duvelisib (Copiktra®)

EOCCO POLICY

Policy Type: PA/SP Pharmacy Coverage Policy: EOCCO222

Description

Duvelisib (Copiktra) is an orally administered inhibitor of phosphoinositide 3-kinase (PI3K) with inhibitory activity predominantly against PI3K-δ and PI3K-γ isoforms expressed in normal and malignant B-cells.

Length of Authorization

- Initial: Three months
- Renewal: 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
duvelisib (Copiktra)	15 mg capsules	Relapsed/refractory chronic lymphocytic leukemia (CLL); Relapsed/refractory small lymphocytic lymphoma (SLL); Relapsed/refractory follicular lymphoma (FL)	56 capsules/28 days
	25 mg capsules		

Initial Evaluation

I. Duvelisib (Copiktra) may be considered medically necessary when the following criteria are met:
   A. Member is 18 years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with, a hematologist or oncologist; **AND**
   C. Member does not have a history of histological transformation (HT); **AND**
   D. Not used in combination with any other oncology therapy; **AND**
   E. Member has not progressed while on therapy with another PI3K inhibitor [e.g. copanlisib (Aliqopa), idelalisib (Zydelig)]; **AND**
   F. A diagnosis of **relapsed/refractory chronic lymphocytic leukemia (CLL) OR relapsed/refractory small lymphocytic lymphoma (SLL)** when the following are met:
      i. Treatment with one of the following has been ineffective or not tolerated or BOTH have been contraindicated:
         a. Bruton tyrosine kinase (BTK) inhibitor [e.g. ibrutinib (Imbruvica), acalabrutinib (Calquence)] **OR**
         b. BCL2 inhibitor [e.g. venetoclax (Venclexta)]; **AND**

ii. Treatment with at least **ONE** of the following additional therapies has been ineffective, not tolerated, or ALL are contraindicated:
   a. fludarabine/cyclophosphamide/rituximab (FCR)
   b. alkylating agent (e.g., chlorambucil, bendamustine, cyclophosphamide)
   c. monoclonal antibody (e.g., ofatumumab, rituximab, obinutuzumab)
   d. purine analog (e.g., fludarabine, pentostatin, cladribine)

II. Duvelisib (Copiktra) is considered investigational when used for all other conditions, including but not limited to:
   A. Relapsed/refractory follicular lymphoma (FL)
   B. Head and Neck Cancer
   C. Stage IIB-IVB Mycosis Fungoides and Sezary Syndrome
   D. Moderate to Severe Rheumatoid Arthritis
   E. Coronavirus Infection (COVID-19)

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. Initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Disease response to treatment defined by stabilization of disease or improvement in disease or disease symptoms.

Supporting Evidence

I. The safety and efficacy of duvelisib (Copiktra) for the treatment of relapsed and refractory CLL/SLL has been studied in a global, multicenter, randomized, open-label, Phase 3, superiority trial in 319 adult patients.
   - The two treatment arms included the duvelisib (Copiktra) and ofatumumab arm. Treatment groups were balanced, had a median number of prior therapies of two with approximately one-third having received three or more prior lines of therapy. Most patients had previously received an alkylating agent (chlorambucil, bendamustine,

cyclophosphamide) 93% in the duvelisib (Copiktra) and 95% in the ofatumumab group, a monoclonal antibody (ofatumumab, rituximab, obinutuzumab) 78% in the duvelisib (Copiktra) and 83% in the ofatumumab group, and purine analog (60% duvelisib (Copiktra); 71% ofatumumab).

