TEPMETKO
Tepotinib 225 mg
Film coating tablets

MEDICINE AUTHORIZED UNDER SPECIAL REGISTRATION CONDITIONS

Made in Germany sold under archived prescription

COMPOSITION

Each film tablet contains:
Inner Phase (Granules)
Tepotinib* ……225,00 mg
mannitol……372,00 mg
microcrystalline cellulose……33,33 mg
crospovidone……8,00 mg
magnesium stearate……3,33 mg
Outer Phase (tablet Cores)
mannitol……83,33 mg
crospovidone……16,67 mg
magnesium stearate……16,67 mg
colloidal silicon dioxide……8,33 mg
microcrystalline cellulose……41,67 mg
Coating:
Opadry II pink (33G240013)……20,83 mg
composed by
Hypromellose……8,33 mg
titanium dioxide……5,17 mg
lactose monohydrate……4,37 mg
polyethylene glycol……1,67 mg
triacetin……1,25 mg
red iron oxide……0,03 mg

***(225mg Tepotinib active moiety/free base as Tepotinib hydrochloride hydrate 250 mg)**

THERAPEUTIC ACTION

Antineoplastic agents, other protein kinase inhibitors

ATC code L01EX21

DESCRIPTION

Tepotinib is an antineoplastic compound. Tepotinib is a reversible, Type I adenosine Triphosphate (ATP)-competitive, orally available inhibitor of the receptor tyrosine kinase mesenchymal-epithelial transition factor (protein related: MET; gene-related: *MET*).

INDICATION

Treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) harboring mesenchymal-epithelial transition (MET) exon 14 skipping alterations.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

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 METdependent tumor cells. In mice implanted with tumor cell lines with oncogenic activation of MET, including METex14 skipping alterations, tepotinib inhibited tumor growth, led to sustained inhibition of MET phosphorylation, and, in one model, decreased the formation of metastases.

Pharmacodynamic effects

Exposure response

Tepotinib exposure-reponse 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

Pharmacokinetic properties

The pharmacokinetics of tepotinib were evaluated in patients with cancer administered 450 mg once daily unless otherwise specified. Tepotinib exposure (AUC_{0-12h} 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_{0-24h} 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_{0-24h} 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-INF} of tepotinib increased by 1.6-fold and C 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 Tmax shifted from 12 hours to 8 hours.

Distribution

The geometric mean (CV%) apparent volume of distribution (V /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 and Model-Informed Approaches

P-gp Substrates: Coadministration of TEPMETKO with dabigatran etexilate (P-gp substrate) increased dabigatran C by 40% and AUC 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).

MATE2 and OCT2 Substrates: No clinically relevant differences in glucose levels were observed when metformin (MATE2 and OCT2 substrate) was coadministered with tepotinib.

CYP2C9 Substrates: Physiologically based pharmacokinetic modeling suggested CYP2C9 inhibition is not clinically significant.

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.

Posology and method of administration

Patient Selection for METex14 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.

Recommended Dosage

The recommended dosage of TEPMETKO is 450 mg orally once daily with food 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.

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	Any grade	Withhold TEPMETKO if ILD is suspected. Permanently discontinue TEPMETKO if ILD is confirmed.
Increased ALT and/or AST without increased total bilirubin	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	ALT and/or AST greater than 3 times ULN with total bilirubin greater than 2 times ULN	Permanently discontinue TEPMETKO
Increased total bilirubin without concurrent increased ALT and/or AST	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	Grado 2	Maintain dose level. If intolerable, consider withholding TEPMETKO until resolved, then resume TEPMETKO at a reduced dose.
	Grade 3	Withhold TEPMETKO until resolved, then resume TEPMETKO at a reduced dose.
	Grade 4	Permanently discontinue TEPMETKO

Contraindications

Patients with a history of hypersensitivity to any of the ingredients of TEPMETKO.

Warning and precautions

Administration should be started only after obtaining the patient's (or his/her family's) consent based on a full explanation of the benefits and risks of treatment with TEPMETKO.

Interstitial lung disease

ILD/pneumonitis, which can be fatal, occurred in patients treated with TEPMETKO. 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.

Hepatotoxicity

Hepatotoxicity occurred in patients treated with TEPMETKO. 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).

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

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.

DRUG INTERACTIONS

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 Pgp inhibitors may increase tepotinib exposure, 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, which may reduce TEPMETKO efficacy. Avoid concomitant use of TEPMETKO with strong CYP3A inducers.

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 , 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.

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.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

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. 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.

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.

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.

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.

Pregnancy Testing

Verify pregnancy status in females of reproductive potential prior to initiating TEPMETKO

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.

