CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

217514Orig1s000

OTHER REVIEW(S)

PMR Fulfillment – Cross-Disciplinary Team Leader Memorandum

Application Type (NDA/BLA)	NDA and sNDA
Application Number(s)/ supplement number	217514 and 217513 202806 S-25 and 204114 S-25
Received Date	August 24, 2022
PDUFA Goal Date	May 24, 2023
Division/Office	Office of Oncologic Diseases/Division of Oncology 2
Clinical Reviewer	Michael Barbato, Jeannette Nashed
Team Leader	Diana Bradford
Signatory	Nicole Drezner
Product: Established Name (Trade name)	Trametinib (MEKINIST) tablets, for oral use; 0.5 mg, 2 mg and powder for oral solution; 4.7 mg Dabrafenib (TAFINLAR) capsules, for oral use; 50 mg, 75 mg and tablets for oral suspension; 10 mg
Applicant	Novartis Pharmaceuticals Corporation

Executive Summary:

On June 22, 2022, FDA granted accelerated approval to dabrafenib in combination with trametinib (NDA 202806 S-22 and 204114 S-22) for the treatment of adult and pediatric patients 6 years of age and older with unresectable or metastatic solid tumors with BRAF V600E mutation who have progressed following prior treatment and have no satisfactory alternative treatment options. The following post-marketing requirements were included in the approval letters:

Dabrafenib (202806)

- 4298-2 Develop age appropriate pediatric formulations (dabrafenib dispersible tablets for oral suspension, and trametinib powder for oral solution), and evaluate these in Study CDRB436G2201 ("Phase II Open-label Global Study to Evaluate the Effect of Dabrafenib in Combination With Trametinib in Children and Adolescent Patients With BRAF V600 Mutation Positive Low Grade Glioma (LGG) or Relapsed or Refractory High Grade Glioma (HGG)").
  Final Report Submission: 10/2022

- 4298-3 Conduct Study CDRB436G2201 ("Phase II Open-label Global Study to Evaluate the Effect of Dabrafenib in Combination With Trametinib in Children and Adolescent Patients With BRAF V600 Mutation Positive Low Grade Glioma (LGG) or Relapsed or Refractory High Grade Glioma [HGG]") to confirm safety and efficacy in pediatric

patients with glioma one year of age and above.
Final Report Submission: 10/2022

Trametinib (204114)

- 4297-2 Develop age appropriate pediatric formulations (dabrafenib dispersible tablets for oral suspension, and trametinib powder for oral solution), and evaluate these in Study CDRB436G2201 ("Phase II Open-label Global Study to Evaluate the Effect of Dabrafenib in Combination With Trametinib in Children and Adolescent Patients With BRAF V600 Mutation Positive Low Grade Glioma (LGG) or Relapsed or Refractory High Grade Glioma (HGG)").
  Final Report Submission: 10/2022
- 4297-3 Conduct Study CDRB436G2201 ("Phase II Open-label Global Study to Evaluate the Effect of Dabrafenib in Combination With Trametinib in Children and Adolescent Patients With BRAF V600 Mutation Positive Low Grade Glioma (LGG) or Relapsed or Refractory High Grade Glioma [HGG]") to confirm safety and efficacy in pediatric patients with glioma one year of age and above.
  Final Report Submission: 10/2022

On August 17, 2022, the Applicant submitted NDA 217513 (trametinib) and NDA 217514 (dabrafenib) for new formulations of trametinib (oral solution) and dabrafenib (tablets for oral suspension) appropriate for patients who cannot swallow pills. The Applicant's proposed indication was for the treatment of pediatric patients 1 year of age and older with low-grade glioma (LGG) with a BRAF V600E mutation who require systemic therapy. On August 24, 2022, the Applicant submitted NDA 202806 S-25 and NDA 204114 S-25, as supplements to the NDAs for dabrafenib and trametinib, respectively, with the intent to allow the indication stated above to be granted for the existing solid dosage forms in addition to the new dosage forms. Dabrafenib is administered orally, twice daily, and trametinib is administered orally, once daily; the recommended dosages for trametinib and dabrafenib are based on age and body weight. The supplementary applications rely entirely upon data submitted to the new NDAs, 217513 and 217514. The review team has recommended regular approval for NDAs 217513 and 217514 and the associated efficacy supplements to the existing NDAs.

Assessment and Recommended Regulatory Action

The review team considers that PMRs 4297-2 and 4298-2 have been fulfilled by the submission of NDAs 217513 and 217513, applications for new age-appropriate pediatric formulations of dabrafenib and trametinib.

The study report for Study CDRB436G2201 was submitted to NDAs 217513 and 217514 (and associated supplements 202806 S-25 and 204114 S-25) to establish the safety and efficacy of dabrafenib in combination with trametinib in patients pediatric patients with glioma (specifically patients with LGG with BRAF V600E mutations) one year of age and above. Therefore, the review team considers that PMRs 4297-3 and 4298-3 requiring the conduct of the study have been fulfilled. In order to obtain results of the final analysis of overall survival from Study G2201 and obtain longitudinal analyses to understand any impact of treatment with dabrafenib and trametinib on visual acuity (an important functional outcome for patients with LGG involving the optic pathway), a post-marketing commitment will be issued with the approval letters for NDAs NDAs 217513 and 217514 (and associated supplements 202806 S-25 and 204114 S-25). The post-marketing commitment is provided below:

> Complete Study CDRB436G2201, entitled "Phase II open-label global study to evaluate the effect of dabrafenib in combination with trametinib in children and adolescent patients with BRAF V600 mutation positive Low Grade Glioma (LGG) or relapsed or refractory High Grade Glioma (HGG)", and provide the final analysis for overall survival (OS) and progression free survival once all patients with LGG have been followed for at least 2 years. Include an analysis of change in visual acuity over the course of treatment with dabrafenib and trametinib for patients who enrolled on the study due to impaired vision.

Please refer to the Approval letters for the post-marketing requirements and commitments for NDAs NDAs 217513 and 217514 (and associated supplements 202806 S-25 and 204114 S-25). The Approval letters will state that the PMRs PMRs 4297-3 and 4298-3 and 4297-2 and 4298-2 have been fulfilled.

