Pharmacy Policy Bulletin: J-0825 PI3K Inhibitors – Commercial and Healthcare Reform	
Number: J-0825	**Category:** Prior Authorization
Line(s) of Business: ☒ Commercial ☒ Healthcare Reform ☐ Medicare	**Benefit(s):** **Commercial:** **Prior Authorization (1.):** **1.** Miscellaneous Specialty Drugs Oral = Yes w/ Prior Authorization **Healthcare Reform:** Not Applicable
Region(s): ☒ All ☐ Delaware ☐ New York ☐ Pennsylvania ☐ West Virginia	**Additional Restriction(s):** None
Version: J-0825-012	**Original Date:** 11/07/2018
Effective Date: 12/20/2024	**Review Date:** 12/04/2024

Drugs Product(s):	• Copiktra (duvelisib) • Itovebi (inavolisib) • Joenja (leniolisib) • Piqray (alpelisib) • Vijoice (alpelisib)
FDA-Approved Indication(s):	• Copiktra o Treatment of adult patients with relapsed or refractory chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) after at least two prior therapies. • Itovebi o In combination with palbociclib and fulvestrant 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. • Joenja o Treatment of activated phosphoinositide 3-kinase delta (PI3Kδ) syndrome (APDS) in adult and pediatric patients 12 years of age and older. • Piqray o Indicated in combination with fulvestrant for the treatment of adults with HR-positive, HER2-negative, *PIK3CA*-mutated, advanced or metastatic breast cancer as detected by an FDA-approved test following progression on or after an endocrine-based regimen. • Vijoice o 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.

Background:	• Copiktra

- Copiktra inhibits the phosphoinositide 3-kinase (PI3K) enzyme, and predominantly inhibits PI3K-δ and PI3K-γ isoforms expressed in normal and malignant B-cells, leading to growth inhibition and reduced cell viability.
- CLL and SLL are indolent cancers involving immature lymphocytes. CLL and SLL are both types of non-Hodgkin lymphoma (NHL), and the disease states are similar in definition except that CLL affects the blood and bone marrow; SLL affects the lymph nodes.
- Copiktra has Risk Evaluation and Mitigation Strategies (REMS) to mitigate the risks of fatal and/or serious toxicities including infections, diarrhea or colitis, cutaneous reactions, and pneumonitis associated with the use of Copiktra by informing healthcare providers of these risks.

- Itovebi
  - Itovebi inhibits PI3K with 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, Itovebi reduced tumor growth.
  - Endocrine-based therapy includes drugs such as aromatase inhibitors (anastrozole, exemestane, letrozole), fulvestrant, and tamoxifen, among others.
- Joenja
  - Joenja is a kinase inhibitor that works by inhibiting PI3Kδ, leading to inhibition of proliferation and activation of B and T cells.
  - APDS is a rare, autosomal dominant, primary immunodeficiency. Individuals with APDS often have low levels of white blood cells, particularly B and T cells. Symptoms may include recurrent infections (particularly in the lungs, sinuses, and ears), bronchiectasis, chronic viral infections (commonly Epstein Barr or cytomegalovirus), lymphadenopathy, and nodular lymphoid hyperplasia. APDS increases the risk of developing B-cell lymphoma. APDS is caused by mutations in the *PIK3CD* or *PIK3R1* genes which lead to overactive PI3Kδ signaling, subsequently causing lack of functioning B and T cells and abnormal proliferation of white blood cells. APDS affects approximately 1 to 2 people per million. APDS was previously known as PASLI disease (p110d-activating mutation causing senescent T cells, lymphadenopathy, and immunodeficiency).
- Piqray
  - Piqray inhibits phosphatidylinositol-3-kinase (PI3K), and predominantly inhibits PI3Kα. In breast cancer cell lines, this resulted in inhibition of downstream targets, leading to reduced tumor growth. In breast cancer cells, PI3K inhibition was observed with an increase in estrogen receptor (ER) transcription.
  - Recommendations for HR-positive, HER2-negative metastatic breast cancer include adjuvant endocrine therapy or chemotherapy (one preferred regimen includes doxorubicin, cyclophosphamide, paclitaxel, and trastuzumab).
  - Endocrine therapy includes tamoxifen for premenopausal patients; or tamoxifen or an aromatase inhibitor (e.g. anastrozole, letrozole, or exemestane) in postmenopausal patients.
- Vijoice
  - PIK3CA-Related Overgrowth Spectrum (PROS) is a group of rare conditions characterized by focal or segmental overgrowth of parts of the body due to mutations in the *PIK3CA* gene. It is estimated that PROS affects 14 people per 1 million. PROS can present with a range of signs

