1. NAME OF THE MEDICINAL PRODUCT

TEPMETKO 225 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 225 mg tepotinib (equivalent to 250 mg tepotinib hydrochloride hydrate).

Excipient with known effect

Each film-coated tablet contains 4.37 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

White-pink, oval, biconvex film-coated tablet with embossment 'M' on one side and plain on the other side. The film-coated tablets have a length of approximately 18 mm, a width of approximately 9 mm, and a thickness of approximately 7 mm.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

TEPMETKO is indicated for the treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) harbouring mesenchymal-epithelial transition factor gene (*MET)* exon 14 (*MET*ex14) skipping alterations.

4.2 Posology and method of administration

Treatment must be initiated and supervised by a physician experienced in the use of anticancer therapies.

Prior to initiation of treatment with TEPMETKO the presence of *MET*ex14 skipping alterations should be confirmed by a validated test method using nucleic acids isolated from plasma or tumour specimens.

Posology

The recommended dose is 450 mg tepotinib (2 tablets) taken once daily. 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.

Dose modification for adverse reactions

If pulmonary symptoms indicative of interstitial lung disease (ILD)-like reactions occur, 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 treated appropriately (see section 4.4).

The recommended dose reduction of TEPMETKO for the management of adverse reactions is 225 mg orally once daily. Permanently discontinue TEPMETKO in patients who are unable to tolerate 225 mg orally once daily.

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

Table 1: Recommended TEPMETKO dosage modifications for adverse reactions"

Adverse Reaction	**Severity**	**Dose Modification**
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 haemolysis	ALT and/or AST greater than 3 times ULN with total bilirubin greater than 2 times ULN	Permanently discontinue TEPMETKO.
Increased total bilirubin without concurrent increased ALT and/or AST	Grade 3	Withhold TEPMETKO until recovery to baseline bilirubin. If recovered to baseline within 7 days, then resume TEPMETKO at a reduced dose; otherwise permanently discontinue.
	Grade 4	Permanently discontinue TEPMETKO.
Other adverse reactions (see section 4.8)	Grade 2	Maintain dose level. If intolerable, consider withholding TEPMETKO until resolved, then resume TEPMETKO at a reduced dose.
	Grade 3	Withhold TEPMETKO until resolved, then resume TEPMETKO at a reduced dose.
	Grade 4	Permanently discontinue TEPMETKO.

Renal impairment

No dose adjustment is recommended in patients with mild or moderate renal impairment (creatinine clearance 30 to 89 mL/min) (see section 5.2). 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 (see section 5.2). 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 (see section 5.2).

Paediatric population

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

Method of administration

TEPMETKO is for oral use. The tablet(s) should be taken with food and should be swallowed whole.

Administration to patients 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 or within 1 hour. Do not chew pieces of the tablet. Rinse with additional 30 mL and drink immediately to ensure that no residues remain in the glass and the full dose is administered.

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 liquid immediately or within 1 hour as per naso-gastric tube manufacturer's instructions. Immediately rinse twice with 30 mL each to ensure that no residues remain in the glass or syringe and the full dose is administered.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

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 appropriately.

Hepatotoxicity

Hepatotoxicity occurred in patients treated with TEPMETKO (see section 4.8). Increased alanine aminotransferase (ALT)/increased aspartate aminotransferase (AST) occurred in 13% of patients treated with TEPMETKO. Grade 3 or 4 increased ALT/AST occurred in 4.2% of patients. A fatal adverse reaction of hepatic failure occurred in one patient (0.2%). Three patients (0.7%) discontinued TEPMETKO due to increased ALT/AST. The median time-to-onset of Grade 3 or higher increased ALT/AST was 30 days (range 1 to 178).

Monitor liver function tests (including ALT, AST, and total bilirubin) prior to the start of TEPMETKO, every 2 weeks during the first 3 months of treatment, then once a month or as clinically indicated, with more frequent testing in patients who develop increased transaminases or bilirubin. Based on the severity of the adverse reaction, withhold, dose reduce, or permanently discontinue TEPMETKO (see section 4.2).