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/s/

DIANA L BRADFORD
03/16/2023 11:29:25 AM

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:	March 14, 2023
Requesting Office or Division:	Division of Oncology 2 (DO2)
Application Type and Number:	NDA 217514
Product Name, Dosage Form, and Strength:	Tafinlar (dabrafenib) tablets for oral suspension, 10 mg
Applicant/Sponsor Name:	Novartis Pharmaceuticals Corporation
TTT ID #:	2022-923-3
DMEPA 2 Safety Evaluator:	Janine Stewart, PharmD
DMEPA 2 Team Leader:	Ashleigh Lowery, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label and carton labeling received on March 14, 2023 for Tafinlar. Division of Oncology 2 (DO2) requested that we review the revised container label and carton labeling for Tafinlar (Appendix A) to determine if it is acceptable from a medication error perspective. In addition, based on administration considerations by DO2 to align the Tafinlar labeling with that of the co-administered product, Mekinist (trametinib) for oral solution, we provided a related recommendation to add language to the Tafinlar carton labeling to limit administration to caregivers only in a previous label and labeling memorandum.[a]

2 DISCUSSION

In their emailed response[b] to our recommendation to add the statement "For administration by caregivers only" to appear under the strength statement to align the Tafinlar labeling with that of the co-administered product, Mekinist (trametinib) for oral solution, Novartis referred us to their Human Factors Engineering Summary Report for Tafinlar 10 mg tablet for oral suspension (Sequence No. 0032). Based on the results from the adult patient user group, Novartis did not

[a] Stewart, J. Label and Labeling Memorandum for Tafinlar (NDA 217514). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2023 MAR 10. TTT ID No.: 2022-923-2.
[b] Zhu. C. Email RE: Tafinlar (dabrafenib) NDA 217514. Novartis Pharmaceuticals Corporation 2023 MAR 13 2023.

identify any risk that would warrant restricting administration to caregivers only. Novartis expressed concern that adding the statement to limit administration to caregivers was not needed and would be restrictive given the different dosing schemes for Tafinlar vs. Mekinist (BID vs. Qday) where the products are not always administered simultaneously. Follow-up email discussions with the review team found the rationale provided by Novartis to be reasonable and reached agreement that the statement limiting administration to caregivers was not necessary.

3 CONCLUSION

We have no additional recommendations at this time.

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JANINE A STEWART
03/14/2023 05:59:05 PM

ASHLEIGH V LOWERY
03/15/2023 10:39:03 AM

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:	March 10, 2023
Requesting Office or Division:	Division of Oncology 2 (DO2)
Application Type and Number:	NDA 217514
Product Name, Dosage Form, and Strength:	Tafinlar (dabrafenib) tablets for oral suspension, 10 mg
Applicant/Sponsor Name:	Novartis Pharmaceuticals Corporation
TTT ID #:	2022-923-2
DMEPA 2 Safety Evaluator:	Janine Stewart, PharmD
DMEPA 2 Team Leader:	Ashleigh Lowery, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label and carton labeling received on March 1, 2023 for Tafinlar. Division of Oncology 2 (DO2) requested that we review the revised container label and carton labeling for Tafinlar (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.[a]

2 CONCLUSION

Upon further consideration of the use of this product, we provide an update to the previous memorandum[b] to include on the principal display panel (PDP) of the carton labeling a statement to limit the administration of this product to caregivers.

3 RECOMMENDATIONS FOR NOVARTIS PHARMACEUTICALS CORPORATION

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

[a] Stewart, J. Label and Labeling Review for Tafinlar (NDA 217514). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2023 FEB 27. TTT ID No.: 2022-923.
[b] Stewart, J. Label and Labeling Review for Tafinlar (NDA 217514). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2023 MAR 09. TTT ID No.: 2022-923-1.

A. On the principal display panel (PDP) of the carton labeling, add the statement "For administration by caregivers only" to appear under the strength statement. We recommend this revision to align the Tafinlar labeling with that of the co-administered product, Mekinist (trametinib) for oral solution.
    a. To reduce crowding of information on the PDP, replace the "Contents:…" list with the quantity statement "210 tablets".
    b. Relocate the "Contents:…" list from the PDP to appear on a side panel with increased prominence as space allows.

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JANINE A STEWART
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ASHLEIGH V LOWERY
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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)

Date of This Memorandum:	March 10, 2023
Requesting Office or Division:	Division of Oncology 2 (DO2)
Application Type and Number:	NDA 217513
Product Name, Dosage Form, and Strength:	Mekinist (trametinib) for oral solution, 4.7 mg per bottle (0.05 mg/mL when reconstituted)
Applicant/Sponsor Name:	Novartis Pharmaceuticals Corporation
TTT ID #:	2022-926-1
DMEPA 2 Safety Evaluator:	Janine Stewart, PharmD
DMEPA 2 Team Leader:	Ashleigh Lowery, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label and carton labeling received on March 6, 2023 for Mekinist. Division of Oncology 2 (DO2) requested that we review the revised container label and carton labeling for Mekinist (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.[a]

2 CONCLUSION

Upon further consideration, we provide an update to the revised administration statement on the principal display panel (PDP) of the carton labeling. In addition, the revised carton labeling may be improved by ensuring all product identifier requirements are met for product tracking and tracing purposes.

3 RECOMMENDATIONS FOR NOVARTIS PHARMACEUTICALS CORPORATION

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

[a] Stewart. J. Label and Labeling Review for Mekinist (NDA 217513). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2023 Feb 23. TTT ID No.: 2022-926.

A. On the PDP, revise the statement "[redacted (b) (4)]. " to read "For administration by caregivers only. We recommend this revision because the term "caregiver' is broad enough to encompass [redacted (b) (4)] who will administer Mekinist [redacted (b) (4)]

B. In June 2021, FDA finalized guidance on product identifiers required under the Drug Supply Chain Security Act.1 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 guidance to determine if the product identifier requirements apply to your product's labeling.

