Medicines & Healthcare products Regulatory Agency

MHRA

Early Access to Medicines Scheme – Treatment protocol – Information for healthcare professionals

Introduction

The aim of the Early Access to Medicines Scheme (EAMS) is to provide earlier availability of promising new unlicensed medicines and medicines used outside their licence, to UK patients that have a high unmet clinical need. The medicinal products included in the scheme are those that are intended to treat, diagnose or prevent seriously debilitating or life-threatening conditions where there are no adequate treatment options. More information about the scheme can be found here: http://www.mhra.gov.uk/Howweregulate/Innovation/EarlyaccesstomedicinesschemeEAMS/index.htm

This information is intended for healthcare professionals and is provided by the pharmaceutical company that manufactures the EAMS medicine. This medicine does not yet have a licence (marketing authorisation) and the information is provided to assist physicians in prescribing this unlicensed medicine. Guidance on prescribing unlicensed medicines can be found on the GMC webpage:
https://www.gmc-uk.org/guidance/ethical_guidance/14327.asp

The scientific opinion is based on assessment of the information supplied to the MHRA on the benefits and risks of this promising new medicine. As such, this is a scientific opinion and should not be regarded as a medicine licensed by the MHRA or a future commitment by the MHRA to license such a medicine, nor should it be regarded as an authorisation to sell or supply such a medicine. A positive scientific opinion is not a recommendation for use of the medicine and should not be interpreted as such. Under EAMS the risk and legal responsibility for prescribing a 'special' remains with the physician, and the opinion and EAMs documentation published by the MHRA are intended only to inform physicians' decision making and not to recommend use. An EAMS scientific opinion does not affect the civil liability of the manufacturer or any physician in relation to the product.

Healthcare professionals should also refer to the summary information on the pharmacovigilance system which is provided in the document 'Early Access to Medicines Scheme – Treatment protocol – Information on the pharmacovigilance system'.

Scientific opinion period: The MHRA will withdraw the EAMS positive scientific opinion when a marketing authorisation (drug licence) is issued for the EAMS product covering the EAMS indication, or if following scientific assessment, the EAMS criteria are considered to be no longer met.

Treatment protocol update(s): In case of substantial new efficacy or safety data, the treatment protocol may need to be updated.

Contact information regarding queries on using this EAMS medicine can be found at the end of this document.

Information for healthcare professionals

This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Tepotinib 225 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Excipient with known effect

Each film-coated tablet contains 4.15 mg lactose.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

White-pink, oval, biconvex film-coated tablet of approximately 18 mm in length with embossment ‘M’ on one side and plain on the other side.

4. CLINICAL PARTICULARS

4.1 EAMS therapeutic indication

Tepotinib is indicated for the treatment of adult patients with advanced 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.

Assessment of *MET*ex14 skipping alterations status

Prior to initiation of treatment with tepotinib the presence of *MET*ex14 skipping alterations should be confirmed by a test method using nucleic acids isolated from either tumour or plasma specimens. Testing for the presence of *MET*ex14 skipping alterations in tissue specimens is recommended because of higher sensitivity. However, plasma specimens may be used in patients for whom a tumour biopsy cannot be obtained. If an alteration is not detected in a plasma specimen, the feasibility of biopsy for tumour tissue testing should be evaluated.

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

Dose interruption, dose reduction or discontinuation of treatment with tepotinib may be required based on adverse reactions. The recommended dose reduction level for the management of adverse reactions is 225 mg (1 tablet) daily. Tepotinib should be permanently discontinued if patients are unable to tolerate 225 mg (1 tablet) daily. Detailed recommendations for dose modification are provided in the table below.

