LifeWise
Health Plan of Washington

PHARMACY / MEDICAL POLICY – 5.01.592

Phosphoinositide 3-kinase (PI3K) Inhibitors

Effective Date:	Mar. 1, 2025	RELATED MEDICAL POLICIES:
Last Revised:	Feb. 11, 2025	None
Replaces:	N/A	

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Introduction

Phosphoinositide 3-kinase inhibitors (PI3K inhibitors) block one or more enzymes, which are part of an important signaling pathway inside cells, essentially working to turn the cell growth to the "off" position. This policy describes when this specific form of chemotherapy may be considered medically necessary.

Note: The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.

Policy Coverage Criteria

Drug	Medical Necessity
Aliqopa (copanlisib) (IV infusion)	**Aliqopa (copanlisib) may be considered medically necessary for individuals with relapsed follicular lymphoma (FL) when the following criteria are met:** • The individual is aged 18 years or older **AND**

Drug	Medical Necessity
	• Has had at least two prior systemic therapies
Copiktra (duvelisib) (oral)	**Copiktra (duvelisib) may be considered medically necessary for individuals with relapsed or refractory chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) when the following criteria are met:** • The individual is aged 18 years or older **AND** • Has had at least two prior systemic therapies
Itovebi (inavolisib) (oral)	**Itovebi (inavolisib) may be considered medically necessary 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 when the following criteria are met:** • The individual is aged 18 years or older **AND** • Has been diagnosed with HR-positive, HER2-negative locally advanced or metastatic breast cancer with *PIK3CA* mutation **AND** • Has disease progression following at least one line of endocrine therapy in the metastatic setting OR recurrence on or within 12 months of completing adjuvant therapy **AND** • Will be given in combination with Ibrance (palbociclib) and fulvestrant as first-line therapy **AND** • Must have an ECOG performance status of 0 or 1 **AND** • Has not experienced disease progression on or following other phosphatidylinositol 3-kinase (PI3K) inhibitors **AND** • Itovebi (inavolisib) is prescribed by or in consultation with an oncologist **AND** • Dose is limited to 9 mg once daily
Joenja (leniolisib) (oral)	**Joenja (leniolisib) may be considered medically necessary for the treatment of individuals with activated phosphoinositide**

Drug	Medical Necessity
	3-kinase delta syndrome (APDS) when the following criteria are met: • The individual is aged 12 years or older **AND** • Diagnosed with activated phosphoinositide 3-kinase delta syndrome (APDS) **AND** • Has documented APDS associated PI3K delta gene mutation with documented variant in either PIK3CD or PIK3R1 **AND** • Joenja is prescribed by or in consultation with an oncologist, medical geneticist, or hematologist **AND** • Dose is limited to 140 mg per day (taken as 70 mg twice daily)
Piqray (alpelisib) (oral)	**Piqray (alpelisib) may be considered medically necessary for the treatment of individuals with breast cancer when the following are met:** • The individual is aged 18 years or older **AND** • Diagnosed with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, PIK3CA-mutated, advanced or metastatic breast cancer as detected by an FDA-approved test **AND** • Has experienced progression on or after an endocrine-based regimen **AND** • Piqray (alpelisib) will be used in combination with fulvestrant **Piqray (alpelisib) may be considered medically necessary for the treatment of individuals with *PIK3CA*-Related Overgrowth Spectrum (PROS) when the following criteria are met:** • The individual is aged 18 years or older **AND** • Diagnosed with *PIK3CA*-related overgrowth spectrum (PROS) **AND**

