PDL DRUG REVIEW

Proprietary Name: Tabrecta®
Common Name: capmatinib
PDL Category: Antineoplastics

Summary

Pharmacology/Usage: Capmatinib, the active ingredient of Tabrecta®, is a kinase inhibitor that targets mesenchymal-epithelial transition (MET), including the mutant variant produced by exon 14 skipping. MET exon 14 skipping results in a protein with a missing regulatory domain that reduces its negative regulation leading to increased downstream MET signaling. Capmatinib inhibited cancer cell growth driven by a mutant MET variant lacking exon 14 at clinically achievable concentrations and demonstrated anti-tumor activity in animal models derived from human lung tumors with either a mutation leading to MET exon 14 skipping or MET amplification.

Indication: For the treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have a mutation that leads to mesenchymal-epithelial transition (MET) exon 14 skipping as detected by an FDA-approved test. This indication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial(s).

There is no pregnancy category for this medication; however, the risk summary indicates that based on findings from animal studies and its mechanism of action, Tabrecta® can cause fetal harm when administered to a pregnant woman. There are no available data on use in pregnant women. Advise pregnant women of the potential risk to the fetus. In addition, verify the pregnancy status for females of reproductive potential prior to starting Tabrecta®, as well as use effective contraception during Tabrecta® treatment and for 1 week after the last dose (for females of reproductive potential and males with female partners of reproductive potential). The safety and efficacy of use in the pediatric population have not been established.

Dosage Form: Film-Coated Tablets: 150mg, 200mg. Swallow tablets whole; Do not break, crush, or chew the tablets.

Recommended Dosage: Select patients for treatment with Tabrecta® based on the presence of a mutation that leads to MET exon 14 skipping in tumor specimens. Information on FDA-approved tests is available at http://www.fda.gov/companiondiagnostics.

The recommended dosage is 400mg PO BID with or without food. Dose modifications may be required for the management of adverse reactions, such as interstitial lung disease (ILD)/pneumonitis, increased ALT and/or AST without increased total bilirubin, increased ALT and/or AST with increased total bilirubin in the absence of cholestasis or hemolysis, increased total bilirubin without concurrent increased ALT and/or AST, or other adverse reactions. Permanently discontinue Tabrecta® in patients who are unable to tolerate 200mg PO BID.

Dose adjustment is not required with mild or moderate renal impairment. Use has not been studied in patients with severe renal impairment.

Drug Interactions: Coadministration of Tabrecta® with a strong CYP3A inhibitor increased capmatinib exposure, which may increase the incidence and severity of adverse reactions of Tabrecta®. Closely monitor patients for adverse reactions during coadministration of Tabrecta® with strong CYP3A inhibitors.

Avoid the coadministration of Tabrecta® with strong and moderate CYP3A inducers.

Coadministration of Tabrecta® increased the exposure of a CYP1A2 substrate, which may increase the adverse reactions of these substrates. If coadministration is unavoidable between Tabrecta® and CYP1A2 substrates where minimal concentration changes may lead to serious adverse reactions, decrease the CYP1A2 substrate dosage per the approved prescribing information.

Coadministration of Tabrecta® increased the exposure of a P-gp substrate and a BCRP substrate, which may increase the adverse reactions of these substrates. If coadministration is unavoidable between Tabrecta® and P-gp or BCRP substrates where minimal concentration changes may lead to serious adverse reactions, decrease the P-gp or BCRP substrate dosage per the approved prescribing information.

Coadministration of Tabrecta® may increase the exposure of MATE1 and MATE2K substrates, which may increase the adverse reactions of these substrates. If coadministration is unavoidable between Tabrecta® and MATE1 or MATE2K substrates where minimal concentration changes may lead to serious adverse reactions, decrease the MATE1 or MATE2K substrate dosage per the approved prescribing information.

Box Warning: There is no box warning listed with this product.

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions= reported % incidence for drug (Tabrecta®) for all grades. Please note that there is no placebo data in the prescribing information to compare with Tabrecta®.* The most frequently reported adverse events included peripheral edema (52%), fatigue (32%), non-cardiac chest pain (15%), back pain (14%), pyrexia (14%), weight decreased (10%), nausea (44%), vomiting (28%), constipation (18%), diarrhea (18%), dyspnea (24%), cough (16%), and decreased appetite (21%).

