linerixibat (Lynavoy)

EOCCO POLICY

Policy Type: PA/SP Pharmacy Coverage Policy: EOCCO250

Description

Linerixibat (Lynavoy) are orally administered reversible ileal bile acid transporter (IBAT) inhibitors.

Length of Authorization

- Initial: Six months
- Renewal: Six months

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
linerixibat (Lynavoy)	Cholestatic pruritis in adults with Primary Biliary Cholangitis (PBC)	40 mg tablets	60 tablets/30 days

Initial Evaluation

I. **Linerixibat (Lynavoy)** may be considered medically necessary when the following criteria are met:

A. Medication is prescribed by, or in consultation with, a hepatologist or gastroenterologist; **AND**

B. Provider attestation member has cholestasis including at least one of the following:

1. Total serum bile acids greater than three times the upper limit of normal for age; **OR**
2. Conjugated bilirubin greater than 1 mg/dL; **OR**
3. Unexplained fat-soluble vitamin deficiency; **OR**
4. Gamma glutamyl transferase (GGT) greater than three times the upper limit of normal for age; **OR**
5. Intractable pruritis explainable only by liver disease; **AND**

C. Other causes of cholestasis have been ruled out (e.g., drug toxicity, hepatitis A, sclerosing cholangitis); **AND**

D. Member does not have decompensated cirrhosis or prior hepatic decompensation events (e.g., variceal hemorrhage, ascites, hepatic encephalopathy); **AND**

E. Provider attestation of presence of moderate to severe pruritis; **AND**

F. Treatment with <u>all</u> the following has been ineffective, contraindicated, or not tolerated:

1. Ursodiol; **AND**
2. Bile acid sequestrant (e.g., cholestyramine, colesevelam); **AND**
3. Rifampin; **AND**
4. Opioid antagonist (e.g., naltrexone); **AND**
5. Serotonin inhibitor (e.g., sertraline, ondansetron); **AND**

G. Member has a diagnosis of **Primary Biliary Cholangitis (PBC); 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 duct; **AND**
iv. Member is 18 years of age and older

II. Linerixibat (Lynavoy) are considered investigational when used for all other conditions, including but not limited to:
A. Benign recurrent intrahepatic cholestasis (BRIC) 1 and 2
B. Biliary Atresia
C. Primary sclerosing cholangitis (PSC)

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. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Member has exhibited improvement or stability of disease symptoms [e.g., improvement in pruritis, quality of sleep] **AND**
IV. Member has not had a liver transplant since the last prior authorization period; **AND**
V. Member has not progressed to decompensated cirrhosis or experience hepatic decompensation events (e.g., variceal hemorrhage, ascites, hepatic encephalopathy); **AND**

Supporting Evidence

I. Primary biliary cholangitis (PBC) is a rare, autoimmune, cholestatic liver disease that impacts nearly 100,000 people in the United States. 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. Bile ducts are destroyed and as a result, there is a build-up of bile and toxins and chronic inflammation, which leads to irreversible fibrosis of the liver. The buildup of bile and toxins may cause symptoms of pruritus in up to 70% of patients with PBC. Debilitating pruritus may lead to cutaneous wounds from scratching and sleep disturbance.
II. 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.

III. Linerixibat (Lynavoy) is the first IBAT inhibitor FDA-approved to treat cholestatic pruritis associated with PBC. Linerixibat (Lynavoy) has demonstrated increased bile acid elimination and reduced serum IL-31, which are hypothesized to contribute to itch signaling in PBC.