Drug	Medical Necessity
	• Has at least one target lesion identified on imaging **AND** • Has documented *PIK3CA* gene mutation **AND** • Piqray is prescribed by or in consultation with an oncologist, geneticist, or hematologist **AND** • Dose prescribed is 250 mg orally once daily
Truqap (capivasertib) (oral)	**Truqap (capivasertib) may be considered medically necessary for the treatment of adult individuals with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative breast cancer when all the following criteria are met:** • The individual is aged 18 years or older **AND** • Has been diagnosed with HR-positive, HER2-negative* locally advanced or metastatic breast cancer **AND** • Has one or more *PIK3CA/AKT1/PTEN*-alterations **AND** • Has experienced disease progression following at least one line of endocrine therapy in the metastatic setting or recurrence on or within 12 months of completing adjuvant therapy **AND** • Truqap (capivasertib) will be used in combination with fulvestrant **AND** • Has not experienced disease progression on or following other PI3K/AKT/PTEN inhibitors such as Piqray (alpelisib) **AND** • Documentation of Piqray (alpelisib) intolerance or specific solitary AKT1 or PTEN mutations not sensitive to Piqray (alpelisib) **AND** • Dose is limited to 400 mg twice daily for 4 days followed by 3 days off

Drug	Medical Necessity
	***Note:** HER2-negative status is defined as 0 or 1+ intensity on immunohistochemical testing or 2+ intensity on immunohistochemical testing and no amplification on in situ hybridization.
Vijoice (alpelisib) (oral)	**Vijoice (alpelisib) may be considered medically necessary for the treatment of individuals with *PIK3CA*-Related Overgrowth Spectrum (PROS) when the following criteria are met:** • The individual is aged 2 years or older **AND** • Diagnosed with *PIK3CA*-related overgrowth spectrum (PROS) **AND** • Has at least one target lesion identified on imaging **AND** • Has documented *PIK3CA* gene mutation **AND** • Vijoice (alpelisib) is prescribed by or in consultation with an oncologist, geneticist, or hematologist **AND** • The dose prescribed is: ○ Individuals aged 2-5 years: 50 mg once daily ○ Individuals aged 6-17 years: ≤ 125 mg once daily ○ Individuals aged 18 years and older: 250 mg once daily
Zydelig (idelalisib) (oral)	**Zydelig (idelalisib) may be considered medically necessary for treatment of individuals with the following:** • Relapsed chronic lymphocytic leukemia (CLL), in combination with rituximab, in individuals for whom rituximab alone would be considered appropriate therapy due to other co-morbidities **AND** • Dose is limited to 300 mg per day (taken as 150 mg twice daily) **Note:** Zydelig is not indicated and is not recommended for first-line treatment of any individual.

Drug	Investigational
All drugs in this policy	**The medications listed in this policy are subject to the product's US Food and Drug Administration (FDA) dosage and administration prescribing information.**

Drug	Investigational
	All other uses of drugs in this policy for conditions not outlined in the policy are considered investigational.

Length of Approval	
Approval	**Criteria**
Initial authorization	**Non-formulary exception reviews for all drugs listed in the policy may be approved up to 12 months.** **All other reviews for Copiktra (duvelisib), Itovebi (inavolisib), Joenja (leniolisib), Piqray (alpelisib) for breast cancer, Truqap (capivasertib), and Zydelig (idelalisib) may be approved up to 3 months.** **All other reviews for Aliqopa (copanlisib), Piqray (alpelisib) for PROS, and Vijoice (alpelisib) may be approved up to 6 months.**
Re-authorization criteria	**Non-formulary exception reviews and all other reviews for Aliqopa (copanlisib), Copiktra (duvelisib), Itovebi (inavolisib), Joenja (leniolisib), Piqray (alpelisib) for breast cancer, Truqap (capivasertib), and Zydelig (idelalisib) may be approved up to 12 months as long as the drug-specific coverage criteria are met, and chart notes demonstrate that the individual continues to show a positive clinical response to therapy.** **Non-formulary exception reviews and all other reviews for Piqray (alpelisib) for PROS and Vijoice (alpelisib) may be approved up to 12 months as long as the drug-specific coverage criteria are met and chart notes demonstrate that the individual continues to show a positive clinical response to therapy as documented by:** • A reduction in the sum of measurable target lesion volume from baseline.

