TEPMETKO®
(tepotinib)
Film-coated Tablets 225mg

1 INDICATIONS AND USAGE

TEPMETKO is indicated for the treatment of adult patients 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)*[see Clinical Studies (12)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Patient Selection for *MET*ex14 Skipping Alterations

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-evaluate the feasibility of biopsy for tumor tissue testing.

2.2 Recommended Dosage

The recommended dosage of TEPMETKO is 450 mg orally once daily with food *[see Clinical Pharmacology (10.3)]* until disease progression or unacceptable toxicity.

Instruct patients to take their dose of TEPMETKO at approximately the same time every day and to swallow tablets whole. Do not chew, crush or split tablets.

Advise patients not to make up a missed dose within 8 hours of the next scheduled dose.

If vomiting occurs after taking a dose of TEPMETKO, advise patients to take the next dose at the scheduled time.

2.3 Dose Modifications for Adverse Reactions

The recommended dose reduction of TEPMETKO for the management of adverse reactions is 225 mg orally once daily.

Permanently discontinue TEPMETKO in patients who are unable to tolerate 225 mg orally once daily.

The recommended dosage modifications of TEPMETKO for adverse reactions are provided in Table 1.

Table 1: Recommended TEPMETKO Dosage Modifications for Adverse Reactions

Adverse Reaction	Severity	Dose Modification
Interstitial Lung Disease (ILD) /Pneumonitis *[see Warnings and Precautions (5.1)]*	Any grade	Withhold TEPMETKO if ILD is suspected. Permanently discontinue TEPMETKO if ILD is confirmed.
Increased ALT and/or AST without increased total bilirubin *[see Warnings and Precautions (5.2)]*	Grade 3	Withhold TEPMETKO until recovery to baseline ALT/AST. If recovered to baseline within 7 days, then resume TEPMETKO at the same dose; otherwise resume TEPMETKO at a reduced dose.
	Grade 4	Permanently discontinue TEPMETKO.
Increased ALT and/or AST with increased total bilirubin in the absence of cholestasis or hemolysis *[see Warnings and Precautions (5.2)]*	ALT and/or AST greater than 3 times ULN with total bilirubin greater than 2 times ULN	Permanently discontinue TEPMETKO.
Increase total bilirubin without concurrent increase ALT and/or AST [*see Warnings and Precautions (5.2)*]	Grade 3	Withhold TEPMETKO until recovery to baseline bilirubin. If recovered to baseline within 7 days, then resume TEPMETKO at a reduced dose; otherwise permanently discontinue.
	Grade 4	Permanently discontinue TEPMETKO.
Other adverse reactions *[see Adverse Reactions (6.1)]*	Grade 3	Withhold TEPMETKO until resolved, then resume TEPMETKO at a reduced dose.
	Grade 4	Permanently discontinue TEPMETKO.

3 DOSAGE FORMS AND STRENGTHS

Tablets: 225 mg, white-pink, oval, biconvex film-coated tablets with embossment “M” on one side and plain on the other side.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Interstitial Lung Disease (ILD)/Pneumonitis

ILD/pneumonitis, which can be fatal, occurred in patients treated with TEPMETKO *[see Adverse Reactions (6.1)]*. ILD/pneumonitis occurred in 2.2% patients treated with TEPMETKO, with one patient experiencing a Grade 3 or higher event; this event resulted in death. Four patients (0.9%) discontinued TEPMETKO due to ILD/pneumonitis.

Monitor patients for new or worsening pulmonary symptoms indicative of ILD/pneumonitis (e.g., dyspnea, cough, fever). Immediately withhold TEPMETKO in patients with suspected ILD/pneumonitis and permanently discontinue if no other potential causes of ILD/pneumonitis are identified *[see Dosage and Administration (2.3)]*.

5.2 Hepatotoxicity

Hepatotoxicity occurred in patients treated with TEPMETKO [*see Adverse Reactions (6.1)*]. Increased alanine aminotransferase (ALT)/increased aspartate aminotransferase (AST) occurred in 13% of patients treated with TEPMETKO. Grade 3 or 4 increased ALT/AST occurred in 4.2% of patients. A fatal adverse reaction of hepatic failure occurred in one patient (0.2%). Three patients (0.7%) discontinued TEPMETKO due to increased ALT/AST. The median time-to-onset of Grade 3 or higher increased ALT/AST was 30 days (range 1 to 178).

