ANNEX I

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 4.4 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

White-pink, oval, biconvex film-coated tablet of approximately 18 x 9 mm in size, embossed with ‘M’ on one side and plain on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

TEPMETKO as monotherapy is indicated for the treatment of adult patients with advanced non-small cell lung cancer (NSCLC) harbouring alterations leading to mesenchymal-epithelial transition factor gene exon 14 (*MET*ex14) skipping, who require systemic therapy following prior treatment with immunotherapy and/or platinum-based chemotherapy.

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 (see sections 4.4 and 5.1).

Posology

The recommended dose is 450 mg tepotinib (2 tablets) taken once daily. Treatment should continue as long as clinical benefit is observed.

If a daily dose is missed, it can be taken as soon as remembered on the same day, unless the next dose is due within 8 hours.

Dose modification for adverse reactions

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

Adverse reaction	**Severity**	**Dose modification**
Interstitial lung disease (ILD) (see section 4.4)	Any grade	Withhold TEPMETKO if ILD is suspected. Permanently discontinue TEPMETKO if ILD is confirmed.
Increased ALT and/or AST without increased total bilirubin (see section 4.4)	ALT and/or AST greater than 5 times up to 20 times ULN	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.
	ALT and/or AST greater than 20 times ULN	Permanently discontinue TEPMETKO.
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 TEPMETKO.
Other adverse reactions (see section 4.8)	Grade 3 or higher	Reduce TEPMETKO to 225 mg until the adverse reaction recovers to ≤ grade 2. A temporary interruption of TEPMETKO treatment for no more than 21 days can also be considered.

ULN=upper limit of normal

Special populations

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. The use of TEPMETKO in patients with severe renal impairment is therefore not recommended.

Renal function estimates that rely on serum creatinine (creatinine clearance or estimated glomerular filtration rate) should be interpreted with caution (see section 4.4).

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. The use of TEPMETKO in patients with severe hepatic impairment is therefore not recommended.

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. No data are available.

Method of administration

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

Assessment of *MET*ex14 skipping alterations status

When detecting the presence of alterations leading to *MET*ex14 skipping using tissue-based or plasma-based specimens, it is important that a well-validated and robust test is chosen to avoid false negative or false positive results. For the characteristics of tests used in clinical studies, see section 5.1.

Interstitial lung disease and pneumonitis

Interstitial lung disease (ILD) or ILD-like adverse reactions including pneumonitis have been reported in patients who received tepotinib monotherapy at the recommended dose regimen and may be fatal (see section 4.8).

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.

Monitoring of liver enzymes

Increase in ALT and/or AST have been reported in patients who received tepotinib monotherapy at the recommended dose regimen (see section 4.8).

Liver enzymes (ALT and AST) and bilirubin should be monitored prior to the start of TEPMETKO treatment and thereafter as clinically indicated. If grade 3 or higher increases (ALT and/or AST greater than 5 times ULN) occur, dose adjustment or discontinuation is recommended (see section 4.2).

QTc prolongation

QTc prolongation was reported in a limited number of patients (see section 4.8). In patients at risk of developing QTc prolongation, including patients with known electrolyte disturbances or taking concomitant medicinal products known to have QTc prolongation effects, monitoring is recommended as clinically indicated (e.g. ECG, electrolytes).

Embryo-foetal toxicity

Tepotinib can cause foetal harm when administered to pregnant women. Pregnancy testing is recommended in women of childbearing potential prior to initiating treatment with TEPMETKO. Women of childbearing potential and males with female partners of childbearing potential should use effective contraception during TEPMETKO treatment and for at least 1 week after the last dose (see section 4.6).

Interaction with other medicinal products

Concomitant use of TEPMETKO with strong CYP and P-gp inducers or dual strong CYP3A and P-gp inhibitors should be avoided (see section 4.5).

Interpretation of laboratory tests

In vitro 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 medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

Effects of other medicinal products on tepotinib

CYP 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 and P-gp inducers (e.g. carbamazepine, phenytoin, rifampicin, St. John's wort) should be avoided.