Documentation Requirements

The individual's medical records submitted for review for all conditions should document that medical necessity criteria are met. The record should include the following:

- Office visit notes that contain the diagnosis, relevant history, physical evaluation, and medication history

Coding

Code	Description
HCPC	
J9057	Injection, copanlisib (Aliqopa), 1 mg

Note: CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). HCPCS codes, descriptions and materials are copyrighted by Centers for Medicare Services (CMS).

Related Information

Consideration of Age

Age limits specified in this policy are determined according to US Food and Drug Administration (FDA) -approved indications, where applicable.

Benefit Application

The drugs in this policy that are administered orally (Copiktra, Itovebi, Joenja, Piqray, Truqap, and Zydelig) are managed through the pharmacy benefit. Drugs administered via IV infusion (Aliqopa) are managed through the medical benefit.

Evidence Review

Description

Chronic Lymphocytic Leukemia (CLL)/Small Lymphocytic Lymphoma (SLL) and Follicular Lymphoma (FL)

CLL and SLL are different manifestations of the same lymphocytic malignancy and are subtypes of Non-Hodgkin Lymphoma (NHL). The primary difference between these conditions is that a majority of leukemic B-cells circulate in the blood in CLL, whereas they are found in lymphoid tissue in SLL. FL is another B-cell lymphoproliferative disorder and subtype of NHL.

Disease Burden

Approximately 7% of newly diagnosed NHL cases are CLL/SLL. In the US in 2021, the incidence of CLL is estimated to be 21,250 and approximately 4,320 people will die of the disease. CLL is the most prevalent adult leukemia in Western countries. CLL is mainly diagnosed in older adults and the average age of people when they are diagnosed is around 70 years of age. Between 1998 and 2011, FL comprised 17% of all NHL diagnosed in the US. It is the second most common form of NHL and the most common form of indolent NHL.

Pathophysiology

CLL/SLL is characterized by a progressive accumulation of mature lymphocytes in the blood, bone marrow, and lymphoid tissues. These conditions typically proceed through a couple of different phases consisting of an early indolent phase where cells are small in size, proliferation is low, and there is prolonged cell survival and a transformation phase characterized by an increase in large immature cells and extramedullary proliferation. Unfavorable prognostic indicators include unmutated immunoglobulin heavy-chain variable (IGHV) status, TP53 mutation, the presence of cytogenic abnormalities (del[13q] or del[11q]), higher levels of flow-cytometry based prognostic markers (CD38, CD49d, and ZAP-70), and serum markers (e.g., thymidine kinase and beta-2 microglobulin).

Individuals with low-grade indolent disease without signs or symptoms for initiating treatment usually receive supportive care and watchful waiting as therapy, given active treatment has not been shown to prolong survival. Signs and symptoms for initiating active treatment include severe fatigue, weight loss, night sweats, fever (without infection), progressive bulky disease (enlarged spleen and/or lymph nodes), progressive anemia or thrombocytopenia, autoimmune anemia, thrombocytopenia unresponsive to corticosteroids, and threatened end-organ function.

FL is caused by a translocation between chromosome 14 and 18 that results in overexpression of the bcl-2 gene. This gene produces a protein that prevents apoptosis. Consequently, cells that overexpress the bcl-2 protein are basically immortal. Other translocations may also be involved. FL tumors are composed of centrocytes and centroblasts, and the volume of these cell types determines the World Health Organization morphological grade.

Individuals with asymptomatic disease usually receive supportive care and watchful waiting as therapy. When individuals are symptomatic, active treatment is initiated, with consideration to age, stage, and International Prognostic Index score.