Recommended dose modifications for tepotinib for adverse reactions

Adverse reaction	**Severity**	**Dose modification**
Interstitial Lung Disease (ILD) (see section 4.4)	Any grade	Withhold tepotinib if ILD is suspected. Permanently discontinue tepotinib if ILD is confirmed.
Increased ALT and/or AST without increased total bilirubin (see section 4.4)	Grade 3	Withhold tepotinib until recovery to baseline ALT/AST. If recovered to baseline within 7 days, then resume tepotinib at the same dose; otherwise resume tepotinib at a reduced dose.
	Grade 4	Permanently discontinue tepotinib.
Increased ALT and/or AST with increased total bilirubin in the absence of cholestasis or haemolysis (see section 4.4)	ALT and/or AST greater than 3 times ULN with total bilirubin greater than 2 times ULN	Permanently discontinue tepotinib.
Increased total bilirubin without concurrent increased ALT and/or AST (see section 4.4)	Grade 3	Withhold tepotinib until recovery to baseline bilirubin. If recovered to baseline within 7 days, then resume tepotinib at a reduced dose; otherwise permanently discontinue.
	Grade 4	Permanently discontinue tepotinib.
Other adverse reactions (see section 4.8)	Grade 2	Maintain dose level. If intolerable, consider withholding tepotinib until resolved, then resume tepotinib at a reduced dose.
	Grade 3	Withhold tepotinib until resolved, then resume tepotinib at a reduced dose.
	Grade 4	Permanently discontinue tepotinib.

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 efficacy of tepotinib in paediatric patients below 18 years of age have not been established.

Method of administration

Tepotinib is for oral use. The tablet(s) should be taken with food and should be swallowed whole (patients should not crush or chew the tablet before swallowing).

4.3 Contraindications

Hypersensitivity to tepotinib 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 (for example, pneumonitis) have been reported, including a fatal case (see section 4.8).

Patients should be monitored for new or worsening pulmonary symptoms indicative for ILD-like reactions (for example, dyspnoea, cough, fever). Tepotinib should be withheld immediately; and patients should be promptly investigated for alternative diagnosis or specific aetiology of interstitial lung disease. Tepotinib must be permanently discontinued if interstitial lung disease is confirmed and the patient be treated according to local clinical practice.

Hepatotoxicity

Increases in ALT and/or AST have been reported (see section 4.8).

Liver enzymes (ALT and AST) and bilirubin should be monitored prior to the start of tepotinib, every 2 weeks during the first 3 months of treatment, then once a month. If Grade 3 or higher increases occur, dose adjustment is recommended (see section 4.2).

Embryo-foetal toxicity

Tepotinib 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 tepotinib treatment and for at least 1 week after the last dose.

Male patients with female partners of childbearing potential should use barrier contraception during Tepotinib 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

Tepotinib 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

Pharmacokinetic interactions

CYP inducers and P-gp inducers

Tepotinib is a substrate for P-glycoprotein (P-gp) (see section 5.2). Strong P-gp inducers may have the potential to decrease tepotinib exposure. Strong CYP inducers may also decrease tepotinib exposure. Concomitant use of strong CYP inducers and P-gp inducers (e.g. carbamazepine, phenytoin, rifampicin, St. John's wort) should be avoided.

Dual strong CYP3A inhibitors and P-gp inhibitors

The effect of strong CYP3A inhibitors or P-gp inhibitors on tepotinib has not been studied clinically. However, metabolism and *in vitro* data suggest concomitant use of medicinal products that are strong CYP3A inhibitors and P gp inhibitors may increase tepotinib exposure (see section 5.2), which may increase the incidence and severity of adverse reactions of tepotinib. Concomitant use of tepotinib with dual strong CYP3A and P-gp inhibitors (e.g. itraconazole) should be avoided.

P-gp substrates

Tepotinib can inhibit the transport of sensitive substrates of P-gp (see section 5.2). Monitoring of the clinical effects of P-gp-dependent substances with a narrow therapeutic index (e.g. digoxin) is recommended during co-administration with tepotinib.

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 tepotinib.

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 tepotinib.

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 tepotinib.

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

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

Pregnancy

There are no clinical data on the use of tepotinib in pregnant women. Studies in animals have shown teratogenicity (see section 5.3). Based on the mechanism of action and findings in animals tepotinib can cause foetal harm when administered to pregnant women.

Tepotinib 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 tepotinib and for at least 1 week after the last dose.

Fertility

No human data on the effect of tepotinib 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

Tepotinib may have minor influence on the ability to drive and use machines. During treatment with tepotinib, fatigue and asthenia have been reported.

4.8 Undesirable effects

Summary of the safety profile

The safety data described reflect exposure to tepotinib 450 mg once daily in 255 patients with advanced NSCLC harbouring *MET*ex14 skipping alterations included in the main clinical study (VISION). Median duration of treatment was 22.3 weeks (range: 0 – 188 weeks).

