BlueCross BlueShield Arizona

An Independent Licensee of the Blue Cross Blue Shield Association

PHARMACY COVERAGE GUIDELINE

JOENJA® (leniolisib)
Generic Equivalent (if available)

This Pharmacy Coverage Guideline (PCG):
- Provides information about the reasons, basis, and information sources we use for coverage decisions
- Is not an opinion that a drug (collectively "Service") is clinically appropriate or inappropriate for a patient
- Is not a substitute for a provider's judgment (Provider and patient are responsible for all decisions about appropriateness of care)
- Is subject to all provisions e.g. (benefit coverage, limits, and exclusions) in the member's benefit plan; and
- Is subject to change as new information becomes available.

Scope
- This PCG applies to Commercial and/or Marketplace plans
- This PCG does not apply to the Federal Employee Program, Medicare Advantage, Medicaid or members of out-of-state Blue Cross and/or Blue Shield Plans

Instructions & Guidance
- To determine whether a member is eligible for the Service, read the entire PCG.
- This PCG is used for FDA approved indications including, but not limited to, a diagnosis and/or treatment with dosing, frequency, and duration.
- Use of a drug outside the FDA approved guidelines, refer to the appropriate Off-Label Use policy.
- The "Criteria" section outlines the factors and information we use to decide if the Service is medically necessary as defined in the Member's benefit plan.
- The "Description" section describes the Service.
- The "Definition" section defines certain words, terms or items within the policy and may include tables and charts.
- The "Resources" section lists the information and materials we considered in developing this PCG
- **We do not accept patient use of samples as evidence of an initial course of treatment, justification for continuation of therapy, or evidence of adequate trial and failure.**
- Information about medications that require prior authorization is available at www.azblue.com/pharmacy. You must fully complete the request form and provide chart notes, lab workup and any other supporting documentation. The prescribing provider must sign the form. Fax the form to BCBSAZ Pharmacy Management at (602) 864-3126 or email it to Pharmacyprecert@azblue.com.

Medical Necessity Requirements for JOENJA (leniolisib)

Criteria for Initial Therapy:

Prescriber Qualifications
- Prescribed by an Immunologist, Hematologist, Pediatrician, or Oncologist, or in consultation with one

Indication
- Activated phosphoinositide 3-kinase delta (PI3Kδ) syndrome (APDS)

Age Requirement
- 12 years of age or older and weighs 45 kilograms or more

ORIGINAL EFFECTIVE DATE: 05/18/2023 | ARCHIVE DATE: | LAST REVIEW DATE: 05/15/2025 | LAST CRITERIA REVISION DATE: 05/15/2025

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Baseline Clinical Evaluation

- Documentation of *PIK3CD* or *PIK3R1* gene mutations
- Nodal or extra-nodal lymphoproliferation
- At least one measurable nodal lesion on CT or MRI scan
- Clinical manifestations of APDS/PASLI (e.g., history of repeated oto-sino-pulmonary infections, bronchiectasis, viral infections (EBV, CMV, HSV), hepatosplenomegaly, autoimmune cytopenias)
- Negative pregnancy test in a woman of childbearing potential

Alternative Therapies

- Failure, contraindication per FDA label, or intolerance, to **ALL** the following:
  - Prophylactic antimicrobials (bacterial and viral)
  - Immunoglobulin replacement if needed
  - Immunosuppressive therapy with rituximab and sirolimus

Brand Specific Criteria

- Have failure, contraindication, or intolerance with **THREE** generic equivalents (when available) for at least three months each. **Note:** Any failure, contraindication, or intolerance to the generic drugs should be reported to the FDA (see Definitions section)

Safety

- No concomitant drug use with:
  - Strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, posaconazole, voriconazole, clarithromycin, etc.)
  - Strong and moderate CYP3A4 inducers (e.g., rifampin, rifabutin, phenobarbital, carbamazepine, armodafinil, bexarotene, bosentan, efavirenz, etc.)
  - CYP1A2 metabolized drugs with a Narrow Therapeutic Index (e.g., theophylline, caffeine, tizanidine, etc.)
  - BCRP, OATP1B1, and OATP1B3 substrates (e.g., estrone-3 sulfate, estradiol-17B-glucuronide, pitavastatin, pravastatin, rosuvastatin, etc.)
- Does not have moderate to severe hepatic impairment

Documentation Requirements

- A completed request form must be submitted, including:
  - Chart notes
  - Lab results (gene mutation confirmation, pregnancy test)
  - Supporting clinical documentation

Initial Therapy Criteria Approval Duration:

- 6 months OR end of plan year

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Criteria for Continuation of Therapy (renewal therapy)

Note: Manufacturer assistance (e.g., coupons, samples, etc.) are not considered for continuation of therapy

Prescriber Qualifications

- Continues to be seen by a physician specializing in or is in consultation with an Immunologist, Hematologist, Pediatrician, or Oncologist