IV. The 2018 American Association for the Study of Liver Diseases (AASLD) and 2021 Evaluation and Management of Pruritus in Primary Biliary Cholangitis Guidelines recommend ursodeoxycholic acid (UDCA or ursodiol) as first line therapy for treatment of PBC. Seladelpar (Livdelzi) and elafibranor (Iqirvo) are second-line, disease-modifying treatments used after inadequate response to ursodeoxycholic acid. Ursodeoxycholic acid, seladelpar (Livdelzi), and elafibranor (Iqirvo) improve cholestatic disease markers and may indirectly benefit pruritus by addressing underlying disease biology. As such, they remain relevant treatment options in patients with PBC and pruritus, though their primary role is disease modification rather than symptom control. For symptomatic control, guidelines recommend cholestyramine as first line treatment for pruritus associated with cholestasis in adults. Alternative pruritus treatment options include rifampicin, fibrates, naltrexone, and sertraline. Linerixibat (Lynavoy) is expected to be an add-on, symptom-directed therapy for pruritus in PBC. Guidelines have not been updated to include recommendations for linerixibat (Lynavoy); however, linerixibat (Lynavoy) is expected to be used as an adjunct treatment to UDCA, seladelpar (Livdelzi) and elafibranor (Iqirvo) and compete with cholestyramine, rifampicin, fibrates, naltrexone, and sertraline.

- **Ursodiol** - commonly used as the first-line treatment option due to its anti-cholestatic properties which are exerted by improved hepatobiliary secretory function and reduced bile toxicity. It is the only medication that may affect liver disease progression and is recommended by the European Association for the Study of the Liver (EASL) guidelines as the initial pharmacological treatment for cholestatic pruritus. While some patients may experience improvement in pruritus during UDCA therapy, clinical studies have generally failed to demonstrate a significant or sustained antipruritic benefit (Kremer, 2017; Talwalkar, 2003).
- Subsequent treatment options are aimed at reducing symptoms of pruritus. Pruritus can be a feature of any cholestatic disease, thus there are many treatment options available with variable evidence.
- **Bile acid sequestrant** - cholestyramine is FDA-approved for the treatment of pruritus associated with cholestasis in adults and is often used as one of the first-line treatment options for pediatric patients with pruritus associated with cholestasis. Despite a limited evidence base, cholestyramine is listed as a first-line treatment by EASL guidelines for the treatment of pruritus associated with cholestasis. A systematic review identified five studies of cholestyramine in PBC (56 treated patients total) in which 45.5% of patients achieved pruritus resolution with cholestyramine. The lack of evidence is largely because the agent entered widespread use before the era of evidence-based medicine. (Zuin, 1991; Duncan, 1984).

- **Rifampin** - commonly used after treatment failure with ursodiol/cholestyramine and is recommended for the treatment of cholestatic pruritus by EASL guidelines, rare disease organizations, and expert reviews. Additionally, there are various reports in literature showing positive results on pruritus due to chronic cholestasis, including retrospective, case controlled, and prospective trials in other cholestatic diseases in children and adults. In a placebo-controlled crossover trial, patients treated with rifampin reported complete disappearance of pruritus in 11 of 14 patients with PBC treated. Additionally, meta-analyses of randomized studies have generally supported rifampin's efficacy, with approximately 60–80% of patients experiencing symptomatic improvement. (Podesta, 1991; Jones 2017; Hegade, 2023).
- **Opioid antagonist** - naltrexone is recommended for the treatment of pruritus associated with cholestatic liver disease by the EASL guidelines as a subsequent option for patients failing cholestyramine and rifampin. Evidence supporting naltrexone comes from several small randomized controlled trials and crossover studies in patients with cholestatic pruritus (many that had PBC). In the randomized placebo-controlled study, naltrexone significantly reduced both daytime and nighttime pruritus scores, and during an open-label extension, 5 of 7 responders maintained benefit over an additional two months. A systematic review identified three naltrexone studies (including two randomized controlled trials) and concluded that naltrexone consistently improved pruritus severity in cholestatic liver disease, although the overall evidence base remains limited by small sample sizes and short follow-up durations. (Terg, 2002; Wolfhagen, 1997; Smith, 2023).
- **Serotonin Inhibitors** - EASL guidelines recommended sertraline as a fourth-line treatment option for patients with cholestatic pruritus. A randomized, double-blind, placebo-controlled trial demonstrated that pruritus scores improved significantly in the sertraline group while worsening in the placebo group (P = 0.009). Ondansetron has been studied in several cholestatic liver diseases with mixed results. One placebo-controlled trial studied intravenous ondansetron in adult patients with cholestatic pruritus and showed improvement in itch intensity by 50%. Another randomized, double-blind cross over study determined there was significant but moderate reduction in visual analogue scale (VAS) score when ondansetron was compared to placebo in patients with chronic liver disease. Another study showed that ondansetron therapy effectively reduced pruritus in 5 out of 13 patients; however, the reduction in itch intensity did not correlate to substantial decrease in objective scratching activity. A fourth clinical trial compared ondansetron to placebo and found no significant differences in pruritus scores or scratching activity (Ebhohon, 2023, Mayo, 2007).

