TEPMETKO™

tepotinibe hydrochloride hydrate

HOW SUPPLIED
Film -coated tablets of 250 mg. Pack with 60 tablets.

ORAL ROUTE
ADULT USE

COMPOSITION
Each film-coated tablet contains:
tepotinib hydrochloride hydrate – 250 mg (equivalent to 225 mg tepotinib).
Excipients: mannitol, colloidal silicon dioxide, crospovidone, magnesium stearate, microcystalline cellulose, hypromellose, lactose monohydrate, macrogol, triacetin, red iron oxides, titanium dioxide.

TECHNICAL INFORMATION FOR HEALTH PROFESSIONALS

1. INDICATIONS

TEPMETKO™ is indicated for the treatment of adult patients with advanced non-small cell lung cancer (NSCLC) harbouring *MET* tyrosine kinase receptor exon 14 (*METex14*) skipping alterations.

2. EFFECTIVENESS RESULTS

The efficacy of tepotinib was evaluated in a single-arm, open-label, multicentre study (VISION) in adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) harbouring *MET*ex14 skipping alterations (n = 146). Patients with Eastern Cooperative Oncology Group Performance Status (ECOG PS) from 0 to 1 were included, they were either treatment-naïve or had progressed in up to 2 lines prior systemic therapies. Neurologically stable patients with central nervous system metastases were permitted. Patients with epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) activating alterations were excluded.

Patients had a median age of 73 years (41 to 94), the majority being ≥ 65 years old (82%) and 45% of the patients were ≥ 75 years old, 48% were female and 52% male. The majority of patients were white (70%), followed by Asian patients (26%) and were never (42%) or former smokers (50%).

The majority of patients had stage IV disease (98%), 87% had adenocarcinoma histology . Ten percent of the patients had stable brain metastases. Patients received tepotinib as first-line (45%) or second- or later line (55%) therapy.

*MET*ex14 skipping was prospectively tested by next-generation sequencing in tumour (RNA-based) and/or plasma (ctDNA-based).

Patients received 500 mg tepotinib hydrochloride hydrate once daily until disease progression or unacceptable toxicity. Median treatment duration was 8.02 months (range 0.03 to 43.33 months).

The primary efficacy outcome measure was confirmed objective response (complete response or partial response) according to Response Evaluation Criteria in Solid Tumors (RECIST v1.1) as evaluated by an Independent Review Committee (IRC). Additional efficacy outcome measures included duration of response and progression-free survival assessed by IRC as well as overall survival.

Table 1. Clinical outcomes in the VISION study by IRC assessment in ITT population

Efficacy parameter	**ITT N = 146**
Objective response rate, % [95% CI]	45.2 [37.0, 53.6]
Complete response, %	0
Partial response, %	45.2
Median duration of response, months [95% CI]	11.1 [8.4, 18.5]
Duration of response β	
≥ 6 months, % of responders	74.2
≥ 9 months, % of responders	43.9
≥ 12 months, % of responders	21.2
Median progression-free survival, monthsα [95% CI]	8.9 [8.2, 11.0]
Median overall survival time, monthsα [95% CI]	17.6 [15.0, 21.0]

IRC=Independent Review Committee, ITT=Intent-to-treat, CI=confidence interval
α Product-limit (Kaplan-Meier) estimates, 95% CI for the median using the Brookmeyer and Crowley method
β Duration of response of ≥ 9 months and ≥ 12 months, respectively, could not be reached by some patients due to their time of enrolment.

Efficacy outcome was independent of the testing modality (liquid biopsy or tumour biopsy) used to establish the *MET*ex14 skipping status. Consistent efficacy results in subgroups by prior therapy, presence of brain metastasis or age were observed.

References

Paik PK, et al. Tepotinib in Non–Small-Cell Lung Cancer with MET Exon 14 Skipping Mutations. N Engl J Med. 2020 May 29 (VISION study).*

*Data updated in the section "Effectiveness Results" due to cut-off of July 2020.

3. PHARMACOLOGICAL CHARACTERISTICS

Mechanism of action

Oncogenic activation of MET has been shown to promote cancer cell proliferation, survival, migration and invasion, and tumour angiogenesis, as well as to mediate resistance to cancer therapies.