[1]The guidance is available from: https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm621044.pdf

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JANINE A STEWART
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ASHLEIGH V LOWERY
03/10/2023 04:03:47 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)

Date of This Memorandum:	March 6, 2023
Requesting Office or Division:	Division of Oncology 2 (DO2)
Application Type and Number:	NDA 217514
Product Name, Dosage Form, and Strength:	Tafinlar (dabrafenib) tablets for oral suspension, 10 mg
Applicant/Sponsor Name:	Novartis Pharmaceuticals Corporation
TTT ID #:	2022-923-1
DMEPA 2 Safety Evaluator:	Janine Stewart, PharmD
DMEPA 2 Team Leader:	Ashleigh Lowery, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label and carton labeling received on March 1, 2023 for Tafinlar. Division of Oncology 2 (DO2) requested that we review the revised container label and carton labeling for Tafinlar (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.[a]

2 CONCLUSION

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

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[a] Stewart, J. Label and Labeling Review for Tafinlar (NDA 217514). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2023 FEB 27. TTT ID No.: 2022-923.

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03/06/2023 09:47:11 PM

ASHLEIGH V LOWERY
03/08/2023 01:39:40 PM

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

PATIENT LABELING REVIEW

Date:	February 28, 2023
To:	Raniya Al-Matari, PhD Regulatory Health Project Manager **Division of Oncology II (DO2)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Sharon R. Mills, BSN, RN, CCRP Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Andrew Nguyen, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Instructions for Use (IFU)
Drug Name (established name); Dosage Form and Route; Application Type/Number:	• MEKINIST (trametinib) tablets, for oral use, NDA 204114/S-025 • MEKINIST (trametinib) for oral solution, NDA 217513 • TAFINLAR (dabrafenib) tablets for oral suspension, NDA 202806/S-025 • TAFINLAR (dabrafenib) capsules, for oral use, NDA 217514
Applicant:	Novartis Pharmaceuticals Corporation

1 INTRODUCTION

On August 17, 2022, Novartis Pharmaceuticals Corporation submitted for the Agency's review two original New Drug Applications (NDAs): NDA 217513 MEKINIST (trametinib) for oral solution and NDA 217514 TAFINLAR (dabrafenib) tablets for oral suspension. The proposed labeling for MEKINIST for oral solution will share combined labeling with the approved dosage form for MEKINIST (trametinib) tablets under NDA 204114. The proposed labeling for TAFINLAR (dabrafenib) tablet for oral suspension will share combined labeling with the approved dosage form TAFINLAR (dabrafenib) capsules under NDA 202806.

On August 24, 2022, Novartis Pharmaceuticals Corporation submitted for the Agency's review two Prior Approval Supplements (PASs)- Efficacy to their approved New Drug Applications, NDA 204114/S-025 for MEKINIST (trametinib) tablets and NDA 202806/S-025 for TAFINLAR (dabrafenib) capsules. As stated in the Applicant's cover letter, "Based on post-meeting addendum comments issued in the meeting minutes on April 13, 2022, FDA recommended that Novartis submit two efficacy supplemental NDAs (one for a dabrafenib solid formulation and one for trametinib solid formulation) for the first-line pediatric LGG indication."

The proposed new indication for MEKINIST (trametinib) is as follows: in combination with dabrafenib, for the treatment of pediatric patients 1 year of age and older with low-grade glioma (LGG) with BRAF V600E mutation who require systemic therapy.

The proposed new indication for TAFINLAR (dabrafenib) is as follows: in combination with trametinib, for the treatment of pediatric patients 1 year and older with low-grade glioma (LGG) with BRAF V600E mutation who require systemic 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 the following requests by the Division of Oncology II (DO2):

- Request dated August 31, 2022, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) and Instructions for Use (IFU) for MEKINIST (trametinib) for oral solution and TAFINLAR (dabrafenib) tablets for oral suspension.
- Request dated September 30, 2022, for DMPP and OPDP to review the Applicant's proposed PPI and IFU for MEKINIST (trametinib) tablets, for oral use and TAFINLAR (dabrafenib) capsules, for oral use.

DMPP and OPDP completed a collaborative review of the PPI for MEKINIST (trametinib) for oral solution and MEKINIST (trametinib) tablets, and the MG for TAFINLAR (dabrafenib) tablets and TAINLAR (dabrafenib), capsules for oral use on January 11, 2023. At that time, review of the newly proposed IFUs for both products were deferred for completion at a later date, once the Division of Medication Errors Prevention and Analysis (DMEPA) provides input regarding the Human Factors issues.

2 MATERIAL REVIEWED

- Draft MEKINIST (trametinib) tablets and MEKINIST (trametinib) for oral solution IFU received on August 17, 2022, revised on December 1, 2022, and revised throughout the review cycle and accessed from SharePoint by DMPP and OPDP February 16, 2023.
- TAFINLAR (dabrafenib) capsules and tablets for oral suspension IFU received on August 17, 2022, revised on December 1, 2022 and February 17, 2023, and accessed from SharePoint by DMPP and OPDP on February 22, 2023.
- Draft MEKINIST (trametinib) tablets and MEKINIST (trametinib) for oral solution Prescribing Information (PI), and TAFINLAR (dabrafenib) capsules and tablets for oral suspension PI received on August 17, 2022, revised by the Review Division throughout the review cycle, and accessed from SharePoint by DMPP and OPDP on February 16, 2023.
- Approved MEKINIST (trametinib) tablets labeling dated June 22, 2022.
- Approved TAFINLAR (dabrafenib) capsules labeling dated June 22, 2022.

3 REVIEW METHODS

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

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

In our collaborative review of the IFUs we:

- simplified wording and clarified concepts where possible
- ensured that the IFUs are consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the IFUs are free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the IFUs meet the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The IFUs are 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 IFUs are 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 and MG.

Please let us know if you have any questions.

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ANDREW D NGUYEN
02/28/2023 12:50:01 PM

LASHAWN M GRIFFITHS
02/28/2023 12:58:56 PM

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

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Date of This Review:	February 23, 2023
Requesting Office or Division:	Division of Oncology 2 (DO2)
Application Type and Number:	NDA 217514
Product Name, Dosage Form, and Strength:	Tafinlar (dabrafenib) tablets for oral suspension, 10 mg
Product Type:	Combination Product
Device Constituent:	Oral Dosing Cup
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Novartis Pharmaceuticals Corporation,
FDA Received Date:	August 17, 2022, November 21, 2022, November 23, 2022, December 1, 2022, and January 9, 2023
TTT ID #:	2022-923
DMEPA 2 Safety Evaluator:	Janine Stewart, PharmD
DMEPA 2 Team Leader:	Ashleigh Lowery, PharmD

1 REASON FOR REVIEW

Novartis Pharmaceuticals Corporation (Novartis) has submitted a New Drug Application (NDA) for Tafinlar® (dabrafenib) tablet for oral suspension (NDA 217514) for use in combination with Mekinist® (trametinib) powder for oral solution for a new indication in the treatment of pediatric patients 1 year of age. Both are proposed products developed as age-appropriate pediatric oral formulations in response to postmarketing requirements.

