CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

217513Orig1s000

PRODUCT QUALITY REVIEW(S)

NDA OPQ Review and Evaluation

NDA 217513
Review # 01

OPQ RECOMMENDATION: APPROVAL

Drug Substance Retest Period: A cross reference is made to trametinib dimethyl sulfoxide drug substance sections of approved NDA #204114, registered as Mekinist®.
FDA Assessment: Retest date of (b) (4) months may be granted when stored at the proposed storage conditions

Drug Product Expiration Dating Period: Proposed shelf life is 24 months and storage condition is "Store in original container in order to protect from light and moisture. Store refrigerated at 2°C - 8°C (36°F - 46°F) until reconstitution" for the powder and "Store the reconstituted solution below 25°C (77°F) and do not freeze. Use within 35 days of reconstitution" for the solution.
FDA Assessment: An expiration dating period of 24 months may be granted when stored at the proposed storage conditions.

Drug Name/Dosage Form	Trametinib/Powder for oral solution
Strength	4.7 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Indication	Trametinib 4.7 mg powder for oral solution in combination with dabrafenib 10 mg dispersible tablets for the treatment of BRAF V600E mutation-positive low-grade glioma in pediatric patients 1 year of age and older
Applicant	Novartis Pharmaceutical Corporation
US agent, if applicable	N/A

[FDA will complete these sections.]

Submit Date(s)	August 17, 2022
Received Date(s)	August 17, 2022
PDUFA Goal Date	February 17, 2023
Division/Office	Division of Oncology 2/Office of Oncologic Diseases
Review Completion Date	January 31, 2023
Established Name	Trametinib
(Proposed) Trade Name	Mekinist
Pharmacologic Class	Kinase inhibitor
Recommendation on Regulatory Action	Approval

FDA assessment is indicated in colored fonts

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
SD 2	*08/17/2022*	*All*
SD4	*09/01/2022*	*All*
SD18	*11/22/2022*	*Biopharm*
SD26	*12/13/2022*	*OPMA*
SD29	*01/04/2023*	*DP*
SD30	*01/09/2023*	*OPMA*
SD33	*01/12/2023*	*OPMA*

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Substance	Rajan Pragani	Haripada Sarker
Drug Product	Tefsit Bekele	Xing Wang
Process and Facility	Diane Goll	Zhaoyang Meng
Microbiology	Julie Nemecek	Bryan Riley
Biopharmaceutics	Mei Ou	Mei Ou
Regulatory Business Process Manager	Janell Artis	
Application Technical Lead	Xing Wang	
ORA Lead	N/A	
Environmental	Tefsit Bekele	Xing Wang

ORBIS Partner Agency Quality Review Team (To be redacted for FOIA)

Agency	PRIMARY REVIEWER	SECONDARY REVIEWER
Anvisa	No reviewers assigned	No reviewers assigned
Israel Ministry of Health	(b) (4)	
Swissmedic Switzerland		

RELATED/SUPPORTING DOCUMENTS

DMFs:

[Applicant will complete]				[FDA will complete]	
DMF #	**Type**	**Holder**	**Item Referenced**	**Status**	**Comments**
Excipients					
(b) (4)	Type IV	(b) (4)		Adequate	Active. Supporting several NDAs/ ANDAs
	Type IV			Adequate	Active. Supporting several NDAs/ ANDAs
	Type V			Adequate	Refer to non-clinical review
Container closure system					
(b) (4)		(b) (4)		Adequate	Active. Supporting several NDAs/ ANDAs
				Adequate	Active. Supporting several NDAs/ ANDAs

Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	102175, 119309	TMT212 (trametinib)
NDA	204114	Mekinist (DS cross referenced)

CONSULTS

[FDA will complete this section.]

None

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Evaluation of the Quality Information

DIFFERENCES IN M3 MODULE IN SUBMISSIONS TO DIFFERENT AGENCIES

#	FDA (US)	Israel	Singapore	Switzerland	Brazil
(b) (4)					

1. EXECUTIVE SUMMARY

[FDA (b) (4) will complete this section.]
The applicant provided sufficient information to assure the identity, strength, purity, and quality of the proposed drug product. The applicant has adequately justified not to implement the (b) (4). All associated manufacturing, testing, packaging facilities were deemed acceptable. Based on the OPQ review team's evaluation of the information provided in the submission, OPQ recommends APPROVAL of NDA 217513 for MEKINIST® (trametinib) for oral solution.