Treatment Alternatives

NCCN Recommended Preferred First-line Regimens Include:

CLL/SLL without del(17p)/TP53 mutation:

- Acalabrutinib ± obinutuzumab
- Ibrutinib
- Venetoclax + obinutuzumab
- Zanubrutinib

CLL/SLL with del(17p)/TP53 mutation:

- Acalabrutinib ± obinutuzumab
- Ibrutinib
- Venetoclax + obinutuzumab
- Zanubrutinib

R/R FL (grade 1-2):

- Bendamustine + obinutuzumab or rituximab
- CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) + obinutuzumab or rituximab
- CVP (cyclophosphamide, vincristine, prednisone) + obinutuzumab or rituximab

- Lenalidomide + rituximab

PI3K Inhibitors

Alpelisib, copanlisib, duvelisib, and idelalisib are oral selective small molecule inhibitors of one or more of the phosphoinositide 3-kinase enzymes, which are part of the PI3K/AKT/mTOR pathway, an important signaling pathway for many cellular functions such as growth control, metabolism, and translation initiation. Within this pathway there are many components, inhibition of which may result in tumor suppression.

There are a number of different classes and isoforms of PI3Ks. Class 1 PI3Ks have a catalytic subunit known as p110, with four types (isoforms) – p110 alpha, p110 beta, p110 gamma and p110 delta. The inhibitors being studied inhibit one or more isoforms of the class I PI3Ks. They are being actively investigated for treatment of various cancers. PI3K signaling is believed to play a role in the proliferation of malignant B- and T-cells and in the formation and maintenance of a supportive tumor microenvironment. The currently approved agents have the following target profiles:

- Alpelisib: targets alpha
- Copanlisib: targets alpha and delta
- Duvalisib: targets gamma and delta
- Idelalisib: targets delta

Summary of Evidence

Aliqopa (copanlisib)

The efficacy of Aliqopa (copanlisib) was evaluated in a single-arm, multicenter, phase 2 clinical trial, CHRONOS-1 in a total of 142 subjects, which included 104 subjects with follicular B-cell non-Hodgkin lymphoma who had relapsed disease following at least two prior treatments. Individuals must have received rituximab and an alkylating agent. The most common prior systemic therapies were chemotherapy in combination with anti-CD20 immunotherapy (89%), chemotherapy alone (41%), and anti-CD20 immunotherapy alone (37%). In CHRONOS-1, 34% of individuals received two prior lines of therapy and 36% received three prior lines of therapy.

One hundred forty-two individuals received 60 mg Aliqopa; 130 individuals received fixed dose 60 mg Aliqopa, and 12 individuals received 0.8 mg/kg equivalent Aliqopa administered as a 1-hour intravenous infusion on Days 1, 8, and 15 of a 28-day treatment cycle on an intermittent schedule (three weeks on and one week off). Treatment continued until disease progression or unacceptable toxicity. Tumor response was assessed according to the International Working Group response criteria for malignant lymphoma. Efficacy based on overall response rate (ORR) was assessed by an Independent Review Committee. Overall Response Rate (ORR) was 59% (61 individuals, 95% CI (49, 68). Of these, 15 individuals achieved a Complete Response. Median Duration of Response was 12.2 months (range 0+, 22.6 months).

Copiktra (duvelisib)

One moderate quality phase 3, randomized open-label, active-controlled clinical trial (DUO) demonstrates statistically significant incremental improvements in progression-free survival (PFS) of 3.4 months, objective response rate (ORR) of 28.5%, and lymph node response rate (LNRR) of 69% with duvelisib vs ofatumumab in individuals with R/R CLL or SLL. One fair quality phase 2, open-label, single arm study (DYNAMO) of duvelisib monotherapy in adults with double-refractory indolent non-Hodgkin lymphoma (iNHL) showed an overall ORR of 46%, a median DoR of 9.9 months, a lymph node response rate (LNRR) of 83%, a median PFS of 8.4 months, and a median OS of 18.4 months. Response appeared better in individuals with SLL than in those with FL. Other potentially supportive studies of duvelisib monotherapy in individuals with CLL or iNHL and off-label studies in individuals with R/R peripheral T-cell lymphoma (PTCL) and for use in combination with chemoimmunotherapy are ongoing.