As part of the approval process for Tafinlar (dabrafenib) tablets for oral suspension the Division of Oncology 2 (DO2) requested that we review the proposed Prescribing Information (PI), Medication Guide (MG), Instructions for Use (IFU), container label, and carton labeling for areas of vulnerability that may lead to medication errors.

Mekinist powder for oral solution (NDA 217513) is reviewed under a separate cover.

1.1 REGULATORY HISTORY

Tafinlar (dabrafenib) was originally approved on May 29, 2013 under NDA 202806 and is currently available as 50 mg and 75 mg capsules. As described above, Novartis submitted NDA 217514 for a new tablet for oral suspension formulation of Tafinlar® for a new indication in combination with trametinib for the treatment of pediatric patients 1 year of age and older with low-grade glioma with a BRAF V600E mutation who require systemic therapy.

Novartis proposes to revise the approved PI and MG for Tafinlar to include both Tafinlar capsules (NDA 202806) and Tafinlar tablets for oral suspension (NDA 217514) in a shared PI.

This submission is cross-referenced between Tafinlar NDAs 217514 (tablet for oral suspension) and 202806/S-025 (capsules), and Mekinist NDAs 217513 (powder for oral solution) and 204114/S-025 (tablets).

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
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

Table 1. Materials Considered for this Review	
Material Reviewed	Appendix Section (for Methods and Results)

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

We performed a risk assessment of the Tafinlar PI, MG, IFU, container label, and carton labeling to identify areas of vulnerability that may lead to medication errors and other areas of improvement.

Prescribing Information and Medication Guide

We reviewed the Applicant's proposed revisions to the Highlights (HL) and Full prescribing information (PI) for the proposed indication for Low Grade Glioma (LGG) in patients 1 year and older, the addition of the newly proposed dosage form and strength, as well as the recommended dosage table, preparation, and administration instructions using the proposed 10 mg tablets for oral suspension.

We note Section 2.2 can be improved by adding subheadings to distinguish the pediatric (age 6 and older) and adult dosing information for the Tafinlar capsules from the pediatric (1 year and older) dosing information for Tafinlar tablets for oral suspension.

We also note the omission of information regarding how to manage a missed dose or a vomited dose in Section 2.3. Further Section 16 *Storage and Handling* can be improved to clearly indicate the 2 dosage forms and how they are supplied, stored, and handled. Thus, the PI can be revised to support the safe and effective use of the product.

Our review of the MG found it can be improved to include information for how to manage dosing if vomiting occurs after taking a dose of Tafinlar..

Instructions for Use (IFU)

The proposed Tafinlar tablets for oral suspension is a combination product that is co-packaged with a dosing cup to be used as a device to measure water, disperse the tablets, and for direct oral administration of the dispersed tablets. We note the initial Tafinlar submission did not include a comprehensive use-related risk analysis (URRA) or plans for a Human Factors (HF) validation study. To inform our review of the proposed IFU, we issued an Information Request (IR) for human factors (HF) data on January 5, 2023. The Applicant responded via email on

January 9, 2023 with a completed URRA[a], and their Human Factors Engineering Summary Report with their justification[b] for why they believe a HF validation study is not needed. Our review of the URRA did not identify any new or unique tasks or risks associated with the intended use of this product. Thus, we agree with the applicant's assessment that no further HF evaluations are needed.

Our review of the IFU found it acceptable from a medication error perspective.

Container Label and Carton Labeling

Our review of the container label and carton labeling identified opportunities to increase the prominence of important preparation, administration, storage and handling information. Thus, the container label and carton labeling can be improved to convey important product information.

4 CONCLUSION & RECOMMENDATIONS

We conclude that the proposed Tafinlar PI, Medication Guide, container label, and carton labeling can be improved to promote the safe and effective use of the product. We provide recommendations for DO2 in Section 4.1 and recommendations for Novartis Pharmaceuticals Corporation, in Section 4.2 below.

4.1 RECOMMENDATIONS FOR DIVISION OF ONCOLOGY 2 (DO2)

A. Prescribing Information

1. Dosage and Administration Section

a. To support the safe and effective use of the proposed product, consider including in Section 2.3 information on what to do if vomiting occurs after TAFINLAR administration. For example:

"If vomiting occurs after TAFINLAR administration, do not take an additional dose. Take the next dose at its scheduled time."

2. How Supplied/Storage and Handling Section

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[a]Novartis Pharmaceuticals Corporation, URRA Commercial. East Hanover (NJ): Novartis. 2023 JAN 11. Available at: \\CDSESUB1\EVSPROD\nda217514\0032\m5\53-clin-stud-rep\535-rep-effic-safety-stud\pedglioma\5354-other-stud-rep\drb436-medical-devices\rsk-drb436-urra-comm-app1.pdf

[b] Novartis Pharmaceuticals Corporation, HF Engineering Summary Report. East Hanover (NJ): Novartis. 2023 JAN 11. Available at: \\CDSESUB1\EVSPROD\nda217514\0032\m5\53-clin-stud-rep\535-rep-effic-safety-stud\pedglioma\5354-other-stud-rep\drb436-medical-devices\rpt-drb436-hfesr-comm-app2.pdf

a. Consider adding a description of the flavor of the tablets for oral suspension (e.g., berry flavored) to the description of the tablets for oral suspension.

b. To improve the organization of the information of how Tafinlar is supplied and the storage and handling information, consider revising Section 16 to read as follows:

Tafinlar Capsules

50 mg capsules: Dark red capsule imprinted with 'GS TEW' and '50 mg' available in bottles of 120 (NDC 0078-0682-66). Each bottle contains a silica gel desiccant.

