CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

219293Orig1s000

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)

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

Date of This Review:	October 16, 2024
Requesting Office or Division:	Division of Hematologic Malignancies 1 (DHM 1)
Application Type and Number:	NDA 219293
Product Name, Dosage Form, and Strength:	Danziten (nilotinib) tablets, 71 mg and 95 mg
Applicant Name:	Azurity Pharmaceuticals, Inc.
FDA Received Date:	October 11, 2024
TTT ID #:	2024-8093-3
DMEPA 2 Safety Evaluator:	Jody Kundreskas, PharmD
DMEPA 2 Team Leader:	Nicole Iverson, PharmD, BCPS

1 PURPOSE OF MEMORANDUM

Azurity Pharmaceuticals, Inc. submitted revised outer carton labeling received on October 11, 2024 for Danziten. We reviewed the revised outer carton labeling for Danziten (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

Azurity Pharmaceuticals, Inc. implemented all of our recommendations and we have no additional recommendations at this time.

[a] Kundreskas, J. Review of Revised Label and Labeling for Danziten (NDA 219293). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2024 OCT 08. TTT ID: 2024-8093-2.

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/s/

JODY K KUNDRESKAS
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NICOLE F IVERSON
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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)

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Date of This Review:	October 8, 2024
Requesting Office or Division:	Division of Hematologic Malignancies 1 (DHM 1)
Application Type and Number:	NDA 219293
Product Name, Dosage Form, and Strength:	Danziten (nilotinib) tablets, 71 mg and 95 mg
Applicant Name:	Azurity Pharmaceuticals, Inc.
FDA Received Date:	October 2, 2024
TTT ID #:	2024-8093-2
DMEPA 2 Safety Evaluator:	Jody Kundreskas, PharmD
DMEPA 2 Team Leader:	Nicole Iverson, PharmD, BCPS

1 PURPOSE OF MEMORANDUM

Azurity Pharmaceuticals, Inc. submitted revised container labels and carton labeling received on October 2, 2024 for Danziten. We reviewed the revised container labels and carton labeling for Danziten (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

Azurity Pharmaceuticals, Inc. implemented all of our recommendations. However, we have an additional recommendation for the Applicant to revise the format of the instructions for how to remove the tablets on the outer carton labeling so that they are presented in sentence case to improve readability.

3 RECOMMENDATIONS FOR AZURITY PHARMACEUTICALS, INC.

A. Outer Carton Labeling

1. The instructions for how to remove the tablets are presented using a mixture of sentence case and title case which decreases readability of the information. We recommend revising the formatting so that the instructions are presented in sentence case. Revise to:

   How to remove the tablets:

   1. Bend and tear through perforation to separate the blister

   2. Peel off the paper layer from the aluminum foil and push the tablet through the foil

[a] Kundreskas, J. Label and Labeling Review for Danziten (NDA 219293). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2024 SEP 26. TTT ID: 2024-8093-1.

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10/08/2024 07:19:04 AM

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10/08/2024 03:16:39 PM

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)

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Date of This Review:	September 26, 2024
Requesting Office or Division:	Division of Hematologic Malignancies 1 (DHM 1)
Application Type and Number:	NDA 219293
Product Name, Dosage Form, and Strength:	Danziten (nilotinib) tablets, 71 mg and 95 mg
Applicant Name:	Azurity Pharmaceuticals, Inc.
FDA Received Date:	September 9, 2024
TTT ID #:	2024-8093-1
DMEPA 2 Safety Evaluator:	Jody Kundreskas, PharmD
DMEPA 2 Team Leader:	Nicole Iverson, PharmD, BCPS

1 PURPOSE OF MEMORANDUM

Azurity Pharmaceuticals, Inc. submitted revised container labels and carton labeling received on September 9, 2024 for Danziten. We reviewed the revised container labels and carton labeling for Danziten (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

In their response, the Applicant clarified that the expiration date format (YYYY-MM) utilizes only numerical characters (i.e., 2024-06). We have no additional concerns relating to expiration date format at this time. However, the revised container labels and carton labeling are still unacceptable from a medication error perspective. The Applicant acknowledged our previous carton labeling recommendation regarding differentiation concerns between the 71 mg and 95 mg strengths and provided updates to the labeling. However, we find their proposed change unacceptable due to the (b) (4) between the proprietary name and the 71 mg strength boxing. We note that the Applicant proposed additional revisions to their container labels and carton labeling to include a graphic at the beginning of the proprietary name which we find detracts from the prominence of the proprietary name. Additionally, the Applicant altered the font color for the established name and dosage form, and we find that the change in font color reduces the prominence of the established name. Lastly, we note the potential for confusion relating to unclear tablet removal instructions on the container label and request the Applicant review and revise the instructions for clarity.

3 RECOMMENDATIONS FOR AZURITY PHARMACEUTICALS, INC.

A. General Comments (Container Labels and Carton Labeling)

1. The placement of the graphic at the beginning of the proprietary name competes with the legibility of the proprietary name, which may lead to misinterpretation of the proprietary name. Placing a logo immediately before, within, or after the proprietary name can lead to misinterpretation because logos may look like an additional letter in the proprietary name or detract from legibility. Delete, move, and/or decrease the prominence of the graphic at the beginning of the proprietary name.
2. As currently presented, the established name lacks prominence on the Principal Display Panel (PDP) due to the (b) (4) font color on the white background. The proprietary name and established name along with the product strength, and warnings or cautionary statements should be the most prominent information on the PDP. We recommend increasing the prominence of the established name. Consider the use of different font type or size, bolding, color, or other means to achieve increased prominence. See Guidance for Industry: Safety Considerations

[a] Kundreskas, J. Label and Labeling Review for Danziten (NDA 219293). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2024 AUG 28. TTT ID: 2024-8093.

for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022).

