

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**213217Orig1s000**

**OTHER REVIEW(S)**

## CLINICAL INSPECTION SUMMARY

<b>Date</b>	October 31, 2019
<b>From</b>	Anthony Orenca M.D., F.A.C.P., Medical Officer Min Lu, M.D., M.P.H., Team Leader Kassa Ayalew, M.D., M.P.H., Branch Chief Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations
<b>To</b>	Margret Merino, M.D., Medical Officer R. Angelo de Claro, M.D., Clinical Team Leader Ann Farrell, M.D., Director Rachel McMullen, M.P.H., M.H.A., Project Manager Division of Hematology Products
<b>NDA</b>	213217
<b>Applicant</b>	BeiGene, Ltd.
<b>Drug</b>	Zanubrutinib
<b>NME</b>	Yes
<b>Division Classification</b>	Bruton tyrosine kinase protein inhibitor
<b>Proposed Indication</b>	Treatment of adult patients with mantle cell lymphoma (MCL) who have received at least one prior therapy
<b>Consultation Request Date</b>	July 3, 2019 (Priority Review)
<b>Summary Goal Date</b>	October 1, 2019 (original) November 4, 2019 (extension)
<b>Action Goal Date</b>	November 14, 2019
<b>PDUFA Date</b>	February 27, 2020

### I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Two selected clinical sites (Drs. Keshu Zhou and Jun Zhu) and BeiGene USA, Inc. were inspected for Study BGB-3111-206 in NDA 213217.

The study data derived from these clinical sites, based on the inspections, are considered reliable and the study in support of this application appears to have been conducted adequately.

The sponsor maintained adequate oversight of the clinical trial.

### II. BACKGROUND

Zanubrutinib (BGB-3111) is a second-generation small molecule oral Bruton's tyrosine kinase protein inhibitor, which forms an irreversible covalent bond at Cys481 within the adenosine triphosphate (ATP) binding pocket of the protein. BGB-3111 is potent against Bruton's tyrosine kinase.

Bruton's tyrosine kinase, a member of the tyrosine kinase expressed in TEC family kinases, is a critical component of the B cell antigen receptor (BCR) signaling cascade. Bruton's tyrosine kinase inhibition has emerged as a promising strategy for targeting B-cell malignancies such as mantle cell lymphoma.

The clinical data to support the use of zanubrutinib for treatment of adult patients with mantle cell lymphoma (MCL) who have received at least one prior therapy is based on a single study, that is described below:

### **Study BGB-3111-206**

Study BGB-3111-206 was a Phase 2, single-arm, open-label, multicenter study in patients with histologically documented mantle cell lymphoma who had no response or relapsed after one to four prior treatment regimens. The study was composed of an initial screening phase up to 28 days, a treatment phase, and a follow-up phase. The study is ongoing.

The primary study objective was to evaluate the efficacy of zanubrutinib at a dose of 160 mg orally twice a day in patients with centrally confirmed relapsed or refractory mantle cell lymphoma as measured by overall response rate assessed by an Independent Review Committee in accordance with the 2014 modification of the International Working Group on non-Hodgkin lymphoma Criteria (also known as Cheson's criteria).

The primary efficacy endpoint was overall response rate, defined as the achievement of either a partial response (PR) or complete response as determined by the Independent Review Committee according to the Lugano classification criteria.

The study was conducted in 13 active study centers in China which enrolled patients. A total of 86 patients were enrolled into the study and all received at least 1 dose of study drug. The first study patient received his first dose on March 2, 2017. The data cutoff date for the submitted study report was February 15, 2019.

## **III. RESULTS (by site):**

### **1. Keshu Zhou, M.D., Site #20615**

No.127 Dongming Road, Jinshui District Henan Cancer Hospital  
Zhengzhou, Henan 450008  
China

Inspection dates: October 14 to 17, 2019

A total of 18 subjects were screened and 14 study subjects enrolled. Four enrolled study subjects who received treatment discontinued from the study due to disease progression. Ten subjects are currently participating in an ongoing study. An audit was conducted for all enrolled subjects.

Source documents were verified against the case report forms and NDA subject line listings for study eligibility, informed consent form, ethics committee review/approval, monitoring, test article accountability, concomitant medication, delegation of authority, primary efficacy endpoint, and adverse event/serious adverse event reporting. Records review of the enrolled subjects indicated that the eligibility criteria for enrollment were met.