75 mg capsules: Dark pink capsule imprinted with 'GS LHF' and '75 mg' available in bottles of 120 (NDC 0078-0681-66). Each bottle contains a silica gel desiccant.

Tafinlar Tablets for Oral Suspension

10 mg tablets for oral suspension: white to slightly yellow, round biconvex 6 mm tablet debossed with "D" on one side and "NVR" on the other. Available in bottles of 210 (NDC xxxx-xxxx-xx). Each bottle contains a silica gel desiccant.

Storage and Handling

Store 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]. Store and dispense in the original bottle with the desiccant.

B. Medication Guide

1. How should I take TAFINLAR?

a. In the "How should I take TAFINLAR" section, consider adding information on what to do if vomiting occurs after TAFINLAR administration. For example:

If you vomit after taking a dose of TAFINLAR, do not take an additional dose. Take the next dose at your regular time.

4.2 RECOMMENDATIONS FOR NOVARTIS PHARMACEUTICALS CORPORATION,

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

A. General Comments (Container labels & Carton Labeling)

1. Revise the statement "* (b) (4) ", to read "*Disperse tablets in water prior to ingestion. Do not swallow whole, chew or crush." We recommend this revision to support the safe and effective use of the drug product.

2. Revise the "[redacted] (b) (4)" to read "Recommended Dosage: See Prescribing Information" to use language that is consistent with language used in the PI.

3. To support proper dispensing and storage of the drug product, revise the boxed statement "[redacted] (b) (4)..." to read as follows:

> Dispense and store in original container with the desiccant**.
>
> Dispense with Medication Guide

4. Revise the storage statement on the back panel ("Store in original container to protect...") by adding double asterisks to reference the boxed statement on the principal display panel (PDP) and to read as follows:

   **Store in original container to protect from moisture. Keep container tightly closed. Do not remove desiccant from bottle.

B. Carton Labeling

1. Consider revising and relocating the statement of contents from the back panel to the principal display panel (PDP) to increase the prominence of this important product information and to read as follows:

   - One 210-Count Bottle of 10 mg Dispersible Tablets
   - Two Dosing Cups
   - Instructions for Use

   a. To avoid redundancy, remove the quantity statement that currently appears on the PDP.

2. To improve readability, increase the font size of the product information that appears on the back panel.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Tafinlar received on December 1, 2022 from Novartis Pharmaceuticals Corporation, .

Appears this way on original

Table 2. Relevant Product Information for Tafinlar	
Initial Approval Date	NDA 202806: May 29, 2013 ***proposed*** NDA 217514: N/A
Active Ingredient	dabrafenib
Indication	Tafinlar is a kinase inhibitor indicated as a single agent for the treatment of patients with u metastatic melanoma with BRAF V600E mutation as detected by an FDA-approved test. Tafinlar is indicated, in combination with trametinib, for: • the treatment of patients with unresectable or metastatic melanoma with BRAF V600E c mutations as detected by an FDA-approved test. • the adjuvant treatment of patients with melanoma with BRAF V600E or V600K mutation detected by an FDA-approved test, and involvement of lymph node(s), following comple • the treatment of patients with metastatic non-small cell lung cancer (NSCLC) with BRAF mutation as detected by an FDA-approved test. • the treatment of patients with locally advanced or metastatic anaplastic thyroid cancer (BRAF V600E mutation and with no satisfactory locoregional treatment options. • *the treatment of adult and pediatric patients 6 years of age and older with unresectable solid tumors with BRAF V600E mutation who have progressed following prior treatment satisfactory alternative treatment options. This indication is approved under accelerated based on overall response rate and duration of response. Continued approval for this ind be contingent upon verification and description of clinical benefit in a confirmatory trial(s* ***Proposed:*** • ***the treatment of pediatric patients 1 year of age and older with low-grade glioma (LG BRAF V600E mutation who require systemic therapy*** <u>Limitations of Use</u>: Tafinlar is not indicated for treatment of patients ***with colorectal cancer BRAF solid tumors***
Route of Administration	oral
Dosage Form	Capsules **Proposed:** Tablets for oral suspension
Strength	Capsules: 50 mg and 75 mg **Proposed**: Tablets for oral suspension: 10 mg

<table>
<tr><td>Dose and Frequency</td><td>(See Full Prescribing Information in Appendix G)
Proposed:
Dosing for TAFINLAR Tablets for Oral Suspension (Weight-Adjusted Dose)
<table>
<tr><td></td><td colspan="2">Recommended dose</td></tr>
<tr><td>Body weight</td><td>Total Daily Dose</td><td>(b) (4)</td></tr>
<tr><td>8 to 9 kg</td><td>20 mg twice daily</td><td></td></tr>
<tr><td>10 to 13 kg</td><td>30 mg twice daily</td><td></td></tr>
<tr><td>14 to 17 kg</td><td>40 mg twice daily</td><td></td></tr>
<tr><td>18 to 21 kg</td><td>50 mg twice daily</td><td></td></tr>
<tr><td>22 to 25 kg</td><td>60 mg twice daily</td><td></td></tr>
<tr><td>26 to 29 kg</td><td>70 mg twice daily</td><td></td></tr>
<tr><td>30 to 33 kg</td><td>80 mg twice daily</td><td></td></tr>
<tr><td>34 to 37 kg</td><td>90 mg twice daily</td><td></td></tr>
<tr><td>38 to 41 kg</td><td>100 mg twice daily</td><td></td></tr>
<tr><td>42 to 45 kg</td><td>110 mg twice daily</td><td></td></tr>
<tr><td>46 to 50 kg</td><td>130 mg twice daily</td><td></td></tr>
<tr><td>≥ 51 kg</td><td>150 mg twice daily</td><td></td></tr>
</table></td></tr>
<tr><td>How Supplied</td><td>50 mg capsules: Dark red capsule imprinted with ‘GS TEW’ and ‘50 mg’ available in bottles c
0078-0682-66). Each bottle contains a silica gel desiccant.
75 mg capsules: Dark pink capsule imprinted with ‘GS LHF’ and ‘75 mg’ available in bottles c
0078-0681-66). Each bottle contains a silica gel desiccant.
Proposed:</td></tr>
<tr><td>Storage</td><td>Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (59°F and
USP Controlled Room Temperature].</td></tr>
</table>

APPENDIX B. PREVIOUS DMEPA REVIEWS

On December 7, 2022, we searched for previous DMEPA reviews relevant to this current review using the terms, Tafinlar, dabrafenib, Mekinist, and trametinib. Our search identified 3 previous reviews[c,d,e], and we considered our previous recommendations to see if they are applicable for this current review.

