Primary Biliary Cholangitis

EOCCO POLICY

Policy Type: PA Pharmacy Coverage Policy: EOCCO141

Description

Obeticholic acid (Ocaliva) is a Farnesoid X Receptor (FXR) agonist. Elafibranor (Iqirvo) is a dual PPAR-alpha and PPARδ agonist. Seladelpar (Livdelzi) is a selective PPARδ agonist.

Length of Authorization

- Initial:
  - **Obeticholic acid (Ocaliva):** six months
  - **All other agents:** 12 months
- Renewal: 12 months

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
obeticholic acid (Ocaliva)	Primary Biliary Cholangitis (PBC)	5 mg tablets	30 tablets/30 days
		10 mg tablets	
elafibranor (Iqirvo)		80 mg tablets	30 tablets/30 days
seladelpar (Livdelzi)		10 mg capsules	30 capsules/30 days

Initial Evaluation

I. **Obeticholic acid (Ocaliva)**, **Elafibranor (Iqirvo),** or **seladelpar (Livdelzi)** may be considered medically necessary when the following criteria below are met:
   A. Member is 18 years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with, a gastroenterologist or hepatologist; **AND**
   C. Must not be used in combination with another primary biliary cholangitis (PBC) drug (e.g., obeticholic acid (Ocaliva), elafibranor (Iqirvo), or seladelpar (Livdelzi)); **AND**
   D. A diagnosis of **Primary Biliary Cholangitis (PBC)** (i.e., primary biliary cirrhosis); **AND**
      1. Diagnosis confirmed by <u>two</u> of the following:
         i. Alkaline phosphatase (ALP) level at least 1.67 times the upper limit of normal (ULN, normal range: 44-147 IU/L)
         ii. Positive antimitochondrial antibodies (AMA) test or other PBC-specific autoantibodies, (including sp100 or gp210), if AMA is negative
         iii. Histopathologic evidence seen on biopsy (i.e., nonsuppurative cholangitis and destruction of small or medium-sized bile ducts); **AND**
   E. The member did not have an adequate biochemical response after treatment with a maximally tolerated dose of ursodiol for at least 6 months (defined as an alkaline phosphatase (ALP) level less than or equal to 1.67 times the ULN (44-147 IU/L) or a total bilirubin less than the ULN (1 mg/dL); **AND**

F. Will be used in combination with ursodiol; **OR**
    1. Treatment with ursodiol was not tolerated; **AND**
G. Member does not have decompensated liver disease (e.g. ascites, variceal bleeding, hepatic encephalopathy)

II. Elafibranor (Iqirvo), seladelpar (Livdelzi), and obeticholic acid (Ocaliva) are considered investigational when used for all other conditions, including but not limited to:
    A. Metabolic Dysfunction-Associated Steatohepatitis (MASH)/Non-alcoholic steatohepatitis (NASH)
    B. Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD)/Non-alcoholic fatty liver disease (NAFLD)
    C. Familial partial lipodystrophy
    D. Obesity
    E. Digestive system disease/symptoms (bile acid diarrhea, unspecified diarrhea, gallstones, primary sclerosing cholangitis, biliary atresia, etc.)

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. Initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Medication will not be used in combination with another primary biliary cholangitis (PBC) drug (e.g., elafibranor (Iqirvo), seladelpar (Livdelzi), or obeticholic acid (Ocaliva)); **AND**
IV. Member has a diagnosis of **Primary Biliary Cholangitis (PBC)** (i.e., primary biliary cirrhosis); **AND**
    A. Member does not have decompensated liver disease (e.g., ascites, variceal bleeding, hepatic encephalopathy); **AND**
V. Member has exhibited improvement or stability of disease symptoms (e.g., reduction of pruritus, reduced fatigue, or decrease in alkaline phosphate levels)

