TEPMETKO tablet 225 mg

(Tepotinib 225 mg film-coated tab. ; equivalent to 250 mg tepotinib hydrochloride hydrate 250 mg)

Indication

: Treatment of patients with locally advanced or metastatic non-small cell lung cancer harboring confirmed *MET* exon 14 deletion (skipping).

The efficacy of Tepmetko was based on the response rate and duration of response, and there are no data demonstrating improvement in survival.

Dosage and administration

Patient selection for MET exon 14 deletion (skipping) alterations

MET exon 14 deletion (skipping) should be confirmed by a validated test method, using nucleic acids isolated from plasma or tumour specimens.

Recommended dosage

The recommended dose is 450 mg tepotinib (2 tablets) once daily (equivalent to 500 mg tepotinib hydrochloride hydrate). Treatment should continue as long as clinical benefit is observed
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.

Dose modification for adverse reactions

The recommended dose reduction level for the management of adverse reactions is 225 mg (1 tablet) daily. Detailed recommendations for dose modification are provided in Table.

Table. Recommended TEPMETKO Dosage Modifications for Adverse Reactions

Adverse Reaction	**Severity**	**Dose Modification**
Interstitial Lung Disease (ILD)	Any grade	Withhold Tepmetko if ILD is suspected. Permanently discontinue Tepmetko if ILD is confirmed.

Adverse Reaction	Severity	Dose Modification
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 225 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). The pharmacokinetics and safety of tepotinib in patients with severe renal impairment (creatinine clearance below 30 mL/min) have not been studied.

Hepatic impairment

No dose adjustment 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.

Elderly

No dose adjustment is necessary in patients aged 65 years and above. Of 255 patients with *MET* exon 14 deletion (skipping) alterations in the VISION study who received 450 mg tepotinib once daily, 79% were 65 years or older, and 8% were 85 years or older.

Administration

Tepmetko is for oral use. Tablets should be taken with food and should be swallowed whole.

Precautions in use

1. Warnings

(1) 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. 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

2. Contraindications

(1) Hypersensitivity to Active drug substance or to any of the excipients of the tablet.
(2) Since Tepmetko contains lactose, it should not be administered to patients with genetic problems such as galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption, etc.

3. 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 as a single agent at a dose of 450 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, diarrhoea, 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%).

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

System organ class/Adverse reaction	Tepmetko N=255	
	All grades n (%)	Grade ≥ 3 n (%)
General disorders and administration site conditions		
Oedema[a]	178 (69.8)	24 (9.4)
Gastrointestinal disorders		
Nausea	68 (26.7)	2 (0.8)
Diarrhoea	67 (26.3)	1 (0.4)
Vomiting	33 (12.9)	3 (1.2)
Metabolism and nutrition disorders		
Hypoalbuminaemia[b]	61 (23.9)	14 (5.5)
Hepatobiliary disorders		
Increase in alanine aminotransferase (ALT)	29 (11.4)	8 (3.1)
Increase in alkaline phosphatase (ALP)	20 (7.8)	0 (0)
Increase in aspartate aminotransferase (AST)	19 (7.5)	3 (1.2)
Investigations		
Increase in creatinine[c]	66 (25.9)	1 (0.4)
Increase in amylase[d]	22 (8.6)	8 (3.1)
Increase in lipase	18 (7.1)	9 (3.5)
Respiratory, thoracic and mediastinal disorders		
ILD[e]	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 repiratory failure

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. (see sections Dosage and administration, General cautions)

Increase in liver enzymes

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 (see sections Dosage and administration, General cautions).

Increases in ALP were mainly non-severe, non-serious and asymptomatic in clinical studies. ALP increase did not lead to any dose reductions, temporary discontinuation, or permanent discontinuation. The observed ALP increase was not associated with cholestasis. Based on laboratory values, a worst-on-treatment increase of at least 1 grade was observed for 47.5% of patients for ALP in the VISION study. An increase to grade 3 or higher occurred in 1.6% of patients.

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 section General cautions).

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.

4. General cautions

(1) Embryo-foetal toxicity

Tepmetko can cause foetal harm when administered to pregnant women (see Pregnancy, Lactation and Fertility)
Women of childbearing potential or male patients with female partners of childbearing potenti al 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.

(2) Increase in ALT and/or AST

Increases in ALT and/or AST have been reported.

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 adjustment is recommended.

