercial Pharmacy Formulary. It is unable to be determined if it should be added to the medical benefit cost share list since no pricing is available. No prior authorization criteria will apply.

AUTHORIZATION LIMITATIONS: Approval is for a one-time injection

QUANTITY LIMIT: 1 mL per 999 days

AGE LIMIT: 12 months of age and older

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

INGREZZA SPRINKLE (valbenazine)

Review: Ingrezza Sprinkle is a vesicular monoamine transporter 2 (VMAT2) inhibitor indicated for treatment of adults with tardive dyskinesia or chorea associated with Huntington's disease. Ingrezza Sprinkle is a new formulation that allows patients to sprinkle the contents of the capsule over soft food such as applesauce, yogurt, or pudding, which must be taken within 2 hours of mixing. Like Ingrezza, the recommended dosing for Ingrezza Sprinkle is 40mg once daily and the dose may be increased every two weeks to the recommended dosage of 80mg once daily. A dosage of 40mg or 60mg may be considered based on patient response and tolerability. Ingrezza Sprinkle is available as 40mg, 60mg, and 80mg capsules. It can be taken with or without food, may be swallowed whole but must not be crushed or chewed, and should not be administered via nasogastric, gastrostomy, or other enteral tubes because it may cause obstruction.

The efficacy and safety of Ingrezza Sprinkle was established from clinical trials of Ingrezza. There were no specific Ingrezza Sprinkle trials performed. In a randomized, double-blind, placebo-controlled trial of Ingrezza for tardive dyskinesia, the primary efficacy endpoint showed a significant mean change from baseline in the AIMS dyskinesia score at the end of week 6 for patients taking Ingrezza. In a randomized, double-blind, placebo-controlled trial of Ingrezza for Huntington's disease, the primary efficacy endpoint showed a significant change from baseline in the Total Maximal Chorea score of the Unified Huntington's Disease Rating Scale (UHDRS) in patients taking Ingrezza.

Like Ingrezza, Ingrezza Sprinkle is contraindicated in patients with hypersensitivity to valbenazine or any components. There is a boxed warning for depression and suicidal ideation or behaviors in patients with Huntington's Disease. Other warnings and precautions include hypersensitivity reactions, somnolence and sedation, QT prolongation, Neuroleptic Malignant Syndrome (NMS), and parkinsonism. Use should be avoided in pregnant patients as the risk of major birth defects is unknown and women should be advised not to breastfeed during treatment of Ingrezza Sprinkle. The recommended dosage for patients with moderate or severe hepatic impairment is 40mg once daily. No dose adjustment is required for elderly patients or patients with renal 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: No comments or questions. The committee unanimously voted to accept the recommendations as presented. None were opposed (38 approved, 0 rejected).

Financial Discussion: Dr. Yarczower questioned if we require a prior authorization for amantadine. There is no prior authorization requirement for amantadine. No additional comments or questions. The committee unanimously voted to accept the recommendations as presented. None were opposed (39 approved, 0 rejected).

Outcome: Ingrezza Sprinkle is a pharmacy benefit and will not be added to Commercial, Marketplace, and CHIP formularies. It should be added to the Commercial Policy 465.0 Ingrezza, which has the following prior authorization criteria:

Tardive Dyskinesia

- Medical record documentation of age greater than or equal to 18 years **AND**
- Medical record documentation that Ingrezza is prescribed by, or in consultation with, a psychiatrist or neurologist **AND**
- Medical record documentation of a diagnosis of tardive dyskinesia (TD) as evidenced by one of the following:
    - Moderate to severe abnormal body movement (AIMS score 3 or 4) in greater than or equal to 1 body area **OR**
    - Mild abnormal body movements (AIMS score 1 or 2) in greater than or equal to 2 body areas **AND**
- Medical record documentation that the member was assessed for and determined to have no other causes of involuntary movements **AND**
- Medical record documentation of the member's baseline AIMS score prior to initiating therapy **AND**
- If member's symptoms are related to use of a first-generation antipsychotic, medical record documentation that a switch to a second-generation antipsychotic has been attempted and did not resolve tardive dyskinesia symptoms **OR** provider rationale as to why a switch to a second-generation antipsychotic would not be appropriate for the member **AND**
- Medical record documentation of therapeutic failure on, intolerance to, or contraindication to amantadine

