Prescribing Information

TEPMETKO

Composition

Active substances

Tepotinib as tepotinib hydrochloride hydrate

Excipients

Core: mannitol, microcrystalline cellulose, crospovidone, magnesium stearate, colloidal silicon dioxide
Film: hypromellose, titanium dioxide, lactose monohydrate, polyethylene glycol, triacetin, red iron oxide

Pharmaceutical form and active substance quantity per unit

Each film-coated tablet contains 225 mg Tepotinib (as 250 mg tepotinib hydrochloride hydrate).

Indications/Usess

Tepmetko is indicated for the treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) harbouring a *MET* tyrosine kinase receptor exon 14 (*MET*ex14) skipping mutation.

Dosage/Administration

Treatment must be initiated and supervised by a physician experienced in the use of anticancer therapies. *MET*ex14 skipping alterations should be confirmed by a validated test method, using nucleic acids isolated from plasma or tumour specimens.
Tepmetko is for oral use.

Usual dosage

The recommended dose of Tepmetko is 450 mg tepotinib (2 film-coated tablets) taken once daily.

Duration of treatment

Treatment should continue as long as clinical benefit is observed.

Dose adjustment following undesirable effects

Recommended dose adjustments for Tepmetko for undesirable effects are provided in Table 1.

Table 1: Dose adjustments following undesirable effects

Adverse Reaction	**Severity**	**Dose Adjustment**
Interstitial Lung Disease (ILD) /ILD-like reactions (see section *Warnings and Precautions)*	Any grade	Withhold Tepmetko if ILD is suspected. Permanently discontinue Tepmetko if ILD is confirmed.
Increased ALT and/or AST without increased total bilirubin (see section *Warnings and Precautions*)	Grade 3	Withhold Tepmetko until recovery to baseline ALT/AST. If recovered to baseline within 7 days, then resume Tepmetko at the same dose; otherwise resume Tepmetko at a reduced dose.
	Grade 4	Permanently discontinue Tepmetko.
Increased ALT and/or AST with increased total bilirubin in the absence of cholestasis or hemolysis (see section *Warnings and Precautions*)	ALT and/or AST greater than 3 times ULN with total bilirubin greater than 2 times ULN	Permanently discontinue Tepmetko.
Other adverse reactions (see section *Undesirable effects)*	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.

Special dosage instructions

Patients with impaired hepatic function

No dose adjustment is recommended in patients with mild (Child Pugh Class A) or moderate (Child Pugh Class B) hepatic impairment (see section *Pharmacokinetics*). The pharmacokinetics and safety of tepotinib in patients with severe hepatic impairment (Child Pugh Class C) have not been studied.

Patients with impaired renal function

No dose adjustment is recommended in patients with mild or moderate renal impairment (creatinine clearance 30 to 89 mL/min) (see section *Pharmacokinetics*). The pharmacokinetics and safety of tepotinib in patients with severe renal impairment (creatinine clearance below 30 mL/min) have not been studied.

Elderly patients

No dose adjustment is necessary in patients aged 65 years and above (see section *Pharmacokinetics*). Of 313 patients with *MET*ex14 skipping alterations in the VISION study, 79% were 65 years or older, and 8% were 85 years or older.

Children and adolescents

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

Delayed administration

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.

Mode of administration

The tablet(s) should be taken together with food and should be swallowed whole.

Administration to patient who have difficulty swallowing solids

If the patient is unable to swallow, the tablets can be dispersed in 30 mL of non-carbonated water. No other liquids should be used or added. Drop the tablets in a glass with water without crushing, stir until the tablets dispersed into small pieces (the tablet will not completely dissolve) and swallow the dispersion immediately together with food. Rinse with additional 30 mL to ensure that no residues remain in the glass and drink immediately.
If an administration via a naso-gastric tube (with at least 8 French gauge) is required, disperse the tablets in 30 mL of non-carbonated water as described above. Administer the 30 mL of dispersion immediately together with food as bolus as per naso-gastric tube manufacturer's instructions. Immediately rinse twice with 30 mL of non-carbonated water each to ensure that no residues remain in the syringe.

