CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

216387Orig1Orig2s000

OTHER REVIEW(S)

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	July 20, 2022
Requesting Office or Division:	Division of Hematologic Malignancies 2 (DHM 2)
Application Type and Number:	NDA 216387
Product Name and Strength:	Calquence (acalabrutinib) 100 mg, Tablets
Applicant/Sponsor Name:	AstraZeneca UK Limited
OSE RCM #:	2021-1953-1
DMEPA 2 Safety Evaluator:	Nicole Iverson, PharmD, BCPS
DMEPA 2 Team Leader:	Chi-Ming (Alice) Tu, PharmD, BCPS

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label and professional sample label received on July 18, 2022 for Calquence. We review the revised container label and professional sample label for Calquence (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

1 Page of Draft Labeling has been Withheld in Full as B4(CCI/TS) Immediately Following this Page

[a] Iverson, N. Label and Labeling Review for Calquence (NDA 216387). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2022 MAY 31. RCM No.: 2021-1953.

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/

NICOLE F IVERSON
07/20/2022 12:29:27 PM

CHI-MING TU
07/20/2022 01:00:59 PM

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	July 12, 2022
To:	Denise Felluca Regulatory Project Manager **Division of Hematologic Malignancies II (DHM2)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Barbara Fuller, RN, MSN Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
From:	Susan Redwood, MPH, BSN, RN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Jennifer Chen, PharmD, MBA Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI)
Drug Name (established name):	CALQUENCE (acalabrutinib maleate)
Dosage Form and Route:	tablets, for oral use
Application Type/Number:	NDA 216387
Applicant:	AstraZeneca UK LTD c/o AstraZeneca Pharmaceuticals LP

1 INTRODUCTION

On October 4, 2021, AstraZeneca UK LTD c/o AstraZeneca Pharmaceuticals LP, submitted for the Agency's review an original New Drug Application (NDA) 216387 for CALQUENCE (acalabrutinib maleate) tablets, for oral use. With this submission, the Applicant seeks approval for 100 mg oral tablets for the treatment of adult patients with mantle cell lymphoma (MCL) who have received at least one prior therapy and chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL). The Applicant references their approved NDA (210259) for CALQUENCE (acalabrutinib) capsules.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Hematologic Malignancies II (DHM2) on November 24, 2021, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for CALQUENCE (acalabrutinib maleate) tablets.

2 MATERIAL REVIEWED

- Draft CALQUENCE (acalabrutinib maleate) tablets PPI received on October 4, 2021, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on July 6, 2022.
- Draft CALQUENCE (acalabrutinib maleate) tablets Prescribing Information (PI) received on October 4, 2021, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on July 6, 2022.
- Approved CALQUENCE (acalabrutinib) capsules labeling dated March 24, 2022.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss.

In our collaborative review of the PPI we:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language

- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the PPI is consistent with the approved labeling where applicable.

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

4 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

---

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/

SUSAN W REDWOOD
07/12/2022 09:22:31 AM

JENNIFER W CHEN
07/12/2022 09:32:52 AM

BARBARA A FULLER
07/12/2022 10:14:25 AM

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: 7/11/22

To: Denise Felluca, PharmD, MBA, Regulatory Health Project Manager, Division of Hematologic Malignancies II (DHM2)

From: Jennifer Chen, PharmD, MBA, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Jina Kwak, PharmD, RAC, Team Leader, OPDP

Subject: OPDP Labeling Comments for CALQUENCE® (acalabrutinib) tablets, for oral use

NDA: 216387

In response to DHM2's consult request dated November 5, 2021, OPDP has reviewed the proposed product labeling (PI) and patient package insert (PPI) for the original NDA submission for CALQUENCE® (acalabrutinib) tablets, for oral use.

Labeling: OPDP's comments on the proposed PI are based on the draft labeling received by electronic mail from DHM2 (Denise Felluca) on July 6, 2022, and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed, and comments on the proposed PPI will be sent under separate cover.

Thank you for your consult. If you have any questions, please contact Jennifer Chen at (301) 796-9398 or Jennifer.Chen@fda.hhs.gov.

