Date: 16 August 2021
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Tepmetko

International non-proprietary name: tepotinib as tepotinib hydrochloride monohydrate

Pharmaceutical form: film-coated tablets

Dosage strength: 225 mg

Route(s) of administration: oral

Marketing Authorisation Holder: Merck (Schweiz) AG

Marketing Authorisation No.: 68113

Decision and Decision date: approved (temporary authorisation in accordance with Art. 9a TPA) on 22 June 2021

Note:

Assessment Report as adopted by Swissmedic with all information of a commercially confidential nature deleted.

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About Swissmedic

Swissmedic is the Swiss authority responsible for the authorisation and supervision of therapeutic products. Swissmedic's activities are based on the Federal Act of 15 December 2000 (Status as of 1 January 2020) on Medicinal Products and Medical Devices (TPA, SR 812.21). The agency ensures that only high-quality, safe and effective drugs are available in Switzerland, thus making an important contribution to the protection of human health.

About the Swiss Public Assessment Report (SwissPAR)

- The SwissPAR is referred to in Article 67 para. 1 of the Therapeutic Products Act and the implementing provisions of Art. 68 para. 1 let. e of the Ordinance of 21 September 2018 on Therapeutic Products (TPO, SR 812.212.21).
- The SwissPAR provides information about the evaluation of a prescription medicine and the considerations that led Swissmedic to approve or not approve a prescription medicine submission. The report focuses on the transparent presentation of the benefit-risk profile of the medicinal product.
- A SwissPAR is produced for all human medicinal products with a new active substance and transplant products for which a decision to approve or reject an authorisation application has been issued.
- A supplementary report will be published for approved or rejected applications for an additional indication for a human medicinal product for which a SwissPAR has been published following the initial authorisation.
- The SwissPAR is written by Swissmedic and is published on the Swissmedic website. Information from the application documentation is not published if publication would disclose commercial or manufacturing secrets.
- The SwissPAR is a “final” document, which provides information relating to a submission at a particular point in time and will not be updated after publication.
- In addition to the actual SwissPAR, a concise version of SwissPAR that is more comprehensible to lay persons (Public Summary SwissPAR) is also published.

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1 Terms, Definitions, Abbreviations

1L	First line
2L	Second line
ADA	Anti-drug antibody
ADME	Absorption, Distribution, Metabolism, Elimination
ALK	Anaplastic lymphoma kinase
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
AST	Aspartate amino-transferase
ATC	Anatomical Therapeutic Chemical Classification System
ATP	Adenosine triphosphate
AUC	Area under the plasma concentration-time curve
AUC0-24h	Area under the plasma concentration-time curve for the 24-hour dosing interval
CAS	Chemical Abstracts Service
CI	Confidence interval
CL	Clearance
Cmax	Maximum observed plasma/serum concentration of drug
cMET	Receptor tyrosine kinase mesenchymal-epithelial transition factor
CNS	Central nervous system
CR	Complete remission
CYP	Cytochrome P450
DMSO	Dimethyl sulfoxide
DoR	Duration of response
ECOG	Eastern Cooperative Oncology Group
eGFR	Estimated Glomerular Filtration Rate
EGFR	Epidermal growth factor receptor
ERA	Environmental Risk Assessment
FTIR	Fourier-transform infrared spectroscopy
GC	Gas Chromatography
GLP	Good Laboratory Practice
HCC	Hepatocellular carcinoma
HGF	Hepatocyte growth factor
HS	Headspace
HPLC	High Performance Liquid Chromatography
IC_{50}	Half-maximal inhibitory concentration
ICH	International Council for Harmonisation
ICP-MS	Inductively Coupled Plasma Mass Spectrometry
Ig	Immunoglobulin
INN	International Nonproprietary Name
IRC	Independent Review Committee
ITT	Intention-to-Treat
IUPAC	International Union of Pure and Applied Chemistry
JAN	Japanese Accepted Names
KF	Karl Fischer
LoQ	List of Questions
MAH	Marketing Authorisation Holder
Max	Maximum
MET	Mesenchymal-epithelial transition factor
METex14	MET exon 14
Min	Minimum
MTD	Maximum tolerated dose
N/A	Not applicable
NCCN	National Comprehensive Cancer Network

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NO(A)EL	No Observed (Adverse) Effect Level
NSCLC	Non-small cell lung cancer
OR	Objective response
ORR	Objective response rate
OS	Overall survival
PD	Pharmacodynamics
PFS	Progression-free survival
PIP	Paediatric Investigation Plan (EMA)
PK	Pharmacokinetics
PopPK	Population PK
PR	Partial remission
PSP	Pediatric Study Plan (US-FDA)
PT	Preferred term
QD	once daily
RMP	Risk Management Plan
RP2D	recommended phase 2 dose
SAE	Serious adverse event
SwissPAR	Swiss Public Assessment Report
TEAE	Treatment-emergent adverse event
TPA	Federal Act of 15 December 2000 (Status as of 1 January 2020) on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 (Status as of 1 April 2020) on Therapeutic Products (SR 812.212.21)
UV	Ultraviolet
XRPD	X-ray Powder Diffraction

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2 Background Information on the Procedure

2.1 Applicant's Request(s)

New Active Substance status
The applicant requested the status of a new active entity for the active substance tepotinib as tepotinib hydrochloride monohydrate of the medicinal product mentioned above.

Orphan drug status
The applicant requested Orphan Drug Status in accordance with Article 4 a^{decies} no. 2 of the TPA. The Orphan Status was granted on 14 January 2021.

Temporary authorisation for human medical products
The applicant requested a temporary authorisation in accordance with Art. 9a TPA.

2.2 Indication and Dosage

2.2.1 Requested Indication

TEPMETKO (tepotinib) is indicated for the treatment of adult patients with advanced non-small cell lung cancer (NSCLC) harbouring MET tyrosine kinase receptor exon 14 (METex14) skipping alterations.

2.2.2 Approved Indication

Tepmetko is indicated for the treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) harbouring a *MET* tyrosine kinase receptor exon 14 (*MET*ex14) skipping mutation. The efficacy and safety of Tepmetko have not been studied in patients with other oncogenic driver mutations, including EGFR or ALK tumour aberrations (see section *Warnings and precautions*).

2.2.3 Requested Dosage

The recommended dose of TEPMETKO is 450 mg (equivalent to 2 film-coated tablets) once daily.

2.2.4 Approved Dosage

(see appendix)

2.3 Regulatory History (Milestones)

Application	26 August 2020
Formal control completed	26 August 2020
Predecision	21 January 2021
Answers to Predecision	21 February 2021
Second Predecision	20 May 2021
Answers to second Predecision	2 June 2021
Final Decision	22 June 2021
Decision	approval (temporary authorisation in accordance with Art. 9a TPA)

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3 Medical Context

Lung cancer is the leading cause of cancer death in men and the second leading cause of cancer death in women in the Western world. Non-small cell lung cancer (NSCLC) accounts for 80%-90% of lung cancers and approximately 2% (squamous cell carcinoma) to 3% (adenocarcinoma) of patients with NSCLC have tumours containing mesenchymal-epithelial transition (MET) gene alterations. The receptor tyrosine kinase mesenchymal-epithelial transition factor (cMET) is involved in tumour growth, vasculogenesis, migration, and invasion during cancer growth. In patients with lung cancer, mutations that disrupt MET exon 14 splicing tend to occur in older individuals (median age of 73 years), with a lower proportion of never-smokers relative to patients with other oncogene-driven lung cancers, and they are enriched in sarcomatoid histology, with a prevalence ranging from 8 to 22%.
According to the NCCN Guidelines, capmatinib, another MET inhibitor, is recommended in first line treatment of metastatic NSCLC with MET exon 14 skipping mutations. Otherwise, treatment for patients with advanced METex 14 skipping mutated NSCLC is no different from treatment of NSCLC without any molecular target. The literature regarding the specific treatment outcome of patients with METex14 skipping mutation NSCLC is scarce.

