CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204114Orig1s000

OFFICE DIRECTOR MEMO

Summary Review for Regulatory Action

Date	Electronic stamp date
From	Richard Pazdur, MD
Subject	Office Director Decisional Memo
NDA #	NDA 204114
Applicant Name	GlaxoSmithKline LLC
Date of Submission	August 2, 2012
PDUFA Goal Date	June 3, 2013
Proprietary Name / Established (USAN) Name	Mekinist trametinib
Dosage Forms / Strength	tablets/ 0.5 mg, 1 mg, and 2 mg
Proposed Indication(s)	MEKINIST™ is indicated for the treatment of patients with unresectable or metastatic melanoma with BRAF (b) (4) mutations as detected by an FDA-approved test. **Limitation of use:** (b) (4) MEKINIST (b) (4) prior BRAF inhibitor therapy.
Recommended Action for NME:	Approval

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Division Director	Patricia Keegan
Regulatory Project Manager	Norma Griffin
Medical Officer Review	Marc Theoret
Statistical Review	Huanyu (Jade) Chen
Pharmacology Toxicology Review	Gabriel S. Khasar
CMC Review/	Sue-Ching Lin (DP) & Z. Jean Tang (DS)
Biopharmaceutics Reviewer	Minerva Hughes
Microbiology Review	John Metcalfe
Clinical Pharmacology Review	Ruby Leong
OPDP/DPDP	Tran, Quyn-Van
OSI Reviews	Jean Mulinde
CDTL Review	Suzanne Demko
OSE/DMEPA	James Schlick
OSE/DRISK	Igor Cerny
Ophthalmology Consult	Wiley Chambers

OND=Office of New Drugs
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DSI=Division of Scientific Investigations
DDRE= Division of Drug Risk Evaluation
DRISK=Division of Risk Management
CDTL=Cross-Discipline Team Leader

1. Introduction

On August 2, 2012, GlaxoSmithKline (GSK) submitted this NDA for trametinib (Mekinist), which is a selective, non-competitive inhibitor of MEK1/MEK2 activation and kinase activity. The applicant limited the clinical development program to patients with melanoma containing BRAF V600 mutations based on the intended co-development with GSK's dabrafenib and the predicted synergism of trametinib and dabrafenib, both of which inhibit proteins in the ERK (extracellular signal-related kinase) transduction signaling pathway. The MEK1 and MEK2 proteins are (b) (4) of the RAF proteins in this signaling pathway and mutations in BRAF which result in constitutive activation (e.g., BRAF V600E) and continuous activation of MEK. Unlike BRAF inhibitors, MEK inhibition in BRAF wild-type tumors does not result in paradoxical activation of the signaling pathway.

The safety and effectiveness of trametinib is based primarily on the results of a single trial (Protocol MEK114267), which a randomized (2:1), open-label, active-controlled, multinational comparing trametinib to single agent chemotherapy (dacarbazine or paclitaxel). Patients on the chemotherapy arm were allowed to cross-over to trametinib upon progression. Key inclusion criteria were unresectable Stage III or Stage IV melanoma containing either a BRAF V600E or BRAF V600K mutation and no more than one prior systemic treatment regimen (biologic or chemotherapy but not BRAF or MEK inhibitor therapy). The primary endpoint was progression-free survival (PFS) as determined by the clinical investigator and key secondary endpoints were overall survival (OS) and best overall response rate (ORR).

A total of 322 patients were randomized to trametinib (n=214) 2 mg orally once daily or one of two chemotherapy regimens (n=108), consisting of dacarbazine 1000 mg/m^2 or paclitaxel 175 mg/m^2 by intravenous infusion every 21 days. Of the 322 patients enrolled and randomized, 87% had melanomas with BRAF V600E mutations, 12% with BRAF V600K, and <1% with both mutations detected, 54% were male, the median age was 54 years, all had baseline ECOG performance status of 0 or 1, and 64% had M1c disease.