B. Container Labels

1. The vertically printed instructions "1. Bend & Tear 2. Peel & Push" can be clarified to reduce confusion for end users. As currently presented, it is unclear which part(s) of the packaging must be bent and torn and which part(s) should be peeled and pushed. You may consider providing detailed instructions for tablet removal on the side panel of the outer carton that is opposite to the bar code panel or revising the wording and/or placement of the printed instructions on the container label to clarify the instructions. For example, some blister packages provide written instructions along the perforation line between individual units and within the corner triangle of a unit dose blister, directing users to perform tasks in each area. If revised instructions remain on the container label, ensure that they do not contribute to label clutter.

C. Carton Labeling

1. General Comments (Inner and Outer Carton Labeling)
    a. The 71 mg strength is not clearly differentiated due to the (b) (4) boxing color (b) (4) to the font color used for the proprietary name. Lack of adequate differentiation may contribute to wrong strength errors. Color differentiation is most effective when the color used has no association with a particular feature and there is no pattern in the application of the color scheme. We recommend revising the color scheme of the 71 mg strength such that the strength and the proprietary name appear in their own unique colors (b) (4)

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

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/s/

JODY K KUNDRESKAS
09/26/2024 06:54:49 AM

NICOLE F IVERSON
09/26/2024 11:41:13 AM

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)

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Date of This Review:	August 28, 2024
Requesting Office or Division:	Division of Hematologic Malignancies 1 (DHM 1)
Application Type and Number:	NDA 219293
Product Name, Dosage Form, and Strength:	Danziten (nilotinib) tablets, 71 mg and 95 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant Name:	Slayback Pharma LLC
FDA Received Date:	January 30, 2024 and April 4, 2024
TTT ID #:	2024-8093
DMEPA 2 Safety Evaluator:	Jody Kundreskas, PharmD
DMEPA 2 Team Leader:	Nicole Iverson, PharmD, BCPS

1 INTRODUCTION

As part of the approval process for Danziten (nilotinib) tablets, we reviewed the proposed Danziten Prescribing Information (PI), Medication Guide (MG), container labels, and carton labeling for areas of vulnerability that may lead to medication errors.

1.1 BACKGROUND

Danziten (nilotinib) is a proposed 505(b)(2) drug product and the Listed Drug (LD) is Tasigna (nilotinib), NDA 022068.

2 MATERIALS REVIEWED

This section lists the materials considered for our review of NDA 219293.

Table 1. Materials Considered for this Label and Labeling Review	
Material(s) Reviewed	Appendix Section
Relevant Product Information	A
Labels and Labeling	B
Information Request	D

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We note that the proposed Danziten has the same active ingredient (nilotinib) and route of administration (oral) as the listed drug (LD), Tasigna. However, there are differences as the proposed product will be indicated to treat adult patients with newly diagnosed Philadelphia chromosome positive chronic myeloid leukemia (Ph+ CML) in chronic phase (CP) and adult patients with chronic phase and accelerated phase (AP) Ph+ CML resistant to or intolerant to prior therapy that included imatinib. In addition to the proposed indications for Danziten, the LD is indicated in pediatric patients with newly diagnosed Ph+ CML-CP or resistant or intolerant Ph+ CML-CP and CML-AP. Danziten is not proposed to be indicated in the pediatric population.

The proposed product will be available as 71 mg and 95 mg tablets, whereas Tasigna is approved as 50 mg, 150 mg, and 200 mg capsules. We note that the 50 mg Tasigna strength is indicated for pediatric use, only. We note that the recommended dosage differs for these two products. The recommended dosage of Danziten for newly diagnosed Ph+ CML-CP is 142 mg twice daily and 190 mg twice daily for resistant or intolerant Ph+ CML-CP and CMP-AP. The LD's recommended dosage for these two indications is 300 mg twice daily or 400 mg twice daily, respectively. Due to the different dosage forms, strengths, and recommended dosage, the Division has added a warning and a dosage equivalency table to the Prescribing Information (PI) notifying users that Danziten may not be substitutable with other nilotinib products on a milligram to milligram basis.

Additionally, Danziten is proposed to be supplied in blister packs, whereas Tasigna is supplied in bottles for the 50 mg strength, and blister packs for the 150 mg and 200 mg strengths.

See Appendix A for product characteristics comparison between the LD Tasigna (NDA 022068) and the proposed Danziten (NDA 219293).

We performed a risk assessment of the proposed PI, Medication Guide, container labels, and carton labeling to determine whether there are significant concerns in terms of safety related to preventable medication errors.

We noted that the term (b) (4) is used in the PI and on the carton labeling to describe the inner carton of the proposed product. We requested the Office of Pharmaceutical Quality (OPQ) opine on the use of this term. OPQ stated that the term (b) (4) is not commonly used and assisted us in simplifying the term. As such, we provide a recommendation to the Applicant to clarify this term.

4 CONCLUSION

The proposed Danziten Prescribing Information (PI), Medication Guide (MG), container labels, and carton labeling may be improved to promote safe use of this product from a medication error perspective. We provide the identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error for the Division of Hematologic Malignancies 1 (DHM 1) in Section 5 and for Slayback Pharma LLC in Section 6.

5 RECOMMENDATIONS FOR THE DIVISION OF HEMATOLOGIC MALIGNANCIES 1 (DHM 1)

A. Prescribing Information

1. General Comments
    a. As currently presented, the proprietary name is denoted by the placeholder "TRADENAME". We reference our April 29, 2024 Proprietary Name Request Conditionally Acceptable letter informing you that the proprietary name, Danziten, was found conditionally acceptable. We recommend replacing the placeholder "TRADENAME" with the conditionally acceptable proprietary name, Danziten.

2. Highlights of Prescribing Information
    a. As currently presented, the first bullet under Dosage and Administration contains the recommended dosage for Newly Diagnosed Ph+ CML-CP and for resistant or intolerant Ph+ CML-CP and CML-AP. We recommend displaying the recommended dosage for the different indications as separate bullets to increase readability and to prevent confusion.