Tepotinib is an oral ATP-competitive MET inhibitor belonging to the family of type Ib inhibitors, which implies a high specificity for MET with fewer off target effects as compared with type Ia inhibitors, such as crizotinib.

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4 Quality Aspects

4.1 Drug Substance

INN: Tepotinib

Chemical names: **IUPAC; WHO:**

- 3-{1-[(3-{5-[(1-Methylpiperidin-4-yl)methoxy]pyrimidin-2-yl}phenyl)methyl]-6-oxo-1,6-dihydropyridazin-3-yl}benzonitrile hydrochloride hydrate

CAS Registry:

- 3-(1-(3-(5-(1-Methylpiperidin-4-ylmethoxy)-pyrimidin-2-yl)-benzyl)-1,6-dihydro-6-oxo-pyridazin-3-yl)-benzonitrile hydrochloride hydrate

JAN:

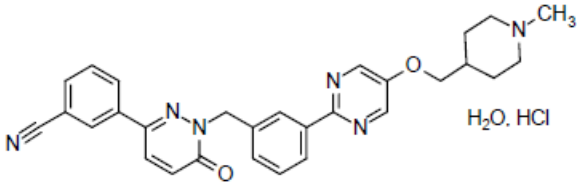
- 3-{1-[(3-{5-[(1-Methylpiperidin-4-yl)methoxy]pyrimidin-2-yl}phenyl)methyl]-6-oxo-1,6-dihydropyridazin-3-yl}benzonitrile monohydrochloride monohydrate

Chemical Abstracts Service/ Registry Number (CAS-RN): Tepotinib hydrochloride hydrate: 1100598-30-8
Tepotinib: 1100598-32-0

Molecular formula: Tepotinib hydrochloride hydrate: $C_{29}H31N_6O_3Cl$ ($C_{29}H_{28}N_6O_2 \cdot HCl \cdot H_2O$)
Tepotinib: $C_{29}H_{28}N_6O_2$

Molecular mass: Tepotinib hydrochloride hydrate: 547.05 (determined); 547.06 (calculated)
Tepotinib: 492.58

Molecular structure:



The molecule does not have chiral centers.

Physico-chemical properties: Tepotinib is a white to off-white powder which is freely soluble in aqueous hydrochloric acid (25% v/v); soluble in DMSO; slightly soluble in methanol, ethanol; very slightly soluble in 2-propanol, acetonitrile, water; practically insoluble in acetone, tetrahydrofuran.

Synthesis: Tepotinib is manufactured using well-defined starting materials and reagents.

Specification: To ensure a consistent quality of tepotinib, the specifications include tests for appearance, identity (FT-IR, HPLC), identification of chloride (chemical precipitation test), assay (HPLC), impurities (HPLC), residual solvents (HS-GC), water content (KF), elemental impurities (ICP-MS), sulfated ash/residue on ignition, microbial limits and polymorphic form (XRPD).

Stability: The bulk drug substance is stored in suitable containers. Based on stability studies, carried out according to the current guideline recommendations, a satisfactory retest period was established.

4.2 Drug Product

Description and composition: Tepmetko drug product is presented as white-pink, oval, biconvex film-coated tablets, with embossment “M” on one side and plain on the other side, containing 225 mg tepotinib, equivalent to 250 mg tepotinib hydrochloride hydrate.
The drug product contains tepotinib hydrochloride hydrate as the only drug substance (active pharmaceutical ingredient) and the following excipients: mannitol, magnesium stearate, microcrystalline cellulose, crospovidone, colloidal silicon dioxide, and Opadry II pink.

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Pharmaceutical development: The overall formulation development strategy was to obtain immediate-release film-coated tablets of suitable size with the intended quality, taking into account safety and efficacy of the drug product, and allowing convenient administration of a dose of 500 mg tepotinib hydrochloride hydrate.

Manufacture: The manufacturing process is described with a sufficient level of detail in order to achieve consistent tablet quality. Appropriate in-process controls are applied.

Specification: The finished product release specifications include appropriate tests for description, dimension (height), identification (HPLC, UV), assay, degradation products (HPLC), resistance to crushing (N), uniformity of dosage units, dissolution and microbial limits.
The test methods are adequately validated according to the recommendations of the current scientific guidelines.

Container-Closure System: The primary packaging of Tepmetko tablets is a transparent blister consisting of a multilayer composite form foil and an aluminium lidding foil, packed into carton boxes.

Stability: Appropriate stability data are presented for industrial-scale batches. Based on these data, a shelf-life was established. Based on stress stability data, it is recommended to store the drug product in the original packaging in order to protect from moisture.

4.3 Quality Conclusions

Satisfactory and consistent quality of drug substance and drug product has been demonstrated.

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5 Nonclinical Aspects

The applicant submitted a comprehensive nonclinical study package that met or exceeded the requirements according to ICH S9 for the applied indication. All relevant safety studies were conducted in compliance with GLP.

Pharmacology

In *in vitro* kinase assays, tepotinib inhibited the activity of MET with IC_{50} values of 1.7 to 1.8 nM, and also showed activity against several MET mutants at 1 µM. Based on crystal structure analyses, tepotinib binds to the ATP pocket of MET, i.e. is a type I, ATP-competitive inhibitor.
In cell-based *in vitro* assays, tepotinib at low nanomolar concentrations induced potent and persistent inhibition of the phosphorylation of MET (induced by hepatocyte growth factor (HGF) or HGF-independent) and downstream effectors. Tepotinib inhibited the proliferation of cells with high-level MET gene amplification (IC_{50} 6.2 nM), whereas no significant effect on the cell proliferation was induced in cancer cells with low expression of non-activated MET. Tepotinib also inhibited anchorage-independent growth of murine fibroblasts co-transfected with human HGF and MET (IC_{50} 1.8 nM) and migration of H441 human NSCLC cells (MET overexpression) at ≥ 0.1 nM.
In studies with mouse xenograft models bearing subcutaneous tumours with MET alterations from various cancer types, including NSCLC, oral administration of tepotinib led to dose-dependent inhibition of tumour growth or regression at tolerated doses (≥ 25 mg/kg/day). Tepotinib at 125 mg/kg/day also showed significant anti-tumour activity in two models with orthotopic implantation of tissue from brain metastases of lung tumour origin. The MET alterations used in the *in vivo* studies included METex14 skipping alterations, high-level MET gene amplification (> 10 MET gene copies), MET overexpression, and constitutive HGF/MET expression. PK/PD studies with single dose administration at ≥ 3 mg/kg showed dose-dependent inhibition of MET phosphorylation in tumour tissue. Tepotinib concentration in tumour tissue was above that in plasma.
In three mouse models with xenografts derived from human NSCLC cells that had both MET overexpression and epidermal growth factor receptor (EGFR) kinase domain mutation, oral administration of 100 mg/kg tepotinib had no significant anti-tumour effect. The results of these studies indicate that tepotinib might have significantly less or no activity against tumours that also depend on drivers other than MET.
The major human plasma metabolite MSC2571109A also showed *in vitro* MET inhibition at low concentrations (IC_{50} 13-26 nM), but had no significant anti-tumour activity *in vivo*.
The results of secondary pharmacodynamics studies indicate that tepotinib has relatively high specificity for MET vs. other kinases. However, several off-target receptor molecules were identified in screening studies, and interactions with the melatonin receptor MT3 (IC_{50} 2.4 nM) and imidazoline receptor I1 (IC_{50} 35 nM) might be clinically relevant.
Although MET signalling is necessary for skin wound healing, no adverse effect on wound healing was observed in mice following oral administration of tepotinib (up to 50 mg/kg/day for up to 10 days). Tepotinib inhibited the hERG channel current *in vitro* with an IC_{50} value approx. 25-fold the clinical $C_{max,free}$. In the *in vivo* safety pharmacology studies and in the repeat-dose toxicity studies, no adverse effects on cardiovascular system, respiratory function, or central nervous system were observed. However, tepotinib exposure in these studies was often below or just within the clinical exposure range. In the clinical studies, there were no reports of significant effects on respiratory rate or CNS function, but cases of QT prolongation were observed. Thus, a risk cannot be excluded.

