PHARMACY COVERAGE GUIDELINE

VIJOICE® (alpelisib) oral
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 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.

Criteria:

➢ **Criteria for initial therapy:** Vijoice (alpelisib) and/or generic equivalent (if available) is considered ***medically necessary*** and will be approved when **ALL** the following criteria are met:

1. Prescriber is a physician specializing in the patient's diagnosis or is in consultation with a Pediatrician or Geneticist

2. Individual is 2 years of age or older

3. Individual has a confirmed diagnosis of severe or life-threatening manifestation of PIK3CA-Related Overgrowth Spectrum (PROS) who requires systemic therapy (see Definitions section)

4. Onset of disease is/was congenital or occurred early in childhood

5. There is segmental/focal overgrowth that is considered sporadic and mosaic (patchy, irregular) that may be in an asymmetric distribution

6. There is **ONE** of the following features: (see Definitions section)
    a. There is **TWO** of the following Spectrum features:
        i. Overgrowth seen in adipose tissue, muscle, nerve, or skeleton
        ii. Vascular malformations are found (capillary, venous, arteriovenous malformations, or lymphatics)
        iii. Epidermal nevus
    b. There is **ONE** of the following Isolated features:
        i. Large isolated lymphatic malformations
        ii. Isolated macrodactyly OR overgrown splayed feet/hands, overgrown limbs
        iii. Truncal adipose overgrowth
        iv. Hemimegalencephaly (bilateral)/dysplastic megalencephaly/focal cortical dysplasia
        v. Epidermal nevus
        vi. Seborrheic keratoses
        vii. Benign lichenoid keratoses

7. Individual has received and completed **ALL** the following **baseline tests** before initiation of treatment and with continued monitoring of the individual as clinically appropriate:
    a. Evidence of somatic (acquired) mutation in the *PIK3CA* gene
    b. Fasting plasma glucose
    c. Hemoglobin A1c
    d. Negative pregnancy test in a woman of childbearing potential

8. **If available**: Individual has failure after adequate trial, contraindication per FDA label, intolerance, or is not a candidate for a **generic equivalent** [Note: Failure, contraindication or intolerance to the generic should be reported to the FDA] (see Definitions section)

9. Will not be combined with other alpelisib containing products (e.g., Piqray)

10. Individual does not have a history of Stevens-Johnson syndrome, erythema multiforme, or toxic epidermal necrolysis

11. Individual does not have type 1 diabetes mellitus or *uncontrolled* type 2 diabetes mellitus

12. Individual does not have severe renal impairment (CrCl ≤ 30 mL/min)

13. Individual is not using other drugs which result in significant drug interactions requiring discontinuation such as strong inducers of CYP3A4 (e.g., rifampin, rifabutin, phenobarbital, carbamazepine, phenytoin, others)

Initial approval duration: 6 months

- **Criteria for continuation of coverage (renewal request):** Vijoice (alpelisib) and/or generic equivalent (if available) is considered ***medically necessary*** and will be approved when **ALL** the following criteria are met **(samples are not considered for continuation of therapy)**:

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1. Individual continues to be seen by a physician specializing in the patient's diagnosis or is in consultation with a Pediatrician or Geneticist

2. Individual's condition has responded while on therapy with response defined as **TWO** of the following:
    a. There is at least a 20% reduction in the target lesion volume
    b. There is no presence of at least a 20% increase in any target lesion or progression of non-target lesions or appearance of new lesions
    c. Improvement in signs or symptoms of PROS (e.g., pain, fatigue, vascular malformations, etc.)

3. Individual has been adherent with the medication

4. **If available**: Individual has failure after adequate trial, contraindication per FDA label, intolerance, or is not a candidate for a **generic equivalent** [Note: Failure, contraindication or intolerance to the generic should be reported to the FDA] (see Definitions section)

5. Individual has not developed any significant adverse drug effects that may exclude continued use such as:
    a. Severe hypersensitivity
    b. Stevens-Johnson syndrome
    c. Erythema multiforme
    d. Toxic epidermal necrolysis
    e. Drug reaction with eosinophilia and systemic symptoms (DRESS)
    f. Severe hyperglycemia, despite treatment
    g. Hyperglycemic hyperosmolar non-ketotic syndrome
    h. Ketoacidosis
    i. Pneumonitis/Interstitial lung disease
    j. Severe diarrhea, despite anti-diarrheal agents
    k. Colitis
    l. Pancreatitis

