NEW DRUG APPROVAL

Brand Name	Tepmetko®
Generic Name	tepotinib
Drug Manufacturer	EMD Serono Inc.

New Drug Approval

FDA Approval Date: February 03, 2021

Review Designation: Type 1 - New Molecular Entity

Type of Review: Priority; Orphan, New Drug Application (NDA): 214096

Dispensing Restriction: Specialty Only, Limited Distribution

Place in Therapy

DISEASE DESCRIPTION & EPIDEMIOLOGY

NSCLC is the most common type of lung cancer, accounting for 84% of all lung cancer diagnoses. This cancer has 3 major types. They are grouped by the kind of lung cell the cancer started in and by how the cells look under a microscope. They have slight differences among them. But they tend to have a similar outlook (prognosis) and are generally treated the same way:

- **Adenocarcinoma.** This is the most common type of NSCLC. It's the most common type of lung cancer in nonsmokers. But it is found more often in smokers or former smokers. It tends to grow in the outer edges of the lungs. It usually grows more slowly than other types of lung cancer.
- **Squamous cell carcinoma (epidermoid carcinoma).** This type of NSCLC develops more often in smokers or former smokers. These cancers tend to start in the middle part of the lungs near the main airways (the bronchi).
- **Large cell carcinoma.** This is the least common type of NSCLC. It tends to quickly grow and spread to other organs. This can make it harder to treat.

Statistics provided below for lung cancer include both small cell and NSCLC.

- In 2020, an estimated 235,760 adults (119,100 men and 116,660 women) in the United States were diagnosed with lung cancer. However, since the mid-2000s, incidence rates have dropped by around 2% each year.
- Black men are about 15% more likely to get lung cancer than white men. Black women are 14% less likely to get lung cancer when compared with white women. People age 65 and older are more likely to develop the disease. The average age of diagnosis is 70.
- Lung cancer is the second most common cancer and the leading cause of cancer death for men and women. It is estimated that 131,880 (69,410 men and 62,470 women) deaths from this disease occurred in 2020.
- Lung cancer makes up around 25% of cancer deaths. However, death rates for the disease have declined by 54% since 1990 in men and 30% in women since 2002. From 2014 to 2018, the death rates for men with lung cancer dropped by 5% each year. The death rates for women with lung cancer declined 4% per year. Research indicates that these declines are due to more people not smoking, more people quitting smoking, and medical advances in diagnosis and treatment.

Efficacy

The efficacy of Tepmetko® was evaluated in a single-arm, open-label, multicenter, non-randomized, multicohort study (VISION, NCT02864992). Eligible patients were required to have advanced or metastatic NSCLC harboring METex14 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 of 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.

Identification of METex14 skipping alterations was prospectively determined using central laboratories employing either a PCR-based or next-generation sequencing-based clinical trial assay using tissue (58%) and/or plasma (65%) samples.

Patients received Tepmetko® 450 mg once daily until disease progression or unacceptable toxicity. The major efficacy outcome measure was confirmed overall response rate (ORR) according to Response Evaluation Criteria in Solid Tumors (RECIST v1.1) as evaluated by a Blinded Independent Review Committee (BIRC). An additional efficacy outcome measure was duration of response (DOR) by BIRC.

The efficacy population included 69 treatment naïve patients and 83 previously treated patients. The median age was 73 years (range 41 to 94 years); 48% female; 71% White, 25% Asian; 27% had Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) 0 and 73% had ECOG PS 1; 43% never smoked; 86% had adenocarcinoma; 98% had metastatic disease; and 10% had CNS metastases. Amongst previously treated patients, 89% received prior platinum-based chemotherapy.

Efficacy Results in the VISION study

Efficacy parameter	Treatment-Naïve N = 69	Previously Treated N = 83
Overall response rate, % (95% CI)[a, b]	43 (32, 56)	43 (33, 55)
Median duration of response, months [c] (95% CI)	10.8 (6.9, NE)	11.1 (9.5, 18.5)
Patients with DOR ≥ 6 months, %	67	75
Patients with DOR ≥ 9 months, %	30	50

CI=confidence interval, NE=Not estimable
a Blinded Independent Review Committee (BIRC) review
b Confirmed Responses
c Product-limit (Kaplan-Meier) estimates, 95% CI for the median using the Brookmeyer and Crowley method.

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Safety

ADVERSE EVENTS

Most common adverse reactions (≥ 20%) were edema, fatigue, nausea, diarrhea, musculoskeletal pain, and dyspnea. The most common Grade 3 to 4 laboratory abnormalities (≥ 2%) were decreased lymphocytes, decreased albumin, decreased sodium, increased gamma-glutamyltransferase, increased amylase, increased ALT, increased AST, and decreased hemoglobin.

WARNINGS & PRECAUTIONS

- Interstitial Lung Disease (ILD)/Pneumonitis: Immediately withhold Tepmetko® in patients with suspected ILD/pneumonitis. Permanently discontinue Tepmetko® in patients diagnosed with ILD/pneumonitis of any severity.
- Hepatotoxicity: Monitor liver function tests. Withhold, dose reduce, or permanently discontinue Tepmetko® based on severity.
- Embryo-fetal toxicity: Tepmetko® can cause fetal harm. Advise of potential risk to a fetus and use of effective contraception.

CONTRAINDICATIONS

- None.

Clinical Pharmacology

MECHANISMS OF ACTION

Tepotinib is a kinase inhibitor that targets 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.

Dose & Administration

ADULTS

Select patients for treatment with Tepmetko® on the presence of METex14 skipping.
Recommended dosage: 450 mg orally once daily with food until disease progression or unacceptable toxicity.

PEDIATRICS

The safety and efficacy of Tepmetko® in pediatric patients have not been established.

GERIATRICS

Of 255 patients with METex14 skipping alterations in VISION who received 450 mg Tepmetko® once daily, 79% were 65 years or older, and 43% were 75 years or older. No clinically important differences in safety or efficacy were observed between patients aged 65 years or older and younger patients.

RENAL IMPAIRMENT

No dosage modification is recommended in patients with mild or moderate renal impairment (creatinine clearance [CLcr] 30 to 89 mL/min, estimated by Cockcroft-Gault). The recommended dosage has not been established for patients with severe renal impairment (CLcr < 30 mL/min).

HEPATIC IMPAIRMENT

No dosage modification is recommended in patients with mild (Child Pugh Class A) or moderate (Child Pugh Class B) hepatic impairment. The pharmacokinetics and safety of tepotinib in patients with severe hepatic impairment (Child Pugh Class C) have not been studied.

Product Availability

DOSAGE FORM(S) & STRENGTH(S)

Tablets: 225 mg