V. Linerixibat (Lynavoy) was studied in a randomized, placebo-controlled, double-blinded Phase 3 study (GLISTEN). The study included 238 adults with a confirmed diagnosis of PBC and moderate to severe cholestatic pruritus at baseline (defined by an itch numeric rating scale [NRS] ≥4). Participants were permitted to continue treatment for PBC if they are currently stable. Baseline characteristics were relatively between both cohorts with a mean age of 55-57 years, majority

of participants were female (95%) and White (61%), and the majority had severe pruritus (57%). At baseline, 97% of patients were receiving UDCA and 47% were receiving concomitant antipruritic drugs (19-26% on fibrates, 8.4% on bile acid sequestrants).

VI. Linerixibat (Lynavoy) demonstrated a statistically significant improvement in itch severity compared with placebo, with a least-squares mean change in itch NRS of −2.86 compared to −2.15, difference of −0.72 (95% CI, -1.15 to -0.28; p=0.0013). Given that a 2-point reduction from baseline is generally considered clinically meaningful in cholestatic pruritus associated with PBC, both treatment and placebo groups achieved improvements that meet thresholds for clinical relevance. However, the incremental benefit of linerixibat (Lynavoy) over placebo remains modest in magnitude. Secondary outcomes such as early change in itch NRS at week 2, sleep interference over 24 weeks, and the proportion of participants achieving a ≥2-point reduction in itch severity were broadly comparable between groups.

VII. Adverse events occurred more frequently in the linerixibat (Lynavoy) group compared to placebo with the most common being diarrhea (61% vs 18%), abdominal pain (18% vs 3%), nausea (10% vs 9%), ALT increase (8% vs 3%), and headache (8% vs 3%). Serious adverse events occurred in 12% of the linerixibat (Lynavoy) group compared to 3% in the placebo group and out of these events, three were deemed treatment related (anemia, arthritis, sinus arrest). Adverse events leading to discontinuation occurred in 14% of participants in the linerixibat (Lynavoy) group. Reasons for discontinuation included gastrointestinal adverse events and elevated liver tests.

VIII. The quality of evidence supporting the clinical significance of IBAT inhibitors for pruritus remains low, and the overall clinical benefit is uncertain. Therefore, the initial authorization period will remain at 6 months to allow for closer monitoring of treatment response in these rare diseases.

Investigational or Not Medically Necessary Uses

I. Linerixibat (Lynavoy) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. BRIC1 and BRIC2
      i. BRIC1 and BRIC2 are milder versions of PFIC1 and PFIC2. BRIC1 and 2 occur on the same genes as PFIC1 and 2, respectively. However, cholestatic events are described as recurrent and unpredictable. Cholestatic episodes often last for a couple of weeks, vary in severity and duration and do not progress to liver failure. Therefore, there is uncertainty whether the duration of disease would offset treatment benefit. Further research and collection of evidence in patients with BRIC1 and BRIC2 is warranted at this time.

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Related Policies

Policy name	Disease state
Primary Biliary Cholangitis	Primary Biliary Cholangitis

Policy Implementation/Update:

Action and Summary of Changes	Date
New Policy	08/2026