Dual strong CYP3A and P-gp inhibitors, and P-gp inhibitors

The effect of strong CYP3A inhibitors or P-gp inhibitors on TEPMETKO 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 TEPMETKO with dual strong CYP3A and P-gp inhibitors (e.g. itraconazole, ketoconazole, ritonavir, saquinavir, nelfinavir) should be avoided. Also for P-gp inhibitors that are not strong inhibitors of CYP3A (e.g. quinidine, verapamil) an increase in exposure for tepotinib cannot be excluded. Therefore, caution and monitoring for adverse reactions is advised in case of concomitant use.

Acid-reducing agents

Co-administration of omeprazole under fed conditions had no clinically relevant effect on the pharmacokinetic profile of a single dose of tepotinib 450 mg and its metabolites (geometric mean ratio for tepotinib of 110% for AUC_{inf} (90% CI: 102; 119) and of 104% for C_{max} (90% CI: 93; 117); similar effect on metabolites observed).

Effects of tepotinib on other medicinal products

P-gp substrates

Tepotinib is an inhibitor of P-gp. Administration of tepotinib 450 mg orally once daily for 8 days increased the AUC of the sensitive P-gp substrate dabigatran etexilate by approximately 50% and C_{max} by approximately 40%. Dose adjustment of dabigatran etexilate may be needed in case of concomitant use. Caution and monitoring for adverse reactions of other P-gp-dependent substances with a narrow therapeutic index (e.g. digoxin, aliskiren, everolimus, sirolimus) is recommended during co-administration with TEPMETKO.

BCRP substrates

Tepotinib can inhibit the transport of substrates of the breast cancer resistance protein (BCRP) *in vitro* (see section 5.2). Monitoring for adverse reactions of sensitive BCRP substrates (e.g. rosuvastatin, methotrexate, topotecan) is recommended during co-administration with TEPMETKO.

Substrates of OCT and MATE

Based on *in vitro* data, tepotinib or its metabolite may have the potential to alter the exposure of substrates of the transporters OCT1 and 2 and MATE1 and 2 (see section 5.2). The most clinically relevant example of substrates of these transporters is metformin. Monitoring of the clinical effects of metformin is recommended during co-administration with TEPMETKO.

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.

Hormonal contraceptives

It is currently unknown whether tepotinib may reduce the effectiveness of systemically acting hormonal contraceptives. Therefore, women using systemically acting hormonal contraceptives should add a barrier method during TEPMETKO treatment and for at least 1 week after the last dose (see section 4.6).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/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. Women using systemically acting hormonal contraceptives should add a barrier method during TEPMETKO treatment and for at least 1 week after the last dose (see section 4.5).

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 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.

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 child 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 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, except for reduced secretion in seminal vesicles of male rats at comparable human clinical exposure (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

Summary of the safety profile

The most common adverse reactions in ≥ 20% of exposed to tepotinib at the recommended dose in the target indication are oedema (77.3% of patients), mainly peripheral oedema (65.6%), nausea (30.2%), hypoalbuminaemia (28.5%), diarrhoea (27.8%) and increase in creatinine (27.1%).

The most common serious adverse reactions in ≥ 1% of patients are peripheral oedema (3.1%), generalised oedema (2.1%) and ILD (1.4%).

The percentage of patients who had adverse events leading to permanent treatment discontinuation is 23.7%. The most common adverse reactions leading to permanent discontinuation in ≥ 1% of patients are peripheral oedema (4.5%), oedema (1.0%), genital oedema (1.0%) and ILD (1.0%).

The percentage of patients who had adverse events leading to temporary treatment discontinuation is 49.1%. The most common adverse reactions leading to temporary discontinuation in ≥ 2% of patients are peripheral oedema (18.6%), increase in creatinine (5.8%), generalised oedema (3.8%), oedema (3.8%), increase in ALT (2.7%), nausea (2.7%) and increase in amylase (2.1%).

