NDA 213176/Original 1
NDA 213176/Original 2

ACCELERATED APPROVAL

TG Therapeutics, Inc.
Attention: Anne Frederick, PhD
Vice President, Global Regulatory Affairs Strategy
343 Thornall Street, Suite 740
Edison, NJ 08837

Dear Dr. Frederick:

Please refer to your new drug application (NDA) dated June 15, 2020, received June 15, 2020, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Ukoniq (umbralisib) tablets.

NDA 213176 provides for the use of Ukoniq (umbralisib) tablets for the following indications which, for administrative purposes, we have designated as follows:

- NDA 213176/Original 1 – treatment of adult patients with relapsed or refractory marginal zone lymphoma (MZL) who have received at least one prior anti-CD20-based regimen
- NDA 213176/Original 2 – treatment of adult patients with relapsed or refractory follicular lymphoma (FL) who have received at least three prior lines of systemic therapy

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved under the provisions of accelerated approval regulations (21 CFR 314.500), effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

Marketing of this drug product and related activities must adhere to the substance and procedures of the referenced accelerated approval regulations.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the Food and Drug Administration (FDA) automated drug registration and listing system

(eLIST).[1] Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information and Medication Guide) as well as annual reportable changes not included in the enclosed labeling. Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As.*[2]

The SPL will be accessible via publicly available labeling repositories.

CARTON AND CONTAINER LABELING

Submit final printed carton and container labeling that are identical to the enclosed carton and container labeling, as soon as they are available, but no more than 30 days after they are printed. Please submit these labeling electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (April 2018, Revision 5)*. For administrative purposes, designate this submission "**Final Printed Carton and Container Labeling for approved NDA 213176**." Approval of this submission by FDA is not required before the labeling is used.

DATING PERIOD

Based on the stability data submitted to date, the expiry dating period for Ukoniq (umbralisib) tablets shall be 36 months from the date of manufacture when stored at 20°C to 25°C (68°F to 77°F) excursions permitted between 15°C to 30°C (59°F to 86°F) [see USP controlled room temperature].

ADVISORY COMMITTEE

Your application for Ukoniq was not referred to an FDA advisory committee because the application did not raise significant public health questions on the role of the drug in the diagnosis, cure, mitigation, treatment, or prevention of a disease.

ACCELERATED APPROVAL REQUIREMENTS

Products approved under the accelerated approval regulations, 21 CFR 314.510, require further adequate and well-controlled clinical trials to verify and describe clinical benefit. You are required to conduct such clinical trials with due diligence. If postmarketing clinical trials fail to verify clinical benefit or are not conducted with due diligence, we may, following a hearing in accordance with 21 CFR 314.530, withdraw

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm
[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

this approval. We remind you of your postmarketing requirement specified in your submission dated February 4, 2021. This requirement, along with required completion dates, is listed below.

3999-1 Conduct a randomized, Phase 3 clinical trial that verifies and describes the clinical benefit of umbralisib in patients with relapsed or refractory follicular lymphoma and marginal zone lymphoma. The trial should include sufficient numbers of racial and ethnic minority patients to better reflect the U.S. patient population and allow for interpretation of the results in these patient populations. Patients should be randomized to receive immunotherapy with or without umbralisib. The primary endpoint should be progression-free survival, with secondary endpoints that include overall survival and objective response rate.

Final Protocol Submission:	06/2021
Trial Completion:	12/2026
Final Report Submission:	06/2027

Submit clinical protocols to your IND 116762 for this product. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each requirement in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial.

Submit final reports to this NDA as a supplemental application. For administrative purposes, all submissions relating to this postmarketing requirement must be clearly designated "**Subpart H Postmarketing Requirement(s)**."

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for these indications has an orphan drug designation, you are exempt from this requirement.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify an unexpected serious risk of elevated drug levels; in patients with moderate or severe hepatic impairment; when umbralisib is administered concomitantly with strong CYP3A and moderate CYP2C9 inhibitors; and to assess a signal of excessive drug toxicity on repeat doses of umbralisib on the single dose pharmacokinetics of sensitive CYP2, CYP3A and P-gp substrates. Additionally, an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify an unexpected serious risk of QT prolongation in patients receiving umbralisib.

Furthermore, the active postmarket risk identification and analysis system as available under section 505(k)(3) of the FDCA will not be sufficient to assess these serious risks.

Finally, we have determined that only clinical trials (rather than nonclinical or observational studies) will be sufficient to identify these unexpected serious risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following trials:

3999-2 Conduct a clinical pharmacokinetic study to determine a safe and appropriate dose of umbralisib in patients with moderate to severe hepatic impairment. Design and conduct the study in accordance with the FDA Guidance for Industry titled "Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling."