Serious adverse events occurred in 45% of patients who received tepotinib. The most common serious adverse events (≥ 2%) included pleural effusion (6.7%), pneumonia (4.7%), dyspnoea (3.9%), general health deterioration (3.5%), peripheral oedema (2.4%), generalised oedema (2.0%), musculoskeletal pain (2.0%) and pulmonary embolism (2.0%).

List of adverse reactions

An asterisk (*) indicates that additional information on the respective adverse reaction is provided below the table.

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)

Adverse reactions in patients with NSCLC harbouring *MET*ex14 skipping alterations who received tepotinib in VISION

System organ class/Adverse reaction	Frequency category	Tepotinib N=255 All grades %	Tepotinib N=255 Grade ≥ 3 %
Metabolism and nutrition disorders			
Hypoalbuminaemia	Very common	23.9	5.5
Respiratory, thoracic and mediastinal disorders			
ILD [α]*	Common	2.4	0.4

Gastrointestinal disorders			
Nausea	Very common	26.7	0.8
Diarrhoea	Very common	26.3	0.4
Abdominal pain[b]	Very common	16.5	0.8
Constipation	Very common	15.7	0
Vomiting	Very common	12.9	1.2
Hepatobiliary disorders			
Increase in alanine aminotransferase (ALT)*	Very common	11.4	3.1
Increase in alkaline phosphatase (ALP)*	Common	7.8	0
Increase in aspartate aminotransferase (AST)*	Common	7.5	1.2
General disorders and administration site conditions			
Oedema	Very common	69.8	9.4
Fatigue/Asthenia	Very common	27.5	1.6
Investigations			
Increase in creatinine*	Very common	25.9	0.4
Increase in amylase*	Common	8.6	3.1
Increase in lipase*	Common	7.1	3.5

[α] includes terms interstitial lung disease, pneumoniti[s], acute respiratory failure

b includes abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper, gastrointestinal pain and hepatic pain

Description of selected adverse reactions

Interstitial lung disease

6 out of 255 patients (2.4%) in the VISION study developed interstitial lung disease (ILD) or ILD-like reactions. The median time to onset was 9.1 weeks (range: 3.0 - 42.1 weeks). Treatment was permanently discontinued in 3 patients and temporarily discontinued in 3 patients. One fatal case of acute respiratory failure secondary to ILD was reported. For clinical recommendations, see sections 4.2 and 4.4.

Hepatotoxicity

In the VISION study, based on laboratory assessment, ALT and AST increases from baseline were reported on 42.0% and 32.9% of patients, respectively. Grade 3 or higher ALT and AST were reported in 3.9% and 2.4% of patients, respectively. A fatal adverse reaction of hepatic failure occurred in one patient (0.4%). The median time to first onset was 6.1 weeks (range: 0.1 – 34.0 weeks) for any grade of ALT and/or AST increase. 9 patients (3.5%) temporarily discontinued treatment, and 2 patients (0.8%) required a dose reduction of tepotinib. The median time to resolution was 5.0 weeks (range: 0.1 – 31.1 weeks). For clinical recommendations, see sections 4.2 and 4.4.

Based on laboratory assessment, ALP increase from baseline was reported in 47.5% of patients. Grade 3 or 4 occurred in 1.6% of patients. The median time to first onset for ALP increase of any grade was 5.7 weeks (range: 0.7 – 28.0 weeks) and the median time to resolution was 9.8 weeks (range: 0.9+* – 45.3+ weeks). The observed ALP increase was not associated with cholestasis, and did not lead to dose modification.

*'+' indicates censored observation

Oedema

Oedema was observed in 69.8% of patients. It includes peripheral oedema, which was the most frequent at 60.0%, generalised oedema , and localised oedema (for example, oedema of the face, periorbital oedema, genital oedema) . the median time to onset of any-grade oedema was 7.86 weeks (range: 0.1 – 58.3 weeks) and the median time to resolution was approximately 67.0 weeks (range: 0.1 – 162.0+ weeks). 4.3% of patients had oedema events leading to permanent treatment discontinuation, of whom 3.5% had peripheral oedema. 23.1% of patients temporarily discontinued treatment and 18.8% of patients had dose reduction due to oedema Most frequently peripheral oedema led to temporary treatment discontinuation and dose reductions (16.9% and 14.1%, respectively). Generalised oedema events led to a dose reduction in 6/13 patients and to temporary treatment discontinuation in 8/13 patients, but did not lead to permanent discontinuation.