The percentage of patients who had adverse events leading to dose reduction is 34.0%. The most common adverse reactions leading to dose reduction in ≥ 2% of patients are peripheral oedema (15.1%), increase in creatinine (3.1%), generalised oedema (2.7%) and oedema (2.4%).

List of adverse reactions

Adverse reactions described in the list below reflect exposure to tepotinib in 484 patients with various solid tumours enrolled in five open-label studies, in which patients received tepotinib as a single agent at a dose of 450 mg once daily. The frequencies of adverse reactions are based on all-cause adverse event frequencies identified in 291 patients exposed to tepotinib at the recommended dose in the target indication, whereas frequencies for changes in laboratory parameters are based on worsening from baseline by at least 1 grade and shifts to ≥ grade 3. Median duration of treatment was 27.6 weeks (range 0 to 220).

Frequencies presented may not be fully attributable to tepotinib alone but may contain contributions from the underlying disease or from other medicinal products used concomitantly.

The severity of adverse reactions was assessed based on the Common Terminology Criteria for Adverse Events (CTCAE), defining grade 1 = mild, grade 2 = moderate, grade 3 = severe, grade 4 = life threatening and grade 5 = death.

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 (VISION)

System organ class/Adverse reaction	TEPMETKO N=291		
	Frequency category	**All grades %**	**Grade ≥ 3 %**
Metabolism and nutrition disorders			
Decrease in albumin *	Very common	76	7.9
Cardiac disorders			
QT prolongation *	Common	2.1	
Respiratory, thoracic and mediastinal disorders			
ILD-like reactions [a]*	Common	2.7	0.3
Gastrointestinal disorders			
Nausea	Very common	30	1.0
Diarrhoea	Very common	28	0.3
Increase in amylase *	Very common	23	4.5
Increase in lipase *	Very common	18	4.5
Vomiting	Very common	14	1.0
Hepatobiliary disorders			
Increase in alkaline phosphatase (ALP) *	Very common	48	1.7
Increase in alanine aminotransferase (ALT) *	Very common	43	4.1
Increase in aspartate aminotransferase (AST) *	Very common	34	3.1
Renal and urinary disorders			
Increase in creatinine *	Very common	55	0.3
General disorders and administration site conditions			
Oedema [b]*	Very common	77	13

* Additional information on the respective adverse reaction is provided below.
a includes terms interstitial lung disease, pneumonitis, acute respiratory failure
b includes terms oedema peripheral, oedema, generalised oedema, oedema genital, face oedema, localised oedema, periorbital oedema, peripheral swelling, scrotal oedema

Description of selected adverse reactions

Interstitial lung disease

Interstitial lung disease (ILD) or ILD-like reactions have been reported in 8 patients (2.7%), including 1 case of grade 3 or higher; serious cases occurred in 4 patients (1.4%), 1 case was fatal. Treatment was permanently discontinued in 5 patients and temporarily in 3 patients. Median time to onset of ILD was 9.4 weeks. For clinical recommendations, see sections 4.2 and 4.4.

Increase in liver enzymes

ALT and/or AST increase led to permanent treatment discontinuation in 1 patient and infrequently led to temporary discontinuation (3.1%) or dose reduction (0.7%) of tepotinib. Median time to first onset for ALT and/or AST increase of any grade reported as an adverse event by investigators was 6.1 weeks and the median time to resolution was 4.9 weeks. 82% of patients recovered from all events. For clinical recommendations, see sections 4.2 and 4.4.

ALP increase did not lead to any dose reductions, temporary treatment discontinuation or permanent discontinuation. The observed ALP increase was not associated with cholestasis. Median time to first onset for ALP increase of any grade reported as an adverse event by investigators was 4.4 weeks and the median time to resolution was 11 weeks. 60% of patients recovered from all events.