3. Section 2 Dosage and Administration
    a. We note under Section 2.1 *Recommended Dosage* that the recommended dosage for the two indications are displayed at the end of the section. To improve readability and to minimize the risk of this important information being overlooked, we recommend relocating this important information to the beginning of Section 2.1 *Recommended Dosage*.
    b. The statement (b) (4) is missing the instruction to

not cut tablets. Failure to provide this instruction may result in drug administration errors. We recommend revising the statement to read "Advise patients to swallow the tablets whole with water and not to cut, crush, or chew the tablets.".

c. Laboratory values are presented with a trailing zero in section 2.5 *Dosage Modifications for Myelosuppression*, which can lead to a tenfold misinterpretation when the decimal point is overlooked (e.g., 1.0 x 10^9/L is read as 10 x 10^9/L). We recommend revising this laboratory value to remove the trailing zeros (e.g., 1 x 10^9/L).

d. Instructions regarding missed doses are present in Section 17, but are missing from Section 2. Add "If a dose of TRADENAME is missed, the patient should take the next scheduled dose at its regular time. The patient should not take two doses at the same time." to Section 2.1.

4. Section 16 How Supplied/Storage and Handling

a. The package type term (b) (4) is unclear. Describing how the product is supplied using unclear terminology may result in confusion on the package contents. We recommend revising the how supplied section as follows:
Outer Carton containing 4 inner carton packs (4x28)
Inner carton containing 2 blister packs (2x14)
Blisters of 14 tablets (1x14)

5. Section 17 Patient Counseling

a. The statement (b) (4) is missing important information. Failure to provide this information may result in drug administration errors. We recommend revising the statement to read "Advise patients to swallow the tablets whole with water and not to cut, crush, or chew the tablets.".

b. The last bullet (b) (4) is duplicative. Remove this bullet.

B. Medication Guide (MG)

1. The statement "Swallow TRADENAME whole with water." is missing important information. Failure to provide this information may result in drug administration errors. Revise the statement to read "Advise patients to swallow the tablets whole with water and not to cut, crush, or chew the tablets.".

6 RECOMMENDATIONS FOR SLAYBACK PHARMA LLC

A. General Comments (Container Labels & Carton Labeling)

1. As currently presented, the expiration date format is presented as YYYY-MM. Two letter abbreviations have led to confusion for the months of March vs May and June vs July. Please clarify whether MM is intended to indicate a 2-letter

abbreviation (e.g., JU) for the month or 2-digit (e.g., 01). FDA recommends 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 forward slash to separate the portions of the expiration date. See Guidance for Industry: Product Identifiers under the Drug Supply Chain Security Act - Questions and Answers (June 2021).

B. Container Labels
    1. There is inadequate differentiation between the 71 mg and 95 mg strengths on the blister labels due to the use of the (b) (4) font color surrounded by (b) (4) boxing for the expression of strength. Lack of adequate differentiation may contribute to wrong strength medication errors. We recommend increasing the visual differentiation between these two strengths. This can be achieved by using different colors, boxing, or some other means to ensure adequate differentiation between the strengths. See Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022).

C. Carton Labeling ((b) (4) and outer carton)
    1. General Comments
        a. There is inadequate differentiation between the 71 mg and 95 mg strengths due to (b) (4) color. Lack of adequate differentiation may contribute to wrong strength medication errors. We recommend using different colors, or some other means to ensure adequate differentiation between the strengths for the carton labeling. See Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022).
        b. It is not immediately clear that the designated strength (i.e., 71 mg and 95 mg) is per single unit (tablet). Failure to clearly express the product strength in milligram per single unit (tablet) may lead to wrong dose errors. We recommend revising the strength statement to make it clear that the designated strength is per unit so there is no confusion as to how much product is contained in a single unit as compared to the total contents of the entire blister card. For example, revise the boxed (b) (4) to state "71 mg per tablet". See Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022).
            i. Additionally, the duplicate statement (b) (4) can be removed to reduce labeling clutter.

c. We note that the statement [redacted] (b) (4) is proposed on the carton labeling. This statement is unnecessary and contributes to clutter. We recommend removing this statement.
d. Most of the information on the Principal Display Panel (PDP) is presented in bold font and appears prominent. Bolding most of the information on the PDP may cause important information to be overlooked. We recommend you consider decreasing the prominence of the "Rx only", "Dosage:", net quantity, and storage statements through debolding.
e. The 2D data matrix barcode is missing from the product identifier. In June 2021, FDA finalized the Guidance for Industry on product identifiers required under the Drug Supply Chain Security Act (DSCSA). The Act requires manufacturers and re-packagers to affix or imprint a product identifier to each package and homogenous case of a product intended to be introduced in a transaction into commerce. The product identifier includes the NDC, serial number, lot number, and expiration date in both a human-readable form and machine-readable (2D data matrix barcode) format. We recommend that you review the guidance to determine if the product identifier requirements apply to your product's labeling. See Guidance for Industry: Product Identifiers under the Drug Supply Chain Security Act - Questions and Answers (June 2021). If you determine that the product identifier requirements apply to your product's labeling, we request you add a place holder to the carton labeling.
f. As currently presented, the statement "Swallow tablets whole. Do not split, chew, or crush tablets" is missing. To minimize wrong administration errors, we recommend adding the following warning statement to the carton labeling: "Swallow tablets whole. Do not cut, crush, or chew tablets.".

2. [redacted] (b) (4) Labeling
a. The net quantity statement is in close proximity to the product strength. From post-marketing experience, the risk of numerical confusion between the strength and net quantity increases when the net quantity statement is located in close proximity to the strength statement. Product selection or dosing errors can occur if the net quantity statement is mistaken for the product strength, leading to under- or over-dosing. We recommend relocating the net quantity statement away from and less prominent than the product strength, such as to the bottom of the PDP. See Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022).
b. The PDP is cluttered. Visually cluttered labels may cause important information to be overlooked. Consider relocating the storage statement to the side or back panel to reduce clutter on the PDP.

c. The package type term [redacted] is unclear. Describing how the product is supplied using unclear terminology may result in confusion on the package contents. We recommend revising the statement, "[redacted] of 2 blister packs (2x14)" to "Carton of 2 blister packs (2x14)".

