Medicines & Healthcare products Regulatory Agency

MHRA Regulating Medicines and Medical Devices

Public Assessment Report

National Procedure

TEPMETKO 225 MG FILM-COATED TABLETS
Tepotinib hydrochloride hydrate

PLGB 11648/0291

Merck Serono Limited

LAY SUMMARY

TEPMETKO 225 mg film-coated tablets
Tepotinib hydrochloride hydrate

This is a summary of the Public Assessment Report (PAR) for TEPMETKO 225 mg film-coated tablets. It explains how this product was assessed and its authorisation recommended, as well as its conditions of use. It is not intended to provide practical advice on how to use this product.

For practical information about using TEPMETKO 225 mg film-coated tablets, patients should read the Patient Information Leaflet (PIL) or contact their doctor or pharmacist.

What are TEPMETKO 225 mg film-coated tablets and what are they used for?
This application is a full-dossier application. This means that the results of pharmaceutical, non-clinical and clinical tests have been submitted to show that this medicine is suitable for treating the specified indications.

TEPMETKO 225 mg film-coated tablets are used in adults to treat a type of lung cancer, called non-small cell lung cancer, that has certain abnormal changes in the mesenchymal-epithelial transition factor gene (MET) and which has spread and/or cannot be removed by surgery.

How do TEPMETKO 225 mg film-coated tablets work?
This medicine contains the active substance tepotinib. It belongs to a group of medicines called protein kinase inhibitors which are used to treat cancer.

Changes in the MET gene can make an abnormal protein which can then cause uncontrolled cell growth and cancer. By blocking this abnormal protein TEPMETKO 225 mg film-coated tablets may slow or stop the cancer from growing. They may also help to shrink the cancer. A doctor will perform a test to check if the cancer has a change in the MET gene to make sure that TEPMETKO 225 mg film-coated tablets are the right treatment.

How are TEPMETKO 225 mg film-coated tablets used?
The pharmaceutical form of this medicine is a film-coated tablet and the route of administration is oral (by mouth).

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

The tablets should be swallowed whole (without crushing or chewing) and should be taken with food or shortly after a meal.

For further information on how TEPMETKO 225 mg film-coated tablets are used, refer to the PIL and Summary (SmPC) available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

This medicine can only be obtained with a prescription.

The patient should always take the medicine exactly as their doctor has told them. The patient should check with their doctor if they are not sure.

What benefits of TEPMETKO 225 mg film-coated tablets have been shown in studies?
TEPMETKO 225 mg film-coated tablets have been studied in patients with non-small cell lung cancer, with certain abnormal changes in the mesenchymal-epithelial transition factor gene (MET), known as METex14 skipping alterations. Patients in the study who took TEPMETKO 225 mg film-coated tablets had an overall response rate (a complete response or partial response to treatment) of 45.2% (95% CI: 37.0, 53.6) and median duration of response of 11.1 months (95% CI: 8.4, 18.5). Overall median progression-free survival was 8.9 months (95% CI: 8.2, 11.0). Overall median survival was 17.6 months (95% CI: 15.0, 21.0).

What are the possible side effects of TEPMETKO 225 mg film-coated tablets?
For the full list of all side effects reported with this medicine, see Section 4 of the PIL or the SmPC available on the MHRA website.

If a patient gets any side effects, they should talk to their doctor, pharmacist or nurse. This includes any possible side effects not listed in the product information or the PIL that comes with the medicine. Patients can also report suspected side effects themselves, or a report can be made on behalf of someone else they care for, directly via the Yellow Card scheme at www.mhra.gov.uk/yellowcard or search for 'MHRA Yellow Card' online. By reporting side effects, patients can help provide more information on the safety of this medicine.

The most common side effects with TEPMETKO 225 mg film-coated tablets (which may affect more than 1 in 10 people) are swelling caused by fluid build-up in the body (oedema); feeling sick (nausea); being sick (vomiting); diarrhoea; abdominal pain; constipation; fatigue or tiredness; higher than normal blood levels of creatinine; reduced protein levels in the blood; and higher than normal blood levels of a certain liver enzyme (alanine aminotransferase).