	and symptoms, including megalencephaly, hypotonia, seizures, intellectual disability, and blood vessel anomalies. o Prior to the FDA approval of Vijoice, treatment with alpelisib was available through an expanded access program for compassionate use. Step therapy through Piqray 250 mg is recommended since it is a cost-effective treatment for PROS. • For information regarding FDA-approved diagnostic tests, please visit: https://www.fda.gov/medical-devices/in-vitro-diagnostics/list-cleared-or-approved-companion-diagnostic-devices-in-vitro-and-imaging-tools. • Prescribing Considerations: o Prophylaxis for *Pneumocystis jirovecii* pneumonia (PJP) should be provided with Copiktra therapy. In addition, consider prophylaxis for cytomegalovirus (CMV) infection, including reactivation, with Copiktra therapy. o Copiktra has black box warnings for fatal and/or serious infections; diarrhea or colitis; cutaneous reactions; and pneumonitis. o PI3K inhibitors should be prescribed under the supervision of a hematologist or oncologist, or immunologist for Joenja. o Safety and effectiveness have not been established in pediatric patients for Copiktra, Itovebi, and Piqray. o Vijoice oral granules are for patients who are only prescribed a 50 mg daily dose. Do not use multiple 50 mg packets or partial packets of Vijoice oral granules for patients prescribed a 125 mg or a 250 mg dose. Do not combine Vijoice tablets and Vijoice oral granules to achieve the prescribed dose.

Approval Criteria

I. Initial Authorization

A. Copiktra

When a benefit, coverage of Copiktra may be approved when all of the following criteria are met **(1. though 4.)**:

1. The member is 18 years of age or older.
2. The member has a diagnosis of one (1) of the following (**a. or b.)**:
  a. Chronic lymphocytic leukemia (CLL) (ICD-10: C91.1)
  b. Small lymphocytic lymphoma (SLL) (ICD-10: C83)
3. Disease is relapsed or refractory.
4. The member is no longer responding to, or is intolerant to, at least two (2) prior therapies (e.g., ibrutinib, alemtuzumab ± rituximab, HDMP + rituximab, obinutuzumab, venetoclax + rituximab, etc.).

B. Itovebi

When a benefit, coverage of Itovebi may be approved when all of the following criteria are met **(1. through 6.)**:

1. The member is 18 years of age or older.
2. The member has a diagnosis of endocrine-resistant, locally advanced or metastatic breast cancer (ICD-10: C50).
3. Disease is HR-positive, HER2-negative.
4. Disease is *PIK3CA*-mutated, as detected by an FDA-approved test.
5. The member is using Itovebi in combination with all of the following **(a. and b.)**:
  a. palbociclib (Ibrance)
  b. fulvestrant
6. The member has experienced recurrence on or after completing adjuvant endocrine therapy.

C. Joenja

When a benefit, coverage of Joenja may be approved when all of the following criteria are met **(1. through 5.):**

1. The member is 12 years of age or older.
2. The patient weighs ≥ 45 kg.
3. The member has a diagnosis of activated phosphoinositide 3-kinase delta (PI3Kδ) syndrome (APDS) (ICD-10: D81.82).
4. The member has a confirmed variant in one (1) of the following genes **(a. or b.):**
   - **a.** *PIK3CD*
   - **b.** *PIK3R1*
5. The member has clinical findings of APDS (e.g., lymphoproliferation, lymphadenopathy, splenomegaly, recurrent infections).

