CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

217513Orig1s000

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.

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/

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 15, 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 #:	2022-926-2
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 14, 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 memo.[a]

2 CONCLUSION

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

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

[a] Stewart. J. Label and Labeling Memorandum for Mekinist (NDA 217513). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2023 MAR 10. TTT ID No.: 2022-926-1.

Reference ID: 5141829

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/s/

JANINE A STEWART
03/15/2023 08:38:28 AM

ASHLEIGH V LOWERY
03/15/2023 10:39:20 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 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.

Reference ID: 5139745

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

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

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/s/

JANINE A STEWART
03/10/2023 12:15:07 PM

ASHLEIGH V LOWERY
03/10/2023 04:03:47 PM

HUMAN FACTORS STUDY REPORT REVIEW
Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

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

Date of This Review:	March 1, 2023
Requesting Office or Division:	Division of Oncology 2 (DO2)
Application Type and Number:	NDA 217513
Product Type:	Combination Product (Drug-Device)
Product, Name, Dosage Form and Strength:	Mekinist (trametinib) for oral solution, 4.7 mg per bottle After reconstitution: 0.05 mg/mL
Device Constituent:	Oral syringe
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Novartis Pharmaceuticals Corporation
FDA Received Date:	August 17, 2022; November 23, 2022; February 3, 2023
TTT ID #:	2022-2984
DMEPA 2 Safety Evaluator:	Ebony Whaley, PharmD, BCPPS
DMEPA 2 Team Leader (Acting):	Colleen Little, PharmD
DMEPA 2 Associate Director for Human Factors:	Lolita White, PharmD
DMEPA 2 Deputy Director	Chi-Ming (Alice) Tu, PharmD, FISMP, BCPS

Reference ID: 5134531

1 REASON FOR REVIEW

This review evaluates the human factors (HF) validation study report submitted under NDA 217513 for Mekinist (trametinib) for oral solution.

This review contains our evaluation of the user interface from the HF validation study. We note that the DMEPA 2 primary review team will evaluate product specific label and labeling under a separate cover.[a]

1.1 PRODUCT INFORMATION

Table 1 presents relevant product information for Mekinist (trametinib) for oral solution that Novartis Pharmaceuticals Corporation submitted on November 23, 2022.

Table 1. Relevant Product Information for Mekinist

Initial Approval Date	Proposed • N/A Currently approved (tablets) • 5/29/2013 under NDA 204114
Active Ingredient	Trametinib
Indication	Proposed in combination with dabrafenib, 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
Route of Administration	Oral or via feeding tube
Dosage Form	Proposed • For oral solution Currently approved • Tablets
Strength	Proposed • 4.7 mg per bottle (0.05 mg/mL after reconstitution) Currently approved • 0.5 mg • 2 mg
Dose and Frequency	

Body weight	Recommended dose total volume of oral solution once daily (trametinib content)
8 kg	6 mL (0.3 mg)
9 kg	7 mL (0.35 mg)
10 kg	7 mL (0.35 mg)
11 kg	8 mL (0.4 mg)

Reference ID: 5134531

<table>
<tr><td></td><td><table>
<tr><td>12 to 13 kg</td><td>9 mL (0.45 mg)</td></tr>
<tr><td>14 to 17 kg</td><td>11 mL (0.55 mg)</td></tr>
<tr><td>18 to 21 kg</td><td>14 mL (0.7 mg)</td></tr>
<tr><td>22 to 25 kg</td><td>17 mL (0.85 mg)</td></tr>
<tr><td>26 to 29 kg</td><td>18 mL (0.9 mg)</td></tr>
<tr><td>30 to 33 kg</td><td>20 mL (1 mg)</td></tr>
<tr><td>34 to 37 kg</td><td>23 mL (1.15 mg)</td></tr>
<tr><td>38 to 41 kg</td><td>25 mL (1.25 mg)</td></tr>
<tr><td>42 to 45 kg</td><td>28 mL (1.4 mg)</td></tr>
<tr><td>46 to 50 kg</td><td>32 mL (1.6 mg)</td></tr>
<tr><td>≥ 51 kg</td><td>40 mL (2 mg)</td></tr>
</table></td></tr>
<tr><td>How Supplied</td><td><u>Proposed</u>
white or almost white powder in amber glass bottles, co-packaged with a press-in bottle adapter and an oral syringe
<u>Currently approved</u>
0.5 mg tablets: Yellow, modified oval, biconvex, film-coated tablets with ‘GS’ debossed on one face and ‘TFC’ on the opposing face and are available in bottles of 30
0.5 mg tablets: Yellow, ovaloid, biconvex, unscored film-coated tablets with beveled edges and with the Novartis logo debossed on one side and ‘TT’ on the other side; available in bottles of 30
2 mg tablets: Pink, round, biconvex, film-coated tablets with ‘GS’ debossed on one face and ‘HMJ’ on the opposing face and are available in bottles of 30
2 mg tablets: Pink, round, biconvex, unscored film-coated tablets with beveled edges and with the Novartis logo debossed on one side and ‘LL’ on the other side; available in bottles of 30</td></tr>
<tr><td>Storage</td><td><u>Proposed</u>
Store in the original container in order to protect from light and moisture.
Before reconstitution, store the dry powder refrigerated at 2°C to 8°C (36°F to 46°F).
After reconstitution, store below 25°C (77°F) and do not freeze.</td></tr>
</table>

[a] Stewart, J. Label and Labeling Review for Mekinist (trametinib) NDA 217513. Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2023 FEB 23. TTT ID#: 2022-926.

	• Discard any unused solution 35 days after reconstitution. (b) (4) [redacted] <u>Currently approved</u> • Store refrigerated at 2°C to 8°C (36°F to 46°F). Dispense in original bottle. Do not remove desiccant. Protect from moisture and light. Do not place medication in pill boxes.
Container Closure/Device Constituent	Proposed oral syringe (20 mL) 
Intended Users	<u>Proposed</u> • Pharmacists (only pharmacists will be permitted to reconstitute) • Healthcare professionals (e.g., physicians, nurses, etc.) • Lay caregivers
Intended Use Environment	<u>Proposed</u> • may be reconstituted and/or administered in a pharmacy, a typical domestic environment or in a non-emergency clinical setting

1.2 REGULATORY HISTORY RELATED TO THE PROPOSED PRODUCT'S HUMAN FACTORS DEVELOPMENT PROGRAM[b]

- On September 13, 2021, the Applicant submitted an HF validation study protocol under IND 119309. We completed our review of the HF validation study protocol February 16, 2022 and provided recommendations for the Applicant in the HF Advice Letter dated March 16, 2022.[c]

[b] On December 3, 2022, we searched for previous DMEPA reviewed relevant to this current review using the terms, IND 119309, NDA 217513, trametinib. We considered our previous recommendations to see if they are applicable for this current review.

[c] Ford, L. Human Factors Validation Study Advice Letter for trametinib (IND 119309). Silver Spring (MD): FDA, CDER, OSE (US); 2022 MAR 16.

- In the Memorandum of Meeting Minutes dated April, 13,2022 under IND 117898 regarding dabrafenib in combination with trametinib[d], we informed the Applicant that the results of the HF validation study should be included in the original filing of the application. The Agency also recommended that the Applicant submit two original NDAs for the proposed dabrafenib dispersible tablet and trametinib for oral solution.
- On August 17, 2022, the Applicant submitted NDA 217513 to seek approval for trametinib for oral solution, which did not include the results of their HF validation study.
- On August 26, 2022, the Applicant submitted a response to the March 16, 2022 HF Advice letter regarding recruitment efforts for the HF validation study. We completed our review of the August 26, 2022 submission and informed the Applicant that we did not have any recommendations or comments.[e]
- On November 23, 2022, the Applicant submitted their HF validation study results report under NDA 217513, which is the subject of this review.

1.3 MATERIALS REVIEWED

We considered the materials listed in Table 2 for this review.