Oedema

The most frequently reported event was peripheral oedema (65.6% of patients), followed by oedema (9.3%) and generalised oedema (5.8%). Median time to onset of any-grade oedema was 9.0 weeks and the median time to resolution was 69 weeks. 17% of patients recovered from all events. 7.2% of patients had oedema events leading to permanent treatment discontinuation, of whom 4.5% had peripheral oedema. 26% of patients temporarily discontinued treatment and 21% of patients had dose reductions due to oedema. Most frequently peripheral oedema led to temporary treatment discontinuation and dose reductions (19% and 15%, respectively). Generalised oedema events led to a dose reduction in 2.7% of patients, to temporary treatment discontinuation in 3.8% and to permanent discontinuation in 0.7%.

Increase in creatinine

Increase in creatinine led to permanent treatment discontinuation in 2 patients (0.7%), temporary treatment discontinuation in 5.8% of patients and dose reduction in 3.1% of patients. Median time to onset of increase in creatinine reported as an adverse event by investigators was 3.1 weeks and the median time to resolution was 11 weeks. 61% of patients recovered from all events. The observed increases in creatinine are thought to occur mainly due to inhibition of renal tubular secretion (see section 4.4).

Hypoalbuminaemia

Hypoalbuminaemia appeared to be long-lasting but did not lead to permanent treatment discontinuation. Dose reduction (1.0%) and temporary discontinuation (1.4%) were infrequent. Median time to onset of any-grade hypoalbuminaemia reported as an adverse event by investigators was 9.4 weeks; a median time to resolution could not be estimated. 27% of patients recovered from all events.

Increase in amylase or lipase

Increases in amylase or lipase reported as an adverse event by investigators were asymptomatic and not associated with pancreatitis. 3.1% of patients temporarily discontinued treatment and there were no permanent treatment discontinuation or dose reduction. Median time to onset of any grade in lipase/amylase increase was 12 weeks and median time to resolution was 5.9 weeks. 65% of patients recovered from all events.

QTc prolongation

QTcF prolongation to > 500 ms was observed in 6 patients (2.1%) and a QTcF prolongation by at least 60 ms from baseline in 15 patients (5.2%) (see section 4.4). The findings were isolated and asymptomatic; the clinical significance is unknown.

Additional information on special populations

Elderly

Of 291 patients with *MET*ex14 skipping alterations in the VISION study who received 450 mg tepotinib once daily, 78% were 65 years or older, and 8% were 85 years or older. The occurrence of grade ≥ 3 events increased with age. Treatment-related serious events were more frequent in patients aged ≥ 75 years and < 85 years (19.8%) or those aged ≥ 85 years (20.8%) when compared to those younger than 65 years (7.8%), although this comparison is limited by the small sample size in patients aged ≥ 85 years.

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 the national reporting system listed in Appendix V.

4.9 Overdose

Tepotinib has been investigated at doses up to 1 261 mg, but experience with doses higher than the recommended therapeutic dose is limited.

The symptoms of overdose are expected to be in the range of known adverse reactions (see section 4.8). There is no specific antidote for TEPMETKO. Treatment of overdose is directed to symptoms.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action

Tepotinib is a reversible Type I adenosine triphosphate (ATP)-competitive small molecule inhibitor of MET. Tepotinib blocked MET phosphorylation and MET-dependent downstream signalling such as the phosphatidylinositol 3-kinase/protein kinase B (PI3K/Akt) and mitogen-activated protein kinase/extracellular-signal regulated kinase (MAPK/ERK) pathways in a dose-dependent manner.

Tepotinib demonstrated pronounced anti-tumour activity in tumours with oncogenic activation of *MET*, such as *MET*ex14 skipping alterations.

Pharmacodynamic effects

Cardiac electrophysiology

A concentration-dependent increase in QTc interval was observed in the concentration-QTc analysis. At the recommended dose, no large mean increases in QTc (i.e. > 20 ms) were detected in patients with various solid tumours. The QTc effect of tepotinib at supratherapeutic exposures has not been evaluated. See sections 4.4. and 4.8.

