POLICY NUMBER UM ONC_1346	SUBJECT Copiktra™ (duvelisib)		DEPT/PROGRAM UM Dept	PAGE 1 OF 4
DATES COMMITTEE REVIEWED 10/10/18, 10/09/19, 12/11/19	APPROVAL DATE December 11, 2019	EFFECTIVE DATE December 11, 2019	COMMITTEE APPROVAL DATES (latest version listed last) 10/10/18, 10/09/19, 12/11/19	
PRIMARY BUSINESS OWNER: UM APPROVED BY: Dr. Andrew Hertler		COMMITTEE/BOARD APPROVAL Utilization Management Committee		
URAC STANDARDS HUM 1		NCQA STANDARDS UM 2	ADDITIONAL AREAS OF IMPACT	
CMS REQUIREMENTS	STATE/FEDERAL REQUIREMENTS		APPLICABLE LINES OF BUSINESS All	

I. PURPOSE

To define and describe the accepted indications for Copiktra (duvelisib) usage in the treatment of cancer.

II. DEFINITIONS

Copiktra (duvelisib): is an inhibitor of phosphatidylinositol 3-kinase (PI3K); it works primarily to inhibit PI3K-delta and PI3K-gamma isoforms expressed in normal and malignant B-cells. In cell lines derived from malignant B-cells and in primary CLL tumor cells, it induced growth inhibition in cells and reduced cell viability. Additionally, duvelisib inhibits several cell signaling pathways, including B-cell receptor signaling and the CXCR12-mediated chemotaxis of malignant B-cells. It also inhibits CXCR12-induced T-cell migration and macrophage colony-stimulating factor and IL-4 driven M2 polarization of macrophages.

Copiktra (duvelisib) is FDA approved for the treatment of adult patients with relapsed or refractory chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma CLL/SLL or follicular lymphoma after at least two prior therapies. Other PI3K inhibitors include idelaslisib and copanlisib.

Copiktra (duvelisib) is available in 15 mg and 25 mg oral capsules.

III. POLICY

New Century Health is responsible for processing all medication requests from network ordering providers. Medications not authorized by New Century Health may be deemed as not approvable and therefore not reimbursable. Treatment request outside the approved FDA manufacturer labeling or CMS approved compendia must follow CMS Medicare Benefit Policy Manual Chapter 15. If references are not produced, delays may occur to the processing of such request.

Inclusion Criteria: Copiktra (duvelisib) may be considered medically necessary when any of the following selection criteria are met:

1. **B-Cell Lymphomas**
    a. The member has a diagnosis of active follicular, gastric and non-gastric MALT, splenic marginal zone, and nodal marginal zone lymphoma **AND**
    b. Copiktra (duvelisib) is being used as second line or subsequent therapy for refractory or progressive disease after at least 2 prior therapies.
2. **Chronic Lymphocytic Leukemia (CLL)/Small Lymphocytic Lymphoma (CLL/SLL)**
    a. The member has a diagnosis of active CLL/SLL **AND**
    b. Copiktra (duvelisib) is being used as a single agent for relapsed or refractory disease with or without del(17p)/TP53 mutation.

Exclusion Criteria: Copiktra (duvelisib) is not considered medically necessary when any of the following selection criteria are met:

1. Copiktra (duvelisib) is being used after disease progression with the same regimen or previous treatment with a PI3K inhibitor (e.g., idelalisib or capanlisib) or BTK inhibitor (e.g., ibrutinib or acalabrutinib).
2. Concurrent use with chronic immunosuppressants (e.g., cyclosporine) or systemic steroids > 20 mg prednisone (or equivalent) daily.
3. History of Richter's transformation or prolymphocytic leukemia, chronic liver disease, prior allogeneic transplant, known central nervous system lymphoma or leukemia, or active infection.
4. Dosing exceeds single dose limit of Copiktra (duvelisib) 25 mg.
5. Treatment exceeds the maximum limit of 60 (25 mg) tablets/month.
6. Indications not supported by CMS recognized compendia or acceptable peer reviewed literature may be deemed as not approvable and therefore not reimbursable.

