PDL NEW DRUG REVIEW

Proprietary Name: Mekinist®
Common Name: trametinib
PDL Category: Antineoplastics

Comparable Products	Preferred Drug List Status
Zelboraf	Non-Recommended

Summary

Indications and Usage: Treatment of patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutation as detected by an FDA-approved test. Mekinist® is not indicated for treatment of those who have received prior BRAF-inhibitor therapy. This is a pregnancy category D medication. Additionally, as Mekinist® can cause fetal harm if taken during pregnancy, it is recommended that females of reproductive potential use highly effective contraception during treatment and for 4 weeks after treatment. Males should be advised that there is a potential risk of impaired fertility with Mekinist® use. The safety and efficacy of use in children under 18 years of age has not been established.

Drug Interactions: Formal drug interaction studies to evaluate CYP450 enzyme interactions were not conducted.

Dosage Forms: Film-coated Tablets: 0.5mg, 1mg, and 2mg

Recommended Dosage: Information on FDA-approved tests for the detection of BRAF V600 mutations in melanoma can be found at http://www.fda.gov/CompanionDiagnostics. Patients selected to be treated with Mekinist® should be based on the presence of BRAF V600E or V600K mutation in tumor specimens.

Take 2mg once daily until disease progression or unacceptable toxicity, one hour before or 2 hours after a meal. Please refer to the prescribing information for specific information regarding dose adjustments in those with cutaneous, cardiac, ocular, pulmonary, or other adverse reaction.

Dose adjustments are not needed for those with mild hepatic impairment, but an appropriate dose has not been established in those with moderate or severe hepatic impairment. Dose adjustments are not required in those with mild or moderate renal impairment; however, the appropriate dose for those with severe renal impairment has not been established.

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions = reported % incidence for drug (Mekinist®) minus reported % incidence for active comparator (chemotherapy).* The most common adverse event reported with Mekinist® includes rash (47%), dermatitis acneiform (18%), dry skin (11%), pruritus (9%), paronychia (9%), diarrhea (27%), stomatitis (13%), abdominal pain (8%), lymphedema (28%), hypertension (8%), and hemorrhage (13%).

Reported laboratory abnormalities included increased AST (44%), increased ALT (19%), hypoalbuminemia (19%), anemia (12%), and increased alkaline phosphatase (6%).

In Trial 1 (see analysis section for details), cardiomyopathy (defined as cardiac failure, left ventricular dysfunction, or decreased left ventricular ejection fraction (LVEF)] was reported in 7% of the Mekinist® group vs 0% in the

chemotherapy-treated group, with the median time to onset of cardiomyopathy in the Mekinist® group being 63 days. Thus, it is recommended to assess LVEF by echocardiogram prior to starting treatment, one month after treatment was started, and then at 2-3 month intervals while on treatment. Treatment should be withheld if absolute LVEF value decreases by 10% from pre-treatment values and is less than the lower limit of normal. Permanently discontinue Mekinist® for symptomatic cardiomyopathy or persistent, asymptomatic LVEF that does not resolve within 4 weeks.

Retinal pigment epithelial detachment (RPED) and retinal vein occlusion (RVO) have been reported with Mekinist® use. It is recommended to perform ophthalmological evaluations at any time with patient-reported visual disturbances or loss of vision. If RPED is diagnosed, withhold treatment and upon resolution Mekinist® may be resumed at a reduced dose. Treatment should be permanently discontinued in those with documented RVO.

Contraindications: There are currently no contraindications listed with this product.

Manufacturer: GlaxoSmithKline

Analysis: Trametinib dimethyl sulfoxide, the active ingredient of Mekinist®, is a kinase inhibitor. It is a reversible inhibitor of mitogen-activated extracellular signal regulated kinase 1 (MEK1) and MEK2 activation and of MEK1 and MEK2 kinase activity. BRAF V600E mutations results in constitutive activation of the BRAF pathway, which includes MEK1 and MEK2. Trametinib inhibits BRAF V600 mutation-positive melanoma cell growth.

The safety and efficacy of Mekinist® was established in a multicenter, randomized, open-label, active-controlled study that included patients with BRAF V600E or V600K mutation-positive, unresectable or metastatic melanoma (Trial 1; N=322). Prior treatment with a BRAF inhibitor or MEK inhibitor was not allowed. Patients were randomized to Mekinist® 2mg QD or chemotherapy consisting of either dacarbazine 1000mg/m^2 IV Q3W or paclitaxel 175mg/m^2 IV Q3W. The primary outcome was progression-free survival (PFS), and results suggested a statistically significant increase in PFR in those treated with Mekinist®. The rate for the number of events was 55% with Mekinist® vs 71% with chemotherapy ($p<0.0001$), while the rate of progressive disease was 50% vs 65%, respectively. There were 10 deaths in the Mekinist® group (5%) vs 7 in the chemotherapy group (6%). The objective response rate (ORR) was 22% with Mekinist® vs 8% with chemotherapy and duration of response of 5.5 months (median) vs not reported, respectively.

Trial 2 assessed the clinical activity of Mekinist® in a single-arm, multicenter study in patients (N=40) with BRAF V600E or V600K mutation-positive, unresectable or metastatic melanoma who had received prior treatment with a BRAF inhibitor. There were no patients in this trial who obtained a confirmed partial or complete response per the study investigators.

It is recommended that Mekinist® be added to the Recommended Drug List as a non-recommended drug, as it is only indicated to treat a specific subset of patients.

PDL Placement:
- ☐ **Recommended**
- ☒ **Non-Recommended**

References

[1] Mekinist [package insert]. Research Triangle Park, NC: GlaxoSmithKline; 2013.