Detection of METex14 skipping status

In clinical studies, identification of *MET*ex14 skipping alterations relied on next generation sequencing using RNA or DNA (1 patient) extracted from formalin-fixed paraffin embedded (FFPE) tumour tissue or using circulating cell free DNA from plasma. Additionally, a RNA-based reverse transcriptase polymerase chain reaction-based method specific for detecting *MET*ex14 skipping alterations from fresh frozen tissue was available to patients in Japan.

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 = 275). 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 received tepotinib as first-line (50%), second-line (32%) or later line (18%) therapy.

Patients who received tepotinib for second- or later line therapy (n = 138) had a median age of 71 years (range 41 to 89), 51% were female and 49% male. The majority of patients were white (55%), followed by Asian patients (38%) and were never (54%) or former smokers (29%). Most patients were ≥ 65 years of age (75%) and 36% of patients were ≥ 75 years of age. The majority of patients (96%) had stage IV disease, 80% had adenocarcinoma histology. Thirteen percent of the patients had stable brain metastases. Eighty-six percent of patients had received prior platinum-based cancer therapy and 53% of patients had received immune-based cancer therapy, including 37% of patients who had received immunotherapy as monotherapy. *MET*ex14 skipping was prospectively detected by testing from tumour tissue in 43% of patients and by testing from plasma in 36% of patients; 21% of patients tested positive with both methods.

Patients received 450 mg tepotinib once daily until disease progression or unacceptable toxicity. Median treatment duration was 6.67 months (range 0.03 to 50.60).

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.

Clinical outcomes in the VISION study by IRC assessment

Efficacy parameter	Overall population N = 275	Previously treated patients N = 138
Objective response rate (ORR), % [α] [95% CI]	49.1 [43.0, 55.2]	44.2 [35.8, 52.9]
Median duration of response (mDoR), months [β] [95% CI]	13.8 [9.9, 19.4]	11.1 [8.4, 18.5]

IRC=Independent Review Committee, CI=confidence interval
α Only includes partial response
β Product-limit (Kaplan-Meier) estimates, 95% CI for the median using the Brookmeyer and Crowley method

Efficacy outcome was independent of the testing modality (in plasma or tumour specimens) 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 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).

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) (see section 4.5).

Biotransformation

Overall, metabolism is a major route of elimination, but no single metabolic pathway accounted for more than 25% of tepotinib elimination. Only one major circulating plasma metabolite has been identified, MSC2571109A. There is only a minor contribution of the major circulating metabolite to the overall efficacy of tepotinib in humans.

In-vitro pharmacokinetic interaction studies

Effects of tepotinib on other transporters: Tepotinib or its major circulating metabolite inhibit P-gp, BCRP, OCT1 and 2 and MATE1 and 2 at clinically relevant concentrations. At clinically relevant concentrations tepotinib presents no risk for organic-anion-transporting polypeptide (OATP) 1B1 and OATP1B3 or organic anion transporter (OAT) 1 and 3.

Effects of tepotinib on UDP-glucuronosyltransferase (UGT): Tepotinib is an inhibitor of UGT1A9 at clinically relevant concentrations, but the clinical relevance is unknown. Tepotinib and its major circulating metabolite are not inhibitors of the other isoforms (UGT1A1/3/4/6 and 2B7/15/17) at clinically relevant concentrations.

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, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP2E1. Tepotinib or its major circulating metabolite do not induce CYP1A2 and 2B6.

Elimination

After intravenous administration of single doses, a total systemic clearance (geometric mean and geoCV%) of 12.8 L/h was observed.

After a single oral administration of a radiolabelled dose of 450 mg tepotinib, tepotinib was mainly excreted via the faeces (approximately 78% of the dose was recovered in faeces), with urinary excretion being a minor excretion pathway.

Biliary excretion of tepotinib is a major elimination pathway. The unchanged tepotinib represented 45% and 7% of the total radioactive dose in faeces and urine, respectively. The major circulating metabolite accounted for only about 3% of the total radioactive dose 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 $AUC_{0\text{-}24h}$.

Dose and time dependence

Tepotinib exposure increases approximately 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 clinically meaningful effect of age (range 18 to 89 years), race, gender or body weight, on the pharmacokinetics of tepotinib. Data on ethnicities other than Caucasian or Asian are limited.