Table 2. Materials Considered for this Review

Material Reviewed	Appendix or Section (for Methods and Results)
Product Information/Prescribing Information	Section 1.1
Background Information on Human Factors Engineering (HFE) Process	A
Human Factors Validation Study Report	B
Information Requests Issued During the Review	C
Labels and Labeling	D

N/A=not applicable for this review

2 OVERALL ASSESSMENT OF MATERIALS REVIEWED

[d] Pierce, M. Memorandum of Meeting Minutes for dabrafenib in combination with trametinib (IND 117898). Silver Spring (MD): FDA, CDER, OND, DO2 (US); 2022 APR 13.
[e] Wu, L. Human Factors General Advice Letter for trametinib (IND 119309). Silver Spring (MD): FDA, CDER, OSE (US); 2022 SEP 16.

Reference ID: 5134531

The sections below provide a summary of the study design, errors/close calls/use difficulties observed, and our analysis to determine if the user interface has been optimized to support the safe and effective use of the proposed product.

2.1 SUMMARY OF STUDY DESIGN

Table 3 presents a summary of the HF validation study design. See Appendix B for more details on the study design.

Table 3. Study Methodology for Human Factors (HF) Validation Study

Study Design Elements	Details
Participants	<table><tr><th>User group</th><th>Total</th></tr><tr><td>Healthcare Professionals (HCPs)- nurses</td><td>n = 15</td></tr><tr><td>Lay caregivers aged ≥ 18 years</td><td>n = 15</td></tr><tr><td>Pharmacists</td><td>n = 15</td></tr><tr><td>Patients aged ≥ 18 years - 5 participants were currently diagnosed with low-grade glioma (LGG) or high-grade glioma (HGG) - 10 participants were proxy participants and were in remission from LGG or HGG or had another form of cancer which had metastasized to the brain</td><td>n = 15</td></tr></table>
Training	Participants were not trained.
Test Environment & Materials	Test Environment The HF study was conducted on a one-to-one in an interview room at a usability lab. The moderator remained in the interview room throughout the interview. In addition, an observer/note taker viewed the interviews anonymously via a one-way mirror. The evaluation sessions were video recorded for subsequent review/ analysis. Test Materials Patients, caregivers, and HCPs were given an unrefrigerated box with a reconstituted bottle inside. Pharmacists received a refrigerated box with powder-in-bottle inside.
Sequence of Study	• Enrollment • Introduction discussion and informed consent

Reference ID: 5134531

	• Simulated use scenario
	  o Pharmacists only: simulated reconstitution
	  ▪ A participant was deemed to have added an acceptable volume of water if they add between 80-120% of 90 mL (72 mL-108 mL) of water.
	  o Patients, caregivers, and HCPs: given a box (carton) with the reconstituted solution inside and were asked to simulate administration of a specific dose (3 mL, 23 mL, or 40 mL). The patient and lay caregiver user groups simulated administration via swallowing and the HCP user group simulated administration via feeding tube.
	  ▪ For the 3 mL dose scenario, a dose between 2.4 mL and 3.6 mL was determined as a pass.
	  ▪ For the 23 mL dose scenario, a dose between 18.4 mL and 27.6 mL was determined as a pass.
	  ▪ For the 40 mL dose scenario, a dose between 32 mL and 48 mL was determined as a pass.
	• Root cause analysis
	• Knowledge based assessment
	• Activities of Daily Living (ADL) and Rapid Estimate of Adult Literacy in Medicine (REALM) assessments
	• Pinch and grip strength measurements

2.2 DISCUSSION OF METHODOLOGY

(b) (4)

(b) (4)

3 RESULTS AND ANALYSIS

We have carefully reviewed each observed event, the Applicant's URRA, the participants' subjective feedback, the Applicant's root cause analysis (RCA), and the Applicant's comments and proposed mitigations below.

Table 4. HF Validation Study Results
Legend: RCA = root cause analysis; UD = use difficulty; UE = use error; URRA = use-related risk analysis, V2C = caregiver participant, V2N = HCP participant, V2PH = pharmacist participant

	Information Supplied by Applicant	DMEPA's Findings and Recommendations
Task: Wash and dry hands before preparation/ administration Scenario: Simulated use Events: UE (n=9) — Participant Type: V2PH (n=2), V2C (n=5), V2N (n=2) Events: CC (n=0) Events: UD (n=0)	Observed events: • Did not wash hands, sanitize, or use gloves during reconstitution, preparation, or administration of the medication	
	Risk associated with Task Errors (Per URRA): • Contamination of devices/solution with pathogen microorganisms. Microbial contamination in the delivery path leading to vomiting or diarrhea	
	Relevant RCA/Subjective Feedback/Observation: • Does not wash their hands between every reconstitution because they wash their hands regularly throughout the day • Washed or sanitized hands before the study began • Did not think washing hands was necessary because they were not touching the patient or the medication • Did not use the IFU • Study artifact o Not in their usual environment or pharmacy setting o Forgot o There was no sink or handwashing station in available	We did not identify subjective feedback indicating labeling confusion or user interface design issues. The RCA and subjective feedback indicate that negative transfer, personal preference, and study artifact contributed to some of the use errors (i.e., lack of sink). We note the study environment included hand sanitizer; however, a sink was not available for participants to wash their hands.
	Applicant Comment and Proposed Mitigations: • In response to the Agency's January 27, 2023 Information Request (IR), the Applicant indicated they implemented a post-validation revision (b) (4) in response to participant performance on this task (see Appendix C). Specifically, the Applicant (b) (4) . The Applicant determined that validation of the revision was not necessary because it is standard practice for pharmacists to wash their hands.	Regarding the post-validation revision, we agree with the Applicant that it is standard practice for pharmacists to wash their hands in their workplace. Also, considering many of the use-related events occurred due to lack of sink in the use environment, negative transfer, or personal preference, we find that the Applicant's post-validation is not necessary. We provide a recommendation in Table 6 below. This recommendation can be implemented without submission of additional HF data.

Table 4. HF Validation Study Results
Legend: RCA = root cause analysis; UD = use difficulty; UE = use error; URRA = use-related risk analysis, V2C = caregiver participant, V2N = HCP participant, V2PH = pharmacist participant

	Information Supplied by Applicant	DMEPA's Findings and Recommendations
Task: Firmly tap the sides of the bottle to loosen the powder Scenario: Simulated use Events: UE (n=2) V2PH; CC (n=0); UD (n=0)	Observed event: • Did not tap the sides of the bottle to loosen the powder, which resulted in reconstitution taking a long time because the powder was clumped • Did not tap the sides of the bottle to loosen the powder	
	Risk associated with Task Error (Per URRA): • Sporadic underdose of <80% up to 7 times in 35 uses leading to planned improvement of health situation not being reached and decreased efficacy (if bottle has not been tapped enough, powder is not loose and the dissolution is not complete)	We note that if users do not loosen the powder and the solution is non-homogeneous, there is also risk of administration of an overdose.
	Relevant RCA/Subjective Feedback/Observation: • Design/layout of pharmacist instructions – 1 participant overlooked pharmacist instruction step #2 and recommended the steps be separated by white space • Did not refer to the pharmacist instructions • Location of pharmacist instructions – expected to find the pharmacist instructions in the PI or IFU	We acknowledge a participant recommended including additional white space on the carton for the reconstitution instructions. However, we also acknowledge the RCA and subjective feedback indicate location of the pharmacist instructions only on the carton contributed to another use error. Our independent review of labeling for similar currently marketed products finds that pharmacist only reconstitution instructions are generally included in the Prescribing Information (PI).
	Applicant Comment and Proposed Mitigations: • The Applicant did not propose additional mitigations in response to participant performance.	(b) (4) We provide recommendations in Table 5 below. These recommendations can be implemented without submission of additional HF data.