Is the overall recommendation in agreement with the individual discipline recommendations? Yes

Recommendation by Subdiscipline:
Drug Substance - Adequate
Drug Product - Adequate
Quality Labeling - Adequate
Manufacturing - Adequate
Biopharmaceutics - Adequate
Microbiology – Adequate

Life Cycle Considerations:
[FDA (b) (4) to include any life-cycle considerations here]
None

2. APPLICATION BACKGROUND

The purpose of this NDA submission is to seek approval for trametinib in combination with dabrafenib for the treatment of pediatric patients 1 year of age and older with low-grade glioma who require systemic therapy.

Dabrafenib and trametinib have been investigated in multiple clinical studies, mostly in adult patients, as both single agents and in combination (hereafter referred to as "D+T") to treat patients with BRAF V600 mutation positive cancers since 2007. Following the initial approval of dabrafenib and trametinib in 2013, the combination therapy with D+T has been approved in over 80 countries worldwide for the treatment of advanced BRAF V600 mutation-positive solid tumors in adults including melanoma, non-small cell lung cancer, and anaplastic thyroid cancer (locally approved indications may vary), and has demonstrated a well established benefit risk profile in adult patients.

This application also seeks approval for novel age-appropriate pharmaceutical forms for dabrafenib (10 mg dispersible tablets) and trametinib (0.05 mg/mL oral solution after reconstitution) that can be conveniently dosed and administered in patients 1 year of age and older who are unable to swallow the solid dosage forms.

On March 28, 2022, FDA granted Breakthrough Therapy designation for dabrafenib in combination with trametinib for the treatment of pediatric patients one year of age and older with LGG with a BRAF V600E mutation who require systemic therapy.

On June 24, 2022, FDA granted Orphan Drug Designation for trametinib for the treatment of malignant glioma with BRAF V600 mutation.

3. SUMMARY OF CMC SPECIFIC PRESUBMISSION AGREEMENTS

The Applicant's Position:

Date	Description	Pre-NDA agreements
09-Aug-2021	Type C meeting (Written Responses only) to seek the FDA's agreement on whether Betadex Sulfobutyl Ether Sodium (USP, Ph. Eur.) can be considered a non-novel excipient when used in the trametinib powder for oral solution formulation.	FDA had no concerns with calling Betadex Sulfobutyl Ether Sodium a non-novel excipient given that Novartis has a Letter of Authorization to reference DMF (b) (4)

The FDA's Assessment: ***Consistent with FDA's records***

[FDA will complete this section.]

4. ENVIRONMENTAL ASSESSMENT

The Applicant's Position:

As set forth in 21 CFR Part 25.31(b), action on a New Drug Application (NDA) is categorically excluded from the requirement to prepare an Environmental Assessment (EA) or an Environmental Impact Statement (EIS) if the action increases the use of the active moiety, but the estimated concentration of the substance at the point of entry into the aquatic environment will be less than 1 part per billion (ppb). "Increased use", as defined in 21 CFR Part 25.5(a), will occur if the drug is "administered at higher dosage levels, for longer duration or for different indications than were previously in effect, or if the drug is a new molecular entity."

Novartis Pharmaceuticals Corporation is filing a New Drug Application for Tafinlar® (dabrafenib) dispersible tablets and Mekinist® (trametinib) powder for oral solution. Dabrafenib is an orally bioavailable inhibitor of B-Raf (BRAF) protein with potential antineoplastic activity. Trametinib is an orally bioavailable, reversible, highly selective, allosteric inhibitor of mitogen-activated extracellular signal regulated kinase 1 (MEK1) and MEK2. In the current NDA, Novartis is seeking approval for the combination of dabrafenib and trametinib in the following indication:

"TAFINLAR in combination with trametinib, 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."
"MEKINIST 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."

Novartis certifies that this submission for Tafinlar and Mekinist qualifies for a categorical exclusion in accordance with 21 CFR Part 25.31(b) as the estimated environmental intake concentration of the active moieties, dabrafenib and trametinib, will be significantly less than 1 ppb, based on the peak production estimates within the next five years.

Further, Novartis states that, to the best of its knowledge, no extraordinary circumstances exist which may significantly affect the quality of the human environment and would thus require the preparation of at least an Environmental Assessment.

The FDA's Assessment: ***Adequate***

The applicant requested categorical exclusion from the requirement for environmental impact assessment per 21 CFR 25.31. The applicant is only required to prepare an environmental analysis report if application increases the use of the active moiety and the estimated concentration of the substance at the point of entry into the aquatic environment will be 1 ppb or greater. The calculation for the expected introduction concentration (EIC) for trametinib was provided and it is significantly less than 1 ppb [redacted] (b) (4) ppb). The applicant's request for categorical exclusion is granted.