Tepotinib is a selective and potent, reversible, Type I adenosine triphosphate (ATP)-competitive small molecule inhibitor or MET. Tepotinib blocks MET phosphorylation and MET-dependent downstream signalling such as the phosphatidylinositol-3-kinase/protein kinase B and mitogen-activated protein kinase/extracellular-signal regulated kinase pathways in a dose-dependent manner.

Treatment of susceptible tumour cells with tepotinib inhibited proliferation, anchorage-independent growth and migration of MET-dependent tumour cells. Treatment of tumour-bearing mice with tepotinib led to effective and sustained inhibition of MET phosphorylation and a change in pharmacodynamic biomarkers, indicating inhibition of tumour cell proliferation, increased tumour cell apoptosis and reduced tumour angiogenesis.

Tepotinib inhibited tumour growth in multiple tumour models derived from diverse cancer types. The anti-tumour activity of tepotinib was particularly pronounced in tumours with oncogenic activation of *MET*, such as *MET*ex14 skipping alterations. Furthermore, tepotinib treatment prevented the formation of metastases.

Tepotinib treatment led also to regression of established intracranial brain metastasis models from NSCLC patient-derived xenografts with oncogenic MET activation. Unbound concentrations of tepotinib in the brain tissue of rats at steady state were approximately 25% of the corresponding concentrations in plasma.

The contribution of the major circulating metabolite to the anti-tumour activity of tepotinib is considered to be negligible.

Pharmacotherapeutic group: Antineoplastic agents, other protein kinase inhibitors.
ATC code: L01EX21

Pharmacodynamics

Cardiac electrophysiology

In an exposure-QTc analysis, the QTcF interval prolongation potential of tepotinib was assessed in 392 patients with various solid tumours following single or multiple daily doses of. tepotinib hydrochloride hydrate ranging from 30 mg to 1,400 mg. Tepotinib did not prolong the QTcF interval to a clinically relevant extent.

Pharmacokinetics

Absorption

A mean absolute bioavailability of 71.6% was observed for a single 500 mg dose of tepotinib hydrochloride hydrate administered in the fed state; the median time to Cmax was 8 hours (range from 6 to 12 hours).

The presence of food (standard high-fat, high-calorie breakfast) increased the AUC of tepotinib by about 1.6-fold and Cmax by 2-fold.

Distribution

In human plasma, tepotinib is highly protein bound (98%).108 The mean volume of distribution (Vz) of tepotinib after an intravenous tracer dose (geometric mean and geoCV%) was 574 L (14.4%).

In vitro studies indicate that tepotinib is a substrate for P-glycoprotein (P-gp). While P-gp inhibitors are not expected to alter tepotinib exposure to a clinically relevant extent, strong P-gp inducers may have the potential to decrease tepotinib exposure.

Biotransformation

Metabolism is not the major route of elimination. No metabolic pathway accounted for more than 25% of tepotinib elimination. Only one major circulating plasma metabolite has been

identified. There is only a minor contribution of the major circulating metabolite to the overall efficacy of tepotinib in humans.

Elimination
After intravenous administration of single doses, a total systemic clearance (geometric mean and geoCV%) of 12.8 L/h was observed.

Tepotinib is mainly excreted via the faeces (approximately 85% total recovery of radioactivity), with urinary excretion being a minor excretion pathway. After a single oral administration of a radiolabelled dose of 500 mg tepotinib hydrochloride hydrate, the unchanged tepotinib represented 45% and 7% of the total radioactivity in faeces and urine, respectively. The major circulating metabolite accounted for only about 3% of the total radioactivity in the faeces.

The effective half-life for tepotinib is approximately 32 h. After multiple daily administrations of 500 mg tepotinib hydrochloride hydrate, median accumulation was 2.5-fold for Cmax and 3.3-fold for AUC0-24h.

Dose and time dependence
Tepotinib hydrochloride hydrate exposure increases dose-proportionally over the clinically relevant dose range up to 500 mg. The pharmacokinetics of tepotinib did not change with respect to time.

Special populations
A population kinetic analysis did not show any effect of age (range 18 to 89 years), race, sex or body weight, on the pharmacokinetics of tepotinib.

Renal impairment
There was no clinically meaningful change in exposure in patients with mild and moderate renal impairment. Patients with severe renal impairment (creatinine clearance less than 30 mL/min) were not included in clinical trials.

