LifeWise
Health Plan of Washington

PHARMACY POLICY – 5.01.615
Pharmacologic Treatment of Chronic Non-Infectious Liver Diseases

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Introduction

Primary biliary cholangitis (PBC), formerly known as primary biliary cirrhosis, is a chronic liver disease. The body's immune system mistakenly attacks the liver's healthy cells in the small bile ducts (intrahepatic bile ducts). Bile is a fluid made by the liver. It removes toxins and waste from the body and helps with digestion. In PBC, the bile ducts become damaged and destroyed over time. Bile then builds up and causes scarring of the liver (cirrhosis). Treatment of PBC is meant to slow down the progression of liver damage. Metabolic dysfunction–associated steatotic liver disease (MASLD) is a common chronic liver condition and is often associated with obesity and type 2 diabetes. It is estimated that about 25% of the US population is affected by MASLD, although many people do not know that they have it. Metabolic dysfunction–associated steatohepatitis (MASH) is the most severe form of MASLD and is characterized by an accumulation of fat in the liver. People with MASH are more likely to develop serious liver complications such as liver failure or liver cancer. This policy describes when drugs used to treat chronic non-infectious liver diseases may be considered medically necessary.

Note: The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.

Policy Coverage Criteria

Drug	Medical Necessity
Primary Biliary Cholangitis	
Iqirvo (elafibranor)	**Iqirvo (elafibranor) may be considered medically necessary for the treatment of primary biliary cholangitis (PBC) in combination with ursodeoxycholic acid (UDCA) in adults with an inadequate response to UDCA, or as monotherapy in adults unable to tolerate UDCA when the following criteria are met:** • The individual is aged 18 years or older **AND** • Meets 1 of the following: ○ Has PBC without cirrhosis **OR** ○ Has PBC with compensated cirrhosis (Child-Pugh A) and no evidence of portal hypertension **AND** • Diagnosis is confirmed by consistently elevated alkaline phosphatase (ALP) for at least 6 months at time of diagnosis and 1 of the following: ○ Positive antimitochondrial (AMA) test **OR** ○ Presence of sp100 or gp210 autoantibodies if AMA negative **OR** ○ Liver biopsy consistent with PBC **AND** • The diagnosis is not associated with a cholestatic drug reaction, complete biliary obstruction, sarcoidosis, and primary sclerosing cholangitis **AND** • The individual has tried ursodeoxycholic acid (UDCA) for at least 1 year and had an inadequate response to UDCA therapy OR the individual has tried UDCA and has a documented intolerance to use of UDCA **AND**

Drug	Medical Necessity
Primary Biliary Cholangitis	
	• Iqirvo (elafibranor) is prescribed by or in consultation with a gastroenterologist or hepatologist **AND** • Iqirvo (elafibranor) will not be used in combination with Livdelzi (seladelpar) **AND** • The dose is limited to 80 mg once daily **AND** • The quantity is limited to 30 tablets per 30 days

Livdelzi (seladelpar)	**Livdelzi (seladelpar) may be considered medically necessary for the treatment of primary biliary cholangitis (PBC) in combination with ursodeoxycholic acid (UDCA) in adults with an inadequate response to UDCA, or as monotherapy in adults unable to tolerate UDCA when the following criteria are met:**
	• The individual is aged 18 years or older
	AND
	• Meets 1 of the following:
	  ○ Has PBC without cirrhosis
	  OR
	  ○ Has PBC with compensated cirrhosis (Child-Pugh A) and no evidence of portal hypertension
	AND
	• Diagnosis is confirmed by consistently elevated alkaline phosphatase (ALP) for at least 6 months at time of diagnosis and 1 of the following:
	  ○ Positive antimitochondrial (AMA) test
	  OR
	  ○ Presence of sp100 or gp210 autoantibodies if AMA negative
	  OR
	  ○ Liver biopsy consistent with PBC
	AND
	• The diagnosis is not associated with a cholestatic drug reaction, complete biliary obstruction, sarcoidosis, and primary sclerosing cholangitis
	AND

Drug	Medical Necessity
Primary Biliary Cholangitis	
	• The individual has tried ursodeoxycholic acid (UDCA) for at least 1 year and had an inadequate response to UDCA therapy OR the individual has tried UDCA and has a documented intolerance to use of UDCA **AND** • Livdelzi (seladelpar) is prescribed by or in consultation with a gastroenterologist or hepatologist **AND** • Livdelzi (seladelpar) will not be used in combination with Iqirvo (elafibranor) **AND** • The dose is limited to 10 mg once daily **AND** • The quantity is limited to 30 capsules per 30 days
Lynavoy (linerixibat)	**Lynavoy (linerixibat) may be considered medically necessary for the treatment of cholestatic pruritus associated with primary biliary cholangitis (PBC) when the following criteria are met:** • The individual is aged 18 years or older **AND** • Meets 1 of the following: ○ Has PBC without cirrhosis **OR** ○ Has PBC with compensated cirrhosis (Child-Pugh A) and no prior or active evidence of hepatic decompensation (e.g., variceal hemorrhage, ascites, hepatic encephalopathy) **AND** • Diagnosis is confirmed by consistently elevated alkaline phosphatase (ALP) for at least 6 months at time of diagnosis and 1 of the following: ○ Positive antimitochondrial (AMA) test **OR** ○ Presence of sp100 or gp210 autoantibodies if AMA negative **OR** ○ Liver biopsy consistent with PBC