The trial demonstrated a statistically significant improvement in the PFS for the trametinib arm compared with chemotherapy [HR 0.47 (95% confidence intervals (CI): 0.34, 0.65)] with an increase in median PFS from 1.5 months in the chemotherapy arm to a median PFS of 4.8 months for the trametinib arm.

Safety evaluation for common adverse reactions was based primarily on the comparative results observed in Protocol MEK114267 (n=211 trametinib-treated patients), with characterization of uncommon and serious adverse reactions supplemented by the results of two additional clinical trials in patients with melanoma treated with trametinib 2 mg daily (n=329 trametinib-treated patients). The most serious adverse reactions of trametinib are cardiomyopathy in approximately 7% of patients in MEK114267 based on serial LVEF measurements, retinal pigment epithelial detachment in less than one percent (0.5%) of patients enrolled in MEK114267 and fourteen patients across the entire clinical trial database, retinal vein occlusion in 0.6% of patients (2/329) receiving the recommended dose of trametinib across clinical trials, interstitial lung disease in 2.4% of trametinib treated patients in Protocol MEK114267, and serious skin rash requiring hospitalization in 6% of trametinib treated patients in Protocol MEK114267. The most common (≥ 10% incidence) adverse reactions were rash, diarrhea, lymphedema, acneiform dermatitis, hypertension, stomatitis, stomach pain, mild-moderate hemorrhage, abdominal pain, dry skin, paronychia, and pruritis.

2. Background

Cutaneous melanoma from malignant transformation of melanocytes in the skin, is the most aggressive malignancy arising from the skin; based on trend analyses, the incidence of melanoma has been increasing over the past several decades. The National Cancer Institute estimates that in 2013 there will be 76, 690 new cases of melanoma and 9,480 deaths due to melanoma in the United States.[1] While 84% of melanoma presents with localized disease which may be cured with surgical excision alone or with adjuvant interferon or investigational agents and has a 5-year survival rate of 98%, for the 4% who present with metastatic disease and receive systemic treatment, the 5-year survival rates is only 15%. Of patients presenting with cutaneous melanoma, approximately 50% will have melanoma bearing BRAF V600 mutations.

There are five drugs that have been approved by the US FDA for the treatment of metastatic melanoma: vemurafenib, ipilimumab, aldesleukin, dacarbazine, and hydroxurea. Hydroxurea which was FDA-approved in the 1970's, is no longer used or recommended by clinical practice guidelines. Dacarbazine and aldesleukin (interleukin-2) were approved by FDA for the treatment of metastatic melanoma in May 1975 and January 1998, respectively, based on evidence of durable objective tumor responses. Their use for the initial treatment of metastatic melanoma has declined following approval of ipilimumab and vemurafenib.

On March 25, 2011, FDA approved ipilimumab (Yervoy, Bristol Myers Squibb) for the treatment of unresectable or metastatic melanoma. The approval of ipilimumab was based on a single, randomized trial which demonstrated a statistically significant improvement in OS for ipilimumab in combination with a peptide vaccine (gp100 peptides) compared to the peptide vaccine alone [HR 0.66 (95% CI: 0.55, 0.85), p=0.0004] with median survival times of 9.95 months and 6.44 months in the combination and gp100 monotherapy arms, respectively.

On August 17, 2011, vemurafenib (ZELBORAF, Genentech Inc.) an inhibitor of some mutated forms of BRAF serine-threonine kinase, including BRAF V600E, was approved for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E mutation as detected by an FDA-approved test[2]. The approval was based on a single, multicenter, randomized (1:1), open-label, active-controlled (dacarbazine) trial conducted in 675 patients with treatment naive, BRAF V600E mutation-positive unresectable or metastatic melanoma as detected by the cobas 4800 BRAF V600 Mutation Test. The trial demonstrated a statistically significant improvement in OS [HR 0.44 (95% CI: 0.33, 0.59); p < 0.0001] and PFS [HR 0.26 (95% CI: 0.20, 0.33); p <0.0001] for patients in the vemurafenib arm. The median survival time not reached in the vemurafenib arm as compared to 7.9 months in the dacarbazine arm. The median PFS was 5.3 months in the vemurafenib arm compared with 1.6 months in the dacarbazine arm.