IV. PROCEDURE

Requests for Copiktra (duvelisib) shall be reviewed for appropriateness per FDA approved product labeling, the National Comprehensive Cancer Network (NCCN) and American Society of Clinical Oncology (ASCO) clinical guidelines, or CMS approved compendia.

1. **Dosage and Administration:**
    a. CLL/SLL/FL: 25 mg orally twice daily, with or without food. All patients should receive Pneumocystis jiroveci (PJP) prophylaxis during treatment and continued after treatment until the absolute CD4+ T cell count is greater than 200 cells/mcL; consider prophylactic antivirals to prevent cytomegalovirus (CMV) infection, including reactivation, during treatment.
2. **Dosage Adjustments:**
    a. Concomitant use with strong CYP3A4 inhibitors: Reduce dose to 15 mg twice daily.
    b. Cutaneous reaction (Grade 1 to 2): Continue current dose, initiate supportive therapy with emollients, antihistamines (for pruritus), or topical steroids, and monitor closely.
    c. Cutaneous reaction (Grade 3): Withhold therapy, initiate supportive therapy with emollients, antihistamines (for pruritus), or topical steroids, and monitor at least weekly until resolved. Resume at a reduced dosage (15 mg twice daily; discontinue use if patient is unable to tolerate 15 mg twice daily). If severe cutaneous reaction does not improve, worsens, or recurs, discontinue use.
    d. Cutaneous reaction (life-threatening, or any Grade Steven-Johnson Syndrome, toxic epidermal necrolysis, or drug rash with eosinophilia and systemic symptoms [DRESS]): Discontinue use.
    e. Hepatic enzyme elevation (Grade 2, ALT or AST 3 to 5 times ULN): Continue current dose, monitor at least weekly until return to less than 3 times ULN.
    f. Hepatic enzyme elevation (Grade 3, ALT or AST greater than 5 to 20 times ULN): Withhold therapy, monitor at least weekly until return to less than 3 times ULN; resume therapy at the same dose if first occurrence or reduced dosage for subsequent occurrence (initial dosage, 25 mg twice daily; dose reduction, 15 mg twice daily; discontinue use if patient is unable to tolerate 15 mg twice daily).
    g. Hepatic enzyme elevation (Grade 4, ALT or AST greater than 20 times ULN): Discontinue use.

h. Infection (Grade 3 or higher): Withhold until resolved; resume at the same or reduced dosage (initial dosage, 25 mg twice daily; dose reduction, 15 mg twice daily; discontinue use if patient is unable to tolerate 15 mg twice daily).

i. Infection (clinical cytomegalovirus (CMV) infection or viremia (positive polymerase chain reaction or antigen test)): Withhold until resolved; resume at the same or reduced dosage (initial dosage, 25 mg twice daily; dose reduction, 15 mg twice daily; discontinue use if patient is unable to tolerate 15 mg twice daily). Monitor patient at least monthly for CMV reactivation if therapy is resumed.

j. Infection (Pneumocystis jiroveci (PJP)): Withhold use if suspected; discontinue use if confirmed.

k. Neutropenia (ANC 0.5 to 1 giga (Gi)/L): Continue current dose, monitor ANC at least weekly

l. Neutropenia (ANC less than 0.5 Gi/L): Withhold therapy, monitor ANC until greater than 0.5 Gi/L; resume therapy at the same dose if first occurrence or reduced dosage for subsequent occurrence (initial dosage, 25 mg twice daily; dose reduction, 15 mg twice daily; discontinue use if patient is unable to tolerate 15 mg twice daily).

m. Non-infectious diarrhea or colitis (mild/moderate Grade 1 to 2 diarrhea [up to 6 stools per day over baseline] and responsive to antidiarrheal agents or asymptomatic Grade 1 colitis): Continue current dose, initiate supportive therapy with antidiarrheal agents as appropriate, and monitor at least weekly until resolved.