Clinical Response

- Improvement in lymphoproliferation as measured by change from baseline in lymphadenopathy
- Improvement in other clinical features such as spleen size, liver size, infection rate , etc.
- Normalization of immunophenotype as measured by percentage of naïve B cells out of total B cells

Adherence

- Adherence to the prescribed therapy regimen has been documented

Brand Specific Criteria

- Have failure, contraindication, or intolerance with **THREE** generic equivalents (when available) for at least three months each. **Note:** Any failure, contraindication, or intolerance to the generic drugs should be reported to the FDA (see Definitions section)

Safety

- No concomitant drug use with:
  - Strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, posaconazole, voriconazole, clarithromycin, etc.)
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  - CYP1A2 metabolized drugs with a Narrow Therapeutic Index (e.g., theophylline, caffeine, tizanidine, etc.)
  - BCRP, OATP1B1, and OATP1B3 substrates (e.g., estrone-3 sulfate, estradiol-17B-glucuronide, pitavastatin, pravastatin, rosuvastatin, etc.)
- Does not have moderate to severe hepatic impairment

Documentation Requirements

- Chart notes
- Supporting clinical documentation with evidence of improvement in given indication
- Lab values that confirm safe use from above criteria

Continuation Therapy Criteria Approval Duration:

- 12 months OR end of plan year

Criteria for Off-Label Use Requests:

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Criteria for a request for non-FDA use or indication, treatment with dosing, frequency, or duration outside the FDA-approved dosing, frequency, and duration, refer to one of the following Pharmacy Coverage Guideline:

1. Off-Label Use of Non-Cancer Medications

2. Off-Label Use of Cancer Medications

Description:

Joenja (leniolisib) is a kinase inhibitor indicated for the treatment of **a**ctivated ***p***hosphoinositide 3-kinase *delta* (PI3Kδ) *s*yndrome (APDS) in adult and pediatric patients 12 years of age and older who weigh 45 kilograms or more. There is no recommended dosage for pediatric patients 12 years of age and older who weigh less than 45 kg.

APDS is an inborn error of immunity resulting from pathogenic variants in either of the genes encoding the PI3Kδ heterodimer. APDS or PASLI disease (***p***110-delta-***a***ctivating mutation causing ***s***enescent T cells, ***l***ymphadenopathy, and ***i***mmunodeficiency) is due to heterozygous gain-of-function mutations of the phosphatidylinositol 3-kinase, catalytic, delta (*PIK3CD*) gene that encodes the p100-delta subunit of PI3K. Senescent T cells are highly inflammatory and secrete cytotoxic mediators and express natural killer cells receptors (NKR) that bypass their antigen specificity. Gain-of-function variants in *PIK3CD* that encodes for catalytic subunit p110δ causes APDS1, whereas loss-of-function variants in *PIK3R1* that encodes for the regulatory subunit p85α causes APDS2.

Phosphoinositide 3-kinase (PI3K, also known as phosphatidylinositol 3-kinase) activates mammalian target of rapamycin (mTOR) and AKT (a murine thymoma viral oncogene homolog and protein kinase) signaling pathways that control T cell metabolism, proliferation, and effector function. Activation shifts intracellular metabolism from beta-oxidation of fatty acids to aerobic glycolysis in effector T cells. T cells switch back to beta-oxidation when there is transition from the effector to memory cell state. PI3K also plays a role in B cell development, class-switch recombination (CSR), and survival of mature B cells.

Patients with APDS/PASLI disease have recurrent sinopulmonary infections with progressive airway damage and bronchiectasis, lymphadenopathy, nodular lymphoid hyperplasia in mucosal tissues, increased incidence of EBV and CMV viremia and EBV-related lymphoma, progressive lymphopenia, elevated serum IgM, and impaired antibody responses. Recurrent sinopulmonary infections and prolonged or intermittent herpesvirus viremia may be due to immunoglobulin dysfunction or related to increases in immature/dysfunctional B and T lymphocytes at the expense of mature/functional cells.

Since there is a sustained PI3K signaling that causes increased activation of the mTOR signaling pathway, patients may benefit from treatment with sirolimus (rapamycin), an mTOR inhibitor, that can partially restore NK cell cytotoxicity. Patients can survive into adulthood. However, most patient have persistent symptoms and life-threatening lymphoproliferation, and/or infections are common.

There are different classes and isoforms of PI3Ks. Class 1 PI3Ks have a catalytic subunit known as p110, with four types (isoforms) – p110 **alpha** (PIK3CA), p110 **beta** (PIK3CB), p110 **gamma** (PIK3CG) and p110 **delta** (PIK3CD). PI3K inhibitor class of medicines have been developed to inhibit one or more of the phosphoinositide

3-kinase enzymes that form part of the PI3K/AKT/mTOR pathway. By inhibiting these enzymes, PI3K inhibitors cause cell death, inhibit the proliferation of malignant cells, and interfere with several signaling pathways.