In clinical trials, the incidence of increased ALT/AST in Asian subjects was higher than that in caucasian subjects, but there was no significant difference in the incidence of increased ALT/AST for Grade 3 or higher

Monitor liver function tests (including ALT, AST, and total bilirubin) prior to the start of TEPMETKO, 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 TEPMETKO [*see Dosage and Administration (2.3)*].

5.3 Embryo-Fetal Toxicity

Based on findings in animal studies and its mechanism of action TEPMETKO can cause fetal harm when administered to a pregnant woman. Oral administration of tepotinib to pregnant rabbits during the period of organogenesis resulted in malformations (teratogenicity) and anomalies at exposures less than the human exposure based on area under the curve (AUC) at the 450 mg daily clinical dose. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential or males with female partners of reproductive potential to use effective contraception during treatment with TEPMETKO and for one week after the final dose. *[See Use in Specific Populations (8.1, 8.3)]*

6 ADVERSE REACTIONS

The following adverse reactions are described in greater detail elsewhere in the labeling:

- Interstitial Lung Disease/Pneumonitis *[see Warnings and Precautions (5.1)]*
- Hepatotoxicity*[see Warnings and Precautions (5.2)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The pooled safety population described in the WARNINGS AND PRECAUTIONS reflect exposure to TEPMETKO in 448 patients with solid tumors enrolled in five open-label, single-arm studies receiving TEPMETKO as single agent at a dose of 450 mg once daily. This included 255 patients with NSCLC positive for *MET*ex14 skipping alterations, who received TEPMETKO in VISION. Among 448 patients who received TEPMETKO, 32% were exposed for 6 months or longer, and 12% were exposed for greater than one year.

The data described below reflect exposure to TEPMETKO 450 mg once daily in 255 patients with metastatic non-small cell lung cancer (NSCLC) with *MET*ex14 skipping alterations in VISION *[see Clinical Studies (12)]*.

Serious treatment-emergent adverse events occurred in 45% of patients who received TEPMETKO. Serious adverse events in > 2% of patients included pleural effusion (7%), pneumonia (5%), edema (3.9%), dyspnea (3.9%), general health deterioration (3.5%), pulmonary embolism (2%), and musculoskeletal pain (2%). Fatal adverse events occurred in one patient (0.4%) due to pneumonitis, one patient (0.4%) due to hepatic failure, and one patient (0.4%) due to respiratory failure from fluid overload.

Permanent discontinuation due to a treatment-emergent adverse event (TEAE) occurred in 20% of patients who received TEPMETKO. The most frequent TEAE(> 1%) leading to permanent discontinuations of TEPMETKO were edema (5%), pleural effusion (2%), dyspnea (1.6%), general health deterioration (1.6%), and pneumonitis (1.2%).

Dosage interruptions due to TEAE occurred in 44% of patients who received TEPMETKO. TEAE which required dosage interruption in > 2% of patients who received TEPMETKO included edema (23%), increased blood creatinine (6%), pleural effusion (4.3%), increased ALT (3.1%), and pneumonia (2.4%).

Dose reductions due to TEAE reaction occurred in 30% of patients who received TEPMETKO. TEAE which required dose reductions in > 2% of patients who received TEPMETKO included edema (19%), pleural effusion (2.7%), and increased blood creatinine (2.7%).

The most common TEAE (≥ 20%) in patients who received TEPMETKO 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.

Table 2 summarizes the TEAE in VISION.