29 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

---

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/

JENNIFER W CHEN
07/11/2022 06:06:33 PM

LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	May 31, 2022
Requesting Office or Division:	Division of Hematologic Malignancies 2 (DHM 2)
Application Type and Number:	NDA 216387
Product Name, Dosage Form, and Strength:	Calquence (acalabrutinib) 100 mg, Tablets
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	AstraZeneca UK Limited
FDA Received Date:	October 4, 2021
OSE RCM #:	2021-1953
DMEPA 2 Safety Evaluator:	Nicole Iverson, PharmD, BCPS
DMEPA 2 Team Leader:	Hina Mehta, PharmD

1 REASON FOR REVIEW

As part of the approval process for Calquence (acalabrutinib) 100 mg, tablets, we reviewed the proposed Calquence Prescribing Information (PI), Patient Information, container label, and professional sample label for areas of vulnerability that may lead to medication errors.

1.1 REGULATORY HISTORY

Calquence (acalabrutinib), capsules were approved on October 31, 2017 under NDA 210259 for the treatment of adult patients with Mantle cell lymphoma (MCL) who have received at least one prior therapy. On November 21, 2019, Calquence was approved the treatment of adult patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL).

Calquence capsule is currently marketed as a 100 mg capsule in the United States. Patient receiving Calquence capsules should avoid co-administration with proton-pump inhibitors (PPIs) and dosing should be staggered with H2 receptor antagonists and antacids (b) (4) Given the number of patients potentially receiving PPIs, the recommendation to avoid concomitant use of acalabrutinib with a PPI may limit its use as a treatment option. In addition, the current split dosing recommendations in the PI for patients taking other acid reducing agents may add complexity to their anti-cancer regimen. Therefore, the Applicant developed acalabrutinib maleate film-coated tablets (free base equivalent), (b) (4) Thus, acalabrutinib maleate film-coated tablets can be co-administered with acid reducing agents and can benefit patients by supporting simplification of their medication regimen. The tablet formulation is intended for the treatment of the same approved indications and the same dose as the approved capsule formulation (NDA 210259). The Applicant plans to remove the capsule formulation from the US market, within 9 months after launch of the tablet formulation.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B

Table 1. Materials Considered for this Review	
Material Reviewed	Appendix Section (for Methods and Results)
Human Factors Study	C – N/A
ISMP Newsletters*	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

AstraZeneca UK Limited submitted a 505 (b)(1) application to obtain marketing approval of Calquence (acalabrutinib) tablets to allow co-administration with acid reducing agents and can benefit patients by supporting simplification of their medication regimen. Calquence tablets will have the same indication and dosing as the currently marketed Calquence capsules. Calquence tablets will be supplied in bottles containing 60 tablets.

We note Calquence (acalabrutinib) tablets will be in a separate PI from the Calquence (acalabrutinib) capsules as AstraZeneca UK Limited intends to remove the capsule formulation from the market. We defer to clinical pharmacology for the determination on allowance of the tablets with co-administration of acid reducing agents.

We performed a risk assessment of the proposed container label, sample label, PI, and Patient Information for Calquence (acalabrutinib) tablets to determine whether there are significant concerns in terms of safety, related to preventable medication errors. We identified areas of the proposed labels and labeling that could be revised to improve clarity and readability of important information. For the Division, we note that the PI lacks clarity in the recommended dosage, administration instructions, dosage form, and how supplied information. We also note large doses appears without a comma for clarity. For the Applicant, we note prominence of the Rx only statement, lack of clarity of the recommended dosage and administration instructions. Additionally, the salt equivalency statement is missing. These factors may confuse the user and inadvertently lead to medication errors. We provide recommendations for the Division in Section 4.1 and the Applicant in Section 4.2 to address these deficiencies.

4 CONCLUSION & RECOMMENDATIONS

We identified areas in the proposed container label, sample label, PI, and Patient Information that can be improved to increase readability and prominence of important information and promote the safe use of the product.

We provide recommendations in Section 4.1 for the Division and Section 4.2 for AstraZeneca UK Limited to address our concerns.

4.1 RECOMMENDATIONS FOR DIVISION OF HEMATOLOGIC MALIGNANCIES 2 (DHM 2)

A. Highlights of Prescribing Information

1. Dosage and Administration

a. We recommend revising the statement, [redacted] (b) (4) to "Recommended dosage is 100 mg orally approximately every 12 hours; swallow whole with water and with or without food." to align to Section 2 Dosage and Administration of the PI.

b. We recommend revising the statement, [redacted] (b) (4) to "Advise patients not to chew, crush, dissolve, or cut tablets." for added clarity.

