CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

216387Orig1Orig2s000

SUMMARY REVIEW

Cross-Discipline Team Leader Review

Date	2-Aug-2022
From	Sherita D. McLamore, Ph.D.
Subject	Cross-Discipline Team Leader (CDTL) Review
NDA	216387
Type of Application	505(b)(1)
Applicant	AstraZeneca UK Ltd
Date of Receipt	04-Oct-2021
PDUFA Goal Date	04-Aug-2022
Proposed Proprietary/Established Names	Acalabrutinib Maleate
Dosage forms / Strength	Tablet/ 100 mg
Route of Administration	Oral
Proposed Indication(s)	Indicated for the treatment of adult patients with: • Mantle cell lymphoma (MCL) who have received at least one prior therapy • Chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL).
Recommended:	Accelerated Approval (MCL indication) Regular Approval (CLL and SLL indication)

This cross-discipline team leader review is based on the primary reviews, memos and documented review input of:

- Clinical (Margret Marino, M.D.)
- ADL (Elizabeth Everhart)
- Pharmacology/Toxicology (Simon Williams, Ph.D.)
- Clinical Pharmacology (Catharine Bulik, Pharm.D)
- DEMPA (Nicole Iverson, Pharm. D.)
- DMPP (Susan Redwood, MPH, BSN, RN)
- OPDP (Jennifer Chen, Pharm. D)
- Drug Product (Yang Nan, Ph.D.)
- Drug Substance (Raymond Frankewich, Ph.D.)
- Microbiology (Huiquan Wu, Ph.D.)
- Manufacturing Process and Facilities (Huiquan Wu, Ph.D.)
- Biopharmaceutics (Min Kang, Ph.D.)

1. Introduction

NDA 216387 was submitted by AstraZeneca UK Ltd. for Acalabrutinib Maleate 100 mg Tablets in accordance with section 505(b)(1) of the Food, Drug and Cosmetic Act. Acalabrutinib is a second generation, orally bioavailable, Bruton Tyrosine Kinase inhibitor that is indicated for the treatment of adult patients with mantle cell lymphoma who have received at least one prior therapy, chronic lymphocytic leukemia or small lymphocytic lymphoma. Acalabrutinib was granted orphan designation for B-cell chronic lymphocytic leukemia/small lymphocytic lymphoma in 2015.

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Acalabrutinib was approved under NDA 210259 in a capsule formulation of the free base in October 2017. The current label for Acalabrutinib restricts its administration with acid reducing agents, including the recommendation that patients avoid co-administration with proton-pump inhibitors. (b) (4). In an effort to circumvent the problems associated with the free base the Applicant has introduced a new solid oral, maleate-salt presentation of acalabrutinib. The new salt tablet formulation is equivalent to 100 mg of the free base formulation and (b) (4)

The recommended dose for the proposed product is identical to that of the approved product e.g. 100 mg taken orally approximately every 12 hours until disease progression or unacceptable toxicity with a MDD 200 mg.

2. Background

As a result of pH dependent solubility and in an effort to improve patient access, this application provides CMC and clinical pharmacology data to support the stability and bioequivalence of a new tablet, salt formulation of acalabrutinib which is consistent with the approved product. (b) (4) The new maleate-salt formulation of acalabrutinib will ultimately replace the existing free base formulation.

This submission primarily included clinical pharmacology and chemistry manufacturing and controls (CMC) information; however, clinical data from two healthy volunteers were also provided.

3. Product Quality

Acalabrutinib (b) (4) is a small chiral crystalline, BCS Class 2 (high permeability low solubility) molecule. The manufacturing process (b) (4) is a part of the approved NDA (NDA 210259) (b) (4) (b) (4). There were no changes to the approved process for the manufacture of acalabrutinib; (b) (4). Based on the information provided, a (b) (4) retest period has been established by the drug substance manufacturer (b) (4).

The drug product is an immediate release, film-coated tablet containing 129 mg acalabrutinib maleate (equivalent to 100 mg acalabrutinib). It is presented orange, oval, biconvex, tablet, with debossment ‘ACA100’ on one side and plain on the other and formulated with compendial, commonly used excipients. The drug product is manufactured by AstraZeneca AB of Sweden at a commercial batch size of (b) (4) which corresponds to (b) (4) tablets. The drug product is manufactured (b) (4) by conventional processes. The primary container closure system was deemed suitable for the intended use and the rubber closure was demonstrated to be compatible with the drug product based on stability studies.

The biopharmaceutics review focused on (1) the acceptability of the proposed in vitro dissolution method and acceptance criterion for the routine quality control testing of the proposed drug product at batch release and on stability and (2) bridging of the pivotal clinical and commercial formulation and (3) the acceptability of the Physiologically-Based Biopharmaceutics Model (PBBM) which was

developed to support a dissolution acceptance criterion of Q = (b) (4)% in (b) (4)min for the drug product. Based on the information provided, the proposed dissolution method and acceptance criterion and bridging studies were deemed acceptable to support the approval of this application. The PBBM was considered inadequate and as a result the FDA recommended that the dissolution acceptance criterion be tightened to Q = (b) (4)% in 20 min based on the in vitro dissolution profile data from the clinical batches.