The primary efficacy endpoint data were verifiable. There was no under-reporting of adverse events. There were no limitations during conduct of the clinical site inspection.

In general, this clinical site appeared to be in compliance with Good Clinical Practice. A Form FDA 483 (Inspectional Observations) was not issued at the end of the inspection.

## **2. Jun Zhu, M.D., Site #20601**

No.52 Fucheng Road, Haidian District  
Beijing 100142  
China

Inspection dates: October 21 to 24, 2019

A total of 30 subjects were screened and 26 patients were enrolled. Of the 26 patients who received treatment, seven subjects developed disease progression and discontinued from the study, three study subjects discontinued due to adverse events, and three patients withdrew for other reasons. Thirteen subjects are continuing in an ongoing study.

For this inspection, a complete review of regulatory documentation at the study site was performed. Source records for the five subjects enrolled at the site were reviewed. The records reviewed included medical records, regulatory binder documents, delegation logs and signature logs, training logs, source data worksheets, informed consent forms, monitoring follow-up reports, and pharmacy records.

Source documents for all enrolled subjects were verified against the case report forms and NDA subject line listings for eligibility, adverse events, and serious adverse event reporting. The primary efficacy endpoint raw data were verifiable. There was no under-reporting of adverse events.

There were no limitations during conduct of the clinical site inspection.

In general, this clinical site appeared to be in compliance with Good Clinical Practice. A Form FDA 483 (Inspectional Observations) was not issued at the end of the inspection.

### 3. BeiGene USA, Inc.

2929 Campus Drive, Suite 300, San Mateo, CA 94403

Inspection dates: September 6 to 13, 2019

This inspection evaluated compliance with the sponsor's responsibilities concerning the conduct of Study BGB-3111-206. BeiGene, Ltd., the parent company of Beigene USA, Inc. was founded in 2010. Beigene, USA, Inc. is actively registered as a corporation, and currently does not have any subsidiaries. There are no recent or relevant regulatory actions associated with this firm.

The inspection included review of organizational charts, vendor oversight, transfer of obligations, investigator agreements, financial disclosures, monitoring plans, monitoring reports, monitor qualifications, safety reports, adverse events, protocol deviations, and standard operating procedures. Monitoring Reports for Study BGB-3111-206, specifically Sites 601 (Dr. Zhu), Site 602 (Dr. Zou) and Site 615 (Dr. Zhou) were selected and reviewed. No underreporting of significant adverse events to the Agency was noted.

Adverse event query logs were found in the Rave Electronic Data Capture (EDC) database. The Argus safety database maintained the query logs for serious adverse events (SAEs) and adverse events of special interest (AESIs).

The following Suspected Unexpected Safety Adverse Reaction (SUSAR) reports including source data, correspondence files and a selected sample of database audit trail queries were reviewed: BEIGENE-2017-00348, BEIGENE-2017-00368 and BEIGENE-2017-00443.

A Form FDA 483 was not issued at the end of the study inspection. In general, the sponsor appeared to be in compliance with Good Clinical Practice. Clinical trial oversight and monitoring by the sponsor appeared to be adequate.

*{See appended electronic signature page}*

Anthony Orenca, M.D.  
Good Clinical Practice Assessment Branch  
Division of Clinical Compliance Evaluation  
Office of Scientific Investigations

CONCURRENCE:

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CONCURRENCE:

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Kassa Ayalew, M.D., M.P.H.

Branch Chief

Good Clinical Practice Assessment Branch

Division of Clinical Compliance Evaluation

Office of Scientific Investigations

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

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Date of This Memorandum: October 18, 2019  
Requesting Office or Division: Division of Hematology Products (DHP)  
Application Type and Number: NDA 213217  
Product Name and Strength: Brukinsa (zanbrutinib) capsule, 80 mg  
Applicant/Sponsor Name: BeiGene  
OSE RCM #: 2019-1364-1  
DMEPA Team Leader: Hina Mehta, PharmD

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## 1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label and carton labeling received on October 8, 2019 for Brukinsa (zanbrutinib). We reviewed the revised container label and carton labeling for Brukinsa (zanbrutinib) (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.<sup>a</sup>

## 2 CONCLUSION

The revised container label and carton labeling are acceptable from a medication error perspective. We have no further recommendations at this time.