Commonly used off-label treatments, whose use has also declined following approval of vemurafenib and ipilimumab, include temozolomide alone or in combination with other drugs, dacarbazine-based combination chemotherapy regimens, and interferon alone or in combination with chemotherapy, as well as investigational immunotherapy treatments.

3. CMC and Biopharmaceutics/Device

CMC

There are no issues that preclude approval. CMC and biopharmaceutics reviewers have provided an overall acceptability recommendation of the manufacturing of the drug product and drug substance for trametinib. Manufacturing site inspections were acceptable. The proposed commercial product was adequately bridged to the product administered in the major efficacy trial using in vitro dissolution. The specifications for genotoxic impurities have been qualified by nonclinical toxicology. Stability testing supports an expiry of 12 months for the

[1] http://www.cancer.gov/cancertopics/types/melanoma
[2]http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label_ApprovalHistory#labelinfo

0.5 mg and 2 mg tablets and 9 months for the 1 mg tablets when stored at 2° to 8°C (36°F to 46°F) and protected from moisture and light.

See action letter for CMC PMCs.

4. Nonclinical Pharmacology/Toxicology

There are no pharmacology/toxicology issues that preclude approval.

The NDA contained *in vitro* pharmacology studies demonstrating inhibition of MEK1/MEK2 kinase activity directly as well as that mediated by constitutively activated BRAF in BRAF B600E mutation-positive cells and also demonstrated that trametinib inhibited of BRAF V600 mutation-positive melanoma in tumor xenograft models. The NDA contained evidence of selective MEK inhibition with minimal off-target activity based on *in vitro* studies.

In rats, target organ toxicity was observed in the skin, the gastrointestinal (GI) tract, lymphoid organs, bone marrow (reversible neutropenia), liver, and adrenal gland at doses of 0.5 to 1 mg/m^2. In addition, evidence of toxicity with possible impairment of fertility was noted in female rats (decreased corpora lutea). In dogs, target organ toxicity was observed in the skin, GI tract, lymphoid organs, and lungs at doses of 0.6-0.45 mg/m^2 daily.

In safety pharmacology assessments, inhibition of the hERG channel was observed only at micromolar concentrations (1.5-3.7) and QT prolongation was not observed in dogs, indicating a low potential for QT prolongation in humans. Evidence of cardiomyopathy (decreased left ventricular ejection fraction, increased hear weight) was observed only in mice who were able to tolerate trametinib doses and exposures exceeding those administered in clinical and other non-clinical studies by 3-7-fold.

Trametinib administration resulted in embryofetal lethality in reproductive toxicology studies. 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 post-implantation loss, including total loss of pregnancy, compared to control animals.

Carcinogenicity studies with trametinib have not been conducted. Trametinib was not genotoxic in studies evaluating reverse mutations in bacteria, chromosomal aberrations in mammalian cells and micronuclei in the bone marrow of rats.

5. Clinical Pharmacology

There are no clinical pharmacology issues that preclude approval. As noted by the clinical pharmacologist, evaluation of PK in patients with organ impairment and adequate assessment of effects on QTc were not conducted. See PMRs in action letter required to assess these effects.

The mean absolute bioavailability of a single 2 mg oral dose of trametinib is 72%, with a median time to achieve peak concentrations (Tmax) of 1.5 hours and the estimated elimination half-life is 3.9 to 4.8 days. Trametinib is highly protein bound (97.4%). Administration of a single 2 mg dose of trametinib with a high-fat, high-calorie meal resulted in a 70% decrease in Cmax and a 24% decrease in AUC0-168h, compared to fasted conditions. Since

the decrease in exposure was considered clinically relevant and given the potential for confusion as to what constitutes a "high fat meal" product labeling recommends taking trametinib in a fasting state.