[c] Thomas, S. Label and Labeling Review for Tafinlar and Mekinist (NDA 202806/S-22 and NDA 204114/S-24). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2022 FEB 24. RCM No.: 2021-2202.

[d] Little, C. Label and Labeling Review for Tafinlar and Mekinist (NDA 202806/S-8 and NDA 204114/S-7). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 MAR 26. RCM No.: 2018-546.

[e] Gao, T. Label and Labeling Review for Mekinist (NDA 204114/S-022). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 DEC 10. RCM No.: 2021-2371.

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,[f] along with postmarket medication error data, we reviewed the following Tafinlar labels and labeling submitted by Novartis Pharmaceuticals Corporation, .

- Container label received on August 17, 2022
- Carton labeling received on August 17, 2022
- Instructions for Use received on January 9, 2023, available from \\CDSESUB1\EVSPROD\nda217514\0031\m1\us\proposed.docx
- Prescribing Information (Image not shown) received on January 9, 2023, available from \\CDSESUB1\EVSPROD\nda217514\0031\m1\us\proposed.docx
- Medication Guide received on January 9, 2023, available from \\CDSESUB1\EVSPROD\nda217514\0031\m1\us\proposed.docx

G.2 Label and Labeling Images

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

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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: January 13, 2023

To: Raniya Al-Matari, PhD, Regulatory Project Manager
Division of Oncology 2 (DO2)

From: Andrew Nguyen, PharmD, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Emily Dvorsky, PharmD, Team Leader, OPDP

Subject: OPDP Labeling Comments for TAFINLAR® (dabrafenib) capsules, for oral use; TAFINLAR® (dabrafenib) tablets for oral suspension; MEKINIST® (trametinib) tablets, for oral use; MEKINIST® (trametinib) for oral solution

NDA: 202806, Supplement 025 AND 217514
204114, Supplement 025 AND 217513

Background:
In response to DO2's consult requests dated August 31, 2022 and September 30, 2022, OPDP has reviewed the proposed Prescribing Information (PI) and Medication Guide for supplement 25 for TAFINLAR® (dabrafenib) capsules, for oral use, the original application for TAFINLAR® (dabrafenib) tablets for oral suspension, supplement 25 for MEKINIST® (trametinib) tablets, for oral use, and the original application for MEKINIST® (trametinib) for oral solution. The proposed labeling for TAFINLAR® (dabrafenib) tablets for oral suspension will share combined labeling with the approved label for TAFINLAR® (dabrafenib) capsules, for oral use under NDA 202806 while the proposed labeling for MEKINIST® for oral solution will share combined labeling with the approved label for MEKINIST® (trametinib) tablets, for oral use under NDA 204114. The supplements include updates to labeling to expand the approved indication for the combination of TAFINLAR and MEKINIST to include pediatric patients 1 year and older with low-grade glioma (LGG) with BRAF V600E mutation who require systemic therapy.

PI/Medication Guide:
OPDP's review of the proposed PI is based on the draft labeling sent by electronic mail to OPDP on December 22, 2022, 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 on January 11, 2023.

Thank you for your consult. If you have any questions, please contact Andrew Nguyen at 240-402-0512 or andrew.nguyen@fda.hhs.gov.

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/s/

ANDREW D NGUYEN
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Clinical Inspection Summary

Date	January 13, 2023
From	Lee Pai-Scherf, MD Michele Fedowitz, MD, Acting Team Leader Jenn Sellers, MD, PhD, Acting Branch Chief Good Clinical Practice Assessment Branch (GCPAB) DCCE, OSI
To	Michael Barbato, MD and Jeannette Nashed, NP Diana Bradford, MD, Team Leader Martha Donoghue, MD, Deputy Division Director Division of Oncology 2 (DO2), OOP
NDA/BLA #	NDA 217513. NDA 217514.
Applicant	Novartis Pharmaceuticals Corp.
Drug	Trametinib and Dabrafenib
NME (Yes/No)	No
Therapeutic Classification	Tyrosine Kinase Inhibitors
Proposed Indication(s)	BRAF V600 mutation-positive glioma
Consultation Request Date	September 16, 2022
Summary Goal Date	January 16, 2023
Action Goal Date	February 16, 2023
PDUFA Date	February 17, 2023

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Clinical data from Study CDRB436G2201, low-grade glioma (LGG) Cohort were submitted to the Agency in support of New Drug Applications (NDA 217513 and NDA 217514) for dabrafenib in combination with trametinib in children and adolescents with BRAF V600 mutation positive LGG. Three clinical investigators Drs. Ashley Plant (site # 5008), Jordan Hansford (site # 4001), and Maria Luisa Garrè (site # 3801), as well as the imaging contract research organization (CRO), [redacted] (b) (4) were inspected.

At Dr Plant's site, the tumor assessment for a key secondary endpoint of investigator assessed overall response rate (ORR) per response assessment in neuro-oncology (RANO) criteria was not performed according to the protocol, as described below. For this reason, OSI suggests a sensitivity analysis at Dr. Plant's site for the purpose of analysis of this key secondary endpoint. The tumor assessments for the secondary endpoint were performed according to the protocol at the other inspected sites.

With the exception of the tumor assessment methodology for one of the key secondary endpoints observed at Dr. Plant's site, Study CDRB436G2201 overall appears to have been conducted adequately and the data generated by the inspected clinical investigators, the

imaging CRO appear acceptable in support of the respective indication in the NDAs.

II. BACKGROUND

Novartis submitted NDA 217513 (trametinib) and NDA 217514 (dabrafenib) seeking approval for trametinib in combination with dabrafenib, for the treatment of pediatric patients 1 year of age and older with BRAF V600E mutation positive low-grade glioma (LGG) who require systemic therapy.