Hepatic impairment
Following a single oral dose of 500 mg, tepotinib hydrochloride hydrate exposure was similar in healthy subjects and patients with mild hepatic impairment (Child-Pugh Class A), and was slightly lower (-13% AUC and -29% Cmax) in patients with moderate hepatic impairment (Child-Pugh Class B) compared to healthy subjects. However, the free plasma concentrations of tepotinib were in a similar range in the healthy subjects, patients with mild hepatic impairment and in patients with moderate hepatic impairment. The pharmacokinetics of tepotinib have not been studied in patients with severe (Child Pugh Class C) hepatic impairment.

Pharmacokinetic interaction studies
Clinical studies
Effect of tepotinib on CYP3A4 substrates: Multiple administrations of 500 mg tepotinib hydrochloride hydrate orally once daily had no clinically relevant effect on the PK of the sensitive CYP3A4 substrate midazolam.

Effect of tepotinib on P-gp substrates: Tepotinib is an inhibitor of P-gp. Multiple administrations of tepotinib hydrochloride hydrate 500 mg orally once daily had a mild effect on the pharmacokinetics of the sensitive P-gp substrate dabigatran etexilate, increasing its AUCt by approximately 50% and Cmax by approximately 40%.

Effect of acid-reducing agents on tepotinib: Co-administration of omeprazole had no marked effect on the pharmacokinetic profile of tepotinib and its metabolites when administered under fed conditions.

In-vitro studies

Effects of tepotinib on other transporters: Tepotinib or its major circulating metabolite inhibit BCRP, OCT2 and MATE 2 at clinically relevant concentrations. At clinically relevant concentrations tepotinib represents a remote risk for bile salt export pump (BSEP) whilst it presents no risk for organic anion transporter polypeptide (OATP)B3, organic anion transporter (OAT)1 and 3.

Effects of tepotinib on UDP-glucuronosyltransferase (UGT): The perpetrator risk of tepotinib or its major circulating metabolite on UGT 1A1, 1A9 and 2B17 is considered unlikely, whilst it is excluded for the other isoforms (UGT1A3/4/6, and 2B7/15).

Effect of tepotinib on CYP 450 enzymes: At clinically relevant concentrations neither tepotinib nor the major circulating metabolite represent a risk of inhibition of CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP2E1. Tepotinib or its major circulating metabolite do not induce CYP1A2, and 2B6.

Non-clinical safety

Oral repeat-dose toxicity studies have been conducted in rats up to 26 weeks and dogs up to 39 weeks.

Increased hepato-biliary parameters concomitant with pronounced cholangitis and pericholangitis were seen in dogs starting at doses of 30 mg tepotinib hydrochloride hydrate per kg per day (approximately 18% the human exposure at the recommended dose of TEPMETKO™ 500 mg once daily based on AUC). Slightly increased liver enzymes were seen in rats starting at doses 15 mg tepotinib hydrochloride hydrate per kg per day (approximately 3% of the human exposure at the recommended dose of TEPMETKO™ 500 mg once daily based on AUC). In dogs vomiting and diarrhoea were seen starting at 2.5 mg tepotinib hydrochloride hydrate per kg per day and at exposures approximately 0.3% of the human exposure at the recommended dose of 500 mg TEPMETKO™ based on AUC. All changes proved to be reversible or showed indications of reversibility or improvements.

A no-observed-adverse-effect-level (NOAEL) was established at 45 mg tepotinib hydrochloride hydrate per kg per day in the 26-week study in rats and at 10 mg tepotinib hydrochloride hydrate per kg per day in the 39-week study in dogs (both equivalent to approximately 4% of the human exposure at the recommended dose of 500 mg TEPMETKO™ based on AUC).

Genotoxicity

No mutagenic or genotoxic effects of tepotinib were observed in in vitro and in vivo studies. The major circulating metabolite was also shown to be non-mutagenic.

Carcinogenicity

No studies have been performed to evaluate the carcinogenic potential of tepotinib.

Reproduction toxicity

In a first oral embryo-foetal development study, pregnant rabbits received doses of 50, 150, and 450 mg tepotinib hydrochloride hydrate per kg per day during organogenesis. The dose of 450 mg/kg was discontinued due to severe maternal toxic effects. In the 150 mg per kg group, two

animals aborted and one animal died prematurely. Mean foetal body weight was decreased at doses of ≥ 150 mg per kg per day. 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, were observed at 50 and 150 mg per kg per day.