Drug	Medical Necessity
Primary Biliary Cholangitis	

	AND
	• Does not have a total bilirubin greater than 2.0 times Upper Limit of Normal (ULN) and alanine aminotransferase (ALT) greater than 6 times ULN
	AND
	• The individual has moderate to severe pruritus
	AND
	• Has tried and had an inadequate response or intolerance to 2 of the following medications for cholestatic pruritus:
	  ○ Anion-exchange resins (e.g., cholestyramine, colestipol)
	  ○ Rifampin
	  ○ Naltrexone
	  ○ Sertraline
	AND
	• Lynavoy (linerixibat) is prescribed by or in consultation with a gastroenterologist or hepatologist
	AND
	• The dose is limited to 40 mg twice daily
	AND
	• The quantity is limited to 60 tablets per 30 days

Rezdiffra (resmetirom)	**Rezdiffra (resmetirom) may be considered medically necessary for the treatment of stage F2 or F3 liver fibrosis due to metabolic dysfunction-associated steatohepatitis (MASH) when ALL the following criteria are met:**
	• The individual is aged 18 years or older
	AND
	• Has evidence of stage F2 or F3 fibrosis confirmed by 1 of the following:
	  ○ Liver biopsy from within 3 years preceding treatment
	  ○ Vibration-controlled transient elastography (VCTE) within 6 months preceding treatment
	  ○ Magnetic resonance elastography (MRE) within 6 months preceding treatment
	  ○ Enhanced Liver Fibrosis (ELF) test within 6 months preceding treatment

Drug	Medical Necessity
Primary Biliary Cholangitis	

	AND
	• Has 1 or more of the following metabolic risk factors that are managed according to standard of care:
	  ○ Elevated fasting plasma glucose indicative of diabetes or pre-diabetes
	  ○ Hypertension
	  ○ Hypertriglyceridemia
	  ○ Obesity
	  ○ Reduced high-density lipoprotein (HDL) cholesterol
	AND
	• Meets 1 the following
	  ○ Consumes 15 standard drinks or less per week if male
	  ○ Consumes 10 standard drinks or less per week if female
	AND
	• Does not have cirrhosis (F4 fibrosis)
	AND
	• Medication is being used as an adjunct to a reduced-calorie diet and increased physical activity
	AND
	• Rezdiffra (resmetirom) will not be started at the same time as Wegovy (semaglutide) for the treatment of MASH
	AND
	• Medication is prescribed by or in consultation with an endocrinologist, gastroenterologist or hepatologist
	AND
	• The dose is limited to 100 mg daily
	AND
	• The quantity is limited to 30 tablets per 30 days

Drug	Investigational
• **Iqirvo (elafibranor)** • **Livdelzi (seladelpar)** • **Lynavoy (linerixibat)** • **Rezdiffra (resmetirom)**	**All other uses of Iqirvo (elafibranor), Livdelzi (seladelpar), Lynavoy (linerixibat), and Rezdiffra (resmetirom) for conditions not outlined in this policy are considered investigational.**

Drug	Investigational
	The medications listed in this policy are subject to the product's US Food and Drug Administration (FDA) dosage and administration prescribing information.

Length of Approval	
Approval	**Criteria**
Initial authorization	**All drugs listed in the policy may be approved up to 12 months.**

Re-authorization criteria	**Iqirvo (elafibranor) and Livdelzi (seladelpar) may be approved up to 12 months as long as the drug-specific coverage criteria are met, and chart notes demonstrate that the individual continues to show a reduced alkaline phosphatase (ALP) level from baseline.**
	
	Lynavoy (linerixibat) may be approved up to 12 months as long as the drug-specific coverage criteria are met, and chart notes demonstrate that the individual continues to show an improvement in pruritus from baseline.
	
	Rezdiffra (resmetirom) may be approved up to 12 months as long as the drug-specific coverage criteria are met, and chart notes demonstrate that the individual continues to show a positive clinical response to therapy as documented by:
	• Has not had worsening of fibrosis or MASH
	AND
	• Metabolic risk factors are managed according to standard of care
	AND
	• Meets 1 of the following:
	  ○ Consumes 15 standard drinks or less per week if male
	  ○ Consumes 10 standard drinks or less per week if female
	AND
	• Medication is being used as an adjunct to a reduced-calorie diet and increased physical activity

Documentation Requirements

The individual's medical records submitted for review for all conditions should document that medical necessity criteria are met. The record should include the following:

- Office visit notes that contain the diagnosis, relevant history, physical evaluation and medication history

Coding

N/A

Related Information

Benefit Application

The drugs in this policy are managed through the pharmacy benefit.

Consideration of Age:

Age limits specified in this policy are determined according to FDA-approved indications, where applicable.