The timetable you submitted on February 4, 2021 states that you will conduct this trial according to the following schedule:

Draft Protocol Submission:	06/2021
Final Protocol Submission:	09/2021
Trial Completion:	03/2024
Final Report Submission:	09/2024

3999-3 Conduct a clinical pharmacokinetic study to evaluate the effect of repeat doses of a strong CYP3A and a moderate CYP2C9 inhibitor on the single dose pharmacokinetics of umbralisib to address the potential for excessive drug toxicity. Design and conduct the study in accordance with the FDA

Guidance for Industry entitled "Clinical Drug Interaction Studies — Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions Guidance for Industry"

The timetable you submitted on February 4, 2021 states that you will conduct this trial according to the following schedule:

Draft Protocol Submission: 06/2021
Final Protocol Submission: 09/2021
Trial Completion: 12/2024
Final Report Submission: 06/2025

3999-4 Conduct a clinical pharmacokinetic study to evaluate the effect of repeat doses of umbralisib on the single dose pharmacokinetics of a sensitive CYP2C8, CYP2C9, CYP2C19, and CYP3A and P-gp substrate to address the potential for excessive drug toxicity. Design and conduct the study in accordance with the FDA Guidance for Industry entitled "Clinical Drug Interaction Studies — Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions Guidance for Industry."

The timetable you submitted on February 4, 2021 states that you will conduct this trial according to the following schedule:

Draft Protocol Submission: 06/2021
Final Protocol Submission: 09/2021
Trial Completion: 10/2024
Final Report Submission: 04/2025

3999-5 Conduct a clinical study to characterize QTc prolongation risk with umbralisib at steady-state maximal concentrations. The QT study can be conducted as a dedicated study or as a sub-study of ongoing trials. Design and conduct the QT study in accordance with the ICH E14 Guidances for industry titled, *E14 Clinical Evaluation of QT/QTc* and *E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs Questions and Answers (R3) Guidance for Industry*.

The timetable you submitted on February 4, 2021 states that you will conduct this trial according to the following schedule:

Final Protocol Submission: 06/2021
Trial Completion: 12/2026
Final Report Submission: 06/2027

FDA considers the term *final* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.[3]

Submit clinical protocols to your IND 116762 with a cross-reference letter to this NDA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final reports to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **Required Postmarketing Protocol Under 505(o), Required Postmarketing Final Report Under 505(o), Required Postmarketing Correspondence Under 505(o).**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

3999-6 Submit a final report containing data from clinical trials, post-marketing reports, compassionate use/expanded access program, real-world evidence, and other sources to further characterize the safety and efficacy of umbralisib monotherapy and in combination with immunotherapy among U.S. racial and ethnic minority patients with follicular lymphoma or marginal zone lymphoma.

[3] See the guidance for Industry *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (October 2019).* https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

The timetable you submitted on February 4, 2021, states that you will conduct this study according to the following schedule:

Final Report Submission: 06/2028

3999-7 Conduct a clinical pharmacokinetic study with repeat doses of a strong CYP3A inducer on the single dose pharmacokinetics of umbralisib to assess the magnitude of decreased drug exposure and to determine appropriate dosing recommendations. Design and conduct the study in accordance with the FDA Guidance for Industry entitled "Clinical Drug Interaction Studies — Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions Guidance for Industry"

The timetable you submitted on February 4, 2021, states that you will conduct this study according to the following schedule:

Draft Protocol Submission: 06/2021
Final Protocol Submission: 09/2021
Trial Completion: 12/2023
Final Report Submission: 06/2024

A final submitted protocol is one that the FDA has reviewed and commented upon, and you have revised as needed to meet the goal of the study or clinical trial.

Submit clinical protocols to your IND 116762 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled "**Postmarketing Commitment Protocol**," "**Postmarketing Commitment Final Report**," **or** "**Postmarketing Commitment Correspondence**."

PROMOTIONAL MATERIALS

Under 21 CFR 314.55, you are required to submit, during the application pre-approval review period, all promotional materials, including promotional labeling and advertisements, that you intend to use in the first 120 days following marketing approval (i.e., your launch campaign). If you have not already met this requirement, you must immediately contact the Office of Prescription Drug Promotion (OPDP) at (301) 796-1200. Please ask to speak to a regulatory project manager or the appropriate reviewer to discuss this issue.

As further required by 21 CFR 314.55, submit all promotional materials that you intend to use after the 120 days following marketing approval (i.e., your post-launch materials) at least 30 days before the intended time of initial dissemination of labeling or initial publication of the advertisement. We ask that each submission include a detailed cover letter together with three copies each of the promotional materials, annotated references, and approved Prescribing Information, Medication Guide, and Patient Package Insert (as applicable).

For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format-Promotional Labeling and Advertising Materials for Human Prescription Drugs*.[4]

REPORTING REQUIREMENTS

We remind you that you must comply with the reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

POST APPROVAL FEEDBACK MEETING

New molecular entities and new biologics qualify for a post approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

[4] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.

If you have any questions, call Natasha Kormanik, Senior Regulatory Project Manager, at (240) 402-4227.

Sincerely,

{See appended electronic signature page}

Marc R. Theoret, MD
Supervisory Associate Director (Acting)
Office of Oncologic Diseases
Center for Drug Evaluation and Research

ENCLOSURE(S):

- Content of Labeling
  - Prescribing Information
  - Medication Guide
- Carton and Container Labeling

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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