D. Piqray

When a benefit, coverage of Piqray may be approved when all of the following criteria are met **(1. through 6.)**:

1. The member is 18 years of age or older.
2. The member has a diagnosis of advanced or metastatic breast cancer. (ICD-10: C50)
3. The member is using Piqray in combination with fulvestrant.
4. The member has experienced disease progression on or after an endocrine-based regimen.
5. The member has tumor status of HR-positive, HER2-negative.
6. The member is *PI3KCA* mutation-positive as detected by an FDA-approved test.

E. Vijoice

When a benefit, coverage of Vijoice may be approved when all of the following criteria are met **(1., 2., and 3.):**

1. The member is 2 years of age or older.
2. The member has a diagnosis of PIK3CA related overgrowth spectrum (PROS) with severe manifestations (No ICD-10 Code).
3. If the request is for Vijoice 250 mg, the member has experienced therapeutic failure or intolerance to Piqray 250 mg.

II. Reauthorization

When a benefit, reauthorization of a PI3K inhibitor may be approved when the following criterion is met **(A.)**:

A. The prescriber attests that the member is tolerating therapy and has experienced a therapeutic response defined as either one (1) of the following **(1. or 2.)**:
   1. Disease improvement
   2. Delayed disease progression

III. An exception to some or all of the criteria above may be granted for select members and/or circumstances based on state and/or federal regulations.

IV. Coverage of oncology medications listed in this policy may be approved on a case-by-case basis per indications supported in the most current NCCN guidelines.

Limitations of Coverage

I. Vijoice oral granules are for members who are only prescribed a 50 mg daily dose.

II. Coverage of drug(s) addressed in this policy for disease states outside of the FDA-approved indications should be denied based on the lack of clinical data to support effectiveness and safety in other conditions unless otherwise noted in the approval criteria.

III. For Commercial or HCR members with a closed formulary, a non-formulary product will only be approved if the member meets the criteria for a formulary exception in addition to the criteria outlined within this policy.

Authorization Duration

- Commercial and HCR Plans: If approved, up to a 12 month authorization may be granted.

Automatic Approval Criteria

None

References:

1. Copiktra [package insert]. Needham, Massachusetts: Verastem, Inc.; December 2021.
2. Itovebi [package insert]. San Francisco, CA: Genentech USA, Inc.; October 2024.
3. Joenja [package insert]. Saint Qunetine Fallavier, France: Pharming Technologies B.V.; March 2023.
4. Piqray [package insert]. East Hanover, New Jersey: Novartis Pharmaceuticals Corporation; January 2024.
5. Vijoice [package insert]. East Hanover, New Jersey: Novartis Pharmaceuticals Corporation; April 2024.
6. TG Therapeutics. TG Therapeutics Announces Voluntary Withdrawal of the BLA/sNDA for U2 to Treat Patients with CLL and SLL. Available at: https://ir.tgtherapeutics.com/news-releases/news-release-details/tg-therapeutics-announces-voluntary-withdrawal-blasnda-u2-treat. Accessed May 10, 2022.
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8. NCCN Guidelines. B-Cell Lymphomas v.5.2021 National Comprehensive Cancer Network. Available at: https://www.nccn.org/professionals/physician_gls/pdf/b-cell.pdf. Accessed January 10, 2022.
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10. National Comprehensive Cancer Network. NCCN Guidelines Version 5.2024 Breast Cancer. Available at: https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf. Accessed October 21, 2024.
11. National Library of Medicine. Activated PI3K-delta syndrome. Available at: https://medlineplus.gov/genetics/condition/activated-pi3k-delta-syndrome/. Accessed March 29, 2023.