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 studies.

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% lower AUC and 29% lower C_{max}) in patients with moderate hepatic impairment (Child-Pugh Class B) compared to healthy subjects. Based on unbound tepotinib concentrations, AUC was about 13% and 24% higher in patients with mild and moderate hepatic impairment, respectively, compared to healthy subjects. The pharmacokinetics of tepotinib have not been studied in patients with severe (Child Pugh Class C) hepatic impairment.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology or repeated dose toxicity.

Genotoxicity

No mutagenic or genotoxic effects of tepotinib were observed in *in vitro* and *in vivo* studies. However, the maximally feasible dose used in the *in vivo* micronucleus test in rats provided an estimated systemic exposure close to 3-fold lower than the clinical plasma exposure. The major circulating metabolite was 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 (approximately 61% of the human exposure at the recommended dose of TEPMETKO 450 mg once daily based on AUC) was discontinued due to severe maternal toxic effects. In the 150 mg per kg group (approximately 40% of the human exposure at the 450 mg clinical dose), 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 mg per kg (approximately 14% of the human exposure at the 450 mg clinical dose) 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 (approximately 1.3% of the human exposure at the 450 mg clinical dose), 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, except for reduced secretion in seminal vesicles of male rats in a 4-week repeat-dose toxicity study at 450 mg per kg per day (comparable to human exposure at the 450 mg clinical dose).

Environmental risk assessment

Environmental risk assessment studies have shown that tepotinib has the potential to be very persistent and toxic to the environment.

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 (E171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require special storage conditions.

6.5 Nature and contents of container

Aluminium/Polyvinyl chloride-polyethylene-polyvinylidene chloride-polyethylene-polyvinyl chloride (Al/PVC-PE-PVDC-PE-PVC) blister. Pack of 60 film-coated tablets.

6.6 Special precautions for disposal

This medicinal product may pose a risk to the environment (see section 5.3). Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Merck Europe B.V.
Gustav Mahlerplein 102
1082 MA Amsterdam
The Netherlands

8. MARKETING AUTHORISATION NUMBER

EU/1/21/1596/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Merck Healthcare KGaA, Frankfurter Strasse 250, 64293 Darmstadt, Germany

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

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

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 Europe B.V.
Gustav Mahlerplein 102
1082 MA Amsterdam
The Netherlands

12. MARKETING AUTHORISATION NUMBER

EU/1/21/1596/001

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 tablets
tepotinib

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Merck Europe B.V.

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 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 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 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

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 to treat adults with lung cancer that has spread to other parts of the body or cannot be removed by surgery. The medicine is given, when the cancer cells have an alteration in the *MET* (mesenchymal-epithelial transition factor) gene and previous treatment has not helped to stop your disease.

An alteration in the *MET* gene can lead to production of an abnormal protein, which can then cause uncontrolled cell growth and cancer. By blocking the action of the abnormal protein, TEPMETKO may slow or stop the cancer from growing. It may also help to shrink the cancer.

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 before taking this medicine if you have any questions.

Lung or breathing problems
TEPMETKO can sometimes cause sudden breathing difficulties that may be associated with a fever and cough. Tell your doctor right away if you develop any new or worsening symptoms (see section 4) as these may be signs of a serious lung condition (interstitial lung disease) which needs immediate attention. Your doctor may need to treat you with other medicines and interrupt your TEPMETKO treatment.

Monitoring of liver function
Your doctor will carry out blood tests to check how well your liver is working before you are treated with TEPMETKO, and as necessary during treatment.

Monitoring of heart function
Your doctor may carry out ECG tests as necessary during treatment to check whether TEPMETKO affects your heart rhythm.

Contraception
This medicine should not be used in pregnancy as it can harm the unborn baby. Men and women should use effective contraception during TEPMETKO treatment and for at least 1 week after the last dose. Your doctor will give you guidance on appropriate methods of contraception. See 'Pregnancy' below.