B. Prescribing Information

1. Dosage and Administration Section

a. Section 2.1 Recommended Dosage

i. We recommend revising the statement, [redacted] (b) (4) to "For patients with MCL, CLL, or SLL, the recommended dosage of CALQUENCE is 100 mg taken orally approximately every 12 hours until disease progression or unacceptable toxicity."

ii. We recommend revising the statement, [redacted] (b) (4) to "Advise patients not to chew, crush, dissolve, or cut the tablets." for added clarity.

2. Dosage Forms and Strengths

a. A description of the dosage form is not provided (e.g. imprinting, shape, and color). A description of the dosage form is required per 21 CFR

201.57(c)(4)(ii). Therefore, revise the statement, [redacted] (b) (4) to "Tablets: 100 mg tablet ,orange, oval, film-coated, biconvex, debossed with 'ACA100' on one side and plain on the other." in accordance with 21 CFR 201.57(c)(4)(ii).

3. Clinical Studies

    a. 14.2 Chronic Lymphocytic Leukemia

        i. The strength of Obinutuzumab (e.g. 1,000 mg) is presented as a large number and appears without comma to improve readability. Numbers greater than or equal to 1,000 should contain a comma to prevent the reader from misinterpreting thousands "1000" as hundreds "100" or ten-thousands "10000". We recommend revising the strength statement of Obinutuzumab to include a comma, for example, to read as 1,000 instead of 1000.

4. Patient Counseling Information

    a. Dosing Instructions

        i. We recommend revising the statement, [redacted] (b) (4) . to "Advise patients that CALQUENCE tablets should be swallowed whole with a glass of water, without chewing, crushing, dissolving, or cutting the tablets *[see Dosage and Administration (2.1)]*." for added clarity.

C. Patient Information

1. How should I take CALQUENCE?

    a. We recommend revising the statement, [redacted] (b) (4) to "Do not chew, crush, dissolve, or cut tablets." to align with the Prescribing Information.

4.2 RECOMMENDATIONS FOR ASTRAZENECA UK LIMITED

We recommend the following be implemented prior to approval of this NDA:

A. Container Label and Sample Label

1. We recommend revising the statement, [redacted] (b) (4) to "Recommend Dosage: See Prescribing Information".

2. The Rx Only statement appears prominent on the principal display panel. Decrease the prominence by debolding the Rx Only statement.

3. We recommend including the statement, “Do not chew, crush, dissolve, or cut tablets.” on the principal display panel to mitigate product administration errors.

4. (b) (4) We recommend revising the statement, (b) (4) to “Each tablet contains 100 mg of acalabrutinib (equivalent to 129 mg acalabrutinib maleate).”

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Calquence received on October 4, 2021 from AstraZeneca UK Limited, and the listed drug (LD).

Table 2. Relevant Product Information for Calquence and the Listed Drug		
Product Name	Calquence tablets	Calquence capsules[a]
Initial Approval Date	N/A	October 31, 2017
Active Ingredient	acalabrutinib	
Indication	• Mantle cell lymphoma (MCL) who have received at least one prior therapy. • Chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL).	
Route of Administration	Oral	
Dosage Form	100 mg	
Strength	Tablets	Capsules
Dose and Frequency	100 mg taken orally approximately every 12 hours until disease progression or unacceptable toxicity.	
How Supplied	• 60 count bottle containing 60 tablets with a child-resistant closure • 100 mg, orange, oval, biconvex, tablet, with debossment 'ACA100' on one side and plain on the reverse	• 60 count bottle containing 60 capsules • 100 mg, hard gelatin capsules with yellow body and blue cap, marked in black ink with 'ACA 100 mg'
Storage	Store at 20°C-25°C (68°F-77°F); excursions permitted to 15°C-30°C (59°F-86°F) [see USP	Store at 20°C-25°C (68°F-77°F); excursions permitted to 15°C-30°C (59°F-86°F) [see USP

[a] Calquence [Prescribing Information]. Drugs@FDA. U.S. Food and Drug Administration. 2019 NOV 21. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/210259s006s007lbl.pdf.

	Controlled Room Temperature].	Controlled Room Temperature].

APPENDIX B. PREVIOUS DMEPA REVIEWS

On March 5, 2022, we searched for previous DMEPA reviews relevant to this current review using the terms, Calquence. Our search identified 2 previous reviews[b,c], and we considered our previous recommendations to see if they are applicable for this current review.