Itovebi (inavolisib)

The approval was based on results from the Phase 3 INAVO120 trial, a randomized, double-blind, placebo-controlled study that evaluated the efficacy and safety of Itovebi in combination with Ibrance and fulvestrant in adults with *PIK3CA*-mutated, HR-positive, HER2-negative, locally advanced or mBC. The primary endpoint of progression-free survival (PFS) was met, with the Itovebi triplet regimen demonstrating a 57% reduction in the risk of progression or death compared with Ibrance and fulvestrant alone (median PFS: 15.0 months vs. 7.3 months; hazard ratio [HR]: 0.43, 95% CI: 0.32, 0.59). An interim analysis of overall survival based on 63% of the planned data was not statistically significant but supported the benefit-risk profile. The Itovebi triplet regimen showed a 36% reduction in the risk of death (HR: 0.64).

Joenja (leniolisib)

Joenja (leniolisib) is a kinase inhibitor indicated for the treatment of activated phosphoinositide 3-kinase delta syndrome in adults and pediatric individuals 12 years of age and older. The safety and efficacy of Joenja was evaluated in the placebo-controlled study part of study 2201, which involved a12-week blinded, randomized, placebo-controlled study conducted in adults and pediatric individuals 12 years of age and older. The study specifically focused on an individual with confirmed APDS-associated genetic PI3Kδ mutation with a documented variant in either PIK3CD or PIK3R1.

In this trial, a total of thirty-one individuals were randomized 2:1 to receive either Joenja 70 mg (n = 21) or placebo (n =10) twice daily for 12 weeks. The primary efficacy endpoints were the improvement in the lymphoproliferation, measured by the change from baseline in lymphadenopathy using the log10 – transformed sum of product diameters and the normalization of immunophenotypes as measured by the percentage of naïve B cells out of total B cells.

At the end of week 12, the least square (LS) mean change in the lymphadenopathy from baseline in treatment group was -0.27 compared to -0.02 in the placebo group, with p-value of 0.0006. At week 12, the LS mean change in percentage of naïve B cells out of total B cell was 37.39% in the treatment group compared to 0.09% in the placebo group, with p- value of 0.0002.

The common adverse reactions observed in the trial included headache, sinusitis, and atopic dermatitis.

Piqray (alpelisib)

Piqray (alpelisib) inhibits phosphatidylinositol-3-kinase (PI3K), predominantly PI3Kα. Alpelisib plus fulvestrant was studied in a single Phase 3 trial, the multicenter, randomized, double-blind, placebo-controlled SOLAR-1 trial. The trial included 572 individuals with hormone receptor positive, HER2-advanced BC with relapse or progression on or after prior endocrine therapy. A total of 85.6% of individuals in the trial were considered endocrine resistant. Individuals were randomized to alpelisib plus fulvestrant, or placebo plus fulvestrant until disease progression or unacceptable adverse events (AEs). Individuals were divided into cohorts based on *PIK3CA*-mutation status, which was not an inclusion criterion. Of note, alpelisib is approved in mutation-positive individuals only. Overall, 341 individuals were mutation positive (59.6%). At the interim

data cutoff (June 12, 2018), the primary endpoint of PFS in individuals with the *PIK3CA* mutation significantly favored alpelisib plus fulvestrant over fulvestrant alone per investigator assessment (11.0 mo vs 5.7 mo, HR 0.64, 95% CI 0.5-0.85, p<0.001) as well as blinded independent central review (BICR) (11.1 mo vs 2.7 mo, HR 0.48, 95% CI 0.32-0.71). At 12 months, progression-free survival (PFS) was 46.2% with alpelisib plus fulvestrant vs 32.9% with fulvestrant alone. PFS did not differ significantly between groups in individuals without the *PIK3CA* mutation (7.4 mo alpelisib plus fulvestrant vs 5.6 mo fulvestrant, HR 0.85, 95% CI 0.58-1.25).

