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Subject: Leniolisib Phosphate (Joenja®)

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DESCRIPTION:

Leniolisib phosphate (Joenja) is an oral kinase inhibitor approved by the United States (US) Food and Drug Administration (FDA) in March 2023 for the treatment of activated phosphoinositide 3-kinase (PI3K) delta syndrome (APDS) in adults and pediatric patients 12 years and older. Leniolisib is the first FDA-approved treatment specifically for APDS. APDS is an ultra-rare primary immunodeficiency disease (PID) caused by an autosomal-dominant pathogenic mutation in the phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit δ (*PIK3CD*) (APDS1) or phosphoinositide-3-kinase regulatory subunit 1 (*PIK3R1*) (APDS2) genes that encode PI3K delta, an important protein for the normal development and function of white blood cells. Leniolisib blocks PI3K delta inhibiting the hyperactive signaling pathways and dysregulation of B and T cells. APDS was previously known as p110δ-activating mutation causing senescent T cells, lymphadenopathy, and immunodeficiency (PASLI) disease. Patients with APDS have low numbers of white blood cells, particularly certain types of B cells and T cells, and develop recurrent infections, most often in the sinuses, ears, and respiratory tract and as herpesvirus viremia. Patients also often present with lymphoproliferation (e.g., lymphadenopathy, splenomegaly, hepatomegaly), delayed growth, organ damage (e.g., lung, liver), autoimmunity (e.g., cytopenias) and enteropathy. APDS can be diagnosed at any age but is most often identified in early childhood. Definitive diagnosis is made through genetic testing. The prevalence of APDS is estimated at 1 to 2 cases per million, and likely affects fewer than 500 patients in the U.S.

Existing treatments for APDS include supportive therapies to manage symptoms, such as long-term antibiotic prophylaxis and immunoglobulin replacement therapy. Furthermore, immunosuppressive therapies are also used to reduced lymphoproliferation and include treatments such as rituximab and rapamycin. Procedures such as splenectomies and repeated otosinopulmonary surgeries may be needed. In very severe cases of APDS, a hematopoietic stem cell transplant (HSCT) may be curative but comes with numerous risks and potential serious complications. In addition, HSCTs are not effective for all people with APDS and it will not correct non-immune pathological manifestations such as kidney disease. Leniolisib is currently the only FDA-approved therapy that aims to treat the underlying cause of the disease.

The safety and efficacy of leniolisib leading to FDA-approved was based on results from the placebo-controlled portion of Study 2201 (NCT02435173), a 12-week blinded, randomized, placebo-controlled study in adult and pediatric patients 12 years of age and older with confirmed APDS-associated genetic PI3Kδ mutation with a documented variant in either *PIK3CD* or *PIK3R*. Patients had nodal and/or

extranodal lymphoproliferation, as measured by index nodal lesion selected by the Cheson methodology on CT or MRI, and clinical findings and manifestations compatible with APDS (e.g., history of repeated oto-sino-pulmonary infections, organ dysfunction). Immunosuppressive medications or PI3Kδ inhibitors (selective or non-selective) were prohibited within 6 weeks of baseline and throughout the study. In addition, patients who had previous or concurrent B cell depleters (e.g., rituximab) within 6 months of baseline were excluded from the study, unless absolute B lymphocytes in the blood were normal. B cell depleters were prohibited throughout the study. Glucocorticoid doses equivalent to 25 mg or less of prednisone daily were allowed within 2 weeks prior to, and throughout, the study. Thirty-one patients were randomized 2:1 to receive either leniolisib 70 mg (n=21) or placebo (n=10) twice a day for 12 weeks. The co-primary efficacy endpoints were: [1] improvement in lymphoproliferation as measured by a change from baseline in lymphadenopathy measured by the log10-transformed sum of product diameters of the index lymph nodes (the ≤6 of the largest lymph nodes as measured by MRI or CT scan) and [2] the improvement of immunophenotype as measured by the percentage of naïve B cells out of total B cells (as assessed by flow cytometry) after 12 weeks. The pharmacodynamics (PD) analysis set included all patients who received any study drug with no protocol deviations and with relevant impact on endpoints. The safety analysis set included all patients who received any study drug. The median age of included patients was 20 years (38.7% less than 18 years) and the pathogenic variants distribution was 80.65% *PIK3CD* and 19.35% *PIK3R1*. Patients received baseline glucocorticoids (58.1%), immunoglobulin replacement therapy (67.7%), antibiotic prophylaxis (41.9%), or prior sirolimus treatment (22.6%).