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<sup>a</sup> Garrison N. Label and Labeling Review for Brukinsa (zanbrutinib) (NDA 213217). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 SEP 04. RCM No.: 2019-1364.

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HINA S MEHTA  
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**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: October 15, 2019

To: Ann Farrell, MD  
Director  
**Division of Hematology Products (DHP)**

Through: LaShawn Griffiths, MSHS-PH, BSN, RN  
Associate Director for Patient Labeling  
**Division of Medical Policy Programs (DMPP)**

Barbara Fuller, RN, MSN, CWOCN  
Team Leader, Patient Labeling  
**Division of Medical Policy Programs (DMPP)**

From: Ruth Mayrosh, PharmD  
Patient Labeling Reviewer  
**Division of Medical Policy Programs (DMPP)**

Nisha Patel, PharmD  
Regulatory Review Officer  
**Office of Prescription Drug Promotion (OPDP)**

Subject: Review of Patient Labeling: Patient Package Insert (PPI)

Drug Name (established name): BRUKINSA (zanubrutinib)

Dosage Form and Route: capsules, for oral use

Application Type/Number: NDA 213217

Applicant: BeiGene USA, Inc.

## 1 INTRODUCTION

On June 27, 2019, BeiGene USA, Inc. submitted for the Agency's review an original New Drug Application (NDA) 213217 for BRUKINSA (zanubrutinib) capsules. The proposed indication for BRUKINSA (zanubrutinib) capsules is for the treatment of adult patients with mantle cell lymphoma (MCL) who have received at least one prior therapy.

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 Hematology Products (DHP) on July 5, 2019, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for BRUKINSA (zanubrutinib) capsules.

## 2 MATERIAL REVIEWED

- Draft BRUKINSA (zanubrutinib) capsules PPI received on June 27, 2019, and received by DMPP and OPDP on October 4, 2019.
- Draft BRUKINSA (zanubrutinib) capsules Prescribing Information (PI) received on June 27, 2019, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on October 4, 2019.

## 3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6<sup>th</sup> to 8<sup>th</sup> grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8<sup>th</sup> 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. We reformatted the PPI document using the Arial font, size 10.

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)

#### **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.

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

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

## Memorandum

**Date:** October 10, 2019

**To:** Rachel McMullen, Regulatory Project Manager  
Division of Hematology Products (DHP)  
  
Virginia Kwitkowski, Associate Director for Labeling, DHP

**From:** Nisha Patel, Regulatory Review Officer  
Office of Prescription Drug Promotion (OPDP)

**CC:** Trung-Hieu (Brian) Tran, Team Leader, OPDP

**Subject:** OPDP Labeling Comments for BRUKINSA™ (zanubrutinib) capsules, for oral use

**NDA:** 213217

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In response to DHP's consult request dated July 5, 2019, OPDP has reviewed the proposed product labeling (PI) and patient package insert (PPI) for the original NDA submission for BRUKINSA™ (zanubrutinib) capsules, for oral use (Brukinsa).

**PI and PPI:** OPDP's comments on the proposed labeling are based on the draft PI emailed to OPDP on October 7, 2019, 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 Nisha Patel at (301) 796-3715 or [nisha.patel@fda.hhs.gov](mailto:nisha.patel@fda.hhs.gov).

## Product Labeling

Section	Statement from draft	Comment
17 Patient Counseling Information	<p><u>Embryo-Fetal Toxicity</u></p> <p>Advise males with female sexual partners of reproductive potential to <b>use effective contraception during BRUKINSA treatment and for at least</b> (b) (4) <b>after the final dose of BRUKINSA</b> [see <i>Use in Specific Populations (8.3)</i>]. (emphasis added)</p>	<p>We note that the bolded text is not included in Section 8.3 of the full PI. Should this information be added to Section 8.3 for consistency with Section 17 of the full PI?</p>

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NISHA PATEL  
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# Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH  
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: October 7, 2019

From: CDER DCRP QT Interdisciplinary Review Team

Through: Christine Garnett, Pharm.D.  
Clinical Analyst  
Division of Cardiovascular and Renal Products /CDER

To: Rachel McMullen, RPM  
DHP

Subject: QT-IRT Consult to NDA 213217 (SDN 002)

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

This memo responds to your consult to us dated 9/27/2019 regarding the Division's request to provide labeling recommendations related to QT effects. The QT-IRT reviewed the following materials:

- Previous QT-IRT review for IND 125326 dated 04/02/2019 in DARRTS;
- [Summary of Clinical Pharmacology](#) and [Nonclinical Overview](#) (Submission 0001);
- Sponsor's response to information request (Submission ); and
- [Proposed label](#) (Submission 0005).