In the second embryo-foetal development study, pregnant rabbits received oral doses of 0.5, 5, and 25 mg tepotinib hydrochloride hydrate per kg per day during organogenesis. Two malformed foetuses with malrotated hind limbs were observed (one in the 5 mg/kg group (approximately 0.21% of the human exposure at the recommended dose of TEPMETKO™ 500 mg once daily based on AUC) and one in the 25 mg/kg group), together with a generally increased incidence of foetuses with hind limb hyperextension.

Fertility studies of tepotinib to evaluate the possible impairment of fertility have not been performed. No morphological changes in male or female reproductive organs were seen in the repeat-dose toxicity studies in rats and dogs.

4. CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients.

5. WARNINGS AND PRECAUTIONS

Interstitial lung disease

Interstitial lung disease (ILD) or ILD-like adverse reactions have been reported in 6 patients (2.4%) with advanced NSCLC with *MET*ex14 skipping alterations who received tepotinib monotherapy at the recommended dosage regimen (n=255), including 1 case of grade 3 or higher; serious cases occurred in 2 patients (0.8%), 1 case was fatal.

Patients should be monitored for pulmonary symptoms indicative for ILD-like reactions (e.g., dyspnea, cough, fever). TEPMETKO™ should be withheld and patients should be promptly investigated for alternative diagnosis or specific aetiology of interstitial lung disease. TEPMETKO™ must be permanently discontinued if interstitial lung disease is confirmed and the patient be treated accordingly.

Increase in ALT and/or AST

Increase in ALT and/or AST has been reported (see "Description of selected adverse reactions"). Liver enzymes (ALT and AST) and bilirubin should be monitored prior to the start of TEPMETKO™ and thereafter as clinically indicated. If grade 3 or higher increases occur, dose modification is recommended (see "Dose modification for adverse reactions").

Embryo-foetal toxicity

TEPMETKO™ can cause foetal harm when administered to pregnant women (see "Pregnancy and lactation").

Women of childbearing potential or male patients with female partners of childbearing potential should be advised of the potential risk to a foetus.

Women of childbearing potential should use effective contraception during TEPMETKO™ treatment and for at least 1 week after the last dose.

Male patients with female partners of childbearing potential should use barrier contraception during TEPMETKO™ treatment and for at least 1 week after the last dose.

Interpretation of laboratory tests
Nonclinical studies suggest that tepotinib or its main metabolite inhibit the renal tubular transporter proteins OCT2 and MATE2 (see "Pharmacokinetics"). Creatinine is a substrate of these transporters, and the observed increases in creatinine (see "Adverse reactions") may be the result of inhibition of active tubular secretion rather than renal injury. Renal function estimates that rely on serum creatinine (creatinine clearance or estimated glomerular filtration rate) should be interpreted with caution considering this effect.

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

Warning: Contains lactose (4.37 mg of lactose monohydrate/tablet). This medicine should not be used by people with glucose-galactose malabsorption syndrome.

PREGNANCY AND LACTATION
Contraception in males and females
Pregnancy testing is recommended in women of childbearing potential prior to initiating treatment with TEPMETKO™.

Women of childbearing potential should use effective contraception during TEPMETKO™ treatment and for at least 1 week following the last dose.

Male patients with female partners of childbearing potential should use barrier contraception during TEPMETKO™ treatment and for at least 1 week after the last dose.

Pregnancy
There are no clinical data on the use of TEPMETKO™ in pregnant women. Studies in animals have shown teratogenicity (see "Non-clinical safety"). Based on the mechanism of action and findings in animals TEPMETKO™ can cause foetal harm when administered to pregnant women.

TEPMETKO™ should not be used during pregnancy, unless the clinical condition of the woman requires treatment with tepotinib. Women of childbearing potential or male patients with female partners of childbearing potential should be advised of the potential risk to a foetus.

Breast-feeding
There are no data regarding the secretion of tepotinib or its metabolites in human milk or its effects on the breast-fed infant or milk production. Breast-feeding should be discontinued during treatment with TEPMETKO™.

Fertility
No human data on the effect of TEPMETKO™ on fertility are available. No morphological changes in male or female reproductive organs were seen in the repeat-dose toxicity studies in rats and dogs (see "Non-clinical safety").