Reference ID: 5134531

Table 4. HF Validation Study Results
Legend: RCA = root cause analysis; UD = use difficulty; UE = use error; URRA = use-related risk analysis, V2C = caregiver participant, V2N = HCP participant, V2PH = pharmacist participant

<table>
<tr><th colspan="2">Information Supplied by Applicant</th><th>DMEPA's Findings and Recommendations</th></tr>
<tr><td rowspan="3">Task: Separate the dosing adapter from the syringe and insert the adapter

Scenario: Simulated use

<table><tr><th>Events:</th><th>Participant Type:</th></tr><tr><td>UE (n=3)</td><td>V2PH</td></tr><tr><td>CC (n=1)</td><td>V2PH</td></tr><tr><td>UD (n=4)</td><td>V2PH</td></tr></table></td><td>Observed events:
• Did not separate the dosing adapter from the oral syringe or insert the dosing adapter into the bottle neck
• Inserted the dosing adapter but it was not flush with the bottle neck, so the bottle cap would not attach. Then, the participant removed the dosing adapter.
• Inserted the dosing adapter but it was not flush with the bottle neck and/or difficulty inserting the dosing adapter all the way
• Initially did not notice the dosing adapter and did not insert the dosing adapter into the bottle neck. Later, the participant inserted the dosing adapter, but it was not flush with the bottle neck at first. Then, the participant eventually corrected.
• Initially unsure of which way to insert the dosing adapter</td><td></td></tr>
<tr><td>Risk associated with Task Errors (Per URRA):
• Microbial contamination leading to vomiting or diarrhea
• Underdose
• Dose omission
• Accidental exposure</td><td>We note the risk of dose omission was included in the risk discussion for this task in the HF results report but was omitted from the URRA.</td></tr>
<tr><td>Relevant RCA/Subjective Feedback/Observation:
• Force required
o Could not push the dosing adapter down further
o Required a greater force to insert the last ridge of the dosing adapter
o Thought they were pushing too hard and didn't want to break the dosing adapter
• Device embodiment confusion – believed they had fully inserted the dosing adapter</td><td>The RCA and subjective feedback indicate that some participants experienced use-related events due to the force required to insert the dosing adapter. We defer to the Office of Pharmaceutical Quality (OPQ) to provide assessment of the acceptability of the force-related specifications for the dosing adapter. We acknowledge confusion and concern regarding the dosing adapter contributed to some of the use errors, close call, and use difficulties; however, the task of inserting a dosing</td></tr>
</table>

Table 4. HF Validation Study Results
Legend: RCA = root cause analysis; UD = use difficulty; UE = use error; URRA = use-related risk analysis, V2C = caregiver participant, V2N = HCP participant, V2PH = pharmacist participant

	Information Supplied by Applicant	DMEPA's Findings and Recommendations
	• Did not see or use the pharmacist instructions • Expressed concern regarding patients inserting the dosing adapter in their mouth	adapter into a bottle is not a unique task for pharmacists and is common to other marketed products. Additionally, some participants did not refer to the pharmacist instructions on the carton labeling during the simulated-use scenario but completed the tasks successfully after referring to the instructions during the RCA and/or after the moderator prompted them to ensure the dosing adapter was fully inserted.
	Applicant Comment and Proposed Mitigations: • The Applicant did not propose additional mitigations in response to participant performance.	The dosing adapter is supplied connected to the oral syringe. We acknowledge the packaging design might lead some pharmacists to overlook the insertion of the dosing adapter. However, we also note that the (b) (4) Additionally, the IFU includes a step to check that the bottle adapter and states (b) (4) . As such, if the pharmacist did not insert the dosing adapter, we anticipate the lay user may contact their HCP (b) (4) as instructed in the IFU. As previously noted, we recommend including the reconstitution instructions in the PI, which is where pharmacist may typically expect to find reconstitution instructions. We provide a recommendation in Table 5 below. This recommendation can be implemented without submission of additional HF data.

Table 4. HF Validation Study Results
Legend: RCA = root cause analysis; UD = use difficulty; UE = use error; URRA = use-related risk analysis, V2C = caregiver participant, V2N = HCP participant, V2PH = pharmacist participant

	Information Supplied by Applicant	DMEPA's Findings and Recommendations
Task: Check whether there is powder or a liquid solution in the bottle ("If you received the medication from your pharmacist and it was a powder, what would you do?") Scenario: Knowledge task Events: UE (n=7) – Participant Type: V2C (n=4), V2N (n=3); CC (n=0); UD (n=1) – V2C	Observed events: • Indicated they would read the instructions for how to reconstitute the product	
	Risk associated with Task Errors (Per URRA): • Chronic underdose leading to disease progression (if user adds liquid to solution or incorrectly attempts to reconstitute) • Chronic overdose leading to an increased risk of possible side effects such as decreased appetite, headache, neutropenia, rash, renal impairment, bleeding, and eye related adverse events (if user incorrectly attempts to reconstitute)	
	Relevant RCA/Subjective Feedback/Observation: • Previous experience with reconstitution • Use of pharmacist instructions (on carton labeling) o Did not notice the statement "To the pharmacist" that is located before the reconstitution instructions on the carton labeling o Felt they would be able to reconstitute • IFU o Low IFU use/briefly read the IFU o Did not use the IFU o Struggled to comprehend IFU Step 3: The participant stated it could come as either a powder or a solution but later stated they would call their pharmacist and ask whether the pharmacist would reconstitute or themselves.	We identified RCA and subjective feedback that suggests some patients and caregivers may perform the reconstitution tasks if the product is dispensed in powder form because the reconstitution instructions are provided on the carton (e.g., "I would follow the instructions here) and the steps would be "easy" to perform at home. We acknowledge that several participants provided a correct response after referring to the IFU during the RCA including the participant who initially had difficulty comprehending IFU Step 3.
	Applicant Comment and Proposed Mitigations: • The Applicant implemented revisions to the proposed carton	We acknowledge the Applicant implemented a carton labeling revision to align with the sentence structure of

Reference ID: 5134531

Table 4. HF Validation Study Results
Legend: RCA = root cause analysis; UD = use difficulty; UE = use error; URRA = use-related risk analysis, V2C = caregiver participant, V2N = HCP participant, V2PH = pharmacist participant

	Information Supplied by Applicant	DMEPA's Findings and Recommendations
	labeling following the HF validation study. Specifically, in response to the Agency's January 27, 2023 IR (see Appendix C), the Applicant provided the following discussion regarding this post-validation carton labeling change (not all inclusive): o Revised the statement "Pharmacy only reconstitution" to "(b) (4) (b) (4) and "(b) (4) which per the Applicant was not implemented in response to the HF validation study results but instead was implemented align with the sentence structure of the IFU and to align with general best practices for using action-oriented language within labeling.	the IFU and with general best practices for using active language. We agree with the revision; however, we find additional revisions are necessary. We note the formatting ((b) (4) and location of pharmacist instructions on the carton labeling led some non-pharmacist participants (e.g., lay caregivers) to refer to the carton labeling instead of the IFU. As such, we find the formatting and]location of the pharmacist instructions on the carton labeling should be revised to mitigate the risk of non-pharmacists from attempting to perform pharmacist only reconstitution tasks. We find it may be less likely for non-pharmacist users to refer to the pharmacist instructions if the information is less prominent and is not numbered. We provide recommendations in Table 6 below. These recommendations can be implemented without submission of additional HF data. Additionally, we note the Important Information section and IFU Step 3 inform users to contact their pharmacist or healthcare provider if the product is powder. However, we find the IFU Step 3 statement can be improved to reiterate that lay users should not attempt to reconstitute. We provide a recommendation in Table 5 below. We find the recommendation can be implemented without the submission of additional HF data.