- The primary endpoint of Progression-free Survival (PFS) was significantly longer for the duvelisib (Copiktra) arm compared with the ofatumumab arm (13.3 months vs 9.9 months, HR = 0.52, P < 0.0001).
- The key secondary endpoint of Overall Response Rate (ORR) was also significantly higher compared with ofatumumab (73.8% vs 45.3%; P < 0.0001), but the OS was not statistically different and the median overall survival (OS) was not reached on either treatment arm with a 12-month probability of survival of 86% (HR = 0.99; 95% CI, 0.65-1.50) for both treatments. This could be due to the availability of multiple CLL therapies to rescue patients on either arm following disease progression, including administration of duvelisib in a separate, optional extension study to 89 patients who had confirmed progressive disease on ofatumumab in the DUO study.
- Almost all patients in the study experienced an AE, 124 duvelisib (Copiktra)-treated patients had discontinued treatment, with the most common reasons being AEs (35%), disease progression (22%), subject withdrawal (8%), and death (8%).
- Fatal adverse reactions within 30 days of the last dose occurred in 36 patients (8%) treated with duvelisib (Copiktra) 25 mg twice daily. Serious adverse reactions were reported in 289 patients (65%). The most frequent serious adverse reactions that occurred were infection (31%), diarrhea or colitis (18%), pneumonia (17%), rash (5%), and pneumonitis (5%). Adverse reactions resulted in treatment discontinuation in 156 patients (35%), most often due to diarrhea or colitis, infection, and rash. Duvelisib (Copiktra) was dose reduced in 104 patients (24%) due to adverse reactions, most often due to diarrhea or colitis and transaminase elevation. The median time to first dose modification or discontinuation was 4 months (range: 0.1 to 27), with 75% of patients having their first dose modification or discontinuation within 7 months.

II. Histological transformation (HT) refers to the evolution of a clinically indolent disease (e.g. FL) to a clinically aggressive disease [e.g. diffuse large B-cell lymphoma (DLBCL)] defined as those lymphomas in which survival of the untreated patient is measured in months. The HT that occurs in patients with CLL/SLL has been termed Richter's transformation. When histological transformation is present, these patients are generally treated differently than their primary diagnosis. The goal of therapy for most patients is to eliminate the aggressive component of the disease (i.e. the histologically transformed cells) while minimizing toxicity. The most common treatment regimens for patients with HT include conventional chemotherapy with immunotherapy and high dose therapy followed by hematopoietic cell transplantation. There is no clinical trial data to support the use of duvelisib (Copiktra) in patients with HT.

III. Per the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology, CLL/SLL, recognizes duvelisib (Copiktra) as a preferred regimen for r/r CLL/SLL (Category 2A recommendation). Ibrutinib (Imbruvica), acalabrutinib (Calquence), venetoclax (Venclexta) plus rituximab are Category 1 recommendation, based on the results of the Phase 3 randomized studies (ASCEND, RESONATE and MURANO, respectively). Idelalisib (Zydelig) plus rituximab and duvelisib (Copiktra) are also preferred regimens in these populations with a category 2A recommendation due to their toxicity profile (colitis, diarrhea, and increased risk of infections).

Investigational or Not Medically Necessary Uses

I. Duvelisib (Copiktra) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Relapsed/refractory follicular lymphoma (FL)
      i. The safety and efficacy of duvelisib (Copiktra) for the treatment of relapsed and refractory FL has been studied in a single-arm, Phase 2, open-label study in 129 patients.
         - Duvelisib (Copiktra) 25 mg twice daily was administered in patients with FL (N = 83) who were refractory to rituximab and to either chemotherapy or radioimmunotherapy. Patients were refractory to rituximab either alone or in combination (127 patients [98%]), 119 patients (92%) had disease refractory to an alkylating agent or purine analog, and 117 patients (91%) had disease refractory to combination therapy with rituximab and an alkylating agent.
         - Patients had a median of three prior lines of therapy (range: 1 to 10), and 40% receiving four or more prior regiments, with 94% being refractory to their last therapy and 81% being refractory to 2 or more prior lines of therapy.
         - The primary endpoint was met with Overall Response Rate (ORR) being 47% (95% CI, 38% to 56%). The key secondary endpoint of duration of response (DOR was 10 months (95% CI, 6.5 to 10.5 months)
         - Due to treatment emergent adverse events (TEAE), forty patients (31%) discontinued duvelisib (Copiktra). In 85 (66%) of patients TEAEs were managed with dose interruption or reduction.
         - The most frequent grade 3 or greater TEAEs were neutropenia (24.8%), diarrhea (14.7%), anemia (14.7%), and thrombocytopenia (11.6%). Seventeen deaths (13.2%) occurred on treatment

ii. Almost all patients in the study assessing the safety and efficacy of duvelisib (Copiktra) were refractory to rituximab (98.4%), alkylating agent/purine analog (92.2%) and alkylating agent (90.7%).

