CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204114Orig1s000

OTHER REVIEW(S)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

PMR/PMC Description: Cardiomyopathy

PMR/PMC Schedule Milestones:		
	Final protocol Submission Date:	
	Study/Clinical trial Completion Date:	
	Final Report Submission Date:	09/30/2020
	Other: Final Analysis Plan Submission	9/30/2013
	Other: Interim Report Submission	09/30/2014
	Other: Interim Report Submission	09/30/2015
	Other: Interim Report Submission	09/30/2016
	Other: Interim Report Submission	09/30/2017
	Other: Interim Report Submission	09/30/2018
	Other: Interim Report Submission	09/30/2019

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☒ Unmet need
- ☒ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☐ Other

Metastatic melanoma is a life threatening condition with historical median survival times of 6 to 9 months and less than 10% of patients surviving beyond five years. Metastatic melanoma accounts for approximately 4% of all newly diagnosed melanoma cases. There are few FDA-approved treatments for metastatic melanoma—vemurafenib, ipilimumab, aldesleukin, and dacarbazine (DTIC).

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

Goals:

- (b) (4) and characterize risk of (b) (4) sequelae of trametinib-related cardiomyopathy
- Provide evidence-based dose modification and monitoring recommendations to inform labeling of cardiomyopathy

Risks:

- Assess a known serious risk
  - cardiomyopathy is increased in trametinib-treated patients; in a randomized (2:1) controlled trial in patients with BRAF V600E or V600K mutation-positive melanoma, cardiomyopathy occurred in 7% (14/211) of patients treated with dabrafenib and in none of the patients treated with chemotherapy (n=99)
  - cardiomyopathy was symptomatic in some patients
  - safety database of trametinib at the time of the NDA was not adequate to provide evidence-based recommendations for optimal dose modification and monitoring
  - longer follow-up in the primary clinical trial is likely not adequate to sufficiently characterize this risk, nearly half of chemotherapy-treated patients crossed over to receive trametinib at the time of disease progression
- Assess signals of serious risks
  - safety database is not of sufficient size to adequately identify and characterize the risk of known serious sequelae of cardiomyopathy, such as congestive heart failure, arrhythmias, thromboembolic events, and sudden cardiac death
  - signals of serious sequelae of cardiomyopathy were observed across the development program of trametinib, including trials of trametinib administered as monotherapy or in combination with other anti-cancer products, across multiple primary malignancy types.
  - five cases of sudden death occurred in the development program of trametinib, and there was one in a patient with documented dilated cardiomyopathy and normal coronary arteries
  - the background incidence of cardiovascular complications and mortality across oncologic patient populations confounds assessment of individual cases, comparative data using a trametinib unexposed control group is important in assessment of cardiovascular adverse event

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☐ Pediatric Research Equity Act
☒ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

☒ Assess a known serious risk related to the use of the drug?
☒ Assess signals of serious risk related to the use of the drug?
☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☒ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Submit cumulative safety analyses annually, and for one year after the last patient has completed clinical trial treatment, to identify and characterize the risk of cardiomyopathy and subsequent sequelae, including safety evaluations adequate to inform labeling of patient populations at highest risk for developing these toxicities and to provide evidence-based dose modification and monitoring recommendations, in all ongoing and subsequently initiated randomized controlled clinical trials through 2020 that use trametinib alone or in combination with other anti-cancer drugs.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies

Continuation of Question 4

☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☒ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
Risk of cardiomyopathy and serious sequelae thereof can be defined and characterized in planned or ongoing randomized clinical trials intended to support the efficacy trametinib in oncologic indications.
☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

☐ Other

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:
☐*This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

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/s/

MARC R THEORET
05/24/2013

JEFFERY L SUMMERS
05/24/2013

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

PMR/PMC Description: **Ocular Toxicity**

PMR/PMC Schedule Milestones:

Final protocol Submission Date:	-
Study/Clinical trial Completion Date:	
Final Report Submission Date:	09/30/2016
Other: Final Analysis Plan Submission	09/30/2013
Other: Interim Report Submission	09/30/2014

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☒ Unmet need
- ☒ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☐ Other

Metastatic melanoma is a life threatening condition with historical median survival times of 6 to 9 months and less than 10% of patients surviving beyond five years. Metastatic melanoma accounts for approximately 4% of all newly diagnosed melanoma cases. There are few FDA-approved treatments for metastatic melanoma—vemurafenib, ipilimumab, aldesleukin, and dacarbazine (DTIC).

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

Goals:

- Define and characterize risk of trametinib-related toxicity to the retina described as retinal pigment epithelial detachments (RPED)
- Provide evidence-based dose modification and monitoring recommendations to inform labeling of RPED

Risks:

- Assess a known serious risk
  - incidence of RPED across the entire development program of trametinib is approximately 1%, with varied outcomes in response to dose modifications
  - safety database of trametinib at the time of the NDA was not adequate to provide evidence-based recommendations for optimal dose modification and monitoring
  - longer follow-up in the primary clinical trial is likely not adequate to sufficiently characterize this risk, nearly half of chemotherapy-treated patients crossed over to receive trametinib at the time of disease progression

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☐ Pediatric Research Equity Act
☒ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

☒ Assess a known serious risk related to the use of the drug?
☐ Assess signals of serious risk related to the use of the drug?
☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☒ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Submit integrated safety analyses from an adequate number of randomized controlled clinical trial(s) to identify and characterize the risk of retinal pigmented epithelial detachments (RPED), including safety evaluations adequate to inform labeling of patient populations at highest risk and to provide evidence-based dose modification and monitoring recommendations in labeling of RPED events.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
Continuation of Question 4

☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☒ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
Risk of ocular toxicity can be assessed in an adequate number of patients from ongoing (or planned) randomized clinical trials intended to support the efficacy trametinib in additional oncology indications.
☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness

☐ Nonclinical study, not safety-related (specify)

☐ Other

5. Is the PMR/PMC clear, feasible, and appropriate?

   ☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
   ☒ Are the objectives clear from the description of the PMR/PMC?
   ☒ Has the applicant adequately justified the choice of schedule milestone dates?
   ☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☐ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

_____

(signature line for BLAs)

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/s/

MARC R THEORET
05/24/2013

JEFFERY L SUMMERS
05/24/2013

REGULATORY PROJECT MANAGER
PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW
OF THE PRESCRIBING INFORMATION

To be completed for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Supplements

Application: NDA 204114

Application Type: New NDA

Name of Drug: MEKINIST (trametinib) 0.5 mg, 1 mg, 2 mg tablets

Applicant: GlaxoSmithKline, LLC

Submission Date: July 2, 2013

Receipt Date: July 3, 2013

1.0 Regulatory History and Applicant's Main Proposals

This is a new NDA for treatment of unresectable or metastatic melanoma with BRAF V600E or V600K mutations as detected by an FDA-approved test. The regulatory history includes the following: There was an End of Phase 1/PP3 (CMC) meeting held in November 9, 2010. There were two End of Phase 1/PP3 meetings held – on July 30, 2010 and on February 24, 2011 (with IND 105032). There were also two pre NDA meetings held – CMC on February 15, 2012 and with IND 105032 on May 9, 2012. . Orphan Drug Exclusivity was granted December 20, 2010. Fast Track designation issued June 29, 2012.

2.0 Review of the Prescribing Information (PI)

This review is based on the applicant's submitted Microsoft Word format of the PI. The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix). The initial review of this PI was conducted during the filing review (10/2/2012).

3.0 Conclusions/Recommendations

Selected Requirements of Prescribing Information (SRPI) format deficiencies were identified in the review of this PI. For a list of these deficiencies see the Appendix.

All SRPI format deficiencies and other labeling issues identified above were conveyed to the applicant in the 74-day, deficiencies identified letter. The Appendix contains the most recent review of the PI which were conveyed in the FDA proposed edits of 5/10/2013.

4.0 Appendix

Selected Requirements of Prescribing Information (SRPI)

The Selected Requirement of Prescribing Information (SRPI) version 2 is a 48-item, drop-down checklist of critical format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and labeling guidances.

Highlights (HL)

GENERAL FORMAT

YES 1. Highlights (HL) must be in two-column format, with ½ inch margins on all sides and in a minimum of 8-point font.

Comment:

YES 2. The length of HL must be less than or equal to one-half page (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been is granted in a previous submission (i.e., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is less than or equal to one-half page then select "YES" in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

- **For the Filing Period (for RPMs)**
  - *For efficacy supplements:* If a waiver was previously granted, select "**YES**" in the drop-down menu because this item meets the requirement.
  - *For NDAs/BLAs and PLR conversions:* Select "**NO**" in the drop-down menu because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.
- **For the End-of Cycle Period (for SEALD reviewers)**
  - The SEALD reviewer documents (based on information received from the RPM) that a waiver has been previously granted or will be granted by the review division in the approval letter.

Comment:

YES 3. All headings in HL must be presented in the center of a horizontal line, in UPPER-CASE letters and **bolded**.

Comment:

YES 4. White space must be present before each major heading in HL.

Comment:

YES 5. Each summarized statement in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each information summary (e.g. end of each bullet).

Comment:

YES 6. Section headings are presented in the following order in HL:

Section	Required/Optional
• **Highlights Heading**	Required
• **Highlights Limitation Statement**	Required
• **Product Title**	Required
• **Initial U.S. Approval**	Required
• **Boxed Warning**	Required if a Boxed Warning is in the FPI
• **Recent Major Changes**	Required for only certain changes to PI*
• **Indications and Usage**	Required
• **Dosage and Administration**	Required
• **Dosage Forms and Strengths**	Required
• **Contraindications**	Required (if no contraindications must state "None.")
• **Warnings and Precautions**	Not required by regulation, but should be present
• **Adverse Reactions**	Required
• **Drug Interactions**	Optional
• **Use in Specific Populations**	Optional
• **Patient Counseling Information Statement**	Required
• **Revision Date**	Required

* RMC only applies to the Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions sections.

Comment:

YES 7. A horizontal line must separate HL and Table of Contents (TOC).

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

YES 8. At the beginning of HL, the following heading must be **bolded** and appear in all UPPER CASE letters: **"HIGHLIGHTS OF PRESCRIBING INFORMATION"**.

Comment:

Highlights Limitation Statement

YES 9. The **bolded** HL Limitation Statement must be on the line immediately beneath the HL heading and must state: "**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE)**."

Comment:

Product Title

YES 10. Product title in HL must be **bolded.**

Comment:

Initial U.S. Approval

YES 11. Initial U.S. Approval in HL must be placed immediately beneath the product title, **bolded,** and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment:

Selected Requirements of Prescribing Information (SRPI)

Boxed Warning

12. All text must be **bolded**.

Comment:

N/A 13. Must have a centered heading in UPPER-CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the Warning (e.g., "**WARNING: SERIOUS INFECTIONS**").

Comment:

N/A 14. Must always have the verbatim statement "***See full prescribing information for complete boxed warning***." centered immediately beneath the heading.

Comment:

N/A 15. Must be limited in length to 20 lines (this does not include the heading and statement "***See full prescribing information for complete boxed warning.***")

Comment:

N/A 16. Use sentence case for summary (combination of uppercase and lowercase letters typical of that used in a sentence).

Comment:

Recent Major Changes (RMC)

N/A 17. Pertains to only the following five sections of the FPI: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.

Comment:

N/A 18. Must be listed in the same order in HL as they appear in FPI.

Comment:

N/A 19. Includes heading(s) and, if appropriate, subheading(s) of labeling section(s) affected by the recent major change, together with each section's identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, "Dosage and Administration, Coronary Stenting (2.2) --- 3/2012".

Comment:

N/A 20. Must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage

YES 21. If a product belongs to an established pharmacologic class, the following statement is required in the Indications and Usage section of HL: [(Product) is a (name of class) indicated for (indication)]."