(3) Interpretation of laboratory tests

Nonclinical studies suggest that tepotinib or its main metabolite inhibit the renal tubular transporter proteins organic cation transporter (OCT) 2 and multidrug and toxin extrusion transporters (MATE) 1 and 2 (see section Information for specialist, pharmacokinetics information). Creatinine is a substrate of these transporters, and the observed increases in creatinine (see section 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.

(4) Effects on the ability to drive and use machines

Tepmetko has no influence on the ability to drive and use machines.

5. Interactions

(1) P-gp inducers

Tepotinib is a substrate for P-glycoprotein (P-gp) (see section Information for specialist, pharmacokinetics information). 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.

(2) P-gp substrates

Tepotinib can inhibit the transport of sensitive substrates of P-gp (see section Information for specialist, pharmacokinetics information). 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.

(3) BCRP substrates

Tepotinib can inhibit the transport of sensitive substrates of the breast cancer resistance protein (BCRP) (see section Information for specialist, pharmacokinetics information). Monitoring of the clinical effects of sensitive BCRP substrates is recommended during co-administration with Tepmetko.

(4) Metformin

Based on *in vitro* data, tepotinib or its metabolite may have the potential to alter the exposure to co-administered metformin in humans through inhibition of metformin’s renal excretion or hepatic uptake mediated via OCT1 and 2 and MATE1 and 2 (see section Information for specialist, pharmacokinetics information). Monitoring of the clinical effects of metformin is recommended during co-administration with Tepmetko.

6. Pregnancy, lactation and fertility

Contraception in males and females
Pregnancy testing is recommended in women of childbearing potential prior to initiating treat ment 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 d uring Tepmetko treatment and for at least 1 week after the last dose.

(1) Pregnancy

There are no clinical data on the use of Tepmetko in pregnant women. Studies in animals have shown teratogenicity (see section Information for specialist, toxicity test information). 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 re quires 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.

(2) Lactation

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.

(3) 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 section Information for specialist, toxicity test information).

7. Paediatric population

Safety and effectiveness of Tepmetko in paediatric patients below 18 years of age have not been established.

8. 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.

9. Cautions in storage and handling

(1) Keep out of reach of children.

(2) Storing the pharmaceutical into another container may cause accidents or not be appropriate to keep its quality.

10. Information for specialists

(1) Pharmacological action

Mode 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 signaling 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.

(2) Pharmacokinetics information

Absorption

A mean absolute bioavailability of 71.6% was observed for a single 450 mg dose of tepotinib administered in the fed state; the median time to C_{max} 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 C_{max} by 2-fold.

Distribution

In human plasma, tepotinib is highly protein bound (98%). 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.

Metabolism

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 450 mg tepotinib, 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 450 mg tepotinib, median accumulation was 2.5-fold for C_{max} and 3.3-fold for AUC_{0-24h}.

Dose and time dependence

Tepotinib exposure increases dose-proportionally over the clinically relevant dose range up to 450 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 450 mg, tepotinib exposure was similar in healthy subjects and patients with mild hepatic impairment (Child-Pugh Class A), and was slightly lower (-13% AUC and -29% C_{max}) 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 interactions

● *Clinical studies*

Effect of tepotinib on CYP3A4 substrates: Multiple administrations of 450 mg tepotinib 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 450 mg orally once daily had a mild effect on the pharmacokinetics of the sensitive P-gp substrate dabigatran etexilate, increasing its AUC_t by approximately 50% and C_{max} 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, OCT1 and 2, organic-anion-transporting polypeptide (OATP) 1B1 and MATE1 and 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 OATP1B3, 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.

(3) Clinical trial information

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 had an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 to 1 and were either treatment-naïve or had progressed on 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 (range 41 to 94), 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%). Most patients were ≥ 65 years of age (82%) and 45% of patients were ≥ 75 years of age.

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 450 mg tepotinib 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. 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[a] [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, months[a] [95% CI]	8.9 [8.2, 11.0]
Median overall survival time, months[a] [95% CI]	17.6 [15.0, 21.0]

IRC=Independent Review Committee, ITT=Intent-to-treat, CI=confidence interval

a 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.

(4) Toxicity test information

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 Tepotinib 450 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 Tepotinib 450 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 450 mg Tepotinib 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 450 mg Tepotinib 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, a nd 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 2 5 mg tepotinib hydrochloride hydrate per kg per day during organogenesis. Two malformed fo etuses 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 Tepotinib 450 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.