UKONIQ™ (umbralisib) tablets, for oral use

This is a brief summary. Before prescribing, please refer to the full Prescribing Information.

1.1. Marginal Zone Lymphoma

UKONIQ is indicated for the treatment of adult patients with relapsed or refractory marginal zone lymphoma (MZL) who have received at least one prior anti-CD20-based regimen.

This indication is approved under accelerated approval based on overall response rate *[see Clinical Studies (14.1)]*. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

1.2. Follicular Lymphoma

UKONIQ is indicated for the treatment of adult patients with relapsed or refractory follicular lymphoma (FL) who have received at least three prior lines of systemic therapy.

This indication is approved under accelerated approval based on overall response rate *[see Clinical Studies (14.2)]*. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

4. CONTRAINDICATIONS

None.

5. WARNINGS AND PRECAUTIONS

5.1. Infections

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 (range: 1 day to 21 months) *[see Adverse Reactions (6.1)]*.

Monitor for any new or worsening signs and symptoms of infection. For Grade 3 or 4 infection, withhold UKONIQ until infection has resolved. Resume UKONIQ at the same or a reduced dose *[see Dosage and Administration (2.3)]*.

Provide prophylaxis for *Pneumocystis jirovecii* pneumonia (PJP) during treatment with UKONIQ *[see Dosage and Administration (2.2)]*. Withhold UKONIQ in patients with suspected PJP of any grade and permanently discontinue in patients with confirmed PJP *[see Dosage and Administration (2.2)]*.

Monitor for cytomegalovirus (CMV) infection during treatment with UKONIQ in patients with a history of CMV infection. Consider prophylactic antivirals during treatment with UKONIQ to prevent CMV infection, including CMV reactivation *[see Dosage and Administration (2.2)]*. For clinical CMV infection or viremia, withhold UKONIQ until infection or viremia resolves. If UKONIQ is resumed, administer the same or reduced dose and monitor patients for CMV reactivation by PCR or antigen test at least monthly *[see Dosage and Administration (2.2)]*.

5.2. Neutropenia

Serious neutropenia occurred in patients treated with UKONIQ. Grade 3 neutropenia developed in 9% of 335 patients and Grade 4 neutropenia developed in 9% *[see Adverse Reactions (6.1)]*. The median time to onset of Grade 3 or 4 neutropenia was 45 days.

Monitor neutrophil counts at least every 2 weeks for the first 2 months of UKONIQ and at least weekly in patients with neutrophil counts $<1 \times 10^9$/L (Grade 3-4). Consider supportive care as appropriate. Withhold, reduce dose, or discontinue UKONIQ depending on the severity and persistence of neutropenia *[see Dosage and Administration (2.3)]*.

5.3. Diarrhea or Non-infectious Colitis

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% *[see Adverse Reactions (6.1)]*. The median time to onset for any grade diarrhea or colitis was 1 month (range: 1 day to 23 months), with 75% of cases occurring by 2.9 months.

For patients with severe diarrhea (Grade 3, i.e., > 6 stools per day over baseline) 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. Upon resolution, resume UKONIQ at a reduced dose. For recurrent Grade 3 diarrhea or recurrent colitis of any grade, discontinue UKONIQ. Discontinue UKONIQ for life-threatening diarrhea or colitis *[see Dosage and Administration (2.3)]*.

5.4. Hepatotoxicity

Serious hepatotoxicity occurred in patients treated with UKONIQ. Grade 3 and 4 transaminase elevations (ALT and/or AST) occurred in 8% and <1%, respectively, in 335 patients *[see Adverse Reactions (6.1)]*. The median time to onset for Grade 3 or higher transaminase elevations was 2.2 months (range: 15 days to 4.7 months).

Monitor hepatic function at baseline and during treatment with UKONIQ. For ALT/AST greater than 5 to less than 20 times ULN, withhold UKONIQ until return to less than 3 times ULN, then resume at a reduced dose. For ALT/AST elevation greater than 20 times ULN, discontinue UKONIQ *[see Dosage and Administration (2.3)]*.

5.5. Severe Cutaneous Reactions

Severe cutaneous reactions, including a fatal case of exfoliative dermatitis, occurred in patients treated with UKONIQ. Grade 3 cutaneous reactions occurred in 2% of 335 patients and included exfoliative dermatitis, erythema, and rash (primarily maculo-papular) *[see Adverse Reactions (6.1)]*. The median time to onset of Grade 3 or higher cutaneous reaction was 15 days (range: 9 days to 6.4 months).

