

**SUMMARY OF PRODUCT CHARACTERISTICS,  
LABELLING AND PACKAGE LEAFLET**

## **SUMMARY OF PRODUCT CHARACTERISTICS**

▼ 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

TEPMETKO 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 Therapeutic indications

TEPMETKO 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 TEPMETKO the presence of *MET*ex14 skipping alterations should be confirmed by a validated 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 TEPMETKO may be required based on adverse reactions. The recommended dose reduction level for the management of adverse reactions is 225 mg (1 tablet) daily. TEPMETKO 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.

<b>Recommended dose modifications for TEPMETKO for adverse reactions</b>		
<b>Adverse reaction</b>	<b>Severity</b>	<b>Dose modification</b>
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 hemolysis (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 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 (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 (e.g. 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 (e.g. dyspnoea, cough, fever). TEPMETKO should be withheld immediately 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 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 TEPMETKO, 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

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. In case of blood creatinine increase while on treatment, it is recommended that further assessment of the renal function be performed to exclude renal impairment.

## 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**

### 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 TEPMETKO.

#### *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 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 5.3).

## 4.7 Effects on ability to drive and use machines

TEPMETKO 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 to 188 weeks).

Serious adverse events occurred in 45% of patients who received tepotinib. The most common serious adverse events ( $\geq 2\%$ ) 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 ( $\geq 1/10$ )

Common ( $\geq 1/100$  to  $< 1/10$ )

Uncommon ( $\geq 1/1,000$  to  $< 1/100$ )

Rare ( $\geq 1/10,000$  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 TEPMETKO in VISION**

System organ class/Adverse reaction	Frequency category	TEPMETKO N=255	
		All grades %	Grade $\geq 3$ %
<u>Metabolism and nutrition disorders</u>			
Hypoalbuminaemia*	Very common	23.9	5.5
<u>Respiratory, thoracic and mediastinal disorders</u>			
ILD-like reactions <sup>a*</sup>	Common	2.4	0.4
<u>Gastrointestinal disorders</u>			
Nausea	Very common	26.7	0.8
Diarrhoea	Very common	26.3	0.4
Abdominal pain <sup>b</sup>	Very common	16.5	0.8
Constipation	Very common	15.7	0
Vomiting	Very common	12.9	1.2
<u>Hepatobiliary disorders</u>			
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
<u>General disorders and administration site conditions</u>			
Oedema*	Very common	69.8	9.4
Fatigue/Asthenia	Very common	27.5	1.6
<u>Investigations</u>			
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

<sup>a</sup> includes terms interstitial lung disease, pneumonitis, acute respiratory failure

<sup>b</sup> 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 to 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 to 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 to 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 to 28.0 weeks) and the median time to resolution was 9.8 weeks (range: 0.9+\* to 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 (e.g. oedema of the face, periorbital oedema, genital oedema). The median time to onset of any-grade oedema was 7.9 weeks (range: 0.1 to 58.3 weeks) and the median time to resolution was approximately 67.0 weeks (range: 0.1 to 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 3.1 weeks (range: 0.1 to 78.4 weeks) and the median time to resolution was 12.1 weeks (range: 0.4+ to 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.

### 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 9.4 weeks (range: 0.1 to 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 increase in 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 11.9 weeks (range: 0.1 to 96.3 weeks). Median time to resolution was 6.0 weeks (range: 0.6+ to 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.

### Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via:

Yellow Card Scheme

Website: [www.mhra.gov.uk/yellowcard](http://www.mhra.gov.uk/yellowcard) or search for MHRA Yellow Card in the Google Play or Apple App Store.

## **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 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. > 20 ms) 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 metastases were permitted. Patients with symptomatic central nervous system 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).

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 <sup>α</sup> [95% CI]	11.1 [8.4, 18.5]
<u>Duration of response</u> <sup>β</sup>	
≥ 6 months, % of responders	74.2
≥ 9 months, % of responders	43.9
≥ 12 months, % of responders	21.2
Median progression-free survival, months <sup>α</sup> [95% CI]	8.9 [8.2, 11.0]
Median overall survival time, months <sup>α</sup> [95% CI]	17.6 [15.0, 21.0]

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

<sup>α</sup> Product-limit (Kaplan-Meier) estimates, 95% CI for the median using the Brookmeyer and Crowley method

<sup>β</sup> 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 *METex14* 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 TEPMETKO 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).

#### Conditional approval

This medicinal product has been authorised under a so-called ‘conditional approval’ scheme. This means that further evidence on this medicinal product is awaited. The MHRA will review new information on this medicinal product at least every year and this SmPC will be updated as necessary.

## 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: 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 ( $V_z$ ) 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  $AUC_{0-24h}$ .

## 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<sub>t</sub> by approximately 50% and C<sub>max</sub> 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 a 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 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 per 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  $\geq 150$  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 TEPMETKO 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 oxides (E172)  
Titanium dioxide

### **6.3 Shelf life**

3 years.