Pharmacokinetics

The pharmacokinetics of tepotinib in the nonclinical species selected for safety assessment (rat, dog, and rabbit) was sufficiently characterised. Oral bioavailability was about 20-30% in male rats and dogs and slightly higher in female rats (55%). Female rats also showed consistently higher plasma exposure than males in all studies; a tendency towards higher exposure was also noted in the dog studies. Across species, T_{max} was between 2 h and 6 h. Plasma elimination half-lives after single oral administration were 3.2 h in rats and 7.6 h in dogs. Some accumulation upon repeated dosing occurred in rats (ratio ≤ 2), dogs (up to 8.9 in dogs at 30 mg/kg/day in the chronic study), and

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pregnant rabbits (6.5-7.6 at ≥ 50 mg/kg/day). In dogs, there were significant inter-individual differences in tepotinib exposure, with individual animals showing much higher plasma levels than other animals of the same dose group. The high plasma concentrations correlated with changes in clinical chemistry parameters and histopathology.
In an *in vitro* study, tepotinib blood-to-plasma ratios were > 1 in nonclinical species (mouse, rat, rabbit, dog, and monkey), whereas there was an equal distribution of tepotinib in human blood and plasma (ratio 1.0 at 1 µM). In studies with oral administration of ^{14}C-tepotinib to mice or rats, there was wide tissue distribution, with the highest radioactivity concentrations present in lungs, stomach, small and large intestine, liver, and kidneys. In tumour-bearing mice, drug-related radioactivity persisted longer in tumour tissue than in other tissues. Studies with intravenous administration showed high concentrations in liver and intestine shortly after dosing, which is consistent with the main excretion route (biliary/faecal across all species). In pigmented rats, drug-related radioactivity persisted in melanin-containing tissues. Studies on the distribution of tepotinib or metabolites to milk or via the placental barrier were not conducted.
The plasma protein binding of tepotinib in mouse, rat, rabbit, monkey, and human was ≥ 97%. In dog, plasma protein binding was slightly lower (ca. 94%). The metabolite MSC2571109 also showed high plasma protein binding (≥ 97.5%) across species. Based on the results of additional studies, tepotinib and MSC2571109 mainly bind to serum albumin.
In *in vitro* metabolism studies with hepatocytes, diastereomeric N-oxides (M508-1 and M508-2), the dimethyl metabolite M478, and two glucuronide conjugates (mouse-specific M684 and human-specific M668) were detected as main metabolites of tepotinib. Based on the results of these studies, rat and dog were selected as the nonclinical species for safety assessment. However, in the clinical mass balance study, metabolite MSC2571109A was identified as the major plasma metabolite. This metabolite was detected at significantly lower levels in plasma from rats and dogs and, thus, represents a disproportionate human metabolite (see below, Toxicology). The minor human plasma metabolites M508-1, M508-2, M478, and MSC2571107A (enantiomer of MSC2571109A) were also detected in plasma from the nonclinical species.

Toxicology
Studies to evaluate the toxicity of tepotinib following repeated dose administration were conducted in rats and dogs. The route of administration (oral) and frequency of dosing (daily) in the nonclinical studies are consistent with the proposed clinical setting. The duration of the long-term studies (26 weeks in rats and 39 weeks in dogs) exceeds the requirements according to ICH S9.
In studies with periods ranging from 2 to 4 weeks, the maximum tolerated doses (MTD) of tepotinib in rats and dogs were determined at 450 mg/kg/day and 120 mg/kg/day, respectively, associated with plasma exposures within (female rats) or below (male rats and dogs) clinical exposure in terms of AUC. Higher doses caused mortality in rats and markedly decreased food consumption in dogs.
The liver/hepatobiliary system was the main target organ in both species. Increases in liver enzymes (e.g. ALT, AST, alkaline phosphatase) and increases in bile acids and bilirubin (dogs only) were observed across studies. Microscopic changes in dogs included bile duct hyperplasia, increased numbers of periportal cholangioles, pericholangitis and pericholangiolar fibrosis, and necrosis in bile duct epithelium and liver cells. In rats, liver cell hypertrophy was seen in the chronic study at the high dose of 135 mg/kg/day; in the 4-week study, hepatocellular necrosis, mononuclear infiltrates and mild hypertrophy of bile duct epithelium were observed at the MTD of 450 mg/kg/day. Liver changes observed in the long-term studies in rats and dog were reversible or showed a trend to reversibility. In the clinical studies, increases in ALT and AST were frequently observed, but there were no relevant increases in bilirubin as a marker for cholestatic liver damage.
Gastrointestinal disorders were frequently seen with tepotinib in the dog studies, which is consistent with respective reports in the clinical trials. In rats treated with doses at or above the MTD of 450 mg/kg/day, local toxicity occurred in stomach and/or large intestine (ulceration, necrosis). However, these findings are considered high-dose effects and of low clinical relevance.
Decreased serum albumin was generally observed in rats and dogs following tepotinib treatment, which is consistent with clinical reports of hypoalbuminaemia; this is considered a class-related effect of MET inhibitors.

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In rats, alveolar macrophage aggregates (foam cells) were seen in all repeat-dose toxicity studies. These findings might correlate with interstitial lung disease observed in the clinical trials (identified risk). Other tepotinib-related histological changes identified in the nonclinical studies, e.g. in adrenals, lymphoid tissues, pancreas, or mammary gland, are considered of low clinical relevance since the effects were rather mild.
At the NOAELs in the chronic toxicity studies, tepotinib plasma exposures were about 4% the clinical exposure. The lack of safety margins is acceptable considering the requested indication (treatment of advanced cancer).
Tepotinib tested negative for genotoxicity in a standard test battery according to ICH S2(R1). The metabolite MSC2571109A showed no mutagenic potential *in vitro* in the bacterial mutation assay or in mammalian cells. Carcinogenicity studies with tepotinib have not been conducted and are not warranted for the requested indication according to ICH S9.
In preliminary embryo-foetal development studies in rabbits, oral treatment with tepotinib induced skeletal malformations at plasma exposures below the clinical exposure. Due to the teratogenic potential, tepotinib should not be used during pregnancy, and women of childbearing potential should use contraception.
Dedicated studies on fertility and pre-/postnatal development with tepotinib have not been conducted and are not warranted for the requested indication according to ICH S9. Evaluation of sperm samples and reproductive organs in the repeat-dose toxicity studies did not reveal tepotinib-related changes. The risk for effects on fertility is therefore considered low.
Although not required per ICH S9, the pharmacological properties and *in vitro* genotoxicity of the disproportional human metabolite MSC2571109A were examined in dedicated studies (see above). Additional studies are not needed. Specific safety assessment for the minor human-specific metabolite M668 (glucuronide conjugate) is also not required.
Tepotinib showed phototoxic potential in the *in vitro* 3T3 neutral red uptake assay, but tested negative for phototoxicity in an *in vivo* study in rats at plasma exposures that were within clinical exposure. This indicates a low risk for patients.
The control levels for impurities are considered adequate.
The summary of the main safety findings in the nonclinical part of the safety specification in the RMP is considered adequate.
According to the ERA, tepotinib fulfils the criteria for persistence and toxicity. Bioaccumulation in fish was not investigated but was considered unlikely due to the rapid shift of tepotinib to sediment. Based on these data, a risk to the environment resulting from the use of tepotinib cannot be excluded.