Monitor patients for new or worsening cutaneous reactions. Review all concomitant medications and discontinue any potentially contributing medications. Withhold UKONIQ for severe (Grade 3) cutaneous reactions until resolution. Monitor at least weekly until resolved. Upon resolution, resume UKONIQ at a reduced dose. Discontinue UKONIQ if severe cutaneous reaction does not improve, worsens, or recurs. Discontinue UKONIQ for life-threatening cutaneous reactions or SJS, TEN, or DRESS of any grade *[see Dosage and Administration (2.3)]*. Provide supportive care as appropriate.

5.6 Allergic Reactions Due to Inactive Ingredient FD&C Yellow No. 5

UKONIQ contains FD&C Yellow No. 5 (tartrazine), which may cause allergic-type reactions (including bronchial asthma) in certain susceptible persons. Although 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 hypersensitivity.

5.7 Embryo-Fetal Toxicity

Based on findings in animals and its mechanism of action, UKONIQ can cause fetal harm when administered to a pregnant woman.

In animal reproduction studies, administration of umbralisib to pregnant mice during the period of organogenesis caused adverse developmental outcomes including embryo-fetal mortality and fetal malformations at maternal exposures comparable to those in patients at the recommended dose of 800 mg. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential and males with female partners of reproductive potential to use effective contraception during treatment and for one month after the last dose *[see Use in Specific Populations (8.1, 8.3)]*.

6. ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Infections *[see Warnings and Precautions (5.1)]*
- Neutropenia *[see Warnings and Precautions (5.2)]*
- Diarrhea and Non-infectious Colitis *[see Warnings and Precautions (5.3)]*
- Hepatotoxicity *[see Warnings and Precautions (5.4)]*
- Severe Cutaneous Reactions *[see Warnings and Precautions (5.5)]*

6.1. Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be compared to rates in the clinical trials of another drug and may not reflect the rates observed in the general patient population.

The pooled safety population described in WARNINGS AND PRECAUTIONS reflects exposure to UKONIQ as monotherapy at a dosage of 800 mg orally once daily in 335 adults with hematologic malignancies in studies TGR-1202-101, TGR-1202-202, UTX-TGR-205, and UTX-TGR-501. Among these 335 patients who received UKONIQ, 52% were exposed for 6 months or longer and 30% were exposed for greater than one year.

Relapsed or Refractory Follicular Lymphoma and Marginal Zone Lymphoma

The safety of UKONIQ was evaluated in a pooled safety population that included 221 adults with marginal zone lymphoma (37%) and follicular lymphoma (63%) enrolled in three single-arm, open-label trials (Study TGR-1202-101, TGR-1202-202, and UTX-TGR-205) and one open-label extension trial (Study UTX-TGR-501) *[see Clinical Studies (14.1, 14.2)]*. These trials required hepatic transaminases ≤ 2.5 times upper limit of normal (ULN), total bilirubin ≤ 1.5 times ULN, and creatinine clearance ≥ 30 mL/min. No patients had prior exposure to a PI3K inhibitor. Patients received UKONIQ 800 mg orally once daily. Among these 221 patients who received UKONIQ, 60% were exposed for 6 months or longer and 34% were exposed for greater than one year.

The median age was 66 years (range: 29 to 88 years), 43% were female, and 97% had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1. Race was reported in 92% of patients; of these patients, 89% were White, 6% were Black, and 3% were Asian. Patients had a median of 2 prior therapies (range 1 to 10).

Serious adverse reactions occurred in 18% of patients who received UKONIQ. Serious adverse reactions that occurred in ≥2% of patients were diarrhea-colitis (4%), pneumonia (3%), sepsis (2%), and urinary tract infection (2%). Fatal adverse reactions occurred in <1% of patients who received UKONIQ, including exfoliative dermatitis.

Permanent discontinuation of UKONIQ due to an adverse reaction occurred in 14% of patients. Adverse reactions which resulted in permanent discontinuation of UKONIQ in ≥5% of patients included diarrhea-colitis (6%) and transaminase elevation (5%).

Dose reductions of UKONIQ due to an adverse reaction occurred in 11% of patients. Adverse reactions which required dose reductions in ≥4% of patients included diarrhea-colitis (4%).

Dosage interruptions of UKONIQ due to an adverse reaction occurred in 43% of patients. Adverse reactions which required dosage interruption in ≥5% of patients included diarrhea-colitis (18%), transaminase elevation (7%), neutropenia (5%), vomiting (5%), and upper respiratory tract infection (5%).