Table 4. HF Validation Study Results
Legend: RCA = root cause analysis; UD = use difficulty; UE = use error; URRA = use-related risk analysis, V2C = caregiver participant, V2N = HCP participant, V2PH = pharmacist participant

	Information Supplied by Applicant	DMEPA's Findings and Recommendations
Task: Gently swirl the bottle for 30 seconds to mix the solution. If foam appears, allow the bottle to stand until the foam disappears. Scenario: Simulated use Events: UE (n=21); CC (n=0); UD (n=0) Participant Type: V2C (n=10), V2N (n =11)	Observed events: • Did not swirl the bottle for 30 seconds before administering the medication • Briefly swirled the bottle but not for 30 seconds	
	Risk associated with Task Errors (Per URRA): • Sporadic administration of an underdose of <80% up to 7 times in 35 uses resulting in planned improvement of health situation is not being reached and decreased efficacy (if user does not swirl the bottle and the solution is non-homogeneous)	We also note that if users do not swirl the bottle and the solution is non-homogeneous, there is also risk of administration of an overdose.
	Relevant RCA/Subjective Feedback/Observation: • IFU o Comprehension of IFU information – thought swirling only applied if medication came as powder not a solution o Did not use IFU o Low IFU use • Use of pharmacist instructions • Expectation for information to be on the bottle label or carton • Perception of correct mixing requirement – swirled briefly and believed a 30 second swirl would be too much since they had already shaken and inverted the bottle • Medication appearance – did not believe medicine needed to be shaken because it appeared clear	We identified RCA and subjective feedback that suggests some patients and caregivers either did not refer to the IFU or referred to the pharmacist instructions, which led them to be unaware of this step.
	Applicant Comment and Proposed Mitigations: • The Applicant did not propose mitigations in response to	The carton labeling indicates the reconstitution instructions are for pharmacists. However, we note some

Table 4. HF Validation Study Results
Legend: RCA = root cause analysis; UD = use difficulty; UE = use error; URRA = use-related risk analysis, V2C = caregiver participant, V2N = HCP participant, V2PH = pharmacist participant

<table>
<tr><th colspan="2">Information Supplied by Applicant</th><th>DMEPA's Findings and Recommendations</th></tr>
<tr><td></td><td>participant performance.</td><td>non-pharmacist participants (i.e., lay caregivers, nurses) referred to the pharmacist only instructions on the carton labeling instead of to the IFU. As previously noted, we find revising the formatting and location of the pharmacist instructions on the carton labeling will minimize the risk of non-pharmacist users referring to the pharmacist instructions. We provide a recommendation in Table 6 below. We find the recommendation can be implemented without the submission of additional HF data.</td></tr>
<tr><td rowspan="4">Task: Separate the dosing adapter from the syringe and insert the adapter (If there was no dosing adapter inserted in the bottle, what should you do?)

Scenario: Knowledge task

<table><tr><th>Events:</th><th>Participant Type:</th></tr><tr><td>UE (n=8)</td><td>V2C (n=5), V2N (n=3)</td></tr><tr><td>CC (n=0)</td><td></td></tr><tr><td>UD (n=0)</td><td></td></tr></table></td><td>Observed events:
• Stated they would insert the syringe in the bottle and/or would pour the medication into a cap or cup and then withdraw using syringe</td><td></td></tr>
<tr><td>Risk associated with Task Errors (Per URRA):
• Microbial contamination leading to vomiting or diarrhea
• Underdose
• Dose omission
• Accidental exposure</td><td>We note the risk of dose omission was included in the risk discussion but was omitted from the URRA.</td></tr>
<tr><td>Relevant RCA/Subjective Feedback/Observation:
• Experience transfer
• Did not use IFU</td><td>The RCA and subjective feedback did not indicate confusion with the user interface.</td></tr>
<tr><td>Applicant Comment and Proposed Mitigations:
• The Applicant revised the IFU statements "If not inserted, separate the adapter from the syringe and insert it. Contact your healthcare provider if you are unsure or missing the adapter" to indicate instead the user should contact their pharmacist or HCP ("(b) (4), </td><td>We note the IFU tested in the HF validation study instructed users to "Contact your healthcare provider if you are unsure or missing the adapter". We also note the Applicant implemented a post-validation revision to the IFU to indicate that if the adapter is not inserted, the user should contact your pharmacist or healthcare provider.</td></tr>
</table>

Table 4. HF Validation Study Results
Legend: RCA = root cause analysis; UD = use difficulty; UE = use error; URRA = use-related risk analysis, V2C = caregiver participant, V2N = HCP participant, V2PH = pharmacist participant

	Information Supplied by Applicant	DMEPA's Findings and Recommendations
	[redacted](b) (4)"). In their response to the Agency's January 27, 2023 IR, the Applicant indicated this revision was implemented because the only user group tested to insert the bottle adapter was pharmacists. The Applicant determined no further validation is necessary because the revision is not intended to address the risk that a pharmacist does not insert the adapter.	We find the revision acceptable. We did not identify additional areas of improvement and have no recommendations at this time.
Task: If air bubbles are present, dispense the solution back into the bottle Scenario: Simulated use Events: / Participant Type: UE (n=6) / V2C CC (n=0) UD (n=0)	Observed events: • Large air bubble was present resulting in incorrect doses of 39 mL instead of 40 mL, 37 mL instead of 40 mL, 3.5 mL instead of 3 mL (this participant intentionally measured additional volume to account for the air bubble), and 42.5 mL instead of 40 mL. • Large air bubble was present, but correct dose was measured (i.e., 40 mL, 23 mL)	
	Risk associated with Task Errors (Per URRA): • Sporadic administration of an underdose of <80% up to 7 times in 35 uses resulting in planned improvement of health situation is not being reached and decreased efficacy.	We note failure with this task might also result in overdose, in the instance where the user attempts to draw additional volume beyond the intended dose to account for air bubbles. Based on discussion with the OND review team (i.e., clinical, clinical pharmacology), we find the risk associated with the dosing errors with this task is acceptable from a clinical perspective.
	Relevant RCA/Subjective Feedback/Observation: • Did not notice air bubble • Confusion over air bubbles – mistook the air bubbles for	The RCA and subjective feedback indicated some participants either overlooked a large air bubble or did not remove the air bubble because they did not consider

Table 4. HF Validation Study Results
Legend: RCA = root cause analysis; UD = use difficulty; UE = use error; URRA = use-related risk analysis, V2C = caregiver participant, V2N = HCP participant, V2PH = pharmacist participant

	Information Supplied by Applicant	DMEPA's Findings and Recommendations
	"space" • Did not use IFU • Unwilling to follow guidance/indifference - observed the air bubbles, but perceived them as not serious since not injecting the medication • Perception of bubbles – didn't think the air bubbles were large so did not attempt to remove • Focused on dosing and may have not paid attention to the bubbles	it large. Additionally, some participants did not refer to the IFU and thus were unaware of this step.
	Applicant Comment and Proposed Mitigations: • The Applicant noted all caregivers administered a clinically effective dose, with most caregivers compensating for air bubbles by measuring more medication rather than pushing medication back into the syringe to remove the air bubble. • The Applicant did not propose mitigations in response to participant performance.	IFU Step 10 states "If large air bubbles appear in the syringe, push the oral solution back into the amber bottle and then pull down on the plunger again to draw up your dose" and includes graphics that depict large air bubbles. We did not identify areas of improvement and have no recommendations at this time.
Task: Store syringe in a clean and dry place at room temperature ("How would you store the oral syringe?") Scenario: Knowledge task Events: UE; Participant Type: V2C (n=6),	Observed events: • Unable to find the information in the IFU • Stated they would store the oral syringe in a Ziploc bag, in a plastic container, with their kitchen utensils, in the medicine cabinet, and/or in the dishwasher rack • Stated they would discard the syringe (would not store) • Stated they would flush the syringe the normal saline or obtain another one • Some participants also noted they would not keep the folding box (i.e., carton)	
	Risk associated with Task Errors (Per URRA): • Sporadic underdose of <80% up to 7 times in uses which	

Reference ID: 5134531

Table 4. HF Validation Study Results
Legend: **RCA** = root cause analysis; **UD** = use difficulty; **UE** = use error; **URRA** = use-related risk analysis, **V2C** = caregiver participant, **V2N** = HCP participant, **V2PH** = pharmacist participant