Comment:

Dosage Forms and Strengths

YES 22. For a product that has several dosage forms, bulleted subheadings (e.g., capsules, tablets, injection, suspension) or tabular presentations of information is used.

Comment:

Contraindications

YES 23. All contraindications listed in the FPI must also be listed in HL or must include the statement "None" if no contraindications are known.

Comment:

N/A 24. Each contraindication is bulleted when there is more than one contraindication.

Comment:

Adverse Reactions

YES 25. For drug products other than vaccines, the verbatim **bolded** statement must be present: "**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**".

Comment:

Patient Counseling Information Statement

YES 26. Must include one of the following three **bolded** verbatim statements (without quotation marks):

If a product **does not** have FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION"**

If a product **has** FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling."**
- **"See 17 for PATIENT COUNSELING INFORMATION and Medication Guide."**

Comment:

Revision Date

YES 27. **Bolded** revision date (i.e., "**Revised: MM/YYYY** or **Month Year**") must be at the end of HL.

Comment:

Contents: Table of Contents (TOC)

GENERAL FORMAT

YES 28. A horizontal line must separate TOC from the FPI.

Comment:

YES 29. The following **bolded** heading in all UPPER CASE letters must appear at the beginning of TOC: "**FULL PRESCRIBING INFORMATION: CONTENTS"**.

Comment:

N/A

30. The section headings and subheadings (including title of the Boxed Warning) in the TOC must match the headings and subheadings in the FPI.

Comment:

N/A 31. The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in UPPER-CASE letters and **bolded**.

Comment:

YES 32. All section headings must be **bolded** and in UPPER CASE.

Comment:

YES 33. All subsection headings must be indented, not bolded, and in title case.

Comment:

YES 34. When a section or subsection is omitted, the numbering does not change.

Comment:

YES 35. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading "**FULL PRESCRIBING INFORMATION: CONTENTS"** must be followed by an asterisk and the following statement must appear at the end of TOC: "*Sections or subsections omitted from the Full Prescribing Information are not listed."

Comment:

Full Prescribing Information (FPI)

GENERAL FORMAT

YES 36. The following heading must appear at the beginning of the FPI in UPPER CASE and **bolded**: "**FULL PRESCRIBING INFORMATION".**

Comment:

YES 37. All section and subsection headings and numbers must be **bolded**.

Comment:

YES 38. The **bolded** section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. If a section/subsection is omitted, the numbering does not change.

Boxed Warning
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use

Selected Requirements of Prescribing Information (SRPI)

9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

YES 39. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under Section 17 (Patient Counseling Information). All patient labeling must appear at the end of the PI upon approval.

Comment:

YES 40. The preferred presentation for cross-references in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, [*see Warnings and Precautions (5.2)*].

Comment:

N/A 41. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

Boxed Warning

N/A 42. All text is **bolded**.

Comment:

N/A 43. Must have a heading in UPPER-CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the Warning (e.g., "**WARNING: SERIOUS INFECTIONS**").

Comment:

N/A 44. Use sentence case (combination of uppercase and lowercase letters typical of that used in a sentence) for the information in the Boxed Warning.

Comment:

Contraindications

YES 45. If no Contraindications are known, this section must state "None".

Comment:

Adverse Reactions

YES 46. When clinical trials adverse reactions data is included (typically in the "Clinical Trials Experience" subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice."

Comment:

N/A 47. When postmarketing adverse reaction data is included (typically in the "Postmarketing Experience" subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure."

Comment:

Patient Counseling Information

YES 48. Must reference any FDA-approved patient labeling, include the type of patient labeling, and use one of the following statements at the beginning of Section 17:

- "See FDA-approved patient labeling (Medication Guide)"
- "See FDA-approved patient labeling (Medication Guide and Instructions for Use)"
- "See FDA-approved patient labeling (Patient Information)"
- "See FDA-approved patient labeling (Instructions for Use)"
- "See FDA-approved patient labeling (Patient Information and Instructions for Use)"

Comment:

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/s/

NORMA S GRIFFIN
05/22/2013

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

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

Memorandum

Date: May 14, 2013

To: Norma Griffin
Regulatory Project Manager
Division of Oncology Products 2 (DOP2)

From: Quynh-Van Tran, PharmD, BCPP
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: **MEKINIST (trametinib) tablets, for oral use (Mekinist)**
NDA 204114
OPDP Review of Prescribing Information (PI), Patient Information Leaflet (PPI) and container labeling

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In response to DOP2 September 18, 2012 consult request, OPDP has reviewed the proposed PI (FDA version sent via email to OPDP on May 6, 2013), PPI [Division of Medical Policy Programs (DMPP)'s version on May 14, 2013] and container labeling for Mekinist (version submitted by the sponsor on May 7, 2013).

Please see the attached PI and container labeling with our comments incorporated therein.

We agree with DMPP's comments on the PPI and offer no additional comment.

Thank you for the opportunity to provide comments on the proposed PI, PPI and container labeling for Mekinist. If you have any questions, please contact Quynh-Van Tran at (301) 796-0185, or quynh-van.tran@fda.hhs.gov.

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/s/

QUYNH-VAN TRAN
05/14/2013

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

PATIENT LABELING REVIEW

Date:	May 14, 2013
To:	Patricia Keegan, MD Director **Division of Oncology Products 2 (DOP2)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Barbara Fuller, RN, MSN, CWOCN Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Nathan Caulk, MS, BSN, RN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
Subject:	DMPP Review of Patient Labeling: Patient Package Insert (PPI)
Drug Name (established name):	MEKINIST (trametinib)
Dosage Form and Route:	tablets, for oral use
Application Type/Number:	NDA 204-114
Applicant:	GlaxoSmithKline, LLC

1 INTRODUCTION

On August 3, 2012, GlaxoSmithKline, LLC submitted for the Agency's review an original New Drug Application (NDA) 204-114 for MEKINIST (trametinib) tablets with the proposed indication for the treatment of patients with unresectable or metastatic melanoma with BRAF V600 mutations as detected by an FDA-approved test. On September 18, 2012, the Division of Oncology Products 2 (DOP2) requested that the Division of Medical Policy Programs (DMPP) review the Applicant's proposed Patient Package Insert (PPI) for MEKINIST (trametinib) tablets.

This review is written in response to a request by DOP2 for DMPP to review the Applicant's proposed Patient Package Insert (PPI) for MEKINIST (trametinib) tablets.

2 MATERIAL REVIEWED

- Draft MEKINIST (trametinib) tablets PPI received on August 3, 2012, revised by the Review Division throughout the review cycle, and received by DMPP on May 6, 2013.
- Draft MEKINIST (trametinib) tablets Prescribing Information (PI) received on August 3, 2012, revised by the Review Division throughout the review cycle, and received by DMPP on May 6, 2013.
- Approved ABRAXANE (paclitaxel protein-bound particles for injectable suspension)(albumin-bound) comparator labeling dated October 11, 2012.

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. In our review of the PPI the target reading level is at or below an 8th grade 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. We have reformatted the PPI document using the Verdana font, size 11.

In our review of the PPI we have:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information

- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the PPI is consistent with the approved comparator labeling where applicable.

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP on the correspondence.
- Our review of the PPI is appended to this memorandum. Consult DMPP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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/s/

NATHAN P CAULK
05/14/2013

BARBARA A FULLER
05/14/2013

LASHAWN M GRIFFITHS
05/14/2013

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Label, Labeling and Packaging Review - Final

Date:	May 13, 2013
Reviewer:	James Schlick, RPh, MBA Division of Medication Error Prevention and Analysis
Team Leader:	Todd Bridges, RPh Division of Medication Error Prevention and Analysis
Drug Name and Strength:	Mekinist (Trametinib) Tablets 0.5 mg, 1 mg, and 2 mg
Application Type/Number:	NDA 204114
Applicant:	GlaxoSmithKline
OSE RCM #:	2012-1589-1

*** This document contains proprietary and confidential information that should not be released to the public.***

Contents

1 INTRODUCTION

This review evaluates the proposed container labels for Mekinist (Trametinib), NDA 204114, submitted in response to the Division of Medication Error Prevention and Analysis' comments in the November 15, 2012 OSE Review# 2012-1589 and comments sent to the Applicant on May 3, 2013.

2 METHODS AND MATERIALS REVIEWED

2.1 LABELS

Using the principles of human factors and Failure Mode and Effects Analysis[1] along with post marketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Container Labels submitted May 7, 2013 (Appendix A)

2.2 PREVIOUSLY COMPLETED REVIEWS

DMEPA previously reviewed this product in OSE Review 2012-1589, and we looked at the review to ensure all our recommendations were implemented.

3 CONCLUSION

DMEPA finds the Applicant's revisions to the labels acceptable.
If you have questions or need clarifications, please contact Sue Kang, OSE project manager, at 301-796-4216.

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

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/s/

JAMES H SCHLICK
05/13/2013

TODD D BRIDGES
05/13/2013

Medical Officer's Review of NDA 204114
Ophthalmology Consultant

NDA 204114	Consult Request Date: 10/17/12
Consult Review	Review completed: 5/ 7/13
Product Name:	Mekinist (trametinib)
Sponsor:	GlaxoSmithKline

Proposed Indication: A kinase inhibitor indicated for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutations as detected by an FDA-approved test indicated for this use, who have not received BRAF inhibitor therapy

Requested: This is an original NDA for the NME, trametinib, which is the first application for a MEK inhibitor submitted to the Office of Hematology and Oncology Products. DOP2 requests your review of ocular events, including retinal vein occlusion and serous retinopathy, and your recommendations concerning labeling of ocular disorders as well as any post-marketing requirements to assess the risk of these events. Information concerning ocular events is included in the following Modules. Each includes the eCTD link for access:

A) eCTD 0002, Module 2.7.4 (Summary of Clinical Safety) at
\\cdsesub1\EVSPROD\NDA204114\\0002\m2\27-clin-sum\summary-clin-safety.pdf
See Section 2.5 (Tables 26 and 27), Section 2.5.3, and Section 8

B) eCTD 0002, Module 5.3.5.1.3 (Study Report Body [MEK114267]) at
\\cdsesub1\EVSPROD\NDA204114\\0002\m5\53-clin-stud-rep\535-rep-effic-safety-stud\metastatic-melanoma\5351-stud-rep-contr\mek114267\mek114267-report.pdf
See Section 7.7.3 and Section 13 (Case Narratives)

C) eCTD 0002, Module 5.3.5.2.3 (Study Report Body [MEK113583]) at
\\cdsesub1\EVSPROD\NDA204114\\0002\m5\53-clin-stud-rep\535-rep-effic-safety-stud\metastatic-melanoma\5352-stud-rep-uncontr\mek113583\mek113583-report.pdf
See Section 8.5.3 and Section 12 (Case Narratives)

D) eCTD 0002, Module 5.3.5.2.3 (Study Report Body [MEK111054]) at
\\cdsesub1\EVSPROD\NDA204114\\0002\m5\53-clin-stud-rep\535-rep-effic-safety-stud\metastatic-melanoma\5352-stud-rep-uncontr\mek111054\mek111054-report.pdf
See Section 10.6.3 and Section 17 (Case Narratives).

Marc Theoret is the Medical Officer serving as the primary clinical reviewer for this NDA.

Reviewer's Comments: *The initial submission included ophthalmic terminology which was inexact and sometimes confusing. The submitted medical records did not support the proposed labeling. A request was made for the angiograms of all patients with retinal vein occlusions and "central serous chorioretinopathy."*

The following information was submitted following the April 17, 2013, teleconference.