Leniolisib significantly reduced lymphadenopathy. The difference in the adjusted mean change (95% CI) between leniolisib (n=18) and placebo (n=8) was −0.25 (−0.38, −0.12; p=0.0006). One patient receiving leniolisib was excluded from the PD analysis set because the baseline index node fully resolved by D85. In the safety analysis set, 26% of patients in the leniolisib group (n=19) achieved complete absence of index lymphadenopathy, whereas the other 74% achieved partial response. In the placebo group (n=9), 45% achieved partial response, 44% had stable disease, and 11% had an unknown response. Leniolisib decreased spleen size as well. The adjusted mean difference (95% CI) in bidimensional size between the groups was −13.5 cm^2 (−24.1, −2.91; p=0.0148) and in 3D volume was −186 cm^3 (−297, −76.2; p=0.0020). Of the patients in the safety analysis set with baseline splenomegaly, in the leniolisib group (n=13), 38% achieved complete response, 54% achieved partial response, and 8% had stable disease at 12 weeks. In the placebo group (n=5), 20% achieved complete response with the remaining 80% experiencing worsening disease. As an indication of improvement in immunodeficiency, leniolisib significantly increased the percentage of naïve B cells. The difference in the adjusted mean change (95% CI) between leniolisib (n=8) and placebo (n=5) from baseline to day 85 was 37.3 percentage points (24.06, 50.54; p=0.0002). Leniolisib also had greater reductions in serum IgM (mean decrease from baseline, 208 vs.10 mg/dL) and CXCL13 levels (mean decrease from baseline of 287 vs. a 59 pg/mL increase with placebo). Leniolisib improved key lymphocyte subsets notably decreasing elevated transitional B cells and CD38+ plasmablasts, switched and non-switched memory B-cells, normalizing the inverted CD4:CD8 T-cell ratio, and increasing the naïve CD8+ T-cell and CD4+ T cell percentages (decreasing the CD4+ T(EMRA) subset). Leniolisib had minimal effects on memory T cells and effector memory T cells. Additionally, leniolisib decreased TNF-alpha and other systemic inflammatory markers. There were no significant changes in patient- and clinician-reported outcomes at 12 weeks; however, investigators described positive improvements including increased tolerance for physical activity and decreased fatigue in 70% of patients with leniolisib compared with 44.4% with placebo.

Adverse events (AEs) were reported in 85.7% of patients receiving leniolisib and in 90% of the placebo group; these events were mostly grade 1 (74.2%). Study drug-related AEs occurred in 8 patients; the incidence was lower in the leniolisib arm (23.8%) than in the placebo arm (30%). Transient alopecia was reported in 2 of 21 patients receiving leniolisib. In total, 5 patients reported a serious AE, with none judged as related to study medication. No deaths were reported within 30 days of the end of trial, and no AEs led to discontinuation of study treatment.

POSITION STATEMENT:

Comparative Effectiveness

The FDA has deemed the drug(s) or biological product(s) in this coverage policy to be appropriate for self-administration or administration by a caregiver (i.e., not a healthcare professional). Therefore, coverage (i.e., administration) in a provider-administered setting such as an outpatient hospital, ambulatory surgical suite, physician office, or emergency facility is not considered medically necessary.

Initiation of leniolisib phosphate (Joenja) **meets the definition of medical necessity** when **ALL** of the following criteria are met ("1" to "8"):

1. Member has a documented diagnosis of activated phosphoinositide 3-kinase (PI3K) delta syndrome (APDS) as confirmed by a pathogenic variant in the *PIK3CD* or *PIK3R1* gene – *documentation of the genetic test results must be submitted*
2. Member has clinical findings and manifestations compatible with APDS such as repeated oto-sino-pulmonary infections, herpesvirus viremia infections, chronic non-malignant lymphoproliferation, organ damage (e.g., lung, liver), autoimmunity (e.g., cytopenias), and/or enteropathy - *medical record documentation of the findings must be submitted*
3. Prescriber has assessed the member's baseline (defined as prior to therapy with leniolisib and within 180 days of the prior authorization request) clinical findings and manifestations of APDS, such as, but not limited to, frequency and severity of infections, severity of organ damage, frequency of hospitalizations, extent of nodal and/or extranodal lymphoproliferation, and immunophenotype (the percentage of naive B cells out of total B cells via flow cytometry)* – *medical record documentation of the member's baseline findings must be submitted*

   **This requirement can be waived for members already receiving treatment such as those transitioning from active treatment in a clinical trial or coming from another health plan*
4. Leniolisib is prescribed by a specialist with experience in the management of primary immunodeficiency diseases (for example, a geneticist or immunologist)
5. Leniolisib will **NOT** be used in combination with a B-cell depleting antibody for the treatment of APDS [for example, belimumab (Benlysta), inebilizumab (Uplinza), obinutuzumab (Gazyva), ocrelizumab (Ocrevus), ofatumumab (Kesimpta), rituximab products, and ublituximab (Briumvi)]
6. Member is 12 years of age or older **OR** meets the minimum age as listed in the FDA-approved product labeling for leniolisib
7. Member weighs 45 kg (99 lbs) or greater **OR** meets the minimum weight as listed in the FDA-approved product labeling for leniolisib
8. Dosage of leniolisib does not exceed 70 mg twice daily (60 tablets per 30 days)

Approval duration: 6 months

Continuation of leniolisib phosphate (Joenja) **meets the definition of medical necessity** when **ALL** of the following criteria are met ("1" to "7")

