RXADVANCE
2 Park Central Drive
Southborough, MA 01772

NEW DRUG APPROVAL

Brand Name	Tabrecta™
Generic Name	capmatinib
Drug Manufacturer	Novartis Pharmaceuticals Corporation

New Drug Approval

FDA Approval Date: May 06, 2020
Review Designation: Priority; Orphan
Type of Review: New Drug Application 213591

Place in Therapy

DISEASE DESCRIPTION & EPIDEMIOLOGY

NSCLC is a disease in which malignant cancer cells form in the tissues of the lung. It is the most common type of lung cancer with up to 90% of all lung carcinomas falling into the non-small cell category. NSCLC occurs when healthy cells become abnormal and grow rapidly. One danger of this form of cancer is that there's a high likelihood that the cancer cells will spread from the lungs to other organs and body parts. Cancer metastasis consists of a sequential series of events, and MET exon 14 skipping is recognized as a critical event for metastasis o

Worldwide, lung cancer occurred in approximately 1.8 million patients in 2012 and caused an estimated 1.6 million deaths. In the United States, lung cancer occurs in approximately 230,000 patients and causes over 135,000 deaths annually.

Both the absolute and relative frequency of lung cancer have risen dramatically. Around 1953, lung cancer became the most common cause of cancer deaths in men, and in 1985, it became the leading cause of cancer deaths in women. Lung cancer deaths have begun to decline in both men and women, reflecting a decrease in smoking.

The term lung cancer, or bronchogenic carcinoma, refers to malignancies that originate in the airways or pulmonary parenchyma. Approximately 95 percent of all lung cancers are classified as either small cell lung cancer (SCLC) or non-small cell lung cancer (NSCLC). This distinction is essential for staging, treatment, and prognosis. Other cell types comprise approximately 5 percent of malignancies arising in the lung.

Efficacy

During the clinical trial, participants received Tabrecta 400 mg orally twice daily until disease progression or unacceptable toxicity. The major efficacy outcome measure was overall response rate (ORR), which reflects the percentage of participants that had a certain amount of tumor shrinkage. An additional efficacy outcome measure was duration of response (DOR). The efficacy population included 28 patients who had never undergone treatment for NSCLC and 69 previously treated patients. The ORR for the 28 participants was 68%, with 4% having a complete response and 64% having a partial response. The ORR for the 69 participants was 41%, with all having a partial response. Of the responding participants who had never undergone treatment for NSCLC, 47% had a duration of response lasting 12 months or longer compared to 32.1% of the responding participants who had been previously treated.

NEW DRUG APPROVAL

Safety

ADVERSE EVENTS

The most common adverse reactions (≥ 20%) are peripheral edema, nausea, fatigue, vomiting, dyspnea, and decreased appetite

WARNINGS & PRECAUTIONS

- Interstitial Lung Disease (ILD)/Pneumonitis: Monitor for new or worsening pulmonary symptoms indicative of ILD/pneumonitis. Permanently discontinue TABRECTA in patients with ILD/pneumonitis.
- Hepatotoxicity: Monitor liver function tests. Withhold, dose reduce, or permanently discontinue TABRECTA based on severity.
- Risk of Photosensitivity: May cause photosensitivity reactions. Advise patients to limit direct ultraviolet exposure.
- Embryo-Fetal Toxicity: Can cause fetal harm. Advise patients of the potential risk to a fetus and to use effective contraception.

CONTRAINDICATIONS

None

Clinical Pharmacology

MECHANISMS OF ACTION

Capmatinib is a kinase inhibitor that targets 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 murine tumor xenograft models derived from human lung tumors with either a mutation leading to MET exon 14 skipping or MET amplification. Capmatinib inhibited the phosphorylation of MET triggered by binding of hepatocyte growth factor or by MET amplification, as well as METmediated phosphorylation of downstream signaling proteins and proliferation and survival of MET-dependent cancer cells.

Dose & Administration

ADULTS

400 mg orally twice daily with or without food.

PEDIATRICS

Safety and effectiveness of TABRECTA in pediatric patients have not been established.

GERIATRICS

In GEOMETRY mono-1, 57% of the 334 patients were 65 years or older and 16% were 75 years or older.

No overall differences in the safety or effectiveness were observed between these patients and younger patients.

RENAL IMPAIRMENT

NEW DRUG APPROVAL

No dosage adjustment is recommended in patients with mild (baseline creatinine clearance [CLcr] 60 to 89 mL/min by Cockcroft-Gault) or moderate renal impairment (CLcr 30 to 59 mL/min).TABRECTA has not been studied in patients with severe renal impairment (CLcr 15 to 29 mL/min).

HEPATIC IMPAIRMENT

None

Product Availability

DOSAGE FORM(S) & STRENGTH(S)

Tablets: 150 mg and 200 mg