3. Outer Carton Labeling
   a. The net quantity statement does not appear on the PDP of the outer carton labeling. Failure to include the net quantity statement on the PDP may result in confusion regarding the contents of the carton. We recommend including a net quantity statement (e.g., 112 tablets) on the PDP and ensure it is located away from and less prominent than the product strength. See Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022).
   b. The package type term [redacted] is unclear. Describing how the product is supplied using unclear terminology may result in confusion on the package contents. We recommend revising the statement, "Outer Carton of 4 [redacted] packs (4x28)" to "Outer Carton containing 4 inner carton packs (4x28)".

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. RELEVANT PRODUCT INFORMATION

Table 2 presents relevant product information for Danziten received on January 30, 2024 from Slayback Pharma LLC, and the Listed Drug (LD).

Table 2. Relevant Product Information for Danziten and the Listed Drug (LD).		
Product Name	Danziten	Tasigna[a] (NDA 022068)
Initial Approval Date	N/A	October 29, 2007
Active Ingredient	nilotinib	

[a] Tasigna [Prescribing Information]. Drugs@FDA. U.S. Food and Drug Administration. 02/2024. [cited 2024 MAY 30]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/022068s041lbl.pdf.

Table 2. Relevant Product Information for Danziten and the Listed Drug (LD).		
Product Name	Danziten	Tasigna[a] (NDA 022068)
Indication	• Adult Patients With Newly Diagnosed Ph+ CML-CP TRADENAME is indicated for the treatment of adult patients with newly diagnosed Philadelphia chromosome positive chronic myeloid leukemia (Ph+ CML) in chronic phase. • Adult Patients With Resistant or Intolerant Ph+ CML-CP and CML-AP TRADENAME is indicated for the treatment of adult patients with chronic phase and accelerated phase Philadelphia chromosome positive chronic myelogenous leukemia (Ph+ CML) resistant or intolerant to prior therapy that included imatinib.	• Adult and Pediatric Patients With Newly Diagnosed Ph+ CML-CP Tasigna is indicated for the treatment of adult and pediatric patients greater than or equal to 1 year of age with newly diagnosed Philadelphia chromosome positive chronic myeloid leukemia (Ph+ CML) in chronic phase. • Adult Patients With Resistant or Intolerant Ph+ CML-CP and CML-AP Tasigna is indicated for the treatment of adult patients with chronic phase and accelerated phase Philadelphia chromosome positive chronic myelogenous leukemia (Ph+ CML) resistant or intolerant to prior therapy that included imatinib. • Pediatric Patients With Resistant or Intolerant Ph+ CML-CP and CML-AP Tasigna is indicated for the treatment of pediatric patients greater than or equal to 1 year of age with chronic phase and accelerated phase Philadelphia chromosome positive chronic myeloid leukemia (Ph+ CML) with resistance or intolerance to prior tyrosine-kinase inhibitor (TKI) therapy.
Dosage Form	tablets	capsules
Strength	71 mg and 95 mg	50 mg, 150 mg, and 200 mg
Route of Administration	oral	

Table 2. Relevant Product Information for Danziten and the Listed Drug (LD).		
Product Name	Danziten	Tasigna[a] (NDA 022068)
Dose and Frequency	(b) (4) Dosage in Adult Patients with Newly Diagnosed Ph+ CML-CP: The recommended dosage of TRADENAME is 142 mg orally twice daily with or without food. Dosage in Adult Patients with Resistant or Intolerant Ph+ CML-CP and CML-AP: The recommended dosage of TRADENAME is 190 mg orally twice daily with or without food.	• Recommended Dosage Dose Tasigna twice daily at approximately 12-hour intervals on an empty stomach. No food should be consumed for at least 2 hours before the dose is taken and for at least 1 hour after the dose is taken. Advise patients to swallow the capsules whole with water. For patients who are unable to swallow capsules, the contents of each capsule may be dispersed in 1 teaspoon of applesauce (puréed apple). The mixture should be taken immediately (within 15 minutes) and should not be stored for future use. Tasigna may be given in combination with hematopoietic growth factors, such as erythropoietin or G-CSF if clinically indicated. Tasigna may be given with hydroxyurea or anagrelide if clinically indicated. Dosage in Adult Patients with Newly Diagnosed Ph+ CML-CP: The recommended dosage of Tasigna is 300 mg orally twice daily. Dosage in Adult Patients with Resistant or Intolerant Ph+ CML-CP and CML-AP: The recommended dosage of Tasigna is 400 mg orally twice daily.

Table 2. Relevant Product Information for Danziten and the Listed Drug (LD).		
Product Name	Danziten	Tasigna[a] (NDA 022068)
		Dosage in Pediatric Patients with Newly Diagnosed Ph+ CML-CP or Resistant or Intolerant Ph+ CML-CP and CML-AP: The recommended dosage of Tasigna for pediatric patients is 230 mg/m2 orally twice daily, rounded to the nearest 50 mg dose (to a maximum single dose of 400 mg) (see Table 1). If needed, attain the desired dose by combining different strengths of Tasigna capsules. Continue treatment as long as clinical benefit is observed or until unacceptable toxicity occurs.

