PDL NEW DRUG REVIEW

Proprietary Name: Tafinlar®
Common Name: dabrafenib
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 mutation as detected by an FDA-approved test. Tafinlar® is not indicated for treatment of those with wild-type BRAF melanoma. This is a pregnancy category D medication. Additionally, females of reproductive potential should use highly effective contraception during treatment and for 4 weeks after treatment. A non-hormonal method of contraception should be used since Tafinlar® can cause hormonal contraceptives to be ineffective. Males should be advised that there is a potential risk of impaired spermatogenesis with Tafinlar® use, so it is recommended that fertility and family planning options be sought prior to starting treatment. The safety and efficacy of use in children under 18 years of age has not been established.

Drug Interactions: Dabrafenib is primarily metabolized by CYP2C8 and CYP3A4, thus strong inhibitors or inducers of CYP3A4 or CYP2C8 may increase/decrease dabrafenib levels. It is recommended to substitute strong inhibitors or strong inducers of CYP3A4 or CYP2C8 during dabrafenib treatment. If concomitant use is unavoidable, then monitor closely for adverse reactions when taking strong inhibitors or loss of efficacy when taking strong inducers.

While not formally studied, drugs that alter the pH of the upper GI tract (eg PPIs, H2-receptor antagonists, antacids) may reduce the bioavailability of dabrafenib. The effect on efficacy of dabrafenib is not known.

Dosage Forms: Capsules: 50mg, 75mg

Recommended Dosage: Prior to administration, the presence of BRAF V600E mutation must be confirmed. Information on the FDA-approved tests for detection of BRAF V600 mutations in melanoma is available at http://www.fda.gov/CompanionDiagnostics. The recommended dose is 150mg twice daily, approximately every 12 hours, until disease progression or unacceptable toxicity occurs. Please refer to the prescribing information for specific recommendations on dose reductions in those with febrile drug reactions, other intolerable Grade 2 adverse reaction (AR), or any Grade 3 or 4 AR.

Dose adjustment is not needed for those with mild hepatic impairment. An increased exposure may occur in those with moderate to severe hepatic impairment; however, an appropriate dose for this population set has not been established. Dose adjustments are not needed for those with mild or moderate renal impairment, and an appropriate dose has not been established in those with severe renal impairment.

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions = reported % incidence for drug (Tafinlar®) minus reported % incidence for dacarbazine (the comparator chemotherapeutic agent).* The most common adverse event reported with Tafinlar® includes hyperkeratosis (37%), alopecia (20%), palmar-plantar erythrodysesthesia syndrome (PPES, 20%), rash (17%), headache (24%), pyrexia (18%), arthralgia (25%), back pain (5%), myalgia (11%), papilloma (25%), constipation (0%), cough (5%), nasopharyngitis (7%).

Laboratory abnormalities reported include hyperglycemia (7%), hypophosphatemia (23%), increased alkaline phosphatase (5%), and hyponatremia (5%).

In Trial 1 (see analysis section for full details), there was an increased incidence of cutaneous squamous cell carcinoma (cuSCC, 7%), keratoacanthoma, and melanoma. It is recommended to perform dermatologic evaluations prior to starting therapy, every 2 months while on therapy, and for up to 6 months following discontinuation of Tafinlar®.

Serious febrile drug reactions were reported during Trial 1, defined as serious cases of fever or fever of any severity accompanied by hypotension, rigors or chills, dehydration, or renal failure in the absence of another identifiable cause. This occurred in 3.7% of the Tafinlar® treated population as compared with none in those treated with dacarbazine. The incidence of fever (serious and non-serious) was 28% in those treated with Tafinlar® vs 10% in those treated with dacarbazine. The median time to initial onset of fever was 11 days and the median duration of fever was 3 days.

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

Manufacturer: GlaxoSmithKline

Analysis: Dabrafenib, the active ingredient of Tafinlar®, is a kinase inhibitor and inhibits some mutated forms of BRAF kinases. It also inhibits wild-type BRAF and CRAF kinases, as well as other kinases such as SIK1, NEK11, and LIMK1.

Registration Trial 1 was a multicenter, randomized, open-label, active-controlled study (N=250) including adults with previously untreated BRAF V600E mutation-positive, unresectable or metastatic melanoma. Patients were randomized to Tafinlar® or dacarbazine 1000mg/m^2 IV every 3 weeks. The primary outcome was progression-free survival (PFS). Results suggested a statistically significant increase in PFS in those treated with Tafinlar®. The incidence of events was 42% with Tafinlar® as compared with 65% with dacarbazine ($p<0.0001$). The median for PFS was 5.1 months with Tafinlar® vs 2.7 months with dacarbazine. There were 2 deaths in the Tafinlar® group and no deaths in the dacarbazine group. For the confirmed tumor responses, there was a 52% objective response rate with Tafinlar® as compared with 17% with dacarbazine, with a 5.6 months median duration of response vs not reported with dacarbazine.

In Trial 2, activity of Tafinlar® for the treatment of BRAF V600E mutation-positive melanoma, metastatic to the brain was assessed in a single treatment arm, two-cohort study. Cohort A had no prior local therapy for brain metastases and cohort B had at least one local therapy for brain metastases. The primary outcome was the estimation of the overall intracranial response rate (OIRR) in each cohort. Results suggested that the OIRR was 18% in cohort A and in cohort B, with a median of 4.6 months for both cohorts.

It is recommended that Tafinlar® 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] Tafinlar [package insert]. Research Triangle Park, NC: GlaxoSmithKline; 2013.