Increase in creatinine

Based on laboratory assessment, increase in creatinine from baseline were reported in 52.9% of patients. Grade 3 occurred in one patient (0.4%). The observed increases in creatinine are thought to occur due to competition of renal tubular secretion (see section 4.4) . The median time to onset of increased creatinine was 3.14 weeks (range: 0.1 – 78.4 weeks) and the median time to resolution was 12.1 weeks (range: 0.4+ – 104.3 weeks). Two patients permanently discontinued treatment due to increase in creatinine, 6.3% of patients temporarily discontinued treatment and 2.7% patients required a dose reduction due to increased creatinine.

Hypoalbuminaemia

Based on laboratory assessment, decrease in albumin from baseline by one grade was reported in 38.4% of patients. Shift of 2 grades and 3 grades were observed in 29.8% and 2.7%, respectively. The median time to onset of any-grade hypoalbuminaemia was 9.43 weeks (range: 0.1 – 150.3 weeks) and the median time to resolution ranged between 0.3+ and 124.9+ weeks. Hypoalbuminaemia appeared to be long-lasting but did not lead to permanent treatment discontinuation. Dose reduction (0.8%) and temporary discontinuation (1.2%) were infrequent.

Increase in amylase or lipase

Based on laboratory assessment, increases in amylase and lipase from baseline were reported in 21.6% and 17.3% of patients, respectively. Grade 3 or 4 increased amylase and lipase were reported in 4.3% and 3.9% of patients, respectively. No pancreatitis was observed in the VISION study. The median time to onset of any grade in lipase/amylase increase was 11.93 weeks (range: 0.1 – 96.3 weeks). Median time to resolution was 6.0 weeks (range 0.6+ - 186.4+ weeks). 2.4% of patients temporarily discontinued treatment. No patient required dose reduction or permanent treatment discontinuation.

Additional information on special populations

Elderly

Of 255 patients with METex14 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. No clinically important differences in safety were observed between patients aged 65 years or older and younger patients.

Adverse event/Adverse drug reaction reporting

All Healthcare Professionals (HCPs) involved in the care of patients on the EAMS will be instructed to report all adverse events (serious and non-serious), any exposure during pregnancy (including exposure from male participants of the EAMS) and lactation, medication errors, and overdose, within 24 hours to Merck UK Pharmacovigilance, as specified in the relevant documentation within the physician's pack which shall contain a relevant EAMS AE reporting form. HCPs will be required to confirm to Merck that they understand their obligation to report adverse events before EAMS registration.

The contact details for reporting adverse events can be found under Contact information below.

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, tepotinib 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 signalling pathways. Tepotinib also inhibited melatonin 2 and imidazoline 1 receptors at clinically achievable concentrations.

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

Pharmacodynamic effects

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 recommended dose, no large mean increases in QTc (i.e. > 20ms) were detected. 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 one cohort of 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). The primary objective was to evaluate the activity of tepotinib by determining objective response rate (ORR).

Patients with measurable disease as determined by RECIST v1.1, with *MET*ex14 skipping alterations in plasma and/or tissue, as determined by the central laboratory or by an assay with appropriate regulatory status and with an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 to 1 were enrolled. Neurologically stable patients with central nervous system (CNS) metastases were permitted. Patients with symptomatic CNS metastases or leptomeningeal carcinomatosis were excluded, as were patients with clinically uncontrolled cardiac disease. Patients who had received treatment with any inhibitor of MET or HGF (hepatocyte growth factor), and those with epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) activating alterations were also excluded.

Patients received 450 mg tepotinib once daily until disease progression or unacceptable toxicity.

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

The primary outcome measure was 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). Secondary outcome measures included duration of response, progression-free survival assessed by IRC and overall survival.

The population included 65 treatment-naïve (45%) and 81 previously-treated (55%) patients. The median age was 73 years (range 41 to 94), 52% of patients were male. 70% of patients were White , 26% were Asians. 42%of patients were never-smokers and 50% were former smokers. Most patients were ≥ 65 years of age (82%), with 45% ≥ 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.

Median treatment duration was 8.02 months (range 0.03 to 43.33 months).