	Information Supplied by Applicant	DMEPA's Findings and Recommendations
(n=13) / V2N (n=7) CC (n=0) UD (n=0)	poses risk that planned improvement of health situation is not reached and decreased efficacy (in the instance a user disposes the syringe and uses a different syringe with different graduations/accuracy) • Sporadic overdose of >120% than intended up to 7 times in 35 uses which poses risk of possible side effects such as decreased appetite, headache, neutropenia, rash, renal impairment, bleeding, and eye related adverse events (in the instance a user disposes the syringe and uses a different syringe with different graduations/accuracy) • Leachables ingestion resulting in allergic reaction or toxic effect on the patient (in the instance a user disposes the syringe and uses a different syringe)	
	Relevant RCA/Subjective Feedback/Observation: • IFU o IFU design/layout: assumed the information would be at the end of the administration steps or after cleaning of the syringe and/or expected the information to be on the side of the IFU that includes cleaning instructions o Did not use the IFU • Would expect the pharmacist to explain all the information they needed	The RCA and subjective feedback indicate that the location of the oral syringe storage information could be information can be improved. For example, a participant stated it was difficult to find the information in the IFU and they would assume it would be after cleaning steps in the IFU.
	Applicant Comment and Proposed Mitigations: • The Applicant did not propose mitigations in response to participant performance.	IFU Section C includes instructions for cleaning the oral syringe. However, this IFU section does not inform users where or how to store the oral syringe after cleaning. As such, given the subjective feedback and general order of use, we note the oral syringe storage information in the IFU should be located in close proximity to the oral

Table 4. HF Validation Study Results
Legend: RCA = root cause analysis; UD = use difficulty; UE = use error; URRA = use-related risk analysis, V2C = caregiver participant, V2N = HCP participant, V2PH = pharmacist participant

	Information Supplied by Applicant	DMEPA's Findings and Recommendations
		syringe cleaning instructions. We provide a recommendation in Table 5 below. We find the recommendation can be implemented without the submission of additional HF data.
Task: Disposal ("How should you dispose of the medication?") Scenario: Knowledge task Events: UE (n=9); Participant Type: V2PH (n=2), V2C (n=6), V2N (n=1) CC (n=0) UD[f] (n=0)	Observed events: • Stated an incorrect response including dispose using coffee grounds, discard in the trash or sharps, or discard down the sink or toilet	
	Risk associated with Task Errors: • User may be exposed to drug product	
	Relevant RCA/Subjective Feedback/Observation: • Instructions for pharmacist are unclear • Did not use IFU • Safe disposal misconception: believed disposing the solution into domestic wastewater would be the safest method of disposal • Convenience: stated it would be convenient to dispose of the solution via domestic wastewater	The RCA and subjective feedback indicated confusion with the term "wastewater" and lack of clarity regarding the instructions the pharmacist or HCP should give to a lay user regarding correct disposal (e.g., the IFU and Prescribing Information do not provide pharmacists or HCPs with detailed information regarding correct disposal). We note that after RCA and discussion with the moderator, the participants provided a correct or reasonable response (e.g., follow hospital policy, refer to the PI) to the knowledge task question.
	Applicant Comment and Proposed Mitigations:	The IFU states "(b) (4)

[f] The HF validation study results report lists participant V2PH04's performance in at the beginning of section 9.8.1.12 as a UE, but as a UD at the end of section 9.8.1.12. Based on our review of the RCA and subjective feedback, we consider V2PH04's performance for this task as a UE.

Table 4. HF Validation Study Results
Legend: RCA = root cause analysis; UD = use difficulty; UE = use error; URRA = use-related risk analysis, V2C = caregiver participant, V2N = HCP participant, V2PH = pharmacist participant

	Information Supplied by Applicant	DMEPA's Findings and Recommendations
	• The Applicant did not propose mitigations in response to participant performance.	[redacted] (b) (4) ". We find the terminology used may not be readily understood by lay users. Additionally, we note the disposal guidance for pharmacist and HCPs is unclear. We provide recommendations in Table 5 below. We find the recommendations can be implemented without the submission of additional HF data.
Task: [In the event of spillage] Wash your hands with soap and water ("If the medication got into your eyes or skin, what would you do?") Scenario: Knowledge task Events: UE (n=3); Participant Type: V2PH (n=1), V2C (n=2) CC (n=0) UD (n=0)	Observed events: • Responded incorrectly and stated they would: o Use a wet cloth to wash solution off the skin o Contact their pharmacist and look at the IFU • Did not provide a response	
	Risk associated with Task Errors (Per URRA): • Product is accidentally spilled onto skin leading to potential allergy	
	Relevant RCA/Subjective Feedback/Observation: • IFU o IFU layout: unable to locate the information in the IFU (could not locate Section C) o Did not refer to the correct section of the IFU o Did not use the IFU	The RCA and subjective feedback indicate that the location of the information in the IFU is not prominent and may be overlooked.
	Applicant Comment and Proposed Mitigations: • The Applicant did not propose mitigations in response to participant performance.	We note the IFU includes a dedicated section titled [redacted] (b) (4) " which informs users how to address an accidental exposure. This section is located on the right panel of the IFU. We find the location and title of the spillage cleaning instructions section can be improved. We provide a recommendation in Table 5 below. We find the recommendation can be

Reference ID: 5134531

Table 4. HF Validation Study Results
Legend: RCA = root cause analysis; UD = use difficulty; UE = use error; URRA = use-related risk analysis, V2C = caregiver participant, V2N = HCP participant, V2PH = pharmacist participant

	Information Supplied by Applicant	DMEPA's Findings and Recommendations
		implemented without the submission of additional HF data.
Task: Spillage cleaning ("If you spilled any medication, how would you clean it?") Scenario: Knowledge task Events: UE (n=10); CC (n=0); UD (n=0) Participant Type: V2PH (n=1), V2C (n=8), V2N (n=1)	Observed events: • Did not state the spillage cleaning method as listed in the IFU	
	Risk associated with Task Errors (Per URRA): • Accidental exposure leading to potential allergy	
	Relevant RCA/Subjective Feedback/Observation: • Did not use IFU • Expected information to be on the carton • Believed that standard cleaning approaches would be sufficient • Available hospital supplies/current practice	The RCA and subjective feedback indicate some participants were expected to find the information on the carton. We also note that healthcare institutions may have their own in-house policies and procedures for cleaning medication spills.
	Applicant Comment and Proposed Mitigations: • The Applicant did not propose mitigations in response to participant performance.	Refer to the row above (Wash your hands with soap and water knowledge task) for our assessment of this task and suggested recommendation to decrease use risk.

3.1 ANALYSIS OF OTHER CRITICAL AND NON-CRITICAL TASK ERRORS

The HF validation study showed use errors, use difficulties, and close calls with the tasks listed below in this section. However, based on our review of the available assessment of these use error/use difficulties/close calls, the available participants' subjective feedback (including when participants' subjective feedback did not indicate any potential issue with the user interface), and the Applicant's root cause analysis, we find the proposed labels and labeling include information that is prominently placed to address the use errors, use difficulties, and close calls with the tasks below.

We also find the labels and labeling are in alignment with best labeling practices. Subsequently, we did not identify further need for risk mitigation strategies at this time to address the use errors related to the tasks below and determine that the residual risks are acceptable.

Pharmacist reconstitution tasks

- Remove the child-resistant cap from the bottle, by pushing it down and turning counterclockwise
- Place the cap back onto the bottle and turn it clockwise to close it and make sure the cap is securely attached.
- Repeatedly turn the bottle upside and then back upright (or gently shake)
- Label the bottle with the expiry date
- Inform the patient or caregiver of the dose and the expiry date knowledge task (What information would you tell the patient/caregiver when you give them the medication?)
- Check the solution expiry date
- Check the solution expiry date knowledge task (When does the solution expire?)

Lay caregiver and HCP administration tasks

- Gently swirl the bottle for 30 seconds to mix the solution knowledge task (If foam appears on the solution after you swirl the bottle, what should you do ?): 1 caregiver participant stated that they would try to shake the bottle more if they saw foam. Additionally, 2 HCP participants stated they would either check the bottle label to see if foaming was normal and/or would call the pharmacy. None of the participants referred to the IFU, which led them to be unaware of this step. We note the subjective feedback and RCA did not indicate confusion with the user interface.
- Check if there is a bottle adapter already inserted in the bottle neck task: A caregiver participant initially removed the dosing adapter and attempted to withdraw the medication because they thought the syringe would not fit into the dose adapter. The

Reference ID: 5134531

participant believed the dosing adapter was a cover and was used to products where you can directly insert the syringe into the bottle. We note the presence of a bottle adapter is not unique for the proposed oral solution.