Why were TEPMETKO 225 mg film-coated tablets approved?
It was concluded that TEPMETKO 225 mg film-coated tablets have been shown to be effective in the treatment of non-small cell lung cancer, that has certain abnormal changes in the mesenchymal-epithelial transition factor gene (MET). Furthermore, the side effects observed with use of this product are considered to be typical for this type of treatment. Therefore, the MHRA decided that the benefits are greater than the risks and recommended that this medicine can be approved for use.

TEPMETKO 225 mg film-coated tablets have been authorised with a Conditional Marketing Authorisation (CMA). CMAs are intended for medicinal products that address an unmet medical need, such as a lack of alternative therapy for a serious and life-threatening disease. CMAs may be granted where comprehensive clinical data is not yet complete, but it is judged that such data will become available soon.

What measures are being taken to ensure the safe and effective use of TEPMETKO 225 mg film-coated tablets?
A Risk Management Plan (RMP) has been developed to ensure that TEPMETKO 225 mg film-coated tablets is used as safely as possible. Based on this plan, safety information has been included in the SmPC and the PIL, including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore, new safety signals reported by patients/healthcare professionals will be monitored and reviewed continuously.

Other information about TEPMETKO 225 mg film-coated tablets

A Marketing Authorisation for TEPMETKO 225 mg film-coated tablets was granted in Great Britain (consisting of England, Scotland and Wales) on 24 September 2021.

The full PAR for TEPMETKO 225 mg film-coated tablets follows this summary.

This summary was last updated in November 2021.

TABLE OF CONTENTS

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) considered that the application for TEPMETKO 225 mg film-coated tablets (PLGB 11648/0291) could be approved.

The product is approved for the following indication:
For the treatment of adult patients with advanced non-small cell lung cancer (NSCLC) harbouring mesenchymal-epithelial transition factor gene (MET) exon 14 (METex14) skipping alterations.

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

In vitro, tepotinib inhibited tumour cell proliferation, anchorage-independent growth, and migration of MET-dependent tumour cells. In mice implanted with tumour cell lines with oncogenic activation of MET, including METex14 skipping alterations, tepotinib inhibited tumour growth, led to sustained inhibition of MET phosphorylation, and, in one model, decreased the formation of metastases.

This application was approved under Regulation 50 of The Human Medicines Regulation 2012, as amended (previously Article 8(3) of Directive 2001/83/EC, as amended), as a full-dossier application. Safety pharmacology and pivotal toxicology studies were conducted in accordance with Good Laboratory Practice (GLP). All clinical data submitted were from studies conducted in accordance with Good Clinical Practice (GCP).

This application was evaluated as part of Project Orbis.
Project Orbis is a programme coordinated by the US Food and Drug Administration (FDA) to review and approve promising cancer treatments. It could involve the regulatory authorities of Australia (TGA), Canada (Health Canada), Singapore (HSA), Brazil (ANVISA), Switzerland (Swissmedic) and the MHRA (UK). Project Orbis provides a framework for concurrent submission and review of oncology products among selected international partners. Each regulator makes independent decisions regarding approval of the application.

This product has been authorised as a Conditional Marketing Authorisation (CMA). CMAs are granted in the interest of public health and are intended for medicinal products that fulfil an unmet medical need and the benefit of immediate availability outweighs the risk posed from less comprehensive data than normally required. Unmet medical needs include, for example, treatment or diagnosis of serious and life-threatening diseases where no satisfactory treatment methods are available. CMAs may be granted where comprehensive clinical data is not yet complete, but it is judged that such data will become available soon. Adequate evidence of safety and efficacy to enable the MHRA to conclude that the benefits are greater than the risks is required, and has been provided for TEPMETKO 225 mg film-coated tablets. The CMA for TEPMETKO 225 mg film-coated tablets, including the provision of any new information, will be reviewed every year and this report will be updated as necessary.