The most common (≥15%) adverse reactions, including laboratory abnormalities, were increased creatinine, diarrhea-colitis, fatigue, nausea, neutropenia, transaminase elevation, musculoskeletal pain, anemia, thrombocytopenia, upper respiratory tract infection, vomiting, abdominal pain, decreased appetite, and rash.

Table 3 provides the adverse reactions in the pooled safety population of 221 patients with marginal zone lymphoma and follicular lymphoma who received the recommended dosage.

Table 3: Adverse Reactions Reported (≥10%) in Patients With Marginal Zone Lymphoma and Follicular Lymphoma Who Received UKONIQ in Pooled Safety Population

	UKONIQ N=221	
Adverse Reactions	**All Grades (%)**	**Grade 3 or 4 (%)**
Gastrointestinal Disorders		
Diarrhea	58	10
Nausea	38	<1
Vomiting	21	<1
Abdominal pain[a]	19	3
General Disorders and Administration Site Conditions		
Fatigue[b]	41	3
Edema[c]	14	<1
Pyrexia	10	0
Musculoskeletal and Connective Tissue Disorders		
Musculoskeletal pain[d]	27	2
Infections		
Upper respiratory tract infection[e]	21	<1
Metabolism and Nutrition Disorders		
Decreased appetite	19	2
Skin and Subcutaneous Tissue Disorders		
Rash[f]	18	3
Psychiatric Disorders		
Insomnia	14	<1

[a] Abdominal pain includes Abdominal pain, abdominal pain upper, abdominal pain lower, abdominal discomfort
[b] Fatigue includes Fatigue, asthenia, lethargy
[c] Edema includes Edema peripheral, face edema, pulmonary edema, fluid overload, generalized edema
[d] Musculoskeletal pain includes Back pain, myalgia, pain in extremity, musculoskeletal pain, neck pain, spinal pain, musculoskeletal chest pain, musculoskeletal discomfort
[e] Upper respiratory tract infection includes Upper respiratory tract infection, sinusitis, nasopharyngitis, rhinitis
[f] Rash includes Rash, rash maculo-papular, rash erythematous, rash pruritic, rash macular, exfoliative dermatitis

Clinically relevant adverse reactions in <10% of patients who received UKONIQ included urinary tract infection (9%), dyspnea (7%), pneumonia (6%), sepsis (3%), colitis (2%), pneumonitis (<1%), and exfoliative dermatitis (<1%).

Table 4 provides the laboratory abnormalities in the pooled safety population of 221 patients with marginal zone lymphoma and follicular lymphoma who received the recommended dosage.

Table 4: Select Laboratory Abnormalities (>20%) That Worsened from Baseline in Patients with Marginal Zone Lymphoma and Follicular Lymphoma Who Received UKONIQ in Pooled Safety Population

	UKONIQ N=221	
Laboratory Parameter	**Any Grades[a] (%)**	**Grade 3 or 4[b] (%)**
Hematologic		
Neutrophil decreased	33	16
Hemoglobin decreased	27	3
Platelets decreased	26	4
Chemistry		
Creatinine increased	79	0
Alanine aminotransferase increased	33	8
Aspartate aminotransferase increased	32	7
Potassium decreased	21	4

[a] Laboratory values were categorized using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.03 grading system.

8. USE IN SPECIFIC POPULATIONS

8.1. Pregnancy

Risk Summary

Based on findings from animal studies and the mechanism of action *[see Clinical Pharmacology (12.1)]*, UKONIQ can cause fetal harm when administered to a pregnant woman. There are no available data on UKONIQ use in pregnant women to evaluate for a drug-associated risk. In animal reproduction studies, administration of umbralisib to pregnant mice during organogenesis resulted in adverse developmental outcomes, including alterations to growth, embryo-fetal mortality, and structural abnormalities at maternal exposures (AUC) comparable to those in patients at the recommended dose of 800 mg *(see Data)*. Advise pregnant women of the potential risk to a fetus.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data

In an embryo-fetal development study in mice, pregnant animals were administered oral doses of umbralisib at 100, 200, and 400 mg/kg/day during the period of organogenesis. Malformations were observed at doses of 200 mg/kg/day (cleft palate) and 400 mg/kg/day (cleft palate and nasopharyngeal fistula). Additional findings occurred starting at the dose of 100 mg/kg/day and included folded retina, delayed ossification of sternebrae and vertebrae, increased resorptions, and increased post-implantation loss. The exposure (AUC) at a dose of 100 mg/kg/day in mice is approximately equivalent to the human exposure at the recommended dose of 800 mg.