Table 2. Relevant Product Information for Danziten and the Listed Drug (LD).		
Product Name	Danziten	Tasigna[a] (NDA 022068)
How Supplied	• TRADENAME (nilotinib) 71 mg tablets are pink, coated, oblong tablets, debossed with "N5" on one side and plain on other side. Outer carton of 4 (b) (4) packs of (4x28), (b) (4) of 2 blister packs (2x14), and Blisters of 14 tablets (1x14) • TRADENAME (nilotinib) 95 mg tablets are yellow, coated, oblong tablets, debossed with "N2" on one side and plain on other side. Outer carton of 4 (b) (4) packs of (4x28), (b) (4) of 2 blister packs (2x14), and Blisters of 14 tablets (1x14) TRADENAME (nilotinib) 71 mg and 95 mg tablets are supplied in blister packs.	• Tasigna (nilotinib) 50 mg capsules are red opaque cap and light yellow opaque body hard gelatin capsules, size 4 with black radial imprint "NVR/ABL." Bottle of 120 capsules • Tasigna (nilotinib) 150 mg capsules are red opaque hard gelatin capsules, size 1 with black axial imprint "NVR/BCR." Carton of 4 blister packs of (4x28) and Blisters of 28 capsules • Tasigna (nilotinib) 200 mg capsules are light yellow opaque hard gelatin capsules, size 0 with the red axial imprint "NVR/TKI." Carton of 4 blister packs of (4x28) and Blisters of 28 capsules Tasigna 50 mg capsules are supplied in bottles and Tasigna 150 mg and 200 mg capsules are supplied in blister packs.
Storage	TRADENAME (nilotinib) tablets should be stored at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F) [see USP Controlled Room Temperature].	Tasigna (nilotinib) capsules should be stored at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F) [see USP Controlled Room Temperature].

Table 2. Relevant Product Information for Danziten and the Listed Drug (LD).		
Product Name	**Danziten**	**Tasigna**[a] (NDA 022068)
Container Closure	TRADENAME (nilotinib) 71 mg and 95 mg tablets are supplied in blister packs (b) (4) (b) (4)	• 50 mg Square HDPE bottles (b) (4) • 150 mg and 200 mg (b) (4) blister packs with (b) (4)

APPENDIX B. LABELS AND LABELING

B.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[b] along with postmarket medication error data, we reviewed the following Danziten labels and labeling submitted by Slayback Pharma LLC.

- Prescribing Information and Medication Guide received on January 30, 2024, available from \\CDSESUB1\EVSPROD\nda219293\0001\m1\us\prescribing-information-label.pdf
- Container label(s) received on January 30, 2024
- Carton labeling received on January 30, 2024
- Product Sample received on April 4, 2024

B.2 Container Labels and Carton Labeling Images

Container labels:

Foil Labels:

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

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

APPENDIX D. INFORMATION REQUEST

FDA Information Request sent on March 11, 2024:

We refer to your submission of NDA 219293 for Danziten (nilotinib) tablets received on January 30, 2024.

We are reviewing your submission and have the following information request.

To facilitate our review, provide 3 full intend-to-market samples of your proposed 71 mg and 95 mg presentations, including the blister labels and carton labeling. Empty or placebo-filled representation of the intend-to-market samples are required to minimize exposure to your product.

Please provide a response by April 2, 2024. If you have a question, please feel free to reach out to me.

Applicant response received via email on April 4, 2024:

Located at: \\CDSESUB1\evsprod\NDA219293\0006

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/s/

JODY K KUNDRESKAS
08/28/2024 07:52:12 AM

NICOLE F IVERSON
08/28/2024 01:06:02 PM

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

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

Memorandum

Date: August 27, 2024

To: Tawanna Stokes, Regulatory Project Manager
Division of Hematologic Malignancies I (DHM1)

From: Samia Alam, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Jina Kwak, Team Leader, OPDP

Subject: OPDP Labeling Comments for TRADENAME (nilotinib) tablets, for oral use

NDA: 219293

Background:

In response to DHM1's consult request dated February 12, 2024, OPDP has reviewed the proposed Prescribing Information (PI) and Medication Guide for the original NDA submission for TRADENAME (nilotinib) tablets, for oral use. As per the RPM's email dated August 16, 2024, carton/container labeling is not available for review.

PI/Medication Guide:

OPDP's review of the proposed PI is based on the draft labeling emailed to OPDP on August 16, 2024, and our comments are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed for the proposed Medication Guide, and comments were sent under separate cover on August 21, 2024.

Thank you for your consult. If you have any questions, please contact Samia Alam at (240) 402-3695 or Samia.Alam@fda.hhs.gov.

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

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/s/

SAMIA ALAM
08/27/2024 10:14:59 AM

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 21, 2024
To:	Tawanna Stokes Regulatory Project Manager **Division of Hematologic Malignancies I (DHM1)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Barbara Fuller, MSN, BSN, RN Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Susan Redwood, MPH, BSN, RN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Samia Alam, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG)
Drug Name (established name):	DANZITEN (nilotinib)
Dosage Form and Route:	tablets, for oral use
Application Type/Number:	NDA 219293
Applicant:	Azurity Pharmaceuticals Inc.

1 INTRODUCTION

On January 30, 2024, Azurity Pharmaceuticals Inc. submitted for the Agency's review a 505 (b)(2) originalNew Drug Application (NDA) 219293 for DANZITEN (nilotinib) tablets. With this application, the applicant seeks approval for the following indications:

- Adult patients with newly diagnosed Philadelphia chromosome positive chronic myeloid leukemia (Ph+ CML) in chronic phase.
- Adult patients with chronic phase (CP) and accelerated phase (AP) Ph+ CML resistant to or intolerant to prior therapy that included imatinib.

The proposed proprietary name, DANZITEN was found conditionally acceptable by the Division of Medication Error Prevention and Analysis (DMEPA) on April 29, 2024.

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 I (DHM1) on March 1, 2024 and February 13, 2024, respectively, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for DANZITEN (nilotinib) tablets, for oral use.