This application was evaluated for fulfilment of orphan designation criteria and was examined by the Commission on Human Medicines (CHM). The applicant withdrew the application for orphan designation.

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product at all sites responsible for the manufacture, assembly and batch release of this product.

A Risk Management Plan (RMP) and a summary of the pharmacovigilance system have been provided with this application and are satisfactory.

Advice was sought from the Commission of Human Medicines (CHM) on 06 May 2021 as this is an application for a new active substance.

A national marketing authorisation was granted in the Great Britain (GB, consisting of England, Scotland and Wales) on 24 September 2021.

II QUALITY ASPECTS

II.1 Introduction

This product consists of film-coated tablets containing 225 mg tepotinib (as hydrochloride hydrate).

In addition to tepotinib, this product also contains the excipients mannitol, colloidal anhydrous silica, crospovidone, magnesium stearate and microcrystalline cellulose in the tablet core and hypromellose, lactose monohydrate, macrogol, triacetin, red iron oxide (E172) and titanium dioxide in the film-coating.

The finished product is packaged in aluminium/polyvinyl chloride-polyethylene-polyvinylidene chloride-polyethylene-polyvinyl chloride blisters in a pack size of 60 film-coated tablets.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current regulations concerning materials in contact with food.

II.2 ACTIVE SUBSTANCE

rINN: Tepotinib

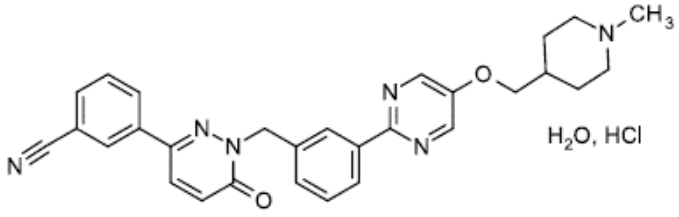
Chemical Name: 3-{1-[(3-{5-[(1-Methylpiperidin-4-yl)methoxy]pyrimidin-2-yl}phenyl)methyl]-6-oxo-1,6-dihydropyridazin-3-yl}benzonitrile hydrochloride hydrate

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

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

Molecular Formula: Tepotinib hydrochloride hydrate:
$C_{29}H_{31}N_6O_3Cl$ ($C_{29}H_{28}N_6O_2 \cdot HCl \cdot H_2O$)
Tepotinib: $C_{29}H_{28}N_6O_2$

Chemical Structure:



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

Appearance: White to off-white powder.

Solubility: Freely soluble in aqueous hydrochloric acid (25%), soluble in DMSO, slightly soluble in ethanol and in methanol, very slightly soluble in 2-propanol, in acetonitrile and in water, practically insoluble in acetone and tetrahydrofuran.

Synthesis of the active substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specifications are in place for all starting materials and reagents, and these are supported by relevant Certificates of Analysis.

Appropriate proof-of-structure data have been supplied for the active substance. All potential known impurities have been identified and characterised.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Batch analysis data are provided and comply with the proposed specification. Satisfactory Certificates of Analysis have been provided for all working standards.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current regulations concerning materials in contact with food.

Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.

II.3 DRUG PRODUCT

Pharmaceutical development

A satisfactory account of the pharmaceutical development has been provided.

All excipients comply with either their respective European/national monographs, or a suitable in-house specification. Satisfactory Certificates of Analysis have been provided for all excipients.

With the exception of lactose monohydrate, no excipients of animal or human origin are used in the final products. The supplier of lactose monohydrate has confirmed that it is sourced from healthy animals under the same conditions as milk for human consumption. Confirmation has been given that the magnesium stearate used in the tablets is of vegetable origin.

This product does not contain or consist of genetically modified organisms (GMO).

Manufacture of the product

A description and flow-chart of the manufacturing method has been provided.

Satisfactory batch formulation data have been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results.

