umbralisib (Ukoniq®)

EOCCO POLICY

Policy Type: PA/SP Pharmacy Coverage Policy: EOCCO231

Description

Umbralisib (Ukoniq) is a multikinase inhibitor of phosphatidylinositol-3-kinase-delta (PI3Kδ) and casein kinase 1-epsilon (CK1ε).

Length of Authorization

- N/A

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
umbralisib (Ukoniq)	200 mg tablet	Relapsed or Refractory Marginal Zone Lymphoma; Relapsed or Refractory Follicular Lymphoma	28 tablets/28 days

Initial Evaluation

I. **Umbralisib (Ukoniq)** is considered investigational when used for all conditions, including but not limited to relapsed or refractory Marginal Zone Lymphoma and relapsed or refractory Follicular Lymphoma.

Renewal Evaluation

I. N/A

Supporting Evidence

I. The activation of the PI3K pathway is commonly seen with marginal zone lymphoma (MZL) and follicular lymphoma (FL) which results in lymphoma cell growth and is one of the most frequently dysregulated pathways in cancer. Umbralisib (Ukoniq) is a multikinase inhibitor of phosphatidylinositol-3-kinase-delta (PI3Kδ) and casein kinase 1-epsilon (CK1ε) FDA-approved for the treatment of relapsed or refractory MZL in patients who have received at least one prior anti-CD20-based regimen and in relapsed or refractory FL in patients who have received at least three prior lines of systemic therapy.

II. Umbralisib (Ukoniq) is the fourth PI3K inhibitor on the market approved for FL and the first PI3K inhibitor approved for MZL. This once daily oral agent joins chemotherapy, immunotherapy, radioimmunotherapy, and other oral based regimens for the treatment of MZL and FL.

III. **Relapsed or refractory marginal zone lymphoma:** As of February 2021, NCCN guidelines have included umbralisib (Ukoniq) with other recommended regimens for the treatment of MZL. Preferred second-line therapies include regimens containing bendamustine, CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone), rituximab, lenalidomide, ibrutinib, Other recommended regimens additionally include ibritumomab tiuxetan, and PI3K inhibitors such as copanlisib, duvelisib, and idelalisib.

IV. **Relapsed or refractory follicular lymphoma:** As of February 2021, NCCN guidelines have included umbralisib (Ukoniq) with other recommended regimens. Preferred second-line therapies include regimens containing bendamustine, CHOP, lenalidomide, and rituximab, . Other recommended regimens additionally include ibritumomab tiuxetan, PI3K inhibitors such as copanlisib, duvelisib, and idelalisib, and tazemetostat, an enhancer of zeste homolog 2 (EZH2) inhibitor.

V. Umbralisib (Ukoniq) is being studied in an ongoing, open-label, single-arm trial in 69 patients with MZL who have progressed with one or more prior lines of therapy, including a CD20-directed regimen, in 117 patients with FL, and 22 patients with small lymphocytic lymphoma (SLL) who have progressed with two or more prior lines of therapy, including a CD20-directed regimen and an alkylating agent. The clinical trial is still ongoing and will further evaluate umbralisib (Ukoniq) in combination with ublituximab for the treatment of FL, MZL, SLL, mantle cell lymphoma (MCL) and in combination with ublituximab and bendamustine for the treatment of large B-cell lymphoma (DLBCL).

VI. Efficacy outcomes studied included primary endpoint of overall response rate (ORR) and secondary endpoints of disease control rate (DCR), duration of response (DOR), progression free survival (PFS), time to response (TTR), and number of patients experiencing a change in tumor volume.

VII. The overall response rate was 49.3% (95% CI 37-62) in the MZL cohort and 45.3% (95% CI 36-55) in the FL cohort. Progression-free survival (PFS) was a median of 10.6 months (95% CI 7.2-13.7) in the FL cohort; PFS was not reached for the MZL cohort.