NDA 216387 included 5 manufacturing, testing, and packaging facilities and all facilities associated with this application were considered adequate to perform the responsibilities listed in the NDA.

Overall Product Quality Recommendation:
The Office of Pharmaceutical Quality (drug substance, drug product, drug process, microbiology, biopharmaceutics and facilities) recommends APPROVAL of NDA 216387. Based on the available stability data, the applicant proposed, and the OPQ accepts the expiration dating period of **24-months** for the drug product when stored at stored under USP controlled room.

6. Clinical Pharmacology

The Applicant submitted study results of one pivotal bioequivalence study and one food effect and drug-drug interaction (DDI) study to support the proposed 100 mg (dose expressed as base equivalent) tablet formulation for acalabrutinib. The pivotal study results suggested that the proposed 100 mg tablet formulation is bioequivalent to the approved 100 mg capsule formulation. The tablet formulation can be administered with or without food because no clinically meaningful differences in AUC and Cmax were observed in the food effect assessment. The dosing recommendations with regard to the co-administration with acid reducing agents for the approved capsule formulation are not needed for the tablet formulation, because co-administration of rabeprazole, a proton pump inhibitor, did not result in clinically meaningful differences in acalabrutinib exposure in the DDI assessment. Other dosing recommendations for the approved capsule formulation generally apply to the proposed tablet formulation. Refer to the clinical pharmacology review for details regarding the study evaluations and PK results. The proposed tablet formulation is considered approvable from a clinical pharmacology perspective.

7. Non-Clinical Pharmacology/Toxicology

Because the proposed acceptance criteria for the impurities are above the qualification threshold as per ICH Q3B (R2), the applicant included toxicology studies to support the proposed drug product impurity acceptance criteria. The toxicology assessments included two repeat-dose comparative toxicology studies in rats and two bacterial reverse mutation assays. The bacterial reverse mutation assays were negative with and without external metabolic activation systems at up to (b) (4) µg/plate of the impurities tested. In the 4-week repeat-dose toxicology studies, Wistar rats (n=10/sex) were administered 100 mg/kg of acalabrutinib maleate spiked with (b) (4)% impurities by oral gavage. The observed toxicities were limited, non-adverse, and comparable between the groups. Based on the levels of the impurities in the animal studies, the proposed specification limits are justified and NDA 216387 is recommended for approval from a Pharmacology/Toxicology perspective.

8. Clinical/Statistical-Efficacy

No new clinical efficacy data was included in this submission; however, the Applicant provided clinical data from 2 healthy volunteers. The clinical study report and datasets for each study were included. The clinical review was limited to the safety data included for these studies and

the safety outcomes in these studies were consistent with the safety profile established with acalabrutinib capsules, with no new safety signals identified.

9. Safety
There was no new safety data submitted with this application.

The most common adverse reactions associated with acalabrutinib include anemia, neutropenia, upper respiratory tract infection, thrombocytopenia, headache, diarrhea, and musculoskeletal pain. The USPI for the approved product includes instructions to avoid co-administration with proton pump inhibitors (PPIs) and to stagger dosing with H2-receptor antagonists and antacids. The USPI for the proposed product is devoid of the aforementioned recommendations.

10. Advisory Committee Meeting N/A

11. Pediatrics N/A

12. Other Relevant Regulatory Issues N/A

13. Labeling
Labeling negotiations are ongoing at the time of this review.

14. Recommendations/Risk Benefit Assessment

- **Recommended Regulatory Action**

The evaluation of this NDA was primarily based on clinical pharmacology and CMC data with clinical data from 2 healthy volunteers. As there are no outstanding issues precluding the approval of this application and based on the recommendations from all review disciplines, the CDTL recommends **APPROVAL** of NDA 216387 Original 1 for Calquence (acalabrutinib) tablets, 100 mg for the treatment of adult patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma and **ACCELERATED APPROVAL** of NDA 216387 Original 2 for Calquence (acalabrutinib) tablets, 100 mg for the treatment of adult patients with mantle cell lymphoma (MCL) who have received at least one prior therapy with the following post-marketing requirement (PMR):

PMR 3291-1 Complete a randomized, double-blind, placebo-controlled clinical trial of acalabrutinib in combination with standard immunochemotherapy versus immunochemotherapy alone in patients with mantle cell lymphoma to obtain data on clinical efficacy and safety.

Final Protocol Submission:	10/2023
Trial Completion:	11/2024

- **Risk Benefit Assessment**

Please refer to NDA 210259.

APPEARS THIS WAY ON ORIGINAL

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/s/

SHERITA D MCLAMORE
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