Table 2: TEAE in ≥ 10% of Patients with NSCLC with *MET*ex14 Skipping Alterations Who Received TEPMETKO in VISION

Adverse Reactions	TEPMETKO (N = 255)	
	All Grades (%)	Grades 3 to 4 (%)
General disorders and administration-site conditions		
Edema [a]	70	9
Fatigue [b]	27	1.6
Gastrointestinal disorders		
Nausea	27	0.8
Diarrhea	26	0.4
Abdominal Pain [c]	16	0.8
Constipation	16	0
Vomiting [d]	13	1.2
Musculoskeletal and Connective Tissue Disorders		
Musculoskeletal Pain [e]	24	2.4
Respiratory, thoracic, and mediastinal disorders		
Dyspnea [f]	20	2
Cough [g]	15	0.4
Pleural effusion	13	5
Metabolism and nutrition disorders		
Decreased appetite	16	1.2
Infections and Infestations		
Pneumonia [h]	11	3.9

[a] Edema includes eye edema, face edema, generalized edema, localized edema, edema, genital edema, peripheral edema, peripheral swelling, periorbital edema, and scrotal edema.

[b] Fatigue includes asthenia and fatigue.

[C] Abdominal Pain includes abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper, gastrointestinal pain, and hepatic pain.

[d] Vomiting includes retching and vomiting.

[e] Musculoskeletal Pain includes arthralgia, arthritis, back pain, bone pain, musculoskeletal chest pain, musculoskeletal pain, myalgia, non-cardiac chest pain, pain in extremity, and spinal pain.

[f] Dyspnea includes dyspnea, dyspnea at rest, and dyspnea exertional.

[g] Cough includes cough, and productive cough.

[h] Pneumonia includes pneumonia, pneumonia aspiration, and pneumonia bacterial

Clinically relevant TEAEin < 10% of patients who received TEPMETKO included ILD/pneumonitis, rash, fever, dizziness, pruritus, and headache.

Table 3 summarizes treatment-emergent shifts from baseline in laboratory findings occurring in VISION.

Table 3: Select Laboratory Abnormalities (≥ 20%) That Worsened from Baseline in Patients Who Received TEPMETKO in VISION

Laboratory Abnormalities	TEPMETKO[1]	
	Grades 1 to 4 (%)	Grades 3 to 4 (%)
Chemistry		
Decreased albumin	76	9
Increased creatinine	55	0.4
Increased alkaline phosphatase aminotransferase	50	1.6
Increased ALT	44	4.1
Increased AST	35	2.5
Decreased sodium	31	8
Increased potassium	25	1.6
Increased gamma-glutamyltransferase	24	5
Increased amylase	23	4.6
Hematology		
Decreased lymphocytes	48	11
Decreased hemoglobin	27	2
Decreased leukocytes	23	0.8

[1] The denominator used to calculate the rate varied from 207 to 246 based on the number of patients with a baseline value and at least one post-treatment value.

A clinically relevant laboratory abnormality in < 20% of patients who received TEPMETKO was increased lipase in 18% of patients, including 3.7% Grades 3 to 4.

Increased Creatinine

A median increase in serum creatinine of 31% was observed 21 days after initiation of treatment with TEPMETKO. The serum creatinine increases persisted throughout treatment and were reversible upon treatment completion.

7 DRUG INTERACTIONS

7.1 Effects of Other Drugs on TEPMETKO

Dual Strong CYP3A Inhibitors and P-gp Inhibitors

The effect of strong CYP3A inhibitors or P-gp inhibitors on TEPMETKO has not been studied clinically. However, metabolism and in vitro data suggest concomitant use of drugs that are strong CYP3A inhibitors and P-gp inhibitors may increase tepotinib exposure *[see Clinical Pharmacology (10.3)]*, which may increase the incidence and severity of adverse reactions of TEPMETKO. Avoid concomitant use of TEPMETKO with dual strong CYP3A inhibitors and P-gp inhibitors.

Strong CYP3A Inducers

The effect of strong CYP3A inducers on TEPMETKO has not been studied clinically. However, metabolism and in vitro data suggest concomitant use may decrease tepotinib exposure *[see Clinical Pharmacology (10.3)]*, which may reduce TEPMETKO efficacy. Avoid concomitant use of TEPMETKO with strong CYP3A inducers.