Finished Product Specification
The finished product specifications at release and shelf-life are satisfactory. The test methods have been described and adequately validated. Batch data have been provided that comply with the release specifications. Certificates of Analysis have been provided for any working standards used.

Stability
Finished product stability studies have been conducted in accordance with current guidelines, using batches of the finished product stored in the packaging proposed for marketing. Based on the results, a shelf-life of 3 years, with the storage conditions 'Store in the original package in order to protect from moisture', is acceptable.

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.

II.4 Discussion on chemical, pharmaceutical and biological aspects
The grant of a marketing authorisation is recommended.

III NON-CLINICAL ASPECTS

III.1 Introduction
The following non-clinical studies were submitted with this application:

- Primary Pharmacodynamic studies
- Secondary Phamacodynamic study of wound healing in mice
- *In vitro* safety pharmacology studies
- *In vivo* safety pharmacology studies in dogs and rats
- *In vitro* safety pharmacology studies on the Tepotinib metabolite MSC2571109A
- Single dose pharmacokinetic studies in mouse, rat, dog and monkey
- Repeat-dose oral toxicity studies in rats and three pivotal repeat-dose oral toxicity studies in dogs
- *In vitro* and *in vivo* absorption, distribution, metabolism and excretion (ADME) studies of tepotinib and/or the metabolite MSC2571109A
- Single dose toxicity studies in mice and rats
- *In vitro* and *in vivo* genotoxicity studies
- *In vitro* genotoxicity studies on metabolites and impurities
- Embryo-fetal development studies in rabbits
- *In vitro* and *in vivo* phototoxicity studies

The primary pharmacodynamic studies were not conducted or required to meet Good Laboratory (GLP) standards. The safety pharmacology *in vitro* study (hERG channel study) and the core battery of *in vivo* studies on the cardiovascular, respiratory and central nervous system were conducted in compliance with GLP regulations.

In vitro and *in vivo* studies performed for characterising the absorption, distribution, metabolism and excretion (ADME) properties of tepotinib and the drug-drug interaction potential of tepotinib and/or the metabolite MSC2571109A were stated to have been performed under non-GLP conditions but in accordance with internal quality standards and good scientific practices.

Most *in vivo* and *in vitro* toxicology studies and especially all pivotal studies were conducted in compliance with GLP regulations.

III.2 Pharmacology

In primary pharmacodynamic studies tepotinib potently inhibited MET kinase activity in a dose-dependent manner with binding IC50 values in the single digit nanomolar range. This effect occurred in kinase assays using the isolated MET kinase domain and in tumour cells expressing full-length MET stimulated with hepatocyte growth factor (HGF) and in tumour cells with a MET gene amplification (resulting in HGF-independent MET activation). The inhibitory activity of tepotinib persisted over a prolonged period and serum proteins only moderately interfered with it.

In various kinase screens against a panel of more than 400 different recombinant kinases, tepotinib demonstrated a very high selectivity for MET.

Tepotinib blocked MET signal transduction, and treatment of susceptible tumour cells with tepotinib inhibited tumour cell proliferation, anchorage-independent growth and HGF-dependent cell migration in a dose-dependent manner. Both effects correlated with inhibition of MET activation.

In vivo, tepotinib was tested in mice bearing human tumour xenografts derived from various cancer indications including non-small cell lung cancer (NSCLC), hepatocellular carcinoma (HCC) and gastric cancer. The antitumour activity of tepotinib monotherapy was dose dependent.

In vivo efficacy was observed particularly in tumour models with oncogenic alterations of the MET gene, including two tumours with MET exon 14 skipping alterations (METex14), one tumour expressing recombinant oncogenic Tpr-Met fusion protein, and in several tumours with high-level amplification of the MET gene (high-level MET gene amplification is defined as an average MET gene copy number (GCN) in the tumour of > 10). Presence of these oncogenic alterations was often associated with strong responses to tepotinib monotherapy treatment, including complete tumour regressions. Antitumour activity (mainly tumour growth inhibition) was also observed in some tumours with overexpression of MET (without concomitant MET amplification or other oncogenic MET alterations) and tumours with HGF/MET autocrine loops, but on average to a lesser extend compared to tumours with oncogenic alterations.