Embryo-foetal toxicity

TEPMETKO can cause foetal harm when administered to pregnant women (see section 4.6).

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 organic cation transporter (OCT) 2 and multidrug and toxin extrusion transporters (MATE) 1 and 2 (see section 5.2). Creatinine is a substrate of these transporters, and the observed increases in creatinine (see section 4.8) 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.

Lactose content

TEPMETKO contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

P-gp substrates

Tepotinib can inhibit the transport of sensitive substrates of P-gp (see section 5.2). Concomitant use of TEPMETKO increases the concentration of P-gp substrates, which may increase the incidence and severity of adverse reactions of these substrates. Avoid concomitant use of TEPMETKO with certain P-gp substrates where minimal concentration changes may lead to serious or life-threatening toxicities. If concomitant use is unavoidable, reduce the P-gp substrate dosage if recommended in its approved product labeling.

BCRP substrates

Tepotinib can inhibit the transport of sensitive substrates of the breast cancer resistance protein (BCRP) (see section 5.2). 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 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 5.2). Monitoring of the clinical effects of metformin is recommended during co-administration with TEPMETKO.

4.6 Fertility, 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 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.

Pregnancy

There are no clinical data on the use of TEPMETKO in pregnant women. Studies in animals have shown teratogenicity (see section 5.3). 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 and for one week after final 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 5.3).

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

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

- Interstitial Lung Disease (see section 4.4)
- Hepatotoxicity (see section 4.4)

Clinical trials experience

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

The pooled safety population described in section 4.4 reflect exposure to TEPMETKO in 448 patients with solid tumors enrolled in five open-label, single-arm studies receiving TEPMETKO as single agent at a dose of 450 mg once daily. This included 255 patients with NSCLC positive for *MET*ex14 skipping alterations, who received TEPMETKO in VISION. Among 448 patients who received TEPMETKO, 32% were exposed for 6 months or longer, and 12% were exposed for greater than one year.

The data described below reflect exposure to TEPMETKO 450 mg once daily in 255 patients with metastatic non-small cell lung cancer (NSCLC) with *MET*ex14 skipping alterations in VISION (see section 5.1).

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

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

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

Dose reductions due to a treatment-emergent adverse event occurred in 30% of patients who received TEPMETKO. Treatment-emergent adverse events which required dose reductions in > 2% of patients who received TEPMETKO included edema (19%), pleural effusion (2.7%), and increased blood creatinine (2.7%).

The most common adverse reactions (≥ 20%) in patients who received TEPMETKO were edema, fatigue, nausea, diarrhea, musculoskeletal pain, and dyspnea. The most common Grade 3 to 4 laboratory abnormalities (≥ 2%) were decreased lymphocytes, decreased albumin, decreased sodium, increased gamma-glutamyltransferase, increased amylase, increased ALT, increased AST, and decreased hemoglobin.

Table 2 summarizes the adverse reactions in VISION.

Table 2: Adverse reactions in ≥ 10% of patients with NSCLC with *MET*ex14 skipping alterations who received TEPMETKO in VISION

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

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

[b] Fatigue includes asthenia and fatigue.

Adverse Reactions	TEPMETKO (N = 255)	
	All Grades (%)	Grades 3 to 4 (%)

[c] Abdominal Pain includes abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper, gastrointestinal pain, and hepatic pain.
[d] Vomiting includes retching and vomiting.
[e] Musculoskeletal Pain includes arthralgia, arthritis, back pain, bone pain, musculoskeletal chest pain, musculoskeletal pain, myalgia, non-cardiac chest pain, pain in extremity, and spinal pain.
[f] Dyspnea includes dyspnea, dyspnea at rest, and dyspnea exertional.
[g] Cough includes cough, and productive cough.
[h] Pneumonia includes pneumonia, pneumonia aspiration, and pneumonia bacterial.

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

Table 3 summarizes the laboratory abnormalities observed in VISION.