Huntington's Disease

- Medical record documentation of age greater than or equal to 18 years **AND**
- Medical record documentation that Ingrezza is prescribed by, or in consultation with, a neurologist or psychiatrist **AND**
- Medical record documentation of a diagnosis of Huntington's Disease **AND**
- Medical record documentation of symptoms of chorea **AND**
- Medical record documentation of patient's baseline Total Maximal Chorea Score prior to initiating therapy **AND**
- Medical record documentation of one of the following:
    - If patient has a history of prior suicide attempt, bipolar disorder, or major depressive disorder: Medical record documentation that patient was evaluated and treated by a psychiatrist **OR**
    - For all others: Medical record documentation of a mental health evaluation performed by the prescriber **AND**
- Medical record documentation of therapeutic failure on, intolerance to, or contraindication to tetrabenazine

AUTHORIZATION DURATION: Initial approval will be for a period of one (1) year. Reevaluation of coverage will be every one (1) year and will require documentation of:

- For Tardive Dyskinesia: Medical record documentation of an improvement in tardive dyskinesia (TD) as evidenced by a reduction from baseline in the patient's AIMS score
- For Huntington's Disease: Medical record documentation of an improvement in chorea associated with Huntington's Disease as evidenced by a reduction in the Total Maximal Chorea Score from baseline

GPI LEVEL: GPI-10

QUANTITY LIMIT: 1 capsule per day

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.

COBENFY (xanomeline/trospium chloride)

Review: Cobenfy is a combination of xanomeline and tropsium chloride indicated for the treatment of schizophrenia in adults. The mechanism of action of xanomeline in the treatment of schizophrenia is unclear, but it is believed to be due to agonist activity in M1 and M4 muscarinic acetylcholine receptors in the central nervous system. Tropsium antagonizes the muscarinic receptors primarily in the peripheral tissues. Cobenfy offers a novel mechanism of action from first- and second-generation antipsychotics by targeting M1 and M4 receptors expressed in brain regions that are implicated in psychosis and cognition.

The recommended starting dose is 50 mg/20 mg capsule orally twice daily for at least 2 days. The dosage should be increased to 100 mg/20 mg capsule twice daily for at least five days. Then the dosage can be increased to 125 mg/30 mg capsule twice daily based on tolerability and response. The maximum recommended dosage is 125 mg/30 mg twice daily. In geriatric patients, a slower titration should be considered and the maximum recommended dosage is 100 mg/20 mg capsules twice daily. Cobenfy is supplied as 50 mg/20 mg capsules, 100 mg/20 mg capsules, and 125 mg/30 mg capsules.

The efficacy of Cobenfy was evaluated in EMERGENT-2 and EMERGENT 3, two placebo-controlled studies in adult patients with schizophrenia according to DSM-5 criteria. Patients randomized to Cobenfy were started on an initial dose of 50 mg/20 mg orally twice daily for the first 2 days, then if tolerated the dose was increased to 100 mg/20 mg twice daily on Days 3 to 7, then on Day 8, the dose was titrated to 125 mg/30 mg twice daily if the patient could tolerate it. All patients could return to 100 mg/20 mg twice daily for the remainder of the treatment period.

The primary efficacy measures was change from baseline in the Positive and Negative Syndrome Scale (PANSS) total score at Week 5, a 30-item scale measuring the symptoms of schizophrenia. Total scores range from 30 to 210 with higher scores reflecting greater overall symptoms severity.

In both studies, patients randomized to Cobenfy showed a statistically significant reduction from baseline to Week 5 in the PANSS total score compared to placebo group (Table 4). Secondary endpoints measuring change from baseline to Week 5 in Clinical Global Impression-Severity (CGI-S) score was statistically significant for Cobenfy compared to placebo. CGI-S measures the patients current illness state and overall clinical state on a 1 to 7 point scale.

Table 4. Primary Efficacy Results for Change from Baseline in PANSS Total Score at Week 5 in Adults with Schizophrenia (EMERGENT-2 and EMERGENT-3)

			Primary Efficacy Endpoint: PANSS Total Score		
Study Number	Treatment Group	N	Mean Baseline Score (SD)	LS Mean Change from Baseline (SE)	Placebo-subtracted Difference (95% CI) [a]
1	COBENFY	117	98.2 (8.9)	-21.2 (1.7)	-9.6 (-13.9, -5.2)*
	Placebo	119	97.7 (9.4)	-11.6 (1.6)	
2	COBENFY	114	96.9 (8.8)	-20.6 (1.6)	-8.4 (-12.4, -4.3)*
	Placebo	120	96.5 (8.8)	-12.2 (1.6)	

The PANSS Total Score may range from 30 to 210; higher scores reflect greater symptom severity.
SD: standard deviation; SE: standard error; LS Mean: least-squares mean; CI: confidence interval.
[a] Difference (drug minus placebo) in LS mean change from baseline.
*Statistically significantly superior to placebo.

