

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

217729Orig1s000

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: September 6, 2023

Requesting Office or Division: Division of Hematologic Malignancies 1 (DHM 1)

Application Type and Number: NDA 217729 and NDA 203341/S-025

Product Name, Dosage Form, and Strength: Bosulif (bosutinib)
NDA 217729: Capsule- 50 mg, and 100 mg
NDA 203341/S-025: Tablets- 100 mg, 400 mg, and 500 mg

Applicant/Sponsor Name: Pfizer Inc.

TTT ID #: 2023-4232-1 and 2023-4380-1

DMEPA 2 Safety Evaluator: Tayler Nalesnik, PharmD, MS

DMEPA 2 Team Leader: Nicole Iverson, PharmD, BCPS

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels received on August 25, 2023 for Bosulif. We reviewed the revised container labels for Bosulif (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 and a recommendation from the Division requesting removal of the Bosulif (b) (4) on the side panel of the container labels. We note the Applicant has identified the format of the expiration date on the container labels as 'YYYY-MMM'. (b) (4)

2 CONCLUSION

The proposed carton labeling is acceptable from a medication error perspective. We have no further recommendations at this time.

^a Nalesnik, Tayler. Label and Labeling Review for Bosulif (NDA 217729 and NDA 203341/S-025). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2025 07 25. TTT ID No.: 2023-4232 and 2023-4380.

APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON AUGUST 25, 2023

Container labels



(b) (4)

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/s/

TAYLER E NALESNIK
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NICOLE F IVERSON
09/07/2023 11:14:39 AM

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

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

Memorandum

Date: September 1, 2023

To: Brad McKenzie, Regulatory Project Manager
Division of Hematologic Malignancies I (DHM1)

From: Valerie Guerrier, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Jina Kwak, Team Leader, OPDP

Subject: OPDP Labeling Comments for BOSULIF® (bosutinib) capsules, for oral use

NDA: 217729

Background:

In response to DHM1's consult request dated March 31, 2023, OPDP has reviewed the proposed Prescribing Information (PI), Patient Package Insert (PPI)/Instructions for Use (IFU), and carton and container labeling for the original NDA submission for BOSULIF® (bosutinib) capsules, for oral use.

PI/PPI/IFU:

OPDP's review of the proposed PI is based on the draft labeling accessed from SharePoint on August 24, 2023, and our comments are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed for the proposed PPI/IFU, and comments were sent under separate cover on August 31, 2023.

Carton and Container Labeling:

OPDP's review of the proposed carton and container labeling is based on the draft labeling accessed from SharePoint on August 24, 2023, and we do not have any comments at this time.

Thank you for your consult. If you have any questions, please contact Valerie Guerrier at (240) 402-2162 or Valerie.Guerrier@fda.hhs.gov.

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VALERIE GUERRIER
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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: August 30, 2023

To: Bradley J. McKenzie, PharmD
Regulatory Project Manager
Division of Hematologic Malignancies 1 (DHM1)

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

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

Valerie Guerrier, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

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

Drug Name (established name): BOSULIF (bosutinib)

Dosage Form and Route, Application Type/Number, Supplement Number: tablets, for oral use, NDA 203341/S-025
capsules, for oral use, NDA 217729

Applicant: PF Prism. C.V.
c/o Pfizer Inc.

1 INTRODUCTION

On March 30, 2023, PF Prism. C.V. c/o Pfizer Inc. submitted for the Agency's review a Prior Approval Supplement (PAS) – Efficacy to their approved New Drug Application (NDA) 203341/S-025 for BOSULIF (bosutinib) tablets. With this supplement, the Applicant seeks a pediatric indication and a request for pediatric exclusivity, which will extend the use of BOSULIF (bosutinib) for the treatment of pediatric patients 1 year of age and older with newly-diagnosed chronic phase Ph+ chronic myelogenous leukemia (CML), or pediatric patients 1 year of age and older with chronic phase, (b) (4) Ph+ CML with resistance or intolerance to prior therapy.

On March 30, 2023, PF PRISM. C.V. c/o Pfizer Inc. submitted for the Agency's review an original New Drug Application (NDA) 217729 for BOSULIF (bosutinib) capsules. The purpose of this submission is to develop an age-appropriate dosage form for the treatment of pediatric patients 1 year of age and older.