Nonclinical Conclusions
Overall, the submitted preclinical documentation is considered sufficient to support the approval of tepotinib in the applied indication. The results of the pharmacology studies indicate that tepotinib is a potent MET inhibitor with the ability to elicit an *in vivo* response against tumours that are dependent on increased MET activity. Tepotinib-associated findings in the toxicity studies generally correlate with findings in the clinical studies. The relevant safety data are included in the information for healthcare professionals.

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6 Clinical and Clinical Pharmacology Aspects

6.1 Clinical Pharmacology

The PK of tepotinib has been studied in healthy subjects as well as in cancer patients with various types of tumours in the dose range of 30 -1400 mg.

ADME

Absorption
After single oral dose administration of 500 mg tepotinib, measurable plasma concentrations were detected after a median t_{lag} of ~0.5 h. C_{max} was reached after median times of ~12 h under fasted conditions and ~8 h under fed conditions. Thereafter, concentrations declined in a mono-exponential fashion.

Food effect
A relevant food effect was observed: Upon intake of the intended marketing formulation with a high-fat, high-calorie meal, tepotinib AUC was increased to about 1.6-fold and C_{max} to about 2-fold. Consequently, tepotinib should be taken in combination with food.

The mean absolute bioavailability of tepotinib following oral administration of 500 mg tepotinib together with a high-fat, high-calorie meal, was 72% (range: 62% to 81%).

PK after multiple doses and dose-proportionality
Following intake of multiple doses of 500 mg tepotinib QD, tepotinib accumulated ~ 3-fold. Attainment of steady state has not been formally assessed.

Following the intake of both single and multiple doses, C_{max} and AUC of tepotinib increased in an almost dose-proportional manner in the dose range of 30-500 mg, but in a less than dose-proportional manner at doses above 500 mg, probably due to limited solubility.

Distribution
The blood to plasma ratio was ~0.8, indicating that a certain amount of tepotinib and/or its metabolites is distributed into blood cells. Tepotinib was highly bound to plasma proteins with a fraction unbound of 1.8 - 2.5%. Following i.v. administration, the mean total volume of distribution (Vz) was 574 L.

Metabolism
Tepotinib was primarily cleared by metabolism. In total, 10 different Phase I and Phase II metabolites were found in humans. In vitro data indicated that CYP3A4 and CYP2C8 were involved in the metabolism of tepotinib, but did not seem to be the main enzymes responsible for metabolic clearance of tepotinib. However, the exact contribution of CYPs was unclear, and no other responsible enzymes have been identified.

In a mass balance study, tepotinib and the major circulating metabolite M506 accounted for 55% and 40.4%, respectively, of total radioactivity (AUC_{0-240h}) in plasma. In addition, a minor circulating metabolite, M668, was detected, which accounted for 3.4% of total radioactivity in plasma.

M506 is a chiral mixture predominantly consisting of the R-enantiomer MSC2571109A, with 64.6% of parent compound exposure, and the S-enantiomer MSC2571107A, with ~ 4.5% of parent compound exposure. Thus, the R-enantiomer MSC2571109A constitutes the major circulating metabolite of tepotinib. However, MSC2571109A accounts for only 3% of radioactivity in excreta, indicating that it does not represent a major elimination pathway.

Elimination

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Tepotinib was cleared renally (7% of an oral dose) and by metabolic elimination (48% of an oral dose). Biliary excretion might also be relevant but the extent is unknown.

In a mass balance study, 77.9% of the administered dose was recovered in faeces, tepotinib accounting for 45% of the dose. In light of the absolute bioavailability of 72%, the unchanged tepotinib in faeces probably reflects a fraction that has not been absorbed and a fraction that has been eliminated by biliary secretion. Besides unchanged tepotinib, the des-methyl metabolite M478 accounted for 9%, the direct N-glucuronide M668 for 6% and M506 for about 3% of the administered dose recovered in faeces. In addition, 5 minor metabolites each accounted for less than 2% of the dose.
13.6% of the dose was recovered in urine, and tepotinib was the main renally eliminated component, at 7% of the administered radioactive dose, and two metabolites, M508-1 and M508-2, accounted for about 2% and 3%, respectively, of the administered dose.

Following i.v. administration, the mean total CL was 13 L/h and the terminal half-life was 31 hours. These values were consistent with the parameters estimated in the population PK analysis.

Special Populations

The effect of mild and moderate hepatic impairment, but not severe hepatic impairment, was assessed in a dedicated study.
The effect of mild and moderate hepatic impairment on the exposure of both total and unbound tepotinib and on the major metabolite MSC2571109 was only weak.
No dose adjustment is required in patients with mild or moderate hepatic impairment. No data was available for patients with severe hepatic impairment.

The effect of renal impairment on the PK of tepotinib was not assessed in a dedicated study in view of the minor role of renal excretion for tepotinib and its metabolites (13% of a radioactive dose). However, since the PK dataset from the VISION study included 37 subjects with moderate renal impairment (eGFR ≥ 30 and < 60mL/min), the effect of decreased renal function was assessed in the population PK analysis. Despite the limited PK data in these subjects, a significant effect of eGFR on the clearance of tepotinib was identified. However, the effect on the exposure of tepotinib was small (<20%) and not considered clinically relevant.
No dose adjustment is recommended in patients with mild or moderate renal impairment. This recommendation was supported by the available data on efficacy and safety in these patients. No data is available for patients with severe renal impairment.

Based on the results of the population PK analysis for tepotinib and MSC2571109A, no dose adjustments based on demographic factors (age, body weight, gender or ethnicity) were required.

Interactions

Although tepotinib was primarily cleared by metabolism, not all responsible enzymes have been identified. CYP3A4 and CYP2C8 are likely to be involved, but the extent was unclear. Thus, there remained uncertainty about the enzyme involved in tepotinib metabolism, which limited the possibilities for theoretical assessments of the drug-drug interaction potential with respect to tepotinib as a victim.
This uncertainty will be addressed by additional drug-drug interaction studies to be conducted as post-marketing commitments. These studies will investigate the interaction potential via CYP3A4 and P-gp.
Tepotinib had an interaction potential as a perpetrator, which warrants cautious concomitant use of certain other medications.
Dose adjustments and recommendations with regard to concomitant medications are addressed in detail in the attached information for healthcare professionals; see Appendix.

Pharmacodynamics

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Mechanism of Action and Primary Pharmacology
Tepotinib is a reversible, adenosine triphosphate-competitive small molecule MET inhibitor. Tepotinib inhibits MET phosphorylation and, thereby, downstream MET signalling.

Secondary Pharmacology (Safety)
Exposure-response analyses indicated that the upper limit of the 90% CIs for the ΔQTcF values were <20 msec at the therapeutic dose of 500 mg and also at the highest tested dose of 1400 mg (2.8-fold the therapeutic dose). A QT effect at higher exposures was not investigated. However, in the safety assessment, QT prolongations were identified.