Trametinib is not significantly metabolized via CYP450. Based on studies with ^{14}C-trametinib, the major route of elimination is the liver (>80%) with renal elimination responsible for less than 20%. Two major active metabolites are formed through acetylation (M5) or hydroxylation (M7). At steady state, trametinib is the major component (≥ 75%) in plasma, with the remainder equally split between M5 and M7.

The population PK analysis assessed the influence of covariates including age, body weight, height, sex, albumin, total bilirubin, international normalized ratio (INR), mild to moderate renal impairment, tumor types (e.g., melanoma vs. others), BRAF V600 mutation (E vs. K vs. others), study, and mild hepatic impairment. The pharmacometrics review concluded that none of these covariates had a clinically important influence on the CL/F and V/F of trametinib. Effects of race and CYP3A4 inhibitors/inducers were not tested in the model since the majority of patients in the datasets were Caucasian (97%), and did not receive CYP3A4 inhibitors (97%) or inducers (99%).

6. Clinical Microbiology

There are no clinical microbiology issues that preclude approval.

7. Clinical Efficacy

Efficacy is supported by a single trial (Protocol MEK114267), which is a Phase 3, open-label, randomized (2:1) trial comparing the safety and efficacy of trametinib to single agent chemotherapy (dacarbazine or paclitaxel). Key eligibility criteria were a diagnosis of Stage IIIc or Stage IV cutaneous melanoma, BRAF V600E/K mutation-positive tumor as determined with the "GSK BRAF mutation assay," no more than one prior regimen for treatment of unresectable or metastatic disease, no prior treatment with a BRAF or MEK inhibitor.

The primary objective was to demonstrate superior PFS as determined by the investigator, with trametinib as compared to chemotherapy in patients with V600E/K locally advanced or metastatic melanoma. The secondary objectives were to further characterize the efficacy, safety, and tolerability of trametinib as a single agent to characterize PFS in the subgroup who received no prior chemotherapy in the advanced or metastatic setting. To characterize PFS in the subgroup who received one prior chemotherapy regimen in the advanced or metastatic setting, to characterize PFS and overall response rate in the subgroup of subjects with BRAF V600 K mutation-positive melanoma, to characterize efficacy (PFS, overall response rate, and duration of response) following crossover from chemotherapy to trametinib. An exploratory objective was to evaluate and compare changes in health related quality of life (HRQOL) between the two study arms. An additional objective was to further validate a BRAF mutation assay.

Patients were randomized (2:1) to receive trametinib 2 mg orally once daily or to receive chemotherapy (either dacarbazine 1000 mg/m^2 once every 3 weeks or paclitaxel 175 mg/m^2 every 3 weeks, at the discretion of the investigator). Treatment continued until disease progression, death or withdrawal. At the time of disease progression, patients randomized to chemotherapy were permitted to receive open-label treatment with trametinib. Randomization was stratified by LDH level (above the upper limit of normal vs. equal to or below the upper limit of normal) and prior chemotherapy for advanced or metastatic disease (yes vs. no).

Results:

A total of 322 patients were enrolled and randomized to trametinib (n=214) or chemotherapy (n=108). Three patients (1%) in the trametinib arm and nine (8%) in the chemotherapy arm never received protocol-specified

therapy. Of the 108 patients randomized to chemotherapy, 62 (57%) received dacarbazine, 37 (34%) received paclitaxel, and 9 (8%) did not initiate chemotherapy.

The median age for randomized patients was 54 years, 54% were male, >99% were white, and all patients had baseline ECOG performance status of 0 or 1. Most patients had metastatic disease (94%), were Stage M1c (64%), had elevated LDH (36%), no history of brain metastasis (97%), and received no prior chemotherapy for advanced or metastatic disease (66%). The distribution of BRAF V600 mutations was BRAF V600E (87%), V600K (12%), or both (<1%). The median duration of follow-up was approximately 5 months in both treatment arms (range: 0 to 10 months). Fifty-one (47%) patients crossed over from the chemotherapy arm at the time of disease progression to receive MEKINIST.