iii. The NCCN B-cell Lymphomas guideline set duvelisib (Copiktra) as a second-line therapy for FL that is relapsed or refractory to at least two prior therapies, a category 2A recommendation. Anti–CD20 antibody–based chemoimmunotherapy [e.g., obinutuzumab (Gazyva), ofatumumab (Arzerra)] is the standard initial treatment for newly diagnosed and relapsed/refractory FL. Options for treatment at first relapse include alternate non–cross-resistant chemoimmunotherapy regimens or combination lenalidomide + rituximab. Rituximab monotherapy may be appropriate for patients with late relapse as well, particularly if disease burden is low.

iv. Patients with Grade 3b FL were excluded from the clinical trial. Grade 3b FL is often referred to as follicular large cell lymphoma and patients commonly present with a more clinically aggressive course. It is commonly treated with regimens used for clinically aggressive lymphomas, such as a Diffuse Large B-Cell Lymphoma (DLBCL).

v. Although, the primary outcome of ORR was met, the quality of evidence is low considering the single arm, Phase 2, open-label trial design. Furthermore, patients included in this trial experienced significant TEAEs and limited efficacy. Given these considerations treatment with duvelisib (Copiktra) in the setting of relapsed/refractory follicular lymphoma (FL) is considered experimental/investigational.

B. Head and Neck Cancer

i. A Phase 1b/2, open label, non-randomized, single group study of duvelisib (Copiktra) in combination with pembrolizumab in subjects with recurrent or metastatic head and neck squamous cell cancer is still recruiting.

C. Stage IIB-IVB Mycosis Fungoides and Sezary Syndrome

i. A Phase 1 open label, non-randomized, single group study with an expansion cohort of duvelisib (Copiktra) and nivolumab in Mycosis Fungoides (MF) and Sezary Syndrome (SS) is not yet recruiting.

D. Moderate to Severe Rheumatoid Arthritis

i. A Phase 2, double blind, placebo-controlled, randomized study to evaluate multiple dose levels of duvelisib (Copiktra) with background methotrexate in subjects with active rheumatoid arthritis and an inadequate response to methotrexate alone was completed in 2018 but no results have been published.

E. Coronavirus Infection (COVID-19)

ii. A Phase 2, double blind, placebo-controlled, randomized study to evaluate whether a two-week exposure to duvelisib (Copiktra), reduces inflammation in the

lungs in patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and COVID-19 who do not require mechanical ventilation at study initiation. The study is not yet recruiting.

References

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4. Wierda WG, Byrd JC, Abramson JS, et al. Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma, Version 4.2020, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw*. 2020;18(2):185-217. doi:10.6004/jnccn.2020.0006
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6. Verastem, Inc. A Study of Duvelisib in Combination With Pembrolizumab in Head and Neck Cancer. ClinicalTrials.gov Identifier: NCT04193293
7. National Cancer Institute (NCI). Duvelisib and Nivolumab for the Treatment of Stage IIB-IVB Mycosis Fungoides and Sezary Syndrome. ClinicalTrials.gov Identifier: NCT04652960
8. Verastem, Inc. A Double-Blind Study Evaluating Duvelisib in Subjects With Moderate to Severe Rheumatoid Arthritis and an Inadequate Response to Methotrexate Alone (ASPIRA). ClinicalTrials.gov Identifier: NCT0185170
9. Emory University, Verastem, Inc., University of Pennsylvania. Duvelisib Ameliorates Manifestations of Pneumonia in Established Novel Coronavirus Infection (COVID-19) (DAMPEN-CI). ClinicalTrials.gov Identifier: NCT04487886

Policy Implementation/Update:

Action and Summary of Changes	Date
Added criteria: age requirement, requirement of monotherapy, requirement of non-progression on a different PI3K inhibitor, requirement of one or more prior therapy if diagnosed with CLL/SLL Removed criteria: requirement for pneumocystis jirovecii pneumonia (PCP) prophylaxis and no history of allogenic stem cell transplant Moved the follicular lymphoma indication to investigational uses Criteria updated to policy format	2/2021
Policy created	11/2018