## 1 QT-IRT Responses

**Question:** The zanubrutinib 320 mg QD dosing regimen is under consideration for inclusion as a potential dosing option in the label. The Division is requesting QT-IRT review of the available data related to acceptability of the 320 mg QD dose from a cardiac electrophysiology perspective.

**QT-IRT's response:** The observed maximum exposure in cancer patients during treatment at the 320 mg QD dose level could be 40% higher than what was observed in the thorough QT study (a single dose of 480 mg in healthy subjects). Considering a lack of concentration-QTc relationship in the studied exposure range in the TQT study, the QT-IRT finds it acceptable to extend the conclusion of no clinically relevant effect to the newly proposed therapeutic dose of 320 mg QD.

It should be noted that the in vitro hERG studies do not provide a high safety margin at the 320 mg QD dose level. In the highest clinically relevant exposure scenario (i.e. with strong CYP3A4 inhibitor), C<sub>max</sub> could increase by 2.6-fold. This is far beyond the exposure range that has been evaluated in the TQT study. We propose to highlight this limitation in the product label.

Below is the QT-IRT's recommendation for Section 12.2 of the product label. Our recommendations are suggestions only, and we defer the final label decision to the Division.

At the therapeutic dose of 160 mg BID or 320 mg QD, there were no clinically relevant effects on the QT<sub>c</sub> interval. Drug effect on the QT<sub>c</sub> interval above the therapeutic exposure has not been evaluated.

## 2 BACKGROUND

Zanubrutinib is an inhibitor of Bruton's tyrosine kinase indicated for the treatment of adult patients with mantle cell lymphoma (MCL) who have received at least one prior therapy. The proposed therapeutic dose is 160 mg (two 80 mg capsules) orally twice daily, approximately every twelve hours, swallow whole with water and with or without food. The review team is considering the 320 mg QD dosing regimen as a potential dosing option in the label.

Previously the QT-IRT concluded a lack of significant QT<sub>c</sub> prolonging effect from a thorough QT study in healthy subjects. The highest dose that was evaluated was a single dose of 480 mg (C<sub>max</sub>: 398 ng/mL, observed in the TQT study), which covers the steady state therapeutic exposure in cancer patients (C<sub>max</sub> 344 ng/mL as reported in [highlight of clinical pharmacology](#) or C<sub>max</sub> 346 ng/mL as reported in the [investigator's brochure](#) under IND 125326). Therefore, the QT-IRT proposed the following label language in section 12.2: "*At the mean maximum exposure of the 160 mg BID dose, there were no clinically relevant effects on the QT<sub>c</sub> interval.*" The QT assessment does not suggest a dose- or concentration-dependent increase in the QT<sub>c</sub> interval within the exposure range studied.

In the [Summary of clinical pharmacology](#) under the NDA submission, the sponsor updated the C<sub>max</sub> values at the 160 mg BID and 320 mg QD doses from the patient population. The geometric mean C<sub>max</sub> are reported to be 289 ng/mL or 547 ng/mL at the 160 mg BID or 320 mg QD dose levels, respectively. The arithmetic mean C<sub>max</sub> are reported to be 328 ng/mL or 619 ng/mL at the 160 mg BID or 320 mg QD doses, respectively.

In the sponsor's recent response to information request, the predicted geometric C<sub>max</sub> is 204.3 ng/mL or 387.3 ng/mL at the 160 mg BID or 320 mg QD dose, respectively, in patients with B-cell malignancy. The sponsor has not provided an explanation for the approximately 40% difference between the observed and predicted C<sub>max</sub>.