6.2 Dose Finding and Dose Recommendation

For monotherapy, the Phase I, open-label, dose-escalation, non-randomised first-in-human study EMR200095-001 determined a recommended phase 2 dose (RP2D) of 500 mg tepotinib once daily. The definition of the RP2D was based on a nonclinical PK/pharmacodynamic and tumour growth model analysis of MET inhibition in on-treatment subject biopsies, and a PopPK model.
The expansion cohorts in c-MET altered patients were to be enrolled in regimen 3 (tablet formulation, 500 mg once daily in 21 day cycles). None of the patients treated with RP2D 500 mg experienced a dose limiting toxicity (DLT). No maximum tolerated dose of tepotinib was defined in study EMR200095-001.
Dose was confirmed in phase 1 and 2 studies.

6.3 Efficacy

The applicant submitted one pivotal study: VISION (MS200095-0022). VISION is a multicentre, open-label, single-arm phase 2 study in patients with locally advanced or metastatic NSCLC harbouring METex14 skipping alterations (cohort A). The study is ongoing and includes a confirmatory cohort C, investigating n=100 additional patients with METex14 skipping mutation NSCLC, with results anticipated in 2023. The submitted supportive studies investigated either differing cancer types (studies EMR200095-004 and EMR200095-005 in patients with hepatocellular carcinoma [HCC]) or combination therapy with gefitinib (study EMR200095-006). Therefore, these studies were not considered supportive to evaluate the efficacy of tepotinib monotherapy in patients with METex14 skipping mutation NSCLC.

Patients with locally advanced or metastatic NSCLC of all subtypes and who were either treatment-naïve or pretreated with no more than 2 lines of prior therapy, measurable disease and ECOG performance status of 0-1 were eligible. METex14 skipping alterations were to be determined centrally confirmed in either plasma and/or tissue.

Primary endpoint was objective response rate (ORR: complete remission [CR] or partial remission [PR]) assessed by an independent review committee (IRC). Relevant secondary endpoints were duration of response (DoR), progression-free survival (PFS) by IRC, and overall survival (OS).

At data cut-off on 01 July 2020, overall n=152 patients were included in the safety analysis set and n=151 patients in the ITT analysis set of cohort A.

Overall, the majority of patients was male (52.0%) and white (71.1%), with a median age of 73.1 years (range 41-94 years). Most of the patients were aged 65 years or older (82.2%). N=69 patients received first line (1L) tepotinib and n=83 second line (2L) or later. Demographic characteristics were balanced between treatment-naïve and pretreated patients. Most of the patients had adenocarcinoma (86.2%), and 98% presented with stage IV disease at study entry.

The primary endpoint of ORR based on IRC was 44.9% (95% CI: 32.9, 57.4) in patients treated 1L and 45.1% (95% CI: 34.1, 56.5) in patients treated 2L or later. The median DoR based on IRC was

10.8 months (95% CI: 6.9, n.d.) in 1L patients and 11.1 months (95% CI: 9.5, 18.5) in 2L or later patients. The median PFS based on IRC was 8.5 months (95% CI: 6.8, 11.3) and 10.9 months (95% CI: 8.2, 12.7) in 1L and 2L or later, respectively. Median OS was 17.6 months (95% CI: 9.7, 29.7) in 1L patients and 19.7 months (95% CI: 15.0, 21.0) in 2L or later patients.

6.4 Safety

The safety review included data from n=448 patients who received at least one dose of tepotinib 500 mg, including n=279 patients from the VISION study. The second most common tumour entity was HCC (n=121, 32.4%).

The most frequently reported adverse events of any grade were generally consistent in the VISION cohort A+C and the pooled population. The most common TEAEs (≥ 20% of patients) by PT in the VISION population were: oedema peripheral (60.0%), nausea (26.7%), diarrhoea (26.3%), blood creatinine increased (25.1%), and hypoalbuminaemia (23.1%). A higher rate of dyspnoea, pleural effusion and cough in the VISION cohort compared to the pooled population may be explained by the underlying disease. A higher incidence of ascites and abdominal pain in the pooled population could be attributable to the high rate of patients with HCC contributing to the pool.

The most common ≥ grade 3 adverse events (overall rate 54.7%) were disease progression (7.0%), oedema peripheral (5.6%), hyponatraemia (4.6%), lipase increased (4.3%), AST increased (3.8%), hypoalbuminaemia (3.5%), ALT increased (3.2%), ascites, pleural effusion (2.9% each), amylase increased, and pneumonia (2.7% each). TEAEs by PT and rates were similar to VISION cohort A+C. The higher rates of ascites, lipase increased, AST increased and hyponatraemia might be related to the high number of patients with HCC in the pooled population.

Treatment-related TEAEs leading to death were reported in a similar proportion in the pooled population (n=5/1.0%) compared to VISION cohort A+C (n=3/1.1%).
The overall rate of SAEs was comparable between VISION cohort A+C and the pooled population (45.1% and 44.6%, respectively). The most common SAEs reported in both analysis sets were pleural effusion, disease progression, pneumonia, oedema (generalised + peripheral), dyspnoea and general physical health deterioration.

The adverse events of special interest (interstitial lung disease, creatinine increased, hepatobiliary toxicity, and QTc interval prolongation) are listed as warnings in the information for healthcare professionals (please refer to the information for healthcare professionals for further information).

6.5 Final Clinical and Clinical Pharmacology Benefit Risk Assessment

Metastatic NSCLC has a poor prognosis, including for patients with METex14 skipping mutations. Patients are currently treated corresponding to patients with no established molecular driver with immunotherapy, either as monotherapy or in combination with platinum doublets in the first-line (1L) setting.

The VISION study reached its primary endpoint of overall response rate (ORR) in pre-treated and treatment-naïve NSCLC patients whose tumours harbour a MET exon 14 skipping mutation that is considered clinically meaningful. Efficacy results in 1L patients do not appear to be superior to standard of care. However, considering soft factors such as oral administration, ambulatory treatment option, monotherapy, and the improved (although still relevant) toxicity profile compared to chemo-immunotherapy, the inclusion of the 1L indication is acceptable.

The safety profile of tepotinib is acceptable overall in light of the life-threatening disease. However, potentially severe hepatotoxicity, interstitial lung disease and QTc prolongation were identified as

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serious safety concerns. These issues are adequately addressed in the information for healthcare professionals.
Due to the limited size of the efficacy database, including uncertainties due to the single-arm nature of the submitted study and the limited follow-up, a temporary marketing authorisation was granted for tepotinib.

In the context of the temporary authorisation in accordance with Art. 9a TPA, conditions to be fulfilled for an ordinary authorisation were defined. In order to confirm currently available results, updated efficacy and safety results of VISION (cohort A and C) have to be submitted, and these are anticipated in April 2023. Furthermore, two clinical interaction studies with a strong cytochrome P450 3A4 (CYP3A4) and P-gp inhibitor and with a strong CYP3A4 and P-gp inducer need to be conducted, and results are expected in 2022.

6.6 Approved Indication and Dosage

See information for healthcare professionals in the Appendix.

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7 Risk Management Plan Summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken in order to further investigate and monitor the risks as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. Marketing Authorisation Holders are responsible for the accuracy and correctness of the content of the published RMP summaries. As the RMPs are international documents, their summaries might differ from the content in the information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorisations.

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8 Appendix

8.1 Approved Information for Healthcare Professionals

Please be aware that the following version of the information for healthcare professionals relating to Tepmetko was approved with the submission described in the SwissPAR. This information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the reference document, which is valid and relevant for the effective and safe use of medicinal products in Switzerland, is the information for healthcare professionals approved and authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following information for healthcare professionals has been translated by the MAH. The Authorisation Holder is responsible for the correct translation of the text. Only the information for healthcare professionals approved in one of the official Swiss languages is binding and legally valid.

