leniolisib (Joenja™)

EOCCO POLICY

Policy Type:PA/SP Pharmacy Coverage Policy: EOCCO282

Description

Leniolisib (Joenja) is an orally administered phosphoinositide 3-kinase delta (PI3Kδ) inhibitor.

Length of Authorization

- Initial: Three months
- Renewal: 12 months

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
leniolisib (Joenja)	Activated phosphoinositide 3-kinase delta (PI3Kδ) syndrome (APDS)	70 mg tablets	60 tablets/30 days

Initial Evaluation

I. **Leniolisib (Joenja)** may be considered medically necessary when the following criteria are met:
   A. Member is 12 years of age or older; **AND**
   B. Member weighs ≥ 45 kg; **AND**
   C. Medication is prescribed by, or in consultation with, an immunologist, geneticist, or a provider specializing in the management of immunodeficiencies; **AND**
   D. Medication will not be used in combination with immunosuppressive therapy (e.g., B lymphocyte depletion therapy, rituximab); **AND**
   E. A diagnosis of **Activated phosphoinositide 3-kinase delta (PI3Kδ) syndrome (APDS)** when the following are met:
      1. Documentation of APDS-associated mutation with pathogenic variants in PIK3CD or PIK3R1 genes; **AND**
      2. Documentation of at least one measurable enlarged lymph node lesion observed by computed tomography (CT scan) or magnetic resonance imaging (MRI scan); **AND**
      3. Documentation of baseline naïve B cell percentage as assessed by flow cytometry; **AND**
      4. Member has one of the following clinical findings and manifestations of APDS as documented in the medical records:
         i. History of repeated infections (e.g., sinus, ear, or lung infections, herpes viral infection) requiring long-term antibiotic or antiviral prophylaxis; **OR**
         ii. Organ dysfunction (e.g., bronchiectasis, liver impairment); **OR**
         iii. History of nodal or extra-nodal lymphoproliferation; **AND**

5. Treatment with one agent in each of the following classes has been ineffective, contraindicated, or not tolerated:
    i. Systemic corticosteroids (e.g., prednisone, methylprednisolone, budesonide)
    ii. Immunoglobulin G (IgG) replacement therapy (IRT)
    iii. Other immunosuppressants (e.g., rituximab, sirolimus)

II. Leniolisib (Joenja) is considered investigational when used for all other conditions except APDS

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. Medication will not be used in combination with immunosuppressive therapy (e.g., B lymphocyte depletion therapy, rituximab); **AND**
IV. Documentation showing that the member has exhibited improvement or stability of disease symptoms as noted by one of the following:
    - Reduction in nodal or extra-nodal lymphoproliferation (lymph node size) from pre-treatment baseline
    - Increase in naïve B cell percentage from pre-treatment baseline

Supporting Evidence

I. Leniolisib (Joenja) is a phosphoinositide 3-kinase delta (PI3Kδ) inhibitor FDA-approved for the treatment of activated phosphoinositide 3-kinase delta syndrome (APDS) in adult and pediatric patients (≥ 12 years of age). It is available as a 70 mg oral tablet administered twice daily. Use in patients under the age of 12 has not yet shown safety and efficacy.
II. The recommended dosage of leniolisib (Joenja) 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.
III. APDS is a rare primary immunodeficiency caused by mutations in PIK3CD or PIK3R1 genes, characterized by severe, recurrent sinopulmonary infections, lymphoproliferation, bronchiectasis, cytopenias, and may progress to permanent lung damage or lymphoma. APDS affects approximately 1 to 2 persons per million in the US. Given the rarity and complexity of diagnosis and management of APDS, the treatment of APDS must be initiated by, or in

consultation with, an immunologist, geneticist, or a provider specializing in the management of immunodeficiencies.

IV. Leniolisib (Joenja) was evaluated for the treatment of APDS via a clinical trial, which enrolled patients with 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 (Day -1 and the visit prior to first study drug administration) 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. At this time, safety, and efficacy of leniolisib (Joenja) in combination with B cell depleting immunosuppressive therapy (e.g., rituximab) is not known. Additionally, the proposed therapeutic goal for the use of leniolisib (Joenja) is to improve the naïve B lymphocyte counts. Use of B cell depleting therapies may antagonize the effect of leniolisib (Joenja).

V. In the absence of curative treatments, management of APDS is symptom-based and consists of non-specific therapies including ongoing antimicrobial prophylaxis, immunosuppressants (e.g., corticosteroids, rituximab, sirolimus), immunoglobulin replacement therapy (IRT), surgeries (e.g., tonsillectomy, splenectomy), and hematopoietic stem cell transplant (HSCT).

VI. There are no treatment guidelines for the management of APDS and the pharmacotherapy approaches remain patient-specific and heterogeneous. Leniolisib (Joenja) is the first targeted PI3Kδ inhibitor, and the first drug FDA-approved for the treatment of APDS. Leniolisib (Joenja) is expected to be the first-line therapy for all patients with a confirmed diagnosis of APDS with other therapeutic interventions (e.g., antibiotics, IRT, corticosteroids) being utilized as adjunct therapies.