There are no black box warnings for Cobenfy. Warnings include risk of urinary retention, risk of use with hepatic impairment, risk of use in patients with biliary disease, decreased gastrointestinal motility, risk of angioedema, risk of narrow-angle glaucoma, increases in heart rate, anticholinergic adverse reactions in patients with renal impairment, and central nervous system effects, including dizziness, confusion, hallucinations, and somnolence. Cobenfy is contraindicated in patients with pre-existing urinary retention, because patients with clinically significant bladder outlet obstruction and incomplete bladder emptying may be at increased risk of urinary retention. The most common adverse reactions reported in clinical

trials were nausea, dyspepsia, constipation, vomiting, hypertensions, abdominal pain, diarrhea, tachycardia, dizziness, and gastroesophageal reflux disease.

The safety and efficacy of Cobenfy in pediatric patients have not been established. Controlled clinical studies did not include patients older than 65 years of age to determine if they respond differently from younger adult patients. Because Cobenfy can increase the risk of urinary retention in geriatric patients, including older males with bladder outlet obstruction due to benign prostatic hyperplasia (BPH), a slower titration and lower maximum dosage is recommended in geriatric patients.

The recommended dosage in patients with mild renal impairment is the same as the recommended dosage for patients with normal renal function. Use of Cobenfy is not recommended in patients with moderate or severe renal impairment.

Use of Cobenfy is contraindicated in patients with moderate or severe hepatic impairment. It is not recommended in patients with mild hepatic impairment due to higher xanomeline exposures compared to patients with normal hepatic function.

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. Shepherd asked the effect on the PANNS scale. Kim R confirmed it was a statistically significant reduction in the PANSS score to week 5. There was a difference from placebo of 9.6 in the first trial and 8.4 in the second trial. No additional comments or questions. The committee unanimously voted to accept the recommendations as presented. None were opposed (33 approved, 0 rejected).

Financial Discussion: No comments or questions. The committee unanimously voted to accept the recommendations as presented. None were opposed (39 approved, 0 rejected).

Outcome: Cobenfy is a pharmacy benefit and will be added to the Specialty tier or Brand NP tier (for members with a three-tier formulary) of the Commercial, Marketplace, and GHP Kids. The following prior authorization criteria will apply:

- Medical record documentation of a diagnosis of schizophrenia **AND**
- Medical record documentation that member is 18 years of age or older **AND**
- Medical record documentation that member does not have pre-existing urinary retention **AND**
- Medical record documentation of therapeutic failure on, intolerance to, or contraindication to three formulary atypical antipsychotics

AUTHORIZATION DURATION: Lazcluze is configured as a prior authorization for new starts only. Lazcluze 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:

- 50 mg/20 mg, 100 mg/20 mg, 125 mg/30 mg capsules: 2 capsules per day, 30 day supply per fill
- Cobenfy Starter Pack: 56 capsules per 180 days

GPI LEVEL: GPI-10

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.

AUCATZYL (obecabtagene autoleucel)

Review: Aucatzyl is a CD19-directed genetically modified autologous T cell immunotherapy indicated for the treatment of adults with relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL). Anti-CD19 CAR-positive T cells engage with CD19-expressing target cells (cancer and normal B cells), which leads to activation of the anti-CD19 CAR-positive T cells, resulting in anti-tumor activity and killing of CD19-expressing target cells. Aucatzyl is the second CAR-T to be approved for the treatment of ALL in all adults, and it will directly compete with already approved Tecartus. Aucatzyl does not require a Risk Evaluation and Mitigation Strategy (REMS) program, which is unlike other CAR-T therapies. It is designed to reduce the excessive activation of the programmed T cells, which can potentially improve safety, including what appears to be lower rates of CRS and ICANS compared to Tecartus.
Aucatzyl is for autologous use only and is dosed as 410 x 10^6 CD19 CAR-positive viable T cells, to be given as a split dose. It is supplied in 5 infusion bags which can be supplied in one of three color-coded bags: blue (10x106), orange (100x106), and red (300x106). The dosing regimen is determined by the tumor burden assessed by bone marrow blast percentage from a sample obtained 7 days prior to lymphodepletion. The second split dose may be postponed or discontinued due to adverse events. The treatment scheduled with fludarabine (FLU) and cyclophosphamide (CY) is summarized in Figure 1 above.