5. FACILITIES

Drug substance manufacturing, quality control and stability storage and testing facilities are listed below:

---------- [Applicant to fill] ----------			[FDA to fill]
Site/address	**FEI/DUNS**	**Responsibility**	**Recommendation**
(b) (4)			

Site/address	FEI/DUNS	Responsibility	Recommendation
(b) (4)			

Drug product manufacturing, packaging, quality control and stability storage and testing facilities are listed below:

---------- [Applicant to fill] ----------			[FDA to fill]
Site/address	FEI/DUNS	Responsibility	Recommendation
(b) (4)			

The FDA's Assessment: *Adequate*

Firms have acceptable compliance history and are approvable.

IR on combination product will be issued to Applicant:
Your product is a combination product defined under 21 CFR part 3.2(e). Combination products are subject to the current good manufacturing practices (CGMP) requirements applicable to each constituent part (drug, device, biological product) of the combination product. However, as reflected in the final rule on CGMPs for combination products (21 CFR part 4), manufacturers have the option to demonstrate compliance both with the drug CGMP regulations (21 CFR parts 210, 211) and with the device quality system (QS) regulation (21 CFR part 820) through a streamlined approach. In addition, for combination products that include a biological product constituent part, manufacturers must demonstrate compliance with the CGMP requirements specific to biological products in 21 CFR parts 600 through 680. In some cases, the combination product may be exempt from the device QS regulation (refer to the guidance for industry and FDA staff Current Good Manufacturing Practice Requirements for Combination Products (January 2017). Your combination product includes a device constituent part, an oral dosing syringe that is co-packaged with the drug product and does not result in a new use of the device constituent part. This device constituent part is exempt from the CGMP requirements of the device QS regulation (21 CFR 820), except for certain general requirements concerning records (21 CFR 820.180) and complaint files (21 CFR 820.198) that would be required if it were marketed separately as a medical device. Since a drug based CGMP streamlined approach is being used for the combination product and the device constituent part CGMP exemptions cover all of the part 820 provisions included in 21 CFR 4.4(b)(1), the Agency will consider the combination product manufacturer to be CGMP compliant as long as the CGMP operating system is compliant with parts 210 and 211 (no demonstration of compliance with part 820 will be necessary). The guidance for industry and FDA staff Current Good Manufacturing Practice Requirements for Combination Products (January 2017) indicates that "manufacturers should document their evaluation…if they believe a device constituent part is exempt from any or all provisions under the device QS regulations." Therefore, your documentation demonstrating compliance with 21 CFR part 4 should include your evaluation, or a copy of correspondence from the Agency confirming the exemption and must be available upon inspection.

Please revise the Field 24 of your FDA Form 356h to indicate that your proposed product is a combination product and identify the combination product type.

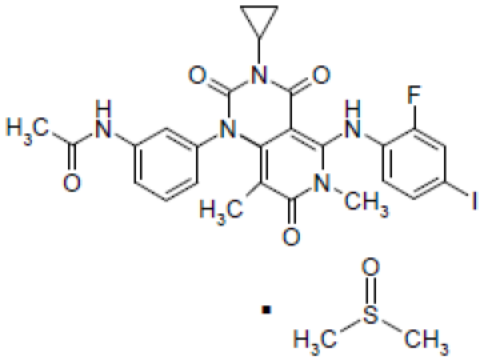
Response Sequence 24, SD 24, dated Dec 8, 2022, **Adequate**: Novartis acknowledges the Agency's comment and confirms that a copy of this Information Request confirming that the device constituent part is exempt from the CGMP requirements of the device QS regulation (21 CFR 820) will be available upon inspection. A revised FDA 356h Form indicating that the proposed product is a co-packaged combination product is provided with this response.

6. DRUG SUBSTANCE

A cross reference is made to trametinib dimethyl sulfoxide drug substance sections of approved NDA #204114, registered as Mekinist®.

a. General Description and Structure

Refer to Mekinist® (approved NDA #204114)

Structure	
	
USAN Name	Trametinib dimethyl sulfoxide
IUPAC Name	Equimolecular combination of N-(3-{3-cyclopropyl-5-[(2-fluoro-4-iodophenyl)amino]-6,8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydropyrido[4,3-*d*]pyrimidin-1(2*H*)-yl}phenyl)acetamide with (methylsulfinyl)methane
Molecular Weight	693.53 g/mol
Molecular Formula	$C_{26}H_{23}FIN_5O_4 \cdot C_2H_6OS$
Solubility	Trametinib dimethyl sulfoxide shows low aqueous solubility over a wide range of pH values
Polymorphism	One solid state has been identified for trametinib dimethyl sulfoxide, Form 1.
pK_a	Calculated basic pKa = 0.25 (acetamide)
Add others as needed	

