BlueCross BlueShield Arizona

An Independent Licensee of the Blue Cross Blue Shield Association

PHARMACY COVERAGE GUIDELINE

ITOVEBI™ (inavolisib) 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:** Itovebi (inavolisib) 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 an Oncologist

2. Individual is 18 years of age or older

3. Individual has a confirmed diagnosis of **ONE** of the following:
    a. Breast cancer that is endocrine-resistant, *PIK3CA*-mutated, hormone receptor (HR)-positive, human epidermal growth-factor receptor 2 (HER2)-negative, locally advanced or metastatic, following recurrence on or after completing adjuvant endocrine therapy

b. Other request for a specific oncologic direct treatment use that is found and listed in the National Comprehensive Cancer Network (NCCN) Guidelines with Categories of Evidence and Consensus of 1 and 2A

4. Individual's disease progressed during or within 12 months of completing adjuvant endocrine therapy with an aromatase inhibitor or tamoxifen

5. Individual does not have any history of leptomeningeal disease or carcinomatous meningitis

6. Individual does not have metaplastic breast cancer

7. Individual does not have known and untreated, or active CNS metastases

8. Individual has not received prior systemic therapy for locally advanced or metastatic disease

9. Requested agent to be used in combination with Ibrance (palbociclib) and fulvestrant (brand Faslodex or generic)

10. **ONE** of the following:
    a. For premenopausal and perimenopausal women, administer a luteinizing hormone releasing hormone (LHRH) agonist (e.g., goserelin or leuprolide) in accordance with local clinical practice
    b. For men, consider administering an LHRH agonist (e.g., goserelin or leuprolide) in accordance with local clinical practice

11. Individual has completed **ALL** the following **baseline tests** before initiation of treatment and will have continued monitoring of the individual as clinically appropriate:
    a. There is documentation of one or more *PIK3CA* mutations in plasma specimen
    b. Fasting plasma glucose (FPG)/blood glucose (FBG) is less than 126 mg/dL, optimize if abnormal
    c. Hemoglobin A1c is less than 6%, optimize if abnormal
    d. Documentation of a negative pregnancy test in a woman of childbearing potential
    e. Eastern Cooperative Oncology Group (ECOG) performance status scale of 0-1

12. **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)

13. Individual is not currently taking any other drug that may cause a severe adverse reaction or a significant drug interaction that may require discontinuation

14. Requested agent will not be used with other phosphatidylinositol 3-kinase (PI3K) inhibitors (e.g., Piqray (alpelisib), Vijoice (alpelisib), Aliqopa (copanlisib), Copiktra (duvelisib), or Zydelig (idelalisib))

15. Individual does not have severe renal impairment (eGFR less than 30 mL/min)

16. Individual does not have moderate to severe hepatic impairment

Initial approval duration: 6 months

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- **Criteria for continuation of coverage (renewal request):** Itovebi (inavolisib) 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)**:

  1. Individual continues to be seen by a physician specializing in the patient's diagnosis or is in consultation with an Oncologist
  2. Individual has documentation of positive clinical response to therapy defined as there is no evidence of disease progression or unacceptable drug toxicity
  3. Individual has been adherent with the medication
  4. Individual **has not had** more than two (2) dose reductions to relieve adverse effects
  5. **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)
  6. Individual has not developed any significant adverse drug effects that may exclude continued use such as:
     a. Hyperglycemia, if clinically appropriate, withhold dose, reduce dose, or permanently discontinue based on severity, recurrence, persistence, or duration of adverse reaction
     b. Stomatitis, if clinically appropriate, withhold dose, reduce dose, or permanently discontinue based on severity, recurrence, persistence, or duration of adverse reaction
     c. Diarrhea, if clinically appropriate, withhold dose, reduce dose, or permanently discontinue based on severity, recurrence, persistence, or duration of adverse reaction
     d. Any life-threatening adverse reaction
  7. Individual is not currently taking any other drug that may cause a severe adverse reaction or a significant drug interaction that may require discontinuation
  8. Requested agent will not be used with other phosphatidylinositol 3-kinase (PI3K) inhibitors (e.g., Piqray (alpelisib), Vijoice (alpelisib), Aliqopa (copanlisib), Copiktra (duvelisib), or Zydelig (idelalisib))
  9. Individual does not have severe renal impairment (eGFR less than 30 mL/min)
  10. Individual does not have moderate to severe hepatic impairment