"As agreed during the April 17, 2013, teleconference with the FDA, GSK is providing all source documentation that was collected from the clinical sites for the cases reported as retinal vein occlusion (RVO) that were reported in section 2.5.3.1 of the NDA Integrated Summary of Safety:

Subject ID	**Study**	**Event**	**Source Documentation**
402315	**MEK114267**	**RVO (Grade 4)**	**Source exam notes, photographs and OCT**
402015	**MEK114267**	**RVO (Grade 3)**	**Source exam notes**
2404	**MEK111054**	**RVO (Grade 3)**	**Source exam notes and OCT**
273	**BRF113220**	**RVO (Grade 1)**	**Source exam notes and OCT**

Drs. Deborah Kelly of GSK and (b) (4) have reviewed this source documentation and provide the following summary for the Agency's use: Two of the four RVO cases can be reasonably confirmed based on either raw imaging data or written interpretations of the angiograms. One of the remaining two cases appears not to have been treatment emergent. The last case of RVO may have been reported correctly and was treatment emergent; however, the diagnosis cannot be confirmed using available data.

Reviewer's Comments: *I agree with the summary described above. One of the reported RVO cases occurred prior to drug product administration. One of the cases includes no documentation (positive or negative) to confirm the diagnosis of RVO. The occurrence of two cases of RVO in a population of approximately 300 patients is considered higher than the expected background rate.*

FDA Request 2:

Central serous retinopathy (CSR) comprises a very small subset of retinopathies. The clinical presentations listed in Safety Summary name CSR as a diagnosis, but several of the cases do not describe the clinical features or clinical course of a CSR (e.g., Protocol MEK114267, Subject 403077). Some of the cases appear to interchange the terms macular edema, CSR and chorioretinopathy (Protocol MEK113583, Subject 109004, 202006). These terms are not interchangeable. In some cases, there are no clinical characteristics, reports of findings on Ocular Coherence Tomography (OCT) or FA, except to say that there was CSR. Without describing the features seen on the test or providing an image of the test results, it is not possible to draw any conclusions about the cases. The FA and OCT images should be provided.

GSK Response (As provided via email on April 15, 2013)

Source documentation was not systematically collected for these cases. A summary of the cases is presented in Module 5.3.5.3 section 2.5.3.2. In this summary which was reviewed by (b) (4) the characteristics of the cases of CSR observed with trametinib are discussed in the context of classic CSR and specific differences with regard to (i) bilateral occurrence, (ii) lack of gender relationship , and (iii) faster resolution are mentioned. GSK is in the process of gathering all the source documentation feasible from the clinical sites and will provide all available documentation by the end of business Monday, April 22. It should be noted, though, that obtaining source documentation for every patient will likely not be feasible. Although there may be differences between the behavior of classic central serous retinopathy and trametinib- related retinal pigment epithelial and neurosensory detachments, the findings consistently demonstrate that this abnormality falls under the general category of "chorioretinopathy", resolves spontaneously, and visual symptoms also improve. Following submission of the source documentation that can be gathered, GSK respectfully requests a teleconference with the clinical review team, including the FDA consulting ophthalmologist, during the week of April 22 to discuss the cases; given that FA and OCT images for all cases are not likely to be available.

GSK Response Following April 17, 2013 Telconference:

As agreed during the April 17, 2013 teleconference with the FDA, GSK is providing all source documentation that was collected from the clinical sites for the cases reported as central serous retinopathy (CSR) that were reported in section 2.5.3.2 of the NDA Integrated Summary of Safety:

Subject ID	Study	Event	Source Documentation
109004	MEK113583	CSR (Grade 3)	Source exam notes
1278	BRF113220	CSR (Grade 3)	Source exam notes, OCT, fundus photographs, fundus autofluorescence, and Published Case Study
403077	MEK114267	CSR (Grade 3)	Source exam notes and OCT
1314	MEK111054	CSR (Grade 2)	OCT
1105	MEK111054	CSR (Grade 2)	Source exam notes

Subject ID	Study	Event	Source Documentation
1210	MEK111054	CSR (Grade 2)	Source exam notes and OCT
1112	MEK111759	CSR (Grade 2)	Source exam notes
317	BRF113220	CSR (Grade 2)	Source exam notes
412	BRF113220	CSR (Grade 2)	Source exam notes
129	TAC113886	CSR (Grade 2)	Source exam notes
4202	MEK111759	CSR (Grade 2)	Source exam notes, fundus photography, IVFA, OCT
202006	MEK113583	CSR (Grade 1)	Source exam notes, IVFA, OCT
1208	MEK112111	CSR (Grade 1)	Source exam notes
403536	MEK114267	CSR (Grade 1)	Source images (OCT, IVFA, photos, fundus autofluorescence)

Drs. Deborah Kelly of GSK and (b) (4) have reviewed this source documentation and provide the following summary for the Agency's use: All source documentation currently available for the 14 cases of CSR-like findings addressed in the trametinib NDA were reviewed. Imaging studies were available to review for 7 of the 14 cases. A reasonable description of the findings was present and available for the remaining cases. There were no cases of classic central serous retinopathy. The trametinib related adverse event seen in this chorioretinal abnormality appears to present primarily as **bilateral, multifocal, serous, central, pigment epithelial detachments**. In the course of evaluating these cases OCT, fluorescein angiography (FA), fundus autofluorescence, and ICG imaging studies were reviewed. There has been a distinct lack of hyperfluoresence and leakage of dye on FA associated with this condition. Furthermore, no true neurosensory detachments were identified on review of available OCT images. Although in three of these cases central serous retinopathy was diagnosed by the treating ophthalmologist, there was consistent commentary by examining ophthalmologists that this condition is different than classic CSR. Additional findings of note are an occasional thickening or accumulation of reflective material on OCT in the outer retina, RPE or Bruch's membrane. The condition is associated clinically with visual acuity disturbances, and generally resolves quickly (often within days to weeks) following cessation of trametinib, although OCT abnormalities persisted beyond a month in at least several cases. **This condition appears to be an acute, reversible, drug induced multiple pigment epithelial detachment syndrome**. Brief case synopses with image grabs have been provided below in Appendix B

Reviewer's Comments: *Concur with above summary. These cases are more appropriately described as pigment epithelial detachments, and the term "central serous" should be avoided because the cases are not consistent with classic central serous retinopathy.*

FDA Request 3:
The cases of papillary edema are more likely to be related to brain metastasis than to the study drug.

GSK Response (As provided via email on April 15, 2013)
GSK acknowledges and agrees with the Agency's comments. Please note these cases, including the potential relation to brain metastases, are discussed not only in the ISS (Module 5.3.5.3, Section 2.5.3), but also in the 120 Day update.

Summary DTOP Comments:
The April 23, 2013, submission from GSK provided a more complete description of the Retinal Vein Occlusions and the Pigment Retinal Detachments. One of the RVO cases was pre-existing, another one was not well documented, but two cases are consistent with RVO events. The retinal pigment epithelial detachments (previously referred to as (b) (4) do not occur as or follow a typical (b) (4) clinical course. They also do not have typical Fluorescein Angiography findings. I think it is important to label them descriptively and not as (b) (4) to avoid clinicians thinking that they will behave as such. The RVO cases are relatively rare and may or may not have visual symptoms at the time of the event. Since it is not possible to predict when they might happen, there is no way to decide on schedule of exams. This suggests that ophthalmic exams should occur when symptoms occur.

Question to be resolved post-marketing:
The optimal dosing instructions for patients who develop a retinal pigment epithelial detachment (RPED) remains unknown. Most RPED resolved with either discontinuation of trametinib or with a dose reduction of trametinib. If a dose reduction is used, it is unclear whether the original dosing regimen can be resumed at some point in time. It would be useful to compare different dosing options in patients who develop RPEDs.

DTOP Labeling Recommendations:
The following Warning/Precaution and Dose Modification Information is recommended for the labeling:

Highlights:
• Retinal pigment epithelial detachments resulting in decreased visual acuity have occurred while on treatment with MEKINIST. Dose modification or dose interruption may be required. (2.2, 5.2)

• Retinal Vein Occlusion (RVO): Retinal vein occlusions have occurred. Treatment discontinuation is recommended. (2.2, 5.3)

Dosing Changes
If a patient has a retinal vein occlusion, it is recommended that dosing of trametinib be discontinued.

If a patient has a retinal pigment epithelial detachment, it is recommended that the dose be reduced for up to two weeks or until the RPED resolves. If the RPED does not resolve, it is recommended that trametinib be discontinued until the RPED resolves.

Warnings/Precautions
5.3 Retinal Pigment Epithelial Detachment
In clinical studies of trametinib monotherapy enrolling 329 patients with metastatic melanoma, approximately 4% developed Retinal Pigment Epithelial Detachments (RPED) during trametinib treatment. The detachments were often bilateral and multifocal occurring in the macular region of the retina. The detachments led to visual acuity disturbances, but generally resolved within days to weeks following dose reduction or cessation of trametinib, although Ocular Coherence Tomography (OCT) abnormalities persisted beyond a month in at least several cases.

It is recommended that ophthalmological evaluation be performed at baseline and anytime a patient reports visual disturbances.

5.4 Retinal Vein Occlusion (RVO)
In clinical studies of trametinib monotherapy enrolling 329 patients with metastatic melanoma, approximately 1% developed a RVO during trametinib treatment. RVOs may lead to macular edema, decreased visual function, neovascularization and glaucoma.

It is recommended that ophthalmological evaluation be performed at baseline and anytime a patient reports visual disturbances. Permanently discontinue trametinib if patients experience retinal vein occlusion . [see Dosage and Administration (2.2)].

Wiley A. Chambers, M.D.
Supervisory Medical Officer, Ophthalmology

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/s/

WILEY A CHAMBERS
05/08/2013

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Pediatric and Maternal Health Staff
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-0700
FAX 301-796-9744

Maternal Health Team Review

Date: April 18, 2013

From: Tammie Howard, RN, MSN
Regulatory Reviewer, Maternal Health Team
Pediatric and Maternal Health Staff

Through: Melissa S. Tassinari, PhD, DABT
Acting Team Leader, Maternal Health Team
Pediatric and Maternal Health Staff

Lynne P. Yao, MD
Associate Director, OND
Pediatric and Maternal Health Staff

To: Division of Oncology Products 2 (DOP2)

Drug: Mekinist (trametinib) NDA 204114

Subject: Mekinist (trametinib) is a new molecular entity (NME) submitted for NDA approval

Applicant: GlaxoSmithKline, LLC (GSK)

Materials Reviewed: Mekinist product labeling

Consult Question: DOP2 requested that PMHS-MHT attend milestone meetings and provide labeling comments for this new NDA.

INTRODUCTION

GlaxoSmithKline, LLC (GSK) submitted a New Drug Application (NDA) for Mekinist (trametinib) tablets on August 3, 2012. Trametinib is a New Molecular Entity (NME) with a proposed indication for treatment of patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutation as detected by an FDA approved test indicated for this use, who have not received BRAF inhibitor therapy.

B-RAF, a Raf kinase, is a protein in a signaling pathway that affects cell division, differentiation and secretion. Mutations in the B-RAF gene can result in stimulation of tumor cell growth, such as in melanomas, colorectal cancers and non-small cell lung cancers. [1] Trametinib is an inhibitor of mitogen-activated extracellular signal regulated kinase 1 (MEK1) and MEK2 activation and of MEK1 and MEK2 kinase activity. MEK proteins are upstream regulators of the extracellular signal-related kinase (ERK) pathway, which promotes cellular proliferation. V600E BRAF mutations result in constitutive activation of the BRAF pathway which includes MEK1 and MEK2.

The Pediatric and Maternal Health Staff-Maternal Health Team (PMHS-MHT) was consulted by DOP2 on September 18, 2012 to attend milestone meetings during the review cycle and provide labeling comments for this new NDA. This review includes PMHS-MHT comments and recommendations for Mekinist (trametinib) labeling.