Contraindications

Hypersensitivity to the active substance or to any of the excipients listed under *Composition*.

Warnings and precautions

Interstitial lung disease/pneumonitis

Interstitial lung disease (ILD) or ILD-like reactions which may be fatal 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 section *Undesirables effects)*.

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 appropriately (see section *Dosage/Administration*).

Hepatotoxicity

Increases in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) have been reported (see section *Undesirable effects*). Liver enzymes (including ALT, AST and bilirubin) should be monitored prior to initiation of treatment with Tepmetko, then every two weeks during the first three months of treatment and then once monthly or as clinically indicated. in patients found to have elevated transaminases or bilirubin levels, more frequently tests should be performed. Depending on severity of adverse drug reactions, Tepmetko must be temporarily discontinued, the dose reduced or discontinued permanently (see section *Dosage/Administration*).

Embryofoetal toxicity

Tepmetko can cause foetal harm when administered to pregnant women (see section *Pregnancy, lactation*).

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

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

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

QTc prolongation

In the main clinical study, QTc prolongation was reported in a limited number of patients (see section *Undesirable effects*). In patients at risk of developing QTc prolongation, including patients with known long QT syndrome or clinically relevant bradyarrhythmia, ECG monitoring is recommended as clinically indicated.

Increase in creatinine

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) 2 (see section *Interactions*). Creatinine is a substrate of these transporters, and the observed increases in creatinine (see section *Undesirable effects*) may be the result of inhibition of active tubular secretion rather than actual 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. Alternative markers of renal function should be considered in line with local clinical practice if persistent elevations in serum creatinine are observed.

Oncogenic drivers

The efficacy and safety of Tepmetko have not been studied in patients with EGFR or ALK tumour aberrations in line with the mutual exclusivity of oncogenic drivers in NSCLC (see section *Clinical efficacy*). For recommended patient selection prior to Tepmetko treatment, see section *Dosage/Administration*.

Lactose

Patients suffering from galactose intolerance, complete lactase deficiency or glucose-galactose-malabsorption syndrome (rare hereditary diseases) should not use this drug.

Interactions

Effect of other medicinal products on the pharmacokinetics of tepotinib

Avoid concomitant administration

CYP3A- and/or P-gp-inducers:

In healthy participants, co-administration of a single 450 mg tepotinib dose with the strong CYP3A-/P-gp-inducer carbamazepine (300 mg twice daily during 14 days) resulted in a decrease of the AUC_{inf} of Tepotinib by 35% (geometric mean ratio of 65.2%, 90% confidence interval of 59.8% to 71.0%) and of the C_{max} of tepotinib by 11% (geometric mean AUC ratio of 89.3%, 90% confidence interval of 83.4% to 95.6%), compared to administration of tepotinib alone.

This could reduce the efficacy of Tepmetko. Concomitant administration of Tepmetko with strong CYP3A- and/or P-gp-inducers (e.g. carbamazepine, phenytoin, rifampicin, St. John's wort) should be avoided.

Strong CYP3A- and P-gp-inhibitors:

In healthy participants, co-administration of a single 450 mg dose tepotinib with the strong CYP3A- and P-gp-inhibitor itraconazole (200 mg once per day during 11 days) resulted in a 22% increase in the AUC_{inf} of tepotinib (geometric mean ratio of 122.4%, 90% confidence interval of 111.5% to 134.3%), with no change in the C_{max} of tepotinib, compared with tepotinib alone.

This could lead to increased or increased occurrence of adverse events. Therefore, concomitant administration of Tepmetko with potent CYP3A- and P-gp-inhibitors should be done with caution and monitoring for adverse events.

Other interactions

Acid-reducing agents:

Co-administration of omeprazole (40 mg daily for 5 days) had no marked effect on the pharmacokinetic profile of tepotinib when administered under fed conditions.