- Insert the tip of the oral syringe into the opening of the bottle adapter and pull the plunger to measure the dose tasks: A caregiver participant removed the plunger and poured the medication directly into the syringe barrel. The participant estimated the 23 mL dose and measured 21 mL prior to referring to the IFU but performed the task correctly after reading the IFU. The participant stated they have not previously used an oral syringe. After completion of administration and referring to the IFU, the participant measured 20 mL using the correct method but did not administer the medication because it could "overmedicate them" (e.g., administer an additional dose), and the participant indicated they just wanted to see if they could correctly withdraw the medication. We note the participant's inexperience with oral syringes contributed to the use error. We also note the proposed oral syringe is standard and use of an oral syringe is not unique for oral solutions.
- Pull the plunger to measure the dose: 2 caregiver participants and 1 HCP participant administered incorrect doses of 23.5 mL instead of 23 mL, 24 mL instead of 23 mL, and 40.5 mL instead of 40 mL. The RCA and subjective feedback indicated participants did not notice they withdrew the incorrect amount and believed they had measured the correct amount. The participants did not note confusion with the user interface. We note the proposed oral syringe is standard and use of an oral syringe is not unique for oral solutions. We also note the OND review team determined the small volume dosing errors observed in the HF validation study are acceptable from a clinical perspective.
- Carefully turn the bottle upside down
- Continue to hold the plunger in place, turn the bottle back around and place it onto a flat surface
- [If administering orally] Place the end of the oral syringe inside the mouth with the tip touching inside of either cheek
- Whilst still holding the plunger, remove the oral syringe from the bottle by gently pulling straight up.
- Clean the oral syringe
- Use a new syringe for each new bottle knowledge task (When should you start to use a new oral syringe?)
- Disposal knowledge task (How should you dispose of the oral syringe?)
- [Before and after administration] Flush the feeding tube in line with the feeding tube manufacturer's instructions

Reference ID: 5134531

4 LABELS AND LABELING

Tables 5 and 6 below include the identified medication error issues with the submitted product samples, packaging, label and labeling, our rationale for concern, and our proposed recommendations to minimize the risk for medication error. Additionally, we note that the DMEPA 2 primary review team evaluated the product specific label and labeling under a separate cover and additional label and labeling comments will be sent to the Applicant based on the outcome of that review.[g]

Table 5. Identified Issues and Recommendations for Division of Oncology 2 (DO2)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Full Prescribing Information – Section 2 Dosage and Administration			
1.	The Prescribing Information (PI) does not include reconstitution instructions.	In the human factors (HF) validation study, subjective feedback for the firmly tap the sides of the bottle to loosen the powder task, indicated some pharmacist participants expected to find the reconstitution instructions in the PI or Instructions for Use (IFU). Confusion regarding how to prepare the product might result in wrong technique and wrong dose medication errors.	We recommend including reconstitution instructions in Section 2. See example below: 1. Tap bottle to loosen powder. 2. Add 90 mL of distilled or purified water for reconstitution. 3. Replace cap and invert or gently shake for up to 5 minutes until fully dissolved. 4. Separate the dosing adapter from oral syringe and insert the adapter into bottle neck. 5. Write the discard after date. The solution expires 35 days after reconstitution. 6. Dispense solution in original container with the oral syringe provided.
Full Prescribing Information – Section 16 How Supplied/Storage and Handling			

[g] Stewart, J. Label and Labeling Review for Mekinist (trametinib) NDA 217513. Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2023 FEB 23. TTT ID#.: 2022-926.

Reference ID: 5134531

Table 5. Identified Issues and Recommendations for Division of Oncology 2 (DO2)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
1.	Section 16 does not provide pharmacists and healthcare professionals (HCPs) with clear information regarding disposal.	In the HF validation study, subjective feedback for the disposal knowledge task indicated subjective feedback indicated a lack of clarity regarding the disposal instructions the pharmacist or HCP should give to lay users. Based on the use-related risk analysis (URRA), failure to properly dispose of the solution might result in exposure to the drug product.	We recommend clarifying the disposal information in Section 16.
Instructions for Use			
1.	IFU Step 3 can be improved to reiterate that lay caregivers) should not attempt to reconstitute the product.	In the HF validation study, 7 participants indicated that if they received the medication and it was a powder (i.e., due to a dispensing error), they would read the instructions for how to reconstitute the product in order to attempt reconstitution. Based on the URRA, if caregivers attempt to reconstitute the product there is risk of chronic underdose or chronic overdose.	Revise the 1st bullet in IFU Step 3 from "(b) (4) " to "If you have powder, do not (b) (4) Mekinist and contact your pharmacist or healthcare provider".
2.	The location of the oral syringe storage information is not prominent and may be overlooked.	In the HF validation study, several participants were unable to the find the information regarding how to store the oral syringe or experienced difficulty finding the information. Additionally, subjective feedback indicated that participants expected to find the information at the end of the IFU	We recommend relocating the oral syringe storage information to appear immediately after the cleaning the oral syringe information. Alternatively, we recommend repeating the oral syringe storage information immediately after the cleaning the oral syringe information.

Reference ID: 5134531

Table 5. Identified Issues and Recommendations for Division of Oncology 2 (DO2)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		or in close proximity to the cleaning the oral syringe instructions. Based on the URRA, failure to properly store the oral syringe might result in underdose, overdose, or leachables ingestion.	
3.	The IFU does not clearly describe how to dispose of unused medication. Additionally, the statement, (b) (4) includes unclear terminology.	In the HF validation study, subjective feedback for the disposal knowledge task indicated subjective feedback indicated participant confusion with the term "(b) (4)". Based on the URRA, failure to properly dispose of the solution might result in exposure to the drug product.	Clarify the disposal information such that it is more readily understood by lay users and provides instructions on how to properly dispose unused medication.
4.	The location of the spillage cleaning instructions is not prominent and may be overlooked.	In the HF validation study, several participants were unable to locate the spillage cleaning instructions in the IFU. Based on the URRA, failure to properly clean spillage of the product might result accidental exposure leading to potential allergy.	Include spillage cleaning instructions in the Important Information You Need to Know Before Taking MEKINIST section. Additionally, consider revising the title of the section from (b) (4)" to "Clean up Spilled MEKINIST".

Reference ID: 5134531

Table 6. Identified Issues and Recommendations for Novartis Pharmaceuticals Corporation (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Carton Labeling			
1.	The reconstitution instructions on the carton labeling directed to the pharmacist can be improved to decrease vulnerability to medication error.	In the HF validation study, several lay caregiver and HCP participants referred to the reconstitution instructions on the carton labeling; however, your proposed product is designed such that only pharmacists should reconstitute the proposed product. We are concerned that the formatting (b) (4) and location (b) (4) of the reconstitution instructions increases the prominence of this information and may encourage lay caregivers and HCPs to perform reconstitution tasks.	Revise reconstitution instructions on carton labeling as follows: "To the pharmacist: Reconstitute before dispensing. Tap bottle to loosen powder. Add 90 mL of distilled or purified water for reconstitution. Replace cap and invert or gently shake for up to 5 minutes until fully dissolved. Separate the dosing adapter from oral syringe and insert the adapter into bottle neck. Write the discard after date. The solution expires 35 days after reconstitution. Dispense solution in original container with the oral syringe provided." Additionally, relocate the reconstitution instructions to the panel with the storage information and move the manufacturer information (currently below the storage information) to another panel.
2.	We acknowledge you implemented the post-validation revision to add "(b) (4) to the reconstitution	In the HF validation study, 9 use errors occurred in which participants did not wash hands, sanitize, or use gloves during reconstitution, preparation, or administration of the medication. We note the subjective feedback and root cause analysis (RCA) indicate that study artifact,	Remove (b) (4) from the reconstitution instructions. Additionally, refer to carton labeling recommendation #1 above.

Table 6. Identified Issues and Recommendations for Novartis Pharmaceuticals Corporation (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	instructions based on participant performance in your HF study; however, we find this revision may contribute to vulnerability of medication error.	negative transfer, and personal preference contributed to the use errors. We are concerned that the revision to add (b) (4) to the carton labeling does not address the use errors. Furthermore, the addition of the proposed carton labeling revision adds clutter and detracts from more critical product information. Additionally, we find the task of washing hands is standard practice for preparation of all medications.	

