Livmarli (maralixibat)

NOTICE

This policy contains information which is clinical in nature. The policy is not medical advice. The information in this policy is used by Wellmark to make determinations whether medical treatment is covered under the terms of a Wellmark member's health benefit plan. Physicians and other health care providers are responsible for medical advice and treatment. If you have specific health care needs, you should consult an appropriate health care professional. If you would like to request an accessible version of this document, please contact customer service at 800-524-9242.

BENEFIT APPLICATION

Benefit determinations are based on the applicable contract language in effect at the time the services were rendered. Exclusions, limitations or exceptions may apply. Benefits may vary based on contract, and individual member benefits must be verified. Wellmark determines medical necessity only if the benefit exists and no contract exclusions are applicable. This medical policy may not apply to FEP. Benefits are determined by the Federal Employee Program.

DESCRIPTION

The intent of the Livmarli (maralixibat) drug policy is to ensure appropriate selection of patients for therapy based on product labeling, clinical guidelines, and clinical studies. The indications below including FDA-approved indications and compendial uses are considered covered benefits provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indications
Livmarli (maralixibat) is indicated for the treatment of cholestatic pruritis in patients with Alagille syndrome 1 year of age and older.

POLICY

Required Documentation
Submission of the following information is necessary to initiate the prior authorization review:

- Initial requests: Genetic testing results confirming a diagnosis of Alagille syndrome (ALGS) (If applicable).
- Continuation requests: Chart notes or medical records documenting a benefit from therapy (e.g., improvement in pruritis).

Prescriber Specialties
The medication must be prescribed by or in consultation with a hepatologist.

Criteria for Initial Approval
Cholestatic pruritis in Alagille syndrome (ALGS)
Authorization of 6 months may be granted for treatment of cholestatic pruritis in Alagille syndrome (ALGS) when all of the following criteria are met:

A. Member has a diagnosis of ALGS confirmed by either of the following:
    1. Genetic testing
    2. Member has both of the following:
        i. Bile duct paucity
        ii. Three of the five major clinical features of ALGS:
            a. Cholestasis
            b. Cardiac defect (e.g., stenosis of the peripheral pulmonary artery and its branches)
            c. Skeletal abnormality (e.g., butterfly vertebrae)
            d. Ophthalmologic abnormality (e.g., posterior embryotoxon)
            e. Characteristic facial features (e.g., triangular-shaped face with a broad forehead and a pointed chin, bulbous tip of the nose, deeply set eyes, and hypertelorism).
B. Member has evidence of cholestasis defined as the presence of one or more of the following:
    1. Total serum bile acid greater than 3 times the upper limit of normal (ULN) for age
    2. Conjugated bilirubin greater than 1mg/dL
    3. Fat soluble vitamin deficiency otherwise unexplainable
    4. Gamma-glutamyl transferase (GGT) greater than 3 times the ULN for age
    5. Intractable pruritis explainable only by liver disease
C. Member does not have a history or presence of other concomitant liver disease
D. Member has not received a liver transplant
E. Member is 1 year of age or older

Continuation of Therapy
Authorization of 12 months may be granted for all members (including new members) requesting continuation of therapy when the member is experiencing benefit from therapy (e.g., improvement in pruritis).

Livmarli (maralixibat) is considered **not medically necessary** for members who do not meet the criteria set forth above.

Dosage and Administration
Approvals may be subject to dosing limits in accordance with FDA-approved labeling, accepted compendia, and/or evidence-based practice guidelines.