Effect of tepotinib on the pharmacokinetics of other medicinal products

Avoid concomitant administration

P-gp substrates:
Tepotinib can inhibit the transport of sensitive substrates of P-gp, which can lead to more frequent or severe adverse reactions of these substrates. Multiple administrations of tepotinib 450 mg orally once daily together with the sensitive P-gp substrate dabigatran etexilate, increased its AUC_t 1.5-fold and its C_{max} 1.4 fold. Concomitant administration of tepotinib with substrates of P-gp with a narrow therapeutic index (e.g. digoxin, dabigatran) should be avoided. If co-administration cannot be avoided, the product information of the respective medicinal product should be consulted with regard to possible measures (such as dose adjustments or monitoring of undesirable effects).

Caution when concomitant administration
BCRP substrates:
Based on in vitro studies, tepotinib can inhibit the transport of sensitive substrates of the breast cancer resistance protein (BCRP). Monitoring of the clinical effects of sensitive BCRP substrates (e.g. rosuvastatin) is recommended during co-administration with Tepmetko.

OCT2- and MATE2-substrates:
Based on in vitro data, tepotinib or its metabolite have the potential to increase the AUC of co-administered OCT2- and MATE2 substrates, such as metformin in humans, by inhibiting the renal excretion of these agents mediated via organic cation transporter (OCT) 2 and multidrug and toxin extrusion transporter (MATE) 2. No clinically relevant differences in glucose levels were observed when metformin (an OCT2 and MATE2 substrate) was coadministered with tepotinib. Monitoring of the clinical effects of metformin is recommended during co-administration with Tepmetko.
The inhibition of OCT2 and MATE2 by tepotinib or its metabolite can also contribute to an increase in creatinine (see section *Warnings and precautions*).

OATP1B1 substrates:
Based on in vitro data, Tepotinib or its active metabolite can inhibit the transport of sensitive substrates of the organic anion transporter polypeptide (OATP) 1B1. Monitoring of the clinical effects of sensitive OATP1B1 substrates (e.g. rosuvastatin) is recommended during co-administration with Tepmetko.

Other interactions
OATP1B3 and organic anion transporter (*OAT) 1 and 3 substrates:*
Based on in vitro data, tepotinib, at clinically relevant concentrations, poses a remote risk of bile salt export pump (BSEP) inhibirion but not OATP1B3 or OAT1 and 3 inhibition.

UDP-glucuronosyltransferase (UGT):
Based on in vitro data, tepotinib or its major circulating metabolite at clinically relevant concentrations is not expected to inhibit UGT1A1, 1A9, 2B17 UGT1A3/4/6, and 2B7/15.

CYP 450 enzymes:

Based on in vitro data, tepotinib or its major circulating metabolite at clinically relevant concentration is not expected to inhibit CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP2E1 or induce CYP1A2, and 2B6.
Multiple administrations of 450 mg tepotinib orally once daily had no clinically relevant effect on the PK of the sensitive CYP3A4 substrate midazolam.

Pregnancy, 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 must use effective contraception during Tepmetko treatment and for at least 1 week after the last dose.
Male patients with female partners of childbearing potential must 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 section *Preclinical data*). Based on the mechanism of action and findings in animals, Tepmetko can cause foetal harm when administered to pregnant women.
Tepmetko must not be used during pregnancy, unless the clinical condition of the woman requires treatment. Women of childbearing potential or male patients with female partners of childbearing potential must be advised of the potential risk to a foetus.

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. A risk to the infant cannot be excluded. Breast-feeding must be discontinued during treatment with Tepmetko and for at least 1 week after the last dose.

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 *Preclinical data*).

Effects on ability to drive and use machines

No corresponding studies have been performed. Patients are to be advised that during treatment with Tepmetko fatigue, nausea and vomiting can occur.