In an embryo-fetal development study in rabbits, pregnant animals were administered oral doses of umbralisib at 30, 100, and 300 mg/kg/day during the period of organogenesis. Administration at 300 mg/kg/day resulted in maternal toxicity (decreased food consumption and body weight) and reduced fetal weights. The exposure (AUC) at 300 mg/kg/day in rabbits is approximately 0.03 times the exposure in human patients at the recommended dose of 800 mg.

8.2. Lactation

Risk Summary

There are no data on the presence of umbralisib in human milk or the effects on the breastfed child or milk production. Because of the potential for serious adverse reactions from umbralisib in the breastfed child, advise women not to breastfeed during treatment with UKONIQ and for one month after the last dose.

8.3. Females and Males of Reproductive Potential

UKONIQ may cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)]*.

Pregnancy Testing

Verify pregnancy status in females of reproductive potential prior to initiating UKONIQ.

Contraception

Females

Advise female patients of reproductive potential to use highly effective contraception during treatment with UKONIQ and for at least 4 months after the last dose.

Males

Advise males with female partners of reproductive potential to use effective contraception during treatment with UKONIQ and for one month after the last dose.

Infertility

Males

Based on the findings from mice and dogs, UKONIQ may impair male fertility *[see Nonclinical Toxicology (13.1)]*. Trend for reversibility was noted in dogs 30 days after the last dose.

8.4. Pediatric Use

Safety and effectiveness of UKONIQ have not been established in pediatric patients.

8.5. Geriatric Use

Of the 221 patients with MZL or FL who received UKONIQ in clinical studies, 56% of patients were 65 years of age and older, while 19% were 75 years of age and older. No overall differences in effectiveness or pharmacokinetics were observed between these patients and younger patients. In patients 65 years of age and older, 23% experienced serious adverse reactions compared to 12% in patients younger than 65 years of age. There was a higher incidence of infectious serious adverse reactions in patients 65 years of age or older (13%) compared to patients younger than 65 years of age (4%).

8.6. Renal Impairment

No dose adjustment is recommended in patients with mild or moderate renal impairment (creatinine clearance [CLcr] 30 to 89 mL/min estimated by Cockcroft-Gault equation) *[see Clinical Pharmacology (12.3)]*. UKONIQ has not been studied in patients with severe renal impairment ([CLcr] < 30 mL/min).

8.7. Hepatic Impairment

No dose adjustment is recommended for patients with mild hepatic impairment (total bilirubin ≤ upper limit of normal [ULN] and AST > ULN or total bilirubin >1 to 1.5 × ULN and any AST) *[see Clinical Pharmacology (12.3)]*. UKONIQ has not been studied in patients with moderate (total bilirubin > 1.5 to 3 × ULN and any AST) or severe hepatic impairment (total bilirubin > 3 × ULN and any AST).

14. CLINICAL STUDIES

14.1. Marginal Zone Lymphoma

The efficacy of UKONIQ was evaluated in a single-arm cohort of Study UTX-TGR-205 (NCT02793583), an open-label, multi-center, multi-cohort trial. 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 800 mg orally once daily until disease progression or unacceptable toxicity.

A total of 69 patients with MZL [extranodal (N=38), nodal (N=20), and splenic (N=11)] were enrolled in this cohort. The median age was 67 years (range: 34 to 88 years), 52% were female, 83% were White, 7% were Black, 3% were Asian, 7% were Other, and 97% had a baseline ECOG performance status of 0 or 1. Patients had a median number of prior lines of therapy of 2 (range: 1 to 6), 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 are shown in Table 5.

Table 5: Efficacy Results in Patients with MZL (Study 205)

Endpoint	Total (N=69)
ORR, n (%)[a]	34 (49)
95% CI	37.0, 61.6
CR, n (%)	11 (16)
PR, n (%)	23 (33)
DOR	
Median, months (95% CI)[b]	NR (9.3, NE)
Range, months	0.0+, 21.8+

CI, confidence interval; CR, complete response; DOR, duration of response; IRC, Independent Review Committee; ORR, overall response rate; NE, not evaluable; NR, not reached; PR, partial response.
[a] Per IRC according to Revised International Working Group Criteria
[b] Based on Kaplan-Meier estimation
+ Denotes censored observation

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 (extranodal, nodal, and splenic, respectively).