The majority of *in vivo* tumour models were run as subcutaneous xenografts. In addition, tepotinib was also tested in an orthotopic HCC tumour and in established, intracranial xenografts derived from brain metastases of primary human lung tumours. All tumours harboured high-level MET gene amplification and responded with tumour shrinkage to tepotinib treatment.

Tepotinib showed anti-tumour activity against tumour explants derived from human brain metastases of primary tumours with high MET gene amplification in orthotopically implanted mice, indicating that tepotinib can elicit an anti-tumour response across the blood brain barrier (BBB); tepotinib was present in brain tissue following a 24-hour IV infusion study despite the lack of radio-labelled tepotinib exposure in the brains of healthy animals after a single low dose (6 mg/kg) oral exposure study.

The assessment of MET phosphorylation in a pharmacokinetic/pharmacodynamic (PK/PD) study with the highly sensitive gastric tumour xenograft Hs746T (METex14 skipping and

high-level MET amplification) confirmed the long-lasting, persistent inhibition of MET upon a single dose application of tepotinib. The inhibition of MET phosphorylation was accompanied by a reduction of human interleukin (IL)-8 plasma levels, a reduction of phospho-histone H3 and cyclin D1 levels, and upregulation of p27 in tumour tissue. These data provided *in vivo* evidence for the mechanism of action of tepotinib, i.e. tepotinib-mediated inhibition of tumour cell proliferation, induction of cell cycle arrest, and reduction of factors that promote tumour angiogenesis (IL-8).

A single dose PK/PD study and a repeat-dose efficacy study with the human pancreatic xenograft KP-4 showed that sustained MET inhibition is needed to achieve maximal antitumour activity. The data of these studies allowed a quantitative estimate of the dose-exposure-PD-efficacy relationship and was used for PK/PD modelling to support finding of the biologically active dose and dose regimen selection in clinical trials.

In a secondary pharmacodynamic *in vivo* study in mice, the once daily oral administration of up to 50 mg/kg tepotinib for 3 or 10 days had no effect on wound healing (i.e. wound width, visual severity score, wound area, percentage of re-epithelialization and granulation tissue maturity) in comparison to vehicle.

In vitro tepotinib or its free base inhibited Kv11.1 (hERG) channel current with an IC50 of 1.2 μM. This concentration is 24-fold higher than the steady state mean human free Cmax of 0.05 μM and therefore not considered clinically relevant. In addition, tepotinib inhibited cardiac ion channel hNav1.5 (up to 26%) at the tested concentration of 10 μM. Moreover, a slight increase in the refractory period of guinea pig papillary muscles was recorded up to 11% at 10 and 30 μM tepotinib (free base). However, these effects, observed at concentrations more than 100-fold higher than the steady state mean free Cmax of 0.05 μM in humans, did not find any correlation in the *in vivo* cardiovascular studies conducted in rats and dogs.

In an oral cardiovascular study in rats by telemetry no effects on heart rate and arterial blood pressure were seen following a once daily oral administration of tepotinib (free base) of up to 50 mg/kg/day for 8 days. No effect on heart rate, arterial blood pressure, and electrocardiogram (ECG) parameters were seen in dogs following a single oral administration of tepotinib at 70 mg/kg. Also, no relevant effects on the various parameters characterising regional and systemic haemodynamics were found in dogs following a single intraduodenal administration at the dose of 70 mg/kg. The slight positive inotropic effect did not correlate to any relevant cardiovascular observation clinically. Exposure to tepotinib in these last two studies was relatively low.

There were no effects on arterial blood pressure and ECG derived parameters in the repeat-dose toxicity studies in dogs (up to 39 weeks). In particular, in the 39-week study no cardiovascular changes were seen up to the high dose of 30 mg/kg.