Risk category D. This medicine should not be used by pregnant women without medical advice. Inform your physician immediately if you suspect a pregnancy.

6. DRUG INTERACTIONS

P-gp inducers

Tepotinib is a substrate for P-glycoprotein (P-gp) (see "Pharmacokinetics"). Strong P-gp inducers may have the potential to decrease tepotinib exposure. Concomitant use of strong P-gp inducers (e.g. carbamazepine, phenytoin, rifampicin, St. John's wort) should be avoided.

P-gp substrates

Tepotinib can inhibit the transport of sensitive substrates of P-gp (see "Pharmacokinetics"). Monitoring of the clinical effects of P-gp-dependent substances with a narrow therapeutic index (e.g. digoxin) is recommended during co-administration with TEPMETKO™.

BCRP substrates

Tepotinib can inhibit the transport of sensitive substrates of the breast cancer resistance protein (BCRP) (see "Pharmacokinetics"). Monitoring of the clinical effects of sensitive BCRP substrates is recommended during co-administration with TEPMETKO™.

Metformin

Based on in vitro data, tepotinib or its metabolite may have the potential to increase the AUC of co-administered metformin in humans through inhibition of its renal excretion mediated via organic cation transporter (OCT) 2 and multidrug and toxin extrusion transporter (MATE)2 (see "Pharmacokinetics"). Monitoring of the clinical effects of metformin is recommended during co-administration with TEPMETKO™.

7. STORAGE PRECAUTIONS OF THE MEDICINE

Store at room temperature (between 15 ° C and 30 ° C) in the original package to protect from moisture.

Expiry date: 36 months from the date of manufacture printed on the packaging.

Batch number and manufacture and expiry dates: see packing. Do not use the medicine with the shelf life expired. Keep the medicine in the original package.

Characteristics of the medicine: white-pink, oval and biconvex coated tablets, with "M" engraving on one side.

Before using, note the appearance of the medicine.

Every medicine should be kept out of reach of children.

8. DOSAGE AND HOW TO USE

Patient selection for *MET*ex14 skipping alterations

*MET*ex14 skipping should be confirmed by a validated test method, using nucleic acids isolated from plasma or tumour specimens.

Recommended dosage

The recommended dose of TEPMETKO™ is 500 mg (2 tablets) once daily with food (equivalent to 450 mg of tepotinib). The patient should administer TEPMETKO™ at approximately the same time each day. Treatment should continue until disease progression or unacceptable toxicity

If a daily dose is missed, it 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™, patients should take the next dose at the scheduled time.

Dose modification for adverse reactions
The recommended dose reduction of TEPMETKO™ for the management of adverse reactions is 250 mg orally once daily. The recommended dosage modifications of TEPMETKO™ for adverse reactions are provided in Table 2.

Table 2. Recommendation for dose change and / or permanent discontinuation due to 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™.
Other adverse reactions	Grade 3 or higher	Reduce TEPMETKO™ to 250 mg until the adverse reaction recovers to ≤ Grade 2. A temporary interruption of TEPMETKO™ treatment for no more than 21 days can also be considered.

Renal impairment
No dose adjustment is recommended in patients with mild or moderate renal impairment (creatinine clearance 30 to 89 mL/min) (see "Pharmacokinetics"). The pharmacokinetics and safety of tepotinib in patients with severe renal impairment (creatinine clearance below 30 mL/min) have not been studied; therefore, the use of TEPMETKO™ in this group of patients is not recommended.

Hepatic impairment
No dose adjustment is recommended in patients with mild (Child Pugh Class A) or moderate (Child Pugh Class B) hepatic impairment (see "Pharmacokinetics"). The pharmacokinetics and safety of tepotinib in patients with severe hepatic impairment (Child Pugh Class C) have not been studied; therefore, the use of TEPMETKO™ in this group of patients is not recommended.

Elderly
No dose adjustment is necessary in patients aged 65 years and above (see "Pharmacokinetics"). Of 255 patients with *MET*ex14 skipping alterations in the VISION study who received 500 mg tepotinib hydrochloride hydrate once daily, 79% were 65 years or older, and 8% were 85 years or older.