Based on discussion with DHM1 on August 25, 2023, DMPP created an Instructions for Use (IFU) to provide clear instructions for patients who cannot swallow BOSULIF (bosutinib) capsules whole to prepare the capsules by mixing with applesauce or yogurt and swallowing the mixture. DMPP conferred with the Division of Medication Error, Prevention, and Analysis (DMEPA) on the IFU on August 30, 2023.

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 1 (DHM1) on March 31, 2023 for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for BOSULIF (bosutinib) tablets and capsules.

2 MATERIAL REVIEWED

- Draft BOSULIF (bosutinib) tablets and capsules PPI received on March 30, 2023, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on August 24, 2023.
- Draft BOSULIF (bosutinib) tablets and capsules Prescribing Information (PI) received on March 30, 2023, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on August 24, 2023.
- Approved BOSULIF (bosutinib) tablets labeling dated May 14, 2021.

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)

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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/s/

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VALERIE GUERRIER
08/31/2023 06:41:45 AM

LASHAWN M GRIFFITHS
08/31/2023 07:04:06 AM

MEMORANDUM

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

DATE: 7/31/2023

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

FROM: Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Decline to conduct on-site inspections**

RE: NDA 217729

The Office of Study Integrity and Surveillance (OSIS) determined that inspections are not needed for the sites listed below. The rationale for this decision is noted below.

Rationale

ICON, Groningen: The Office of Regulatory Affairs (ORA) conducted an inspection for the site in October 2022. The inspection was conducted under the following submission: BLA 761322.

The following item was discussed with the site:

- Rescreening procedures were performed on 2 subjects prior to obtaining their signatures on the informed consent form.

After review of the discussion items, OSIS concluded that subject safety was not impacted and data from the reviewed studies were reliable.

ICON Utrecht: Although OSIS has no inspection history for this site, an inspection will not be needed because no subjects were randomized at the site.

(b) (4): OSIS conducted a Remote Regulatory Assessment (RRA) for the site in (b) (4). The RRA was conducted under the following submission: (b) (4).

The following objectionable conditions were observed:

(b) (4)

After review of the objectionable conditions and the written response from the site, OSIS concluded that data from the reviewed studies were reliable but recommended that the review division consider requesting additional information (b) (4)

Sites

Facility Type	Facility Name	Facility Address
Clinical	ICON, PLC.	Van Swietenlaan 6, 9728 NZ Groningen, The Netherlands
Clinical	ICON, PLC.	Euclideslaan 1, YinYang Building, 3584 BL Utrecht, The Netherlands
Analytical		(b) (4)

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/s/

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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:	July 25, 2023
Requesting Office or Division:	Division of Hematologic Malignancies 1 (DHM 1)
Application Type and Number:	NDA 217729 and NDA 203341/S-025
Product Name, Dosage Form, and Strength:	Bosulif (bosutinib) NDA 217729: Capsule- (b) (4), 50 mg, and 100 mg NDA 203341/S-025: Tablets- 100 mg, 400 mg, and 500 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Pfizer Inc.
FDA Received Date:	March 30, 2023, April 28, 2023, and July 13, 2023
TTT ID #:	2023-4232 and 2023-4380
DMEPA 2 Safety Evaluator:	Tayler Nalesnik, PharmD
DMEPA 2 Team Leader:	Hina Mehta, PharmD

1 REASON FOR REVIEW

Pfizer submitted a New Drug Application (NDA) for Bosulif (bosutinib) under NDA 217729 to propose a new dosage form, capsules, and to propose the indication for the treatment of pediatric patients 1 year of age and older with newly diagnosed chromosome positive chronic myelogenous leukemia (Ph+ CML) or resistance/intolerance to prior therapy. In conjunction a prior approval supplement to Bosulif (bosutinib) tablets NDA 203341/S-025 was also submitted by Pfizer. We evaluated the proposed Bosulif prescribing information (PI), patient package insert (PPI), and container labels for areas of vulnerability that may lead to medication errors.