5 CONCLUSION AND RECOMMENDATIONS

Our review of the results of the human factors (HF) validation study identified use errors, close calls, and use difficulties with critical tasks; however, based on our review, we find the residual risks are acceptable or can be further mitigated via additional labels and labeling revisions for these use-related events. Thus, in this specific instance, we find the simulated use HF validation study results are acceptable provided our recommendations are implemented.

We provide recommendations that we advise are implemented during this review cycle of NDA 217513. These changes can be implemented without submitting additional HF validation testing results for Agency review. Above, we have provided recommendations in Table 5 for the Division and Table 6 for the Applicant. We ask that the Division convey Table 6 in its entirety to the Applicant so that recommendations are implemented prior to approval of this NDA 217513.

5.1 RECOMMENDATIONS FOR NOVARTIS PHARMACEUTICALS CORPORATION

Our review of the results of your human factors (HF) validation study for Mekinist (trametinib) for oral solution identified areas of vulnerability in your labels and labeling that may lead to medication errors. We provide recommendations in Table 6, and we recommend that you implement these recommendations and submit the revised labels and

labeling. We have determined that in this instance, you may implement these revisions without submitting additional HF validation data for Agency review.

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. BACKGROUND INFORMATION ON HUMAN FACTORS ENGINEERING PROCESS

The background information can be accessed in the HF results report. See Appendix B.

APPENDIX B. HUMAN FACTORS VALIDATION STUDY RESULTS REPORT

The HF study results report can be accessed in EDR via:
\\CDSESUB1\EVSPROD\nda217513\0021\m3\32-body-data\32p-drug-prod\tmt212-powder-for-oral-solution-4-7mg-01\32p2-pharm-dev\pharmaceutical-development-hfesr.pdf

APPENDIX C. INFORMATION REQUESTS ISSUED DURING THE REVIEW

On 1/27/2023, we issued an Information Request (IR) to request a description of participant performance in the HF validation study for instances where the participant did not administer the intended dose. Additionally, we requested a side-by-side comparison of and justification for post validation revisions to the user interface. On 2/3/2023, the Applicant did provide an acceptable response on that can be accessed in EDR via:

\\CDSESUB1\EVSPROD\nda217513\0038\m5\53-clin-stud-rep\535-rep-effic-safety-stud\glioma\5354-other-stud-rep\hf-validation-study\human-factors-study.pdf

APPENDIX D. LABELS AND LABELING

D.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[h] along with postmarket medication error data, we reviewed the following Mekinist labels and labeling submitted by Novartis Pharmaceuticals Corporation received on August 17, 2022 and November 23, 2022.

- Container label received on August 17, 2022
- Carton labeling received on November 23, 2022
- Instructions for Use and Prescribing Information (Images not shown) available from \\CDSESUB1\EVSPROD\nda217513\0021\m1\us\proposed-clean.pdf

D.2 Label and Labeling Images

Container label

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

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EBONY A WHALEY
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COLLEEN L LITTLE
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LOLITA G STERRETT
03/02/2023 10:31:16 AM

CHI-MING TU
03/02/2023 01:21:50 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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SHARON R MILLS
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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)

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

Date of This Review:	February 23, 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)
Product Type:	Combination Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Novartis Pharmaceuticals Corporation
FDA Received Date:	August 17, 2022, November 21, 2022, November 23, 2022 and December 1, 2022, January 9, 2023, February 1, 2023
TTT ID #:	2022-926
DMEPA 2 Safety Evaluator:	Janine Stewart, PharmD
DMEPA 2 Team Leader:	Ashleigh Lowery, PharmD

Reference ID: 5131291

1 REASON FOR REVIEW

Novartis Pharmaceuticals Corporation has submitted New Drug Applications (NDAs) for Mekinist® (trametinib) powder for oral solution (NDA 217513) for use in combination with Tafinlar® (dabrafenib) tablet for oral suspension (NDA 217514) for a new indication in the treatment of pediatric patients 1 year of age and older with BRAF V600E mutation-positive low-grade glioma. Both proposed products were developed as age-appropriate pediatric oral formulations in response to postmarketing requirements.

As part of the approval process for Mekinist (trametinib) powder for oral solution, the Division of Oncology 2 (DO2) requested that we review the proposed Prescribing Information (PI), Patient Information, Instructions for Use (IFU) container label, and carton labeling for areas of vulnerability that may lead to medication errors. The submitted human factors validation study is being reviewed under separate cover.

Tafinlar® (dabrafenib) tablet for oral suspension (NDA 217514) label and labeling is reviewed under a separate cover.

1.1 REGULATORY HISTORY

Mekinist (trametinib) was originally approved on May 29, 2013 under NDA 204114 and is currently available as 0.5 mg and 2 mg tablets. As described above, Novartis submitted NDA 217513 for a new powder for oral solution formulation of Mekinist® for a new indication in combination with dabrafenib 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 Mekinist to include both Mekinist tablets (NDA 204144) and Mekinist powder for oral solution (NDA 217513) in a shared PI.

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

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

Reference ID: 5131291

Table 1. Materials Considered for this Review	
Material Reviewed	Appendix Section (for Methods and Results)
Other	F – N/A
Labels and Labeling	G

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

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

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

Prescribing Information

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)min patents 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 powder for oral suspension.

We note Section 2.3 can be improved by adding subheadings to distinguish preparation and administration of Mekinist for oral solution from the administration information for Mekinist tablets.

Further, Section 16 *Storage and Handling* can be improved to clearly indicate Mekinist oral solution must be stored in the original bottle. Thus, the PI can be revised to support the safe and effective use of the product.

Patient Information

We note the patient information can be improved to include information for how to manage dosing if vomiting occurs after taking a dose of Mekinist.

Instructions for Use

(b) (4)

In addition, we note Step 5 states "Gently swirl the bottle for 30 seconds to mix the solution" prior to administration. However, it is unclear why an oral solution requires additional mixing after reconstitution. We communicated with OPQ via email on February 9, 2023 regarding this dosage form-related discrepancy. In their response, OPQ stated the product is a solution once

it is reconstituted and remains a solution. Thus, we propose revisions to support the safe and effective use of the product.

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 Mekinist PI, Patient Information, IFU, 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.

Note that DMEPA 2 is evaluating the HF validation study results under separate cover and based on the outcome of that review, additional label and labeling comments may be forthcoming.

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 MEKINIST administration. For example:

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

b. In section 2.3 under Preparation and Administration revise the preparation instructions to appear as numbered steps and to include instructions to begin by tapping the bottle to loosen the powder and to remind providers to insert the bottle adapter. We recommend this revision to ensure the powder readily dissolves into solution and that patients receive the bottle fitted with the adapter to facilitate dose measurement as described in the IFU. Consider the following revision:

1. Tap bottle until all powder flows freely
2. Add 90 mL of distilled or purified water.
3. Replace cap and invert the bottle repeatedly or gently shake for up to 5 min, until fully dissolved.

Reference ID: 5131291

4. Insert the bottle adapter pressing hard until fully inserted.
5. Dispense solution in original container with the dosing syringe provided.

c. Revise Mekinist for Oral Solution storage information after reconstitutions to include the requirement that the solution should be stored in the original bottle to read as follows:

> After reconstitution, store in original bottle below 25°C (77°F) and do not freeze.

2. How Supplied/Storage and Handling Section

a. Consider adding a description of the flavor of the reconstituted solution (e.g., strawberry flavored) to complete the description of the powder for oral solution.

b. Revise the after-reconstitution storage statement to include the requirement to store the oral solution in the original bottle.

B. Patient Information

1. How should I take MEKINIST?

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

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

C. IFU

1. How should I store MEKINIST?

a. In the '*Mekinist oral solution*' section, there are instructions to "Keep MEKINIST oral solution in the box it comes in …". Per OPQ's review of the stability data, once reconstituted in the amber bottle the Mekinist solution does not need to be stored in the original box. The reconstituted solution stored in amber bottle exposed to normal light is stable for 35 days. Therefore, we recommend revising the statement to read as follows:

> Store MEKINIST oral solution away from direct light and may be stored in the box it comes in.

b. In the '*Oral syringe'* section, the statement "(b) (4) " may be revised as follows to allow for instances where the original box is not available and to remove (b) (4)

> Store your oral syringe with your MEKINIST oral solution.