Safety and efficacy data from 110 subjects with BRAF V600 mutation positive LLG enrolled in study CDRB436G2201 were submitted to support the proposed indication**.** The primary efficacy endpoint is overall response rate (ORR) by blinded independent review (BICR) per response assessment in neuro-oncology (RANO) criteria. Key secondary endpoints are investigator assessed ORR per RANO criteria, duration of response (DOR), Progression-Free Survival (PFS) as assessed by BIRC and investigator per RANO criteria.

Subjects must sign the informed consent form before any study-specific procedures are performed. Tumor assessment was assessed at baseline, every 8 weeks during the first year, subsequently every 16 weeks thereafter until disease progression, death, lost to follow-up or withdrawal of consent/assent.

The first subject was enrolled on 12/28/2017. The data cut-off date was **08/23/2021**. The study enrolled subjects at 58 clinical sites worldwide. Fifteen subjects with LLG were in USA across 7 clinical sites.

Three clinical investigators were identified for inspection by DO2 and OSI: Ashley Plant (site # 5008), Jordan Hansford (site # 4001), and Maria Luisa Garrè (site # 3801). (b) (4) the CRO responsible for central review of radiographic images was chosen for inspection of the conduct of the central imaging review and for evaluation of the primary efficacy endpoint of a larger number of subjects.

III. RESULTS (by site):

1. **Dr. Ashley Plant (site # 5008)**
   225 E. Chicago Ave
   Chicago, IL 60611

   Inspection dates: 10/3 - 10/07/2022

   Dr. Plant was inspected as a routine PDUFA inspection for Study CDRB436G2201, LGG Cohort. This was the first FDA inspection for this investigator.

   At the time of the inspection, the site had screened 4 subjects and enrolled 3 subjects in

the LLG cohort of the study. Of the 3 subjects enrolled, 1 subject discontinued the study due to progression of disease and 2 have completed treatment in the control arm and are currently in follow-up.

Records reviewed included, but were not limited to subject medical records, IRB approval letters and correspondence, monitoring reports, consent forms, financial disclosure reports, case report forms, investigational product accountability records, site training documentation and responsibility logs.

Source records for all 3 subjects enrolled (ID (b) (6)) at the site were audited for protocol adherence, inclusion and exclusion criteria, adverse event reporting, test article accountability and verification informed consent was obtained according to the regulations. There was no underreporting of AEs or SAEs or significant protocol deviations.

All 3 subjects had imaging scans performed at protocol specified timepoints and all scans were submitted to the imaging CRO for central review for assessment and determination of primary efficacy endpoint.

Tumor response/progression was assessed at the site by the investigator according to RANO criteria, at protocol specified timepoints. All imaging source records, and patient level source records used to determine the secondary endpoint of investigator assessed response were available at the site. However, during the inspection, it was noted that for the overall evaluation of the imaging scans for tumor response/progression, the investigator did not follow the protocol. Generally, the investigator did not compare the findings of newly acquired scans to that of the baseline or best response scans as required by the protocol, but rather to the immediately previous scan. While the inspection was able to verify that the source radiology documents were used to populate the eCRF imaging measurements, and the eCRF matched the measurements in the submitted data listings, there was unclear documentation at the site regarding how the eCRF measurements were obtained. Mainly, there was poor documentation of the calculation of the measurements and the overall evaluation of tumor response/progression according to RANO criteria.

Reviewer's comment: Because the investigator did not follow the protocol to evaluate the imaging and because the documentation for the measurements submitted to the agency is unclear, OSI suggests a sensitivity analysis at Dr. Plant's site for the purpose of analysis of the secondary endpoint of investigator assessed ORR per RANO criteria.

The inspection found no regulatory violations at the site. No Form FDA 483 was issued to Dr. Plant at the conclusion of the inspection.

2. **Dr. Jordan Hansford (site # 4001)**
   Murdoch Children Research Institute
   50 Flemington Road

Parkville, VIC 3052
Australia

Inspection dates: 11/7 – 11/11/2022

Dr. Hansford was inspected as a routine PDUFA inspection for Study CDRB436G2201, LGG Cohort. This was the first FDA inspection for this investigator.

At the time of the inspection, the site enrolled 8 subjects in the LLG cohort of the study, one subject had discontinued study due to toxicity.

Records reviewed included, but were not limited to protocol integrity and compliance, local and institutional ethic committee documentation approvals, monitoring, electronic medical records, financial disclosure forms, staff training, drug accountability and informed consent procedures.

Source records for all 8 subjects enrolled (ID (b) (6)) were reviewed for inclusion/exclusion criteria, reporting of adverse events and severe adverse events, protocol deviations and informed consent forms and source documentation of study endpoint data. All imaging scans were performed according to the protocol specified timepoints and were submitted to the imaging CRO for central assessment. All protocol specified assessments were completed according to the protocol, with exception of some ophthalmology assessments that were not completed due to COVID-19 pandemic restrictions. These were previously reported to the NDA.

The inspection found no regulatory violations at the site. No Form FDA 483 was issued to Dr. Hansford at the conclusion of the inspection. Based on the results of the inspection, data generated at Dr. Hansford's site appear acceptable in support of the proposed indication in the NDA.

3. **Dr. Maria Luisa Garrè (site # 3801)**
Largo Gerolamo Gasini 5
Genova, GE 16147
ITALY

Inspection dates: 10/24 – 10/28/2022

Dr. Garrè was inspected as a routine PDUFA inspection for Study CDRB436G2201, LGG Cohort. This was the first FDA inspection for this investigator.

At the time of the inspection, the site screened 8 subjects and enrolled 7 subjects in the LLG cohort and 1 subject in the HGG cohort of the study, 6 subjects are receiving IP treatment, 1 subject in follow-up phase and 1 subject had died (ID (b) (6)

cohort).

Records reviewed included, but were not limited to ethics committee approvals, study correspondence, drug accountability, facility adequacy, staff qualifications, and monitoring procedures.

Source records for all 8 subjects enrolled at the site (ID [redacted] (b) (6) were reviewed. The inspection covered the safety of study subjects along with serious adverse event reporting, protocol deviations, subject eligibility, overall protocol compliance, and the verification of source documentation related to study endpoint criteria. All imaging scans were performed according to the protocol specified timepoints and were submitted to the imaging CRO for central assessment.

The inspection found no regulatory violations at the site. No Form FDA 483 was issued to Dr. Garrè at the conclusion of the inspection. Based on the results of the inspection, data generated at Dr. Garrè's site appear acceptable in support of the proposed indication in the NDA.