VII. The safety and efficacy of leniolisib (Joenja) were evaluated in a Phase 3, blinded, randomized, placebo controlled clinical trial (Study 2201-02). Patients (N=31): 12 to 75 years old with mutation in PIK3CD or PIK3R1, a history of clinical symptoms of APDS, and at least one measurable lymph node enlargement, were randomized 2:1 to receive leniolisib (Joenja) or placebo. While concurrent use of immunosuppressants was prohibited during the trial, patients were allowed to take glucocorticoids (e.g., prednisone) ≤ 25 mg per day (58%) and previously established IRT (68%). The negative change in the index lymph node diameters and the positive change in the naïve B cells percentage (baseline to day 85) were measured as co-primary endpoints. Leniolisib (Joenja) treatment for 85 days reported a baseline mean log10-sum of product diameter (SPD) reductions in the index lesions (lymph nodes) of -0.27 for leniolisib (Joenja) versus -0.02 for placebo (treatment difference of -0.25 (95%CI, -0.38, -0.12; p 0.0006). Additionally, the change in naïve B cell percentage from baseline to day 85 (only assessed in patients who had <48% baseline naïve B cells, and who were not censored during trial; n=13) showed a 37.39% increase in naïve B cell percentage in the treatment group versus a 0.09% increase in placebo (*p* 0.0002).

VIII. The analysis of naïve B cell percent improvement was confounded due to the censoring of 13 patients from the treatment group and five from the placebo group (protocol deviations, ≥48% naïve B cells at baseline, and lack of baseline or day 85 data). However, in a supportive analysis inclusive of all patients (excluding those without baseline or day 85 measurements), the naïve B cells percentage improvement was consistent and showed a mean difference between leniolisib (Joenja, n = 13) and placebo (n = 8) at 27.94% (95% CI: 15.02, 40.85; p 0.0003).

IX. Key and exploratory secondary outcomes such as improvements in spleen size, autoimmune cytopenia, and patient-reported quality of life (SF-36) at 12 weeks were not statistically significant; however, showed a favorable trend toward leniolisib (Joenja).

X. A single-arm, open-label extension (OLE) trial (N=35) for leniolisib (Joenja) did not report additional safety signals. Further reduction of SPD of index lesions and spleen volume were reported as well as up to 32% increase in naïve B cells with up to 252 days of treatment. These outcomes remain observational. During OLE, the patient reported QoL measures (mean change from baseline of the SF-36 and the WPAI-CIQ) remained unchanged. Additionally, study participants continued to receive antibiotics at a similar rate as those in Study 2201-02.

XI. The quality of evidence is considered low. Although objective measures, the changes in SPD index lesions and naïve B cells have not been validated or correlated with clinically meaningful outcomes in APDS such as patients' quality of life, reduction in infections, bronchiectasis, and incidence of lymphoma or death. Study 2201-02 had a small sample size, a short outcome assessment time frame, and a confounded data set due to the censoring of patients as well as the allowance of concurrent use of systemic corticosteroids and IRT. Although indicative of short-term benefits; significant hesitancy remains when considering the long-term application and the true effect of leniolisib (Joenja). Further clinical trials may help elucidate the efficacy and confirmation of the benefit of leniolisib (Joenja).

XII. Leniolisib (Joenja) is currently being evaluated in a Phase 3 trial in children aged four to 11 years.

XIII. Based on treatment exposure in all participants (N=31), adverse events (AEs) were reported by 85.7% of patients in leniolisib (Joenja) and in 90.0% in the placebo group; most commonly grade 1 (74.2%). Serious AEs were reported in five (16%) patients, none of whom were ascribed to the study drug. The most common AE in the treatment arm versus placebo included headache (24% vs 20%), sinusitis (19% vs 0%), and atopic dermatitis (14% vs 0%).

XIV. There were no treatment discontinuations or deaths during the clinical trial. Although no contraindications are listed, the leniolisib (Joenja) label includes warnings related to embryo-fetal toxicity. The real-world safety profile of leniolisib (Joenja) remains undetermined.

XV. Due to the lack of long-term efficacy data, and the low confidence in the clinically meaningful outcomes in APDS, true efficacy benefits and place in therapy for leniolisib (Joenja) remain relatively uncertain. Although expected to be a first-line agent, majority of the APDS patients may remain candidates for standard-of-care front-line therapies such as antibiotic and antiviral prophylaxis, use of systemic corticosteroids, Immunoglobulin G (IgG) replacement therapy (IRT), and other immunosuppressants (e.g., rituximab, sirolimus). Given the long-term safety, efficacy, real-world practice experience and therapy cost, these agents may remain practical alternatives to leniolisib (Joenja).

Investigational or Not Medically Necessary Uses

I. Leniolisib (Joenja) has not been FDA-approved, or sufficiently studied for safety and efficacy for any other condition(s) than APDS

References

1. Rao VK, Webster S, et al. A randomized, placebo-controlled phase 3 trial of the PI3Kδ inhibitor leniolisib for activated PI3Kδ syndrome. Blood. 2023 Mar 2;141(9):971-983.
2. Joenja (leniolisib). Package Insert. Pharming Healthcare Inc, Warren NJ. March 2023.
3. Coulter TI, Cant AJ. The Treatment of Activated PI3Kδ Syndrome. Front Immunol. 2018 Sep 7;9: 2043.

Related Policies

Currently, there are no related policies.

Policy Implementation/Update:

Policy Implementation/Update:	Date
Policy created	08/2023