No significant effects were seen in a respiratory study in male rats following a single oral administration of tepotinib up to 200 mg/kg. No effects on respiratory rate were seen in a 4-week and a 13-week repeat-dose toxicity study in dogs.

No effects on the central nervous system (CNS) were seen in a functional observational battery (FOB) study in rats following a single oral administration of tepotinib up to 200 mg/kg. Additionally, tepotinib did not induce any effects on autonomic nervous system reflexes during a 4-week and a 13-week repeat-dose toxicity studies in dogs at doses up to 40 mg/kg/day.

In an *in vitro* off-target profiling study the major circulating human metabolite MSC2571109A inhibited 3 off-targets (A3h, M1h, M2h) and one enzyme activity (PDE6) > 50% at 10 μM). However, no inhibitory activity on these targets is anticipated in the clinical setting when considering that the measured steady state free Cmax of 0.007 μM of MSC2571109A (following tepotinib administration at the therapeutic dose of 500 mg) is more than 1400-fold lower than the concentration of 10 μM tested in this study.

No effects were observed up to a concentration of 2.7 μM of MSC2571109A in a hERG assay. This concentration is approximately 385-fold higher than the measured free Cmax of 0.007 μM MSC2571109A at steady state, at a tepotinib dose of 500 mg, indicating no risk for hERG inhibition in the clinical situation. In an *in vitro* cardiac ion channel profiler study MSC2571109A showed no significant effects at concentrations up to 30 μM.

In conclusion, *in vitro* and *in vivo* safety pharmacology studies with tepotinib or its free base did not show any relevant off-target, cardiovascular, respiratory or CNS effects up to concentrations or exposure levels (Cmax) comparable or above the steady state mean free Cmax in patients at the therapeutic dose of 500 mg. *In vitro* safety pharmacological investigations of metabolite MSC2571109A suggest no anticipated risk for potential off-target or cardiovascular (QT prolongation) effects at the therapeutic dose.

III.3 Pharmacokinetics

Toxicokinetic (TK) studies were used to characterise repeat-dose PK parameters. Due to animal welfare reasons no dedicated repeat-dose PK studies were conducted. *In vivo* studies (e.g. toxicokinetics in dogs), and human trials, demonstrated that absorption and consequently oral bioavailability of tepotinib increases if the drug is dosed as micronized material under fed state conditions.

Following single oral doses (liquid formulation), tepotinib was rapidly absorbed in mice with a tmax around 1 hour and more slowly absorbed in rat, dog and monkey (tmax between 4 to 12 hours). Clinically, following oral administration of a tablet formulation (TF1) at the proposed clinical dose of 500 mg, tmax ranged between 2 and 24 hours.

In repeat-dose oral toxicity studies in rats with daily oral doses up to 2000 mg/kg in 4-week studies and up to 135 mg/kg in 26-week studies) tepotinib was administered using the same formulation as for oral rat PK studies (vehicle: 0.25% aqueous Methocel). Tmax was between 3 to 6 hours post dose. Exposure increased with increasing tepotinib doses but less than dose proportionally. Accumulation (up to maximally 3-fold) of tepotinib was observed after multiple doses at all dose levels.

After a single IV dose, the estimated clearance of tepotinib was described as moderate in mouse, high in rat and dog and low in monkey. The terminal half-life was short to moderate in all non-clinical species (2 to 10 hours). The applicant’s report stated that this finding suggested that extensive systemic accumulation of tepotinib after multiple daily doses may be unlikely.

However, in the repeat dose oral toxicity studies, toxicokinetics (TK) in the rat revealed accumulation of tepotinib (up to maximally 3-fold) at all dose levels. Similarly, in the dog, a dose-dependent accumulation was generally observed across studies with average accumulation up to 2.4 to 6.9-fold at the highest dose levels tested. The TK studies were used to characterise repeat-dose PK parameters. Following a single intravenous administration, the terminal half-life (t1/2) in the rat was 2.6 h (male) or 3.2h (female), whilst in the dog it was

7.6h (data available for female only). Following oral administration of micronized or non-micronized tepotinib to rats (female only) the t1/2 was approximately 4 hours. The Applicant's justification linking accumulation to flip-flop kinetics occurring at high dose of tepotinib could be accepted. The safety profile of tepotinib following repeated dosing is based on steady state which takes into consideration any accumulation phenomenon.