Truqap (capivasertib)

The approval of Truqap is based on results from the Phase 3 CAPItello-291 trial, which included 708 adult participants with HR-positive, HER2-low or -negative breast cancer, of whom 289 had tumors with *PIK3CA/AKT1/PTEN* alterations. In the *PIK3CA/AKT1/PTEN*–altered population, the median progression-free survival (PFS) was 7.3 months in the Truqap–Faslodex group, compared with 3.1 months in the placebo–Faslodex group (hazard ratio [HR], 0.50; 95% confidence interval [CI], 0.38–0.65; P<0.001), reducing the risk of disease progression or death by 50%. In the overall population, the median PFS was 7.2 months in the Truqap–Faslodex group, compared with 3.6 months in the placebo–Faslodex group (HR, 0.60; 95% CI, 0.51–0.71; P<0.001). According to the FDA, an exploratory analysis of PFS in participants whose tumors did not have a *PIK3CA/AKT1/PTEN* alteration showed an HR of 0.79 (95% CI, 0.61–1.02), indicating that the treatment benefit in the overall population was primarily attributable to the results seen in the subgroup of participants whose tumors had a *PIK3CA/AKT1/PTEN* alteration.

Vijoice (alpelisib)

Vijoice is approved for use in individuals with severe manifestations of *PIK3CA*-related overgrowth spectrum (PROS) who require systemic therapy. PROS refers to a heterogenous group of disorders associated with vascular malformations and segmental overgrowth. This disorder is characterized by early-onset, progressive symptoms accompanied by high morbidity and mortality. Vijoice works by inhibiting phosphatidylinositol-3-kinase (PI3K), predominantly PI3Kα. Use in PROS was approved based on the EPIK-P1 real-world study that included individuals 2 years and older who were assessed by the treating physician as having severe or life-threatening symptoms of PROS. Treatment efficacy was measured as a reduction in lesion volume of at least 20%, which occurred in 27% of individuals at week 24. Of the individuals who responded to treatment, 60% had a response lasting for 12 months or more. Piqray (alpelisib) is

available in similar strengths (50 mg, 150 mg, and 200 mg tablets; Vijoice available as 50 mg, 125 mg, and 200 mg tablets) and could be used for adult individuals with PROS.

Zydelig (idelalisib)

Zydelig (idelalisib) is the first selective and reversible inhibitor of PI3K to receive FDA approval. It was approved for relapsed chronic lymphocytic leukemia on the basis of one multicenter, randomized, double-blind, Phase 3 study. The individuals were randomly assigned to receive rituximab with either idelalisib or placebo. The individuals in the placebo group who had disease progression were able to crossover to receive idelalisib. Individuals in the idelalisib group who had disease progression could receive an increased dose.

The addition of idelalisib to rituximab therapy resulted in an improved overall response rate (81% with idelalisib vs 13% with placebo). There were no complete responses. A higher proportion of individuals with a reduction of lymphadenopathy of 50% or greater was observed with idelalisib (93% vs 4%). Improved progression-free survival (93% vs 46%) was also seen at 24 weeks with idelalisib; PFS median was not reached with idelalisib vs 5.5 months with placebo. (HR 0.15; 95% CI 0.08-0.28). Overall survival rate at 12 months was (92% vs 80%; HR 0.28; 95% CI 0.09-0.86).

Idelalisib for treatment of relapsed FL and SLL is shown in the DELTA study, which is an open-label, single arm, Phase 2 study. Phase 3 trials are ongoing and need to be assessed given the estimated primary completion date (December 2015) and estimated study completion date (April 2016) to establish whether there is an improvement in duration of response, and disease-related symptoms. In comparison, a phase 1b-2 multicenter study assessing ibrutinib as treatment for relapsed CLL in a similar population showed that at 26 months, the estimated progression-free survival rate was 75% and the rate of overall survival was 83%.