Criteria for Diagnosis of Prediabetes and Diabetes in Nonpregnant Individuals

Test	Prediabetes	Diabetes
A1C	5.7% - 6.4%	6.5% or higher
Fasting Plasma Glucose (FPG)	100 mg/dl to 125 mg/dL	126 mg/dL or higher
Oral Glucose Tolerance Test (OGTT)	140 to 199 mg/dL	200 mg/dL or higher
Random Plasma Glucose Test		In an individual with classic symptoms of hyperglycemia or hyperglycemic crisis, a

Test	Prediabetes	Diabetes
		random plasma glucose ≥200 mg/dL (≥11.1 mmol/L). Random is any time of the day without regard to time since previous meal.

American Diabetes Association Standards of Care

Lifestyle Behavior Change and Pharmacologic Interventions for Prevention or Delay of Diabetes and Associated Comorbidities Recommendations:

- Refer adults with overweight or obesity at high risk of type 2 diabetes, as seen in the Diabetes Prevention Program (DPP), to an intensive lifestyle behavior change program to achieve and maintain a weight reduction of at least 7% of initial body weight through healthy reduced-calorie diet and ≥150 min/week of moderate-intensity physical activity.
- Prescribe an eating pattern known to be effective in preventing type 2 diabetes to individuals with prediabetes. A variety of eating patterns, such as Mediterranean style, intermittent fasting, and low carbohydrate, have shown benefit.
- Given the cost-effectiveness of lifestyle behavior modification programs for diabetes prevention, such diabetes prevention programs should be offered to adults at high risk of type 2 diabetes.
- Metformin for the prevention of type 2 diabetes should be considered in adults at high risk of type 2 diabetes, as typified by the DPP, especially those aged 25–59 years with BMI ≥35 kg/m^2, higher fasting plasma glucose (e.g., ≥110 mg/dL [≥6 mmol/L]), and higher A1C (e.g., ≥6.0% [≥42 mmol/mol]), and in individuals with prior gestational diabetes mellitus.

Pharmacologic Therapy for Adults with Type 2 Diabetes:

A person-centered shared decision-making approach should guide the choice of glucose-lowering medications for adults with type 2 diabetes. Use medications that provide sufficient effectiveness to achieve and maintain intended treatment goals with consideration of the effects on cardiovascular, kidney, weight, and other relevant comorbidities; hypoglycemia risk; cost and access; risk for adverse reactions and tolerability; and individual preferences. Medications for glucose lowering in type 2 diabetes may include:

- Metformin

- Sodium-Glucose Cotransporter 2 (SGLT2) Inhibitors: bexagliflozin, canagliflozin, dapagliflozin, empagliflozin, ertugliflozin
- Glucagon-Like Peptide-1 Receptor Agonist (GLP-1 RA): dulaglutide, liraglutide, semaglutide
- Dual Glucose-Dependent Insulinotropic Polypeptide (GIP) and Glucagon-Like Peptide-1 Receptor Agonist (GLP-1 RA): tirzepatide
- Dipeptidyl Peptidase 4 (DPP-4) inhibitors: alogliptin, linagliptin, saxagliptin, sitagliptin
- Pioglitazone
- Sulfonylureas (2nd generation): glimepiride, glipizide, glyburide
- Insulin

American College of Cardiology/American Heart Association Hypertension Definitions and Staging System

Definitions	Blood Pressure (mmHg)
Stage 1 Hypertension	Systolic 130 to 139 mmHg or diastolic 80 to 89 mmHg
Stage 2 Hypertension	Systolic ≥140 mmHg or diastolic ≥90 mmHg
Severe Hypertension	Systolic >180 mmHg or diastolic >120 mmHg

American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines

Lifestyle and Psychosocial Approaches

- In adults who have overweight or obesity, weight loss is recommended with a goal of at least 5% of body weight reduction to prevent or treat elevated blood pressure and hypertension
- In adults with or without hypertension, a heart-healthy eating pattern, such as the DASH eating plan, is recommended to prevent or treat elevated blood pressure and hypertension

- In adults with or without hypertension, increasing physical activity, through a structured exercise program that includes aerobic exercise and/or resistance training, is recommended to prevent or treat elevated blood pressure and hypertension

Medical Management of Blood Pressure

The decision to initiate antihypertensive treatment should be based on blood pressure (BP) level and risk for cardiovascular disease (CVD). Based on BP level alone, all adults with hypertension benefit from antihypertensive therapy at a threshold of ≥140/90 mm Hg. Adults with hypertension and clinical CVD (coronary heart disease, stroke, or HF) are at increased risk for CVD events and benefit from antihypertensive therapy at a lower BP threshold of ≥130/80 mm Hg to prevent recurrent events. Among adults without clinical CVD, identification of individuals at increased risk for CVD selects those who derive greatest benefit from antihypertensive therapy at a threshold of ≥130/80 mm Hg. When initiating pharmacological therapy, primary consideration should be given to comorbidities (e.g., coronary artery disease, HF, stroke, diabetes, CKD) for which specific BP-lowering medication classes are indicated. Initial medication management may include the following:

- Angiotensin-Converting Enzyme (ACE) Inhibitor: benazepril, captopril, enalapril, fosinopril, lisinopril, moexipril, perindopril, quinapril, ramipril, trandolapril
- Angiotensin II Receptor Blocker (ARB): azilsartan, candesartan, eprosartan, irbesartan, losartan, olmesartan, telmisartan, valsartan
- Calcium Channel Blocker (CCB)-dihydropyridines: amlodipine, felodipine, isradipine, nicardipine LA and SR, nisoldipine
- CCB-nondihydropyridines: diltiazem ER, verapamil IR/SR/delayed onset ER
- Diuretics
    - Aldosterone antagonist: eplerenone, spironolactone
    - Loop: bumetanide, furosemide, torsemide
    - Potassium sparing: amiloride, triamterene
    - Thiazide-type: chlorthalidone, hydrochlorothiazide, indapamide
- Beta blockers

    - Cardioselective: atenolol, betaxolol, bisoprolol, metoprolol tartrate, metoprolol succinate
    - Cardioselective and vasodilatory: nebivolol
    - Non-cardioselective: nadolol, propranolol IR, propranolol LA
    - Intrinsic sympathomimetic activity: acebutolol, penbutolol, pindolol
- Combined alpha and beta blockers: carvedilol, labetalol
- Direct renin inhibitor: aliskiren
- Alpha-1 blockers: doxazosin, prazosin, terazosin
- Central alpha-2-agonist and other centrally acting drugs: clonidine, methyldopa, guanfacine
- Direct vasodilators: hydralazine, minoxidil
- Dual endothelin receptor antagonist: aprocitentan

CDC Classification of Obesity in Adults

BMI Category	BMI Range (kg/m^2)
Obesity	30 or greater
Class 1 Obesity	30 to less than 35
Class 2 Obesity	35 to less than 40
Class 3 Obesity	40 or greater

American Association for the Study of Liver Diseases (AASLD) Practice Guidance: Liver Protective Healthy Behaviors and Lifestyle Interventions

- Weight loss improves hepatic steatosis, NASH, and hepatic fibrosis in a dose-dependent manner.
- Individuals with NAFLD who are overweight or obese should be prescribed a diet that leads to a caloric deficit. When possible, diets with limited carbohydrates and saturated fat and enriched with high fiber and unsaturated fats (e.g., Mediterranean diet) should be encouraged due to their additional cardiovascular benefits.

- Individuals with NAFLD should be strongly encouraged to increase their activity level to the extent possible. Individualized prescriptive exercise recommendations may increase sustainability and have benefits independent of weight loss.

American Association for the Study of Liver Diseases (AASLD) Guidance Statements Lipid Lowering Medications

- Statins are safe and recommended for cardiovascular disease (CVD) risk reduction in individuals with NAFLD across the disease spectrum, including compensated cirrhosis.
- Limited data exist on the safety and efficacy of statins in individuals with decompensated cirrhosis, although statin use with careful monitoring could be considered in individuals with high CVD risk.
- Hypertriglyceridemia can be managed through lifestyle changes and supplementation with omega-3 fatty acids, icosapent ethyl, or fibrates.

Evidence Review

Primary Biliary Cholangitis (PBC)

Primary Biliary Cholangitis, or PBC, is considered an autoimmune disease because of its hallmark serologic signature, antimitochondrial antibody (AMA), and specific bile duct pathology. PBC is a chronic cholestatic disease with a progressive course that may extend over many decades. The major symptoms of PBC are fatigue and itching and there is not a good correlation between these symptoms and stage of disease, although individuals with more advanced disease generally have more symptoms. Data suggests that PBC has a higher prevalence in women than men.

Alkaline Phosphatase (ALP)

Alkaline phosphatase is an enzyme found throughout the body, but is mostly found in the liver, bones, kidneys, and digestive system. When the liver is damaged, ALP may leak into the bloodstream.

Ursodeoxycholic Acid (UDCA)

Ursodeoxycholic acid or UDCA was the first drug approved for the treatment of individuals with PBC in the United States. Several randomized trials, combined analyses and long-term observational studies have shown that UDCA not only improves biochemical indices but also delays histologic progression and improves survival without transplantation. UDCA is the initial drug of choice for PBC therapy.

Summary of Evidence

Iqirvo (elafibranor)

In the Phase 3 ELATIVE trial (NCT04526665), the composite primary endpoint of biochemical response (alkaline phosphatase [ALP] <1.67 times upper limit of normal [ULN], total bilirubin [TB] ≤ULN, and ALP decreases ≥15% from baseline) was achieved in 51% of individuals treated with Iqirvo (with or without UDCA) versus 4% of individuals who received placebo (with or without UDCA), for a 47% treatment difference. Secondary endpoints showed normalization in ALP levels in only Iqirvo-treated individuals (15% for Iqirvo with or without UDCA versus 0% for placebo with or without UDCA). Most individuals (95%) received study treatment (Iqirvo or placebo) in combination with UDCA. Iqirvo received accelerated approval based on the surrogate endpoint of reduction in ALP, which the FDA believed could be relied on as reasonably likely to predict clinical benefit, including an improvement in transplant-free survival. As with all FDA accelerated approvals, continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial(s). For Iqirvo, confirmation of clinical benefit will be evaluated in the ongoing Phase 3 ELFIDENCE study (NCT06016842). The most common adverse reactions with Iqirvo reported in ≥10% of study participants were weight gain, abdominal pain, diarrhea, nausea and vomiting. The label for Iqirvo includes warnings regarding myalgia, myopathy, and rhabdomyolysis; fractures; adverse effects on fetal and newborn development; drug-induced liver injury; hypersensitivity reactions; and biliary obstruction. Iqirvo is not recommended for people who have or develop decompensated cirrhosis (e.g., ascites, variceal bleeding, and hepatic encephalopathy).