The most common reason for treatment discontinuation in both arms was disease progression (54% for those randomized to trametinib and 67% for those randomized to chemotherapy), followed by adverse events (10% and 6%, respectively).

The key efficacy results are summarized in the table below. Based on analyses performed by Dr. Chen, the outcomes in the chemotherapy arm were similar in subgroups based on chemotherapy selected (dacarbazine or paclitaxel).

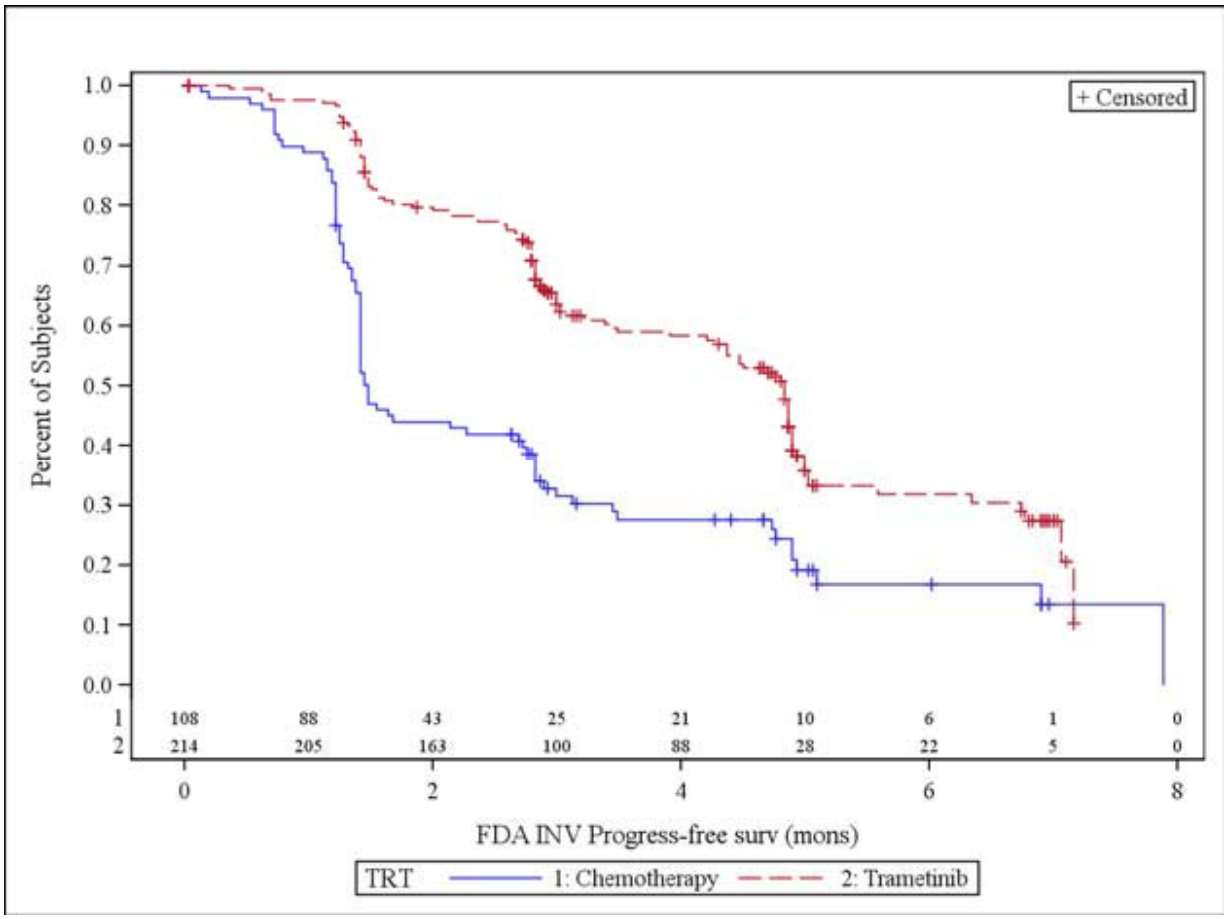
Table 1: Key Efficacy Results from Protocol MEK114267