Paediatric population
Safety and effectiveness of TEPMETKO™ in paediatric patients below 18 years of age have not been established; therefore, the use of TEPMETKO™ in this group of patients is not recommended.

Administration
TEPMETKO™ is for oral use. Tablets should be swallowed whole.

9. ADVERSE REACTIONS

The safety profile of TEPMETKO™ reflects exposure to tepotinib in 448 patients with various solid tumours enrolled in five open-label, single-arm studies, in which patients received tepotinib hydrochloride hydrate as a single agent at a dose of 500 mg once daily. This includes 255 patients with advanced NSCLC harbouring *MET*ex14 skipping alterations included in the main clinical study (VISION). Patient characteristics in the VISION study were: median age of 72 years (range: 41 to 94 years); age less than 65 years 21%; 48% male, 52% female; 67% White, 28% Asian. The median duration of exposure in this study was 22.3 weeks (range 0 to 188 weeks).

The most common adverse reactions observed in the VISION study were oedema, mainly peripheral oedema (60.0% of patients), nausea, diarrhea, increase in creatinine and hypoalbuminaemia. Most common serious adverse reactions were reported for generalised oedema (2.0%) and peripheral oedema (2.4%).

Peripheral oedema was the most frequent cause of permanent treatment discontinuation (3,5%), temporary treatment discontinuation (16,9%) or dose reduction (14.1%).

Adverse reactions are presented by system organ class and frequency. Frequencies are defined as: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000).

Table 3. Adverse reactions in patients with NSCLC harbouring *MET*ex14 skipping alterations (VISION)

System organ class/Adverse reaction	Frequency category	{Tradename} N=255	
		All grades n (%)	Grade ≥ 3 n (%)
General disorders and administration site conditions			
Oedema[a]	Very common	178 (69.8)	24 (9.4)
Gastrointestinal disorders			
Nausea	Very common	68 (26.7)	2 (0.8)
Diarrhoea	Very common	67 (26.3)	1 (0.4)
Vomiting	Very common	33 (12.9)	3 (1.2)
Metabolism and nutrition disorders			
Hypoalbuminaemia[b]	Very common	61 (23.9)	14 (5.5)
Hepatobiliary disorders			
Increase in alanine aminotransferase (ALT)	Very common	29 (11.4)	8 (3.1)
Increase in aspartate aminotransferase (AST)	Common	19 (7.5)	3 (1.2)
Investigations			
Increase in creatinine[c]	Very common	66 (25.9)	1 (0.4)
Increase in amylase[d]	Common	22 (8.6)	8 (3.1)
Increase in lipase	Common	18 (7.1)	9 (3.5)
Respiratory, thoracic and mediastinal disorders			
ILD[e]	Common	6 (2.4)	1 (0.4)

a includes terms oedema peripheral, oedema, generalised oedema, oedema genital, face oedema, localised oedema, periorbital oedema, peripheral swelling, scrotal oedema
b includes terms hypoalbuminaemia, blood albumin decreased
c includes terms blood creatinine increased, hypercreatinaemia
d amylase increased, hyperamylasaemia
e includes terms interstitial lung disease, pneumonitis, acute respiratory failure

Description of selected adverse reactions

Interstitial lung disease

Interstitial lung disease (ILD) or ILD-like reactions were reported in the clinical study program in advanced NSCLC patients with *MET*ex14 skipping alterations who received tepotinib monotherapy at the recommended dosage regimen. For details and clinical recommendations, see “Dosage and how to use” and “Warning and precautions”.

Increase in ALT and/or AST

Increases in ALT and/or AST were mostly non-serious and of low grade. ALT and/or AST increase did not lead to permanent study drug discontinuation and infrequently led to temporary discontinuation or dose reduction.

Based on laboratory values, a worst-on-treatment increase of at least 1 grade was observed for 42.0% of patients for ALT and 32.9% of patients for AST in the VISION study An increase to grade 3 or higher occurred in 3.9% of patients for ALT and 2.4% of patients for AST.

Increase in creatinine
Based on laboratory values, shifts of at least 1 grade in creatinine were documented for 52,9% of patients; one patient had a shift to a grade 3 creatinine increase. The observed increases in creatinine are thought to occur due to competition of renal tubular secretion (see "Warning and precautions").

Increase in amylase or lipase
Increases in amylase or lipase were generally asymptomatic and not associated with pancreatitis and could be managed without dose reduction.