Undesirable effects

Summary of the safety profile

The safety profile of Tepmetko reflects exposure to tepotinib in 506 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 313 patients with advanced NSCLC harbouring *MET*ex14 skipping alterations included in the main clinical study (VISION).

The most common adverse reactions observed in the main clinical study (VISION) were oedema (80.2% of patients), mainly peripheral oedema (72.5%), nausea (31%), diarrhoea (28.8%), increase in creatinine (30.4%),hypoalbuminaemia (33.9%) and fatigue (15.7%). Most common serious adverse reactions were reported for generalised oedema (1.9%) and peripheral oedema (3.2%).

Peripheral oedema was the most frequent cause of permanent treatment discontinuation (5.4%), temporary treatment discontinuation (19.8%) or dose reduction (15.7%).

List of adverse reactions

The following definitions apply to the frequency terminology used hereafter:

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)

Frequency not known (cannot be estimated from the available data)

Table 2: Adverse reactions in patients with solid tumours receiving the target dose

System organ class/Adverse reaction	**Tepmetko N=506**			
	All grades		**Grade ≥ 3**	
	n (%)	**Frequency category**	**n (%)**	**Frequency category**
Metabolism and nutrition disorders				
Hypoalbuminaemia [a]	150 (29.6)	Very common	25 (4.9)	Common
Appetite decreased	116 (22.9)	Very common	10 (2.0)	Common
Respiratory, thoracic and mediastinal disorders				
Dyspnoea [b]	97 (19.2)	Very common	11 (2.2)	Common
Pleural effusion	60 (11.9)	Very common	14 (2.8)	Common
ILD/ILD-like reactions [c],*	10 (2.0)	Common	1 (0.2)	Uncommon

Gastrointestinal disorders				
Diarrhoea	141 (27.9)	Very common	7 (1.4)	Common
Nausea	135 (26.7)	Very common	7 (1.4)	Common
Vomiting	73 (14.4)	Very common	7 (1.4)	Common
Increase in amylase [d]	44 (8.7)	Common	13 (2.6)	Common
Increase in lipase [e]	44 (8.7)	Common	23 (4.5)	Common
Hepatobiliary disorders				
Increase in alanine aminotransferase (ALT)	77 (15.2)	Very common	16 (3.2)	Common
Increase in alkaline phosphatase (ALP)	50 (9.9)	Common	5 (1.0)	Common
Increase in aspartate aminotransferase (AST)	69 (13.6)	Very common	17 (3.4)	Common
Renal and urinary disorders				
Increase in creatinine [f]	123 (24.3)	Very common	7 (1.4)	Common
General disorders and administration site conditions				
Oedema [g]	357 (70.6)	Very common	52 (10.3)	Common
Fatigue	95 (18.8)	Very common	12 (2.4)	Common
Generalised oedema	29 (5.7)	Common	10 (2.0)	Common

* ILD as per Integrated Assessment
a includes terms hypoalbuminaemia, blood albumin decreased
b includes terms dyspnoea, dyspnoea at rest, exertional dyspnoea
c includes terms interstitial lung disease, pneumonitis, acute respiratory failure, lung fibrosis and radiation pneumonitis
d includes terms amylase increased, hyperamylasaemia
e includes terms lipase increased, hyperlipasaemia
f includes terms blood creatinine increased, hypercreatinaemia
g includes terms oedema peripheral, oedema, oedema genital, face oedema, localised oedema, periorbital oedema, peripheral swelling, scrotal oedema

Description of selected adverse reactions

Interstitial lung disease/pneumonitis

Interstitial lung disease (ILD) or ILD-like adverse reactions have been reported in 8 patients (2.6%) with advanced NSCLC with METex14 skipping alterations who received tepotinib monotherapy at the recommended dosage regimen (n=313), including 1 case of grade 3 or higher; serious cases occurred in 4 patients (1.3%), 1 case was fatal (see sections *Dosage/Administration* and *Warnings and precautions*).