6. Dose is at least 50 mg daily

7. Will not be combined with other alpelisib containing products (e.g., Piqray)

8. Individual does not have a history of Stevens-Johnson syndrome, erythema multiforme, or toxic epidermal necrolysis

9. Individual does not have type 1 diabetes mellitus or *uncontrolled* type 2 diabetes mellitus

10. Individual does not have severe renal impairment (CrCl $\leq$ 30 mL/min)

11. Individual is not using other drugs which result in significant drug interactions requiring discontinuation such as strong inducers of CYP3A4 (e.g., rifampin, rifabutin, phenobarbital, carbamazepine, phenytoin, others)

Renewal duration: 12 months

ORIGINAL EFFECTIVE DATE: 05/19/2022 | ARCHIVE DATE: | LAST REVIEW DATE: 05/15/2025 | LAST CRITERIA REVISION DATE: 05/16/2024

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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:

Vijoice (alpelisib) is a kinase inhibitor that is indicated for the treatment of adult and pediatric patients 2 years of age and older with severe manifestations of PIK3CA-Related Overgrowth Spectrum (PROS) who require systemic therapy. This indication is approved under accelerated approval based on response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

Alpelisib is available as 2 different brand names (Piqray and Vijoice). The indications and dosages differ between products. Piqray is indicated for the treatment of treatment (in combination with fulvestrant) of hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, PIK3CA-mutated (as detected by an FDA-approved test), advanced or metastatic breast cancer in adults following progression on or after an endocrine-based regimen.

Activating mutations in *PIK3CA* have been found to induce a spectrum of overgrowths and malformations comprising a wide group of clinically recognizable disorders commonly known as PROS.

PROS groups lesions with heterogeneous, segmental, overgrowth phenotypes, with or without vascular anomalies, and includes fibroadipose hyperplasia or overgrowth, hemihyperplasia multiple lipomatosis, CLOVES (congenital lipomatous overgrowth, vascular malformations, epidermal nevi, and skeletal anomalies) syndrome, macrodactyly, fibroadipose infiltrating lipomatosis/facial infiltrative lipomatosis, macrocephaly-capillary malformation (MOCM, MCAP), dysplastic megalencephaly, and Klippel-Trenaunay syndrome.

PROS involves a range of clinical findings in which the core features are congenital or early-childhood onset of segmental/focal overgrowth with or without cellular dysplasia. PROS-related complications can include hemorrhages; embolisms; vascular or lymphatic anomalies; congenital neurological complications; developmental delays; functional impairments; organ abnormalities, including cardiac and renal; superficial infections; chronic pain; skeletal anomalies; and psychological impact. Prior to the identification of *PIK3CA* as the causative gene, PROS was separated into distinct clinical syndromes based on the tissues and/or organs involved.

Predominant areas of overgrowth include the brain, limbs (including fingers and toes), trunk (including abdomen and chest), and face, all usually in an asymmetric distribution. Brain overgrowth may be accompanied by secondary overgrowth of specific brain structures. Vascular malformations may include capillary, venous, and arterial or mixed (capillary-lymphatic-venous or arteriovenous) malformations. Lymphatic malformations may occur in various locations and can cause swelling, pain, and localized bleeding secondary to trauma. Lipomatous overgrowth may occur.

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Definitions:

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

Manifestation of PIK3CA-Related Overgrowth Spectrum (PROS):

a. CLAPO syndrome (capillary malformation of the lower lip, lymphatic malformation of the face and neck, asymmetry of face and limbs, and partial or generalized overgrowth)
b. CLOVES syndrome (congenital lipomatous overgrowth, vascular malformations, epidermal nevi, and scoliosis/skeletal and spinal anomalies)
c. Dysplastic megalencephaly, hemimegalencephaly and focal cortical dysplasia
d. Fibroadipose hyperplasia or overgrowth
e. Fibroadipose infiltrating lipomatosis/facial infiltrative lipomatosis
f. Hemihyperplasia multiple lipomatosis
g. Isolated macrodactyly or overgrown splayed feet/hands, overgrown limbs
h. Isolated tissue dysplasia-overgrowth phenotypes: lymphatic malformations, vascular malformations, venous malformations, lipomatosis
i. Klippel-Trenaunay syndrome
j. Megalocephaly-capillary malformation syndrome