BACKGROUND

Trametinib and Pregnancy

The occurrence of malignancy during pregnancy is uncommon (approximately 1 in 1,000 to 1 in 6,000 pregnancies), with most occurring in breast and cervical cancers, melanoma and lymphoma.[2,3,4] However, melanoma occurs in a majority male population with a 67% higher incidence in men versus women. The age of fifty-three is the median age of diagnosis, with forty-two percent of cases occurring in those younger than fifty-five. [5]

Trametinib is a NME and a there are no human pregnancy data available. In animal developmental reproductive studies, trametinib was embyrotoxic and abortifacient in rabbits at doses greater than or equal to a dose resulting in exposure approximately 0.3 times the human exposure at the recommended clinical dose. Developmental toxicities consisted of increased incidence of cleft palate and increased post-implantation loss. In rats, there was maternal toxicity and an increase in post-implantation loss at a dose resulting in exposures 1.8 fold higher

[1] Website: http://www.genenames.org/data/hgnc_data.php?hgnc_id=1097, accessed March 27, 2013.
[2]Website: http://www.cancer net/coping/emotional-and-physical-matters/sexual-and-reproductive-health/cancer-during-pregnancy, accessed March 4, 2013.
[3] Esin S, et al., Management of precursor B-lymphoblastic lymphoma/leukaemia of thoracic spine in a pregnancy presenting with acute paraplegia. Journal of Obstetrics and Gynecology. 2012;32(5):485-6.
[4] Perez CA, et al., Primary mediastinal large B-cell lymphoma during pregnancy. Case Reports in Hematology. 2012;Article ID 197347, 1-3.
[5] Website: http://www.cancernetwork.com/cancer-management/moles-melanomas/article/10165/1802671# Brady MS, et al. Melanoma and other skin cancers. Cancer Management: Online Edition. 2013, accessed April 8, 2013.

than the human exposure at the recommended clinical dose. Rats demonstrated decreased fetal weights at doses greater than or equal to 0.3 times the human exposure at the recommended clinical dose. These data are reported in current trametinib pregnancy labeling.

Trametinib and Lactation

It is not known if Trametinib is present in human milk. A search of the Micromedex database resulted in no human or animal data available regarding trametinib and lactation. In addition, there are no available human lactation data available for other BRAF kinase inhibitors.

REVIEW OF SUBMITTED MATERIALS

Sponsor Proposed Trametinib Labeling

The PMHS-MHT reviewed the sponsor's proposed trametinib labeling, submitted August 3, 2012 and participated in several labeling/team meetings during the review period. A summary of PMHS-MHT labeling recommendations appear immediately following Discussion and Conclusions with labeling excerpts provided in **Appendix A**.

DISCUSSION AND CONCLUSIONS

The Proposed Pregnancy and Lactation Labeling Rule (PLLR) published in May 2008. While still complying with current regulations during the time when the Final Rule is in clearance, PMHS-MHT is structuring the Pregnancy and Nursing mothers label information in the spirit of the Proposed Rule. The first paragraph in the pregnancy subsection of labeling provides a risk summary of available data from outcomes of studies conducted in pregnant women (when available), and outcomes of studies conducted in animals, as well as the required regulatory language for the designated pregnancy category. The paragraphs that follow provide more detailed descriptions of the available human and animal data, and when appropriate, clinical information that may affect patient management. The goal of this restructuring is to provide relevant animal and human data to inform prescribers of the potential risks of the product during pregnancy. Similarly for nursing mothers, human data, when available, are summarized. When only animal data are available, just the presence or absence of drug in milk is noted and presented in the label, not the amount. Additionally, information on pregnancy testing, contraception, and infertility that has been located in other sections of labeling are now presented in a subsection, Females and Males of Reproductive Potential.

The PMHS-MHT has reviewed the proposed trametinib labeling, and labeling recommendations are provided below.

MHT Summary of Labeling Comments and Recommendations

Highlights of Prescribing Information

The bullet point (b) (4) under Warnings and Precautions was revised to "Embryo-Fetal Toxicity", to reference the section in the full prescribing information, to comply with requirement of current Safety Endpoints and Labeling Development Team (SEALD) labeling

review tool. Language regarding embryo-fetal toxicity was revised to display preferred labeling language.

Under Use in Specific Populations, the language for the bullet, Nursing Mothers, was revised to display preferred labeling language in a more concise format. A bullet point titled Females and Males of Reproductive Potential was added to reference section 8.6, to reference information regarding possible impairment of fertility in full prescribing information.

5 Warnings and Precautions

The title of section (b) (4) was revised to "Embryo-Fetal Toxicity" to comply with requirement of the current SEALD labeling review tool. The summary statement "Trametinib was embyrotoxic and abortifacient in rabbits at doses greater than or equal to a dose resulting in exposure approximately 0.3 times the human exposure at the recommended clinical dose." was added to provide a concise description of risk.

Language regarding contraception for females of reproductive potential and to indicate when contact with the patient health care provider is needed was revised to appear in active voice. Appropriate labeling cross references were added. Language was revised to ensure use of appropriate regulatory language.

8 Use in Specific Populations- Pregnancy

The Pregnancy section was restructured and the sub-headings Risk Summary and Animal Data were added to provide an organized presentation of data, in the spirit of the proposed rule as described above. Language regarding contraception for females of reproductive potential was (b) (4) placed in section 8.6, Females and Males of Reproductive Potential, under Contraception, Females.

8.3 Nursing Mothers

The Nursing Mothers section states that it is unknown whether trametinib is present in human milk, with appropriate regulatory language.

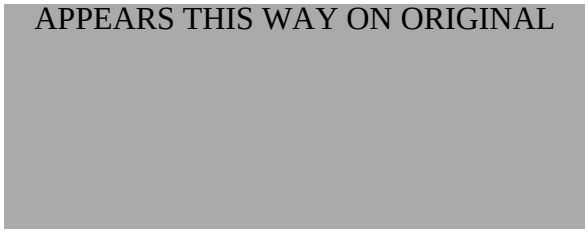
8.6 Females and Males of Reproductive Potential

Information on pregnancy testing, contraception, and infertility that has been located in other sections of labeling are now presented in the subsection, Females and Males of Reproductive Potential. The sub-headings Contraception and Infertility were added to provide an organized presentation of data, in the spirit of the proposed rule as described above. Male and Female sub-headings were added under Contraception and Infertility indicating information pertaining to each.

17 Patient Counseling Information

Language regarding pregnancy, lactation, and infertility was revised to describe the potential risk, actions to mitigate the risk and provide instructions for contacting a health care provider.

Appendix A- PMHS-MHT Mekinist Labeling Recommendation Excerpts



Appendix A-PMHS-MHT Mekinist Labeling Recommendation Excerpts

Highlights of Prescribing Information

WARNINGS AND PRECAUTIONS

- Embryofetal Toxicity: Can cause fetal harm. Advise females of reproductive potential of potential risk to the fetus. (5.5, 8.1)

USE IN SPECIFIC POPULATIONS

- Nursing Mothers: Discontinue drug or nursing. (8.3)
- Females and Males of Reproductive Potential: Counsel female patients on pregnancy planning and prevention. May impair fertility. (8.6)

5 Warnings and Precautions

5.5 Embryo-Fetal Toxicity

MEKINIST can cause fetal harm when administered to a pregnant woman. Trametinib was embyrotoxic and abortifacient in rabbits at doses greater than or equal to a dose resulting in exposure approximately 0.3 times the human exposure at the recommended clinical dose. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus *[See Use in Specific Populations (8.1).*

Advise female patients of reproductive potential to use highly effective contraception during treatment with MEKINIST and for four months after treatment. Advise patients to contact their healthcare provider if they become pregnant, or if pregnancy is suspected, while taking MEKINIST.*[See Use in Specific Populations (8.1),(8.6)]*

8 Use in Specific Populations- Pregnancy (8.1), Nursing Mothers (8.3), Females and Males of Reproductive Potential (8.6)

8.1 Pregnancy

Pregnancy Category D

Risk Summary

MEKINIST can cause fetal harm when administered to a pregnant woman. Trametinib was embyrotoxic and abortifacient in rabbits at doses greater than or equal to a dose resulting in exposures approximately 0.3 times the human exposure at the recommended clinical dose based on AUC. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus *[see Warnings and Precautions (5.4)]*.

Animal Data

In reproductive toxicity studies, administration of trametinib to rats during the period of organogenesis resulted in decreased fetal weights at doses greater than or equal to 0.031 mg/kg/day (approximately 0.3 times the human exposure based on AUC at the recommended dose). In rats, at a dose resulting in exposures 1.8 fold higher than the

human exposure at the recommended dose, there was maternal toxicity and an increase in post-implantation loss.
In pregnant rabbits, administration of trametinib during the period of organogenesis resulted in decreased fetal body weight and increased incidence of variations in ossification at doses greater than or equal to 0.039 mg/kg/day (approximately 0.08 times the human exposure at the recommended dose based on AUC). In rabbits administered trametinib at 0.15 mg/kg/day (approximately 0.3 times the human exposure at the recommended dose based on AUC) there was an increase in the incidence of cleft palate and increased post-implantation loss, including total loss of pregnancy, compared to control animals.

8.3 Nursing Mothers

It is not known whether this drug is present in human milk. Because many drugs are present in human milk and because of the potential for serious adverse reactions in nursing infants from MEKINIST, a decision should be made whether to discontinue nursing or to discontinue the drug taking into account the importance of the drug to the mother.

8.6 Females and Males of Reproductive Potential

Contraception
Females
MEKINIST can cause fetal harm when administered during pregnancy. Advise female patients of reproductive potential to use highly effective contraception during treatment and for four months after treatment. Advise patients to contact their healthcare provider if they become pregnant, or if pregnancy is suspected, while taking MEKINIST *[see Use in Specific Populations (8.1)]*.

Infertility
Females

Trametinib may impair fertility in female patients *[Nonclinical Toxicology (13.1)]*.

17 Patient Counseling Information

- MEKINIST can cause fetal harm if taken during pregnancy. Instruct female patients to use highly effective contraception during treatment and for four months after treatment. Advise patients to contact their healthcare provider if they become pregnant, or if pregnancy is suspected, while taking MEKINIST [*see Use in Specific Populations (8.1),(8.6)]*.
- Nursing infants may experience serious adverse reactions if the mother is taking MEKINIST. Advise lactating mothers to discontinue nursing while taking MEKINIST [*see Use in Specific Populations (8.3)]*.

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/s/

TAMMIE B BRENT HOWARD
04/18/2013

MELISSA S TASSINARI
04/18/2013

LYNNE P YAO
04/18/2013

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA/BLA # NDA 204114, MEKINIST (trametinib)
Product Name:

PMR/PMC Description: Hepatic Impairment Pharmacokinetic Trial

PMR/PMC Schedule Milestones:

Final Protocol Submission:	09/30/2013
(b) (4)	
Final Report Submission:	12/31/2015
Other:	

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☒ Small subpopulation affected
- ☐ Theoretical concern
- ☐ Other

The mass balance study suggests that hepatic elimination appears to be the major route of elimination. Patients with hepatic impairment may have a higher trametinib exposure than that of patients with normal hepatic function, which could cause more toxicity.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

The goal of the clinical pharmacokinetic trial is to determine appropriate trametinib doses in patients with (b) (4) hepatic impairment.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☐ Pediatric Research Equity Act
☒ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

☐ Assess a known serious risk related to the use of the drug?
☒ Assess signals of serious risk related to the use of the drug?
☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☒ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Conduct a pharmacokinetic trial to determine the appropriate dose of trametinib in patients with hepatic impairment in accordance with the FDA Guidance for Industry entitled "*Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling*."

