NDA 210259/S-010

SUPPLEMENT APPROVAL

AstraZeneca UK Limited
c/o AstraZeneca Pharmaceuticals LP
Attention: Thomas Fehn, PharmD, MBA
Regulatory Affairs Director
One MedImmune Way
Gaithersburg, MD 20878

Dear Dr. Fehn:

Please refer to your supplemental new drug application (sNDA) dated and received May 23, 2024, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Calquence (acalabrutinib) capsules.

We also refer to our letter dated March 22, 2024, notifying you, under Section 505(o)(4) of the FDCA, of new safety information that we have determined should be included in the labeling for the Bruton tyrosine kinase inhibitor products. This information pertains to the risk of hepatotoxicity including drug-induced liver injury (DILI). Additionally, we notified you of new safety information that we determined should be included in the labeling for Calquence (acalabrutinib) pertaining to the risk of cardiac arrhythmia including ventricular arrhythmia.

This supplemental new drug application provides for revisions to the labeling for Calquence (acalabrutinib). The agreed upon changes to the language included in our March 22, 2024, letter are as follows (additions are noted by underline and deletion are noted by ~~strikethrough~~).

1. Highlights of Prescribing Information:

   Recent Major Changes:
   Warnings and Precautions, Cardiac Arrhythmias (5.5) 6/2024
   Warnings and Precautions, Hepatotoxicity, Including Drug-Induced Liver Injury (5.6) 6/2024

   Warnings and Precautions:
   Hepatotoxicity, ~~i~~including D~~d~~rug-~~i~~induced L~~l~~iver ~~i~~injury (b) (4) Monitor hepatic function throughout treatment. (5.6)

2. Section 5, Warnings and Precautions:

   5.5 Cardiac Arrhythmias

   Serious cardiac arrhythmias have occurred in patients treated with CALQUENCE. Grade 3 atrial fibrillation or flutter occurred in 1.1% of 1029 patients treated with CALQUENCE, with all grades of atrial fibrillation or flutter reported in 4.1% of all patients. Grade 3 or higher ventricular arrhythmia~~s~~ events were reported in 0.9% of patients. The risk may be increased in patients with cardiac risk factors, hypertension, previous arrhythmias, and acute infection. Monitor for symptoms of arrhythmia (e.g., palpitations, dizziness, syncope, dyspnea) and manage as appropriate.

   5.6 Hepatotoxicity, ~~l~~including D~~d~~rug-~~l~~induced L~~l~~iver ~~l~~injury (b) (4)

   Hepatotoxicity, including severe, life-threatening, and potentially fatal cases of drug-induced liver injury (DILI), ha(b) (4)s (b) (4) occurred in patients treated with Bruton tyrosine kinase inhibitors, including CALQUENCE.

   Evaluate bilirubin and transaminases at baseline and throughout treatment with CALQUENCE. For patients who develop abnormal liver tests after CALQUENCE, monitor more frequently (b) (4) for liver test abnormalities and clinical signs and symptoms of hepatic toxicity (b) (4) If DILI is suspected, withhold CALQUENCE. Upon confirmation of DILI, discontinue CALQUENCE.

3. Section 6, Adverse Reactions

   - Cardiac Arrhythmias *[see Warnings and Precautions (5.(b) (4)5)]*
   - Hepatotoxicity, including DILI *[see Warnings and Precautions (5.(b) (4)6)]*

4. Subsection 6.2, Postmarketing Experience:

   The following adverse reactions have been identified during postapproval use of CALQUENCE. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.
   - Hepatobiliary disorders: ~~D~~drug-induced liver injury

5. Section 17, Patient Counseling Information:

   Hepatotoxicity, ~~l~~including Drug-Induced Liver Injury (b) (4):

   Inform patients that liver problems, including (b) (4) (b) (4) drug-induced liver injury and abnormalities in liver tests, may develop during CALQUENCE treatment. Advise patients to contact their healthcare provider

immediately if they experience (b) (4) abdominal discomfort, dark urine, or jaundice *[see Warnings and Precautions (5.(b) (4)6)]*.

6. Patient Package Insert:

- **Heart rhythm problems (** (b) (4) **cardiac arrhythmias)** have happened in people treated with CALQUENCE, which may be serious or lead to death.

- **Liver problems.** Liver problems can happen during treatment with CALQUENCE, which may be severe or life-threatening, or lead to death. Contact your healthcare provider if you experience stomach pain or discomfort, urine of dark color or yellowing of your skin. Your healthcare provider will request tests to monitor your liver function during treatment with CALQUENCE.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

WAIVER OF ½ PAGE LENGTH REQUIREMENT FOR HIGHLIGHTS

Please note that we have previously granted a waiver of the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of Prescribing Information.

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 FDA automated drug registration and listing system (eLIST), as described at FDA.gov.[1] Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information and Patient Package Insert), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, 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 from publicly available labeling repositories.

[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.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in Microsoft Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(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 none of these criteria apply to your application, you are exempt from this requirement.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. 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.*[3]

You must submit final promotional materials and Prescribing Information, accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at FDA.gov.[4] Information and Instructions for completing the form can be found at FDA.gov.[5]

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any new safety- related information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety-related information that appears in the revised labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4).

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[3] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.
[4] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf

PATENT LISTING REQUIREMENTS

Pursuant to 21 CFR 314.53(d)(2) and 314.70(f), certain changes to an approved NDA submitted in a supplement require you to submit patent information for listing in the Orange Book upon approval of the supplement. You must submit the patent information required by 21 CFR 314.53(d)(2)(i)(A) through (C) and 314.53(d)(2)(ii)(A) and (C), as applicable, to FDA on Form FDA 3542 within 30 days after the date of approval of the supplement for the patent information to be timely filed (see 21 CFR 314.53(c)(2)(ii)). You also must ensure that any changes to your approved NDA that require the submission of a request to remove patent information from the Orange Book are submitted to FDA at the time of approval of the supplement pursuant to 21 CFR 314.53(d)(2)(ii)(B) and 314.53(f)(2)(iv).

REPORTING REQUIREMENTS

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

If you have any questions, contact Jessica Kim, Safety Regulatory Project Manager, at 240-402-0883, or via email at Jessica.Kim1@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Shan M. Pradhan, M.D.
Associate Director for Safety
Office of Oncologic Diseases
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURE(S):

- Content of Labeling
  - Prescribing Information
  - Patient Package Insert

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/

SHAN PRADHAN
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