Hepatoxicity

Hepatotoxicity has occurred in patients treated with Tepmetko. In the main clinical study, an increase of at least 1 grade was observed for 49.5% of patients for ALT and 39.9% of patients for AST. An increase to grade 3 or higher occurred in 4.9% of patients for ALT and 3.6% of patients for AST. No patients treated with Tepmetko discontinued treatment due to elevated ALT/AST. The median time to onset of an elevated ALT/AST increase to grade 3 or higher was 9.9 weeks (time range 3.1 to 37.4 weeks) (see sections *Dosage/Administration* and *Warnings and precautions*).

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 51.6% of patients for ALP in the main clinical 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 59.9% of patients in the main clinical study; three patients had a shift to a grade 3 creatinine increase. A median increase in serum creatinine of 30% was observed 21 days after initiation of treatment with Tepmetko. The serum creatinine increases persisted throughout treatment and were reversible upon treatment completion (see section *Warnings 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, - an increase of at least 1 grade was observed for 24.9% of patients for amylase and 21.2% of patients for lipase in the main clinical study. An increase to grade 3 or higher occurred in 5.3% of patients for amylase and 5.3% of patients for lipase.

QTc prolongation
In the main clinical study (patients with *MET*ex14 skipping alterations, n=313),; QTcF prolonged to > 500 ms was observed in 8 patients (2.6%) and QTcF prolonged by at least 60 ms from baseline in 19 patients (6.1%) (see section *Warnings and precautions*). The findings were isolated and asymptomatic, the clinical significance is unknown. In an exposure-response QTc analysis, no significant changes in the QTc interval (> 20 ms) were found on average at the therapeutic dose, but a concentration-dependent prolongation was found (see section *Properties/Effects*, *Cardiac electrophysiology*).

Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il/

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, Tepotinib should be withheld and symptomatic treatment initiated.

Properties/Effects

ATC code

L01EX21

Mechanism of action

The mesenchymal-epithelial transition factor (MET) and its ligand, the hepatocyte growth factor (HGF), are involved in carcinogenesis and tumour progression. Oncogenic activation of MET signalling 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 of MET. Tepotinib inhibits HGF-dependent and -independent MET phosphorylation and MET-dependent downstream signalling through the phosphatidylinositol 3-kinase/protein kinase B and mitogen-activated protein kinase/extracellular-signal regulated kinase pathways in a dose-dependent manner.

Pharmacodynamics

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 of MET-dependent tumours from different tumour types. The anti-tumour activity of Tepotinib was particularly pronounced in tumours with oncogenic activation of MET, such as *MET*ex14 skipping.
The contribution of the major circulating metabolite to the anti-tumour activity of tepotinib is considered to be negligible.

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 ranging from 27 mg to 1,261 mg. At the therapeutic dose, no major changes in the QTc interval (> 20 ms) were detected on average, but a concentration-dependent prolongation was found. The effect on the QTc interval at high exposure was not investigated.

Clinical efficacy

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 = 313). Patients had an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 or 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.

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

Patients had a median age of 72 years (range 41 to 94), 51% were female and 49% male. The majority of patients were white (62%), followed by Asian patients (34%) and were never (49%) or former smokers (45%). Most patients were ≥ 65 years of age (79%) and 41% of patients were ≥ 75 years of age.

The majority of patients had stage IV disease (94%), 81% had adenocarcinoma histology. Thirteen percent of the patients had stable brain metastases. Patients received tepotinib as first-line (52%) or second- or later line (48%) therapy.

*MET*ex14 skipping alterations were 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 7.5 months (range 0 to 72 months).

In the initial efficacy analysis 152 adult patients with locally advanced or metastatic NSCLC harbouring *MET*ex14 skipping alterations with a follow up of at least 9 months were evaluated (see Table 3).

