Original Effective Date: 08/30/2023
Current Effective Date: 12/17/2025
Last P&T Approval/Version: 10/29/2025
Next Review Due By: 10/2026
Policy Number: C25485-A

Joenja (leniolisib)

PRODUCTS AFFECTED

Joenja (leniolisib)

COVERAGE POLICY

Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Coverage Guideline must be read in its entirety to determine coverage eligibility, if any. This Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide Molina Healthcare complete medical rationale when requesting any exceptions to these guidelines.

Documentation Requirements:
Molina Healthcare reserves the right to require that additional documentation be made available as part of its coverage determination; quality improvement; and fraud; waste and abuse prevention processes. Documentation required may include, but is not limited to, patient records, test results and credentials of the provider ordering or performing a drug or service. Molina Healthcare may deny reimbursement or take additional appropriate action if the documentation provided does not support the initial determination that the drugs or services were medically necessary, not investigational or experimental, and otherwise within the scope of benefits afforded to the member, and/or the documentation demonstrates a pattern of billing or other practice that is inappropriate or excessive.

DIAGNOSIS:
Activated phosphoinositide 3-kinase delta (PI3Kδ) syndrome (APDS)

REQUIRED MEDICAL INFORMATION:
This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. If a drug within this policy receives an updated FDA label within the last 180 days, medical necessity for the member will be reviewed using the updated FDA label information along with state and federal requirements, benefit being administered and formulary preferencing. Coverage will be determined on a case-by-case basis until the criteria can be updated through Molina Healthcare, Inc. clinical governance. Additional information may be required on a case-by-case basis to allow for adequate review. When the requested drug product for coverage is dosed by weight, body surface area or other member specific measurement, this data element is required as part of the medical necessity review. The Pharmacy and Therapeutics Committee has determined that the drug benefit shall be a mandatory generic and that generic drugs will be dispensed whenever available.

A. ACTIVATED PHOSPHOINOSITIDE 3-KINASE DELTA SYNDROME (APDS):
   1. Documentation of diagnosis of activated phosphoinositide 3-kinase delta syndrome (APDS) AND
   2. Documentation of APDS/PASLI- associated PIK3CD/PIK3R1 gene mutation [DOCUMENTATION REQUIRED]

AND

3. Documentation of baseline manifestations including, but not limited to, nodal or extra-nodal lymphoproliferation, history of sinopulmonary infections or organ dysfunction (e.g., bronchiectasis, liver disease, etc.) [DOCUMENTATION REQUIRED]
   AND
4. Documentation member has had a trial with insufficient response or has a labeled contraindication to sirolimus therapy

CONTINUATION OF THERAPY:

A. ACTIVATED PHOSPHOINOSITIDE 3-KINASE DELTA SYNDROME (APDS):

1. Adherence to therapy at least 85% of the time as verified by the prescriber or member medication fill history OR adherence less than 85% of the time due to the need for surgery or treatment of an infection, causing temporary discontinuation
   AND
2. Prescriber attests to or clinical reviewer has found no evidence of intolerable adverse effects or drug toxicity
   AND
3. Documentation of positive clinical response as demonstrated by disease stability or mild progression indicating a slowing of decline (e.g., lymph node size, infections, organ dysfunction, etc.) [DOCUMENTATION REQUIRED]

DURATION OF APPROVAL:

Initial authorization: 12 months, Continuation of Therapy: 12 months

PRESCRIBER REQUIREMENTS:

Prescribed by or in consultation with an immunologist, infectious disease specialist, allergist, otolaryngologist, or physician specializing in the treatment of APDS [If prescribed in consultation, consultation notes must be submitted with initial request and reauthorization requests]

AGE RESTRICTIONS:

12 years of age and older

QUANTITY:

70 mg twice daily (See Special Considerations)

PLACE OF ADMINISTRATION:

The recommendation is that oral medications in this policy will be for pharmacy benefit coverage and patient self-administered.