Examples of severe clinical manifestations include:

- Excessive tissue growth, scoliosis, vascular tumors, cardiac or renal manifestations, severe vascular malformations, chronic gastrointestinal bleeding, severe dyspnea, disabling chronic pain, severe epilepsy, severe manifestations despite previous debulking surgery

The National Institute of Health (NIH) Clinical Diagnostic Criteria for PROS include the following:

• Required:
  o Presence of somatic PIK3CA mutation*
  o Congenital or early childhood onset
  o Overgrowth sporadic and mosaic (other terms: patchy, irregular)
  o Features described in either A or B
• A: Spectrum (TWO or more of the following features) **
  o Overgrowth: adipose, muscle, nerve, skeletal
  o Vascular malformations: capillary, venous, arteriovenous malformations, lymphatic
  o Epidermal nevus
• B: Isolated features (at least ONE of the following features)
  o Large isolated lymphatic malformations
  o Isolated macrodactyly*** OR overgrown splayed feet/hands, overgrown limbs
  o Truncal adipose overgrowth
  o Hemimegalencephaly (bilateral)/dysplastic megalencephaly/focal cortical dysplasia
  o Epidermal nevus
  o Seborrheic keratoses
  o Benign lichenoid keratoses

*- If no mutation identified, consider as presumptive PROS
**- Typically, progressive, can manifest as: Scoliosis (Kyphosis), Limb overgrowth, CNS (HC, Cerebellar tonsillar ectopia, Chiari, Megalencephaly, Mega corpus callosum, Regional lipomatous undergrowth with overgrowth, Infiltrating lipomatosis, Wilms tumor/ovarian cystadenoma.

***- Other terms: macrodystrophia lipomatosa, macrodactylia fibrolipomatosis, and gigantism.

Resources:

Vijoice (alpelisib) product information, revised by Novartis Pharmaceuticals Corporation 04-2024. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed February 18, 2025.

Frieden IL, Chu DH. Klippel-Trenaunay syndrome: Clinical manifestations, diagnosis, and management. In: UpToDate, Levy ML, Corona R (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Literature current through February 2025. Topic last updated February 07, 2025. Accessed March 10, 2025.

ClinicalTrials.gov Bethesda (MD): National Library of Medicine (US). Identifier NCT04285723: Retrospective Chart Review Study of Patients With PIK3CA-Related Overgrowth Spectrum (PROS) Who Have Received Alpelisib as Part of a Compassionate Use Program (EPIK-P1). Available from: http://clinicaltrials.gov. Last update posted February 09, 2023. Last verified May 2022. Accessed March 21, 2023. Re-evaluated March 10, 2025.

Mirzaa G, Graham JM, Keppler-Noreuil K. PIK3CA-Related Overgrowth Spectrum. GeneReviews® - NCBI Bookshelf (nih.gov). National Institute of Health. National Library of Medicine. National Center for Biotechnology Information. Available at www.ncbi.nlm.nih.gov. Topic last updated December 23, 2021. Accessed May 17, 2022. Re-evaluated March 10, 2025.

McCuaig CC. Update on classification and diagnosis of vascular malformations. Current Opinion Pediatrics 2017 Aug; 29(4): 448-454. Accessed March 10, 2025.

Keppler-Noreuil KM, Rios JJ, Parker VER, et al. PIK3CA-Related Overgrowth Spectrum (PROS): Diagnostic and Testing Eligibility Criteria, Differential Diagnosis, and Evaluation. Am J Med Genet Part A. 2015 February: 287-295. Accessed March 22, 2023. Re-evaluated March 10, 2025.

Kuentz P, St Onge J, Duffourd Y, et al: Molecular diagnosis of PIK3CA-related overgrowth spectrum (PROS) in 162 patients and recommendations for genetic testing. Genetics Medicine 2017 Sept; 19; (9): 989-997. Accessed March 20, 2024. Re-evaluated March 10, 2025.

National Organization for Rare Disorders (NORD) 2022: PIK3CA-Related Overgrowth Spectrum. Accessed March 20, 2024. Re-evaluated March 10, 2025.