Efficacy Parameter	Trametinib N=214	Chemotherapy N=108
Progression-free survival		
Median PFS in months	4.8	1.5
Hazard ratio[1] (95% CI)	0.47 (0.34, 0.65)	
p-value	<0.0001	
Overall survival		
Number of deaths	35 (16%)	29 (27%)
Median S in months	NR	NR
Hazard ratio[2] (95% CI)	0.54 (0.33, 0.89)	
p-value	Not significant	
Objective Responses		
Overall response rate (95% CI)	22% (17%, 28%)	8% (4%, 15%)
Complete response (rate)	4 (2%)	0
Partial responses (rate)	43 (25%)	9 (8%)
Duration of response		
Median duration in months (95% CI)	5.5 (4.1, 5.9)	NR (3.5, NR)

[1] Pike unstratified
[2] Cox unstratified

In supportive analyses based on independent radiologic review committee assessment, the PFS results were consistent with those of the primary efficacy analysis.

Figure 1: Investigator-Assessed Progression-free Survival



Additional trials informing assessment of efficacy

Protocol MEK113583 was a single arm, two cohort trial which evaluated the anti-tumor activity (objective response rate) of trametinib in patients with unresectable or metastatic, BRAF V600 mutation-positive melanoma. The two cohorts included patients who had not been exposed to prior BRAF inhibitor therapy and a second cohort of patients who had received a BRAF inhibitor. This latter cohort enrolled 40 patients, all of whom were treated with trametinib at a dose of 2 mg orally once daily until disease progression or unacceptable toxicity. The median age was 58 years, 63% were male, all were white, 98% had baseline ECOG PS of 0 or 1, and the majority of patients' tumors had BRAF V600E mutations (83%)

No patient in this cohort of Protocol MEK113583 achieved a confirmed partial or complete response as determined by the clinical investigators. Based on the unanticipated absence of anti-tumor activity, the results of this cohort are described in the physician package insert and a Limitation of Use has been added to the Indications and Usage section of the package insert.

8. Safety

The safety database of 329 patients with metastatic melanoma, receiving trametinib at the recommended dose and schedule in two open-label single-arm trials (n=118) or in an open-label, randomized, active-controlled trial (n=211), was of adequate size to identify serious adverse reactions occurring at an incidence of 1.0%.

The safety data described in the NDA consists primarily of data obtained in the major efficacy trial (Protocol MEK114267), which provides comparative safety data from 211 trametinib-treated patients and 99 chemotherapy-treated patients. This is supplemented by an integrated safety database on 329 patients with metastatic melanoma receiving the recommended dose of trametinib 2 mg orally once daily (n=329).

There were no specific contraindications to treatment identified and no patient population at increased risk. See the Warnings and Precautions section of the physician package insert and in patient labeling for a description of the following SAEs: cardiomyopathy, retinal pigment epithelial detachment, retinal vein occlusion, interstitial lung disease, and serious cutaneous toxicity. See table below for select adverse reactions occurring in ≥10% of patients receiving trametinib and at a higher incidence than in the control arm.