DRUG INFORMATION

ROUTE OF ADMINISTRATION:

Oral

DRUG CLASS:

Activated Phosphoinositide 3-kinase Delta Syndrome Agent

FDA-APPROVED USES:

Indicated for the treatment of activated phosphoinositide 3-kinase delta (PI3Kδ) syndrome (APDS) in adult and pediatric patients 12 years of age and older.

COMPENDIAL APPROVED OFF-LABELED USES:

None

APPENDIX

APPENDIX:
None

BACKGROUND AND OTHER CONSIDERATIONS

BACKGROUND:
Activated Phosphoinositide 3-Kinase Delta Syndrome (APDS)
Activated phosphoinositide 3-kinase delta syndrome (APDS), previously known as p110δ-activating mutation causing senescent T cells, lymphadenopathy, and immunodeficiency (PASLI) disease, is a complex, ultra-rare genetic disorder. This genetic disorder is caused by an autosomal-dominant mutation in either the phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit δ (PIK3CD) or the phosphoinositide-3-kinase regulatory subunit 1 (PIK3R1) gene. There are two types of APDS: APDS1 is due to changes in the PIK3CD gene and APDS2 is due to changes in the PIK3R1 gene. Both have similar symptoms and are inherited in an autosomal dominant pattern in families. Treatment for APDS is focused on managing symptoms, preventing infections, and lowering inflammation. It includes antibiotics to treat infections, anti-inflammatory drugs, immunoglobulin replacement, and hematopoietic stem-cell transplant (HSCT). The most common symptoms of APDS are frequent upper respiratory tract infections, sinus infections, ear infections, bronchitis, and pneumonia (lung infection). Most people with APDS get their first infection in early childhood, but symptoms can begin at any age. Other symptoms include gastrointestinal irritation, lymph node swelling, enlarged liver and spleen and an increased risk for lymphoma. Over time, frequent ear and respiratory tract infections can lead to permanent hearing loss and scarring of the lungs (bronchiectasis). As of 2020, fewer than 250 patients with APDS had been identified in published literature. APDS can be diagnosed at any age but is most often identified in early childhood. Patients may present with symptoms of mild developmental delay, bronchitis, bronchiectasis, immune cytopenias, splenomegaly, and/or lymphadenopathy. APDS should be suspected in patients with a history of recurrent respiratory infections, lymphoproliferation, and raised immunoglobulin M (IgM) levels. APDS is a significant cause of primary antibody deficiency (PAD) and should be considered among the differential diagnoses of patients presenting with atypical or severe PAD complications.

Currently patient's with APDS are treated with supportive therapies used to manage symptoms, such as long-term antibiotic prophylaxis and immunoglobulin replacement therapy. Immunosuppressive therapies aimed at reducing lymphoproliferation include treatment with rituximab (anti-CD20 monoclonal antibody) and rapamycin (sirolimus) to target the activation of the mammalian target of rapamycin (mTOR) pathway.

Joenja (leniolisib) Efficacy
Approval was based on results from the global Phase 3 study (NCT02435173), which was a triple-blind, randomized, placebo-controlled study that evaluated Joenja over 12 weeks at a dose of 70 mg Joenja or placebo every 12 hours, administered orally. The study population were Patients 12 to 75 years of age with confirmed APDS/PASLI-associated PI3Kδ mutation with a documented variant in either PIK3CD or PIK3R1. The study was designed in two parts: Part I: non-randomized, open-label, within-patient up-titration dose-finding part (n=6)- Phase 2, Part II: randomized, subject-, investigator-, and sponsor-blinded, placebo-controlled, fixed-dose part (n=31)- Phase 3. Patients were required to have nodal and/or extranodal lymphoproliferation, and clinical findings and manifestations compatible with APDS/PASLI such as a history of repeated oto-sino-pulmonary infections and/or organ dysfunction (e.g., lung, liver). In Part II patients were also required to have ≥ 1 measurable nodal lesion on CT or MRI scan. Patients were excluded if they had previous or concurrent use of immunosuppressive medication, current use of medication known to be strong inhibitors or moderate or strong inducers of isoenzyme CYP3A, if the treatment could not be discontinued or switched to a different medication prior to starting study treatment, and current use of medications that are metabolized by isoenzyme CYP1A2 and have a narrow therapeutic index. Additionally, patients were excluded if they had received live vaccines (including any attenuated live vaccines) starting from 6 weeks before study entry, during the study, and up to 7 days

after the last dose of Joenja.