### **6.4 Special precautions for storage**

This medicinal product does not require special temperature storage conditions. Store in the original package in order to protect from moisture.

### **6.5 Nature and contents of container**

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

**6.6 Special precautions for disposal**

No special requirements.

**7. MARKETING AUTHORISATION HOLDER**

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

**8. MARKETING AUTHORISATION NUMBER**

PLGB 11648/0291

**9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first authorisation: DD month YYYY

**10. DATE OF REVISION OF THE TEXT**

MM/YYYY



## **LABELLING AND PACKAGE LEAFLET**

## **A. LABELLING**

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**CARTON**

**1. NAME OF THE MEDICINAL PRODUCT**

TEPMETKO 225 mg film-coated tablets  
tepotinib

**2. STATEMENT OF ACTIVE SUBSTANCE**

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

**3. LIST OF EXCIPIENTS**

Contains lactose.  
See package leaflet for further information.

**4. PHARMACEUTICAL FORM AND CONTENTS**

60 film-coated tablets

**5. METHOD AND ROUTE OF ADMINISTRATION**

Oral use.  
Read the package leaflet before use.

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

**8. EXPIRY DATE**

EXP

**9. SPECIAL STORAGE CONDITIONS**

Store in the original package in order to protect from moisture.

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

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

**12. MARKETING AUTHORISATION NUMBER**

PLGB 11648/0291

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY**

**15. INSTRUCTIONS ON USE**

**16. INFORMATION IN BRAILLE**

tepmetko

**17. UNIQUE IDENTIFIER – 2D BARCODE**

2D barcode carrying the unique identifier included.

**18. UNIQUE IDENTIFIER - HUMAN READABLE DATA**

PC  
SN  
NN

**MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS**

**BLISTER**

**1. NAME OF THE MEDICINAL PRODUCT**

TEPMETKO 225 mg film-coated tablets  
tepotinib

**2. NAME OF THE MARKETING AUTHORISATION HOLDER**

Merck Serono Ltd

**3. EXPIRY DATE**

EXP

**4. BATCH NUMBER**

LOT

**5. OTHER**

**B. PACKAGE LEAFLET**

## Package leaflet: Information for the patient

### TEPMETKO 225 mg film-coated tablets tepotinib

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects which you may get. See the end of section 4 for how to report side effects.

#### **Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.**

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, nurse or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, nurse or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

#### **What is in this leaflet**

1. What TEPMETKO is and what it is used for
2. What you need to know before you take TEPMETKO
3. How to take TEPMETKO
4. Possible side effects
5. How to store TEPMETKO
6. Contents of the pack and other information

#### **1. What TEPMETKO is and what it is used for**

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

TEPMETKO is used in adults to treat a type of lung cancer, called non-small cell lung cancer, that has certain abnormal changes in the mesenchymal-epithelial transition factor gene (*MET*) and which has spread and/or cannot be removed by surgery.

The changes in the *MET* gene can make an abnormal protein which can then cause uncontrolled cell growth and cancer. By blocking this abnormal protein TEPMETKO may slow or stop the cancer from growing. It may also help to shrink the cancer.

Your doctor will perform a test to check if your cancer has a change in the *MET* gene to make sure that TEPMETKO is right for you.

#### **2. What you need to know before you take TEPMETKO**

##### **Do not take TEPMETKO**

- if you are allergic to tepotinib or any of the other ingredients of this medicine (listed in section 6).

### **Warnings and precautions**

Talk to your doctor or pharmacist before taking TEPMETKO if any of the following apply to you:

- if you have or have had any other lung problems.
- if you have or have had liver problems.
- if you are pregnant or plan to become pregnant.
- if you are breastfeeding.

Tell your doctor or pharmacist immediately if you develop any new or worsening symptoms during treatment (see section 4). TEPMETKO may cause sudden breathing difficulties that may be associated with fever and cough.

### **Blood tests**

Your doctor will take blood tests before and regularly during treatment with TEPMETKO. Based on the results, your doctor may decide to interrupt your treatment, reduce your tepotinib dose or stop treatment permanently.

### **Children and adolescents**

TEPMETKO is not to be used in children and adolescents under the age of 18 years.

### **Other medicines and TEPMETKO**

Tell your doctor if you are using, have recently used or might use any other medicines.

The following medicines may affect how well TEPMETKO works:

- carbamazepine or phenytoin – used to treat seizures or fits
- rifampicin – used to treat tuberculosis (TB).
- St. John's wort – a herbal medicine used to treat depression
- itraconazole – used to treat fungal infections

TEPMETKO may affect how well the following medicines work and/or increase side effects of these medicines:

- digoxin – used to treat irregular heart beat or other heart problems
- metformin – used to treat diabetes mellitus

### **Pregnancy**

Do not take TEPMETKO if you are pregnant or suspect you are pregnant, unless advised by your doctor. TEPMETKO may harm the unborn baby.