Aucatzyl was evaluated for efficacy in an open-label, multi-center, single-arm study called the FELIX study (NCT 04404660) in patients with relapsed or refractory B-cell acute lymphoblastic leukemia (ALL). Patients were included if they were refractory, had first relapse following a remission lasting less than or equal to 12 months, relapsed/refractory after 2 or more prior lines of therapy, or relapsed/refractory 3 months or more after allogenic stem cell transplantation (SCT). Also to be included, patients had to have ≥5% blasts in bone marrow at screening. Patients were excluded if they had isolated extra medullary disease, active or serious infections requiring systemic antimicrobials, active graft versus host disease, or history/presence of CNS disorders.

Treatment was administered in-patient and started with lymphodepleting chemotherapy (fludarabine for 4 days and cyclophosphamide for 2 days starting with the fludarabine), followed by Aucatzyl as a split dose given at 410x106 CD19 CAR-positive viable T cells. 112 patients underwent leukapheresis , with 18 discontinuing without going on to receive Aucatzyl. Reasons included: death (n=11), adverse event (1), physician decision (1), and manufacturing failure (5). Of the 94 patients left, 65 had ≥5% blasts in the bone marrow, prior to the start of lymphodepleting therapy, and were considered as efficacy-evaluable patients.

The median age was 51 years (range: 20 to 77 years) with 7 (11%) patients ≤25 years of age and 14 (22%) patients ≥65 years of age. 35 (54%) patients were refractory to the most recent line of therapy, and 32 (49%) patients were relapsed within 12 months of first-line therapy. The median number of prior lines of therapy was 2 (range 1 to 6). 17 (26%) patients had Ph+ ALL, 13 (20%) had extramedullary disease, and 59 (91%) had bridging therapy between leukapheresis and lymphodepleting chemotherapy. 59 (89%) patients received the target dose, and 5 (8%) patients received only the first dose (primarily due to adverse reaction). The median time from leukapheresis to Aucatzyl was 35 days (range 26 to 74 days days).

The major efficacy outcome was rate and duration of complete remission within 3 months after infusion. Additional endpoints were rate and duration of overall complete remission (including complete remission and complete remission with incomplete hematologic recovery at any time). Efficacy results are summarized in Table 1 of the review.

Aucatzyl has black box warnings for cytokine release syndrome (CRS), Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS) and T-cell malignancies. There are no contraindications listed.

Warnings and precautions include CRS, neurologic toxicities (ICANS), prolonged cytopenia, infections, hypogammaglobulinemia, Hemophagocytic Lymphohistiocytosis/Macrophage Activation Syndrome (HLH/MAS), hypersensitivity reactions, and secondary malignancies. For CRS and ICANS, the prescribing information recommends that patients be closely monitored during and following treatment, for at least 14 days at the healthcare facility following the first infusion, and continued monitoring for at least 4 weeks after the first infusion. Patients are to be evaluated for hospitalization at first signs of CRS, and treated with supportive care based on severity and per guidelines. For T cell malignancies, they may present as soon as weeks following infusions and may include fatal outcomes.

The most common serious adverse reactions of any Grade included infections (pathogens unspecified), febrile neutropenia, ICANS, CRS, fever, bacterial infectious disorders, encephalopathy, fungal infections, hemorrhage, respiratory failure, hypotension, ascites, HLH/MAS, thrombosis and hypoxia. 9 patients had fatal adverse reactions which included infections (sepsis, pneumonia, peritonitis), ascites, pulmonary embolism, acute respiratory distress syndrome, HLH/MAS and ICANS. Of the 9 patients, 5 had pre-existing and ongoing neutropenia. No overall differences in safety or efficacy were observed between patients 65 years and older compared to younger patients.

Per NCCN guidelines, Aucatzyl is recommended for relapsed/refractory disease Ph+ B-ALL after ABL1 kinase domain mutation testing, if following therapy that has included TKIs. It is recommended to consider HCT after Aucatzyl. Aucatzyl is also recommended for relapsed/refractory disease, Ph- B-ALL after molecular characterization and MRD assessment as a preferred regimen. It is also recommended to consider HCT after Aucatzyl. NCCN also documents that Aucatzyl is not associated with a REMS program.

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 (30 approved, 0 rejected).

Financial Discussion: No comments or questions. The committee unanimously voted to accept the recommendations as presented. None were opposed (37 approved, 0 rejected).