Based on laboratory values, a worst-on-treatment increase of at least 1 grade was observed for 21.6% of patients for amylase and 17.3% of patients for lipase in the VISION study. An increase to grade 3 or higher occurred in 4,3% of patients for amylase and 3.5% of patients for lipase.

Warning: this product is a new medicine, and although research has indicated acceptable efficacy and safety, even if indicated and used correctly, unpredictable or unknown adverse events may occur. In this case, notify adverse events through the VigiMed System, available on the Anvisa Portal.

10. OVERDOSAGE

Tepotinib hydrochloride hydrate has been investigated at doses up to 1,400 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 poisoning call 0800 722 6001, if you need more guidance.

LEGAL WORDING

M.S. 1.0089.0414
Pharmacist in charge: Alexandre Canellas de Souza CRF-RJ nº 23277

Manufactured by:
Merck Healthcare KGaA
Darmstadt – Germany

Packed by:
Ares Trading Uruguay S.A.
Montevideu – Uruguay

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Rio de Janeiro - RJ - CEP 22710-571

SALE UNDER MEDICAL PRESCRIPTION.
This package insert was approved by Anvisa on 28/jun/2021.

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HOW SUPPLIED
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ORAL ROUTE
ADULT USE

COMPOSITION
Each film-coated tablet contains:
tepotinib hydrochloride hydrate – 250 mg (equivalent to 225 mg tepotinib).
Excipients: mannitol, colloidal silicon dioxide, crospovidone, magnesium stearate, microcystalline cellulose, hypromellose, lactose monohydrate, macrogol, triacetin, red iron oxides, titanium dioxide.

INFORMATION TO PATIENT

1. WHAT IS THIS MEDICINE INDICATED FOR?

TEPMETKO™ is used to treat lung cancer in adults which has spread to other parts of the body and has an alteration in the mesenchymal-epithelial transition factor gene (*MET*).

2. HOW DOES THIS MEDICINE WORK?

TEPMETKO™ contains the active substance tepotinib which belongs to a group of medicines called protein kinase inhibitors which are used to treat cancer.

The alteration in the *MET* gene can lead to a dysfunctional protein which can lead uncontrolled cell growth and cancer. By blocking this dysfunctional protein TEPMETKO™ may slow or stop the cancer from growing. It may also help to shrink the cancer.

3. WHEN SHOULD I DO NOT USE THIS MEDICINE?

Do not take TEPMETKO™ if you are allergic to tepotinib or any of the other ingredients of this medicine (listed in "Composition").

4. WHAT SHOULD I KNOW BEFORE USING THIS MEDICINE?

Warnings and precautions
Talk to your doctor before taking TEPMETKO™.

Lung or breathing problems
TEPMETKO™ may cause sudden breathing difficulties that may be associated with fever and cough. Tell your doctor right away if you develop any new or worsening symptoms (see "What are the harms that this medicine may cause?"). Your doctor may need to treat you with other medicines and interrupt your TEPMETKO™ treatment.

Contraception
Men and women should use effective contraception during TEPMETKO™ treatment and for at least 1 week after the last dose. TEPMETKO™ can harm the unborn baby.

Patients with kidney or liver problems
If you have problems with your kidney or liver, talk to your doctor before using this medicine.

TEPMETKO™ can cause abnormal liver function test results. Your doctor will order the necessary tests to check your liver function before starting treatment and during treatment with TEPMETKO™.

Children and adolescents
TEPMETKO™ has not been studied in patients below the age of 18 years; therefore, the use of TEPMETKO ™ in this group of patients is not recommended.

Pregnancy and breast-feeding
Pregnancy: **This medicine should not be used by pregnant women without medical advice. Inform your physician immediately if you suspect a pregnancy.**
TEPMETKO™ may harm the unborn baby. You should use an effective method of contraception to avoid becoming pregnant during TEPMETKO™ treatment and for at least 1 week after the last dose. If you are male, you should use barrier contraception to prevent your partner from getting pregnant, whilst you are treated with TEPMETKO™ and for at least 1 week after the last dose.

Breast-feeding: Do not breast-feed during treatment with TEPMETKO™ unless advised by your doctor.

Driving and using machines
TEPMETKO™ has no influence on the ability to drive or use machines.