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety

☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☒ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☒ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

☐ Other

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☐ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for NDAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA/BLA # NDA 204114, MEKINIST (trametinib)
Product Name:

PMR/PMC Description: QT/QTc interval prolongation

PMR/PMC Schedule Milestones:

Final Protocol Submission:	Submitted
(b) (4)	(b) (4)
Final Report Submission:	04/30/2015
Other:	

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☒ Theoretical concern
- ☐ Other

In the NDA submission, the applicant included an interim analysis of the QT/QTc intervals on 50 patients with solid tumors enrolled in the first-in-human Study MEK111054. The final study report for the dedicated cardiovascular safety study will be submitted post-marketing.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

The goal of the clinical trial is to assess the risk for trametinib to potentially prolong the QT/QTc interval.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☐ Pediatric Research Equity Act
☒ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

☐ Assess a known serious risk related to the use of the drug?
☒ Assess signals of serious risk related to the use of the drug?
☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☒ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Complete a clinical trial to evaluate the potential for trametinib to prolong the QT/QTc interval in an adequate number of patients administered repeat doses of trametinib in accordance with the principles of the FDA Guidance for Industry entitled "*E14 Clinical Evaluation of QT/QTc Interval Prolongation*." Submit the final report that includes central tendency, categorical and concentration-QT analyses, along with a thorough review of cardiac safety data.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☒ Thorough Q-T clinical trial

☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

_____

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

_____

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

_____

☐ Other

_____

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☐ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

_____

(signature line for NDAs)

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/s/

RUBY LEONG
04/08/2013

HONG ZHAO
04/08/2013

JEFFERY L SUMMERS
04/10/2013

M E M O R A N D U M

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

CLINICAL INSPECTION SUMMARY

DATE: January 3, 2013

TO: Marc Theoret, M.D.
Suzanne Demko, PA-C, Clinical Team Leader
Norma Griffin, Regulatory Project Manager
Division of Oncology Products II
Office of Hematology and Oncology Products

FROM: Jean Mulinde, M.D., Medical Officer
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

THROUGH: Janice Pohlman, M.D., M.P.H.
Team Leader, Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

Susan D. Thompson, M.D.
Acting Branch Chief, Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: NDA 204114

APPLICANT: GlaxoSmithKline, LLC

DRUG: Trametinib [Mekinist™]

NME: Yes

REVIEW PRIORITY: Standard Review

INDICATION: For the treatment of unresectable or metastatic melanoma with a BRAF V600 mutation.

CONSULTATION REQUEST DATE: September 6, 2012
CLINICAL INSPECTION SUMMARY DATE: February 18, 2013
DIVISION ACTION GOAL DATE: April 15, 2013
PDUFA DATE: June 3, 2013

I. BACKGROUND:

Mekinist™ (trametinib, GSK1120212) is a selective (b) (4) noncompetitive inhibitor of MEK1/MEK2 activation and kinase activity. MEK1 and MEK2 are proteins in the central signal transduction pathway and are critical for cell proliferation and survival. Trametinib has been developed specifically to address known oncogenic mutations in upstream mitogen-activated protein kinase (MAPK) pathway proteins BRAF and Ras, which signal through MEK1 and MEK2. The RAS/RAF/MEK/ERK pathway is a critical proliferation pathway in many human cancers and this pathway can be constitutively activated by alterations in specific proteins, including BRAF. BRAF mutations have been identified at a high frequency in specific cancers, including approximately 40-60% of melanoma. The frequency of this activating mutation, and the pathway addiction to which it leads, thus makes mutated BRAF an attractive target for antineoplastic therapy such as trametinib. Trametinib is being developed by GSK as monotherapy, and in combination with dabrafenib (NDA 202806, which is being concurrently submitted for review), for the treatment of BRAF V600 mutation positive unresectable or metastatic melanoma. Trametinib is provided as 2 mg capsules to be taken once daily. Based on the Applicant's summary of pivotal Phase 2/3 data, the use of trametinib in subjects with unresectable or metastatic melanoma has resulted in a significant reduction in risk of disease progression and death.

Of note, as there was no commercially available Food and Drug Administration (FDA)-approved BRAF mutation assay at the time of clinical studies initiation for trametinib, an analytically validated "investigational use only" (IUO) allele-specific polymerase chain reaction (PCR) assay was used to screen subjects for eligibility into the GSK-sponsored clinical study, MEK114267. This assay, developed by Response Genetics Institute (RGI), could distinguish BRAF V600E and BRAF V600K mutation subtypes and only subjects with BRAF V600E or V600K mutation-positive tumors were eligible for study participation. GSK has partnered with bioMerieux in the co-development of a companion diagnostic (cDx) assay to be available at the time of trametinib approval; this diagnostic is undergoing simultaneous review in CDRH.

In support of the efficacy and safety of Mekinist™ (trametinib, GSK1120212), for the treatment of patients with unresectable or metastatic melanoma with BRAF V600 mutation, the Applicant has submitted data from one pivotal Phase 3 study (MEK114267) and two Phase 2 studies (MEK113583 and MEK111054). A brief description of Study MEK114267, the study for which inspections were issued, follows.

PROTOCOL MEK114267, ENTITLED "A PHASE III RANDOMIZED, OPEN-LABEL STUDY COMPARING TRAMETINIB (GSK1120212) TO CHEMOTHERAPY (DACARBAZINE OR PACLITAXEL) IN SUBJECTS WITH ADVANCED OR METASTATIC BRAF V600E/K MUTATION-POSITIVE MELANOMA."

Study MEK114267 was a randomized, open-label, multicenter, Phase 3 study to evaluate the efficacy and safety of single agent trametinib compared with chemotherapy (either dacarbazine or paclitaxel). Key eligibility criteria required subjects have: 1) histologically confirmed, Stage III unresectable (Stage IIIC) or metastatic (Stage IV) cutaneous melanoma, which is also determined to be BRAF V600E/K mutation-positive by the central reference laboratory, 2) received no prior treatment or up to 1 prior regimen of chemotherapy for advanced or metastatic melanoma, 3) measurable disease according to Response Evaluation Criteria in Solid Tumors (RECIST V1.1), 4) adequate screening organ function as defined in the protocol, 5) (b) (4) Performance Status of 0-1, and 6) no history or current evidence / risk of retinal vein occlusion (RVO) or central serous retinopathy (CSR) as defined in the protocol. Once determined to be eligible, subjects were randomized 2:1 to receive either: trametinib 2 mg once daily or one of the following 2 chemotherapies, (chosen at the discretion of the investigator provided the subject had not received that type of chemotherapy prior to randomization): dacarbazine 1000 mg/m^2 every 3 weeks or paclitaxel 175 mg/m^2 every 3 weeks. Subjects remained on treatment until disease progression, death, the occurrence of an unacceptable adverse event (AE), or withdrawal from the study. Subjects randomized to the chemotherapy arm were allowed to crossover to receive trametinib after independent confirmation of progression; subjects were then followed for response, progression, survival, and further anti-cancer therapy while receiving GSK1120212.

The study was conducted at 86 clinical investigator sites in 19 countries: Argentina (1), Australia (8), Austria (2), Belgium (6), Canada (8), Czech Republic (2), France (8), Germany (9), Greece (3), Italy (4), New Zealand (2), Norway (1), Poland (3), Russia (4), Sweden (5), Switzerland (1), Ukraine (6), United Kingdom (9), and USA (4). A total of 344 subjects were randomized into the trial. Two hundred fourteen (214) subjects were treated with GSK1120212 and 108 subjects were treated with chemotherapy. At the time of data cut-off (26-Oct-2011), there were 35 deaths in the trametinib arm compared with 29 deaths in the chemotherapy arm representing 16% and 27% of these arms, respectively; however, most subjects in both treatment arms were still ongoing in the study (either continuing to receive randomized study treatment or being observed in follow-up). According to the NDA submission seven entities provided clinical site monitoring support: GSK (all countries not otherwise listed), (b) (4) provided central laboratory services and Response Genetics, Inc. provided BRAF screening testing during the study. (b) (4) provided central review of computerized tomography images (CT), magnetic resonance images (MRI), skin lesion photos, MUGA scans, and echocardiograms ((b) (4) . was responsible for transfer of all items from sites to (b) (4) . An independent data monitoring committee (IDMC) was utilized for this study to ensure external objective medical and/or statistical review of safety issues. An Independent Review Committee (IRC) was used to assess disease response and progression

(b) (4). provided IRC services). Clinical sites were required to submit electronic files with acquired scans and photographs of skin lesions, which were then submitted to the IRC for review. Data was collected by clinical investigators on electronic case report forms (eCRFs), which were transmitted to GSK and combined with data from other sources in a validated data system. According to the NDA, eCRFs (including queries and audit trails) were retained by GSK, and copies of eCRFs were sent to the investigator to maintain as the investigator copy.

The primary endpoint was progression free survival (PFS), which was defined as the time from randomization to date of radiographic/photographical disease progression or death due to any cause, based on the investigator's assessment. Subjects who had not progressed or died at the time of analysis were censored at the last adequate assessment. Key secondary endpoints for this study included: 1) overall survival (OS), which is defined as the time from randomization to death due to any cause, and 2) PFS as assessed by IRC.

Safety measurements included assessment of adverse events, physical findings and vital signs, laboratory evaluations, echocardiograms, and ECGs. Adverse events of special interest included: skin related toxicities, diarrhea, ocular events, cardiovascular events including hypertension, hepatic events, and pneumonitis.

The clinical investigator sites were selected for inspection based on enrollment characteristics, patterns of protocol violations reported for the sites, and patterns of serious adverse event reporting. In addition, a sponsor inspection was conducted to evaluate the sponsor's overall conduct of the study.

II. RESULTS (By Site)

Name of CI	Protocol # Site# Subject#	Inspection Dates	Final Classification
Mohammed Milhem, M.D. University of Iowa Hospitals and Clinics Holden Comprehensive Cancer Center 5970Z JPP 200 Hawkins Drive Iowa City, IA 52242 US	Protocol: MEK114267 Site: #84362 Subjects: 11	September 24-26, 2012	NAI
Lev Demidov, M.D. Cancer Research Center Kasirskoye Shosse, 24 Moscow, 115478 Russia	Protocol: MEK114267 Site: #86717 Subjects: 10	December 3-7, 2012	Pending (Preliminary Classification NAI)

Name of CI	Protocol # Site# Subject#	Inspection Dates	Final Classification
Caroline Robert, M.D. Institut Gustave Roussy Service de Dermatologie 39, rue Camille Desmoulins Villejuif, 94805 France	Protocol: MEK114267 Site: #86614 Subjects: 11	November 26-29, 2012	Pending (Preliminary Classification NAI)
GlaxoSmithKline 1250 South Collegeville Road Collegeville, PA 19426	Protocol: MEK114267	November 6-8, 2012	NAI

Key to Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
Pending = Preliminary classification based on information in 483, if issued, and preliminary communication with the field; the EIR has not been received from the field and complete review of EIR is pending.

1. **Mohammed Milhem, M.D.**
   University of Iowa Hospitals and Clinics
   Holden Comprehensive Cancer Center
   5970Z JPP
   200 Hawkins Drive
   Iowa City, IA 52242
   Site #84362

   a) What was inspected:
   For Study MEK114267, at this site, 18 subjects were screened, and 11 subjects were enrolled. At the time of data cut-off (26-Oct-2011), death had been reported for the following three subjects (400261, 400263, and 400264). Deaths were reported for four additional subjects after the data cut-off date (400251, 400252, 400265, and 400266). All enrolled subjects' records were reviewed during the inspection. The record audit included comparison of source documentation and eCRFs to NDA line listings with particular attention paid to inclusion/exclusion criteria compliance, primary efficacy and key secondary endpoint data, concomitant medication usage, identification of adverse events, and reporting of AEs in accordance with the protocol. The FDA field investigator also evaluated informed consent documentation, randomization procedures, monitoring logs, and IRB approvals and correspondence. There were no limitations to the inspection.

   b) General observations/commentary:
   Consistent with the routine clinical investigator compliance program assessments, during the inspection, data found in source documents and those measurements reported by the Applicant to the Agency in NDA 204114 were compared. While

minor record keeping errors were noted in the Establishment Inspection Report, the investigator's execution of the protocol was found to be generally adequate, and a Form FDA 483, Inspectional Observations was not issued to the clinical investigator.

c) Assessment of data integrity:
The data provided by Dr. Milhem's site for Study MEK114267 that were submitted to the Agency in support of NDA 204114 appear to be reliable and acceptable for use in support of the pending application.

