CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

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

Risk Evaluation and Mitigation Strategy (REMS) Review

Date:	March 14, 2013
Reviewer:	Igor Cerny, Pharm.D. Senior Clinical Reviewer Division of Risk Management
Through:	Cynthia LaCivita Division of Risk Management
Division Director	Claudia Manzo, Pharm. D., Division of Risk Management
Subject:	Evaluation to determine if a risk evaluation and mitigation strategy (REMS) is needed
Drug Name(s):	Trametinib (Mekinist™)
Therapeutic Class:	mitogen-activated extracellular signal regulated kinase 1 (MEK1) and MEK2 inhibitor
Dosage and Route:	0.5 mg, 1.0 mg, and 2.0 mg tablets orally, once daily
Application Type/Number:	NDA 204-114
Submission Number:	eCTD Sequence 0002
Applicant/sponsor:	GlaxoSmithKline
OSE RCM #:	2012-1790

1. INTRODUCTION

This review by the Division of Risk Management (DRISK evaluates if a risk evaluation and mitigation strategy (REMS) is needed for the new molecular entity (NME) trametinib (Mekinist™). On August 3, 2012, the Division of Oncology Products 2 (DOP-2) received a new drug application (NDA) for trametinib with a proposed indication (indication includes modifications from DOP-2) of the treatment of unresectable or metastatic melanoma with BRAF V600E or V600K mutations, as detected by an FDA approved test, who have not received BRAF inhibitor therapy. This compound is being developed by GlaxoSmithKline.

The Applicant is seeking approval on the basis of a single randomized, open-label, active-controlled Phase 3 study (**MEK114267**) in 322 patients with unresectable or metastatic BRAF V600 mutation-positive melanoma, conducted in North America, South America, Europe, Australia, and New Zealand.

The Applicant has submitted a risk management plan which consists of professional labeling. The Applicant did not submit a proposed REMS.

2. BACKGROUND

Cutaneous melanoma is generally recognized as the most aggressive form of all skin cancers. Worldwide it is estimated that on an annual basis, 160,000 people will be diagnosed with melanoma, and approximately 48,000 people are expected to die of the disease.[1] In the US, the incidence of malignant melanoma has increased over the last several decades, and is now the fifth most common cancer in men and the seventh most common cancer in women.[2] Although only 8% of patients are first diagnosed with stage III (regional metastasis) melanoma, and 4% with stage IV (distant metastasis) disease; however, those with unresectable or metastatic melanoma have a grave prognosis, ranking second only to acute leukemia in terms of loss of years of potential life.[3]

Oncogenic mutations in the upstream mitogen-activated protein kinase (MAPK) pathway proteins BRAF and Ras signal through mitogen-activated extracellular signal regulated kinase 1(MEK1) and MEK2. Trametinib is a reversible inhibitor of MEK1 and MEK2 in this signal transduction pathway which plays an important role in cell proliferation and survival.

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[1] GLOBOCAN. *Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 10.*International Agency for Research on Cancer, Lyon, France; 2010

[2] Siegel R, Ward E, Brawley O, Jemal A. Cancer statistics, 2011. The impact of eliminating socioeconomic and racial disparities on premature cancer deaths. CA Cancer J Clin 2011;61:212-36.

[3] Howlader N, Noone AM, Krapcho M, et al (eds). SEER Cancer Statistics Review, 1975-2008, National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/csr/1975_2008/, based on November 2010 SEER data submission, posted to the SEER web site, 2011.

Cytotoxic chemo- and immunotherapies have traditionally been the mainstays of systemic therapy for unresectable or metastatic melanoma. However, the objective response rate (ORR) for **dacarbazine** (approved in 1975) for the treatment of metastatic melanoma is 10-20% and few melanoma patients achieved durable tumor control. **Proleukin (aldesleukin**, approved 1998), a human recombinant interleukin-2 (IL-2) product is approved for the immunotherapy of melanoma; however, its ORR is 16% (complete remission in only 6%) as it is effective only in selected patient subsets.

Two recently-approved agents, Yervoy (ipilimunmab) and Zelboraf (venurafenib), may potentially have greater efficacy than cytotoxic therapies. **Yervoy (**approved March 25, 2011 is a human cytotoxic T-lymphocyte antigen 4 (CTLA-4)-blocking antibody for the treatment of unresectable or metastatic melanoma. In the pivotal trial leading to approval, Yervoy provided a 4-month overall survival (OS) benefit over active treatment with an investigational peptide vaccine with incomplete Freund's adjuvant (gp100). In this pivotal trial, the BRAFV600 mutation status was not investigated. The ipilimumab label has a black box warning for severe and fatal immune-mediated adverse reactions such as fatal immune-mediated enterocolitis (including gastrointestinal perforation); fatal immune-mediated hepatitis (including hepatic failure); fatal immune-mediated toxicities of the skin (including toxic epidermal necrolysis); fatal nervous system toxicity; and endocrinopathies. At the time of approval, FDA determined that a **REMS** (Communication Plan only) was necessary for ipilimumab to ensure the benefits of the drug outweigh the risks of these immune-mediated adverse events.

Zelboraf (approved August 17, 2011) is an inhibitor of some mutated forms of BRAF serine-threonine kinase, including BRAF V600E. It is indicated for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E mutation as detected by an FDA-approved test. It is not recommended for use in patients with wild-type BRAF melanoma. In the pivotal randomized, open-label Phase 3 study (BRIM-3), patient selection was based on the presence of BRAFV600E mutation-positive tumor. Mean OS was not reported but the hazard ratio was 0.44 while the median progression free survival (PFS) was 5.3 months versus 1.6 months for dacarbazine. BRAF V600 mutation-positive status was detected by the cobas® 4800 BRAF V600 Mutation Test. Vemurafenib is associated with an increased incidence of cutaneous squamous cell carcinomas, serious hypersensitivity reactions, severe dermatologic reactions, and QT prolongation. However, it has no black box warning or REMS. Risks are managed through labeling and a medication guide.

On July 30, 2012, GlaxoSmithKline submitted an NDA for **Dabrafenib** (Tafinlar™) for the treatment of BRAF V600 mutation positive unresectable or metastatic melanoma. In the pivotal randomized, open-label, multi-center, active control (dacarbazine) Phase 3 study (BREAK-3), patients with BRAF V600E mutation positive disease were recruited. Mean OS was not reported but the hazard ratio was 0.30 while the median progression free survival (PFS) was 5.1 months versus 2.7 months for dacarbazine. Dabrafenib is associated with serious non-infectious febrile events, cutaneous squamous cell carcinomas, increased risk of non-cutaneous malignancies, new primary melanomas, and uveitis. The Sponsor has proposed managing these risks primarily through labeling.

3. REGULATORY HISTORY

Trametinib is a new molecular entity (NME) which is not approved or marketed in the United States or any other country. IND 102175 was submitted for trametinib on April 14, 2008, and the drug was granted orphan drug exclusivity on December 20, 2010.

On May 14, 2012, GlaxoSmithKline requested Fast track Designation for trametinib based on the criteria that trametinib:

- Treats a "Serious or Life-Threatening Condition;" and
- Demonstrates "the Potential to Address Unmet Medical Needs"

Fast Track Designation was granted by the FDA on June 29, 2012. However, the Sponsor withdrew their Priority Review request on September 27, 2012.

(b) (4)

4. MATERIAL REVIEWED

- August 3, 2012 Original NDA 204114 submission. Sections reviewed include:
  - Section 1.16, Risk Management Plan for Trametinib
  - Section 2.4, NonClinical Overview
  - Section 2.5, Clinical overview
  - Section 2.7.3, Summary of Clinical Efficacy
  - Section 2.7.4, Summary of Clinical Safety
  - Section 2.7.6, Synopses of Individual Studies
  - Section 5, Clinical Study Report MEK114267
- November 1, 2012 Slides from DOP-2 Mid-Cycle Clinical/Stat Presentation

5. OVERVIEW OF CLINCIAL PROGRAM

5.1. EFFICACY FINDINGS

The primary evidence in support of trametinib for the treatment of unresectable or metastatic BRAF V600 mutation-positive melanoma comes from Pivotal Phase 3 Study **MEK114267.** Supporting data is provided by the following studies:

- Phase 2 Study MEK113583, featuring 97 subjects with unresectable or metastatic BRAF V600 mutation-positive melanoma into 2 cohorts with and without prior treatment with a BRAF-inhibitor; and
- Phase I Study MEK111054 with 30 subjects with BRAF mutation-positive, unresectable or metastatic melanoma who had not received a prior therapy with a BRAF inhibitor.

Study MEK114267 was an international, multi-center, randomized (2:1), open label, active-controlled trial. This study enrolled 322 subjects with unresectable or metastatic

BRAF V600 mutation-positive melanoma, randomized to treatment with trametinib 2 mg (N=214) or chemotherapy (N=108) consisting of either dacarbazine 1000 mg/m^2 intravenously every 3 weeks or paclitaxel 175 mg/m^2 intravenously every 3 weeks. Randomization was stratified according to prior use of chemotherapy for advanced or metastatic disease. The primary efficacy outcome measure was progression-free survival (PFS).

Key inclusion criteria included:

- Histologically confirmed, Stage III unresectable (Stage IIIc) or metastatic (Stage IV) cutaneous melanoma, which was BRAF V600E and V600K mutation-positive by the laboratory testing;
- Either no prior treatment or up to 1 prior chemotherapy regimen for advanced or metastatic melanoma.

Key exclusion criteria included the following:

- Any prior use of BRAF/MEK inhibitors, or ipilimumab in the advanced or metastatic Setting (in a single arm, trial evaluating overall response rates with trametinib in 40 patients with BRAF V600E and V600K mutation-positive, unresectable or metastatic melanoma who had received prior therapy with a BRAF inhibitor, no patient achieved a confirmed, partial or complete response)

RESULTS:

All of the randomized patients had a baseline ECOG performance status of either 0 or 1. Approximately 87% had tumor tissue with mutations in BRAF V600E, whereas only 12% had the V600K mutation, and <1% had both. The vast majority of patients (94%) had metastatic disease while 65% were Stage M1c.

The Applicant employed the use of a blinded independent review committee (BICR). The BICR assessed that the trametinib-treated patients had a statistically significant prolongation in PFS compared to those receiving chemotherapy with median PFS times of 4.9 months (95% CI: 4.6, 5.0) for trametinib and 1.5 months (95% CI: 1.4, 2.8) for the chemotherapy arm. The hazard ratio was calculated to be 0.42 (95% CI: 0.29, 0.59; p<0.0001, stratified log-rank test). Approximately 19% of the trametinib-treated patients were assessed by the BICR to have experienced a confirmed objective tumor response (mean duration 5.6 months); however, all of these were partial responses.

5.2. SAFETY

A total of 329 metastatic melanoma patients received trametinib in this NDA, all starting at a dose of 2 mg daily. The bulk of the safety analyses were drawn primarily from study MEK114267.

The most frequent cause of on-study death was attributed to progression of disease (85% of trametinib deaths). Five subjects in the trametinib safety population died due to 6 fatal SAEs; however, all except one (renal failure) were not considered drug-related.

Cellulitis (3%) was the most frequently reported SAE in the trametinib safety population followed by pulmonary embolism (2%). In Study MEK114267, an identical percentage (9%) of subjects on trametinib and on chemotherapy experienced AEs that led to discontinuation; however, the nature of these adverse events differed between these two groups. The AEs leading to discontinuation in the chemotherapy group included diarrhea, flushing, and neuropathy, for trametinib these included ejection fraction decreased, left ventricular dysfunction, pneumonitis, rash, and renal failure.

In Study MEK114267, AEs that were more common with trametinib than chemotherapy (differences of at least 5% for AEs, and at least 2% for Grades 3-4) included:

- vascular disorders (such as lymphedema and hypertension): 14 Grade 3-4 events versus 4 for chemotherapy;
- skin and subcutaneous tissue disorders:11 Grade 3-4 AEs for trametinib versus zero Grade 3-4 events with chemotherapy;
- gastrointestinal disorders (3 Grade 3-4 events each arm);
- infections (one Grade 3-4 for trametinib versus zero for chemotherapy);
- AST increase: 1 Grade 3-4 event with trametinib; zero with chemotherapy;
- Ejection fraction decreased: 1 Grade 3-4 with trametinib; none with chemo
- cough or epistaxis: zero Grade 3-4 events in each arm

Specific major safety concerns are discussed in more detail below:

Cardiomyopathy: In MEK114267, 2% of patients discontinued trametinib due to cardiomyopathy, one case categorized as severe. The median time to onset of left ventricular dysfunction and decreased ejection fraction was 70 days and occurred within the first month in 36% of patients. Cardiomyopathy eventually resolved in 71% of patients. Decreases of ejection fraction of ≥10% and below normal limits occurred in 17% of patients. The labeling being considered by FDA recommends (b) (4) [redacted] Labeling will also direct how and when to withhold trametinib as well as how and when to reintroduce dosing. However, the safety of resumption trametinib reintroduction in patients with trametinib induced cardiac dysfunction has not been adequately studied.

Central Serous Retinopathy (CSR) and Retinal Vein Occlusion (RVO): Across the trametinib NDA, approximately 1% developed CSR and 1% developed RVO. The four cases of RVO were reported between 99 and 314 days after initiating trametinib, whereas 13 cases of CSR were reported with onset ranging from 1 to 90 days after initiating trametinib. The labeling will instruct the prescriber (b) (4) [redacted]

Rash: In MEK114267, 87% of trametinib-treated patients experience rash as compared to 13% in chemotherapy patients. Approximately12% of trametinib-treated patients reported a severe rash as compared to none in the chemotherapy arm. The median time to rash onset was 15 days while the median time to recovery was 48 days. The labeling will (b) (4)

Infections and Infestations: Of the 56 fatal SAE cases considered **not**-related to trametinib, infections/infestations occurred in 23 patients (41%), far and away the largest individual MedDRA SOC within the 56 cases. These events included sepsis, pneumonia, septic shock, Staphylococcus bacteremia, infected skin ulcer, Pseudomonas infection, and lung Infection. The timeframe for these events was generally quite variable.

Pneumonitis: Three cases of pneumonitis were reported in this NDA. Cases started anywhere from 53 to 80 days after treatment initiation, and required 4 to 27 days to resolve (in one case with sequelae). In two of the three cases trametinib was discontinued.

Embryo-Fetal Toxicity: trametinib could cause fetal harm when administered to a pregnant woman. The labeling will advise female patients of child-bearing age to use highly effective methods of contraception during therapy and for four months following discontinuation.

6.0 Applicant's Proposed Risk Management Plan

The Applicant has submitted a Risk Management Plan (RMP) for trametinib. In this plan, in addition to the Applicant's pharmacovigilance monitoring, risk minimization activities are centered around addressing trametinib-associated risks through labeling.

7.0 PROPOSED POSTMARKETING STUDIES/REQUIREMENTS

The Applicant has not submitted any proposed postmarketing studies. At this current writing, only the Clinical Pharmacology staff (Dr. Ruby Leong, 2/14/12 email) is proposing the following two post-marketing requirements (PMR):

- Conduct a trial to determine the appropriate trametinib dose in patients with hepatic impairment
- Complete a clinical trial evaluating the potential for trametinib to prolong the QT/QTc interval

At this time, no clinical PMRs are being proposed.

6. ODAC

This product will not be presented to the ODAC.

7. DISCUSSION

At the November 1, 2012 Mid-cycle meeting, the DOP-2 Clinical/Statistical team indicated that the data submitted by the Applicant had ongoing data analysis and quality problems and that the results were considered unverified. However, as data come in from the Applicant, the review division is more comfortable with the results which show a 3.4 month benefit over chemotherapy for PFS and a hazard ratio of 0.42. Adverse events of concern include cardiomyopathy/decreased left ventricular ejection fraction, the ophthalmologic events CSR and RVO, rash, infections/infestations, and pneumonitis.

The proposed indication for trametinib is for the treatment of unresectable or metastatic melanoma with BRAF V600E or V600K mutations. This is a seriously ill population with limited therapeutic options, all of which are associated with serious adverse events. The serious adverse events for the most closely related approved agent, vemurafenib, are handled through labeling. Risks associated with vemurafenib include an increased incidence of cutaneous squamous cell carcinomas, serious hypersensitivity reactions, severe dermatologic reactions, and QT prolongation. The adverse events for a closely related yet-to-be-approved agent, dabrafenib include: serious non-infectious febrile events, cutaneous squamous cell carcinomas, increased risk of non-cutaneous malignancies, new primary melanomas, and uveitis and iritis.

In addition, it is expected that the post marketing requirements (one to ascertain the appropriate dose in patients with hepatic impairment, and another to assess the potential for trametinib to prolong the QT/QTc interval) will assist in further characterizing the agent's adverse event profile. If serious adverse events can be further characterized and appear to occur at a higher frequency or are of a greater severity than has been noted heretofore, specific risk mitigation strategies can be considered.

Thus based upon: the overall risk/benefit assessment of trametinib by DOP2 and DRISK; the risk/benefit profile of trametinib compared to that of similar agents; and the overall 3.4 month benefit on PFS, DOP-2 and DRISK concur that risks can be addressed through labeling and a REMS is not necessary to ensure the benefits outweigh the risks.

8. CONCLUSION

DRISK recommends managing the identified safety risks associated with trametinib through labeling, including a Medication Guide as part of labeling and not a REMS. The need for a REMS can be re-evaluated if new safety data becomes available that warrants more extensive risk mitigation.

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/s/

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03/14/2013
REMS Review

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