More than 90% of the individuals were reported to have at least one adverse event. The common adverse events included pyrexia, fatigue, nausea, chills, and diarrhea. Serious adverse events included pneumonia, pyrexia, and febrile neutropenia. Adverse events leading to study-drug discontinuation were reported in 8%. Gastrointestinal and skin disorders lead to 6 discontinuations in the idelalisib group.

In March 2016, the FDA released a safety alert stating that 6 clinical trials studying first-line CLL and early-line iNHL have been terminated due to concerns of decreased overall survival and increased risk of serious adverse events (mostly infections including PCP pneumonia and CMV that could lead to sepsis and death). Health care authorities (FDA, Health Canada) reiterated that idelalisib is only indicated for relapsed CLL, relapsed SLL, and relapsed FL. NCCN CLL/SLL 2.2022

guidelines and NCCN B-Cell Lymphomas 5.2021 guidelines list idelalisib as a treatment option for these indications. It now carries a black box warning for "fatal and serious toxicities: hepatic, severe diarrhea, colitis, pneumonitis, infections, and intestinal perforation."

2019 Update

Reviewed prescribing information for all drugs in policy. No new information was identified that would require changes to this policy.

2020 Update

Reviewed prescribing information for all drugs in policy. No new information was identified that would require changes to this policy.

2021 Update

Reviewed prescribing information for all drugs in policy. No new information was identified that would require changes to this policy for Aliqopa (copanlisib), Copiktra (duvelisib), and Zydelig (idelalisib). Added coverage criteria for Ukoniq (umbralisib) for the treatment of marginal zone lymphoma (MZL) and follicular lymphoma (FL).

2022 Update

Reviewed prescribing information for all drugs in policy and the NCCN Guidelines (v5.2021) for B-Cell Lymphoma and NCCN Guidelines (v2.2022) for Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma. Removed from Copiktra (duvelisib) coverage for the treatment of relapsed or refractory (R/R) follicular lymphoma (FL) as this indication was voluntarily withdrawn by the manufacturer and no longer listed in the prescribing information. Copiktra received accelerated approval for the treatment of R/R FL with the requirement that an additional confirmatory trial be conducted prior to full approval. The manufacturer made the determination to not pursue the additional confirmatory trial and opted to voluntarily withdraw Copiktra coverage for the treatment of R/R FL. Removed from Aliqopa (copanlisib) coverage for the treatment of chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL). Aliqopa is not FDA approved for CLL or SLL and the NCCN Guidelines do not list or recommend

use of Aliqopa for CLL or SLL. Added coverage to Vijoice (alpelisib) and Piqray (alpelisib) for treatment of PROS.

2023 Update

Reviewed prescribing information for all drugs in this policy. Added coverage criteria for Joenja (leniolisib) for the treatment of activated phosphoinositide 3-kinase delta syndrome (APDS) in adults and pediatric individuals 12 years of age and older.

2024 Update

Added coverage criteria for Truqap (capivasertib) for the treatment of certain individuals with breast cancer. Removed Zydelig coverage criteria for the treatment of certain individuals with follicular lymphoma or small lymphocytic lymphoma as use for this indication was removed from the prescribing information. Updated Piqray (alpelisib) coverage criteria to include treatment of certain pre- and peri-menopausal women with breast cancer.

2025 Update

Reviewed prescribing information for all drugs in this policy. Clarified that the medications listed in this policy are subject to the product's FDA dosage and administration prescribing information. Clarified that non-formulary exception review authorizations for all drugs listed in this policy may be approved up to 12 months. Added coverage criteria for Itovebi (inavolisib).