[b] Rahimi, L. Label and Labeling Review for Calquence (NDA 210259). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 SEP 12. RCM No.: 2017-1197.

(b) (4)

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[d] along with postmarket medication error data, we reviewed the following Calquence labels and labeling submitted by AstraZeneca UK Limited.

- Container label received on October 4, 2021
- Professional Sample label received on October 4, 2021
- Prescribing Information and Patient Information (Image not shown) received on October 4, 2021, available from \\CDSESUB1\evsprod\nda216387\0001\m1\us\annotated-draft-label-maleate.pdf

G.2 Label and Labeling Images

1 Page of Draft Labeling has been Withheld in Full as B4(CCI/TS) Immediately Following this Page

[d] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/

NICOLE F IVERSON
05/31/2022 12:11:25 PM

HINA S MEHTA
06/01/2022 11:21:59 AM

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 5/19/2022

TO: Division of Hematologic Malignancies II (DHM II)
Office of Oncologic Diseases (OOD)

FROM: Division of New Drug Study Integrity (DNDSI)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Decline to conduct an on-site inspection**

RE: NDA 216387

OSIS received an inspection request consult from the Division of Hematologic Malignancies II on May 2, 2022, for the below clinical and analytical sites. The requested review goal date is July 4, 2022, and the PDUFA date is August 4, 2022.

The Division of New Drug Study Integrity (DNDSI) within the Office of Study Integrity and Surveillance (OSIS) declines to conduct inspections for the sites listed on the consult. The rationale for this decision is noted below.

Rationale

Inspections of the sites listed below are not able to be completed. Specifically, the requested review goal date of July 4, 2022, to meet the PDUFA date of August 4, 2022, does not provide sufficient time for the inspections to be completed and for OSIS to submit a review to the review division.

We note that OSIS's inspection histories for the sites are listed below, which provides inspection coverage for three of the four sites identified in the consult for inspection.

(b) (4): OSIS inspected the site in (b) (4) which falls within the surveillance interval. The inspection was conducted under the following submissions: (b) (4) The final classification for the inspection was No Action Indicated (NAI).

Parexel, Baltimore: The Office of Regulatory Affairs (ORA) inspected the site in October 2018. The inspection was conducted under the following submission: NDA 210874. The final classification for the inspection was NAI. We note that the current studies were conducted within 2 years of the previous inspection.

Parexel, Glendale: ORA inspection the site in April 2015. The inspection was conducted under the following submission: NDA 206500. The final classification for the inspection was NAI.

JBR Clinical Research, Salt Lake City: OSIS has no inspection history for this site.

Inspection Sites

Facility Type	Facility Name	Facility Address
Analytical	(b) (4)	
Clinical	PAREXEL Early Phase Clinical Unit	MedStar Harbor Hospital, 3001 South Hanover Street, 7th Floor, Baltimore, MD
Clinical	PAREXEL International, Inc. Early Phase Clinical Unit	Glendale Adventist Medical Center Campus, 1560 East Chevy Chase, Suite 140, Glendale, CA
Clinical	JBR Clinical Research	650 East, 4500 South, Suite 100, Salt Lake City, UT

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/

NICOLA M FENTY-STEWART
05/19/2022 04:06:26 PM

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 2/24/2022

TO: Division of Hematologic Malignancies II (DHM II)
Office of Oncologic Diseases (OOD)

FROM: Division of New Drug Study Integrity (DNDSI)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Decline to conduct an on-site inspection**

RE: NDA 216387

The Division of New Drug Study Integrity (DNDSI) within the Office of Study Integrity and Surveillance (OSIS) determined that an inspection is not warranted at this time for the site listed below. The rationale for this decision is noted below.

Rationale

The Office of Regulatory Affairs (ORA) inspected the site in October 2018. The inspection was conducted under the following submission: NDA 210874.

The final classification for the inspection was No Action Indicated (NAI).

OSIS notes that the current studies were conducted within approximately two years of the previous inspection and no objectionable conditions were observed (OSIS Review – Oct 2018 Inspection).

Therefore, based on the rationale described above, an inspection is not warranted at this time.

Inspection Site

Facility Type	Facility Name	Facility Address
Clinical	PAREXEL Early Phase Clinical Unit	MedStar Harbor Hospital, 3001 South Hanover Street, 7th Floor, Baltimore, MD

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/

JAMES J LUMALCURI
02/24/2022 04:40:25 PM