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▼ 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 new or serious adverse reactions. See the "Undesirable effects" section for advice on the reporting of adverse reactions.

Tepmetko is temporarily authorised – see "Properties/Effects" section.

Tepmetko

Composition

Active substances

Tepotinibum ut Tepotinibi hydrochloridum monohydricum

Excipients

Core: Mannitolum, Cellulosum microcristallinum, Crospovidonum, Magnesii stearas, Silica colloidalis anhydrica
Film: Hypromellosum, Titanii dioxidum (E171), Lactosum 4.37 mg, Macrogolum 3350, Triacetinum, Ferri oxidum rubrum (E172)

Pharmaceutical form and active substance quantity per unit

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

Indications/Uses

Tepmetko is indicated for the treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) harbouring a *MET* tyrosine kinase receptor exon 14 (*MET*ex14) skipping mutation. The efficacy and safety of Tepmetko have not been studied in patients with other oncogenic driver mutations, including EGFR or ALK tumour aberrations (see section *Warnings and precautions*).

Dosage/Administration

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

Usual dosage

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

Duration of treatment

Treatment should continue as long as clinical benefit is observed.

Dose adjustment following undesirable effects

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

Table 1: Dose adjustments following undesirable effects

Adverse Reaction	**Severity**	**Dose Adjustment**
Interstitial Lung Disease (ILD) /ILD-like reactions (see section *Warnings and precautions)*	Any grade	Withhold Tepmetko if ILD is suspected. Permanently discontinue Tepmetko if ILD is confirmed.
Increased ALT and/or AST without increased total bilirubin (see section *Warnings and precautions*)	Grade 3	Withhold Tepmetko until recovery to baseline ALT/AST. If recovered to baseline within 7 days, then resume Tepmetko at the same dose; otherwise resume Tepmetko at a reduced dose.
	Grade 4	Permanently discontinue Tepmetko.
Increased ALT and/or AST with increased total bilirubin in the absence of cholestasis or hemolysis (see section *Warnings and precautions*)	ALT and/or AST greater than 3 times ULN with total bilirubin greater than 2 times ULN	Permanently discontinue Tepmetko.
Other adverse reactions (see section *Undesirable effects)*	Grade 3 or higher	Reduce Tepmetko to 225 mg until the adverse reaction recovers to ≤ Grade 2. A temporary interruption of Tepmetko treatment for no more than 21 days can also be considered.

Special dosage instructions

Patients with impaired hepatic function

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

Patients with impaired renal function

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

Elderly patients

No dose adjustment is necessary in patients aged 65 years and above (see section *Pharmacokinetics*). Of 255 patients with *MET*ex14 skipping alterations in the VISION study, 79% were 65 years or older, and 8% were 85 years or older.

Children and adolescents

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

Delayed administration

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

Mode of administration

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

Contraindications

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

Warnings and precautions

Interstitial lung disease

Interstitial lung disease (ILD) or ILD-like reactions, which may be fatal, were reported in the clinical study program in advanced NSCLC patients with *MET*ex14 skipping alterations who received tepotinib monotherapy at the recommended dosage regimen (see section *Undesirable effects)*. Patients should be monitored for pulmonary symptoms indicative for ILD-like reactions. Tepmetko should be withheld and patients should be promptly investigated for alternative diagnosis or specific

aetiology of interstitial lung disease. Tepmetko must be permanently discontinued if interstitial lung disease is confirmed and the patient be treated appropriately (see section *Dosage/Administration*).

Hepatotoxicity

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

Embryofetal toxicity

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

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

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

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

QTc prolongation

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

Increase in creatinine

Nonclinical studies suggest that tepotinib or its main metabolite inhibit the renal tubular transporter proteins organic cation transporter (OCT) 2 and multidrug and toxin extrusion transporters (MATE) 2 (see section *Interactions*). Creatinine is a substrate of these transporters, and the observed increases in creatinine (see section *Undesirable effects*) may be the result of inhibition of active tubular secretion rather than actual renal injury. Renal function estimates that rely on serum creatinine (creatinine clearance or estimated glomerular filtration rate) should be interpreted with caution

considering this effect. Alternative markers of renal function should be considered in line with local clinical practice if persistent elevations in serum creatinine are observed.

Oncogenic drivers

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

Lactose

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

Interactions

Effect of other medicinal products on the pharmacokinetics of tepotinib

Avoid concomitant administration

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 drugs that are strong CYP3A inhibitors and P-gp inhibitors may increase tepotinib exposure, which may increase the incidence and severity of adverse reactions of Tepmetko. Concomitant use of Tepmetko with dual strong CYP3A inhibitors and P-gp inhibitors (e.g. itraconazole, ketoconazole, ritonavir, saquinavir, nelfinavir) should be avoided.

Strong CYP3A and/or P-gp inducers:

The effect of strong CYP3A and/or P-gp inducers on Tepmetko has not been studied clinically. However, metabolism and *in vitro* data suggest concomitant use may decrease tepotinib exposure, which may reduce Tepmetko efficacy. Concomitant use of Tepmetko with strong CYP3A and/or P-gp inducers (e.g. carbamazepine, phenytoin, rifampicin, St. John’s wort) should be avoided.

Other interactions

Acid-reducing agents:

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

Effect of tepotinib on the pharmacokinetics of other medicinal products

Avoid concomitant administration

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

Caution with concomitant administration

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

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

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

Other interactions
OATP1B3 and organic anion transporter (OAT) 1 and 3 substrates:

Based on *in vitro* data, tepotinib, at clinically relevant concentrations, poses a remote risk of bile salt export pump (BSEP) inhibition but not OATP1B3 or OAT1 and 3 inhibition.

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

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

Pregnancy, lactation

Contraception in males and females
Pregnancy testing is recommended in women of childbearing potential prior to initiating treatment with Tepmetko.
Women of childbearing potential must use effective contraception during Tepmetko treatment and for at least 1 week after the last dose.
Male patients with female partners of childbearing potential must use barrier contraception during Tepmetko treatment and for at least 1 week after the last dose.

Pregnancy

There are no clinical data on the use of Tepmetko in pregnant women. Studies in animals have shown teratogenicity (see section *Preclinical data*). Based on the mechanism of action and findings in animals, Tepmetko can cause foetal harm when administered to pregnant women.
Tepmetko must not be used during pregnancy, unless the clinical condition of the woman requires treatment. Women of childbearing potential or male patients with female partners of childbearing potential must be advised of the potential risk to a foetus.

Lactation

There are no data regarding the secretion of tepotinib or its metabolites in human milk or its effects on the breast-fed infant or milk production. A risk to the infant cannot be excluded. Breast-feeding must be discontinued during treatment with Tepmetko and for at least 1 week after the last dose.

Fertility

No human data on the effect of Tepmetko on fertility are available. No morphological changes in male or female reproductive organs were seen in the repeat-dose toxicity studies in rats and dogs (see section *Preclinical data*).

Effects on ability to drive and use machines

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

Undesirable effects

Summary of the safety profile

The safety profile of Tepmetko reflects exposure to tepotinib in 448 patients with various solid tumours enrolled in five open-label, single-arm studies, in which patients received tepotinib as a single agent at a dose of 450 mg once daily. This includes 255 patients with advanced NSCLC harbouring *MET*ex14 skipping alterations included in the main clinical study (VISION).