1.1 BACKGROUND INFORMATION

Bosutinib (bosutinib) tablets were approved on September 4, 2012, as a kinase inhibitor indicated for the treatment of adult patients with chronic, accelerated, or blast phase Philadelphia chromosome positive (Ph+) chronic myelogenous leukemia (CML) with resistance or intolerance to prior therapy. It was originally approved in 100 mg and 500 mg tablet strengths. On December 19, 2017, Bosulif was approved for the treatment of adult patients with newly diagnosed Ph+ CML. A new 400 mg tablet strength was also approved at the time.

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
ISMP Newsletters*	C – N/A
FDA Adverse Event Reporting System (FAERS)*	D – N/A
Other	E – N/A
Labels and Labeling	F

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

Pfizer Inc. is proposing a new dosage form and strength (50 mg and 100 mg tablets) for Bosulif (bosutinib) under NDA 217729 and a prior approval supplement under NDA 203341/S-025 to fulfill the pediatric written request for an indication in pediatric patients 1 year of age and

older. Both the currently approved 100 mg, 400 mg, and 500 mg tablets and proposed 50 mg and 100 mg capsules will have the same PI. (b) (4)

We acknowledge the proposed capsule dosage form overlaps in the 100 mg strength with the marketed 100 mg tablet. We note the labeling is differentiated by color between the dosage forms.

We performed a risk assessment of the proposed PI, PPI, and container labels for Bosulif (bosutinib) to identify areas of vulnerability that may lead to medication errors and other areas for improvement. We note the capsules can be swallowed whole or may be opened and mixed with applesauce or yogurt for administration and Section 2 contains a table with amount of soft food needed per dose. We communicated with the Office of Pharmaceutical Quality (OPQ) to seek clarification on the preparation and administration of capsules regarding the amount of applesauce or yogurt required based on the strength of capsule. For example, for the 250 mg dose, the PI states to sprinkle over 25 mL and would that amount be dependent on the combination of capsule strength was used (e.g. 5 x 50 mg capsules or 2 x 100 mg and 1 x 50 mg capsule). Subsequently, OPQ confirmed that the doses listed in table 2 in Section 2 of the PI can be any combination of Bosulif capsules.

Additionally, we note the statement “ (b) (4) ” in Section 16 of the PI. We confirmed with OPQ that the capsules should be stored and dispensed in the original container.

We note the proposed container labels of the capsule dosage form follow the format and layout of the currently approved and marketed tablets. Our review of the proposed PI, PPI, and container labels identified areas that may be revised to improve clarity and readability of important information. We provide recommendations for the Division and the Applicant to address these deficiencies in Section 4 below.

4 CONCLUSION & RECOMMENDATIONS

We identified areas in the proposed PI, PPI, and container label 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 Pfizer to address our concerns.

4.1 RECOMMENDATIONS FOR DIVISION OF HEMATOLOGIC MALIGNACIES 1 (DHM 1)

A. Full Prescribing Information

1. Dosage and Administration

- I. We recommend revising the statement on swallowing the tablet whole for clarity and consistency among other products. Revise to “Swallow tablets whole. Do Not cut, crush, or chew tablets.”

II. We recommend removing the statement [REDACTED] (b) (4) [REDACTED] as this statement contradicts the fact that the capsule can be opened. If needed, the statement "Capsules may be swallowed whole." may be added.

2. How Supplied

I. As the capsules need to be kept in the original container we recommend revising the statement to read "Store and Dispense in original container."

B. Patient Package Insert

1. As the capsules need to be kept in the original container we recommend included the statement "Keep BOSULIF capsules in original container."

4.2 RECOMMENDATIONS FOR PFIZER INC.

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

A. Container Labels

1. As currently presented, the format of the expiration date is not defined, and we are unable to assess the proposed expiration date format from a medication safety perspective. To minimize confusion and reduce the risk for deteriorated drug medication errors, we recommend identifying the expiration date on the drug package label to 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. FDA recommends a hyphen or forward slash to separate portions of the expiration date.
2. As the capsules need to be kept in the original container, we recommend including a statement on the principal display panel instructing pharmacists to dispense on original bottle. Include the following statement "Attention: Store and dispense Bosulif in original container."
3. As currently presented, the graphic and manufacturer name competes with the prominence of the product name on the principal display panel. The proprietary name and established or proper name along with the product strength, route of administration, and warnings or cautionary statements should be the most prominent information on the principal display panel (PDP). We recommend decreasing the prominence of the graphic and manufacturer name and moving it to the bottom of the label.
4. We recommend revising the storage instructions on the side panel of the container labels to the following: "Store 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]. Store and dispense in original container."

