LifeWise
Health Plan of Washington

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

Effective Date:	Sept. 1, 2024	RELATED MEDICAL POLICIES:
Last Revised:	Aug. 13, 2024	None
Replaces:	N/A	

Select a hyperlink below to be directed to that section.

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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. 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) (oral)	**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:** • Individual is 18 years of age or older **AND** • Individual has PBC without cirrhosis **OR** • Individual 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 one 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** • Iqirvo (elafibranor) prescribed by or in consultation with a gastroenterologist or hepatologist **AND** • Iqirvo (elafibranor) will not be used in combination with Ocaliva (obeticholic acid)

Drug	Medical Necessity
Primary Biliary Cholangitis	
	AND • The dose is limited to 80 mg once daily **Note:** See **Documentation Requirements** prior to request for approval.
Ocaliva (obeticholic acid) (oral)	**Ocaliva (obeticholic acid) 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:** • Individual is 18 years of age or older **AND** • Individual has PBC without cirrhosis **OR** • Individual 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 one 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 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	
	• Ocaliva (obeticholic acid) prescribed by or in consultation with a gastroenterologist or hepatologist **AND** • Ocaliva (obeticholic acid) will not be used in combination with Iqirvo (elafibranor) **AND** • The dose is limited to 10 mg once daily **Note:** See **Documentation Requirements** prior to request for approval.

Drug	Investigational
• **Iqirvo (elafibranor)** • **Ocaliva (obeticholic acid)**	**All other uses of Iqirvo and Ocaliva for conditions not outlined in this policy are considered investigational.**

Length of Approval	
Approval	**Criteria**
Initial authorization	**Iqirvo and Ocaliva may be approved up to 6 months.**
Re-authorization criteria	**Future re-authorization 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.**

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: • Alkaline phosphatase (ALP) lab values

Coding

N/A

Related Information

Benefit Application

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

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.

Obeticholic Acid (OCA)

Ocaliva (obeticholic acid, OCA) is a farnesoid X receptor (FXR) agonist indicated for the treatment of primary biliary cholangitis (PBC) in combination with ursodeoxycholic acid (UDCA) in adults without cirrhosis or with compensated cirrhosis who do not have evidence of portal hypertension, with an inadequate response to UDCA, or as monotherapy in adults unable to

tolerate UDCA. This indication was approved under accelerated approval based on a reduction in alkaline phosphatase (ALP). An improvement in survival or disease-related symptoms has not been established.

The efficacy and safety of OCA in individuals with PBC was evaluated in a 12-month, double-blind, placebo-controlled, Phase III trial (POISE). Participants who had an inadequate response to ursodiol (UDCA) were randomized in a 1:1:1 ratio to receive obeticholic acid (10 mg and 5-10 mg) and placebo. Criteria for inclusion included definite or probable PBC diagnosis, ALP ≥ 1.67 of upper limit of normal (ULN) or total bilirubin > ULN, trial and failure of UDCA for at least 12 months or intolerability to UDCA. The primary composite endpoint of the study was an ALP level of less than 1.67 times the upper limit of the normal range, with a reduction of at least 15% from baseline and a total bilirubin level at or below the upper limit of the normal range at 12 months.

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

Ocaliva (obeticholic acid)

Trials in Primary Biliary Cholangitis

The safety and efficacy of obeticholic acid (OCA) for the treatment of individuals with primary biliary cholangitis who have not achieved treatment goal with UDCA alone or cannot tolerate UDCA was established in a placebo-controlled 12-month double-blind randomized-controlled study. Individuals with alkaline phosphatase level of at least 1.67 times the upper limit of normal or an abnormal total bilirubin level of <2 times the upper limit of normal were included in the study. Individuals were randomly assigned 1:1:1 ratio to receive once-daily oral placebo (n=73), OCA 5-10mg dose (n=70) and obeticholic acid 10 mg (n=73) to be added to ursodiol. Majority of the participants in the study were female (90%) with a mean alkaline phosphatase value of 323 U/L and mean total bilirubin of 0.65 mg/dl. The primary endpoint of the study was an alkaline phosphatase level of <1.67 time the upper limit of normal with a reduction of ≥15%

from baseline, and a total bilirubin level at or below upper limit of the normal range at 12 months.