According to the Nonclinical Summary, a moderate inhibition of hERG channel current was observed in Chinese Hamster Ovary (CHO) cells and HEK 293 cells with IC<sub>50</sub> values of 9.11 μM and 3.8 μM, respectively. No effects on blood pressure, heart rate or ECG were noted in telemetry-instrumented conscious dogs at doses of 10, 30 and 100 mg/kg. Assuming a molecular weight of 471.5 g/mol and a free fraction of 6%, the ratio between hERG IC<sub>50</sub> and free C<sub>max</sub> is calculated to be in the range of 55 (IC<sub>50</sub> from HEK and C<sub>max</sub> from observation) and 185 (IC<sub>50</sub> from CHO and C<sub>max</sub> from simulation).

Thank you for requesting our input into the development of this product. We welcome more discussion with you now and in the future. Please feel free to contact us via email at [cdcrpqt@fda.hhs.gov](mailto:cdcrpqt@fda.hhs.gov)

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LABEL AND LABELING REVIEW  
Division of Medication Error Prevention and Analysis (DMEPA)  
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\*\*\*

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Date of This Review:	September 4, 2019
Requesting Office or Division:	Division of Hematology Products (DHP)
Application Type and Number:	NDA 213217
Product Name and Strength:	Brukinsa (zanubrutinib) capsules, 80 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	BeiGene USA, Inc. (BeiGene)
FDA Received Date:	June 27, 2019 and August 20, 2019
OSE RCM #:	2019-1364
DMEPA Safety Evaluator:	Nicole Garrison, PharmD, BCPS
DMEPA Team Leader:	Hine Mehta, PharmD

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## 1 REASON FOR REVIEW

As part of the approval process for NDA 213217 Brukinsa (zanubrutinib) capsules, 80 mg, this review evaluates the proposed container labels, carton labeling, Patient Information, and Prescribing Information (PI) for areas that may lead to medication errors.

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

BeiGene submitted a 505(b)(1) application to obtain marketing approval of Brukinsa capsules. Brukinsa is indicated for the treatment of adult patients with mantle cell lymphoma (MCL) who have received at least one prior therapy.

We performed a risk assessment of the proposed container labels, carton labeling, Patient Information, and Prescribing Information for Brukinsa to determine whether there are significant concerns in terms of safety related to preventable medication errors. We have identified areas in the proposed labels and labeling that can be revised to improve clarity and readability of important information.

For the Division, we recommend revising dosing instructions for clarity and replacing symbols with the intended meaning.

For the Applicant, we recommend changes to the container labels and carton labeling to improve readability and prominence of important information. Specifically, we recommend bringing prominence to the dosage form, decreasing prominence of the Rx Only statement,

including the lot number, expiration date, and linear barcode on the container labels. Additionally, we recommend revising the usual dosage and administration statements. We also note the product's serial number is absent from the drug package and refer the Applicant to the Guidance on Product Identifiers Under the Drug Supply Chain Security Act Questions and Answers<sup>a</sup>.

#### 4 CONCLUSION & RECOMMENDATIONS

We conclude that the proposed Patient Information is acceptable from a medication error perspective. However, the container labels and carton labeling can be improved to increase the readability and prominence of important information on the label to promote the safe use of the product. We provide recommendations below in Section 4.1 for the Division and Section 4.2 for Beigene USA, Inc. to address our concerns. We advise these recommendations are implemented prior to approval of this product.

##### 4.1 RECOMMENDATIONS FOR THE DIVISION

###### A. Highlights of Prescribing Information

###### 1. Dosage and Administration Section

- a. Revise the statement, "Recommended dose: 160 mg (b) (4) orally twice daily, (b) (4) swallow whole with water and with or without food." to "Recommended dose: 160 mg orally (b) (4) swallow whole with water and with or without food." We recommend this revision to be consistent with Section 2 Dosage and Administration Section of the Full Prescribing Information.

###### B. Full Prescribing Information

###### 1. Dosage and Administration Section

- a. Revise the statement, "The recommended dose of BRUKINSA is 160 mg (b) (4) taken orally (b) (4) until disease progression or unacceptable toxicity." to "The recommended dose of BRUKINSA is 160 mg taken orally (b) (4) until disease progression or unacceptable toxicity."