The FDA's Assessment: ***Adequate***

Drug substance information for trametinib dimethyl sulfoxide to support NDA 217513 is cross-referenced from NDA 204114. Refer to the review of NDA 204114 Supplement 024 (3/7/22), which assessed the most recent drug substance updates. This information applies to all drug substance FDA assessment sections listed below this entry.

b. Drug Substance Manufacturing Process

Refer to Mekinist® (approved NDA #204114)

The FDA's Assessment: ***Adequate***

i. Starting Materials

Refer to Mekinist® (approved NDA #204114)

The FDA's Assessment: ***Adequate***

ii. Control of Intermediates

Refer to Mekinist® (approved NDA #204114)

The FDA's Assessment: ***Adequate***

c. **C**haracterization of Drug Substance and Impurities

Refer to Mekinist® (approved NDA #204114)

The FDA's Assessment: ***Adequate***

d. Control of Drug Substance

Refer to Mekinist® (approved NDA #204114)

The FDA's Assessment: ***Adequate***

i. Key Analytical Methods and Summary of Validation Data

Refer to Mekinist® (approved NDA #204114)

The FDA's Assessment: ***Adequate***

ii. Summary of batch data

Refer to Mekinist® (approved NDA #204114)

The FDA's Assessment: ***Adequate***

e. Container Closure System

Refer to Mekinist® (approved NDA #204114)

The FDA's Assessment: ***Adequate***

f. Stability Data

Refer to Mekinist® (approved NDA #204114)

The FDA's Assessment: ***Adequate***

Retest date of (b) (4) months may be granted when stored at the proposed storage conditions.

R. Regional Information

Refer to Mekinist® (approved NDA #204114)

Comparability Protocols for post-approval changes (if applicable)

The FDA's Assessment: ***Not Applicable***

7. DRUG PRODUCT

a. Drug Product Description and Composition

Trametinib 4.7 mg powder for oral solution is a white or almost white powder to be reconstituted with 90 mL of sterile water or purified water or bottled still drinking water prior to administration to achieve a concentration of 0.05 mg/mL of trametinib non-solvated parent.

Table: Composition and batch formula of the trametinib 4.7 mg powder for oral solution

Component	Quantity[1]		Batch Formula (kg)	Function	Quality Standards	IID Limit (mg)
	(mg/bottle)	% w/w				
Trametinib dimethyl sulfoxide	(b) (4)			Active ingredient	Novartis monograph	N/A
Betadex sulfobutyl ether sodium				(b) (4)	Ph. Eur., USP/NF	[4]
Sucralose					Ph. Eur., USP/NF	414
Citric acid monohydrate					Ph. Eur., USP/NF	315
Dibasic sodium phosphate					Ph. Eur., USP/NF	[4]
Potassium sorbate					Ph. Eur., USP/NF	[4]
Methylparaben					Ph. Eur., USP/NF	30
Flavour strawberry[3]					Novartis monograph	[4]
Total						

(b) (4)

[3] Commercially available flavoring pre-mix. All ingredients comply with EU regulations for flavoring agents and food additives and are also approved for use by FDA regulations or are listed as being generally recognized as safe (GRAS).

[4] No IID limit of this ingredient in powder for oral solution is listed in the FDA IID database.

Updates or edits made to this table during the review cycle captured by the FDA reviewer in red colored fonts

Qualitative composition of flavour strawberry

Ingredient	CoE[1] number	FEMA[2] number
(b) (4)		

Overage used: No. If yes, provide justification:
Overfill used: Yes. If yes, provide justification: To allow for accuracy of the delivered dose after reconstitution.
Commercial Scale: An overfill of (b) (4)% has been selected to ensure a deliverable dose of 4.7 mg of trametinib non-solvated parent per bottle to compensate the small amount of reconstituted solution retained inside the bottle and press-in bottle adapter.

The FDA's Assessment: ***Adequate***

Trametinib (Mekinist) are commercially available as immediate release tablets in 0.5 mg and 2 mg dosage strength for adult and pediatric patients. The basis for developing a liquid oral dosage form is to provide flexibility for patients that have difficulties swallowing the solid oral dosage form. Trametinib pediatric formulation was developed as immediate release, powder for oral administration following reconstitution with 90 mL

water. The applicant stated that clinical studies demonstrated that no dosage adjustment was needed when interchanging formulations. The product consists of 5.3 mg Trametinib dimethyl sulfoxide equivalent to 4.7 mg of trametinib non-solvated per bottle. The strength of the product is appropriately expressed based on the active moiety (non-solvated trametinib). An oral dosing syringe and a press in bottle adaptor are co-packaged to dose and deliver the reconstituted solution from the glass bottle. A (b) (4)% overage is included to ensure deliverable of the desired product dose. The (b) (4) g fill weight per bottle includes an overfill of (b) (4) mg. The (b) (4)% overfill appears excessive and the following information request was sent to the applicant on November 16, 2022.

An overfill of (b) (4)% for trametinib powder for oral solution is appears excessive. Reduce the overfill with justification or justify the inclusion of (b) (4)% overfill.

The applicant responded on November 22, 2022 and stated that three batches of trametinib powder for oral solution were tested for deliverable volume per USP <698>. The target volume after reconstitution is (b) (4) mL and (b) (4) mL of the solution is technically trapped in the system. The extra (b) (4) mL (b) (4)% overfill) is needed in order to compensate for volume trapped in the device. Another (b) (4) mL (b) (4)%) was proposed in order to allow removal of last doses of liquid from the bottle with the syringe connected to the press in bottle adaptor. The (b) (4)% overfill is adequately justified. The applicant's response is acceptable.

All excipients are compendial grade except Flavor strawberry and are tested per the respective monographs. The Flavor strawberry is only (b) (4)% w/w of the proposed drug formulation. The proprietary information which includes the quantitative composition of the flavor strawberry can be found in the referenced DMF (b) (4). The (b) (4) components that make up the flavor (b) (4) are either listed as being generally recognized as safe (GRAS) or approved for use as flavoring agents in food per their respective CFRs. The compounds regarded as GRAS are safe as food additives but not necessarily approved for use in pharmaceutical products. The components in the flavor excipient are not listed in the Inactive Ingredients Database; however, they are safe under the conditions of their intended use due to their low levels in the formulation. Their levels are considerably lower than the qualification limits for impurities. Even if one considers these components as impurities the safety risk associated with their presence in the drug product is low.

The levels of sucralose, citric acid monohydrate and methylparaben excipients in the formulation are lower than those present in other approved oral solution drug products. The MDE for potassium sorbate and dibasic sodium phosphate based on (b) (4) MDD is (b) (4) mg and (b) (4) mg respectively. These levels for the two excipients have not been used in other approved oral solutions. Betadex sulfobutyl ether sodium (b) (4) (b) (4) has also only been used in IV drug products. The non-clinical reviewer was consulted about the safety of potassium sorbate, dibasic sodium phosphate and (b) (4) levels in the formulation. The team confirmed that there are no safety concerns with the levels of excipients. None of the excipients are human or animal origin and no novel excipients are used in the drug product. The product is packaged in 180 mL amber glass

bottle [redacted]. Trametinib powder is co-packaged with a press-in bottle adapter and a 20 mL oral dosing syringe with 0.5 / 1 mL increment.

OPMA assessment of overfill max and min amount:
Each bottle contains an overfill of [redacted] % that allows withdrawal of the labeled amount (4.7 mg of trametinib non-solvated parent / bottle) of the drug product from the bottle after reconstitution with 90 mL of water.
[redacted]

Adequate from a process perspective

The applicant's justification for overfill is: *To allow for accuracy of the delivered dose after reconstitution*. Considering the label claim with the overfill amount was brought up with the drug product reviewer. Per DP Reviewer, [redacted]% overfill is a little excessive and will be addressed by way of IR asking the applicant to justify the inclusion of [redacted]% overfill with data or reduce the overfill.

b. Drug Product Manufacturing Process

(b) (4)

59 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page

8. BIOPHARMACEUTICS

a. BCS Classification

Applicant to fill:	FDA assessment (FDA to fill):
	The BCS designation is not requested by the Applicant.
BCS Classification: BCS II	Acceptable

Information to support the BCS Class II designation request, if applicable.
Link: Summary of biopharmaceutics is available in CTD section 2.7.1 of Tafinlar® NDA #217514 Page#:

Trametinib is administered as a reconstituted oral solution. Therefore, dissolution testing does not apply as an indicator of quality control. The bioavailability of trametinib oral solution is determined by its complete solubilization at time of reconstitution.

The potential impact of manufacturing process changes has been monitored through testing of the soluble content of drug substance after reconstitution of solution. The performance testing during batch release and stability analysis includes soluble content testing by HPLC.

b. Bridging Throughout Drug Product Development (Formulation, Process, or Site Change)

The composition of the proposed commercial formulation is the same as the one used for pivotal pediatric clinical study CDRB436G2201 and in registration stability studies.

Pivotal clinical batches were manufactured at pilot scale at (b) (4) (b) (4) The manufacturing process was then transferred to Sandoz S.R.L., Targu Mures, Romania, which is the proposed commercial manufacturing site.

The manufacturing process has been the same in terms of unit operations and their sequence throughout development with a few minor changes implemented as a consequence of process improvements. These minor adaptations included (b) (4) . A comparison of the equipment used during the various stages of development is provided in section 3.2.P.2.3.

Trametinib is administered as a reconstituted oral solution. The bioavailability of trametinib oral solution is determined by its complete solubilization at time of reconstitution, (b) (4)

(b) (4) The potential impact of manufacturing process changes has been monitored through testing of the soluble content of drug substance after reconstitution of solution. The performance testing during batch release and stability analysis includes soluble content testing by HPLC.

Link: 3.2.P.2.3 Page#: 12 to 14

The FDA's Assessment: ***Adequate***

The Applicant is seeking approval for the proposed drug product, Mekinist® (trametinib) powder for oral solution, 4.7 mg. The proposed drug product is the white or almost white powder to be reconstituted with 90 mL of sterile water or purified water or bottled still drinking water prior to administration to achieve a concentration of 0.05 mg/mL of trametinib non-solvated parent.

This NDA cross-references to the approved drug products from the same Applicant, Tafinlar® (dabrafenib) capsules, 50 mg and 75 mg (NDA 202806 approved on 05/29/2013) and Mekinist® (trametinib) tablets, 0.5 mg and 2 mg (NDA 204114 approved on 05/29/2013) for the benefits of dabrafenib and trametinib combination therapy, as proposed indication in labeling: "*MEKINIST is indicated, 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 recommended dosage in adult patients is 2 mg orally once daily. The proposed powder for oral solution (0.05 mg/mL after reconstitution) is available to subjects who are not able to swallow tablets because of age and disease progression. The recommended dosage in pediatric patients is based on body weight. The recommendation administration is to take Mekinist at least 1 hour before or at least 2 hours after a meal.

The Applicant conducted safety, efficacy, pharmacokinetics, pharmacodynamics, relative bioavailability clinical studies (e.g., CTMT212X2101, CDRB436G2201, CDRB436A2102, CDRB436G2101, and MEK115892) to support this NDA.

From the Biopharmaceutics perspective:

(1) (b) (4) . Therefore, the in vitro dissolution methodology is not proposed or needed as a quality control (QC) test for the proposed drug product, the trametinib powder for oral solution.

(2) The reconstitution time to dissolve a bottle of the proposed trametinib powder, 4.7 mg, in 90 mL of purified water at room temperature has been determined as (b) (4) minutes and proposed as one of the drug product specifications, which is under drug product purview. The reconstitution time has been monitored during development both at drug product release and during stability.

(3) The relative bioavailability, pharmacokinetics, safety, and palatability of the proposed trametinib power for oral solution and the commercial trametinib tablets were evaluated in the clinical study MEK115892 and CTMT212X2101/MEK116540. The late phase formulation of the proposed drug product [redacted] compared to the early phase formulation [redacted][1]. Per the Applicant, the trametinib bioavailability is mainly determined by [redacted] is not expected to affect the trametinib bioavailability. In addition, both the early and late phase formulations have been used in clinical studies [i.e., [redacted] (4.7 mg) used in clinical studies MEK115892 and CTMT212X2101; [redacted] (4.7 mg) used in clinical study CDRB436G2201] while the pharmacokinetics (PK) data/information is under purview of the Office of Clinical Pharmacology (OCP) to establish the scientific bridging. Since there are no formulation/composition changes of the proposed drug product from the pivotal clinical batch (i.e., in pivotal pediatric phase 2 study CDRB436G2201) to the commercial batches. The minor changes with regards to the manufacturing process appears not expected to impact the drug product in vivo performance. There is no change in commercial manufacturing site for final drug product. Therefore, scientific bridging throughout the drug product development appears to be established pending on the assessment of OCP.

c. Biowaiver Request

The Applicant's Position:

The NDA does not contain a biowaiver request

A biowaiver is not needed for trametinib powder for oral solution for the following reasons:

- There is only one strength of dosage form
- The composition of the proposed commercial formulation is the same as the one used for pivotal pediatric clinical study CDRB436G2201 and in registration stability studies
- The manufacturing process has been the same in terms of unit operations and their sequence throughout development with a few minor changes implemented as a consequence of process improvements. None of these changes have required

[1] \\CDSESUB1\EVSPROD\nda217513\0001\m3\32-body-data\32p-drug-prod\tmt212-powder-for-oral-solution-4-7mg-01\32p2-pharm-dev\pharmaceutical-development-formulationdevelopment.pdf

bioavailability bridging [redacted] (b) (4)

- Comparison to marketed solid dosage form has been evaluated by human PK study MEK115892 and popPK data evaluation of clinical study data, namely of the pivotal pediatric study CDRB436G2201

Link: Page#:

The FDA's Assessment: ***Adequate***

Biowaiver request is not submitted or needed.

d. Data to Support IVIVC and/or PBBM Modeling, If Applicable.

No IVIVC has been established as trametinib is administered as a reconstituted oral solution.

Link: Page#:

The FDA's Assessment: ***Adequate***

IVIVC and/or PBBM modeling is not submitted or needed.

9. LABELING

Refer to DMEPA reviews for the most recent USPI and carton/container label. The adequacy of the USPI is currently being evaluated by the clinical division. Below is a brief review of sections 3, 11, 16 and highlight section of the prescribing information.

USPI

Highlights: ***Adequate***

The established name, route of administration, dosage form and strength were provided and found acceptable from the CMC perspective.

Section 2 (if relevant): ***Adequate***

There was no insurrection for the preparation of the oral solution. The following request was conveyed to the applicant during labeling negotiation: "Include preparation instruction, physical description, and storage temperature for oral solution".

Section 3 Dosage Forms and Strengths: ***Adequate***

Under this section the following was included in original submission: (b) (4) . There was no description of the drug product. CMC recommends that the above is replaced with "White to almost white powder containing 4.7 mg of trametinib per bottle".

Section 11 Description: ***Adequate***

If the following excipients used in the drug product, include warning/declaration in the USPI:

(b) (4)

Description of the drug substance, molecular formula, weight, and structure were provided. The pharmacological class, physical/chemical properties, dosage form, strength, and route of administration were provided. A list of inactive ingredients was also provided. The information provided is acceptable. A minor change was recommended for the last paragraph and the updated version is shown below in red.

MEKINIST (trametinib) for oral solution is a white or almost white powder which produces a clear colorless solution when reconstituted with water. Each bottle contains 4.7 mg of trametinib equivalent to 5.3 mg trametinib dimethyl sulfoxide. Each mL of reconstituted trametinib solution contains 0.05 mg of trametinib non-solvated parent. The inactive ingredients of MEKINIST for oral solution are betadex sulfobutyl ether sodium, sucralose, citric acid monohydrate, dibasic sodium phosphate, potassium sorbate, methylparaben, and strawberry flavor.

Section 16 How Supplied/Storage and Handling: ***Adequate***
The storage temperature and how the drug product is supplied is accurately described. A minor change was recommended, and the updated version is shown below in red.

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.. (NDC xxxx-xxxx-xx).
>
> Store refrigerated at 2°C to 8°C (36°F to 46°F). Retain in the original container 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.

Manufacturer Information (Name and Address): ***Provided: Adequate***

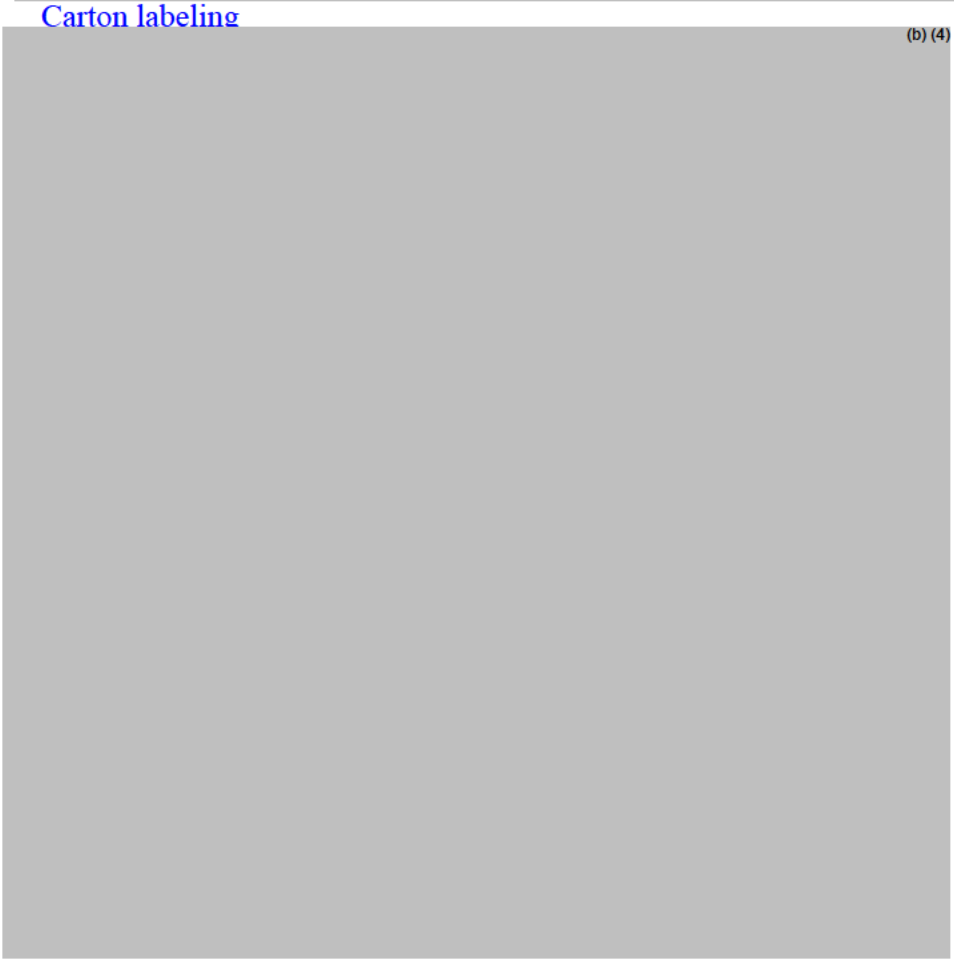
Carton/Container Label ***Adequate***
During an internal labeling meeting, it was discussed that the strength is better represented as 0.05 mg/mL instead of 4.7 mg per bottle. Refer to DMEPA's review for more details. CMC agrees with the 0.05 mg/mL strength expression. CMC also recommends that the applicant

Change " (b) (4) *to"Each bottle contains 4.7 mg of trametinib equivalent to 5.3 mg trametinib dimethyl sulfoxide" on the container label and carton labeling.*

The container/carton label and prescribing information comply with all regulatory requirements, and they are recommended for approval from a CMC perspective pending revision of what are noted above. The container label and carton labeling submitted in the original NDA are shown below.

Container label

Carton labeling



Final Risk Assessments

[FDA will complete this section.]
To the Review Team: *Keep the appropriate Table; delete the rest*

SOLID ORAL

Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments**
Assay, stability	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipment • Site	Low		Low	
Physical stability (solid state)	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	Low		Low	
Content Uniformity	• Formulation • Container closure • Raw material • Process Parameters • Scale/equipment • Site	High	(b) (4)	Low	
Moisture content	• Formulation • Container closure • Process parameters • Scale/equipment • Site	Low		Low	
Microbial Limits	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	Low		Low	
Dissolution – BCS Class II & IV	• Formulation • Container Closure • Raw materials • Process parameters • Scale/equipment • Site	Low		Low	

Recommendation Page

[FDA will complete this section.]

Drug Substance: Approval

Primary Reviewer: Rajan Pragani — Date: December 1, 2022
Secondary Reviewer: Haripada Sarker — Date: December 5, 2022

Drug Product: Approval

Primary Reviewer: Tefsit Bekele — Date: January 31, 2023
Secondary Reviewer: Xing Wang — Date: January 31, 2023

Process and Facility: Approval

Primary Reviewer: Diane Goll — Date: January 19, 2023
Secondary Reviewer: Zhaoyang Meng — Date: January 19, 2023

Biopharmaceutics: Approval

Primary Reviewer: Mei Ou — Date: November 22, 2022
Secondary Reviewer: Mei Ou — Date: November 22, 2022

Application Technical Lead: Approval

Xing Wang — Date: January 31, 2023

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/

XING WANG
01/31/2023 03:34:21 PM

RAJAN PRAGANI
01/31/2023 03:37:22 PM

HARIPADA SARKER
01/31/2023 10:12:19 PM

TEFSIT BEKELE
02/01/2023 06:25:20 AM

MEI OU
02/01/2023 07:40:12 AM

DIANE W GOLL
02/01/2023 08:49:10 AM

ZHAOYANG MENG
02/01/2023 08:50:39 AM

JULIE C NEMECEK
02/01/2023 08:52:18 AM

BRYAN S RILEY
02/01/2023 11:45:20 AM
I concur.