Table 3: Clinical outcomes in the VISION study by IRC assessment

Efficacy parameter	**Overall N = 152**	**Treatment-naïve N = 69**	**Previously treated N = 83**
Objective response rate, % [95% CI]	44.7 [36.7, 53.0]	44.9 [32.9, 57.4]	44.6 [33.7, 55.9]
Complete response, %	0	0	0
Partial response, %	44.7	44.9	44.6
Median duration of response, months[a] [95% CI]	11.1 [8.4, 18.5]	10.8 [6.9, NE]	11.1 [9.5, 18.5]
Duration of response[b]			
≥ 6 months, % of responders	72.1	67.7	75.7
≥ 9 months, % of responders	42.6	32.3	51.4
≥ 12 months, % of responders	20.6	16.1	24.3
Median progression-free survival, months[a] [95% CI]	8.9 [8.2, 11.2]	8.5 [6.8, 11.3]	10.9 [8.2, 12.7]
Median overall survival time, months[a] [95% CI]	17.6 [15.0, 21.0]	17.6 [9.7, 29.7]	19.7 [15.0, 21.0]

IRC=Independent Review Committee, CI=confidence interval, ne=not estimable

[a]: Product-limit (Kaplan-Meier) estimates, 95% CI for the median using the Brookmeyer and Crowley method

[b]: A duration of response of ≥ 9 months or ≥ 12 months, respectively, could not be achieved by some patients due to the timing of their inclusion in the study.

In an extended efficacy analysis additional 161 adult patients with locally advanced or metastatic NSCLC harbouring *MET*ex14 skipping alterations were enrolled into the VISION study. Overall, efficacy results refer to 313 patients with a follow up of at least 18 months.

In the overall population of 313 patients, 161 patients showed either a partial (n = 160) or a complete (n = 1) response, resulting in an ORR of 51.4% (95%-CI 45.8, 57.1%). A median DOR of 18.0 months (95%-CI 12.4, 46.4 months) is observed, with 65.8%, 49.7%, and 38.5% out of 161 patients still showing continued response after 6, 9 or 12 months, respectively. A median PFS of 11.2 months (95%-CI 9.5, 13.8 months) and a median OS of 19.6 months (95%-CI 16.2, 22.9 months) was observed.

In 164 treatment naive patients, 94 patients showed either a partial (n = 93) or a complete (n = 1) response resulting in an ORR of 57.3% (95%-CI 49.4, 65.0%). A median DOR of 46.4 months (95%-CI 13.8, ne months) is observed, with 66.0%, 51.1%, and 40.4% out of 94 patients still showing continued response after 6, 9 or 12 months, respectively. A median PFS of 12.6 months (95%-CI 9.7, 17.7 months) and a median OS of 21.3 months (95%-CI 14.2, 25.9 months) was observed.

In 149 previously treated patients, 67 patients showed a partial response resulting in an ORR of 45.0% (95%-CI 36.8, 53.3%). A median DOR of 12.6 months (95%-CI 9.5, 18.5 months) is observed, with 65.7%, 47.8%, and 35.8% out of 67 patients still showing continued response after 6, 9 or 12 months, respectively. A median PFS of 11.0 months (95%-CI 8.2, 13.7 months) and a median OS of 19.3 months (95%-CI 15.6, 22.3 months) was observed.

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.

Pharmacokinetics

Absorption

The pharmacokinetics of tepotinib were evaluated in patients with cancer administered 450 mg once daily unless otherwise specified.

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. At the recommended dosage, the geometric mean (coefficient of variation [CV]

%) steady state C_{max} was 1,291 ng/mL (48.1%) and the steady state AUC_{0-24h} was 27,438 ng·h/mL (51.7%). The median accumulation was 2.5-fold for C_{max} and 3.3-fold for AUC_{0-24h} after multiple daily doses of tepotinib. Based on a population kinetic model, time to steady-state is approximately 5 days.

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).