Livdelzi (seladelpar)

Seladelpar was studied in two Phase 3 trials and a trial extension, two of which were terminated early due to histological results in a Phase 2 NASH trial. As the histological results were determined to predate exposure to seladelpar by an independent review committee, the final Phase 3 trial (RESPONSE) was conducted in its entirety.

The RESPONSE trial was a well-designed Phase 3 trial which randomized 193 individuals to seladelpar 10 mg once daily or placebo for 12 months. Individuals were adults with PBC with an incomplete response to UDCA or intolerance to UDCA. All individuals who were able to tolerate UDCA continued UDCA throughout the study. Individuals with advanced PBC or hepatic decompensation were excluded. The primary endpoint of biochemical response per POISE criteria was met in 61.7% of individuals on seladelpar and 20% on placebo (difference 41.7 percentage points, 95% CI 27.7-53.4; $p<0.001$). Results were consistent in individuals with cirrhosis vs no cirrhosis, and with seladelpar monotherapy vs UDCA + seladelpar. Normalization of ALP at 12 months occurred in 25% of individuals on seladelpar and 0% on placebo ($p<0.001$). Pruritus as assessed via numerical rating scale (NRS) at 6 months in individuals with moderate-severe pruritus at baseline was significantly reduced with seladelpar vs placebo ($p=0.005$). Total cholesterol, low-density lipoprotein (LDL), and triglycerides decreased with seladelpar while HDL increased.

The ENHANCE trial was a well-designed Phase 3 trial originally designed with a 12-month duration. The trial was terminated early due to histological results in a Phase 2 seladelpar trial in individuals with NASH. Only 3-month trial results are available. The trial randomized individuals to seladelpar 5 mg, 10mg, or placebo. See the RESPONSE trial for inclusion/exclusion criteria. The primary endpoint of biochemical response per POISE criteria occurred significantly more frequently in individuals in the seladelpar arms vs placebo (78.2%, 57.1%, 12.5%, $p<0.001$ for both comparisons). Significantly less pruritus as assessed by numerical rating scale (NRS) and significantly greater alkaline phosphatase (ALP) normalization occurred in the seladelpar arms vs placebo. However, because the trial was terminated early, the trial was underpowered with only 167 individuals of 265 individuals able to provide 3 months data.

Similarly, Mayo published an open-label trial extension which was terminated early due to the Phase 2 NASH results mentioned above. The trial extension enrolled 106 individuals who completed seladelpar trials (Phase 2 trial and the ENHANCE trial) and were treated with seladelpar 2-10 mg once daily for up to 2 years. The trial extension found individuals achieving the biochemical response endpoint increased from year 1 to year 2 (year 1: 63%-66%; year 2: 79%). Normalization of ALP followed the same pattern (year 1: 23%-26%, year 2: 42%). Of note, baseline characteristics between seladelpar dosing arms were not balanced in this trial.

The label for Livdelzi includes warnings for fractures, liver test abnormalities, and biliary obstruction. The most common adverse reactions (reported in ≥5% and higher compared to placebo) are headache, abdominal pain, nausea, abdominal distension, and dizziness.

Lynavoy (linerixibat)

Lynavoy is a reversible inhibitor of the ileal bile acid transporter (IBAT). It decreases the reabsorption of bile acids in the terminal ileum leading to their increased fecal elimination. The efficacy of Lynavoy was evaluated in Study 1 (GLISTEN, NCT04950127), a 24-week, randomized, double-blind, placebo-controlled trial. The study included 238 adult individuals, aged 30 to 80 years, with a confirmed diagnosis of PBC and presence of pruritus at baseline. Individuals were randomized to Lynavoy 40 mg orally twice daily (N = 119) or placebo (N = 119) for 24 weeks. At baseline, 97% of individuals were receiving UDCA, and 47% of individuals were receiving concomitant antipruritic drugs. Thirteen (11%) of Lynavoy-treated and 12 (10%) of placebo-treated individuals had compensated liver cirrhosis (F4, Child-Pugh A). Individuals were excluded from the study if they had hepatic decompensation, chronic viral hepatitis, symptomatic cholelithiasis, active cholecystitis, primary sclerosing cholangitis, alcoholic liver disease, bariatric surgery with ileal bypass, clinically significant diarrhea, or severe renal impairment (eGFR < 30 mL/min/1.73m^2).

Individuals rated their worst itch severity twice daily (in the morning and evening) using the 11-point Worst Itch Numeric Rating Scale (NRS), with possible scores ranging from 0 (no itching) to 10 (worst imaginable itching).

• The Worst Daily Itch Score was computed as the worst (highest) of the two scores recorded in a day.

• The Weekly Itch Score was computed as the average of the Worst Daily Itch Scores across the 7 days in a week.

• The Monthly Itch Score was computed as the worst (highest) Weekly Itch Score within a 4-week period.