7.2 Effects of TEPMETKO on Other Drugs

Certain P-gp Substrates

Tepotinib is a P-gp inhibitor. Concomitant use of TEPMETKO increases the concentration of P-gp substrates *[see Clinical Pharmacology (10.3)]*, 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 changes 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.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on findings in animal studies and the mechanism of action *[see Clinical Pharmacology (10.1)]*, TEPMETKO can cause fetal harm when administered to a pregnant woman. There are no available data on the use of TEPMETKO in pregnant women. Oral administration of tepotinib to pregnant rabbits during the period of organogenesis resulted in malformations (teratogenicity) and anomalies at maternal exposures less than the human exposure based on area under the curve (AUC) at the 450 mg daily clinical dose *(see Data)*. Advise pregnant women of the potential risk to a fetus.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data

In embryo-fetal development studies, pregnant rabbits received oral doses of 0.5, 5, 25, 50, 150, or 450 mg/kg tepotinib hydrochloride hydrate daily during organogenesis. Severe maternal toxicity occurred at the 450 mg/kg dose (approximately 0.75 times the human exposure at the 450 mg clinical dose). At 150 mg/kg (approximately 0.5 times the human exposure by AUC at the 450 mg clinical dose), two animals aborted and one animal died prematurely; mean fetal body weight was also decreased. A dose-dependent increase of skeletal malformations, including malrotations of fore and/or hind paws with concomitant misshapen scapula and/or malpositioned clavicle and/or calcaneous and/or talus, occurred at doses ≥ 5 mg/kg (approximately 0.003 times the human exposure by AUC at the 450 mg clinical dose); there was also an incidence of spina bifida at the 5 mg/kg dose level.

8.2 Lactation

Risk Summary

There are no data regarding the secretion of tepotinib or its metabolites in human milk or its effects on the breastfed infant or milk production. Advise women not to breastfeed during treatment with TEPMETKO and for one week after the final dose.

8.3 Females and Males of Reproductive Potential

Based on animal data, TEPMETKO can cause malformations at doses less than the human exposure based on AUC at the 450 mg clinical dose *[see Use in Specific Populations (8.1)]*.

Pregnancy Testing

Verify pregnancy status in females of reproductive potential prior to initiating TEPMETKO *[see Use in Specific Populations (8.1)]*.

Contraception

Females

Advise females of reproductive potential to use effective contraception during TEPMETKO treatment and for one week after the final dose.

Males

Advise male patients with female partners of reproductive potential to use effective contraception during TEPMETKO treatment and for one week after the final dose.

8.4 Pediatric Use

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

8.5 Geriatric Use

Of 255 patients with *MET*ex14 skipping alterations in VISION who received 450 mg TEMETKO 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.

8.6 Renal Impairment

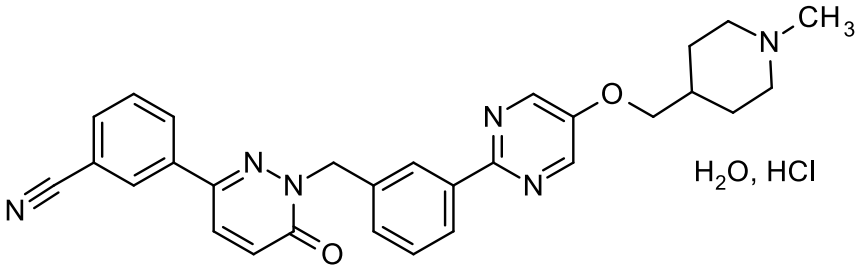
No dosage modification is recommended in patients with mild or moderate renal impairment (creatinine clearance [CLcr] 30 to 89 mL/min, estimated by Cockcroft-Gault). The recommended dosage has not been established for patients with severe renal impairment (CLcr < 30 mL/min) *[see Clinical Pharmacology (10.3)]*.

8.7 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 *[see Clinical Pharmacology (10.3)]*.