Quantity Limits:

Medication	Standard Limit	FDA-recommended dosing
Livmarli (maralixibat) oral solution 9.5 mg/mL	90 mL (3 bottles) per 30 days	380 mcg/kg once daily Start dosing at 190 mcg/kg once daily. After one week, increase to 380 mcg/kg once daily as tolerated. The maximum daily dose volume for patients above 70 kg is 3 mL or 28.5 mg per day

CLINICAL RATIONALE

Background
Alagille syndrome is a multisystem autosomal dominant genetic disorder with a wide range in symptoms and disease severity between patients. Alagille syndrome is a rare disorder, with an estimated incidence of

approximately 1 in 30,000 individuals to 1 in 45,000 individuals. Of note, due to variations in the phenotype, Alagille syndrome is likely underdiagnosed. Almost all cases of Alagille syndrome are caused by mutations in either the jagged canonical notch ligand 1 (JAG1) or the notch receptor 2 (NOTCH2) genes (NORD, 2020). Approximately 94% of patients have a JAG1 mutation, 2.5% have a NOTCH2 mutation, and 3.2% of patients do not have an identified pathogenic JAG1 or NOTCH2 mutation. Signs and symptoms of Alagille syndrome can vary widely between patients, even among those from the same family and with the same mutation. There are seven areas of major clinical features, including cardiac defects (e.g., peripheral pulmonary stenosis, tetralogy of Fallot, aortic stenosis), hepatic manifestations (e.g., cholestasis due to biliary duct paucity, pruritus, xanthomas, cirrhosis), renal abnormalities (e.g., renal dysplasia, renal tubular acidosis), skeletal abnormalities (e.g., butterfly vertebrae, hemivertebrae, pathological long bone fractures), ophthalmologic manifestations (e.g., posterior embryotoxon), dysmorphic facies (i.e., prominent, broad forehead, deep-set eyes with moderate hypertelorism, prominent ears, pointed chin, broad nasal bridge), and vasculature abnormalities (e.g., aneurysms, cerebral arteries abnormalities, middle aortic syndrome). Other signs and symptoms that can be present include short stature, failure to thrive, immunodeficiency, and pancreatic insufficiency. Pruritus is a complication of chronic cholestasis and can negatively affect quality of life; intense pruritus can lead to excoriations, lichenification, and interrupted sleep. Patients can be suspected of having Alagille syndrome if they have bile duct paucity along with three of the following five clinical features: symptoms of liver disease or cholestasis, heart defect, skeletal abnormality, ophthalmologic abnormality, and/or distinctive facial features. A diagnosis of Alagille syndrome is typically confirmed by the presence of a JAG1 or NOTCH2 genetic mutation.

There are no formal guidelines for the treatment of Alagille syndrome, and treatment is driven by which specific signs and symptoms are present. For patients with pruritus, off-label ursodiol, cholestyramine, naltrexone, and Rifadin (rifampin) have all been administered. Off-label antihistamines can be administered as adjunctive therapy in the evening for patients whose pruritus interferes with their sleep. Pruritus associated with Alagille syndrome is typically resistant to therapy, and patients typically will need a combination of agents. For patients with intractable pruritus, biliary resection or ileal resection can be performed. Livmarli (maralixibat) is the first agent approved for the treatment of cholestatic pruritus in patients with Alagille syndrome. It is a reversible inhibitor of the ileal bile acid transporter (IBAT) that decreases reabsorption of bile acids (primarily salt forms) from the terminal ileum. The pathophysiology of pruritus in patients with Alagille syndrome is not completely understood. Although the complete mechanism by which Livmarli improves pruritus in Alagille syndrome is unknown, it may involve inhibition of the IBAT, which results in decreased reuptake of bile salts, as observed by a decrease in serum bile acids. Of note, Bylvay (odevixibat), which is indicated for the treatment of pruritus in patients with progressive familial intrahepatic cholestasis, is in phase III of development for the treatment of Alagille syndrome.