1. An authorization or reauthorization for leniolisib phosphate has been previously approved by Florida Blue for the treatment of APDS, **OR** the member has previously met **ALL** indication-specific criteria
2. Member has had a beneficial response to leniolisib treatment, as determined by the following, depending on the length of treatment
   - Less than 12 months - clinically significant improvement in clinical signs and symptoms of disease, such as, but not limited to, decreased frequency or severity of infections, improvement in organ function, decreased frequency of hospitalizations, reduced lymph node size, increased naïve B-cell percentage, as compared to before treatment with leniolisib - *medical record documentation of improvement vs. baseline must be submitted*
   - 12 months or greater - the member continues to maintain a clinically beneficial response to treatment with leniolisib

3. Leniolisib is prescribed by a specialist with experience in the management of primary immunodeficiency diseases (for example, a geneticist or immunologist)
4. Leniolisib will **NOT** be used in combination with a B-cell depleting antibody for the treatment of APDS [for example, belimumab (Benlysta), inebilizumab (Uplinza), obinutuzumab (Gazyva), ocrelizumab (Ocrevus), ofatumumab (Kesimpta), rituximab products, and ublituximab (Briumvi)]
5. Member is 12 years of age or older **OR** meets the minimum age as listed in the FDA-approved product labeling for leniolisib
6. Member weighs 45 kg (99 lbs) or greater **OR** meets the minimum weight as listed in the FDA-approved product labeling for leniolisib
7. Dosage of leniolisib does not exceed 70 mg twice daily (60 tablets per 30 days)

Approval duration: 12 months

DOSAGE/ADMINISTRATION:

THIS INFORMATION IS PROVIDED FOR INFORMATIONAL PURPOSES ONLY AND SHOULD NOT BE USED AS A SOURCE FOR MAKING PRESCRIBING OR OTHER MEDICAL DETERMINATIONS. PROVIDERS SHOULD REFER TO THE MANUFACTURER'S FULL PRESCRIBING INFORMATION FOR DOSAGE GUIDELINES AND OTHER INFORMATION RELATED TO THIS MEDICATION BEFORE MAKING ANY CLINICAL DECISIONS REGARDING ITS USAGE.

FDA-approved

- Indicated for the treatment of activated phosphoinositide 3-kinase delta (PI3Kδ) syndrome (APDS) in adult and pediatric patients 12 years of age and older.
- The recommended dosage in adult and pediatric patients 12 years of age and older weighing 45 kg or greater is 70 mg administered orally twice daily approximately 12 hours apart, with or without food. There is no recommended dosage for patients weighing less than 45 kg. Verify pregnancy status in females of reproductive potential prior to initiating treatment.

Dose Adjustments

- Hepatic impairment: Use of leniolisib in patients with moderate to severe hepatic impairment is not recommended. The effect of hepatic impairment on leniolisib pharmacokinetics has not been studied; however, 60% of leniolisib is metabolized by the liver.
- Renal impairment: Specific guidelines for dosage adjustments in renal impairment are not available; it appears that no dosage adjustments are needed.

Drug Availability

- 70 mg tablets in bottles of 60 tablets
- Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F). Do not refrigerate. Store and dispense in original container.

PRECAUTIONS:

Boxed Warning

- None

Contraindications

- None

Precautions/Warnings

- **Embryo-Fetal Toxicity**: Leniolisib may cause fetal harm. Advise patients of the potential risk to a fetus and to use effective contraception.
- **Vaccinations**: Live, attenuated vaccinations may be less effective if administered during leniolisib treatment.
- **Risk of Hypersensitivity Reactions Including Anaphylaxis**: Hypersensitivity reactions including anaphylaxis have been reported in the postmarketing setting. If hypersensitivity reactions occur, discontinue Joenja and institute appropriate therapy.

BILLING/CODING INFORMATION:

The following codes may be used to describe:

HCPCS Coding

J8499	Prescription drug, oral, non chemotherapeutic, NOS

ICD-10 Diagnosis Codes That Support Medical Necessity

D81.82	Activated Phosphoinositide 3-kinase Delta Syndrome [APDS]

REIMBURSEMENT INFORMATION:

Refer to section entitled **POSITION STATEMENT**.

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Part D: Florida Blue has delegated to Prime Therapeutics authority to make coverage determinations for the Medicare Part D services referenced in this guideline.

Medicare Advantage: No National Coverage Determination (NCD) and/or Local Coverage Determination (LCD) were found at the time of the last guideline review date.

If this Medical Coverage Guideline contains a step therapy requirement, in compliance with Florida law 627.42393, members or providers may request a step therapy protocol exemption to this requirement if based on medical necessity. The process for requesting a protocol exemption can be found at Coverage Protocol Exemption Request.

DEFINITIONS:

None

RELATED GUIDELINES:

None

OTHER:

None

REFERENCES:

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COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 04/08/26.

GUIDELINE UPDATE INFORMATION:

06/01/23	New Medical Coverage Guideline.
05/15/24	Review and revision to guidelines consisting of updates to the position statement and references. The baseline clinical findings requirements for initiation have been revised.
05/15/25	Review and revision to guidelines consisting of updates to the references.
05/15/26	Review and revision to guidelines consisting of updates to the precautions and references.