The efficacy results summarised in the table below reflect patients in the cohort with at least 9 months of follow-up from the start of treatment (n=146).

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 [α] [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 [α] [95% CI]	8.9 [8.2, 11.0]
Median overall survival time, months [α] [95% CI]	17.6 [15.0, 21.0]

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

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

[β] Duration of response of ≥ 9 months and ≥ 12 months, respectively, could not be reached by some patients due to their time of enrolment.

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

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with tepotinib in all subsets of the paediatric population in treatment of non-small cell lung cancer (NSCLC) (see section 4.2 for information on paediatric use).

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 in healthy subjects; 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) (see section 4.5).

Biotransformation

Metabolism is not the major route of elimination. No metabolic pathway accounted for more than 25% of tepotinib elimination. Only one major circulating plasma metabolite has been identified. There is only a minor contribution of the major circulating metabolite to the overall efficacy of tepotinib in humans.

Elimination

After a single oral administration of a radiolabelled dose of 450 mg tepotinib, approximately 85% of the dose was recovered in faeces (45% unchanged), and 13.6% in urine (7% unchanged). The major circulating metabolite, M506, accounted for about 40.4% of the total radioactivity in plasma.

The elimination half-life for tepotinib is approximately 32 h following oral administration.

Dose and time dependence

Tepotinib exposure increases dose-proportionally over the clinically relevant dose range up to 450 mg. The oral clearance of tepotinib did not change with respect to time. After multiple daily administrations of 450 mg tepotinib, median accumulation was 2.5-fold for C_{max} and 3.3-fold for $AUC_{0\text{-}24h}$.

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

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):*Tepotinib or its major circulating metabolite, M506, do not inhibit UGT1A1, 1A9, 2B17, 1A3/4/6, and 2B7/15 at clinically relevant concentrations.

Effect of tepotinib on CYP 450 enzymes: Tepotinib is substrate of CYP3A4 and CYP2C8. Tepotinib and M506 do not inhibit CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C19, CYP2D6 and CYP2E1.

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 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, 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 per 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 per 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
Microcrystalline cellulose

Film-coating

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

6.2 Incompatibilities

Not applicable

6.3 Shelf life

5 years.

6.4 Special precautions for storage

Store below 25°C. Store all items in original outer packaging, remove only prior to administration.

6.5 Nature and contents of container

Polyamide/ Aluminium/Polyvinyl chloride and Aluminium blister. Packs of 12 wallets of 14 tablets.

6.6 Special precautions for disposal and other handling

No special requirements.

7. SCIENTIFIC OPINION HOLDER

Merck Serono Limited
5 New Square
Bedfont Lakes Business Park
Feltham
Middlesex
TW14 8HA

8. EAMS NUMBER

11648/0004

9. DATE OF SCIENTIFIC OPINION

10 July 2021

Additional information

Healthcare professionals will be provided with the following documents to give to patients:

- EAMS Treatment Protocol – Information for Patients
- EAMS Informed Consent Form

Most importantly, patients should be reminded that if they do experience an adverse event, they should contact their doctor, pharmacist or nurse.

EAMS registration

Merck has appointed Clinigen to act on its behalf to manage the administration of the tepotinib EAMS program via its dedicated access portal, Cliniport. To register a patient with the EAMS, healthcare professionals will need to contact Clinigen directly by email: medicineaccess@clinigengroup.com or telephone: +44 (0) 1932 824100.

All healthcare professionals involved with the management of the EAMS will receive a physician's pack upon set up which includes training material for adverse event (AE) reporting. The material includes provisions for recognising, managing, and reporting AEs. HCPs must confirm they have read and understood their AE reporting obligations prior to EAMS registration. Alternatively, healthcare professionals involved with the management of the EAMS may request adverse event training from the Merck medical team by emailing EAMS-NSCLC@merckgroup.com.

Once registered on Cliniport, healthcare professionals will be able to complete a Patient Access Form, including drug supply information and agreement on their responsibilities within the EAMS. Further information and documentation are available within Cliniport.

Contact information

All enquiries including registration, ordering, product complaints, medical information enquiries and adverse event reporting should be directed to Clinigen via Cliniport or the Clinigen customer services team on email: medicineaccess@clinigengroup.com or telephone: +44 (0) 1932 824100.