NEW DRUG APPROVAL

Brand Name	Ukoniq™
Generic Name	umbralisib
Drug Manufacturer	TG Therapeutics, Inc

New Drug Approval

FDA Approval Date: February 05, 2021

Review Designation: Priority; Orphan

Type of Review: Type 1 - New Molecular Entity

Dispensing Restrictions: Specialty Pharmacy

Place in Therapy

DISEASE DESCRIPTION & EPIDEMIOLOGY

Non-Hodgkin lymphoma (also known as non-Hodgkin's lymphoma, NHL, or sometimes just lymphoma) is a cancer that starts in white blood cells called lymphocytes, which are part of the body's immune system. NHL is a term that is used for many different types of lymphoma that all share some of the same characteristics. There is another main type of lymphoma, called Hodgkin lymphoma, which is treated differently. It most often affects adults, but children can get it too. It usually starts in lymph nodes or other lymph tissue, but it can sometimes affect the skin. Non-Hodgkin lymphoma (NHL) is one of the most common cancers in the United States, accounting for about 4% of all cancers. In 2021, about 81,560 people (45,630 males and 35,930 females) will be diagnosed with NHL. This includes both adults and children. Also, about 20,720 people will die from this cancer (12,170 males and 8,550 females).

Marginal zone lymphomas (MZLs) account for between 5% and 17% of all non-Hodgkin's lymphomas. MZLs consist of 3 different subtypes with extranodal being the most commonly reported, representing 50-70% of MZL, followed by splenic (20%) and nodal (10%). Median age at presentation varies between these lymphoma sub-types, ranging between 50 and 69 years, with an overall greater incidence noted in males compared to females. With an annual incidence of approximately 8,200 newly diagnosed patients in the United States, MZL is the third most common B-cell NHL, accounting for approximately ten percent of all NHL cases.

Follicular lymphoma (FL) is typically an indolent form of non-Hodgkin lymphoma (NHL) that arises from B-lymphocytes. It is the second most common form of NHL. FL is generally not curable and is considered a chronic disease, as patients can live for many years with this form of lymphoma. With an annual incidence in the United States of approximately 13,200 newly diagnosed patients, FL is the most common indolent lymphoma accounting for approximately 17 percent of all NHL cases.

Efficacy

Ukoniq™ accelerated approval was granted based on data from the Phase 2 UNITY-NHL trial (NCT02793583). Table 1 provides a summary of the study design and patient populations. The UNITY-NHL trial consisted of 3 arms:

- Umbralisib oral daily dose in combination with ublituximab intravenous (IV) administration
- Umbralisib oral daily dose
- Umbralisib oral daily dose in combination with ublituximab IV administration and bendamustine IV administration

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The efficacy for both Marginal Zone Lymphoma (MZL) and Follicular Lymphoma (FL) were evaluated in the single-arm cohort of the study.

Table 1. UNITY-NHL (NCT02793583): Study Design Summary

Cohort	Marginal Zone Lymphoma (MZL)	Follicular Lymphoma (FL)
Study Design	Phase 2 open-label, multicenter, multicohort	

Study Population	• A total of 69 patients with MZL [extranodal (n = 38), nodal (n = 20), and splenic (n = 11)] who received at least one prior therapy, including an anti-CD20 containing regimen
	• **Median age:** 67 years (range, 34–88 years)
	  ○ 52% female
	  ○ 83% White, 7% Black, 3% Asian, 7% other
	• 97% had a baseline ECOG performance status of 0 or 1
	• **Median prior lines of therapy:** 2 (range, 1–6); 26% were refractory to their last therapy
	• **Median follow-up time:** 20.3 months (range, 15.0–28.7 months)
	• **Median time to response:** 2.8 months (range, 1.8–21.2 months)
		• 117 patients with relapsed or refractory FL who received at least two prior systemic therapies, including an anti-CD20 monoclonal antibody and an alkylating agent
		• **Median age:** 65 years (range, 29–87 years)
		  ○ 38% female
		  ○ 80% White, 4% Black
		  ○ 73% had stage III–IV disease
		  ○ 38% had bulky disease
		• 97% had a baseline ECOG performance status of 0 to 1
		• **Median prior lines of therapy:** 3 (range, 1–10); 36% were refractory to their last therapy
		• **Median follow-up time:** 20.1 months (range, 13.5–29.6 months)
		• **Median time to response:** 4.4 months (range, 2.2–15.5 months)

Exclusions	Prior exposure to a PI3K inhibitor	Grade 3B FL, large cell transformation, prior allogeneic transplant, history of CNS lymphoma, and prior exposure to a PI3K inhibitor
Interventions	Both cohorts received umbralisib 800 mg orally once daily	
Endpoints	**Primary endpoint (both cohorts):** Independent review committee (IRC) assessed overall response rate (ORR) according to the Revised International Working Group Criteria	
Efficacy Results	• ORR for the 3 MZL subtypes: 44.7% (extranodal), 60.0% (nodal), and 45.5% (splenic) • Complete response (CR): 16%	• ORR: 43% • CR: 3.4%

Safety

ADVERSE EVENTS

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.

WARNINGS & PRECAUTIONS

- Infections: Monitor for fever and any new or worsening signs and symptoms of infection. Evaluate promptly and treat as needed.
- Neutropenia: Monitor blood counts during treatment.

- Diarrhea or Non-infectious colitis: Monitor for the development of diarrhea or colitis and provide supportive care as appropriate.
- Hepatotoxicity: Monitor hepatic function.
- Severe cutaneous reactions: Withhold treatment, reduce dose, or discontinue treatment depending on severity and persistence of severe cutaneous reaction.
- 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.
- Embryo-fatal toxicity: Can cause fatal harm. Advise patients of potential risk to a fetus and to use effective contraception.

CONTRAINDICATIONS

None.

Clinical Pharmacology

MECHANISMS OF ACTION

Umbralisib inhibits multiple kinases. In biochemical and cell-based assays, umbralisib inhibited PI3Kδ and casein kinase CK1ε. PI3Kδ is expressed in normal and malignant B-cells; CK1ε has been implicated in the pathogenesis of cancer cells, including lymphoid malignancies. Umbralisib also inhibited a mutated form of ABL1 in biochemical assays. Umbralisib inhibited cell proliferation, CXCL12-mediated cell adhesion, and CCL19-mediated cell migration in lymphoma cell lines in studies conducted in vitro.

Dose & Administration

ADULTS

800 mg PO once daily.

PEDIATRICS

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

GERIATRICS

Refer to adult dosing.

RENAL IMPAIRMENT

No dose adjustment is recommended in patients with mild or moderate renal impairment.

HEPATIC IMPAIRMENT

No dose adjustment is recommended for patients with mild hepatic impairment.

Product Availability

DOSAGE FORM(S) & STRENGTH(S)

Tablets: 200 mg