In repeat-dose oral toxicity studies in dogs, non-micronized tepotinib was administered in hard gelatin capsules, with daily oral doses up to 40 mg/kg in 4-week studies and up to 30 mg/kg in 13-week studies. Tmax was between 2 and 6 (typically observed at 2 or 4) hours post dose. Exposure increased with increasing doses of tepotinib in an approximately dose proportional manner.

Evidence of the effect of particle size on oral absorption was derived from toxicokinetic studies in rats and dogs, where the AUC exposure was 1.4- to 6.5-fold higher, when smaller particle size batches were administered. In contrast to this, a dedicated *in vivo* PK study in rats did not confirm the difference in exposure observed in toxicokinetic studies, although higher Cmax values were observed with a micronized batch. Clinical studies show that oral exposure and bioavailability is increased when tepotinib is administered in the micronized form and in the fed state.

The volume of distribution at steady state was high in all pre-clinical species (8.2 to 25.8 L/kg) indicating an extensive tissue distribution. Following a single intravenous dose of 14C-labelled tepotinib to humans, the volume of distribution was large (574 L).

Protein binding of tepotinib was moderate to high across species with mean free fractions (fu) of 3% in mouse, 4% in rat, 4- 5% in rabbit, 6-7% in dog, 4-6% in monkey and 1.6-3.4% in human. In human and monkey plasma, the free fraction increased in a concentration-dependent manner. Tepotinib was highly protein bound in human plasma as well as in rat brain tissue. The protein binding of MSC2571109A, the major human circulating metabolite of tepotinib, was independent of concentration and high across all species tested. Average free fractions (fu) were 1.2% in mouse, 1.0% in rat, 2.5% in dog and 1.2% in human plasma.

The *in vitro* blood cell distribution of tepotinib was investigated in mouse, rat, rabbit, dog and monkey, and human blood at concentrations of 0.1 and 1 μM. In animals, the *in vitro* blood cell distribution coefficient (KBC/plasma) was independent of concentration with ratios between 1.9 and 2.6 for all species.

In the mouse, quantitative whole-body autoradiography (QWBA) revealed that drug-related radioactivity showed a tumour-to-plasma ratio ranging from 1.6 (1-hour post dose) to 11.6 (6 hours post dose).

In rats following intravenous injection, medium to high concentrations of drug-related radioactivity in the hepatic tissue and high concentrations in the intestine indicated biliary excretion. Well-perfused organs also showed high concentrations of radioactivity.

Medium levels of drug-related radioactivity were detected in the eyes and skin of pigmented animals throughout the investigation period of 96 hours, leading to the assumption that the test item and/or its metabolites are bound to melanin. This assumption is supported by the fact that no drug-related radioactivity was seen in the eyes of albino rats. Brain concentration ranged between 0.73 and 0.92- fold of plasma concentration in dissection after single oral (4 mg/kg) doses study in rats whilst a brain-to-plasma ratio of 2.87 at steady-state following intravenous administration of tepotinib to rat was observed. Tepotinib demonstrated a very

high binding to rat brain tissue in a concentration-independent manner. The unbound fraction in brain tissue (fu,br) in equilibrium was 0.35% (i.e. 11-fold lower than the 4% fu value in rat plasma).

Investigations on embryo-fetal development in rabbits showed a dose-dependent increase of skeletal malformations at doses ≥ 5 mg/kg/day. These data indicate that tepotinib is able to pass through the rabbit placenta.

In vitro, tepotinib was metabolized by Phase 1 (N-oxidation and de-methylation) and Phase 2 (direct glucuronidation (M668), likely human specific) pathways. CYP3A4 and CYP2C8 contribute to the oxidative metabolism, with other drug metabolizing enzymes (such as flavin-containing monooxygenase) potentially contributing to the formation of the diastereomeric N-oxide metabolites.