4. [redacted] (b) (4)

Inspection dates: [redacted] (b) (4)

[redacted] (b) (4) was inspected as a routine PDUFA inspection for Study CDRB436G2201. This is the first inspection of [redacted] (b) (4). as a CRO. However, under the name [redacted] (b) (4) there were two previous GCP inspections completed [redacted] (b) (4) Both inspections were classified NAI.

This inspection focused on the confirmation of [redacted] (b) (4) sponsor-related responsibilities to perform an independent central imaging review for study CDRB436G2201, LGG Cohort.

The inspection also included verification of source data generated from imaging review by [redacted] (b) (4) with the data submitted to the NDA. Tumor response data from 35 subjects enrolled in study CDRB436G2201 (20 subjects from LGG cohort and 15 subjects from HGG cohort) were reviewed and compared with data submitted to the NDA. Data points verified for each subject included visit number, scan date, sum of diameters (target lesions), % change from baseline, % change from nadir, calculated target lesion response, and radiologic responses. No discrepancies were noted with source data and the data submitted to the NDA.

[redacted] (b) (4) assessment, procedures in performing image analysis, and compliance

with the Imaging Review Charter, protocol, and appropriate regulations were reviewed and appeared adequate.

The inspection found no regulatory violations at the site. No Form FDA 483 was issued to (b) (4) at the conclusion of the inspection. Based on the results of the inspection, imaging review data generated by (b) (4) appear acceptable in support of the proposed indication in the NDA.

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Lee Pai-Scherf, MD
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

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Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE: {*See appended electronic signature page}*

Jenn Sellers, M.D., Ph.D.
Branch Chief (acting)
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CC:

DARRTS: NDA 217513 and NDA 217514
Review Division /Project Manager/Raniya Al-Matari
OSI/DCCE/GCPAB/Program Analyst/Yolanda Patague

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JENN W SELLERS
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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:	January 11, 2023
To:	Raniya Al-Matari, PhD Regulatory Health Project Manager **Division of Oncology II (DO2)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Sharon R. Mills, BSN, RN, CCRP Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Andrew Nguyen, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI), Medication Guide (MG), and Instructions for Use (IFU)
Drug Name (established name); Dosage Form and Route; Application Type/Number:	• MEKINIST (trametinib) tablets, for oral use, NDA 204114/S-025 • MEKINIST (trametinib) for oral solution, NDA 217513 • TAFINLAR (dabrafenib) tablets for oral suspension, NDA 202806/S-025 • TAFINLAR (dabrafenib) capsules, for oral use, NDA 217514
Applicant:	Novartis Pharmaceuticals Corporation

1 INTRODUCTION

On August 17, 2022, Novartis Pharmaceuticals Corporation submitted for the Agency's review two original New Drug Applications (NDAs): NDA 217513 MEKINIST (trametinib) for oral solution and NDA 217514 TAFINLAR (dabrafenib) tablets for oral suspension. The proposed labeling for MEKINIST for oral solution will share combined labeling with the approved dosage form for MEKINIST (trametinib) tablets under NDA 204114. The proposed labeling for TAFINLAR (dabrafenib) tablet for oral suspension will share combined labeling with the approved dosage form TAFINLAR (dabrafenib) capsules under NDA 202806.

On August 24, 2022, Novartis Pharmaceuticals Corporation submitted for the Agency's review two Prior Approval Supplements (PASs)- Efficacy to their approved New Drug Applications, NDA 204114/S-025 for MEKINIST (trametinib) tablets and NDA 202806/S-025 for TAFINLAR (dabrafenib) capsules. As stated in the Applicant's cover letter, "Based on post-meeting addendum comments issued in the meeting minutes on April 13, 2022, FDA recommended that Novartis submit two efficacy supplemental NDAs (one for a dabrafenib solid formulation and one for trametinib solid formulation) for the first-line pediatric LGG indication."

The proposed new indication for MEKINIST (trametinib) is as follows: in combination with dabrafenib, for the treatment of pediatric patients 1 year of age and older with low-grade glioma (LGG) with BRAF V600E mutation who require systemic therapy.

The proposed new indication for TAFINLAR (dabrafenib) is as follows: in combination with trametinib, for the treatment of pediatric patients 1 year and older with low-grade glioma (LGG) with BRAF V600E mutation who require systemic 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 the following requests by the Division of Oncology II (DO2):

- Request dated August 31, 2022, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) and Instructions for Use (IFU) for MEKINIST (trametinib) for oral solution and TAFINLAR (dabrafenib) tablets for oral suspension.
- Request dated September 30, 2022, for DMPP and OPDP to review the Applicant's proposed PPI and IFU for MEKINIST (trametinib) tablets, for oral use and TAFINLAR (dabrafenib) capsules, for oral use..

The requested DMPP and OPDP review of the newly proposed IFUs for both products will be completed at a later date, once the Division of Medication Errors Prevention and Analysis (DMEPA) provides input regarding the Human Factors issues.

2 MATERIAL REVIEWED

- Draft MEKINIST (trametinib) tablets and MEKINIST (trametinib) for oral solution PPI received on August 17, 2022, revised on December 1, 2022, and received by DMPP and OPDP on December 22, 2022.
- TAFINLAR (dabrafenib) capsules and tablets for oral suspension MG received on August 17, 2022, revised on December 1, 2022, and received by DMPP and OPDP on December 22, 2022.
- Draft MEKINIST (trametinib) tablets and MEKINIST (trametinib) for oral solution Prescribing Information (PI), and TAFINLAR (dabrafenib) capsules and tablets for oral suspension PI received on August 17, 2022, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on December 29, 2022.
- Approved MEKINIST (trametinib) tablets labeling dated June 22, 2022.
- Approved TAFINLAR (dabrafenib) capsules labeling dated June 22, 2022.

3 REVIEW METHODS

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

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

In our collaborative review of the PPI and MG we:

- simplified wording and clarified concepts where possible
- ensured that the PPI and MG are consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI and MG are 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 PPI and MG meet the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI and MG are 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 and MG are 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 and MG.

Please let us know if you have any questions.

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

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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.

/s/

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01/11/2023 09:17:10 AM

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