Select laboratory abnormalities included decreased albumin (68%), increased creatinine (62%), increased alanine aminotransferase (37%), increased alkaline phosphatase (32%), increased amylase (31%), increased gamma-glutamyltransferase (29%), increased lipase (26%), increased aspartate aminotransferase (25%), decreased sodium (23%), decreased phosphate (23%), increased potassium (23%), decreased glucose (21%), decreased lymphocytes (44%), decreased hemoglobin (24%), and decreased leukocytes (23%).

Interstitial lung disease (ILD)/pneumonitis, which can be fatal, occurred in 4.5% of patients treated with Tabrecta® in a clinical trial. In addition, 2.4% discontinued treatment due to ILD/pneumonitis. The median time to onset of Grade 3 or higher ILD/pneumonitis was 1.4 months (range 0.2 months to 1.2 years). Monitor for new or worsening pulmonary symptoms indicative of ILD/pneumonitis (e.g. dyspnea, cough, fever). Immediately withhold treatment in patients with suspected ILD/pneumonitis and permanently discontinue Tabrecta® if no other potential causes of ILD/pneumonitis are identified.

Hepatotoxicity occurred in patients treated with Tabrecta®. The median time to onset of Grade 3 or higher increased ALT/AST was 1.4 months. Monitor liver function tests (including AST, ALT, and total bilirubin) prior to the start of Tabrecta®, every 2 weeks during the first 3 months of treatment, then once a month or as clinically indicated, with more frequent testing in patients who develop increased transaminases or bilirubin. Based on the severity of the adverse reaction, withhold, dose reduce, or permanently discontinue treatment.

Based on findings from animal studies, there is a potential risk of photosensitivity reactions with Tabrecta®. It was recommended in a clinical trial that patients use precautionary measures against ultraviolet exposure such as use of sunscreen or protective clothing during treatment with Tabrecta®. Advise patients to limit direct ultraviolet exposure during treatment with Tabrecta®.

Contraindications: There are no contraindications listed with this product.

Manufacturer: Novartis Pharmaceuticals

Analysis: The efficacy of Tabrecta® was assessed in a multicenter, non-randomized, open-label, multi-cohort study (GEOMETRY mono-1) that included patients who were required to have NSCLC with a mutation that leads to MET exon 14 skipping, epidermal growth factor receptor (EGFR) wild-type and anaplastic lymphoma kinase (ALK) negative status, and at least one measurable lesion as defined by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Those with symptomatic CNS metastases, clinically significant uncontrolled cardiac disease, or who received treatment with any MET or hepatocyte growth factor (HGF) inhibitor were not eligible for the study.

The efficacy population included 28 treatment-naïve patients and 69 previously treated patients. The median age was 71 years (range 49 to 90 years), while 60% were female, 75% were white, 24% had Eastern Cooperative Oncology Group (ECOG) performance status 0, 75% had ECOG PS 1, 60% had never smoked, 80% had adenocarcinoma, and 12% had CNS metastases. Furthermore, of previously treated patients, 88% received prior platinum-based chemotherapy.

Patients took Tabrecta® until disease progression or unacceptable toxicity. The major efficacy outcome assessed was overall response rate (ORR) as determined by a Blinded Independent Review Committee (BIRC) per RECIST 1.1. Duration of response was also assessed. Efficacy results can be seen in the table below, which was adapted from the prescribing information.

Efficacy Outcome	Treatment-Naïve (N=28)	Previously Treated (N=69)
Overall Response Rate		
Overall Response Rate	68%	41%
Complete Response	4%	0
Partial Response	64%	41%
Duration of Response		
Median (months)	12.6	9.7
Patients with DOR ≥12 months	47%	32%

Place in Therapy: Tabrecta®, an oral kinase inhibitor, is indicated for the treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have a mutation that leads to mesenchymal-epithelial transition (MET) exon 14 skipping as detected by an FDA-approved test. This indication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial(s). In a non-randomized, open label study, the overall response rate of Tabrecta® in treatment-naïve patients was 68% and in previously treated patients was 41%.

It is recommended that Tabrecta® should be non-recommended with conditions in order to confirm the appropriate diagnosis and clinical parameters for use.

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

References

[1] Tabrecta [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Cor; 2020.