Outcome: Aucatzyl is a medical benefit and will require prior authorization. Aucatzyl will be added to the medical benefit cost share list when processed on the medical benefit. The following prior authorization criteria will apply:

- Medical record documentation that Aucatzyl is prescribed by a hematologist or oncologist **AND**
- Medical record documentation of age greater than or equal to 18 years old **AND**
- Medical record documentation of a diagnosis of relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL) **AND**
- Medical record documentation that the member has not received prior treatment with CAR-T cell therapy or other genetically modified T cell therapy

AUTHORIZATION DURATION: One-time six (6) month authorization for split dose administration of Aucatzyl.

QUANTITY LIMIT: Maximum of two (2) lifetime doses, given on day 1 and day 10 (± 2 days)

RPH SIGNOFF REQUIRED: Yes

OTHER RECOMMENDATIONS FOR TECARTUS: It is recommended to update the Tecartus criteria to align with other CAR-T policies. The following additional prior authorization criteria should apply:

Mantle Cell Lymphoma (MCL)

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

- Medical record documentation of diagnosis of relapsed or refractory mantle cell lymphoma (MCL) **AND**
- Medical record documentation that the member has not received prior treatment with CAR-T cell therapy or other genetically modified T cell therapy.

Acute Lymphoblastic Leukemia (ALL)

- Medical record documentation that Tecartus is prescribed by a hematologist/oncologist **AND**
- Medical record documentation of age greater than or equal to 18 years **AND**
- Medical record documentation of a diagnosis of relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL) **AND**
- Medical record documentation that the member has not received prior treatment with CAR-T cell therapy or other genetically modified T cell therapy

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

CLASS REVIEWS

FERTILITY AGENTS

Agents for Infertility[1]			
Brand Name	**Generic**	**Generic Available?**	**Manufacturer**
Selective Estrogen Receptor Modulator (SERM)			
Clomid*	Clomiphene citrate	Yes	Sanofi-Aventis US
Aromatase Inhibitor (AI)			
Femara	Letrozole	Yes	Novartis Pharma
Human Chorionic Gonadotropin (HCG)			
Ovidrel	Choriogonadotropin alfa	No	EMD Serono
Pregnyl	Chorionic Gonadotropin	Yes	Organon USA Inc
Novarel*	Chorionic Gonadotropin	Yes	Ferring
Human Menopausal Gonadotropin (HMG)			
Menopur	Menotropins	No	Ferring
Gonadotropin-Releasing Hormone (GnRH) Antagonist			
Fyremadel	Ganirelix acetate	Yes	SUN Pharm
Cetrotide	Cetrorelix acetate	Yes	EMD Serono Inc
Gonadotropin-Releasing Hormone (GnRH) Agonist			
Lupron Depot	Leuprolide acetate	Yes	AbbVie Endocrine Inc
Follicle- Stimulating Hormone (FSH)			
Gonal- F	Follitropin alfa/beta	No	EMD Serono
Follistim AQ	Follitropin alfa/beta	No	Organon USA Inc
Dopamine Receptor Agonist			
Parlodel	Bromocriptine mesylate	Yes	SS Pharma

*Brand discontinued

Clinical Summary: Infertility is a disease, condition, or status characterized by any of the following:

- The inability to achieve a successful pregnancy based on a patient's medical, sexual, and reproductive history, age, physical findings, diagnostic testing, or any combination of those factors
- The need for medical intervention, including, but not limited to, the use of donor gametes or donor embryos to achieve a successful pregnancy either as an individual or with a partner
- In patients having regular, unprotected intercourse and without any known etiology for either partner suggestive of impaired reproductive ability, evaluation should be initiated at 12 months when the female partner is under 35 years of age and at 6 months when the female partner is 35 years of age or older.

In the United States, 1 in 5 women aged 15 to 49 with no prior pregnancies are unable to get pregnant after one year of trying. About 1 in 4 women in this same group have difficulty getting pregnant or carrying a pregnancy to full term. There is a rising trend for women to delay childbearing to later of life (in there 30s and 40s, instead of their 20s). A women's chance of having a baby becomes to rapidly to decrease every year after the age of 30.

Infertility can be due to factors seen in both women and men. The individuals involved in conception need to have a functioning reproductive system to have a successful pregnancy. When women have a disruption in ovarian function, fallopian tube obstruction, and/or abnormalities of the uterus, this may be the cause of infertility. When men have a disruption or testicular or ejaculatory function, hormonal disorder, and/or genetic disorder that affects sperm count, this may be the cause of infertility. Some risk factors for infertility in both women and men include increased age, being overweight or obese, smoking, and excessive alcohol or drug use. Sometimes unexplained infertility occurs in which no cause is found.