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Bosulif received on March 30, 2023 from Pfizer Inc..

Table 2. Relevant Product Information for Bosulif	
Initial Approval Date	September 4, 2012
Active Ingredient	bosutinib
Indication	Treatment of adult and pediatric patients greater than or equal to 1 year of age with either newly diagnosed chronic phase Ph+ chronic myelogenous leukemia or chronic, (b) (4) phase Ph+ chronic myelogenous leukemia with resistance or intolerance to prior therapy
Route of Administration	Oral
Dosage Form	Capsule
Strength	(b) (4) 50 mg, and 100 mg
Dose and Frequency	Recommended Dosing Adults patients with newly-diagnosed chronic phase Ph+ CML: 400 mg orally once daily with food. Adult patients with chronic, accelerated, or blast phase Ph+ CML with resistance or intolerance to prior therapy: 500 mg orally once daily with food. Pediatric patients 1 year and older with newly-diagnosed chronic phase Ph+ CML: 300 mg/m² orally once daily with food. Pediatric patients 1 year and older with chronic, (b) (4) phase Ph+ CML with resistance or intolerance to prior therapy: 400 mg/m² orally once daily with food. Dose Escalation Consider dose escalation by increments of 100 mg once daily to a maximum of 600 mg daily in adult patients who do not reach complete hematologic, cytogenetic, or molecular response. Consider dose escalation by increments of 50 mg for those with a BSA <1.1 m² and 100 mg for those with a BSA >1.1 m² once daily to a maximum of 600 mg daily in pediatric patients who do not reach sufficient response after 3 months.
How Supplied	Bosulif Tablets:

Package Configuration	Tablet Strength (mg)	NDC	Tablet Description
120 tablets per bottle	100 mg	0069-0135-01	Yellow, oval, biconvex, film-coated tablets, debossed "Pfizer" on one side and "100" on the other.
30 tablets per bottle	400 mg	0069-0193-01	Orange, oval, biconvex, film-coated tablet debossed with "Pfizer" on one side and "400" on the other.
30 tablets per bottle	500 mg	0069-0136-01	Red, oval, biconvex, film-coated tablets, debossed "Pfizer" on one side and "500" on the other.

Bosulif Capsules:

Package Configuration Count	Capsule Strength (mg)	NDC	Capsule Description
(b) (4)			
30 capsules per bottle	50	0069-0504-30	Size 2 capsule, white body/orange cap with "BOS 50" printed on the body and "Pfizer" printed on the cap in black ink.
150 capsules per bottle	100	0069-1014-15	Size 0 capsule, white

				body/brownish-red cap with "BOS 100" printed on the body and "Pfizer" printed on the cap in black ink.
Storage	Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F)			

APPENDIX B. PREVIOUS DMEPA REVIEWS

On May 19, 2023, we searched for previous DMEPA reviews relevant to this current review using the terms, Bosulif. Our search identified 4 previous reviews^{a,b,c,d}, and we considered our previous recommendations to see if they are applicable for this current review.

^a Ogbonna, Casmir. Label and Labeling Review for Bosulif (NDA 203341/S-013). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2018 03 15. OSE RCM No.: 2017-2543.

^b Ogbonna, Casmir. Label and Labeling Review for Bosulif (NDA 203341/S-010). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2017 08 30. OSE RCM No.: 2017-1431.

^c Rahimi, Leeza. Label and Labeling Review for Bosulif (NDA 203341/S-009). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2017 11 02. OSE RCM No.: 2017-1283.

^d DeFronzo, Kimberly. Label and Labeling Review for Bosulif (NDA 203341). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2012 06 11. OSE RCM No.: 2011-4353.

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,^c along with post market medication error data, we reviewed the following Bosulif labels and labeling submitted by Pfizer Inc.

- Container label received on March 30, 2023 and July 13, 2023
- Prescribing Information (Image not shown) received on March 30, 2023, available from: <\\CDSESUB1\EVSPROD\nda217729\0001\m1\us\lab-0443-16-1a-lab-0639-11-1-combined-annotated.pdf>

F.2 Label and Labeling Images



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^c Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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