### **Contraception**

If you are female and are of childbearing age, you should use an effective method of contraception to avoid becoming pregnant during TEPMETKO treatment and for at least 1 week after the last dose. Talk to your doctor if you take hormonal contraceptives (e.g. "the pill"). You need a second method of contraception during TEPMETKO treatment and for at least 1 week after the last dose.

If you are male, you should use barrier contraception to prevent your partner from getting pregnant, whilst you are treated with TEPMETKO and for at least 1 week after the last dose.

### **Breast-feeding**

It is not known whether TEPMETKO may pass to the baby via breast milk. Do not breast-feed during treatment with TEPMETKO and for at least 1 week after the last dose.

### **Driving and using machines**

You should take special care when driving and using machines as you may feel unusually tired while taking TEPMETKO.



**TEPMETKO contains lactose**

TEPMETKO contains 4.15 mg lactose in each tablet. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

**3. How to take TEPMETKO**

Always take this medicine exactly as your doctor has told you. Check with your doctor if you are not sure.

The recommended dose is 450 mg TEPMETKO (2 tablets) taken once daily. In case of side effects, your doctor may advise you to reduce the dose to 1 tablet daily or interrupt the treatment for some days or stop treatment permanently.

Swallow the tablets whole (without crushing or chewing). Take the tablets with food or shortly after a meal.

**If you take more TEPMETKO than you should**

Symptoms of overdose with TEPMETKO are not known. If you have taken more TEPMETKO than you should, or if someone else has taken your medicine, contact a doctor or hospital for advice. Medical treatment may be necessary.

**If you forget to take TEPMETKO**

If you miss a dose of TEPMETKO, take it as soon as you remember. If your next dose is due within 8 hours, skip the missed dose and take your next dose at your regular time. Do not take a double dose to make up for a missed dose.

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

**If you stop taking TEPMETKO**

Do not stop taking TEPMETKO unless you have discussed with your doctor or your doctor tells you to stop.

If you have any further questions on the use of this medicine, ask your doctor, nurse or pharmacist.

**4. Possible side effects**

Like all medicines, this medicine can cause side effects, although not everybody gets them.

**Serious side effects**

Contact your doctor immediately for any of the following:

- if you develop any new or worsening symptoms such as sudden breathing difficulties, shortness of breath, cough or fever. These may be symptoms of a serious lung condition (interstitial lung disease) which needs immediate medical attention. This side effect is common (may affect up to 1 in 10 people).
- if you develop yellow discolouration of the skin and eyes (jaundice), darkening of the urine, light-coloured stools (faeces), loss of appetite, nausea or vomiting, pain on the upper right side of your stomach area. These are symptoms and signs of liver problems.

**Other side effects**

Very common side effects (may affect more than 1 in 10 people)

- Swelling caused by fluid build-up in the body (oedema)
- Feeling sick (nausea)
- Being sick (vomiting)
- Diarrhoea
- Abdominal pain

- Constipation
- Fatigue or tiredness
- Higher than normal blood levels of creatinine
- Reduced protein levels in the blood
- Higher than normal blood levels of a certain liver enzyme (alanine aminotransferase)

Common side effects (may affect up to 1 in 10 people)

- Higher than normal blood levels of certain liver enzymes (aspartate aminotransferase, alkaline phosphatase)
- Higher than normal blood levels of amylase
- Higher than normal blood levels of lipase

**Reporting of side effects**

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via:

Yellow Card Scheme Website: [www.mhra.gov.uk/yellowcard](http://www.mhra.gov.uk/yellowcard) or search for MHRA Yellow Card in the Google Play or Apple App Store.

By reporting side effects, you can help provide more information on the safety of this medicine.

**5. How to store TEPMETKO**

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and the blister after EXP. The expiry date refers to the last day of that month.

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

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

**6. Contents of the pack and other information**

**What TEPMETKO contains**

- The active substance is tepotinib. Each tablet contains 225 mg tepotinib (as hydrochloride hydrate).
- The other ingredients are mannitol, colloidal anhydrous silica, crospovidone, magnesium stearate and microcrystalline cellulose in the tablet core and hypromellose, lactose monohydrate (see section 2, 'TEPMETKO contains lactose'), Macrogol, triacetin, red iron oxides (E172) and titanium dioxide in the film-coating.

**What TEPMETKO looks like and contents of the pack**

TEPMETKO film-coated tablets are white-pink, oval and biconvex with embossment 'M' on one side and plain on the other side. Each pack contains 60 tablets in aluminium/polyvinyl chloride-polyethylene-polyvinylidene chloride-polyethylene-polyvinyl chloride blisters.

**Marketing Authorisation Holder**

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

**Manufacturer**

Merck Healthcare KGaA  
Frankfurter Strasse 250  
64293 Darmstadt  
Germany

**This leaflet was last revised in MM/YYYY.**

This medicine has been given ‘conditional approval’. This means that there is more evidence to come about this medicine. The MHRA will review new information on this medicine at least every year and this leaflet will be updated as necessary.