Other medicines and TEPMETKO™

The following medicines may reduce how well TEPMETKO™ works:
- cabamazepine or phenytoin – used for seizures or fits
- rifampicin – used for tuberculosis
- St. John's wort – a herbal medicine used for depression

TEPMETKO™ may affect how well the following medicines work and/or increase side effects of these medicines:
- digoxin – used for irregular heart beat or other heart problems
- metformin – used to treat diabetes mellitus

Inform your doctor or surgeon-dentist if you are using some other medicine.
Do not use any medicine without your doctor's knowledge. It can be dangerous to your health.

Warning: Contains lactose (4.37 mg of lactose monohydrate/tablet). This medicine should not be used by people with glucose-galactose malabsorption syndrome. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

5. WHERE, HOW AND FOR HOW LONG CAN I KEEP THIS MEDICINE?

Store at room temperature (between 15 ° C and 30 ° C) in the original package to protect from moisture.
Batch number and manufacture and expiry dates: see packing.
Do not use the medicine with expired shelf life. Keep the medicine in the original packing carton.
Characteristics of the medicine: white-pink, oval and biconvex coated tablets, with "M" engraving on one side.

Before using, note the medicine's appearance. If you notice any change in the appearance of the medicine still in the period of validity, see your doctor or pharmacist to check if you can use it.
Every medicine should be kept out of reach of children.

6. HOW DO I USE THIS MEDICINE?

The recommended dose is 2 tablets of TEPMETKO™ (500 mg) once daily. In case of side effects, your doctor may advise you to reduce the dose to 1 tablet daily or interrupt the treatment for some days.

TEPMETKO™ tablets are for oral use. Swallow the tablets whole without chewing together with food or shortly after a meal. Take your dose of TEPMETKO™ at about the same time each day.

If you vomit after taking a dose of TEPMEKTO™, take your next dose at your regular scheduled time.

Follow the guidance of your doctor, always respecting the timing, dose and duration of treatment.
Do not stop the treatment without the awareness of your doctor.
This medicine should not be broken, opened, or chewed.

7. WHAT SHOULD I DO WHEN I FORGET TO USE THIS MEDICINE?

If you miss a dose of TEPMETKO™, take it as soon as you remember. If your next dose is due within 8 hours, skip the missed dose and take your next dose at your regular time.
In case of doubts, seek guidance from the pharmacist or your doctor, or surgeon-dentist.

8. WHAT ARE THE HARMS THAT THIS MEDICINE MAY CAUSE?

Like all medicines, TEPMETKO™ can cause side effects, although not everybody gets them.

Lung or breathing problems
Tell your doctor right away if you develop any new or worsening symptoms such as sudden breathing difficulties, cough or fever. These may be symptoms of a serious lung condition (interstitial lung disease) which needs immediate medical attention. This side effecte is common (may affect 1% to 10% of patients using this medicine).

Very common side effects (occurring in more than 10% of patients using this medicine):
- Swelling caused by fluid build-up in the body (oedema)
- Nausea
- Diarrhoea
- Vomiting
- Higher than normal blood levels of creatinine
- Reduced protein levels in the blood
- Higher than normal blood levels of a certain liver enzyme (alanine aminotransferase)

Common side effects (occurring in 1% to 10% of patients using this medicine):
- Higher than normal blood levels of a certain liver enzyme (aspartate aminotransferase), amylase or lipase.

Attention: This product is a new medicine, and although research has indicated acceptable efficacy and safety, even if indicated and used correctly, unpredictable or unknown adverse events may occur. In that case, tell your doctor or surgeon-dentist.

9. WHAT TO DO IF SOMEONE USES A QUANTITY HIGHER THAN INDICATED FOR THIS MEDICINE?

Symptoms of overdose with TEPMETKO™ have not been identified. If you have taken more TEPMETKO™ than you should, talk to your doctor.

In case of using a large amount of this medicine, quickly seek medical help and take the packaging or leaflet of the medicine with you, if possible. Call 0800 722 6001, if you need more guidance.

LEGAL WORDING

M.S. 1.0089.0414

Pharmacist in charge: Alexandre Canellas de Souza CRF-RJ nº 23277

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Darmstadt – Germany

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SALE UNDER MEDICAL PRESCRIPTION.

This package insert was approved by Anvisa on 28/jun/2021.