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16. Zydelig Product Information. Gilead Sciences, Inc., Foster City, CA. Revised February 2022.
17. Aliqopa Product Information. Bayer HealthCare Pharmaceuticals Inc. Whippany, NJ. Revised September 2023.
18. Copiktra Product Information. Secura Bio, Inc. Las Vegas, NV. Updated July 2024.
19. Piqray (alpelisib) [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; Revised January 2024.
20. Vijoice (alpelisib) [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; Revised April 2024.
21. Truqap (capivasertib) [prescribing information]. Wilmington, DE; AstraZeneca; Revised September 2024.

History

Date	Comments
12/01/18	New policy approved November 13, 2018. Add to Prescription Drug section. Aliqopa (copanlisib), Copiktra (duvelisib), or Zydelig (idelalisib) may be considered medically necessary when criteria are met. They are considered investigational for all other uses.
01/01/19	Coding update added new HCPCS code J9057 (new code effective 1/1/19). Removed HCPCS code J9999.
01/01/20	Annual Review, approved December 10, 2019. No changes to policy statement.
08/01/20	Annual Review, approved July 23, 2020. Added a daily dose limit to Zydelig (idelalisib).
05/01/21	Annual Review, approved April 13, 2021. Added coverage criteria for Ukoniq (umbralisib) for the treatment of MZL and FL.
03/01/22	Annual Review, approved February 8, 2022. Removed from Copiktra (duvelisib) coverage for the treatment of relapsed or refractory follicular lymphoma as indication was withdrawn due to lack of efficacy in follow-up trials. Removed from Aliqopa (copanlisib) coverage for CLL and SLL as indications are not FDA-approved or supported by NCCN Guidelines. Policy changes for Aliqopa will be effective for dates of service on or after June 3, 2022.
07/01/22	Interim Review, approved June 27, 2022. Removed Ukoniq (umbralisib) from policy for all FDA-approved indications which is for the treatment of MZL and FL. The FDA announced that it has withdrawn approval for Ukoniq due to safety concerns. Moved Piqray (alpelisib) to Policy 5.01.592 from Policy 5.01.540 with no changes to coverage criteria.
10/01/22	Interim Review, approved September 13, 2022. Added coverage to Vijoice (alpelisib) and Piqray (alpelisib) for the treatment of PROS. Changed policy wording from "patient" to "individual" for standardization.
07/01/23	Annual Review, approved June 13, 2023. Reviewed prescribing information for all drugs in this policy. Added coverage criteria for Joenja (leniolisib) for the treatment of activated phosphoinositide 3-kinase delta syndrome (APDS) in adults and pediatric individuals 12 years of age and older.
03/01/24	Annual Review, approved February 13, 2024. Added coverage criteria for Truqap (capivasertib) for the treatment of certain individuals with breast cancer. Removed Zydelig coverage criteria for the treatment of certain individuals with follicular lymphoma or small lymphocytic lymphoma as use for this indication was removed from the prescribing information.
06/01/24	Interim Review, approved May 14, 2024. Updated Piqray (alpelisib) coverage criteria to include treatment of certain pre- and peri-menopausal women with breast cancer.
03/01/25	Annual Review, approved February 11, 2025. Clarified that the medications listed in this policy are subject to the product's FDA dosage and administration prescribing information. Clarified that non-formulary exception review authorizations for all drugs listed in this policy may be approved up to 12 months. Added coverage criteria for Itovebi (inavolisib).

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. The Company adopts policies after careful review of published peer-reviewed scientific literature, national guidelines and local standards of practice. Since medical technology is constantly changing, the Company reserves the right to review and update policies as appropriate. Member contracts differ in their benefits. Always consult the member benefit booklet or contact a member service representative to determine coverage for a specific medical service or supply.

Scope: Medical policies are systematically developed guidelines that serve as a resource for Company staff when determining coverage for specific medical procedures, drugs or devices. Coverage for medical services is subject to the limits and conditions of the member benefit plan. Members and their providers should consult the member benefit booklet or contact a customer service representative to determine whether there are any benefit limitations applicable to this service or supply. This medical policy does not apply to Medicare Advantage.