The most common adverse reactions observed in the main clinical study (VISION) were oedema (69.0% of patients), mainly peripheral oedema (60.0%), nausea (26.7%), diarrhoea (26.3%), increase in creatinine (25.9%) hypoalbuminaemia (23.9%) and fatigue. Most common serious adverse reactions were reported for generalised oedema (2.0%) and peripheral oedema (2.4%).

Peripheral oedema was the most frequent cause of permanent treatment discontinuation (3.5%), temporary treatment discontinuation (16.9%) or dose reduction (14.1%).

List of adverse reactions

The following definitions apply to the frequency terminology used hereafter:

Very common (≥ 1/10)

Common (≥ 1/100 to < 1/10)

Uncommon (≥ 1/1,000 to < 1/100)

Rare (≥ 1/10,000 to < 1/1,000)

Very rare (< 1/10,000)

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

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

System organ class/Adverse reaction	**Tepmetko N=448**			
	All grades		**Grade ≥ 3**	
	n (%)	**Frequency category**	**n (%)**	**Frequency category**

Metabolism and nutrition disorders				
Hypoalbuminaemia [a]	104 (23.2)	Very common	19 (4.2)	Common
Appetite decreased	89 (19.9)	Very common	7 (1.6)	Common
Respiratory, thoracic and mediastinal disorders				
Dyspnoea [b]	74 (16.5)	Very common	10 (2.2)	Common
Pleural effusion	48 (10.7)	Very common	14 (3.1)	Common
ILD/ILD-like reactions [c]	8 (1.8)	Common	1 (0.2)	Uncommon
Gastrointestinal disorders				
Diarrhoea	118 (26.3)	Very common	6 (1.3)	Common
Nausea	106 (23.7)	Very common	5 (1.1)	Common
Vomiting	61 (13.6)	Very common	7 (1.6))	Common
Increase in amylase [d]	30 (6.7)	Common	11 (2.5)	Common
Increase in lipase [e]	34 (7.6)	Common	21 (4.7)	Common
Hepatobiliary disorders				
Increase in alanine aminotransferase (ALT)	49 (10.9)	Very common	14 (3.1)	Common
Increase in aspartate aminotransferase (AST)	45 (10.0)	Very common	14 (3.1)	Common
Renal and urinary disorders				
Increase in creatinine [f]	93 (20.4)	Very common	4 (0.9)	Uncommon
General disorders and administration site conditions				
Oedema [g]	281 (62.7)	Very common	30 (6.7)	Common
Fatigue	84 (18.8)	Very common	10 (2.2)	Common
Generalised oedema	21 (4.7)	Common	7 (1.6)	Common

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

Description of selected adverse reactions

Interstitial lung disease

Interstitial lung disease (ILD) or ILD-like adverse reactions have been reported in 6 patients (2.4%) with advanced NSCLC with *MET*ex14 skipping alterations who received tepotinib monotherapy at the recommended dosage regimen (n=255), including 1 case of grade 3 or higher; serious cases occurred in 2 patients (0.8%), 1 case was fatal (see sections *Dosage/Administration* and *Warnings and precautions*).

Hepatotoxicity
Hepatotoxicity has occurred in patients treated with Tepmetko. In the main clinical study, ALT/AST elevations occurred in 12.2% of patients. In 3.1% of patients, an increase in ALT/AST to grade 3 or higher was observed. In one patient, a fatal case of liver failure occurred. No patients treated with Tepmetko discontinued treatment due to elevated ALT/AST. The median time to onset of an elevated ALT/AST increase to grade 3 or higher was 7.3 weeks (time range: 3.1 to 8.6 weeks) (see sections *Dosage/Administration* and *Warnings and precautions*).

Increase in creatinine
Based on laboratory values, shifts of at least 1 grade in creatinine were documented for 52.9% of patients in the main clinical study; one patient had a shift to a grade 3 creatinine increase. A median increase in serum creatinine of 31% was observed 21 days after initiation of treatment with Tepmetko. The serum creatinine increases persisted throughout treatment and were reversible upon treatment completion (see section *Warnings and precautions*).

Increase in amylase or lipase
Increases in amylase or lipase were generally asymptomatic and not associated with pancreatitis and could be managed without dose reduction.
Based on laboratory values, an increase of at least 1 grade was observed for 21.6% of patients for amylase and 17.3% of patients for lipase in the main clinical study. An increase to grade 3 or higher occurred in 4.3% of patients for amylase and 3.5% of patients for lipase.

QTc prolongation
In the main clinical study (patients with *MET*ex14 skipping alterations, n=255), QTcF prolongation to > 500 ms was observed in 6 patients (2.4%) and a QTcF prolongation by at least 60 ms from baseline in 12 patients (4.7%) (see *Warnings and precautions*). The findings were isolated and asymptomatic; the clinical significance is unknown. In an exposure-response QTc analysis, no significant changes in the QTc interval (> 20 ms) were found on average at the therapeutic dose, but a concentration-dependent prolongation was found (see *Properties/Effects,* Cardiac electrophysiology).

Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Overdose

Tepotinib has been investigated at doses up to 1,261 mg. Symptoms of overdose have not been identified. There is no specific treatment in the event of tepotinib overdose. In case of overdose, Tepotinib should be withheld and symptomatic treatment initiated.

Properties/Effects

ATC code

L01EX21

Mechanism of action

The mesenchymal-epithelial transition factor (MET) and its ligand, the hepatocyte growth factor (HGF), are involved in carcinogenesis and tumour progression. Oncogenic activation of MET signalling has been shown to promote cancer cell proliferation, survival, migration and invasion, and tumour angiogenesis, as well as to mediate resistance to cancer therapies.
Tepotinib is a selective and potent, reversible, Type I adenosine triphosphate (ATP)-competitive small molecule inhibitor of MET. Tepotinib inhibits HGF-dependent and -independent MET phosphorylation and MET-dependent downstream signalling through the phosphatidylinositol 3-kinase/protein kinase B and mitogen-activated protein kinase/extracellular-signal regulated kinase pathways in a dose-dependent manner.

Pharmacodynamics

Treatment of susceptible tumour cells with tepotinib inhibited proliferation, anchorage-independent growth and migration of MET-dependent tumour cells. Treatment of tumour-bearing mice with tepotinib led to effective and sustained inhibition of MET phosphorylation and a change in pharmacodynamic biomarkers, indicating inhibition of tumour cell proliferation, increased tumour cell apoptosis and reduced tumour angiogenesis. Tepotinib inhibited tumour growth of MET-dependent tumours from different tumour types. The anti-tumour activity of Tepotinib was particularly pronounced in tumours with oncogenic activation of MET, such as *MET*ex14 skipping.
The contribution of the major circulating metabolite to the anti-tumour activity of tepotinib is considered to be negligible.

Cardiac electrophysiology
In an exposure-QTc analysis, the QTcF interval prolongation potential of tepotinib was assessed in 392 patients with various solid tumours following single or multiple daily doses of tepotinib ranging from 27 mg to 1,261 mg. At the therapeutic dose, no major changes in the QTc interval (> 20 ms) were detected on average, but a concentration-dependent prolongation was found. The effect on the QTc interval at high exposure was not investigated.

Clinical efficacy

The efficacy of tepotinib was evaluated in a single-arm, open-label, multicentre study (VISION) in adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) harbouring *MET*ex14 skipping alterations (n = 152). Patients had an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 or 1 and were either treatment-naïve or had progressed on up to 2 lines prior systemic therapies. Neurologically stable patients with central nervous system metastases were permitted. Patients with epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) activating alterations were excluded.