Individuals were included in Study 1 if their Monthly Itch Score in the 4 weeks preceding randomization was 4 or greater. The mean (SD) Monthly Itch Score at baseline was 7.3.

Sleep Interference Sleep interference due to pruritus was assessed each morning using the 11-point Sleep Interference NRS, with possible scores ranging from 0 (did not interfere) to 10 (completely interfered).

• The Weekly Sleep Score was computed as the average of the daily sleep scores recorded over the 7 days in a week.

• The Monthly Sleep Score was computed as the worst (highest) Weekly Sleep Score within a 4-week period. The mean (SD) Monthly Sleep Score at baseline was 6.3.

Lynavoy significantly improved pruritus ($P \leq 0.001$) and sleep interference ($P = 0.024$) compared to placebo, with rapid (at Week 2) and sustained (over 24 weeks) effects. In this trial, Lynavoy met both primary and key secondary endpoints: the mean itch score improved versus placebo over 24 weeks (least-square mean difference −0.72 [95% CI, −1.15 to −0.28]; $P = 0.001$). Drug discontinuation due to adverse reactions (ARs) was seen more frequently in Lynavoy-treated individuals (14%) than in placebo-treated individuals (5%). Diarrhea, abdominal pain, increased alanine aminotransferase (ALT), and increased aspartate aminotransferase (AST) were the most common causes of treatment discontinuation. The most common AR was diarrhea (defined as both diarrhea and frequent bowel movements). It was observed in 74 (62%) of individuals in the Lynavoy-treated group compared to 21 (18%) in the placebo-treated group. Most diarrhea events occurred within the first 20 days of initiating treatment. Of those who experienced diarrhea, 56/74 (76%) of Lynavoy-treated individuals and 10/21 (48%) of placebo-treated individuals, did so within the first 20 days. Of the individuals who experienced diarrhea, most were mild (46/74, 62%) or moderate (25/74, 34%) with 4% (3/74) of cases being severe in the Lynavoy-treated group compared to 62% (13/21) mild, 38% (8/21) moderate, and 0% severe cases in the placebo treated group. Discontinuation of treatment due to diarrhea occurred in 4% of individuals in the Lynavoy-treated group compared to < 1% in the placebo group. Liver test elevations (ALT, AST, TB, or ALP) were observed more commonly in Lynavoy-treated individuals (17 [14%]) compared to placebo-treated individuals (7 [6%]). Six (5%) Lynavoy-treated individuals discontinued treatment due to liver test elevations during the study, compared to 2 (2%) of placebo-treated individuals. Elevations in ALT to more than 3 times baseline levels occurred in 8 (7%) of Lynavoy-treated individuals compared to 4 (3%) placebo-treated individuals. Elevations in total bilirubin to more than 2 times baseline levels occurred in 9 (8%) Lynavoy-treated individuals compared to 3 (3%) placebo-treated individuals.

Metabolic Dysfunction–Associated Steatohepatitis (MASH)

Metabolic dysfunction–associated steatotic liver disease (MASLD) is common in the general population. An estimated 25% of adults in the United States (US) have MASLD. MASLD requires the presence of fat in the liver (hepatic steatosis [HS]) without another explanation such as significant alcohol consumption or use of medications that cause HS. Metabolic dysfunction–associated steatohepatitis (MASH) occurs in which HS is accompanied by hepatocellular injury.

The exact prevalence of MASH is uncertain since definitive diagnosis requires liver biopsy, and many individuals with MASLD do not undergo biopsy. It is estimated that the prevalence of MASH in the adult population is between 1.5% and 6.5%. Individuals with MASH may have liver

fibrosis, and liver fibrosis can progress to cirrhosis. Individuals with cirrhosis are at high risk of death from liver failure and liver cancer (hepatocellular carcinoma [HCC]) and may require liver transplantation. MASLD is highly associated with the metabolic syndrome with or without type 2 diabetes mellitus (T2DM) and obesity. Metabolic syndrome has a number of different definitions, but a commonly used one is at least three of: increased waist circumference; elevated triglyceride level; reduced high density lipoprotein (HDL) cholesterol level; elevated blood pressure; and elevated blood glucose (blood sugar). Metabolic syndrome is a major risk factor for cardiovascular disease (CVD), and despite an increased risk of death from liver-related

causes, CVD is the most common cause of death in individuals with MASLD. Statins appear to improve CV outcomes in individuals with MASH. MASH has become a major cause of cirrhosis and is expected to become the leading reason for liver transplantation in the US. Lifestyle changes that result in improvement in metabolic syndrome, including exercise and weight loss, can improve MASH, as can weight loss after bariatric surgery; bariatric surgery also improves T2DM and the metabolic syndrome. Resmetirom is now the first FDA-approved treatment for MASH and was FDA-approved on March 14, 2024.

Rezdiffra (resmetirom)

The efficacy of resmetirom was evaluated based on an efficacy analysis at Month 12 in Trial 1 (NCT03900429), a 54-month, randomized, double-blind, placebo-controlled trial. Enrolled individuals had metabolic risk factors and a baseline or recent liver biopsy showing metabolic dysfunction–associated steatohepatitis (MASH) with fibrosis stage 2 or 3 and a metabolic dysfunction–associated steatotic liver disease (MASLD) Activity Score (MAS) of at least 4. Efficacy determination was based on the effect of resmetirom on resolution of steatohepatitis without worsening of fibrosis and one stage improvement in fibrosis without worsening of steatohepatitis, on post-baseline liver biopsies collected at 12 months.