Supporting Evidence

I. Obeticholic acid (Ocaliva) is a Farnesoid X Receptor (FXR) agonist and elafibranor (Iqirvo) and seladelpar (Livdelzi) are peroxisome proliferator-activated receptor (PPAR) agonists FDA-approved in adults for the treatment of primary biliary cholangitis (PBC) in combination with ursodeoxycholic acid (UDCA or ursodiol) in adults with an inadequate response to UDCA, or as monotherapy in adults unable to tolerate UDCA.
II. Primary biliary cholangitis (PBC) is a rare, autoimmune, cholestatic liver disease that impacts nearly 100,000 people in the United States (U.S.). Most patients diagnosed with PBC are 40 to 60 years old. Primary biliary cholangitis (PBC) is characterized by a T-lymphocyte-mediated

attack on small intralobular bile ducts and bile ducts are destroyed and as a result leading to a build-up of bile, toxins, and chronic inflammation, which causes irreversible fibrosis of the liver. Given the complexity of diagnosis and management of PBC, the treatment must be initiated by, in or consultation with a gastroenterologist or hepatologist.

III. Primary biliary cholangitis (PBC) is considered when patients have an elevated alkaline phosphatase (ALP) without extrahepatic biliary obstruction and symptoms of unexplained itching, fatigue, or jaundice. A diagnosis of PBC is made when there is no evident extrahepatic biliary obstruction, no comorbidity affecting the liver, and at least two of the following are present: an alkaline phosphatase at least 1.5 times the upper limit of normal (44-147 IU/L), presence of antimitochondrial antibodies (AMA) at a titer of 1:40 or higher (or other PBC specific autoantibodies), or histologic evidence of PBC. The 2018 American Association for the Study of Liver Diseases (AASLD) guidelines recommend ursodeoxycholic acid (UDCA or ursodiol) as first line therapy for treatment of PBC. Unfortunately, 30-40% of patients do not respond to UDCA and will require the addition of obeticholic acid (Ocaliva). Guidelines recommend treatment with UDCA for at least 12 months prior to treatment escalation. Despite the 12-month recommendation, guidelines acknowledge that 90% of the improvement on UDCA usually occurs within 6 to 9 months. Numerous studies support that the effect of UDCA generally plateaus after 6 months.

- An observational study published in April 2023 found that a 6-month biochemical response pattern is a good predictor of insufficient response to UDCA. At 6 months, there were 235 patients with ALP >1.9 × ULN which did not meet biochemical response. Of these patients, 89% did not achieve biochemical response after one year of UDCA. Collectively, there is moderate confidence that lack of response to UDCA after 6 months warrants treatment escalation.

IV. Obeticholic acid (Ocaliva) was studied in a randomized, double-blind, placebo-controlled Phase 3 trial (POISE). The study included 216 adults aged 18 years and older with a diagnosis of PBC (defined by presence of two of the following: alkaline phosphatase (ALP) elevated for ≥6 months prior to randomization, positive anti-mitochondria titer, or liver biopsy consistent with PBC). Participants were randomized to receive obeticholic acid (Ocaliva) 5mg, 10mg, or placebo daily, in combination with UDCA. Participants in the lower dose cohort were started on 5mg daily for six months, then given the option to increase to 10mg daily for the last six months. Baseline characteristics were similar between both cohorts, with a mean age of 56 years, mostly female (94%) and most participants were receiving concurrent UDCA (93%). Obeticholic acid (Ocaliva) 10mg and 5mg titration cohorts showed a statistically significantly higher proportion of participants achieving biochemical response compared to placebo over 52 weeks, 48% vs 10%, difference 38%, p<0.0001 and 46% vs 10%, difference 46%, p<0.0001, respectively. Biochemical response defined as ALP level <1.67 times the upper limit of the normal range [ULN], with a decrease of ≥15% from baseline, and a normal total bilirubin level.

- The rate of adverse events occurred more frequently in the obeticholic acid (Ocaliva) 10mg, titration group compared to placebo. The most reported adverse events were pruritis (70%, 56%, 38%), fatigue (25%, 19%, 15%, rash (10%, 7%, 8%), and arthralgia (10%, 6%, 4%). Obeticholic acid (Ocaliva) has black box warnings for hepatic

decompensation and failure and is contraindicated in decompensated cirrhosis. Significant post marketing liver failure, new onset cirrhosis, increased direct and total bilirubin or worsening of jaundice was reported. Due to risk of serious liver injury, the FDA restricted use of obeticholic acid (Ocaliva) in patients with PBC and advanced cirrhosis. Obeticholic acid (Ocaliva) is not to be used in patients with cirrhosis with evidence of portal hypertension (which signifies progression to decompensated cirrhosis).