2. Lev Demidov, M.D.
Cancer Research Center
Kasirskoye Shosse, 24
Moscow, 115478
Russia
Site #86717

a) What was inspected:
For Study MEK114267, at this site, 10 subjects were enrolled, and 8 subjects completed the study. Two subjects withdrew consent and were lost to follow-up. Of the remaining 8 subjects, all experienced disease progression and death (Subjects #403651, #403654, #403664, #403667, and #403671 died after the data cut-off date). All 10 subjects' records were reviewed during the inspection. The record audit included comparison of source documentation and eCRFs to NDA line listings with particular attention paid to informed consent documentation, inclusion/exclusion criteria compliance, primary efficacy and key secondary endpoint data, concomitant medication usage, identification of adverse events, and reporting of AEs in accordance with the protocol. The FDA field investigator also evaluated test article accountability, monitoring and sponsor correspondence with the site, and IRB approvals and correspondence. There were no limitations to the inspection.

b) General observations/commentary:
Consistent with the routine clinical investigator compliance program assessments, during the inspection, data found in source documents and those measurements reported by the Applicant to the Agency in NDA 204114 were compared. A Form FDA 483, Inspectional Observations, was issued to the CI for:

> Failure to ensure that the investigation was conducted according to the signed investigator statement and the investigational plan [21 CFR 312.60].
>
> Specifically for collection of a pharmacokinetic sample for one subject prior to the protocol specified time point for collection (Subject #403672's Cycle 8 PK sample was collected on November 23, 2011, which was prior to Day 1 of Cycle 8).

OSI Reviewer Comment: The Form FDA 483 observation is consistent with a minor deviation from the protocol and it occurred after the data cut-off for this application; therefore, it does not impact NDA analyses. Given the very minor nature of this isolated deviation, OSI believes NAI will be the most appropriate final classification for this inspection, but the final determination will be based upon full review of the EIR when it is received.

c) Assessment of data integrity:
The data provided by Dr. Demidov's site for Study MEK114267 that were submitted to the Agency in support of NDA 204114 appear to be reliable and acceptable for use in support of the pending application.

Note: The EIR and associated exhibits for this inspection were not available at the time this CIS was written. The general observations described above are based on review of the issued 483 and preliminary summary information provided by the ORA investigator. An inspection summary addendum will be generated if conclusions change upon review of the final EIR.

3. Caroline Robert, M.D.
Institut Gustave Roussy
Service de Dermatologie
39, rue Camille Desmoulins
Villejuif, 94805
France
Site #86614

a) What was inspected:
For Study MEK114267, at this site, 36 subjects were screened and 11 subjects were enrolled. All enrolled subjects' records were reviewed during the inspection. The record audit included comparison of source documentation and eCRFs to NDA line listings with particular attention paid to inclusion/exclusion criteria compliance, primary efficacy and key secondary endpoint data, concomitant medication usage, identification of adverse events, and reporting of AEs in accordance with the protocol. The FDA field investigator also evaluated informed consent documentation, randomization procedures, monitoring logs, and IRB approvals and correspondence. There were no limitations to the inspection.

b) General observations/commentary:
Consistent with the routine clinical investigator compliance program assessments, during the inspection, data found in source documents and those measurements reported by the Applicant to the Agency in NDA 204114 were compared. The investigator's execution of the protocol was found to be generally adequate, and a Form FDA 483, Inspectional Observations was not issued to the clinical investigator.

c) Assessment of data integrity:
The data provided by Dr. Robert's site for Study MEK114267 that were submitted to the Agency in support of NDA 204114 appear to be reliable and acceptable for use in support of the pending application.

Note: The EIR and associated exhibits for this inspection were not available at the time this CIS was written. The general observations described above are based on review of preliminary summary information provided by the ORA investigator. An inspection summary addendum will be generated if conclusions change upon review of the final EIR.

4. GlaxoSmithKline
1250 South Collegeville Road
Collegeville, PA 19426

a) What was inspected:
The Sponsor, GlaxoSmithKline, was inspected in accordance with the Sponsor/Monitor/CRO data validation compliance program, CP 7348.810. Study MEK114267 was conducted globally, and during this sponsor/monitor inspection the focus was on clinical site records for the CI sites listed in the table above. The record review included review of documents associated with the IRB approvals, site and investigator qualifications and site selection, delegation of monitoring activities to contractors and actual monitoring activities, Independent Review Committee (IRC) documentation and case review, Data Monitoring Committee (DMC) correspondence and meeting minutes, drug accountability records, serious adverse events, and the Sponsor's handling of protocol deviations and violations.

b) General observations/commentary:
Consistent with the sponsor compliance program assessments, during the inspection data found in source documents and those measurements reported by the Sponsor to the Agency in NDA 204114 were compared and verified. Study MEK114267 was found to be adequately executed by the Sponsor, GlaxoSmithKline. A Form FDA 483 was not issued.

c) Assessment of data integrity:
The data generated, as it pertains to Study MEK114267 were inspected in accordance with the sponsor-monitor oriented BIMO compliance program, CP 7348.810. Study MEK114267 appears to have been conducted adequately by GlaxoSmithKline and the data submitted by the Applicant for this study may be used in support of the pending Application.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Based on the review of inspectional findings for the inspections of GlaxoSmithKline, Dr. Milhem, Dr. Demidov, and Dr. Robert, the data submitted by the Applicant for Study MEK114267 appear reliable in support of NDA 204114.

The preliminary classifications for the inspections of Dr. Demidov, and Dr. Robert, and the final classification for the inspections of GlaxoSmithKline and Dr. Milhem, are No Action Indicated (NAI).

Note: All observations noted above related to the inspections of Dr. Demidov and Dr. Robert are based on communications with the field investigators who conducted these inspections; an inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR for these inspections.

{See appended electronic signature page}

Jean Mulinde, M.D.
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

CONCURRENCE: {See appended electronic signature page}

Janice Pohlman, M.D., M.P.H.
Team Leader, Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

{See appended electronic signature page}

Susan D. Thompson, M.D.
Acting Branch Chief, Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

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/s/

JEAN M MULINDE
01/03/2013

JANICE K POHLMAN
01/03/2013

SUSAN D THOMPSON
01/03/2013

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Label, Labeling and Packaging Review

Date:	November 15, 2012
Reviewer:	James Schlick, RPh, MBA Division of Medication Error Prevention and Analysis
Team Leader:	Todd Bridges, RPh Division of Medication Error Prevention and Analysis
Drug Name and Strengths:	Mekinist (Trametinib) Tablets 0.5 mg, 1 mg, and 2 mg
Application Type/Number:	NDA 204114
Applicant:	GlaxoSmithKline
OSE RCM #:	2012-1589

*** This document contains proprietary and confidential information that should not be released to the public.***

Contents

1 INTRODUCTION

This review evaluates the proposed container labels and insert labeling for Mekinist, NDA 204114, for areas of vulnerability that could lead to medication errors.

1.1 PRODUCT INFORMATION

The following product information is provided in the July 2, 2012 proprietary name submission. GlaxoSmithKline informed the FDA on September 25, 2012 (b) (4) GlaxoSmithKline will only market the 30 count bottle. However, the Applicant (b) (4) s as noted in the November 7, 2012 email to DMEPA.

- Active Ingredient: Trametinib
- Indication of Use: Metastatic melanoma therapy
- Route of Administration: Oral
- Dosage Form: Tablets
- Strength: 0.5 mg, 1 mg, 2 mg
- Dose and Frequency: 1 mg to 2 mg once daily
- How Supplied: Bottle containing: - 30 tablets (one month supply) (b) (4)
- Storage: Room temperature
- Container and Closure Systems: (b) (4) white high-density polyethylene bottle with (b) (4) caps for both 30 count (b) (4)

2 METHODS AND MATERIALS REVIEWED

2.1 LABELS AND LABELING

Using the principals of human factors and Failure Mode and Effects Analysis,[1] along with post marketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Container Labels submitted August 2, 2012 (b) (4) Label submitted October 26, 2012 (Appendix A)
- Insert Labeling submitted August 2, 2012

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

3 MEDICATION ERROR RISK ASSESSMENT

3.1 INTEGRATED SUMMARY OF MEDICATION ERROR RISK ASSESSMENT

Mekinist tablets contain sodium lauryl sulfate, an inactive ingredient that can cause mucosal irritation if there is a sufficient quantity in the tablet. In response to a September 21, 2012 email from DMEPA, the Office of New Drug Quality Assessment explained that Mekinist tablets do not contain a sufficient quantity of sodium lauryl sulfate to possibly cause mucosal irritation if crushed or chewed. Therefore, additional language to swallow the tablet whole and not crush or chew is not necessary from this perspective.

The Mekinist labels and insert labeling direct health care practioners to dispense the tablets in their original container. Patients are also directed to keep the desiccant in the original bottle. Because of these requirements, increasing the prominence of statements to store medication in the original container with the desiccant may help minimize errors related to improper storage.

DMEPA notes the bottle counts for all strengths are directly below the strength presentation. Post marketing data shows that confusion with the strength and bottle count can occur when they are in close proximity with each other on the principal display panel. Post marketing data has also shown that moving the bottle count away from the strength presentation can be an effective strategy to minimize confusion.

4 CONCLUSIONS

DMEPA concludes that the proposed labels and labeling can be improved to increase the readability and prominence of important information on the label to promote the safe use of the product. Specifically, DMEPA notes the statement "30 tablets" and (b) (4)" on the labels should be relocated away from the product strength statement to prevent confusion with the strength. Also, the presentation of storage requirements on the container labels should be revised to increase the prominence of the statements. Lastly, DMEPA notes that additional statements in the Patient Counseling Information, Section 17, should be added to make the section more comprehensive.

5 RECOMMENDATIONS

Based on this review, DMEPA recommends the following be implemented prior to approval of this NDA:

A. Container Labels – 30 count and (b) (4)

1. Relocate the net quantity statement "XX" Tablets" away from the product strength statement. Additionally, relocate the product strength in the 30 count bottles to appear just below "(trametinib) Tablets". Post-marketing data shows that confusion with the strength and bottle count can occur when they are in close proximity with each other on the principal display panel.
2. Ensure the established name is at least ½ the size of the proprietary name and has prominence commensurate with the proprietary name taking into account all pertinent factors including typography, layout, contrast and other printer features per 21 CFR 201.10(g)(2).

3. Revise the storage statement [redacted] (b) (4) to read "Dispense in original bottle. Do not remove desiccant. Protect from moisture and light. Do not place medication in pill boxes." Also, to increase the prominence of the statements, bold the font and change the text color to red.

   For example:

   Dispense in original bottle. Do not remove desiccant. Protect from moisture and light. Do not place medication in pill boxes.