Table 2: Selected Adverse Reactions Occurring in ≥10% of Patients Receiving MEKINIST and at a Higher Incidence than in the Control Arm[f]

	Trametinib (n=211)		Chemotherapy (n=99)	
Adverse Reaction Term	All Grades[a]	Grade 3-4	All Grades[a]	Grade 3-4
Skin and subcutaneous tissue disorders				
Rash	57	8	10	0
Dermatitis acneiform	19	<1	1	0
Dry skin	11	0	0	0
Paronychia	10	0	1	0
Pruritis	10	2	1	0
Gastrointestinal disorders				
Diarrhea	43	0	16	2
Stomatitis[b]	15	2	2	0
Abdominal pain[c]	13	1	5	1
Vascular disorders				
Lymphedema[d]	32	1	4	0
Hypertension	15	12	7	3
Hemorrhage[e]	13	<1	0	0

[a] National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.
[b] Includes the following terms: stomatitis, aphthous stomatitis, mouth ulceration, and mucosal inflammation
[c] Includes the following terms: abdominal pain, abdominal pain lower, abdominal pain upper, and abdominal tenderness
[d] Includes the following terms: lymphedema, edema, and peripheral edema
[e] Includes the following terms: epistaxis, gingival bleeding, hematochezia, rectal hemorrhage, melena, vaginal hemorrhage, hemorrhoidal hemorrhage, hematuria, conjunctival hemorrhage.
[f] Overall incidence ≥ 5% or Grade 3-4 adverse reactions ≥2% higher in trametinib arm compared to chemotherapy

REMS

The clinical review team and DRISK agreed that a REMS is not necessary to ensure safe use of trametinib and that risk communication and mitigation can be addressed through product labeling.

9. Advisory Committee Meeting

Trametinib is a new molecular entity and the first drug approved in this class (MEK inhibitor). It was not referred to ODAC because the safety profile is acceptable for the indication, and the clinical study design for the major efficacy trial is acceptable and similar to that used for previously.

10. Pediatrics

Trametinib was granted orphan drug designation for the "treatment of patients with advanced or metastatic melanoma (Stage IIb through IV) and is therefore exempt from PREA requirements.

11. Decision/Action/Risk Benefit Assessment

- Regulatory Action: Approval

- Risk Benefit Assessment
  Metastatic melanoma is a serious and life-threatening disease, with a 5-year survival rate of only 15%.

  The single trial supporting efficacy in this application demonstrated a statistically significant improvement in PFS for the trametinib arm compared with chemotherapy [HR 0.47 (95% confidence intervals (CI): 0.34, 0.65); p <0.001] with an increase in median PFS from 1.5 months in the chemotherapy arm to a median PFS of 4.8 months for the trametinib arm. In addition, the overall response rate was superior for the trametinib arm compared to chemotherapy (22% vs. 8%) with a median duration of response of 5.5 months for responders in the trametinib arm. An immature analysis of OS did not suggest potentially harmful effects. The most serious adverse reactions of trametinib are cardiomyopathy (7% per-patient incidence), retinal pigment epithelial detachment (0.5%), retinal vein occlusion (0.6%), interstitial lung disease (2.4%), and serious skin rash requiring hospitalization in 6% of trametinib treated patients in Protocol MEK114267. The most common (≥ 10% incidence) adverse reactions were rash, diarrhea, lymphedema, acneiform dermatitis, hypertension, stomatitis, stomach pain, mild-moderate hemorrhage, abdominal pain, dry skin, paronychia, and pruritis.

  As compared to BRAF inhibitors, trametinib has a different toxicity profile which may offer advantages to individual patients. In addition, as compared to ipilimumab, trametinib offers the potential for tumor reduction and tumor control with an alternative toxicity profile. Based on the totality of the data provided, the application contains substantial evidence of effectiveness, an acceptable risk: benefit ratio, and while not superior to recently approved drugs for the treatment of metastatic melanoma, offers a different toxicity profile which may be of importance in treatment selection for individuals with specific co-morbid conditions.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies
  I concur with the division and DRISK that a REMS is not required to ensure safe and effective use of trametinib and that the risks can be conveyed through physician package insert and patient labeling.

- Recommendation for other Postmarketing Requirements and Commitments: See action letter.

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/s/

TAMY E KIM
05/28/2013

RICHARD PAZDUR
05/28/2013