The type of treatment for infertility depends on the cause of infertility, its duration, and the age of the individuals trying to conceive. Treatment options for infertility include timed intercourse, medications, intrauterine insemination (IUI), surgery, and/or assisted reproductive technology (ART), the main type being in vitro fertilization (IVF).

Recommendations Based on Clinical Review:

Commercial (Traditional)/ Exchange (Marketplace)/CHIP (Kids)		
Medication	**Current Policy**	**Recommendations**
Clomid* (clomiphene citrate)	Non-formulary	**Add generic to formulary, no prior authorization required.** *Rationale: ADRM guidelines recommend first line*
Femara (letrozole)	No prior authorization required	No changes
Ovidrel (choriogonadotropin alfa) **Pregnyl (chorionic gonadotropin)** **Novarel* (chorionic gonadotropin)**	**Human Chorionic Gonadotropin (hCG) Policy 572.0** • Medical record documentation that human chorionic gonadotropin (hCG) is prescribed by or in consultation with a reproductive specialist or infertility specialist AND • Medical record documentation of age greater than or equal to 18 years AND • Medical record documentation of use for ovulation induction in females AND • Medical record documentation of therapeutic failure, contraindication, or intolerance to Pregnyl **OR** • Medical record documentation of use for a Food and Drug Administration (FDA) approved indication (hypogonadotropic hypogonadism in males or prepubertal cryptorchidism) AND • Medical record documentation of therapeutic failure, contraindication, or intolerance to Pregnyl **Novarel Policy 573.0** • Medical record documentation that Novarel is prescribed by or in consultation with a reproductive specialist or infertility specialist AND • Medical record documentation of age greater than or equal to 18 years AND • Medical record documentation of use for ovulation induction in females AND • Medical record documentation of therapeutic failure, contraindication, or intolerance to Pregnyl **OR** • Medical record documentation of use for a Food and Drug Administration (FDA) approved indication	**Human Chorionic Gonadotropin (hCG) Policy 572.0** • Medical record documentation that human chorionic gonadotropin (hCG) is prescribed by or in consultation with a reproductive specialist or infertility specialist AND • Medical record documentation of age greater than or equal to 18 years AND • Medical record documentation of use for ovulation induction in females AND • Medical record documentation of therapeutic failure, contraindication, or intolerance to ~~Pregnyl~~ letrozole and clomiphene **OR** • Medical record documentation of use for a Food and Drug Administration (FDA) approved indication (hypogonadotropic hypogonadism in males or prepubertal cryptorchidism) AND • Medical record documentation of therapeutic failure, contraindication, or intolerance to Pregnyl. *Rationale: ADRM guidelines recommend trying letrozole and clomiphene before gonadotropins* **Novarel Policy 573.0** • Medical record documentation that Novarel is prescribed by or in consultation with a reproductive specialist or infertility specialist AND • Medical record documentation of age greater than or equal to 18 years AND • Medical record documentation of use for ovulation induction in females AND • Medical record documentation of therapeutic failure, contraindication, or intolerance to ~~Pregnyl~~ letrozole and clomiphene **OR**

	(hypogonadotropic hypogonadism in males or prepubertal cryptorchidism) AND • Medical record documentation of therapeutic failure, contraindication, or intolerance to Pregnyl	• Medical record documentation of use for a Food and Drug Administration (FDA) approved indication (hypogonadotropic hypogonadism in males or prepubertal cryptorchidism) AND • Medical record documentation of therapeutic failure, contraindication, or intolerance to Pregnyl. *Rationale: ADRM guidelines recommend trying letrozole and clomiphene before gonadotropins.*
Menopur (menotropins)	No prior authorization required	No changes
Fyremadel (ganirelix acetate)	No prior authorization required	No changes
Cetrotide (cetrorelix acetate)	No prior authorization required	No changes
Lupron Depot (leuprolide acetate)	No prior authorization required	No changes
Gonal-F (follitropin alfa/beta) **Follistim AQ (follitropin alfa/beta)**	**Follistim AQ Policy 570.0** <u>For Females:</u> • Medical record documentation that Follistim AQ is prescribed by or in consultation with a reproductive specialist or infertility specialist AND • Medical record documentation of age greater than or equal to 18 years AND • Medical record documentation of one of the following: - Poor/diminished ovarian reserve OR - Tubal factor infertility OR - Follistim AQ is being used with donor eggs OR - In Vitro Fertilization AND • Medical record documentation of therapeutic failure, contraindication, or intolerance to Gonal-f **OR** • Medical record documentation that Follistim AQ is prescribed by or in consultation with a reproductive specialist or infertility specialist AND • Medical record documentation of age greater than or equal to 18 years AND • Medical record documentation that infertility is not due to primary ovarian failure AND • Medical record documentation that Follistim AQ is being using concomitantly with an hCG product AND • Medical record documentation of therapeutic failure, contraindication, or intolerance to Gonal-f AND	**Add prior authorization to Gonal-F.** **Gonal-F Policy** <u>For Females:</u> • Medical record documentation that Gonal-F is prescribed by or in consultation with a reproductive specialist or infertility specialist AND • Medical record documentation of age greater than or equal to 18 years AND • Medical record documentation of one of the following: - Poor/diminished ovarian reserve OR - Tubal factor infertility OR - Gonal-F is being used with donor eggs OR - In Vitro Fertilization AND • Medical record documentation of therapeutic failure, contraindication, or intolerance to Follistim AQ **OR** • Medical record documentation that Gonal-F is prescribed by or in consultation with a reproductive specialist or infertility specialist AND • Medical record documentation of age greater than or equal to 18 years AND • Medical record documentation that infertility is not due to primary ovarian failure AND • Medical record documentation that Gonal-F is being using concomitantly with an hCG product AND • Medical record documentation of therapeutic failure, contraindication, or intolerance to Follistim AQ AND • For patients without a diagnosis of hyperprolactinemic anovulation:

	• For patients without a diagnosis of hyperprolactinemic anovulation: - Medical record documentation of therapeutic failure, contraindication, or intolerance to clomiphene and/or letrozole for a total of 3 cycles OR • For patients with a diagnosis of hyperprolactinemic anovulation, one of the following: - Uncorrected prolactin levels, greater than 25 ng/mL, after 6 months of therapy on bromocriptine or cabergoline OR - Corrected prolactin levels, less than or equal to 25 ng/mL, on bromocriptine or cabergoline with therapeutic failure, contraindication, or intolerance to 3 cycles of clomiphene and/or letrozole <u>For Males:</u> • Medical record documentation that Follistim AQ is prescribed by or in consultation with a reproductive specialist or infertility specialist AND • Medical record documentation of male factor infertility AND • Medical record documentation of therapeutic failure, contraindication, or intolerance to Gonal-f	- Medical record documentation of therapeutic failure, contraindication, or intolerance to clomiphene, letrozole, and/or bromocriptine for a total of 3 cycles OR • For patients with a diagnosis of hyperprolactinemic anovulation, one of the following: - Uncorrected prolactin levels, greater than 25 ng/mL, after 6 months of therapy on bromocriptine or cabergoline OR - Corrected prolactin levels, less than or equal to 25 ng/mL, on bromocriptine or cabergoline with therapeutic failure, contraindication, or intolerance to 3 cycles of clomiphene and/or letrozole <u>For Males:</u> • Medical record documentation that Gonal-F is prescribed by or in consultation with a reproductive specialist or infertility specialist AND • Medical record documentation of male factor infertility AND • Medical record documentation of therapeutic failure, contraindication, or intolerance to Follistim AQ. *Rationale: Gonal-F should require prior authorization for appropriate use.*
Parlodel (bromocriptine mesylate)	No prior authorization required	No changes

Clinical Discussion: It was asked what lines of business covered fertility? This includes Commercial, Exchange, and most self-insured plans. No additional comments or questions. The committee unanimously voted to accept the recommendations as presented. None were opposed (33 approved, 0 rejected).

Recommendations Based on Financial Review:

- Add clomiphene to formulary at the Brand Preferred Tier
- Remove Gonal-F from formulary
- Move Follistim AQ to the Brand Preferred Tier, remove prior authorization

Financial Discussion: It was asked if we should give providers a heads up regarding this change? We will be sure to communicate to the Geisinger fertility clinics. No additional comments or questions. The committee unanimously voted to accept the recommendations as presented. None were opposed (31 approved, 0 rejected).

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

UPDATES

MEDICAL BENEFIT POLICY UPDATES

Drug Optimization Program Update

Recommendations: The following (highlighted) drug products are recommended to be added to the Medical Benefit Drug Optimization Program effective on 6/1/25 and 9/1/25. No other changes are recommended to the program at this time.