V. Elafibranor (Iqirvo) was studied in a randomized, placebo-controlled, double-blind, Phase 3 study. The study included 161 adults aged 18 to 75 years with a diagnosis of PBC (defined by presence of two of the following: ALP elevated for ≥6 months prior to randomization, positive anti-mitochondria titer, or liver biopsy consistent with PBC). Participants were randomized to receive elafibranor (Iqirvo) 80 mg or placebo daily with UDCA. Baseline characteristics were similar between both cohorts, with a mean age of 57 years, mostly female (96%) and most participants were receiving concurrent UDCA (95%). Elafibranor group had a statistically significantly higher proportion of participants achieving biochemical response compared to placebo over 52 weeks (51% vs. 4%), difference of 47% (95% CI: 32, 57; p<0.001). Biochemical response defined as ALP level <1.67 times the upper limit of the normal range [ULN], with a decrease of ≥15% from baseline, and a normal total bilirubin level. Elafibranor (Iqirvo) did not demonstrate a statistically significance difference in the pruritic NRS score compared to placebo, -0.78 (p=0.20).

- The rate of adverse events was similar between elafibranor (Iqirvo) and placebo. Gastrointestinal symptoms (abdominal pain, diarrhea, vomiting, and nausea) occurred more often in the elafibranor (Iqirvo) group compared to placebo (11% vs 2-9%). Pruritus (20.4% vs 26.4%) and fatigue (9.3% vs 13.2%) occurred less often in the elafibranor (Iqirvo) group. Four participants discontinued treatment with elafibranor (Iqirvo) due to increased creatine phosphokinase levels. Deaths occurred in two patients (1.9%) in the elafibranor (Iqirvo) group: one postoperative complication after abdominal hernia repair and one participant died from biliary sepsis and acute kidney injury. Both deaths were not deemed to be treatment related.
- There are no specific contraindications to using elafibranor (Iqirvo). Warning and precautions for elafibranor (Iqirvo) include myalgia, myopathy, and rhabdomyolysis, fractures, adverse effects on fetal and newborn development, drug-induced liver injury, hypersensitivity reactions, and biliary obstruction.

VI. Seladelpar (Livdelzi) was studied in a randomized, placebo-controlled, double-blind, Phase 3 study. The study included 193 adults aged 18 to 75 years with a diagnosis of PBC (defined by presence of two of the following: alkaline phosphatase (ALP) elevated for ≥6 months prior to randomization, positive anti-mitochondria titer, or liver biopsy consistent with PBC). Participants were randomized to receive seladelpar (Livdelzi) 10 mg or placebo daily with UDCA. Baseline characteristics were similar between both cohorts, with a mean age of 57 years, mostly female (95%) and most participants were receiving concurrent UDCA (93%). A greater percentage of the patients in the seladelpar (Livdelzi) group than in the placebo group had a biochemical response (61.7% vs. 20.0%; difference, 41.7 percentage points; 95% confidence interval [CI], 27.7 to 53.4,

P<0.001). Biochemical response defined as ALP level <1.67 times the ULN, with a decrease of ≥15% from baseline, and a normal total bilirubin level. Seladelpar (Livdelzi) demonstrated a statistically significant decrease from baseline in pruritic NRS score compared to placebo, -1.5 (p=0.005). However, a change of -1.5 in pruritic NRS is not considered clinically significant.

- The rate of adverse events was similar between seladelpar (Livdelzi) and placebo. Adverse events that occurred more often in the seladelpar (Livdelzi) group included headache (7.8% vs. 3.1%), abdominal pain (7.0% vs. 1.5%), nausea (6.2% vs. 4.6%), and abdominal distention (6.2% vs. 3.1%). Pruritis occurred less often in the seladelpar (Livdelzi) group (4.7% vs 15.4%). Four participants discontinued treatment with seladelpar (Livdelzi) due to disease progression, increased liver function test, coagulopathy, and papillary thyroid cancer.
- There are no specific contraindications to using seladelpar (Livdelzi). Warning and precautions for seladelpar (Livdelzi) include fractures, liver test abnormalities, and biliary obstruction.