Patients had a median age of 73 years (range 41 to 94), 48% were female and 52% male. The majority of patients were white (71%), followed by Asian patients (25%) and were never (43%) or former smokers (50%). Most patients were ≥ 65 years of age (82%) and 45% of patients were ≥ 75 years of age.

The majority of patients had stage IV disease (98%), 86% had adenocarcinoma histology. Ten percent of the patients had stable brain metastases. Patients received tepotinib as first-line (45%) or second- or later line (55%) therapy.

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

Patients received 450 mg tepotinib once daily until disease progression or unacceptable toxicity. Median treatment duration was 7.03 months (range 0.03 to 43.33 months).

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

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

Efficacy parameter	**Overall N = 152**	**Treatment-naïve N = 69**	**Previously treated N = 83**
Objective response rate, % [95% CI]	44.7 [36.7, 53.0]	44.9 [32.9, 57.4]	44.6 [33.7, 55.9]
Complete response, %	0	0	0
Partial response, %	44.7	44.9	44.6
Median duration of response, months[a] [95% CI]	11.1 [8.4, 18.5]	10.8 [6.9, NE]	11.1 [9.5, 18.5]
Duration of response[b]			
≥ 6 months, % of responders	72.1	67.7	75.7
≥ 9 months, % of responders	42.6	32.3	51.4

≥ 12 months, % of responders	20.6	16.1	24.3
Median progression-free survival, months[a] [95% CI]	8.9 [8.2, 11.2]	8.5 [6.8, 11.3]	10.9 [8.2, 12.7]
Median overall survival time, months[a] [95% CI]	17.6 [15.0, 21.0]	17.6 [9.7, 29.7]	19.7 [15.0, 21.0]

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

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

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

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

Temporary authorisation

The medicinal product Tepmetko has been granted temporary authorisation as the clinical data was incomplete at the time the authorisation application was assessed (Art. 9a TPA). The temporary authorisation is contingent on the timely fulfilment of conditions. After they have been met, the temporary authorisation can be transformed into an ordinary authorisation.

Pharmacokinetics

Absorption

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

A mean absolute bioavailability of 71.6% was observed for a single 450 mg dose of tepotinib administered in the fed state; the median time to C_{max} was 8 hours (range from 6 to 12 hours).

The presence of food (standard high-fat, high-calorie breakfast) increased the AUC of tepotinib about 1.6-fold and C_{max} 2-fold. At the recommended dosage, the geometric mean (coefficient of variation [CV] %) steady state C_{max} was 1,291 ng/mL (48.1%) and the steady state $AUC_{0\text{-}24h}$ was 27,438 ng·h/mL (51.7%). The median accumulation was 2.5-fold for C_{max} and 3.3-fold for $AUC_{0\text{-}24h}$ after multiple daily doses of tepotinib. Based on a population kinetic model, time to steady-state is approximately 5 days.

Distribution

In human plasma, tepotinib is highly protein bound (98%). The mean volume of distribution (Vz) of tepotinib after an intravenous tracer dose (geometric mean and geoCV%) was 574 L (14.4%).

In vitro studies indicate that tepotinib is a substrate for P-glycoprotein (P-gp).

Metabolism

Approximately half of an orally administered dose (about 48%) is excreted as metabolites. In total, 10 different Phase I and Phase II metabolites were found in humans. *In vitro* data indicate that CYP3A4 and CYP2C8 are involved in the metabolism of tepotinib but seem not to be the main enzymes responsible for metabolic clearance of tepotinib. However, no other responsible enzymes have been identified.
Only one major circulating metabolite, M506 (a mixture of two enantiomers), was identified in plasma. In a mass balance study, tepotinib and M506 accounted for 55% and 40.4%, respectively, of the AUC of the total radioactive material in plasma.
No metabolic pathway accounted for more than 25% of tepotinib elimination. Only one major circulating plasma metabolite, namely M506, has been identified. There is only a minor contribution of the major circulating metabolite to the overall efficacy of tepotinib in humans.

Elimination

After intravenous administration of single doses, a total systemic clearance (geometric mean and geoCV%) of 12.8 L/h (7.8%) was observed.
Tepotinib and its metabolites are mainly excreted via the faeces (approximately 85% total recovery of radioactivity), with urinary excretion being a minor excretion pathway. After a single oral administration of a radiolabelled dose of 450 mg tepotinib, unchanged tepotinib represented 45% and 7% of the total radioactivity in faeces and urine, respectively. Some of the unchanged tepotinib in the faeces was probably the unabsorbed active substance. 9% of the administered radioactive dose was excreted as the des-methyl metabolite M478, 6% as the direct N-glucuronide M668, 3% as the chiral major metabolite M506 and less than 2% each as 5 other oxidised metabolites, all excreted in the faeces.
The effective half-life for tepotinib is approximately 32 h.
Linearity/non-linearity

Tepotinib exposure increases dose-proportionally over the clinically relevant dose range of 27 mg (0.06-fold the recommended daily dose) up to 450 mg. Tepotinib exposure increases less than dose-proportionally at doses greater than 450 mg owing to lower oral bioavailability in the supratherapeutic dose range.
The pharmacokinetics of tepotinib did not change with respect to time.
Kinetics in specific patient groups

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

Hepatic impairment

Following a single oral dose of 450 mg, total tepotinib exposure was similar in healthy subjects and patients with mild hepatic impairment (Child-Pugh Class A), and was slightly lower (-13% AUC and -29% C_{max}) in patients with moderate hepatic impairment (Child-Pugh Class B) compared to healthy subjects. In contrast, mean free tepotinib AUCs were about 13% and 24% higher in patients with mild and moderate hepatic impairment, respectively, compared to healthy subjects. The pharmacokinetics of tepotinib have not been studied in patients with severe (Child Pugh Class C) hepatic impairment.

Renal impairment

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

Preclinical data

Repeat dose toxicity

Oral repeat-dose toxicity studies have been conducted in rats up to 26 weeks and dogs up to 39 weeks. The main target organs for tepotinib in these animals were the hepatobiliary system and the gastrointestinal tract.
Increased hepato-biliary parameters concomitant with pronounced cholangitis and pericholangitis were seen in dogs starting at doses of 30 mg tepotinib hydrochloride hydrate per kg per day (approximately 18% the human exposure at the recommended dose of 450 mg based on AUC). Slightly increased liver enzymes were seen in rats starting at doses 15 mg tepotinib hydrochloride hydrate per kg per day (approximately 3% of the human exposure at the recommended dose of 450 mg based on AUC). In dogs gastrointestinal symptoms (vomiting, diarrhoea) were seen starting at 2.5 mg tepotinib hydrochloride hydrate per kg per day (exposures approximately 0.3% of the human exposure at the recommended dose of 450 mg based on AUC). All changes proved to be reversible or showed indications of reversibility or improvements.
Mutagenicity

No mutagenic or genotoxic effects of tepotinib were observed in *in vitro* and *in vivo* studies. The major circulating metabolite was also shown to be non-mutagenic.
Carcinogenicity

No studies have been performed to evaluate the carcinogenic potential of tepotinib.
Reproductive toxicity

Animal studies of tepotinib to evaluate the possible impairment of fertility have not been performed. No morphological changes in male or female reproductive organs were seen in the repeat-dose toxicity studies in rats and dogs.

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

Other information

Shelf life

Do not use this medicine after the expiry date ("EXP") stated on the container.

Special precautions for storage

Store at room temperature (15 – 25°C) and protect from moisture.
Keep out of the reach of children.

Authorisation number

68113 (Swissmedic)

Packs

60 film-coated tablets. [A]

Marketing authorisation holder

Merck (Schweiz) AG, Zug

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