Metabolism

Approximately half of an orally administered dose (about 48%) is excreted as metabolites. In total, 10 different Phase I and Phase II metabolites were found in humans. In vitro data indicate that CYP3A4 and CYP2C8 are involved in the metabolism of tepotinib but seem not to be the main enzymes responsible for metabolic clearance of tepotinib. However, no other responsible enzymes have been identified.
Only one major circulating plasma metabolite, M506 (a mixture of two enantiomers), was identified in plasma. In a mass balance study, tepotinib and M506 accounted for 55% and 40.4%, respectively, of the AUC of total radioactive material in plasma.
No metabolic pathway accounted for more than 25% of tepotinib elimination. Only one major circulating plasma metabolite, namely M506, has been identified. There is only a minor contribution of the major circulationg 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 (7.8%) was observed.
Tepotinib and its metabolites are 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, unchanged tepotinib represented 45% and 7% of the total radioactivity in faeces and urine, respectively. Some of the unchanged tepotinib in the faeces was probably the unabsorbed active substance. 9% of the administered radioactive dose was excreted as the des-methyl metabolite M478, 6% as the direct N-glucuronide M668, 3% as the chiral major metabolite M506 and less than 2% each as 5 other oxidised metabolites, all excreted in the faeces.
The effective half-life for tepotinib is approximately 32 h.

Linearity/non-linearity

Tepotinib exposure increases dose-proportionally over the clinically relevant dose range of 27 mg (0.06 - fold the recommended daily dose) up to 450 mg. Tepotinib exposure increases less than dose-proportionally at doses greater than 450 mg owing to lower oral bioavailability in the supratherapeutic dose range.

The pharmacokinetics of tepotinib did not change with respect to time.

Kinetics in specific patient groups

A population kinetic analysis did not show any clinically relevant effect of age (range 18 to 89 years), race/ethnicity (White, Black, Asian, Japanese, and Hispanic), gender or body weight (35.5 to 136 kg), on the pharmacokinetics of tepotinib.

Hepatic impairment

Following a single oral dose of 450 mg, total 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. In contrast, mean free tepotinib AUCs were about 13% and 24% higher in patients with mild and moderate hepatic impairment, respectively, compared to healthy subjects,. The pharmacokinetics of tepotinib have not been studied in patients with severe (Child Pugh Class C) hepatic impairment.

Renal impairment

There was no clinically meaningful change in exposure in patients with mild and moderate renal impairment based on the results of a population kinetic analysis. The pharmacokinetics of tepotinib has not been studied in patients with severe renal impairment (creatinine clearance less than 30 mL/min).

Preclinical data

Repeat dose toxicity

Oral repeat-dose toxicity studies have been conducted in rats up to 26 weeks and dogs up to 39 weeks. The main target organs for tepotinib in these animals were the hepatobiliary system and the gastrointestinal tract.

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 450 mg 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 450 mg based on AUC). In dogs gastrointestinal symptoms (vomiting, diarrhoea) were seen starting at 2.5 mg tepotinib hydrochloride hydrate per kg per day (exposures approximately 0.3% of the human exposure at the recommended dose of 450 mg based on AUC). All changes proved to be reversible or showed indications of reversibility or improvements.

Mutagenicity

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.

Reproductive toxicity

Animal 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.
In embryofetal development studies with oral administration of 0.5 to 450 mg / kg / day tepotinib hydrochloride hydrate to pregnant rabbits during organogenesis, skeletal malformations (including malrotation of the front and / or rear paws with simultaneous deformation of the scapula and / or misalignment of the clavicle and / or the calcaneus and / or talus) occurred in the fetus, starting from a level of 5 mg / kg / day (about 0.2% of human exposure below the recommended dose of 450 mg based on the AUC). Severe maternal toxicity, including mortality, and reduced body weight of the fetuses occurred at doses ⩾ 150 mg / kg / day.

Other information

Shelf life

The expiry date of the product is indicated on the packaging materials

Special precautions for storage
Store below 25ºC. Store in original package

Authorisation number

169-25-36977-99

Packs with 60 film coated tablets.

Manufacturer
Merck Healthcare KgaA, Darmstadt, Germany

Marketing authorisation holder

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