VII. Elafibranor (Iqirvo) and seladelpar (Livdelzi) are not recommended in patients with decompensated cirrhosis (e.g. ascites, variceal bleeding, and hepatic encephalopathy). The safety and efficacy of both drugs in patients with decompensated liver disease has not been established. Patients should be monitored for evidence of decompensation and product(s) may be considered for discontinuation if patients progress to moderate or severe hepatic impairment.

VIII. Biochemical response is a validated outcome commonly used in PBC trials. Levels of ALP and bilirubin have been shown predict clinical outcomes (e.g. delayed liver transplantation or death) in patients with PBC. Studies have demonstrated that an improved/normalized ALP and bilirubin are directly related to liver-transplant free survival. In patients with ALP <1.67 x ULN and bilirubin normalization (total bilirubin less than 1mg/dL), the 10-year transplant free survival rate is 86% compared to 34% in patients with an uncontrolled ALP and bilirubin.

IX. Obeticholic acid (Ocaliva), elafibranor (Iqirvo) and seladelpar (Livdelzi) were FDA-approved under the accelerated approval pathway based on biochemical response on reduction in alkaline phosphatase (ALP) and continued approval for the treatment of PBC is contingent upon verification and description of clinical benefit in confirmatory trials. Prevention of liver decompensation events and clinically meaningful reduction in pruritis have not been established at this time.

Investigational or Not Medically Necessary Uses

I. Obeticholic acid (Ocaliva), elafibranor (Iqirvo), and seladelpar (Livdelzi) have not been sufficiently evaluated in the following settings:
   A. Metabolic Dysfunction-Associated Steatohepatitis (MASH)/Non-alcoholic steatohepatitis (NASH)
      i. Obeticholic acid (Ocaliva) for treatment of MASH was rejected by the FDA in 2020 due to an inability to demonstrate clinical benefit.

ii. Elafibranor was studied in an international, randomized, double-blinded, placebo-controlled trial (RESOLVE-IT) to evaluate resolution of NASH. Participants were randomized to receive elafibranor 80 mg, 120 mg, or placebo daily for 52 weeks. The study did not find a significant difference between the elafibranor and placebo groups. Additionally, no significant differences as compared to placebo were achieved in the key secondary endpoints, including fibrosis improvement of at least one stage and changes in metabolic parameters (PMID: 26874076).

iii. According to the practice Guideline by the American Association for the Study of Liver Diseases, American College of Gastroenterology, and the American Gastroenterological Association, first line treatment for NASH is weight loss as it generally reduces hepatic steatosis, achieved either by hypocaloric diet alone or in conjunction with increased physical activity. Loss of at least 3-5% of body weight appears necessary to improve steatosis, but a greater weight loss (up to 10%) may be needed to improve necroinflammation.

B. Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD)/Non-alcoholic fatty liver disease (NAFLD)
C. Familial partial lipodystrophy
D. Obesity
E. Digestive system disease/symptoms (bile acid diarrhea, unspecified diarrhea, gallstones, primary sclerosing cholangitis, biliary atresia, etc.)

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Related Policies

Currently there are no related policies.

Policy Implementation/Update

Action and Summary of Changes	Date
Elafibranor (Iqirvo) and seladelpar (Livdelzi) added to policy based on new FDA approval. Supporting evidence of obeticholic acid (Ocaliva) updated. References updated.	**11/2024**
Removed generic obeticholic acid from policy until available on the market	02/2024
Added E/I supporting evidence for NASH indication and digestive system disease/symptoms. Updated supporting evidence for PBC. Updated references. Added related policies.	06/2023
Added generic obeticholic acid to policy QL table, require use of generic prior to brand	05/2023
Added supporting evidence for the investigational use in NASH	07/2020
Prior authorization criteria transitioned to policy format. Updated initial and renewal durations. Addition of specialist requirements. Addition of confirmed diagnosis and Child Pugh A classification. Further clarification of characteristics of inadequate response to ursodeoxycholic acid. Addition of renewal criteria.	12/2019
Policy created	06/2016