n. Non-infectious diarrhea or colitis (mild/moderate Grade 1 to 2 diarrhea [up to 6 stools per day over baseline] and unresponsive to antidiarrheal agents): Withhold therapy, initiate supportive therapy with enteric acting steroids (e.g., budesonide), and monitor at least weekly until resolved. Resume at a reduced dosage (15 mg twice daily; discontinue use if patient is unable to tolerate 15 mg twice daily).

o. Non-infectious diarrhea or colitis (abdominal pain, stool with mucus or blood, change in bowel habits, peritoneal signs, or severe Grade 3 diarrhea [greater than 6 stools per day over baseline]): Withhold therapy, initiate supportive therapy with enteric acting steroids (e.g., budesonide) or systemic steroids, and monitor at least weekly until resolved. Resume at a reduced dosage (15 mg twice daily; discontinue use if patient is unable to tolerate 15 mg twice daily).

p. Non-infectious diarrhea or colitis (recurrent Grade 3 diarrhea or recurrent colitis of any grade): Discontinue use.

q. Non-infectious diarrhea or colitis (life-threatening diarrhea or colitis): Discontinue use.

r. Pneumonitis without suspected infectious cause (moderate, Grade 2, symptomatic pneumonitis): Withhold use, treat with systemic steroid therapy; if pneumonitis recovers to Grade 0 or 1, may resume at reduced dose (15 mg twice daily; discontinue use if patient is unable to tolerate 15 mg twice daily). If non-infectious pneumonitis recurs or patient does not respond to steroid therapy, discontinue use.

s. Pneumonitis without suspected infectious cause (Severe, Grade 3, or life-threatening pneumonitis): Discontinue use, treat with systemic steroid therapy.

t. Thrombocytopenia (Grade 3, platelet count 25 to less than 50 Gi/L with Grade 1 bleed): Continue current dose, monitor platelet counts at least weekly.

u. Thrombocytopenia (Grade 3, platelet count 25 to less than 50 Gi/L with Grade 2 bleed or Grade 4, platelet count less than 25 Gi/L): Withhold therapy, monitor platelet counts until 25 Gi/L or greater; resume therapy at the same dose if first occurrence or reduced dosage for

subsequent occurrence (initial dosage, 25 mg twice daily; dose reduction, 15 mg twice daily; discontinue use if patient is unable to tolerate 15 mg twice daily).

3. **Monitoring:**
    a. Evidence of disease response or stabilization is indicative of efficacy.
    b. Pregnancy test: Before initiation of therapy.
    c. Hepatic function: During treatment; for Grade 2 ALT/AST elevation (greater than 3 to 5 times ULN) monitor at least weekly until return to less than 3 × ULN; for Grade 3 ALT/AST elevation (greater than 5 to 20 times ULN) monitor at least weekly until return to less than 3 × ULN.
    d. Neutrophil counts: At least every 2 weeks for the first 2 months of therapy, and at least weekly in patients with neutrophil counts less than 1.0 giga/L (Grade 3 or 4); monitor until ANC is greater than 0.5 giga/L.
    e. Signs and symptoms of infection.
    f. New or worsening cutaneous reactions; If Grade 1 to 2 reaction occurs, monitor closely and at least weekly for Grade 3 until resolution.
    g. New or worsening diarrhea or colitis: If Grade 1 to 3 diarrhea occurs, monitor at least weekly until resolution.
    h. Pulmonary symptoms and interstitial infiltrates.

V. APPROVAL AUTHORITY

1. Review – UM Department
2. Final Approval – UM Committee

VI. ATTACHMENTS

None

VII. REFERENCES

1. Copiktra PI prescribing information. Verastem Inc, Needham, MA 2019.
2. Clinical Pharmacology Elsevier Gold Standard. 2019.
3. Micromedex® Healthcare Series: Thomson Micromedex, Greenwood Village, Co. 2019.
4. National Comprehensive Cancer Network. Cancer Guidelines and Drugs and Biologics Compendium. 2019.
5. AHFS Drug Information. American Society of Health-Systems Pharmacists or Wolters Kluwer Lexi-Drugs. Bethesda, MD. 2019.