Pediatric Use

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

Geriatric Use

Of 255 patients with METex14 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.

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.

Effects on the ability to drive and use machines

TEPMETKO has no influence on the ability to drive and use machines

ADVERSE EVENTS

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

- Interstitial Lung Disease/Pneumonitis
- Hepatotoxicity

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 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 METex14 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 nonsmall cell lung cancer (NSCLC) with METex14 skipping alterations in VISION.

Serious adverse reactions occurred in 45% of patients who received TEPMETKO. Serious adverse reactions 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 reactions occurred in one patient (0.4%) due to pneumonitis, one patient (0.4%) due to hepatic failure, and one patient (0.4%) due to dyspnea from fluid overload.

Permanent discontinuation due to an adverse reaction occurred in 20% of patients who received TEPMETKO. The most frequent adverse reactions (> 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 an adverse reaction occurred in 44% of patients who received TEPMETKO. Adverse reactions 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 an adverse reaction occurred in 30% of patients who received TEPMETKO. Adverse reactions 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 adverse reactions (≥ 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 adverse reactions in VISION.

Table2 Adverse Reactions in ≥ 10% of Patients with NSCLC with METex14 Skipping Alterations Who Received TEPMETKO in VISION

System organ class/Adverse reaction	TEPMETKO N=255	
	All grades (%)	**Grade ≥ 3 (%)**
General disorders and administration site conditions		
Edema[a]	70	9
Fatigue[b]	27	1,6
Gastrointestinal disorders		
Nausea	27	0,8
Diarrhoea	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 adverse reactions in < 10% of patients who received TEPMETKO included ILD/pneumonitis, rash, fever, dizziness, pruritus, and headache.

Table 3 summarizes the laboratory abnormalities observed in VISION.

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

Laboratory Abnormalities	TEPMETKO*	
	Grades 1 to 4 (%)	Grades 3 to 4 (%)
Chemistry		
Decreased albumin	76	9
Increased creatinine	55	0.4
Increase alkaline phosphatase aminotransferase	50	1.6
Increased alanine aminotransferase	44	4.1

Increased aspartate aminotransferase	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 leukocyes	23	0.8

*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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions

OVERDOSE

Tepotinib has been investigated at doses up to 1,261 mg. Symptoms of overdose have not been identified. There is no specific treatment in the event of tepotinib overdose. In case of overdose, TEPMETKO should be withheld and symptomatic treatment initiated.

In case of overdosage, go to the nearest Hospital or contact the Toxicology Centers:

Ricardo Gutiérrez Pediatric Hospital: (011) 4962-6666 / 2247.

A. Posadas Hospital: (011) 4654-6648 / 4658-7777.

Special precautions for storage

Store TEPMETKO at room temperature between 15°C to 25°C and protect from moisture. Store in original package.

PRESENTATIONS

White-pink, oval, biconvex film-coated tablet with embossment "M" on one side and plain on the other side. Pack size of 60 tablets – 6 blisters with 10 tablets each.

PATIENT COUNSELING INFORMATION

Advise the patient to read the Patient Information.

Interstitial Lung Disease (ILD)/Pneumonitis

Inform patients of the risk of severe or fatal ILD/pneumonitis. Advise patients to contact their healthcare provider immediately to report new or worsening respiratory symptoms.

Hepatotoxicity

Inform patients that they will need to undergo lab tests to monitor liver function. Advise patients to immediately contact their healthcare provider for signs and symptoms of liver dysfunction

Embryo-Fetal Toxicity

Advise males and females of reproductive potential that TEPMETKO can cause fetal harm.

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

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

Lactation

Advise women not to breastfeed during treatment with TEPMETKO and for one week after the final dose.

Drug Interactions

Advise patients to inform their healthcare provider of all concomitant medications, including prescription medicines, over-the-counter drugs and herbal products.

Dosing and Administration

Instruct patients to take 450 mg TEPMETKO once daily with food.

Missed Dose

Advise patients that a missed dose of TEPMETKO can be taken as soon as remembered on the same day, unless the next dose is due within 8 hours. If vomiting occurs after taking a dose of TEPMETKO, advise patients to take the next dose at the scheduled time.

Clinical efficacy and safety

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 are presented in Table 4.

Table 4: Efficacy Results in the VISION study

Efficacy parameter	**Treatment – Näive N=69**	**Previously Treated N=83**
Overall response rate [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 month, %	67	75
Patients with DOR ≥ 9 month, %	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.

Warning for this and all drugs

KEEP MEDICINES OUT OF THE REACH OF CHILDREN.

Medicine authorized by the Ministry of Health. Certificate No. XXXX

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**Manufactures can be modified according to the selected supply route*