2 MATERIAL REVIEWED

- Draft DANZITEN (nilotinib) tablets MG received on January 30, 2024, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on August 16, 2024.
- Draft DANZITEN (nilotinib) tablets Prescribing Information (PI) received on January 30, 2024, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on August 16, 2024.
- Approved comparator TASIGNA (nilotinib) capsules, for oral use labeling dated September 23, 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 MG we:

- simplified wording and clarified concepts where possible

- ensured that the MG is consistent with the PI
- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the MG is consistent with the approved comparator labeling where applicable.

4 CONCLUSIONS

The MG 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 MG 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 MG.

Please let us know if you have any questions.

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/s/

SUSAN W REDWOOD
08/21/2024 08:13:34 AM

SAMIA ALAM
08/21/2024 08:43:31 AM

BARBARA A FULLER
08/21/2024 08:53:44 AM

LASHAWN M GRIFFITHS
08/21/2024 09:07:35 AM

Memorandum

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

Date: April 10, 2024

From: Interdisciplinary Review Team for Cardiac Safety Studies

Through: Christine Garnett, PharmD
Team Lead, Cardiac Safety IRT, DCN

To: Tawanna Stokes, Regulatory Information Specialist
CDER/OND/OOD/Division of Hematologic Malignancies I (DHMI)

Subject: QT Consult to NDA 219293 (SDN 0001)

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 3/7/2024 regarding your QT-related question. We reviewed the following materials:

- Sponsor's Population Pharmacokinetic Analysis Study Report (NDA219293/ SDN 001)
- Tasigna label (Revised 2/2024 link);
- Sponsor proposed labeling (NDA 219293 / SDN 0001; link);
- Annotated labeling comparison (NDA 219293 / SDN 0001 link);
- Previous IRT review for IND 144071 dated 01/06/23 in DARRTS;
- Meeting minutes for IND 144071 dated 01/19/2023 link;
- (b) (4)
- Previous IRT review of reference listed drug (Tasigna) NDA 22068 dated 02/28/2007; 05/25/2007; 06/13/2007; and 05/20/2010 in DARRTS

1 Responses for the Sponsor

Consult request: We are requesting an IRT consult due to the population PK analyses regarding QT prolongation submitted in NDA 219293 Nilotinib. NDA 219293 is a proposed 505(b)(2) application with the listed drug/basis for the submission: NDA 022068 Tasigna.

IRT's response: We defer to the review division on the acceptability of the modeling assumptions and resulting conclusions of the sponsor's bioequivalence analysis.

Should you move to approval, we have the following labeling recommendation.

Our changes are highlighted (addition, ~~deletion~~). Each section is followed by a rationale for the changes made. Additionally, we are omitting sections 2.4, 2.8, 4.0, 6.0, 7.2, 8 and 17, as we do not have any edits to those sections. Please note that this is a suggestion only and that we defer final labeling decisions to the Division.

WARNING: QT PROLONGATION and SUDDEN DEATHS

See full prescribing information for complete boxed warning.

TRADENAME prolongs the QT interval. Prior to TRADENAME administration and periodically, monitor for hypokalemia or hypomagnesemia and correct deficiencies. (5.2) Obtain ECGs to monitor the QTc at baseline, seven days after initiation, and periodically thereafter, and following any dose adjustments. (5.2, 5.3, 5.7, 5.11)

Sudden deaths have been reported in patients receiving TRADENAME. (5.3) Do not administer TRADENAME to patients with hypokalemia, hypomagnesemia, or long QT syndrome. (4, 5.2)

Avoid use of concomitant drugs known to prolong the QT interval and strong CYP3A4 inhibitors. (7.1, 7.2)

Avoid food 2 hours before and 1 hour after taking the dose. (2.1)

Reviewer's comments: *Food increases TRADENAME bioavailability by 61.7% at the 190 mg dose. Bioequivalence comparisons between TRADENAME and TASGNA were done under fasted conditions. Therefore, we do not agree with the proposed deletion of the food related description in BOX WARNING, i.e., "Avoid food 2 hours before and 1 hour after taking the dose [see Dosage and Administration (2.1)]." . We have added back the food related description to the label. The proposed labeling language for this product is consistent with the "QTc Information in Human Prescription Drug and Biological Product Labeling Guidance for Industry" draft guidance (link).*

5.2 QT Prolongation

TRADENAME has been shown to prolong cardiac ventricular repolarization as measured by the QT interval on the surface electrocardiogram (ECG) in a concentration-dependent manner *[see Adverse Reactions (6.1), Clinical Pharmacology (12.2)]*. Prolongation of the QT interval can result in a type of ventricular tachycardia called torsade de pointes, which may result in syncope, seizure, and/or death. Electrocardiograms should be performed at baseline, 7 days after initiation of TRADENAME, and periodically as clinically indicated and following dose adjustments *[see Dosage and Administration (2.4) and Warnings and Precautions (5.11)]*.

TRADENAME should not be used in patients who have hypokalemia, hypomagnesemia, or long QT syndrome. Before initiating TRADENAME and periodically, test electrolyte, calcium, and magnesium blood levels. Hypokalemia or hypomagnesemia must be corrected prior to initiating TRADENAME and these

electrolytes should be monitored periodically during therapy *[see Warnings and Precautions (5.11)]*.

Significant prolongation of the QT interval may occur when TRADENAME is inappropriately taken with *food and/or* strong CYP3A4 inhibitors and/or medicinal products with a known potential to prolong QT. Therefore, *coadministration with food must be avoided and* concomitant use with strong CYP3A4 inhibitors and/or medicinal products with a known potential to prolong QT should be avoided *[see Dosage and Administration (2.1), Drug Interactions (7.1, 7.2)]*. The presence of hypokalemia and hypomagnesemia may further prolong the QT interval *[see Warnings and Precautions (5.7, 5.11)]*.