2. Measuring and taking or giving a dose of MEKINIST oral solution
    a. The proposed product is dispensed to end users after it is reconstituted to an oral solution. However, under IFU Section A, we note Step 5 which states "Gently swirl the bottle for 30 seconds to mix the solution". Further, the URRA included an assessment that failure perform this step poses the risk of the solution being non-homogeneous which could result in underdose (or overdose). It is unclear why a reconstituted oral solution would not remain in solution and would require additional mixing prior to each administration. We communicated with OPQ via email on February 9, 2023 regarding this dosage form-related discrepancy. In their response, OPQ stated the product is a solution once it is reconstituted and remains a solution. Thus we recommend removing the language that instructs users to "gently swirl the bottle for 30 seconds to mix the solution."
3. As proposed, the IFU includes (b) (4) We recommend removing (b) (4) from the IFU.

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. Expressing the strength in a manner that is incongruent with the dosage and administration of the product complicates the calculating of dosage and has led to dosing errors. For clarity, revise the strength statement to read as follows:

    0.05 mg per mL*

    90 mL (when reconstituted)

2. Revise and add an asterisk to the sentence in the equivalency statement on the side panel that reads "After reconstitution…" to read as follows:

    *When reconstituted, each mL contains 0.05 mg of trametinib.

3. For consistency with the PI, revise the statement on the side panel, "(b) (4) …", to read: "Recommended Dosage: See prescribing information".

A. Container Labels

1. Remove the statement on the principal display panel (PDP) which reads "[redacted] (b) (4) and replace with a boxed statement that reads:

> To Pharmacist: Reconstitute before dispensing*. Dispense with the enclosed Patient Information and Instructions for Use.

2. Relocate and revise the "Date solution exp:___" statement to appear below "Discard any unused…" and to read Discard after: MM / DD / YYYY (Pharmacist: enter beyond use date)". We recommend this revision to improve the order of information and to prompt the pharmacy to enter a beyond use date at the time of reconstitution.
3. Revise the information on the side panel that begins beneath the equivalency statement to improve the order information as follows.

   Keep out of the reach of children.

   Recommended Dosage: See Prescribing Information

   Read the Instructions for Use before administering Mekinist.

   Storage: Store in original container to protect from light and moisture.

   Before reconstitution: Store the dry powder refrigerated at 2°C to 8°C (36°F to 46°F).

   After reconstitution: Store the solution at room temperature below 25°C (77°F). Do not freeze.

   Discard any unused solution 35 days after reconstitution.

   Discard after: MM / DD / YYYY (Pharmacist: Enter date)

B. Carton Labeling

1. Remove the statements on the principal display panel (PDP) which read "[redacted] (b) (4)" and replace with a boxed statement that reads:

> To Pharmacist: Reconstitute before dispensing*. Dispense with the enclosed Patient Information and Instructions for Use.

2. To reduce redundancy, remove the "(b) (4)" statement that appears at the bottom of the PDP.
3. Revise the information on the side panel that begins beneath the equivalency statement to improve the order information as follows.

   Keep out of the reach of children.

   Recommended Dosage: See Prescribing Information

   Carefully read the Instructions for Use before administering Mekinist for the first time.

   Storage: Store in original container to protect from light and moisture.

   Before reconstitution: Store the dry powder refrigerated at 2°C to 8°C (36°F to 46°F).

   After reconstitution: Store the solution at room temperature below 25°C (77°F). Do not freeze.

   Discard any unused solution 35 days after reconstitution.

4. Remove the statement on the PDP that reads "(b) (4) . Revise the statement to read "For administration by caregivers and healthcare professionals only. " We recommend this revision to use positive language to convey this limitation of administration.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Mekinist received on August 17, 2022 from Novartis Pharmaceuticals Corporation .

Table 2. Relevant Product Information for Mekinist	
Initial Approval Date	N/A
Active Ingredient	trametinib
Indication	Mekinist is a kinase inhibitor indicated as a single agent for the treatment of BRAF-inhibitor treatment-naïve patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutations as detected by an FDA-approved test. Mekinist is indicated, in combination with dabrafenib, for: • the treatment of patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutations as detected by an FDA-approved test. • the adjuvant treatment of patients with melanoma with BRAF V600E or V600K mutations, as detected by an FDA-approved test, and involvement of lymph node(s), following complete resection. • the treatment of patients with metastatic non-small cell lung cancer (NSCLC) with BRAF V600E mutation as detected by an FDA-approved test. • the treatment of patients with locally advanced or metastatic anaplastic thyroid cancer (ATC) with BRAF V600E mutation and with no satisfactory locoregional treatment options. • the treatment of adult and pediatric patients 6 years of age and older with locally advanced or metastatic solid tumors with BRAF V600E mutation who have progressed following prior treatment or have no satisfactory alternative treatment options *Proposed:* • *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*
Route of Administration	Oral
Dosage Form	Tablet Powder for Oral Solution *(proposed)*
Strength	0.5 mg, 2 mg 4.7 mg per bottle (0.05 mg/mL when reconstituted) *(proposed)*
Dose and Frequency	(See Full Prescribing Information in Appendix G)

Proposed:

Recommended Dosage for MEKINIST for Oral Solution (Weight-based Dose)

Body weight	Recommended dose total volume of oral solution once daily (trametinib content)
8 kg	6 mL (0.3 mg)
9 kg	7 mL (0.35 mg)
10 kg	7 mL (0.35 mg)
11 kg	8 mL (0.4 mg)
12 to 13 kg	9 mL (0.45 mg)
14 to 17 kg	11 mL (0.55 mg)
18 to 21 kg	14 mL (0.7 mg)
22 to 25 kg	17 mL (0.85 mg)
26 to 29 kg	18 mL (0.9 mg)
30 to 33 kg	20 mL (1 mg)
34 to 37 kg	23 mL (1.15 mg)
38 to 41 kg	25 mL (1.25 mg)
42 to 45 kg	28 mL (1.4 mg)
46 to 50 kg	32 mL (1.6 mg)
≥ 51 kg	40 mL (2 mg)

How Supplied

0.5 mg tablets: Yellow, modified oval, biconvex, film-coated tablets with 'GS' debossed on one face and 'TFC' on the opposing face and are available in bottles of 30 (NDC 0078-0666-15).

2 mg tablets: Pink, round, biconvex, film-coated tablets with 'GS' debossed on one face and 'HMJ' on the opposing face and are available in bottles of 30 (NDC 0078-0668-15).

Proposed: MEKINIST for oral solution: white or almost white powder in amber glass bottles, co-packaged with a press-in bottle adapter and an oral dosing syringe. Each bottle contains 4.7 mg of trametinib equivalent to 5.3 mg trametinib dimethylsulfoxide. Each mL of reconstituted strawberry-flavored solution contains 0.05 mg of trametinib.

Storage	Store refrigerated at 2°C to 8°C (36°F to 46°F). Dispense in original bottle. Do not remove desiccant. Protect from moisture and light. Do not place medication in pill boxes. Proposed MEKINIST for oral solution: Store refrigerated at 2°C to 8°C (36°F to 46°F). Store in the original carton to protect from light and moisture. After reconstitution, store below 25°C (77°F) and do not freeze. Discard any unused solution 35 days after reconstitution.

APPENDIX B. PREVIOUS DMEPA REVIEWS

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

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

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

- Container label received on August 1
- Carton labeling received on November 23, 2022
- Prescribing Information, Patient Information, and Instructions for Use for MEKINIST (Image not shown) received on January 9, 2023 available from \\CDSESUB1\EVSPROD\nda217513\0030\m1\us\proposed-clean.docx

G.2 Label and Labeling Images

[a] 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.

[b] 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.

[c] 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.

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

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ASHLEIGH V LOWERY
02/27/2023 11:28:25 AM

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}

Michele Fedowitz, M.D.
Team Leader (acting)
Good Clinical Practice Assessment Branch
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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/s/

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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.

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LASHAWN M GRIFFITHS
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