9 DESCRIPTION

Tepotinib is a kinase inhibitor. TEPMETKO (tepotinib) tablets for oral use are formulated with tepotinib hydrochloride hydrate. The chemical name for tepotinib hydrochloride hydrate is 3-{1-[(3-{5-[(1-methylpiperidin-4-yl)methoxy]pyrimidin-2-yl}phenyl)methyl]-6-oxo-1,6-dihydropyridazin-3-yl}benzonitrile hydrochloride hydrate. The molecular formula is $C_{29}H_{28}N_6O_2 \cdot HCl \cdot H_2O$ and the molecular weight is 547.05 g/mol for tepotinib hydrochloride hydrate and 492.58 g/mol for tepotinib (free base). The chemical structure is shown below:



Tepotinib hydrochloride hydrate is a white to off-white powder with a pKa of 9.5.

TEPMETKO is supplied as film-coated tablets containing 225 mg of tepotinib (equivalent to 250 mg tepotinib hydrochloride hydrate). Inactive ingredients in the tablet core are mannitol (Parteck® M100 and M200), microcrystalline cellulose, crospovidone, magnesium stearate, and colloidal silicon dioxide. The tablet coating consists of hypromellose, titanium dioxide, lactose monohydrate, polyethylene glycol, triacetin, and red iron oxides.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism 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.

In vitro, tepotinib inhibited tumor cell proliferation, anchorage-independent growth, and migration of MET-dependent tumor cells. In mice implanted with tumor cell lines with oncogenic activation of MET, including *MET*ex14 skipping alterations, tepotinib inhibited tumor growth, led to sustained inhibition of MET phosphorylation, and, in one model, decreased the formation of metastases.

10.2 Pharmacodynamics

Exposure-Response

Tepotinib exposure-response relationships and the time course of pharmacodynamic response have not been fully characterized.

Cardiac Electrophysiology

At the recommended dosage, no large mean increases in QTc (i.e. > 20 ms) were detected in patients with various solid tumors. A concentration-dependent increase in QTc interval was observed. The QTc effect of tepotinib at high clinical exposures has not been evaluated.

10.3 Pharmacokinetics

The pharmacokinetics of tepotinib were evaluated in patients with cancer administered 450 mg once daily unless otherwise specified. Tepotinib exposure ($AUC_{0\text{-}12h}$ and C_{max}) increases dose-proportionally over the dose range of 27 mg (0.06 times the recommended daily dosage) to 450 mg. At the recommended dosage, the geometric mean (coefficient of variation [CV] %) steady state C_{max} was 1,291 ng/mL (48.1%) and the $AUC_{0\text{-}24h}$ was 27,438 ng·h/mL (51.7%). The oral clearance of tepotinib did not change with respect to time. The median accumulation was 2.5-fold for C_{max} and 3.3-fold for $AUC_{0\text{-}24h}$ after multiple daily doses of tepotinib.

Absorption

The median T_{max} of tepotinib is 8 hours (range from 6 to 12 hours). The geometric mean (CV%) absolute bioavailability of TEPMETKO in the fed state was 71.6% (10.8%) in healthy subjects.

Effect of Food

The mean $AUC_{0\text{-}INF}$ of tepotinib increased by 1.6-fold and C_{max} increased by 2-fold, following administration of a high-fat, high-calorie meal (approximately 800 to 1,000 calories, 150 calories from protein, 250 calories from carbohydrate, and 500 to 600 calories from fat). The median T_{max} shifted from 12 hours to 8 hours.

Distribution

The geometric mean (CV%) apparent volume of distribution (V_Z/F) of tepotinib is 1,038 L (24.3%). Protein binding of tepotinib is 98% and is independent of drug concentration at clinically relevant exposures.

Elimination

The apparent clearance (CL/F) of tepotinib is 23.8 L/h (87.5%) and the half-life is 32 hours following oral administration of TEPMETKO in patients with cancer.

Metabolism

Tepotinib is primarily metabolized by CYP3A4 and CYP2C8. One major circulating plasma metabolite (M506) has been identified.

Excretion

Following a single oral administration of a radiolabeled dose of 450 mg tepotinib, approximately 85% of the dose was recovered in feces (45% unchanged) and 13.6% in urine (7% unchanged). The major circulating metabolite M506 accounted for about 40.4% of the total radioactivity in plasma.

