PDL DRUG REVIEW

Proprietary Name: Tepmetko®
Common Name: tepotinib
PDL Category: Antineoplastics

Comparable Products	Preferred Drug List Status
Tabrecta	Non-Recommended with Conditions

Summary

Pharmacology/Usage: Tepotinib, the active ingredient of Tepmetko®, is a kinase inhibitor that targets mesenchymal-epithelial transition (*MET*), including variants with exon 14 skipping alterations. Tepotinib inhibits hepatocyte growth factor (HGF)-dependent and -independent MET phosphorylation and MET-dependent downstream signaling pathways. Tepotinib also inhibited melatonin 2 and imidazoline 1 receptors at clinically achievable concentrations.

In vitro, tepotinib inhibited tumor cell proliferation, anchorage-independent growth, and migration of MET-dependent tumor cells.

Indication: For the treatment of adults with metastatic non-small cell lung cancer (NSCLC) harboring mesenchymal-epithelial transition (*MET*) exon 14 skipping alterations. 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 in animal studies and the mechanism of action, Tepmetko® can cause fetal harm when administered to a pregnant woman. There are no available data on the use of Tepmetko® in pregnant women. Advise pregnant women of the potential risk to a fetus. Verify pregnancy status in females of reproductive potential prior to starting treatment. Advise females of reproductive potential and male patients with female partners of reproductive potential to use effective contraception during Tepmetko® treatment and for one week after the final dose. The safety and efficacy of use in pediatric patients have not been established.

Dosage Form: Film-Coated Tablets: 225mg. Swallow tablets whole; do not chew, crush, or split tablets

Recommended Dosage: Select patients for treatment with Tepmetko® based on the presence of *MET* exon 14 skipping alterations in plasma or tumor specimens. Testing for the presence of *MET* exon 14 skipping alterations in plasma specimens is recommended only in patients for whom a tumor biopsy cannot be obtained. If an alteration is not detected in a plasma specimen, re-assess the feasibility of biopsy for tumor tissue testing. An FDA-approved test for detection of *MET* exon 14 skipping alterations in NSCLC for selecting patients for treatment with Tepmetko® is not available.

Take 450mg PO QD with food until disease progression or unacceptable toxicity. Take the dose at about the same time every day. Do not make up a missed dose within 8 hours of the next scheduled dose. In addition, if vomiting occurs after taking a dose of Tepmetko®, advise patients to take the next dose at the scheduled time.

Dose modifications may be required for 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, and other adverse reactions. The recommended dose reduction for the management of adverse reactions is 225mg PO QD. Permanently discontinue Tepmetko® in patients who are unable to tolerate 225mg PO QD. Refer to the prescribing information for further information regarding dosage modifications.

Dose modifications are not recommended in patients with mild or moderate renal impairment, as well as in patients with mild or moderate hepatic impairment. The recommended dosage has not been established with severe renal impairment. The pharmacokinetics and safety of tepotinib in patients with severe hepatic impairment have not been studied.

Drug Interactions: Avoid concomitant use of Tepmetko® with dual strong CYP3A inhibitors and P-gp inhibitors.

Avoid concomitant use of Tepmetko® with strong CYP3A inducers.

Tepotinib is a P-gp inhibitor. Concomitant use of Tepmetko® increases the concentration of P-gp substrates, which may increase the incidence and severity of adverse reactions of these substrates. Avoid concomitant use of Tepmetko® with certain P-gp substrates where minimal concentration may lead to serious or life-threatening toxicities. If concomitant use is unavoidable, reduce the P-gp substrate dosage if recommended in its approved product labeling.

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 (Tepmetko®) for all grades. There was no placebo data found in the prescribing information.* The most frequently reported adverse events included edema (70%), fatigue (27%), nausea (27%), diarrhea (26%), abdominal pain (16%), constipation (16%), vomiting (13%), musculoskeletal pain (24%), dyspnea (20%), cough (15%), pleural effusion (13%), decreased appetite (16%), and pneumonia (11%). Laboratory abnormalities included decreased albumin (76%), increased creatinine (55%), increased alkaline phosphatase aminotransferase (50%), increased alanine aminotransferase (44%), increased aspartate aminotransferase (35%), decreased sodium (31%), increased potassium (25%), increased gamma-glutamyl transferase (24%), increased amylase (23%), decreased lymphocytes (48%), decreased hemoglobin (27%), and decreased leukocytes (23%).

ILD/pneumonitis, which can be fatal, occurred in patients treated with Tepmetko®. This occurred in 2.2% of patients treated with Tepmetko®, with one patient experiencing a Grade 3 or higher event; this event resulted in death. Monitor patients for new or worsening pulmonary symptoms indicative of ILD/pneumonitis. Immediately withhold treatment in patients with suspected ILD/pneumonitis.

Hepatoxicity occurred in patients treated with Tepmetko®. Increased ALT/AST occurred in 13% of patients treated with Tepmetko®. The median time to onset of Grade 3 or higher increased ALT/AST was 30 days. Monitor liver function tests (including ALT, AST, and total bilirubin) prior to the start of treatment, every 2 weeks during the first 3 months of treatment, and 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.

Contraindications: There are no contraindications listed with this product.

Manufacturer: EMD Serono, Inc

Analysis: The safety and efficacy of Tepmetko® were assessed in a single-arm, open-label, multicenter, non-randomized multicohort study (VISION study) that included adults with advanced or metastatic NSCLC harboring *MET* exon 14 skipping alterations, epidermal growth factor receptor (EGFR) wild-type and anaplastic lymphoma kinase (ALK) negative status, at least one measurable lesion as defined by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, and Eastern Cooperative Oncology Group (ECOG) performance status 0 to 1. Patients 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 69 treatment-naïve adults and 83 previously treated adults. The median age of included patients was 73 years (range 41 to 94 years), while 48% were female, 71% were white, 27% had an ECOG performance status of 0, 73% had an ECOG performance status of 1, 43% had never smoked, 86% had adenocarcinoma, 98% had metastatic disease, and 10% had CNS metastases. Of previously treated patients, 89% received prior platinum-based chemotherapy. Patients in this study received Tepmetko® 450mg QD until disease progression or unacceptable toxicity.

The major efficacy outcome measure was confirmed overall response rate (ORR) per RECIST v1.1 as evaluated by a Blinded Independent Review Committee (BIRC). An additional efficacy outcome measure was duration of response (DOR) by BIRC. Efficacy results can be seen in the table below, which was adapted from the prescribing information.

Efficacy parameter	Treatment-naïve (N=69)	Previously treated (N=83)
Overall Response Rate (ORR), %	43%	43%
Median Duration of Response, months	10.8	11.1
Patients with DOR ≥6 months, %	67%	75%
Patients with DOR ≥9 months, %	30%	50%

Place in Therapy: Tepmetko® is an oral kinase inhibitor indicated for the treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) harboring *MET* exon 14 skipping alterations. 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, single-arm study that included adults with advanced or metastatic NSCLC harboring *MET* exon 14 skipping alterations, epidermal growth factor receptor wild-type and anaplastic lymphoma kinase negative status, the overall response rate in treatment-naïve patients was 43% and in previously treated patients was 43%.

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

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

References

[1] Tepmetko [package insert]. Rockland, MA: EMD Serono, Inc; 2021.