Four PI3K inhibitors have received approval for indications involving relapsed or refractory indolent non-Hodgkin lymphoma or chronic lymphocytic leukemia: idelalisib, copanlisib, duvelisib, and umbralisib. All of these inhibit the PI3K**δ** isoform and some also inhibit other isoforms. Alpelisib is a PI3K**α**-specific inhibitor approved for breast cancer (as Piqray) and PIK3CA-related overgrowth spectrum (as Vijoice). Although the other four PI3K inhibitors have shown durable overall response rates or improvements in progression-free survival, or both, they have also shown substantial toxicity.

Due to safety concerns, the FDA has withdrawn its approval for the cancer medicine Ukoniq (umbralisib). Ukoniq was approved to treat two specific types of lymphoma: marginal zone lymphoma (MZL) and follicular lymphoma (FL). Updated findings from the UNITY-CLL clinical trial continued to show a possible increased risk of death in patients receiving Ukoniq. As a result, it was determined the risks of treatment with Ukoniq outweigh its benefits. Based upon this determination, the drug's manufacturer it was voluntarily withdrawing Ukoniq from the market for the approved uses in MZL and FL.

Leniolisib inhibits PI3K-delta by blocking the active binding site of PI3K-delta. In cell-free isolated enzyme assays, leniolisib was selective for PI3K-delta over PI3K-alpha (28-fold), PI3K-beta (43-fold), and PI3K-gamma (257-fold), as well as the broader kinome. In cell-based assays, leniolisib reduced pAKT pathway activity and inhibited proliferation and activation of B and T cell subsets. Gain-of-function variants in the gene encoding the p110-delta catalytic subunit or loss of function variants in the gene encoding the p85-alpha regulatory subunit each cause hyperactivity of PI3K-delta. Leniolisib inhibits the signaling pathways that lead to increased production of PIP3, hyperactivity of the downstream mTOR/AKT pathway, and to the dysregulation of B and T cells.

Definitions:

U.S. Food and Drug Administration (FDA) MedWatch Forms for FDA Safety Reporting
MedWatch Forms for FDA Safety Reporting | FDA

Resources:

Joenja (leniolisib) product information, revised by Pharming Healthcare, Inc. 03-2023. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed February 18, 2025.

Notarangelo L. Hyperimmunoglobulin M Syndrome. In: UpToDate, Orange JS, TePas E (Ed), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Literature current through February 2025. Topic last updated February 08, 2025. Accessed March 12, 2025.

Rao KV, Webster, Sediva A, et al. A randomized, placebo-controlled phase 3 trial of the PI3Kδ inhibitor leniolisib for activated PI3Kδ Syndrome. Blood 2023 March 2; 141 (9): 971-983. Re-evaluated March 12, 2025.

Vanselow S, Wahn V and Schuetz C. Activated PI3Kd syndrome – reviewing challenges in diagnosis and treatment. Front. Immunol. 2023; 14:1208567. doi: 10.3389/fimmu.2023.1208567. Accessed March 13, 2025.

Singh A, Joshi V, Jindal AK, et al.: An updated review on activated PI3 kinase delta syndrome (APDS). Genes Dis 2019 Oct 14; 7(1): 67-74. doi: 10.1016/j.gendis.2019.09.015. Accessed March 13, 2025.

Michalovich D, Nejentsev S. Activated PI3 Kinase Delta Syndrome: From Genetics to Therapy. Front Immunol 2018 Feb 27; 9: 369. doi: 10.3389/fimmu.2018.00369. Accessed March 12, 2025.

Rao KV, Webster S, Dalm VASH, et al. Effective “activated PI3Kδ syndrome”–targeted therapy with the PI3Kδ inhibitor leniolisib. Blood. 2017 Nov 23; 130(21): 2307–2316. Re-evaluated March 12, 2025.

ClinicalTrials.gov Bethesda (MD): National Library of Medicine (US). Identifier NCT02435173: An Open-label, Non-randomized, Within-patient Dose-finding Study Followed by a Randomized, Subject, Investigator and Sponsor Blinded Placebo Controlled Study to Assess the Efficacy and Safety of CDZ173 (Leniolisib) in Patients With APDS/PASLI (Activated Phosphoinositide 3-kinase Delta Syndrome/ p110δ-activating Mutation Causing Senescent T Cells, Lymphadenopathy and Immunodeficiency). Available from: http://clinicaltrials.gov. Last update posted August 10, 2022. Last verified August 2022. Accessed April 05, 2023. Re-evaluated March 12, 2025.

ClinicalTrials.gov Bethesda (MD): National Library of Medicine (US). Identifier NCT02859727: An Open-label, Non-randomized Extension Study to Evaluate the Long Term Safety, Tolerability, Efficacy and Pharmacokinetics of CDZ173 in Patients With APDS/PASLI (Activated Phosphoinositide 3-kinase Delta Syndrome/p110δ-activating Mutation Causing Senescent T Cells, Lymphadenopathy and Immunodeficiency). Available from: http://clinicaltrials.gov. Last update posted October 31, 2022. Last verified October 2022. Accessed April 05, 2023. Re-evaluated March 12, 2025.