The month 12 analysis included 888 F2 and F3 (at eligibility) individuals randomized 1:1:1 to receive placebo (n = 294), resmetirom 80 mg once daily (n = 298), or resmetirom 100 mg once daily (n = 296), in addition to lifestyle counseling on nutrition and exercise. Individuals were on stable doses of medications for diabetes, dyslipidemia, and hypertension.

Efficacy results were based on the percentage of individuals meeting clinical endpoints based on biopsy readings performed by two pathologists (Pathologist A and Pathologist B). Results for the MASH resolution endpoint based on Pathologist A's readings were 27%, 36%, and 13% for resmetirom 80 mg, resmetirom 100 mg, and placebo, respectively. For the same endpoint, results based on Pathologist B's readings were 26%, 24%, and 9% for resmetirom 80 mg,

Rezdiffra 100 mg, and placebo, respectively. Results for the fibrosis endpoint based on Pathologist A's readings were 23%, 28%, and 15% for resmetirom 80 mg, resmetirom 100 mg, and placebo, respectively. For the same endpoint, results based on Pathologist B's readings were 23%, 24%, and 13% for resmetirom 80 mg, resmetirom 100 mg, and placebo, respectively. Examination of age, gender, diabetes status (Yes or No), and fibrosis stage (F2 or F3) subgroups did not identify differences in response to resmetirom among these subgroups.

The most common adverse reactions with resmetirom (reported in ≥5% of individuals and at a higher rate than placebo) are diarrhea, nausea, pruritus, vomiting, constipation, abdominal pain, and dizziness.

Practice Guidelines and Position Statements

2018 Primary Biliary Cholangitis: 2018 Practice Guidance from the American Association for the Study of Liver Diseases (AASLD)

Diagnosis of PBC

According to the AASLD guidelines, the diagnosis of PBC can be established when 2 of the following criteria are met:

- Biochemical evidence of cholestasis based on ALP elevation.
- Presence of AMA, or other PBC-specific autoantibodies, including sp100 or gp210, if AMA is negative.
- Histologic evidence of nonsuppurative destructive cholangitis and destruction of interlobular bile ducts

Primary biliary cholangitis: 2021 practice guidance update from the American Association for the Study of Liver Diseases (AASLD)

The 2018 Practice Guidance was updated to reflect the warning issued by the Food and Drug Administration in May 2021 restricting the use of OCA in individuals with advanced cirrhosis. AASLD recommends careful monitoring of any individual receiving obeticholic acid with any cirrhosis, even if not advanced. AASLD also revised guidelines to include fibrates as a potential off-label alternative for individuals with PBC and inadequate response to UDCA.

Treatment of PBC

The first-line therapy for PBC is UDCA (ursodeoxycholic acid) or ursodiol dosed at 13 to 15 mg/kg/day. UDCA is widely used and has demonstrated the ability to produce a reduction in need for liver transplantation for individuals with PBC. Treatment response to UDCA is monitored using serum ALP and total bilirubin. Improvement in these tests are typically observed within a few weeks, and 90% of improvement occurs within 6 to 9 months. The guidelines recommend that biochemical response to UDCA be evaluated at 12 months after treatment initiation to determine whether individuals should be considered for second-line therapy.

The second-line therapy recommended by AASLD (2018) for PBC is obeticholic acid. Individuals who are inadequate responders to UDCA should be considered for treatment with OCA (starting dose 5 mg per day).

Fibrates can be considered as an off-label alternative for individuals who have an inadequate response to UDCA according to AASLD (2021). The use of fibrates has not been studied in individuals with decompensated liver disease and should be avoided in this population. Therefore, long-term safety of fibrates in individuals with PBC warrants additional studies.

Management of Pruritus

Anion-exchange resins should be used as initial therapy for individuals with PBC who have pruritus. The following agents can be used for pruritus refractory to anion-exchange resins: rifampicin 150 to 300 mg twice daily, oral opiate antagonists such as naltrexone titrated to a dose of 50 mg daily, and sertraline 75 to 100 mg daily.

2021 Update

Reviewed prescribing information for Ocaliva (obeticholic acid). Prescribing information now includes a black box warning describing that hepatic decompensation and failure, sometimes fatal or resulting in liver transplant, have been reported with Ocaliva and that Ocaliva is contraindicated in primary biliary cholangitis (PBC) individuals with decompensated cirrhosis, a prior decompensation event, or with compensated cirrhosis who have evidence of portal hypertension. The indication for Ocaliva has been updated to restrict use to individuals without cirrhosis or with compensated cirrhosis who do not have evidence of portal hypertension.

2022 Update

Reviewed prescribing information for Ocaliva (obeticholic acid). Reviewed 2021 practice guidance update from the American Association for the Study of Liver Diseases (AASLD). No new information was identified that would result in a change to the policy coverage criteria.