B. Insert Labeling

1. Highlights of Prescribing Information - Dosage and Administration
   a. Revise the statement [redacted] (b) (4) to read "Take Mekinist on an empty stomach at least 1 hour before or 2 hours after eating."
2. Dosage and Administration – Section 2.
   a. Revise the statement [redacted] (b) (4) to read "Take Mekinist on an empty stomach at least 1 hour before or 2 hours after eating."
   b. Revise the following statement [redacted] (b) (4) to read "If a dose is missed, do not take the dose if there is less than 12 hours until the next dose"
3. Patient Counseling Information – Section 17.
   a. Add the following statements:

   - "Females who are able to become pregnant should use birth control during treatment and for 4 months after stopping MEKINIST."
   - It is not known if MEKINIST passes into breast milk. Instruct patients who are breastfeeding to talk with their healthcare provider to decide if the patient will take MEKINIST or breastfeed. They should not do both.
   - Instruct patients that if they miss a dose and it is less than 12 hours before their next scheduled dose, do not make up for the missed dose. Take the next dose at their regular time.
   - Do not remove desiccant. Protect from moisture and light. Do not place medication in pill boxes.

   b. Revise the following statement:

(b) (4) [redacted]

to read

"Inform patients to take MEKINIST on an empty stomach, at least one hour before or two hours after eating."

4. Patient Information Leaflet– How should I take MEKINIST?

   a. Revise the following statement (b) (4) [redacted] to read "Take MEKINIST on an empty stomach, at least one hour before or two hours after eating.

   b. Revise the following statement to read (b) (4) [redacted]

      to read

      "If you miss a dose, do not take the missed dose if it is less than 12 hours before your next dose. Take your next dose at the regular scheduled time.

      If it is 12 hours or more until your next dose, take the missed dose as soon as you remember.

      Do not take more than 1 dose of Mekinist at a time."

If you have questions or need clarifications, please contact Frances Fahnbulleh, OSE project manager, at 301-796-0942.

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

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/s/

JAMES H SCHLICK
11/15/2012

TODD D BRIDGES
11/15/2012

RPM FILING REVIEW

Including Memo of Filing Meeting and Filing Meeting Minutes

Application Information		
NDA # 204114	NDA Supplement #:S- Not Applicable	Efficacy Supplement Type SE- Not Applicable
Proprietary Name: Mekinist Established/Proper Name: trametinib Dosage Form: tablets Strengths: 0.5 mg, 1.0 mg, 2.0 mg		
Applicant: GlaxoSmithKline, LLC Agent for Applicant (if applicable): Not Applicable		
Date of Application: August 2, 2012 Date of Receipt: August 3, 2012 Date clock started after UN: Not Applicable		
PDUFA Goal Date: June 3, 2013	Action Goal Date (if different):	
Filing Date: October 2, 2012	Date of Filing Meeting: August 31, 2012	
Chemical Classification: (1,2,3 etc.) (original NDAs only) Type 1		
Proposed indication(s)/Proposed change(s): For the treatment of patients with unresectable or metastatic melanoma with BRAFV600 mutation as detected by an FDA approved test.		

Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:*** ***http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499*** ***and refer to Appendix A for further information.***	☒ 505(b)(1) ☐ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)
Review Classification: ***If the application includes a complete response to pediatric WR, review classification is Priority.*** ***If a tropical disease priority review voucher was submitted, review classification is Priority.***	☒ Standard ☐ Priority ☐ Tropical Disease Priority Review Voucher submitted
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐
Part 3 Combination Product? ☐ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***	☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system (syringe, patch, etc.) ☐ Pre-filled biologic delivery device/system (syringe, patch, etc.) ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Separate products requiring cross-labeling ☐ Drug/Biologic ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)

☒ Fast Track ☒ Rolling Review ☒ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)

Collaborative Review Division (*if OTC product*): Not applicable

List referenced IND Number(s): 102175

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA and Action Goal dates correct in tracking system? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	Yes			
Are the proprietary, established/proper, and applicant names correct in tracking system? ***If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.***	Yes			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? ***For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:*** ***http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm*** ***If no, ask the document room staff to make the appropriate entries.***	Yes			
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** ***http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***		No		
If yes, explain in comment column.				
If affected by AIP, has OC/OMPQ been notified of the submission? **If yes,** date notified:				
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	Yes			

User Fee Status ***If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.***	Payment for this application: ☐ Paid ☒ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.	Payment of other user fees: ☒ Not in arrears ☐ In arrears

505(b)(2) **(NDAs/NDA Efficacy Supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?			NA	
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? **[see 21 CFR 314.54(b)(1)].**			NA	
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug **[see 21 CFR 314.54(b)(2)]?** ***If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs***			NA	
Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm*** **If yes**, please list below:			NA	

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2).Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.

Exclusivity	**YES**	**NO**	**NA**	**Comment**
Does another product (same active moiety) have orphan exclusivity for the same indication? ***Check the Orphan Drug Designations and Approvals list at:*** ***http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm***		No		

If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness **[see 21 CFR 316.3(b)(13)]**? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy***			NA	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ***(NDAs/NDA efficacy supplements only)*** **If yes**, # years requested: ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	Yes			5-year New Chemical Entity Exclusivity
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (***NDAs only***)?		NO		
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.***			NA	

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☒ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	**YES**	**NO**	**NA**	**Comment**
If electronic submission, does it follow the eCTD guidance?[1] **If not,** explain (e.g., waiver granted).	Yes			
Index: Does the submission contain an accurate comprehensive index?	Yes			
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including:	Yes			

[1] http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf

☒ legible ☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only) **If no**, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #			**NA**	
Applications in "the Program" (PDUFA V) (NME NDAs/Original BLAs)	**YES**	**NO**	**NA**	**Comment**
Was there an agreement for any minor application components to be submitted within 30 days after the original submission?			**NA**	
• If yes, were all of them submitted on time?			**NA**	
Is a comprehensive and readily located list of all clinical sites included or referenced in the application?			**NA**	Information is included, however this application does not fall under PDUFA V.
Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?			**NA**	Information is included, however this application does not fall under PDUFA V.
Forms and Certifications				
Electronic *forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise,* ***paper*** *forms and certifications with hand-written signatures must be included.* ***Forms*** *include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674);* ***Certifications*** *include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? ***If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].***	Yes			
Are all establishments and their registration numbers listed on the form/attached to the form?	Yes			
Patent Information (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	Yes			
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and	Yes			Form 3454

(3)? ***Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*				
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature? ***If yes, ensure that the application is also coded with the supporting document category, "Form 3674."*** ***If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant***	Yes			
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature? ***Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].*** ***Note:*** *Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge…"*	Yes			
Field Copy Certification (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***			NA	

Controlled Substance/Product with Abuse Potential	**YES**	**NO**	**NA**	**Comment**
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? ***If yes,*** *date consult sent to the Controlled Substance Staff:* <u>For non-NMEs</u>: *Date of consult sent to Controlled Substance Staff*:			**NA**	

Pediatrics	YES	NO	NA	Comment
PREA Does the application trigger PREA? ***If yes, notify PeRC RPM (PeRC meeting is required)***[2] ***Note**: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.*		No		Orphan Drug Exclusivity issued December 20, 2010
If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?			NA	
If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? ***If no, request in 74-day letter***	Yes			
If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? ***If no, request in 74-day letter***				Sponsor submitted and did not realize it did not trigger PREA.
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)***[3]		No		
Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."***	Yes			
REMS	**YES**	**NO**	**NA**	**Comment**
Is a REMS submitted? ***If yes, send consult to OSE/DRISK and notify OC/ OSI/DSC/PMSB via the CDER OSI RMP mailbox***		No		
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	☒ Package Insert (PI) ☒ Patient Package Insert (PPI) ☐ Instructions for Use (IFU)			

[2] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm
[3] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm

	☐ Medication Guide (MedGuide) ☐ Carton labels ☒ Immediate container labels ☐ Diluent ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request applicant to submit SPL before the filing date.***				
Is the PI submitted in PLR format?[4]	Yes			
If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.***			NA	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	Yes			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (*send WORD version if available*)	Yes			
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	Yes			
OTC Labeling	☒ **Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***				
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***				
If representative labeling is submitted, are all represented SKUs defined?				

[4] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm

If no, request in 74-day letter.				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
Other Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:***	Yes			QT-IRT - 8.27.2012 CDRH – 8.3.2012
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):** May 9, 2012 ***If yes, distribute minutes before filing meeting***		No		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** May 9, 2012 ***If yes, distribute minutes before filing meeting***	Yes			
Any Special Protocol Assessments (SPAs)? **Date(s):** ***If yes, distribute letter and/or relevant minutes before filing meeting***				

ATTACHMENT

MEMO OF FILING MEETING

DATE: August 31, 2012

BLA/NDA/Supp #: NDA 204114

PROPRIETARY NAME: Mekinist

ESTABLISHED/PROPER NAME: trametinib

DOSAGE FORM/STRENGTH: tablets / 0.5 mg, 1 mg, and 2 mg

APPLICANT: GlaxoSmithKline

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): For the treatment of patients with unresectable or metastatic melanoma with BRAFV600 mutation as detected by an FDA approved test.

BACKGROUND: New NME NDA submission.1

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Norma Griffin	Yes
	CPMS/TL:	Karen Jones	Yes
Cross-Discipline Team Leader (CDTL)	Suzanne Demko		Yes
Clinical	Reviewer:	Marc Theoret	Yes
	TL:	Suzanne Demko	Yes
Social Scientist Review (*for OTC products*)	Reviewer:	NA	NA
	TL:		
OTC Labeling Review (*for OTC products*)	Reviewer:	NA	
	TL:		
Clinical Microbiology (*for antimicrobial products*)	Reviewer:	NA	
	TL:		

Clinical Pharmacology	Reviewer:	Ruby Leong	Yes
	TL:	Hong Zhao	Yes
Biostatistics	Reviewer:	Jade Chen	Yes
	TL:	Kun He	Yes
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Gabriel Khasar	Yes
	TL:	Whitney Helms	Yes
Statistics (carcinogenicity)	Reviewer:	NA	
	TL:		
Immunogenicity (assay/assay validation) *(for BLAs/BLA efficacy supplements)*	Reviewer:	NA	
	TL:		
Product Quality (CMC)	Reviewer:	Sue Ching Lin Zhe Jean Tang	Yes
	TL:	Liang Zhou	Yes
Quality Microbiology *(for sterile products)*	Reviewer:		
	TL:		
CMC Labeling Review	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:	Mahesh Ramanadham	Yes
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:	James Schlick	Yes
	TL:		
OSE/DRISK (REMS)	Reviewer:		
	TL:		
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:	Jean Mulinde	Yes
	TL:		
Controlled Substance Staff (CSS)	Reviewer:	NA	NA
	TL:	NA	NA
Other reviewers	Rosane Charlab-Orbach, Genomics Minerva Hughes, Biopharmaceutics Jeff Summers, DOP2 Dep. Dir of Safety Cathryn Lee, DOP 2 Safety RPM Sue Kang, OSE RPM Derek Smith, OC (facilities) Donna Roscoe, CDRH Consultant		Yes
Other attendees	Jewell Martin, ONDQA RPM		Yes

FILING MEETING DISCUSSION

GENERAL • 505(b)(2) filing issues? **If yes,** list issues:	☒ Not Applicable ☐ YES ☐ NO
• Per reviewers, are all parts in English or English translation? **If no**, explain:	☒ YES ☐ NO
• Electronic Submission comments **List comments**:	☒ Not Applicable
CLINICAL **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain:	☒ YES ☐ NO
• Advisory Committee Meeting needed? **Comments**:	☐ YES Date if known: ☒ NO ☐ To be determined

If no, for an NME NDA or original BLA , include the reason. For example: ○ ***the application did not raise significant safety or efficacy issues***	Highlighted as determined by the Team
• Abuse Liability/Potential **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments**:	☒ Not Applicable ☐ YES ☐ NO
CLINICAL MICROBIOLOGY **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL PHARMACOLOGY **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☐ NO
BIOSTATISTICS **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

IMMUNOGENICITY (BLAs/BLA efficacy supplements only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
Environmental Assessment • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **If EA submitted**, consulted to EA officer (OPS)? **Comments**:	☐ Not Applicable ☒ YES ☐ NO ☐ YES ☒ NO ☐ YES ☐ NO
Quality Microbiology (for sterile products) • Was the Microbiology Team consulted for validation of sterilization? (**NDAs/NDA supplements only**) **Comments**:	☐ Not Applicable ☒ YES ☐ NO
Facility Inspection • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? **Comments**:	☐ Not Applicable ☒ YES ☐ NO ☒ YES ☐ NO
Facility/Microbiology Review (BLAs only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

CMC Labeling Review **Comments**:	☐ Review issues for 74-day letter

REGULATORY PROJECT MANAGEMENT

Signatory Authority: Richard Pazdur, Office Director

Date of Mid-Cycle Meeting (for NME NDAs/BLAs in "the Program" PDUFA V): Originally scheduled for November 1, 2012, based on priority review request. However, Sponsor has just recently requested to withdraw 'priority review'. FDA will keep the scheduled November 1, 2012 mid-cycle meeting.