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<sup>a</sup> [Guidance for Industry: Product Identifiers Under the Drug Supply Chain Security Act Questions and Answers. 2018. Available from https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM621044.pdf](https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM621044.pdf)

- b. In Table 1: Recommended Dose Modification for Adverse Reactions, consider replacing the symbols “≥”, “≤”, and “>” with their intended meanings to prevent misinterpretation and confusion.
- c. In Table 1: Recommended Dose Modification for Adverse Reactions in Dose Modification for Use with CYP3A Inhibitors or Inducers, revise the table heading, “(b) (4)” to “Recommended BRUKINSA use” for clarity.

#### 4.2 RECOMMENDATIONS FOR BEIGENE USA, INC. (BEIGENE)

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

##### A. General Comments (Sample and Commercial Container labels & Carton Labeling)

1. The Rx Only statement appears prominent on the principal display panel. Decrease the prominence by debolding the Rx Only statement.
2. Please clarify where the lot number and expiration date will be located on the container labels and carton labeling. We note the lot number statement is required on the immediate container and carton labeling when there is sufficient space per 21 CFR 201.10(i)(1). Additionally, identify the format for the expiration date. To minimize confusion and reduce the risk for deteriorated drug medication errors, identify the format you intend to use. We recommend that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date.
3. Increase the prominence of the dosage form statement, capsules, as currently displayed it lacks prominence.
4. Include the statement, “Do not open, break, or chew the capsules.” on the principal display panel to mitigate product administration errors.

##### B. Sample and Commercial Container Labels

1. Revise the statement, “(b) (4).” to “Dosage: See prescribing information.”
2. The linear barcode is absent from the container labels. The drug barcode is often used as an additional verification before drug administration in the

hospital setting; therefore, it is an important safety feature that should be part of the label whenever possible. Therefore, we request you add the product's linear barcode to each individual [PACKAGE] as required per 21CFR 201.25(c)(2). Ensure that the orientation of the linear barcode is in the vertical position to improve the scannability of the barcode. Barcodes placed in a horizontal position may not scan due to bottle curvature.

### C. Sample and Commercial Carton Labeling

1. Revise the statements, [REDACTED] (b) (4) [REDACTED] to "Dosage: See prescribing information."
2. As currently presented, the manufacturer's logo competes in prominence with the 2D matrix barcode on the principal display panel. Consider relocating the 2D matrix barcode to the side display panel to avoid confusion with the manufacturer's logo.
3. The product's serial number is omitted from the human readable product identifier. In September 2018, FDA released draft guidance on product identifiers required under the Drug Supply Chain Security Act. The Act requires manufacturers and repackagers, respectively, to affix or imprint a product identifier to each package and homogenous case of a product intended to be introduced in a transaction in(to) commerce beginning November 27, 2017, and November 27, 2018, respectively. We recommend that you review the draft guidance to determine if the product identifier requirements apply to your product's labeling. See draft guidance <https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm621044.pdf>

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Brukinsa received on June 27, 2019 from BeiGene USA, Inc. (BeiGene).

Table 2. Relevant Product Information for Brukinsa	
Initial Approval Date	N/A
Active Ingredient	zanubrutinib
Indication	For the treatment of adult patients with mantle cell lymphoma (MCL) who have received at least one prior therapy.
Route of Administration	Oral
Dosage Form	capsules
Strength	80 mg
Dose and Frequency	160 mg orally (b) (4)
How Supplied	Bottle with child-resistant capsules containing 120 capsules. Each capsule is 80 mg.
Storage	Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86) [See USP Controlled Room Temperature].

## APPENDIX B. PREVIOUS DMEPA REVIEWS

On August 19, 2019, we searched for previous DMEPA reviews relevant to this current review using the terms, Brukinsa. Our search did not identify any previous reviews.

## 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,<sup>b</sup> along with postmarket medication error data, we reviewed the following Brukinsa labels and labeling submitted by BeiGene USA, Inc. (BeiGene).

- Container label received on June 27, 2019
- Carton labeling received on June 27, 2019
- Professional Sample container label received on June 27, 2019
- Professional Sample carton labeling received on June 27, 2019
- Patient Information received on August 20, 2019
- Prescribing Information (Image not shown) received on August 20, 2019

### G.2 Label and Labeling Images

#### Container label



3 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

<sup>b</sup> Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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**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.**  
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/s/  
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NICOLE B GARRISON  
09/04/2019 10:16:43 AM

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