Reviewer's comments: *Food increases TRADENAME bioavailability by 61.7% at the 190 mg dose. Bioequivalence comparisons between TRADENAME and TASGNA were done under fasted conditions. Therefore, we do not agree with the proposed deletion of the food related description in section 5.2., of the label. We have added back the food related description to the label. The proposed labeling language for this product consistent with the "QTc Information in Human Prescription Drug and Biological Product Labeling Guidance for Industry" draft guidance (link)*

12.2 Pharmacodynamics

Cardiac Electrophysiology

Nilotinib is associated with concentration-dependent QT prolongation. At a dose of Nilotinib 400 mg *(equivalent to 190 mg TRADENAME)* twice daily given without food in healthy subjects, the maximum mean placebo-adjusted QTcF changes were 10.4 msec (90% CI: 2.85, 18.0). After a single dose of Nilotinib 800 mg (*equivalent to 380 mg TRADENAME,* two times the maximum approved recommended dosage) given with a high fat meal to healthy subjects, the maximum mean placebo-adjusted QTcF changes were) 18.0 msec (90% CI: 9.65, 25.8)~~. *Peak plasma concentrations in the QT study were 26% lower than or comparable with those observed in patients enrolled in the single-arm study*~~ [see Boxed Warning, Warnings and Precautions (5.2), Adverse Reactions (6.1)]. ~~*No new significant QT findings were observed in healthy subject studies with single doses of TRADENAME given with or without food. Throughout the 14 PK studies there were no QT prolongation events associated with TRADENAME.*~~

Reviewer's comment: *We propose to use labeling language for this product consistent with the "QTc Information in Human Prescription Drug and Biological Product Labeling Guidance for Industry" draft guidance (link).*

2 Internal Comments for the Division

N/A

3 BACKGROUND

3.1 Product Information

Nilotinib is an inhibitor of the BCR-ABL kinase that inhibits BCR-ABL-mediated proliferation of leukemic cell lines. The applicant seeks approval for nilotinib tablets via the 505(b)(2) pathway. The reference listed drug (RLD) is Tasigna (nilotinib) capsules, which is marketed in 50 mg, 150 mg, and 200 mg strengths. The to-be-marketed nilotinib formulation is stated to exhibit solubility and dissolution characteristics which permit administration of a lower nilotinib dose and with different instructions for coadministration with food.

The to-be-marketed nilotinib has been developed in 71 mg and 95 mg strengths for administration without regard to fasting status for the treatment of adult patients with newly diagnosed Philadelphia chromosome positive chronic myeloid leukemia (Ph+ CML) in chronic phase and adult patients with chronic phase (CP) and accelerated phase (AP) Ph+ CML resistant to or intolerant to prior therapy that included imatinib. The proposed dose of nilotinib tablets is as follows:

- Newly diagnosed Ph+ CML-CP: 142 mg orally BID.
- Resistant or intolerant Ph+ CML-CP and CML-AP: 190 mg orally BID.

The RLD is indicated for use in adults and pediatric patients, as follows:

- Adult and pediatric patients greater than or equal to 1 year of age with newly diagnosed Philadelphia chromosome positive chronic myeloid leukemia (Ph+ CML) in chronic phase.
- Adult patients with chronic phase (CP) and accelerated phase (AP) Ph+ CML resistant to or intolerant to prior therapy that included imatinib.
- Pediatric patients greater than or equal to 1 year of age with Ph+ CML-CP and CML-AP resistant or intolerant to prior tyrosine-kinase inhibitor (TKI) therapy.

The RLD is dosed on an empty stomach as follows:

- Recommended Adult Dose:
    - Newly diagnosed Ph+ CML-CP: 300 mg orally BID.
    - Resistant or intolerant Ph+ CML-CP and CML-AP: 400 mg orally BID.
- Recommended Pediatric Dose:
    - Newly Diagnosed Ph+ CML-CP or Ph+ CML-CP and CML-AP resistant or intolerant to prior TKI therapy: 230 mg/m2 orally BID, rounded to the nearest 50 mg dose (to a maximum single dose of 400 mg).

The current consultation is in follow up to a previous consultation from the review division (dated December 6, 2022) which was addressed in an IRT review dated January 6, 2023. At that time, the review division asked if the IRT concurred with the sponsor's assessment that nilotinib Tablets do not represent an increased risk of QT prolongation relative to Tasigna.

The IRT's response was to defer to the OCP review team on whether comparing the estimated steady-state PK modeling for nilotinib tablets and Tasigna by applying (b) (4) is sufficient to demonstrate that nilotinib tablets does not result in significantly higher exposures compared to Tasigna. The risk of QTc prolongation with nilotinib has been previously characterized for Tasigna in a TQT study in healthy volunteers at lower concentrations and in patients at higher doses. As long as and Cmax,ss from the nilotinib tablets at the highest therapeutic dose is not higher than the listed product, Tasigna, the sponsor can extend the previously characterized concentration-QT relationship to predict the QT effects. The review also noted that the IRT does not agree to any comparative statements about QT safety unless a comparative QTc study has been conducted.

According to the meeting minutes dated January 19, 2023, the reviewing division communicated the following to the sponsor:

> (a) You will need to address the issue of higher Cmax regarding QT prolongation and other adverse events and provide justification on how the higher Cmax would not be a safety concern.
>
> (b) We do not agree with using the (b) (4) to estimate the concentrations of Nilotinib Tablets at steady state. We recommend using a population PK (popPK) modeling approach using all available data from clinical studies conducted with the to-be-marketed formation to characterize the PK of Nilotinib Tablet and simulate the concentrations at steady state. The PK nonlinearity can be evaluated according to drug concentration change (e.g., drug concentration on CL in the model structure) to improve the accuracy of Cmax estimation following a single dose administration and the reliability for steady state PK prediction. Submit your proposed popPK plan for the Agency to review.
>
> (c) Regarding reliance on previous characterization of QT effects of Tasigna, the previously characterized relationship between nilotinib concentration and QT prolongation following Tasigna administration can be used only to estimate the change in QT based on Nilotinib Tablet Cmax at steady state. However, we do not agree to any comparative statements about QT safety unless a comparative QT study has been conducted.