Comments: - The Review Team discussed the following during the Filing Meeting:

1. **Reminder** - all team members should notify the RPM, the CDTL, their team leader and other team members as soon as issues arise during the review process, instead of waiting until the next scheduled meeting to discuss.
2. The review team agreed to review this submission as a priority review.
3. A mid-cycle meeting was scheduled for November 1, 2012 (based on a 6-month review clock). Mid-cycle slides are due to CDTL by October 24, 2012
4. Standing monthly meetings were set up from September 2012 – January 2013.
5. Labeling meetings need to be scheduled.
6. Clinical sites have been selected for inspections, inspections are being scheduled.
7. Facility manufacturing site inspections are being scheduled.
8. Possible PMRs: disciplines will determine and may go in the 74-day letter.
9. Disciplines determined application is fileable, however Division Director and CDTL requested that all deficiencies be identified and included in the 74-day letter.

REGULATORY CONCLUSIONS/DEFICIENCIES

☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. Review Issues: ☐ No review issues have been identified for the 74-day letter. ☒ Review issues have been identified for the 74-day letter. Review Classification: ☒ Standard Review ☐ Priority Review

ACTIONS ITEMS	
☒	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
☐	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	BLA/BLA supplements: If filed, send 60-day filing letter
☐	If priority review: • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify OMPQ (so facility inspections can be scheduled earlier)
☒	Send review issues/no review issues by day 74
☒	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☐	Update the PDUFA V DARRTS page (for NME NDAs in "the Program")
☐	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found in the CST eRoom at: http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f]
☐	Other

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

NORMA S GRIFFIN
10/02/2012

MONICA L HUGHES
10/02/2012

SRPI Label Review completed with RPM Filing Review 10/2/2012

REGULATORY PROJECT MANAGER PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW OF THE PRESCRIBING INFORMATION

To be completed for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Supplements

Application: NDA 204114

Application Type: New NDA

Name of Drug: Mekinist (trametinib) Tablets; 0.5 mg, 1 mg, and 2 mg

Applicant: GlaxoSmithKline

Submission Date: August 2, 2012

Receipt Date: August 3, 2012

1.0 Regulatory History and Applicant's Main Proposals

This is a new NME NDA submission.

2.0 Review of the Prescribing Information (PI)

This review is based on the applicant's submitted Microsoft Word format of the PI. The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

3.0 Conclusions/Recommendations

No SRPI format deficiencies were identified in the review of this PI.

IF APPLICABLE, LIST OTHER LABELING ISSUES

In addition, the following labeling issues were identified:

1.

All SRPI format deficiencies of the PI and other labeling issues identified above will be conveyed to the applicant in the 74-day letter/an advice letter. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format by DATE (**CHOSE A DATE WITHIN TWO TO THREE WEEKS OF THE LETTER**). The resubmitted PI will be used for further labeling review.

5.0 Appendix

Selected Requirements of Prescribing Information (SRPI)

Selected Requirements of Prescribing Information (SRPI)

The Selected Requirement of Prescribing Information (SRPI) version 2 is a 48-item, drop-down checklist of critical format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and labeling guidances.

Highlights (HL)

GENERAL FORMAT

YES 1. Highlights (HL) must be in two-column format, with ½ inch margins on all sides and in a minimum of 8-point font.

Comment:

YES 2. The length of HL must be less than or equal to one-half page (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been is granted in a previous submission (i.e., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is less than or equal to one-half page then select "YES" in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

- **For the Filing Period (for RPMs)**
  - *For efficacy supplements:* If a waiver was previously granted, select "**YES**" in the drop-down menu because this item meets the requirement.
  - *For NDAs/BLAs and PLR conversions:* Select "**NO**" in the drop-down menu because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.
- **For the End-of Cycle Period (for SEALD reviewers)**
  - The SEALD reviewer documents (based on information received from the RPM) that a waiver has been previously granted or will be granted by the review division in the approval letter.

Comment:

YES 3. All headings in HL must be presented in the center of a horizontal line, in UPPER-CASE letters and **bolded**.

Comment:

YES 4. White space must be present before each major heading in HL.

Comment:

YES 5. Each summarized statement in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each information summary (e.g. end of each bullet).

Comment:

:S 6. Section headings are presented in the following order in HL:

Section	Required/Optional
• **Highlights Heading**	Required

Selected Requirements of Prescribing Information (SRPI)

• **Highlights Limitation Statement**	Required
• **Product Title**	Required
• **Initial U.S. Approval**	Required
• **Boxed Warning**	Required if a Boxed Warning is in the FPI
• **Recent Major Changes**	Required for only certain changes to PI*
• **Indications and Usage**	Required
• **Dosage and Administration**	Required
• **Dosage Forms and Strengths**	Required
• **Contraindications**	Required (if no contraindications must state "None.")
• **Warnings and Precautions**	Not required by regulation, but should be present
• **Adverse Reactions**	Required
• **Drug Interactions**	Optional
• **Use in Specific Populations**	Optional
• **Patient Counseling Information Statement**	Required
• **Revision Date**	Required

* RMC only applies to the Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions sections.

Comment:

YES 7. A horizontal line must separate HL and Table of Contents (TOC).

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

S 8. At the beginning of HL, the following heading must be **bolded** and appear in all UPPER CASE letters: **"HIGHLIGHTS OF PRESCRIBING INFORMATION"**.

Comment:

Highlights Limitation Statement

YES 9. The **bolded** HL Limitation Statement must be on the line immediately beneath the HL heading and must state: "**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE).**"

Comment:

Product Title

YES 10. Product title in HL must be **bolded.**

Comment:

Initial U.S. Approval

N/A 11. Initial U.S. Approval in HL must be placed immediately beneath the product title, **bolded,** and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment: *Not yet approved and sponsor indicated '0000'.*

Boxed Warning

A 12. All text must be **bolded**.

Comment:

N/A

Selected Requirements of Prescribing Information (SRPI)

13. Must have a centered heading in UPPER-CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the Warning (e.g., "**WARNING: SERIOUS INFECTIONS**").

Comment:

N/A 14. Must always have the verbatim statement "***See full prescribing information for complete boxed warning.***" centered immediately beneath the heading.

Comment:

N/A 15. Must be limited in length to 20 lines (this does not include the heading and statement "***See full prescribing information for complete boxed warning.***")

Comment:

N/A 16. Use sentence case for summary (combination of uppercase and lowercase letters typical of that used in a sentence).

Comment:

Recent Major Changes (RMC)

N/A 17. Pertains to only the following five sections of the FPI: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.

Comment:

N/A 18. Must be listed in the same order in HL as they appear in FPI.

Comment:

N/A 19. Includes heading(s) and, if appropriate, subheading(s) of labeling section(s) affected by the recent major change, together with each section's identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, "Dosage and Administration, Coronary Stenting (2.2) --- 3/2012".

Comment:

N/A 20. Must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage

YES 21. If a product belongs to an established pharmacologic class, the following statement is required in the Indications and Usage section of HL: [(Product) is a (name of class) indicated for (indication)]."

Comment:

Dosage Forms and Strengths

YES 22. For a product that has several dosage forms, bulleted subheadings (e.g., capsules, tablets, injection, suspension) or tabular presentations of information is used.

Comment: *Does not have multiple dosage forms.*

Selected Requirements of Prescribing Information (SRPI)

Contraindications

YES 23. All contraindications listed in the FPI must also be listed in HL or must include the statement "None" if no contraindications are known.
Comment:

N/A 24. Each contraindication is bulleted when there is more than one contraindication.
Comment:

Adverse Reactions

YES 25. For drug products other than vaccines, the verbatim **bolded** statement must be present: "**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**".

Comment:

Patient Counseling Information Statement

YES 26. Must include one of the following three **bolded** verbatim statements (without quotation marks):

If a product **does not** have FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION"**

If a product **has** FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling."**
- **"See 17 for PATIENT COUNSELING INFORMATION and Medication Guide."**

Comment:

Revision Date

YES 27. **Bolded** revision date (i.e., "**Revised: MM/YYYY** or **Month Year**") must be at the end of HL.
Comment:

Contents: Table of Contents (TOC)

GENERAL FORMAT

YES 28. A horizontal line must separate TOC from the FPI.
Comment:

YES 29. The following **bolded** heading in all UPPER CASE letters must appear at the beginning of TOC: "**FULL PRESCRIBING INFORMATION: CONTENTS**".
Comment:

YES 30. The section headings and subheadings (including title of the Boxed Warning) in the TOC must match the headings and subheadings in the FPI.
Comment:

N/A 31. The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in UPPER-CASE letters and **bolded**.

Comment:

YES 32. All section headings must be **bolded** and in UPPER CASE.

Comment:

YES 33. All subsection headings must be indented, not bolded, and in title case.

Comment:

YES 34. When a section or subsection is omitted, the numbering does not change.

Comment:

YES 35. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading **"FULL PRESCRIBING INFORMATION: CONTENTS"** must be followed by an asterisk and the following statement must appear at the end of TOC: "*Sections or subsections omitted from the Full Prescribing Information are not listed."

Comment:

Full Prescribing Information (FPI)

GENERAL FORMAT

YES 36. The following heading must appear at the beginning of the FPI in UPPER CASE and **bolded**: **"FULL PRESCRIBING INFORMATION".**

Comment:

YES 37. All section and subsection headings and numbers must be **bolded**.

Comment:

YES 38. The **bolded** section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. If a section/subsection is omitted, the numbering does not change.

Boxed Warning
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

YES 39. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under Section 17 (Patient Counseling Information). All patient labeling must appear at the end of the PI upon approval.

Comment:

YES 40. The preferred presentation for cross-references in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, [*see Warnings and Precautions (5.2)*].

Comment:

YES 41. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

Boxed Warning

N/A 42. All text is **bolded**.

Comment:

N/A 43. Must have a heading in UPPER-CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the Warning (e.g., "**WARNING: SERIOUS INFECTIONS**").

Comment:

N/A 44. Use sentence case (combination of uppercase and lowercase letters typical of that used in a sentence) for the information in the Boxed Warning.

Comment:

Contraindications

YES 45. If no Contraindications are known, this section must state "None".

Comment:

Adverse Reactions

YES 46. When clinical trials adverse reactions data is included (typically in the "Clinical Trials Experience" subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice."

Comment:

N/A 47. When postmarketing adverse reaction data is included (typically in the "Postmarketing Experience" subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure."

Comment:

Patient Counseling Information

YES 48. Must reference any FDA-approved patient labeling, include the type of patient labeling, and use one of the following statements at the beginning of Section 17:

- "See FDA-approved patient labeling (Medication Guide)"
- "See FDA-approved patient labeling (Medication Guide and Instructions for Use)"
- "See FDA-approved patient labeling (Patient Information)"
- "See FDA-approved patient labeling (Instructions for Use)"
- "See FDA-approved patient labeling (Patient Information and Instructions for Use)"

Comment: