PDL DRUG REVIEW

Proprietary Name: Ukoniq®
Common Name: umbralisib
PDL Category: Antineoplastics

Comparable Products	Preferred Drug List Status
Imbruvica	Non-Recommended with Conditions

Summary

Pharmacology/Usage: Umbralisib, the active ingredient of Ukoniq®, is a kinase inhibitor and inhibits multiple kinases. Umbralisib inhibited cell proliferation, CXCL12-mediated cell adhesion, and CCL19-mediated cell migration in lymphoma cell lines in studies conducted in vitro.

Indication: For the treatment of:

- Adults with relapsed or refractory marginal zone lymphoma (MZL) who have received at least one prior anti-CD20-based regimen.
- Adults with relapsed or refractory follicular lymphoma (FL) who have received at least 3 prior lines of systemic therapy.

These indications are approved under accelerated approval based on overall response rate. Continued approval for these indications may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

There is no pregnancy category for this medication; however, the risk summary indicates that based on findings from animal studies and the mechanism of action, Ukoniq® can cause fetal harm when given to a pregnant woman. There are no available data on use in pregnant woman to assess for a drug-associated risk. Advise pregnant women of the potential risk to a fetus. Verify pregnancy status in females of reproductive potential prior to using Ukoniq® and advise this population to use effective contraception during treatment with Ukoniq® and for one month after the last dose. In addition, advise males with female partners of reproductive potential to use effective contraception during treatment with Ukoniq® and for one month after the last dose. The safety and efficacy of use in the pediatric population have not been established.

Dosage Form: Film-Coated Tablets: 200mg. Swallow tablets whole; do not crush, break, cut, or chew.

Recommended Dosage: Take 800mg PO QD with food until disease progression or unacceptable toxicity. If vomiting occurs, do not take an additional dose; continue with the next scheduled dose. If a dose is missed, take a missed dose unless it is less than 12 hours until the next scheduled dose.

Dosage modification may be required for adverse events, such as neutropenia, thrombocytopenia, infection, ALT or AST elevation, diarrhea or noninfectious colitis, severe cutaneous reactions, or other adverse reactions. Refer to the prescribing information for additional information regarding specific dosage modifications.

Provide prophylaxis for *Pneumocystis jirovecii* pneumonia (PJP) during treatment with Ukoniq®. Consider prophylactic antivirals during treatment with Ukoniq® to prevent cytomegalovirus (CMV) infection, including CMV reactivation.

Dose adjustments are not recommended in patients with mild or moderate renal impairment. Ukoniq® has not been studied in patients with severe renal impairment. Dose adjustments are not recommended for patients with mild hepatic impairment; however, Ukoniq® has not been studied in patients with moderate or severe hepatic impairment.

Drug Interactions: There are no drug interactions listed with this product.

Box Warning: There is no box warning listed with this product.

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions= reported % incidence for drug (Ukoniq®) for all grades in the pooled safety population including both indications. There was no placebo data found in the prescribing information.* The most frequently reported adverse events included diarrhea (58%), nausea (38%), vomiting (21%), abdominal pain (19%), fatigue (41%), edema (14%), pyrexia (10%), musculoskeletal pain (27%), upper respiratory tract infection (21%), decreased appetite (19%), rash (18%), and insomnia (14%). Select laboratory abnormalities included neutrophil decreased (33%), hemoglobin decreased (27%), platelets decreased (26%), creatinine increased (79%), alanine aminotransferase increased (33%), aspartate aminotransferase increased (32%), and potassium decreased (21%).

Serious, including fatal, infections occurred in patients treated with Ukoniq®. Grade 3 or higher infections occurred in 10% of 335 patients, with fatal infections occurring in <1%. The most frequent Grade ≥3 infections included pneumonia, sepsis, and urinary tract infection. The median time to onset of Grade ≥3 infection was 2.4 months. Monitor for any new or worsening signs and symptoms of infection. For Grade 3 or 4 infection, withhold Ukoniq® until infection has resolved. Resume treatment at the same or a reduced dose. In addition, monitor for cytomegalovirus infection during treatment with Ukoniq® in patients with a history of CMV infection. Consider prophylactic antivirals during treatment with Ukoniq® to prevent CMV infection. For clinical CMV infection or viremia, withhold Ukoniq® until infection or viremia resolves.

Serious neutropenia occurred in patients treated with Ukoniq®. Grade 3 neutropenia developed in 9% of 335 patients and Grade 4 neutropenia developed in 9%. The median time to onset of Grade 3 or 4 neutropenia was 45 days. Monitor neutropenia counts at least every 2 weeks for the first 2 months of Ukoniq® and at least weekly in patients with neutrophil counts <1 X 10^9/L (Grade 3-4). Consider supportive care as appropriate. Withhold, reduce dose, or discontinue Ukoniq® depending on the severity and persistence of neutropenia.