In Part I, study drug was provided as such: Joenja 10 mg twice daily (Day 1–Day 28), Joenja 30 mg twice daily (Day 29–Day 56), and Joenja 70 mg twice daily (Day 57–Day 84). In Part II study drug was provided as Joenja 70 mg twice daily (Day 1–Day 85). Co-primary outcomes included differences in index lymph node size from baseline as measured by MRI or CT-scan and percentage of naïve B cells in peripheral blood (assessed as proxies for immune dysregulation/deficiency) as measured by flow cytometry. Results demonstrated that that leniolisib achieved a statistically significant reduction in index lymph node size (placebo-adjusted difference, -0.25; 95% CI, -0.38, -0.12; P =.0006) and for the percent improvement in naïve B cell counts (placebo-adjusted difference, 37.30; 95% CI, 24.06-50.54; P =.0002), compared with placebo.

Safety
The most common adverse reactions (incidence greater than 10%) for leniolisib were headache, sinusitis, and atopic dermatitis. Leniolisib carries a risk for embryo-fetal toxicity and the pregnancy status of patients of reproductive potential should be verified prior to starting treatment.

CONTRAINDICATIONS/EXCLUSIONS/DISCONTINUATION:
All other uses of Joenja (leniolisib) are considered experimental/investigational and therefore, will follow Molina's Off- Label policy. Contraindications to Joenja (leniolisib) include: no FDA labeled contraindications currently.

Exclusions/Discontinuation:
Based on findings in animals, Joenja may cause fetal harm when administered to a pregnant woman. Verify the pregnancy status of patients of reproductive potential prior to starting treatment. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use highly effective methods of contraception during treatment and for 1 week after the last dose.

OTHER SPECIAL CONSIDERATIONS:
Joenja (leniolisib) 70 mg twice daily is recommended for member 12 years of age and older who weight at least 45 kilograms. There is no recommended dose for members less than 45 kilograms, per the FDA approved label.

If a dose is missed by more than 6 hours, wait and take the next dose at the usual time.

CODING/BILLING INFORMATION

CODING DISCLAIMER. *Codes listed in this policy are for reference purposes only and may not be all-inclusive or applicable for every state or line of business. Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement. Listing of a service or device code in this policy does not guarantee coverage. Coverage is determined by the benefit document. Molina adheres to Current Procedural Terminology (CPT®), a registered trademark of the American Medical Association (AMA). All CPT codes and descriptions are copyrighted by the AMA; this information is included for informational purposes only. Providers and facilities are expected to utilize industry-standard coding practices for all submissions. Molina has the right to reject/deny the claim and recover claim payment(s) if it is determined it is not billed appropriately or not a covered benefit. Molina reserves the right to revise this policy as needed.*

HCPCS CODE	DESCRIPTION
NA	

AVAILABLE DOSAGE FORMS:

REFERENCES

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7. FDA approves first treatment for activated phosphoinositide 3-kinase delta syndrome. US Food & Drug Administration (FDA). Available at: https://www.fda.gov/drugs/news-events-human- drugs/fda-approves-first-treatment-activated-phosphoinositide-3-kinase-delta-syndrome (Accessed on June 07, 2023).
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SUMMARY OF REVIEW/REVISIONS	DATE
REVISION- Notable revisions: Required Medical Information Contraindications/Exclusions/Discontinuation References	Q4 2025
REVISION- Notable revisions: Coding/Billing Information Template Update Duration of Approval	Q4 2024
REVISION- Notable revisions: Required Medical Information Continuation of Therapy Prescriber Requirements Quantity Other Special Considerations	Q4 2023
NEW CRITERIA	Q3 2023