Specific Populations

No clinically significant effects on tepotinib pharmacokinetics were observed based on age (18 to 89 years), race/ethnicity (White, Black, Asian, Japanese, and Hispanic), sex, body weight (35.5 to 136 kg), mild to moderate renal impairment (CLcr 30 to 89 mL/min), or mild to moderate hepatic impairment (Child-Pugh A and B). The effect of severe renal impairment (CLcr < 30 mL/min) and severe hepatic impairment (Child-Pugh C) on the pharmacokinetics of tepotinib has not been studied.

Drug Interaction Studies

Clinical Studies

P-gp Substrates: Coadministration of TEPMETKO with dabigatran etexilate (P-gp substrate) increased dabigatran C_{max} by 40% and $AUC_{0\text{-}INF}$ by 50%.

Acid-Reducing Agents: No clinically significant differences in tepotinib pharmacokinetics were observed when coadministered with multiple daily doses (40 mg daily for 5 days) of omeprazole (proton pump inhibitor) under fed conditions.

CYP3A Substrates: Coadministration of TEPMETKO had no clinically significant effect on the pharmacokinetics of midazolam (sensitive CYP3A substrate).

In Vitro Studies

Cytochrome P450 Enzymes: Tepotinib is a substrate of CYP3A4 and CYP2C8. Tepotinib and M506 do not inhibit CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C19, CYP2D6 or CYP2E1, and do not induce CYP1A2 or 2B6 at clinically relevant concentrations.

UDP-Glucuronosyltransferase (UGT): Tepotinib and M506 do not inhibit UGT 1A1, 1A9, 2B17, 1A3/4/6 and 2B7/15 at clinically relevant concentrations.

Transporter Systems: Tepotinib is a P-gp substrate. Tepotinib may inhibit intestinal BCRP at clinically relevant concentrations. Tepotinib does not inhibit bile salt export pump (BSEP), organic anion transporter polypeptide (OATP) 1B1, B3, or organic anion transporter (OAT)1 and 3.

11 NONCLINICAL TOXICOLOGY

11.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been performed with tepotinib. Tepotinib and its major circulating metabolite were not mutagenic in vitro in the bacterial reverse mutation (Ames) assay, or a mouse lymphoma assay. In vivo, tepotinib was not genotoxic in a rat micronucleus test.

Fertility studies of tepotinib have not been performed. There were no morphological changes in male or female reproductive organs in repeat-dose toxicity studies in dogs.

12 CLINICAL STUDIES

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 *MET*ex14 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 *MET*ex14 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 65 treatment naïve patients and 81 previously treated patients. The median age was 73 years (range 41 to 94 years); 48% female; 70% White, 26% Asian; 25% had Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) 0 and 75% had ECOG PS 1; 43% never smoked; 87% had adenocarcinoma; 98% had metastatic disease; and 10% had CNS metastases. Amongst previously treated patients, 89% received prior platinum-based chemotherapy.

Efficacy results are presented in Table 4.

Table 4: Efficacy Results in the VISION study

Efficacy parameter	**Treatment-Naïve N = 65**	**Previously Treated N = 81**
Overall response rate, % (95% CI) [a, b]	44.6 (32.3, 57.5)	45.7 (34.6, 57.1)
Median duration of response, months [c] (95% CI)	10.8 (6.9, NE)	11.1 (9.5, 18.5)
Patients with DOR ≥ 6 months, %	72.4	75.7
Patients with DOR ≥ 9 months, %	34.5	51.4

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.

13 HOW SUPPLIED/STORAGE AND HANDLING

TEPMETKO (tepotinib) tablets: 225 mg tepotinib, white-pink, oval, biconvex film-coated tablet with embossment “M” on one side and plain on the other side.

Aluminium/Polyvinyl chloride-polyethylene-polyvinylidene chloride-polyethylene-polyvinyl chloride blister. Pack of 60 film-coated tablets.

Store below 30°C. Store in original package.

Date of revision of the text
Aug 2021

Manufacturer: Merck Healthcare KGaA
Manufacturer address: Frankfurter Straβe 250, 64293 Darmstadt, Germany

Local license holder: Merck Ltd. – Taiwan