On a background of standard of care, the rate of the primary end point was higher in the 5–10-mg group (46%) and in the 10-mg group (47%) than in the placebo group (10%) at month 12 ($P<0.001$ for both comparisons). Response to obeticholic acid was rapid, with a significant difference observed between each obeticholic acid group and the placebo group by week 2 and at each time point thereafter in the double-blind phase ($P<0.001$ for all comparisons).

A total of 193 of 198 individuals (97%) who completed the 12-month double-blind randomized-controlled study were enrolled in the open-label extension study to evaluate sustained reductions in alkaline phosphatase levels and total bilirubin levels. This extension showed a durable response with obeticholic acid for 2 years. Individuals in the placebo arm who were initiated on obeticholic acid in the open-label extension had similar efficacy to those who were started on obeticholic acid during the double-blind phase.

During the double-blind phase, 19 individuals withdrew from the study, 1 individual (1%) died (from an exacerbation of preexisting congestive heart failure and ischemic heart disease as determined by hospital staff), 8 individuals (4%) withdrew because of pruritus, 6 (3%) withdrew because of other adverse events, and 4 (2%) withdrew consent. The most common adverse event that occurred during the double-blind phase across all groups, including placebo, was pruritus, with an incidence reported in 56% of participants in the 5-10 mg group, 68% in 10 mg group and in 38% in the placebo group. High-density lipoprotein (HDL) cholesterol levels decreased in individuals in the two obeticholic acid groups but stabilized within the normal range and were similar to levels observed in individuals in the placebo group after 12 months. At week 2, a sustained decrease from baseline in the triglyceride level and an increase from baseline in the level of low-density lipoprotein (LDL) cholesterol were observed, as compared with the changes from baseline with placebo.

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 patients 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).

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 form 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.

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) patients 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.

References

1. Ocaliva (obeticholic acid) prescribing information. Intercept Pharmaceuticals, Inc. New York, NY. Revised May 2022.
2. Lindor KD, Bolus CL, Boyer J, et al. Primary biliary cholangitis: 2018 Practice guidance from the American Association for the Study of Liver Disease. Hepatology. 2019. 69(1):394-419. doi: 10.1002/hep.30145.
3. Alkaline Phosphatase. Medline Plus. Updated August 3, 2022. Available at: **https://medlineplus.gov/lab-tests/alkaline-phosphatase/** Accessed August 6, 2024.
4. Siddique A, Kowdley KV. Approach to a patient with elevated serum alkaline phosphatase. Clin Liver Dis. 2012 May; 16(2): 199–229.
5. Nevens F, Andreone P, Mazzella G, et al. A placebo-controlled trial of obeticholic acid in primary biliary cholangitis. N Engl J Med. 2016;375:631-43.
6. Lindor KD, Bowlus CL, Boyer J, et al. Primary biliary cholangitis: 2021 practice guidance update from the American Association for the Study of Liver Disease. Hepatology. 2021. 75:1012-1013. doi: 10.1002/hep.32117.
7. Iqirvo (elafibranor) prescribing information. Ipsen Biopharmaceuticals, Inc. Cambridge, MA. Revised June 2024.

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.

Scope: Medical policies are systematically developed guidelines that serve as a resource for Company staff when determining coverage for specific medical procedures, drugs or devices. Coverage for medical services is subject to the limits and conditions of the member benefit plan. Members and their providers should consult the member benefit booklet or contact a customer service representative to determine whether there are any benefit limitations applicable to this service or supply. This medical policy does not apply to Medicare Advantage.

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