14.2. Follicular Lymphoma

The efficacy of UKONIQ was evaluated in a single-arm cohort of Study UTX-TGR-205, an open-label, multi-center, multi-cohort trial (NCT02793583). Patients with relapsed or refractory FL were required to have received at least two 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 800 mg orally once daily until disease progression or unacceptable toxicity.

A total of 117 patients with FL were enrolled in this cohort. The median age was 65 years (range: 29 to 87 years), 38% were female, 80% were White, 4% were Black, 73% had Stage III-IV disease, 38% had bulky disease and 97% had a baseline ECOG performance status of 0 to 1. 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 Independent Review Committee (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 are shown in Table 6.

Table 6: Efficacy Results in Patients With Relapsed or Refractory FL (Study 205)

Endpoint	Total (N=117)
ORR, n (%)[a]	50 (43)
95% CI	33.6, 52.2
CR, n (%)	4 (3.4)
PR, n (%)	46 (39)
DOR	
Median months (95% CI)[b]	11.1 (8.3, 16.4)
Range, months	0.0+, 20.9+

CI, confidence interval; CR, complete response; DOR, duration of response; IRC, Independent Review Committee; ORR, overall response rate; PR, partial response.
[a] Per IRC according to Revised International Working Group Criteria
[b] Based on Kaplan-Meier estimation
+ Denotes censored observation

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

17. PATIENT COUNSELING INFORMATION

Advise patients to read the FDA-approved patient labeling (Medication Guide).

Infections

Advise patients that UKONIQ can cause serious infections that may be fatal. Advise patients to immediately report any signs or symptoms of infection (e.g., fever, chills, weakness) *[see Warnings and Precautions (5.1)]*.

Neutropenia

Advise patients of the need for periodic monitoring of blood counts and to notify their healthcare provider immediately if they develop a fever or any signs of infection *[see Warnings and Precautions (5.2)]*.

Diarrhea or Non-infectious Colitis

Advise patients that they may experience loose stools or diarrhea and should contact their healthcare provider with any persistent or worsening diarrhea. Advise patients to maintain adequate hydration *[see Warnings and Precautions (5.3)]*.

Advise patients of the possibility of colitis and to notify their healthcare provider of any abdominal pain/distress *[see Warnings and Precautions (5.3)]*.

Hepatotoxicity

Advise patients that UKONIQ may cause significant elevations in liver enzymes and the need for periodic monitoring of liver tests. Advise patients to report symptoms of liver dysfunction including jaundice (yellow eyes or yellow skin), abdominal pain, bruising, or bleeding *[see Warnings and Precautions (5.4)]*.

Severe Cutaneous Reactions

Advise patients that UKONIQ may cause a severe skin rash and to notify their healthcare provider immediately if they develop a new or worsening skin rash *[see Warnings and Precautions (5.5)]*.

Embryo-Fetal Toxicity

Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Advise females of reproductive potential to inform their healthcare provider of a known or suspected pregnancy *[see Warnings and Precautions (5.7), Use in Specific Populations (8.1, 8.3)]*.

Advise females of reproductive potential to use effective contraceptive during treatment with UKONIQ and for one month after the last dose *[see Use in Specific Populations (8.3)]*.

Advise males with female partners of reproductive potential to use effective contraceptive during treatment with UKONIQ and for one month after the last dose *[see Use in Specific Populations (8.3)]*.

Lactation

Advise women not to breastfeed during treatment with UKONIQ and for one month after the last dose *[see Use in Specific Populations (8.2)]*.

Infertility

Advise males of reproductive potential that UKONIQ may impair fertility *[see Use in Specific Populations (8.3)]*.

Allergic Reactions Due to Inactive Ingredient FD&C Yellow No. 5

Advise patients that UKONIQ contains FD&C Yellow No. 5 (tartrazine), which may cause allergic-type reactions in certain susceptible persons *[see Warnings and Precautions (5.6)]*.

Administration

Inform patients to take UKONIQ orally once daily at approximately the same time each day with food and how to make up a missed or vomited dose. Advise patients to swallow tablets whole. Advise patients not to crush, break, cut or chew tablets *[see Dosage and Administration (2.1)]*.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit MedWatch or call 1-800-FDA-1088.

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TG Therapeutics, Inc.
343 Thornall Street, Suite 740
Edison, NJ 08837

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