  Renewal duration: 12 months

- 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**

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Description:

Itovebi (inavolisib) is a kinase inhibitor indicated in combination with Ibrance (palbociclib) and fulvestrant (brand Faslodex or generic) for the treatment of adults with endocrine-resistant, *PIK3CA*-mutated, hormone receptor (HR)-positive, human epidermal growth-factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer, as detected by an FDA-approved test, following recurrence on or after completing adjuvant endocrine therapy. Inavolisib is an inhibitor of PI3K with inhibitory activity predominantly against PI3Kα. *In vitro*, inavolisib induced the degradation of mutated PI3K catalytic alpha subunit p110α (encoded by the *PIK3CA* gene), inhibited phosphorylation of the downstream target AKT, reduced cellular proliferation, and induced apoptosis in *PIK3CA*-mutated breast cancer cell lines. *In vivo*, inavolisib reduced tumor growth in *PIK3CA*-mutated, estrogen receptor-positive, breast cancer xenograft models. The combination of inavolisib with palbociclib and fulvestrant increased inhibition of tumor growth compared to each treatment alone or the doublet combinations.

Phosphatidylinositol 3-kinase (PI3K), protein kinase B (AKT), and mammalian target of rapamycin (mTOR) are major nodes in the PI3K/AKT/mTOR intracellular signaling pathway and are critical for cell-cycle modulation, cell growth, metabolism, motility, and survival. The PI3K/AKT/mTOR pathway is generally activated following ligand-receptor tyrosine kinase interactions. Under physiologic conditions, the main role of PI3K is to facilitate the metabolism of inositol phospholipids for intracellular signal transduction.

Dysregulation of the PI3K/AKT/mTOR signaling pathway has been described in multiple solid tumor malignancies: glioblastoma, colorectal, gastric, lung, endometrial, ovarian, prostate, and breast cancers. Up to 70% of breast cancers can have some form of molecular aberration of the PI3K/AKT/mTOR pathway.

There are three classes of PI3K, with Class I being the most responsive to external stimuli. Class I PI3Ks are composed of two subunits: a p110 catalytic subunit and a regulatory adapter subunit, p85. There are four isoforms of the p110 catalytic subunit of PI3K: α, β, γ, and δ. These four isoforms are the respective products of the genes *PIK3CA*, *PIK3CB*, *PIK3CG*, and *PIK3CD*. All cells express *PIK3CA* and *PIK3CB*, while *PIK3CD* is primarily expressed in leukocytes and *PIK3CG* is expressed in multiple tissues, including pancreas, skeletal muscle, liver, and heart.

Definitions:

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

Resources:

Itovebi (inavolisib) product information, revised by Genentech, Inc. 01-2025. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed July 24, 2025.

Ma CX, Sparano JA. Treatment of hormone receptor-positive, HER2-negative advanced breast cancer. In: UpToDate, Burstein HJ, Vora SR (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Literature current through September 2025. Topic last updated January 18, 2025. Accessed October 08, 2025.

National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Breast Cancer Version 4.2025 – Updated April 17, 2025. Available at https://www.nccn.org. Accessed October 08, 2025.

ORIGINAL EFFECTIVE DATE: 11/21/2024 | ARCHIVE DATE: | LAST REVIEW DATE: 11/20/2025 | LAST CRITERIA REVISION DATE: 11/20/2025

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ClinicalTrials.gov Bethesda (MD): National Library of Medicine (US). Identifier NCT04191499: A Phase III, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Efficacy and Safety of Inavolisib Plus Palbociclib and Fulvestrant Versus Placebo Plus Palbociclib and Fulvestrant in Patients With PIK3CA-Mutant, Hormone Receptor-Positive, Her2-Negative, Locally Advanced or Metastatic Breast Cancer. Available from: http://clinicaltrials.gov. Last update posted October 09, 2024. Last verified September 2024. Accessed November 07, 2024. Re-evaluated October 08, 2025.

Off Label Use of Cancer Medications: A.R.S. §§ 20-826(R) & (S). Subscription contracts; definitions.

Off Label Use of Cancer Medications: A.R.S. §§ 20-1057(V) & (W). Evidence of coverage by health care service organizations; renewability; definitions.