MBP 300.0 Medical Benefit Drug Optimization Program (Commercial, Exchange)

I. Policy:
Medical Benefit Drug Optimization Program

II. Purpose/Objective:
To provide a policy of coverage regarding certain complex, rare disease, and specialty drugs, which are required to be obtained from and billed by a Specialty Pharmacy and are not eligible for direct reimbursement to a provider or facility. This policy applies to these medications:

1. AbobotulinumtoxinA (Dysport)
2. Ado-Trastuzumab Emtansine (Kadcyla) [effective 9-1-25]
3. Aripiprazole (Abilify Maintena, Abilify Asimtufii) [effective 6-1-25]
4. Aripiprazole lauroxil (Aristada Initio, Aristada) [effective 6-1-25]
5. Asparaginase (Erwinia [Recombinant]) (Rylaze) [effective 9-1-25]
6. Atezolizumab (Tecentriq)
7. Avelumab (Bavencio)
8. Belatacept (Nulojix) [effective 6-1-25]
9. Belinostat (Beleodaq) [effective 9-1-25]
10. Brentuximab Vedotin (Adcetris) [effective 9-1-25]
11. Bortezomib [effective 9-1-25]
12. Carfilzomib (Kyprolis) [effective 9-1-25]
13. Cemiplimab (Libtayo)
14. Collagenase (Xiaflex) [effective 6-1-25]
15. Daunorubicin and Cytarabine (Liposomal) (Vyxeos) [effective 9-1-25]
16. Daratumumab (Darzalex)
17. Daratumumab and Hyaluronidase (Darzalex Faspro)
18. DaxibotulinumtoxinA (Daxxify)
19. Dostarlimab (Jemperli)
20. Durvalumab (Imfinzi)
21. Eribulin (Halaven)
22. Enfortumab Vedotin (Padcev)
23. Fam-Trastuzumab Deruxtecan (Enhertu)
24. Fluphenazine deconate [effective 6-1-25]
25. Haloperidol deconate [effective 6-1-25]
26. IncobotulinumtoxinA (Xeomin)
27. Inotuzumab Ozogamicin (Besponsa) [effective 9-1-25]
28. Ipilimumab (Yervoy)
29. Mogamulizumab (Poteligeo)
30. Nivolumab (Opdivo)
31. Obinutuzumab (Gazyva)
32. Octreotide (Sandostatin LAR)
33. Olanzapine (Zyprexa Relprevv) [effective 6-1-25]
34. OnabotulinumtoxinA (Botox)
35. Paliperidone (Invega Sustenna, Invega Hafyera, Invega Trinza) [effective 6-1-25]
36. Panitumumab (Vectibix)
37. Pegloticase (Krystexxa) [effective 6-1-25]
38. Pembrolizumab (Keytruda)
39. Polatuzumab Vedotin (Polivy)
40. Ramucirumab (Cyramza)
41. Relatlimab and nivolumab (Opdualag)
42. Retifanlimab (Zynyz)
43. RimabotulinumtoxinB (Myobloc)
44. Risperidone (Perseris, Risperdal Consta, Rykindo, Uzedy) [effective 6-1-25]
45. Rituximab (Rituxan)
46. Rituximab and Hyaluronidase (Rituxan Hycela)
47. Romidepsin (Istodax) [effective 9-1-25]
48. Romiplostim (Nplate) [effective 6-1-25]
49. Tislelizumab (Tevimbra) [effective 6-1-25]
50. Toripalimab (Loqtorzi)
51. Trastuzumab (Herceptin)
52. Tremelimumab (Imjudo

Discussion: What are we hearing from the prescribing community around the white bagging initiatives? There has been some pushback from prescribers, we have re-contracted with some sites, seem to be getting into a groove of implementing new phases and adding medications to the program. The response has been site specific with some more receptive than others. No additional comments or questions.

Outcome: The committee unanimously voted to accept the recommendations as presented. None were opposed (33 approved, 0 rejected).

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

Omnipod 5 Update

Background: Omnipod 5 was approved for use in adults with Type 2 Diabetes Mellitus.

Recommendation: There are no changes to formulary status, but it is recommended to update the prior authorization criteria for Commercial/Exchange/CHIP and Medicare to reflect the new indication.

Type 1 Diabetes Mellitus

- Medical record documentation of a diagnosis of type 1 diabetes mellitus **AND**
- Medical record documentation that member is 2 years of age or older

OR

Type 2 Diabetes Mellitus

- Medical record documentation of a diagnosis of type 2 diabetes mellitus **AND**
- Medical record documentation that member is 18 years of age or older

Outcome: The committee unanimously voted to accept the recommendations as presented. None were opposed (37 approved, 0 rejected).

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

Meeting adjourned at 3:27 pm.

The next bi-monthly scheduled meeting will be held on March 11th, 2025 at 1:00 p.m.

Meeting will be held virtually via phone/Microsoft Teams.