Efficacy

The efficacy and safety of Livmarli (maralixibat) were evaluated in the unpublished phase II ICONIC trial (N = 31, n = 29 at 48 weeks of treatment). All patients were initially enrolled in an 18-week Livmarli (maralixibat) run-in period during which patients received ascending doses of Livmarli (maralixibat) up to 400 mcg/kg orally daily for 6 weeks followed by 12 weeks of stable dosing. This was followed by a 4-week, randomized, double-blind, placebo-controlled, drug-withdrawal period where patients were randomized to either placebo or continuing Livmarli (maralixibat). After the withdrawal period, all patients received Livmarli (maralixibat) 380 mcg/kg orally once daily for 26 weeks. The primary endpoint was the change from baseline in serum bile acid, and secondary endpoints included change from baseline in caregiver-reported itch reported outcome (ItchRO) scale scores. The ItchRO scale assesses pruritus symptoms on a scale from 0 to 4, with a score of 0 indicating no observed or reported symptoms to a score of 4 indicating very severe symptoms; of note, caregivers evaluated patients' pruritus symptoms once in the morning and once in the evening. Patients were enrolled in the trial if they were between 12 months and 18 years of age with a diagnosis of Alagille syndrome and evidence of cholestasis (defined as the presence of at least one of the following signs or symptoms: total serum bile acid > three times the upper limit of normal [ULN] for age, conjugated bilirubin > 1 mg/dL, fat soluble vitamin deficiency otherwise unexplainable, gamma-glutamyl transferase >

three times the ULN, or intractable pruritus explainable only by liver disease). Patients were also required to have an average daily score > 2 points on the ItchRO scale. For the included patients, the mean age was 5.4 years, 66% were male, the mean baseline serum bile acid level was 280 mcmol/L, and the mean baseline caregiver-reported ItchRO score was 3.1 points. During the run-in period, there was a mean decrease of 87 mcmol/L in serum bile acid ($p < 0.001$ vs. baseline) and a mean reduction of 1.7 points in weekly average morning caregiver-reported ItchRO scale. In the treatment withdrawal period of the phase II ICONIC trial, patients who remained on Livmarli (maralixibat) had significantly lower serum bile acid levels and significantly improved ItchRO(Obs) score compared with patients switched to placebo. Twenty-three patients in the trial consented to continue into the long-term extension period of the trial; 15 patients remained on Livmarli (maralixibat) for a median duration of 44.5 months. Patients could receive Livmarli (maralixibat) at up to 400 mcg/kg orally twice daily if serum bile acids were greater than the ULN and/or if pruritus persisted. Compared with trial baseline, the mean change in serum bile acid level was -158.5 mcmol/L ($p = 0.0048$ vs. baseline) and the mean change in ItchRO score was -2.3 points ($p < 0.0001$ vs. baseline). Livmarli (maralixibat) significantly decreased serum bile acid levels and pruritus in pediatric patients with Alagille syndrome and was generally well-tolerated.

Safety

The most common adverse events for Livmarli, which occurred in ≥10% of patients were diarrhea, abdominal pain, vomiting, fat-soluble vitamin deficiency, increased transaminases (ALT, AST), and gastrointestinal bleeding. Livmarli carries warnings for liver test abnormalities, gastrointestinal adverse reactions, and fat-soluble vitamin (FSV) deficiency. Baseline liver tests and serum fat-soluble vitamin levels should be obtained at baseline and monitored during treatment.

PROCEDURES AND BILLING CODES

To report provider services, use appropriate CPT* codes, Alpha Numeric (HCPCS level 2) codes, Revenue codes, and/or ICD diagnostic codes.

- Not applicable (N/A)

REFERENCES

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- Spinner NB, Gilbert MA, Loomes KM, Krantz ID. Alagille syndrome. GeneReviews® [Internet]. December 12, 2019. Last updated December 12, 2019. Accessed October 19, 2021. https://www.ncbi.nlm.nih.gov/books/NBK1273/#__NBK1273_dtls__.
- Genetic and Rare Diseases Information Center. Alagille syndrome. Rare Disease Database. https://rarediseases.info.nih.gov. Updated October 20, 2017. Accessed October 18, 2021.
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POLICY HISTORY

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