Children and adolescents
This medicine has not been studied in patients below 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 – used to treat epileptic seizures (fits) or nerve pain
- phenytoin – used to treat epileptic seizures (fits)
- rifampicin – used to treat tuberculosis (TB)
- St. John's wort – a herbal medicine used to treat depression
- itraconazole or ketoconazole – used to treat fungal infections
- ritonavir, saquinavir or nelfinavir – used to treat HIV infection
- quinidine or verapamil – used to treat irregular heart beat

TEPMETKO may affect how well the following medicines work and/or increase side effects of these medicines:
- dabigatran – used to prevent stroke or venous thrombosis/pulmonary embolism
- digoxin – used to treat irregular heart beat or other heart problems
- aliskiren – used to treat high blood pressure
- everolimus – used to treat cancer
- sirolimus – used to prevent organ rejection in transplanted patients
- rosuvastatin – used to treat high blood fat levels
- methotrexate – used to treat inflammatory diseases or cancer
- topotecan – used to treat cancer
- metformin – used to treat diabetes

Pregnancy and breast-feeding
Pregnancy
Do not take TEPMETKO if you are pregnant or suspect you are pregnant, unless advised by your doctor. This medicine may harm the unborn baby. Pregnancy testing is recommended prior to starting treatment with TEPMETKO.

Contraception in males and females
If you are female and able to have children, 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') as you will need a second method of contraception during this time.

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

Your doctor will give you guidance on appropriate methods of contraception.

Breast-feeding
It is not known whether TEPMETKO may pass to the baby via breast milk. Stop breast-feeding your baby while you are treated with this medicine and for at least 1 week after the last dose.

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

TEPMETKO contains lactose
TEPMETKO contains 4.4 mg lactose monohydrate 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 2 tablets of TEPMETKO taken by mouth once daily. You may continue to take this medicine daily as long as you are benefitting from it and are not having intolerable side effects. In case of intolerable side effects, your doctor may advise you to reduce the dose to 1 tablet daily or interrupt the treatment for some days.

Take the tablets with food or shortly after a meal, swallow them whole and do not chew. This will ensure that the whole dose enters your system.

If you take more TEPMETKO than you should
Experience with overdose of TEPMETKO is limited. Symptoms of overdose will most likely be similar to those mentioned under possible side effects (see section 4). If you have taken more TEPMETKO than you should, talk to your doctor.

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

4. Possible side effects

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

Serious side effects
Lung or breathing problems
Tell your doctor right away if you develop any new or worsening symptoms such as sudden breathing difficulties, cough or fever. These may be signs 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).

Other side effects
Talk to your doctor if you get any other side effects. These can include:

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) or being sick (vomiting)
- Diarrhoea
- Raised levels of creatinine in blood (a sign of possible kidney problems)
- Raised levels of alanine aminotransferase, aspartate aminotransferase or alkaline phosphatase in blood (a sign of possible liver problems)
- Raised levels of amylase or lipase in blood (a sign of possible digestive problems)
- Reduced levels of the protein albumin in blood

Common side effects (may affect up to 1 in 10 people)
- Change in electrical activity of the heart seen on ECG (QT prolongation)

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 the national reporting system listed in Appendix V. 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.

This medicine does not require any special storage conditions.

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 film-coated 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 oxide (E172) and titanium dioxide (E171) in the film-coating.

What TEPMETKO looks like and contents of the pack
TEPMETKO film-coated tablets are white-pink, oval, biconvex, approximately 18x9 mm in size and embossed with ‘M’ on one side and plain on the other side. Each pack contains 60 tablets in a transparent blister, which consists of a multilayer composite form foil and an aluminium lidding.

Marketing Authorisation Holder
Merck Europe B.V.
Gustav Mahlerplein 102
1082 MA Amsterdam
The Netherlands

Manufacturer
Merck Healthcare KGaA
Frankfurter Strasse 250
64293 Darmstadt
Germany

This leaflet was last revised in

Other sources of information
Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.