2023 Update

Reviewed prescribing information for Ocaliva (obeticholic acid). No new information was identified that would result in a change to the policy coverage criteria.

2024 Update

Reviewed prescribing information for Ocaliva (obeticholic acid). Added Iqirvo (elafibranor) coverage criteria. Updated Ocaliva (obeticholic acid) coverage criteria to include a prescriber requirement, a requirement that Ocaliva will not be used in combination with Iqirvo, and a quantity limit.

2025 Update

Reviewed prescribing information for Ocaliva (obeticholic acid), Iqirvo (elafibranor), and Rezdiffra (resmetirom). No new information was identified that would result in a change to the policy coverage criteria. Added Livdelzi (seladelpar) coverage criteria for the treatment of PBC. Updated Iqirvo and Ocaliva criteria to exclude combination use with Livdelzi. Rezdiffra (resmetirom) moved from Policy 5.01.605 to Policy 5.01.615 Pharmacologic Treatment of Chronic Non-Infectious Liver Diseases with no changes to the coverage criteria. Clarified that the medications listed in this policy are subject to the product's FDA dosage and administration prescribing information. Clarified that non-formulary exception review authorizations for all drugs listed in this policy may be approved up to 12 months. Updated Rezdiffra (resmetirom) coverage criteria to clarify that Rezdiffra can be prescribed by or in consultation with a endocrinologist as well. Updated Rezdiffra (resmetirom) coverage criteria to remove the statin requirements and clarify that the individual is being treated for any concomitant conditions.

2026 Update

Removed Ocaliva (obeticholic acid) coverage criteria as the product has been withdrawn from the market due to liver-related safety risks. Reviewed prescribing information for Iqirvo (elafibrano), Livdelzi (seladelpar), and Rezdiffra (resmetirom). Updated Iqirvo, Livdelzi, and Rezdiffra criteria to remove the requirement to exclude combination use with Ocaliva.

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History

Date	Comments
04/01/20	New policy, approved March 10, 2020. Criteria for Ocaliva (obeticholic acid) for primary biliary cholangitis added.
01/01/22	Annual Review, approved December 2, 2021. Updated Ocaliva criteria to restrict use to patients without cirrhosis or with compensated cirrhosis who do not have evidence of portal hypertension.
11/01/22	Annual Review, approved October 24, 2022. No changes to policy statement. Changed the wording from "patient" to "individual" throughout the policy for standardization.
09/01/23	Annual Review, approved August 21, 2023. No changes to the policy statements.
09/01/24	Annual Review, approved August 13, 2024. Added Iqirvo (elafibranor) coverage criteria. Updated Ocaliva (obeticholic acid) coverage criteria to include a prescriber requirement, a requirement that Ocaliva will not be used in combination with Iqirvo, and a quantity limit.

Date	Comments
02/01/25	Annual Review, approved January 14, 2025. Added Livdelzi (seladelpar) coverage criteria for the treatment of PBC. Updated Iqirvo and Ocaliva criteria to exclude combination use with Livdelzi. Rezdiffra (resmetirom) moved from Policy 5.01.605 Medical Necessity Criteria for Pharmacy Edits to Policy 5.01.615 Pharmacologic Treatment of Chronic Non-Infectious Liver Diseases with no changes to the coverage criteria. Clarified that the medications listed in this policy are subject to the product's FDA dosage and administration prescribing information. Clarified that non-formulary exception review authorizations for all drugs listed in this policy may be approved up to 12 months.
11/01/25	Interim Review, approved October 14, 2025. Updated Rezdiffra (resmetirom) coverage criteria to clarify that Rezdiffra can be prescribed by or in consultation with an endocrinologist as well. Updated Rezdiffra (resmetirom) coverage criteria to remove the statin requirements and clarify that the individual is being treated for any concomitant conditions.
03/01/26	Annual Review, approved February 23, 2026. Removed Ocaliva (obeticholic acid) coverage criteria as the product has been withdrawn from the market due to liver-related safety risks. Updated Iqirvo (elafibranor), Livdelzi (seladelpar), and Rezdiffra (resmetirom) coverage criteria to remove the requirement to exclude combination use with Ocaliva.
09/01/26	Interim Review, approved August 11, 2026. Added coverage criteria for Lynavoy (linerixibat) for the treatment of cholestatic pruritus associated with primary biliary cholangitis. Updated criteria for Rezdiffra (resmetirom) adding a quantity limit per 30 days, clarifying fibrosis is confirmed by liver biopsy, VCTE, MRE, or ELF test; replaced concomitant condition requirements with one or more metabolic risk factors managed per standard of care; and removed additional testing requirements. Updated criteria for Iqirvo (elafibranor) and Livdelzi (seladelpar) adding a quantity limit per 30 days and updated the initial length of approval from 6 to 12 months. Removed reference to non-formulary exception reviews.

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. The Company adopts policies after careful review of published peer-reviewed scientific literature, national guidelines and local standards of practice. Since medical technology is constantly changing, the Company reserves the right to review and update policies as appropriate. Member contracts differ in their benefits. Always consult the member benefit booklet or contact a member service representative to determine coverage for a specific medical service or supply. CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). ©2026 Premera All Rights Reserved.

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