Table 3: Select laboratory abnormalities (≥ 20%) that worsened from baseline in patients who received TEPMETKO in VISION

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

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

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

Increased creatinine

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

4.9 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action

Tepotinib is a kinase inhibitor that targets MET, including variants with exon 14 skipping alterations. Tepotinib inhibits hepatocyte growth factor (HGF)-dependent and -independent MET phosphorylation and MET-dependent downstream signaling pathways. Tepotinib also inhibited melatonin 2 and imidazoline 1 receptors at clinically achievable concentrations.

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

Pharmacodynamic effects

Exposure-Response

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

Cardiac electrophysiology

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

Clinical efficacy and safety

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 (98%) had stage IV disease, 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. Efficacy results are presented in Table 4.

Table 4: Clinical outcomes in the VISION study by IRC assessment in ITT population

Efficacy parameter	**ITT** N = 146	**Treatment-naïve** N = 65	**Pre-treated** N = 0 81
Objective response rate, % [95% CI]	45.2 [37.0, 53.6]	44.6 [32.3, 57.5]	45.7 [34.6, 57.1]
Complete response, %	0	0	0
Partial response, %	45.2	44.6	45.7
Median duration of response, months [α] [95% CI]	11.1 [8.4, 18.5]	10.8 [6.9, ne]	11.1 [9.5, 18.5]
Duration of response [β]			
≥ 6 months, % of responders	74.2	72.4	75.7
≥ 9 months, % of responders	43.9	34.5	51.4
≥ 12 months, % of responders	21.2	17.2	24.3
Median progression-free survival, months [α] [95% CI]	8.9 [8.2, 11.0]	8.5 [5.5, 11.3]	10.9 [8.2, 12.7]
Median overall survival time, months [α] [95% CI]	17.6 [15.0, 21.0]	16.3 [9.7, 29.7]	19.7 [15.0, 21.0]

IRC=Independent Review Committee, ITT=Intent-to-treat, CI=confidence interval, ne=not estimable
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.

5.2 Pharmacokinetic properties

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.

Biotransformation

Metabolism is not the major route of elimination. No metabolic pathway accounted for more than 25% of tepotinib elimination. Tepotinib is primarily metabolized by CYP3A4 and CYP2C8. 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, gender 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 interaction studies

Clinical studies

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

Effect of CYP3A/P-gp inducers on tepotinib: In healthy participants, co-administration of a single 450 mg tepotinib dose with the strong CYP3A inducer carbamazepine (300 mg twice daily for 14 days) decreased tepotinib AUC_{inf} by 35% and C_{max} by 11% compared to administration of tepotinib alone.

Effect of CYP3A/P-gp inhibitors on tepotinib: In healthy participants, co-administration of a single 450 mg tepotinib dose with the strong CYP3A inhibitor itraconazole (200 mg once daily for 11 days) increased tepotinib AUC_{inf} by 22% with no change in tepotinib C_{max} compared to administration of tepotinib alone.

Effect of tepotinib on CYP3A4 substrates: Multiple administrations of 450 mg tepotinib orally once daily had no clinically relevant effect on the pharmacokinetics 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 under fed conditions had no marked effect on the pharmacokinetic profile of tepotinib and its metabolites.

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 for 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 UGT1A1, 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,, CYP2C19, CYP2D6 and CYP2E1. Tepotinib or its major circulating metabolite do not induce CYP1A2, and 2B6.

5.3 Preclinical safety data

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 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 TEPMETKO 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 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 450 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 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Mannitol
Colloidal anhydrous silica
Crospovidone
Magnesium stearate
Microcystalline cellulose

Film-coating

Hypromellose
Lactose monohydrate
Macrogol
Triacetin
Red iron oxides (E172)
Titanium dioxide

6.2 Special precautions for storage

Store below 30 °C. Store in the original package in order to protect from moisture.

6.3 Nature and contents of container

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

6.4 Special precautions for disposal

No special requirements.

7. MANUFACTURER

Merck Healthcare KGaA
Frankfurter Strasse 250
64293 Darmstadt
Germany

8. DATE OF REVISION OF THE TEXT

April 2023 CCDS V7