Primary Endpoint	MZL (N=69)	FL (N=117)	SLL (N=22)
ORR, n (%) [95% CI] CR PR	**34 (49.3) [37-62]** 11 (16) [8-27] 23 (33) [22-46]	**53 (45.3) [36-55]** 6 (5) [2-11] 47 (40) [31-50]	**11 (50.0) [28-72]** 1 (5) [0.1-22.8] 10 (45.5) [24-68]
Secondary Endpoint	MZL (N=69)	FL (N=117)	SLL (N=22)
DCR, n (%) [95% CI]	57 (82.6) [72-91]	93 (79.5) [71-86]	19 (86.4) [65-97]
DOR, median (95% CI), months[b]	NR (10.3-NE)[c]	11.1 (8.3-15.6)[d]	18.3 (2.4-NE)
PFS, median (95% CI), months	NR (12.1-NE)	10.6 (7.2-13.7)	20.9 (7.4-24.1)
TTR, median (95% CI), months[b]	2.8 (2.7-2.9)	4.6 (3.0-5.6)	2.7 (2.4-2.8)
Change in tumor volume, n (%)	58/64 (90.6)	95/115 (83.5)	17/19 (89.5)

NR=not reported, NE=not evaluable, [b]calculations based on Kaplan-Meier estimation, [c]DOR was reported in n=34 MZL patients, [d]DOR was reported in n=53 FL patients.

VIII. The quality of evidence is considered low at this time as this was a single arm, open-label study design, with unknown clinical impact on the overall survival rate, health-related quality of life, or symptom improvement in treated patients. Additionally, umbralisib (Ukoniq) was FDA-approved under the accelerated approval pathway and continued approval for the two indications may be contingent upon verification and description of clinical benefit in confirmatory trials.

IX. Safety data was evaluated in 208 patients over a median follow up of 21.4 months. The most common adverse events were diarrhea (59%), nausea (39%), fatigue (31%), vomiting (24%), cough (21%), ALT/AST increase (20%), and neutropenia (15%).

X. Serious adverse events related to umbralisib (Ukoniq) were reported in 36 patients (17%) and included diarrhea (3%), acute kidney injury (1.4%), anemia (1.4%), dehydration (1.4%), febrile neutropenia (1.4%), pneumonia (1.4%), sepsis (1.4%), and urinary tract infection (1.4%). There were no adverse events leading to death.

XI. At the time of data cutoff, 62%, 77%, and 68% of patients had discontinued the drug in the MZL, FL, and SLL cohorts, respectively. Discontinuation rate due to adverse events in the overall population was 15.4%, with 11.5% dose reduction rate, and 59.4% and 45% dose interruption rate in MZL and FL treated patients, respectively.

XII. There are no contraindications to using umbralisib (Ukoniq); however, warnings and precautions include: infections, neutropenia, diarrhea or non-infectious colitis, hepatoxicity, severe cutaneous reactions, allergic reactions, and embryo-fetal toxicity. There are no black box warnings.

XIII. Although umbralisib (Ukoniq) is thought to have comparable efficacy and a more favorable safety profile than some of the other therapies on the market due to its pharmacological properties, confirmatory trials are needed to definitively establish benefit/value of this agent.

Investigational or Not Medically Necessary Uses

I. Umbralisib (Ukoniq) has not been sufficiently studied for safety and efficacy for any condition to date.

References

1. Ukoniq [Prescribing Information]. TG Therapeutics: New York, NY. February 2021.
2. NCCN Guidelines for the treatment of B-Cell Lymphomas. V.2.2021. Updated February 16, 2021.
3. Fowler NH, et al. Umbralisib, a Dual PI3Kδ/CK1ε Inhibitor in Patients With Relapsed or Refractory Indolent Lymphoma. J Clin Oncol. 2021 Mar 8:JCO2003433. doi: 10.1200/JCO.20.03433. Epub ahead of print. PMID: 33683917.

Policy Implementation/Update:

Action and Summary of Changes	Date
Policy created	05/2021