According to the January 19, 2023, meeting minutes, the sponsor stated they would submit the population PK modeling analysis plan for Agency review. The population PK model would include data from all studies using the to-be-marketed formulation under different meal conditions. FDA noted that the simulated Cmax at steady state from an adequate population PK model can be used to characterize the QT effects of Nilotinib Tablet based on the characterized relationship between concentration and QT for Tasigna. If the model simulations showed higher Cmax at steady state of nilotinib tablet compared to Tasigna, the Sponsor would need to consider the impact of a higher Cmax on QT prolongation and other adverse events and provide justification for how a higher Cmax (outside the 80% to 125 % BE criteria) would not be a safety concern. The Sponsor agreed to provide this justification.

The current submission provides a population PK modeling report which offers a different approach to calculate bioequivalence between the reference product and the to-be-marketed product.

3.2 Sponsor's position related to the question

Based on the observed higher upper bound CI for Cmax marginally outside 125%, Agency has recommended to carry out PK modelling and analysis to evaluate the effect of various covariates on the PK, assess and compare the steady state concentrations against the reference listed drug.

The sponsor developed a population pharmacokinetic (PPK) model for nilotinib using all available PK study data to assess the impact of potential covariates on the PK of Nilotinib tablets and listed drug Tasigna®. The sponsor predicted nilotinib exposure under multiple food conditions and dosing regimens and summarized the distribution of key exposure metrics (i.e., steady-state Cmax, Cmin and AUC). The sponsor compared steady state PK following an overnight fasted dose of Nilotinib Tablet and Tasigna® at high and low therapeutic doses.

Based on the dose finding studies and due to the increased relative bioavailability of Nilotinib Tablets as compared to Tasigna, doses of 190 mg and 142 mg of Nilotinib Tablets were selected versus corresponding doses of 400 mg and 300 mg of Tasigna. For these reasons, the following simulation scenarios were considered for the BE testing:

A. 190 mg Nilotinib Tablets and 400 mg Tasigna, both under BID fasted conditions.

B. 142 mg Nilotinib Tablets and 300 mg Tasigna, both under BID fasted conditions.

Table 1 shows the results of the sponsor's analysis of simulated data.

Table 1. Geometric Mean Ratio and Anova Analysis for the BE Testing of Nilotinib Tablets vs Tasigna (N=50)

Scenario (N=50)	Exposure	GMR [90%CI]	Anova p-value [90%CI]
190 mg Nilotinib Tablets vs 400 mg Tasigna	AUCss (ng*h/mL)	1.04 [0.949,1.17]	0.536 [0.0371,0.961]
	Cmaxss (ng/mL)	1.06 [0.97,1.2]	0.388 [0.00918,0.925]
	Cminss (ng/mL)	1.02 [0.89,1.18]	0.478 [0.0646,0.957]
142 mg Nilotinib Tablets vs 300 mg Tasigna	AUCss (ng*h/mL)	1.03 [0.95,1.13]	0.535 [0.0719,0.959]
	Cmaxss (ng/mL)	1.06 [0.97,1.17]	0.411 [0.0358,0.891]
	Cminss (ng/mL)	1 [0.888,1.15]	0.611 [0.103,0.975]

Source: nilotinib-pksim-20230825-fasted-142mg-v2.Rmd; nilotinib-pksim-20230825-fasted-190mg-v2.Rmd

Abbreviations: CI = confidence interval; GMR = geometric mean ratio.

The key goal of the simulations was to assess and compare the pharmacokinetics of test (Tablets) and reference (Tasigna) nilotinib formulations at steady state. As discussed in the previous paragraph, the final population PK model was deemed suitable for this purpose and used to predict concentration time profiles of nilotinib at steady state following BID dosing. Results of the simulations show that BE criteria are met for all exposure metrics (AUCss, Cmaxss and Cminss) and for all evaluated scenarios under fasted conditions. Nilotinib Tablets at a 142 mg or 190 mg dose is predicted to be bioequivalent to Tasigna at a 300 mg or 400 mg dose respectively.

Reviewer's Comment: *The appropriateness of the sponsor's model to assess bioequivalence between the sponsor's product and the reference product can be more appropriately performed by the reviewing division. Should the to-be-marketed nilotinib product be deemed bioequivalent to Tasigna, we have provided suggested labeling.*

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 cderdcrpqt@fda.hhs.gov

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/s/

LESLIE A KENNA
04/10/2024 12:57:06 PM

ELIFORD N KITABI
04/10/2024 02:58:55 PM

CHRISTINE E GARNETT
04/10/2024 03:08:57 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: 4/3/2024

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 219293

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

Rationale

ZenRise, Hyderabad: The Office of Regulatory Affairs (ORA) conducted an inspection for the clinical site in January 2023. The inspection was conducted under the following submissions: ANDAs Non-responsive

The following objectionable conditions were observed:

- Failure to conduct clinical bioavailability/bioequivalence studies in accordance with Good Clinical Practices. Specifically:
  - Failure to report all AEs.
  - Failure to maintain accurate and complete records.
  - Inaccurate language translation, errors, and omissions on informed consent forms.
  - Identification labels were placed over test and reference products' original labels, obscuring the strength, lot number, expiration date, and storage conditions. Additionally, test and reference bottles contained two different study ID numbers because they were transferred from another CRO.

After review of the observations and the written response from the site, OSIS concluded that the objectionable conditions had no impact on data integrity or subject safety and that data from the reviewed studies were reliable. (Final OSIS Review - January 2023).

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

OSIS concluded that data from the reviewed studies were reliable.

Site

Facility Type	Facility Name	Facility Address
Clinical	ZenRise Clinical Research Pvt., Ltd.	Plot No. 201, Mythri Nagar, Madinaguda, Miyapur, Hyderabad, Telangana, India
Analytical		(b) (4)

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/s/

WENDY NG
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