Serious diarrhea or non-infectious colitis occurred in patients treated with Ukoniq®. Any grade diarrhea or colitis occurred in 53% of 335 patients and Grade 3 occurred in 9%. The median time to onset for any grade diarrhea or colitis was 1 month, with 75% of cases occurring by 2.9 months. For patients with severe diarrhea or abdominal pain, stool with mucus or blood, change in bowel habits, or peritoneal signs, withhold Ukoniq® until resolved and provide supportive care with antidiarrheals or enteric acting steroids as appropriate. Discontinue Ukoniq® for life-threatening diarrhea or colitis

Serious hepatotoxicity occurred in patients treated with Ukoniq®. The median time to onset for Grade 3 or higher transaminase elevations was 2.2 months. Monitor hepatic function at baseline and during treatment with Ukoniq®.

Severe cutaneous reactions, including a fatal case of exfoliative dermatitis, occurred in patients treated with Ukoniq®. The median time to onset of Grade 3 or higher cutaneous reaction was 15 days. Monitor patients for new or worsening cutaneous reactions. Withhold treatment for severe cutaneous reactions until resolution. Monitor at least weekly until resolved. Upon resolution, resume Ukoniq® at a reduced dose.

Ukoniq® contains FD & C Yellow No. 5 (tartrazine), which may cause allergic-type reactions (including bronchial asthma) in certain susceptible persons. While the overall incidence of FD & C Yellow No. 5 (tartrazine) sensitivity in the general population is low, it is frequently seen in patients who also have aspirin sensitivity.

Contraindications: There are no contraindications listed with this product.

Manufacturer: TG Therapeutics, Inc

Analysis: *Marginal Zone Lymphoma*- The efficacy of Ukoniq® was assessed in a single-arm, open-label, multicenter, multicohort study. Patients with MZL were required to have received at least one prior therapy, including an anti-CD20 containing regimen. The trial excluded patients with prior exposure to a PI3K inhibitor. Patients received Ukoniq® 800mg PO QD until disease progression or unacceptable toxicity. Of the adults included in this cohort (N=69) the median age was 67 years, 52% were female, 83% were white, and 97% had a baseline Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. Patients had a median number of prior lines of therapy of 2, with 26% being refractory to their last therapy.

Efficacy was based on overall response rate as assessed by an Independent Review Committee (IRC) using criteria adopted from the International Working Group criteria for malignant lymphoma. The median follow-up time was 20.3 months (range 15.0 to 28.7 months). Efficacy results can be seen in the table below, which was adapted from the prescribing information.

Efficacy results in MZL	Total (N=69)
Overall Response Rate (ORR)	34 (49%)
Complete Response (CR)	11 (16%)
Partial Response (PR)	23 (33%)
Duration of Response (median), months	Not reached
Duration of Response (range), months	0.0, 21.8

The median time to response was 2.8 months (range 1.8 to 21.2 months). Overall response rates were 44.7%, 60.0%, and 45.5% for the 3 MZL sub-types (extra-nodal, nodal, and splenic, respectively).

Follicular Lymphoma- The efficacy of Ukoniq® was assessed in a single-arm, open-label, multicenter, multi-cohort study. Patients with relapsed or refractory FL were required to have received at least 2 prior systemic therapies, including an anti-CD20 monoclonal antibody and an alkylating agent. The trial excluded patients with Grade 3b FL, large cell transformation, prior allogeneic transplant, history of CNS lymphoma, and prior exposure to a PI3K inhibitor. Patients received Ukoniq® 800mg PO QD until disease progression or unacceptable toxicity. Of the adults included in this cohort (N=117), the median age was 65 years (range 29 to 87 years), while 38% were female, 80% were white, 73% had Stage III-IV disease, 38% had bulky disease, and 97% had a baseline ECOG performance status of 0 to 1. In addition, patients had a median of 3 prior lines of therapy (range 1 to 10), with 36% refractory to their last therapy.

Efficacy was based on overall response rate as assessed by an IRC using criteria adopted from the International Working Group criteria for malignant lymphoma. The median follow-up time was 20.1 months (range 13.5 to 29.6 months). Efficacy results can be seen in the table below, which was adapted from the prescribing information.

Efficacy results in FL	Total (N=117)
Overall Response Rate (ORR)	50 (43%)

Complete Response (CR)	4 (3.4%)
Partial Response (PR)	46 (39%)
Duration of Response (median), months	11.1
Duration of Response (range), months	0.0, 20.9

The median time to response was 4.4 months (range 2.2 to 15.5 months).

Place in Therapy: Ukoniq®, a multiple kinase inhibitor, is indicated for the treatment of adults with relapsed or refractory marginal zone lymphoma (MZL) who have received at least one prior anti-CD20-based regimen. It is also indicated for the treatment of adults with relapsed or refractory follicular lymphoma (FL) who have received at least 3 prior lines of systemic therapy. These indications are approved under accelerated approval based on overall response rate. Continued approval for these indications may be contingent upon verification and description of clinical benefit in a confirmatory trial. In an open-label, single-arm, multicohort study, patients with MZL had an overall response rate of 49%, while in the cohort of patients with FL the overall response rate was 43%.

It is recommended that Ukoniq® should be non-recommended in order to confirm the appropriate diagnosis and clinical parameters for use.

PDL Placement:

☐ **Recommended**

☒ **Non-Recommended with Conditions**

References

[1] Ukoniq [package insert]. Edison, NJ: TG Therapeutics, Inc; 2021.