Tepotinib was the major component observed in all *in vivo* metabolite studies. Metabolism was by oxidation to chiral N-oxides, enantiomers of a keto alcohol (M506 – the major circulating metabolite in human), by direct glucuronidation and by oxidation to other minor metabolites. Patterns of metabolism were qualitatively broadly similar across species and the enzymes catalysing the formation of different metabolites have been identified for the major metabolites.

Main metabolites present in all species tested were two diastereomeric N-oxides M508-1 and M508-2. In human hepatocytes a glucuronide metabolite, M668, formed via direct glucuronidation of parent drug and most likely representing an N-glucuronide, was not observed in animal species tested.

In vivo in the rat, tepotinib was excreted mainly unchanged in the faeces. The main circulating species in the rat was tepotinib followed by MSC2571109A (R enantiomer), representing 11 to 37% of mean tepotinib AUC and then MSC2571107A (L-enantiomer) representing between 8 and 26% of mean tepotinib AUC. No marked accumulation upon repeat dosing was seen for either metabolite. Minor metabolites were seen in the urine (2 to 6% of the dose) as the chiral N-oxides, M508-1 and M508-2.

Dogs were exposed to metabolites MSC2571107A and MSC2571109A with 2-4-fold higher exposure of the former compared to the latter in plasma with no clear dose, time or sex dependency. Exposure to both metabolites increased roughly in proportion to dose of parent drug with marked accumulation after repeated dosing (Day 267).

In all species tested, the major route of excretion was faecal, with a high fraction of tepotinib being eliminated unchanged. After intravenous administration to rats, 91.1% and 86.1% of 14C-tepotinib related radioactivity was excreted with faeces in males and females respectively whilst 10.8% and 16.9% was recovered in urine in males and females respectively. Biliary secretion was the main route of elimination in that up to 72.9% (males) of the total radioactivity was found in bile within 24 hours.

Results from a study in female dogs with orally dosed 14C-tepotinib at 10 mg/kg indicated that 91.4% of drug related radioactivity was eliminated in faeces and 0.497% in the urine during 192 hours after administration.

Based on mechanistic static modelling of *in vitro* studies, at the proposed clinical dose of 500 mg, tepotinib and its metabolite MSC2571109A have the potential to induce the major cytochrome P450 isoenzyme 3A4 whilst MSC2571109A has the potential to reduce the

clearance of drugs metabolized by the cytochrome P450 isoenzymes 3A4/5 at the proposed clinical dose of 500 mg. Tepotinib and its metabolite MSC2571109A have the potential to inhibit several UGT isoforms. However, taking into account clinical exposure, risk for UGT1A1/9 and 2B17 is considered unlikely whilst it is excluded for the other tested isoforms.

III.4 Toxicology

Tepotinib was tested in repeat-dose toxicity studies with once daily oral administration for up to 26 weeks in rats and for up to 39 weeks in dogs. The vehicle used in rats was 0.25% aqueous hydroxypropyl methylcellulose, whereas in dogs tepotinib was administered as powder in hard gelatin capsules.

In the initial repeat-dose toxicity studies in rats at doses up to 270 mg/kg/day, no observed adverse effect levels (NOAELs) were 90 mg/kg/day in the first two 4-week studies and 45 mg/kg/day in the 26-week study, however a maximum tolerated dose (MTD) was not identified. Histopathology revealed slight liver cell hypertrophy and slight activation of the thyroid follicular epithelium and macrophage aggregates in the mesenteric lymph nodes at 270 mg/kg/day in the 4-week study and 135 mg/kg/day in the 26-week study. At the high doses in the 4-week and the 26-week studies treatment-related incidences of alveolar macrophage aggregates (foam cells) were seen in the lungs in some females. The macrophage aggregates in the lungs and lymph nodes were reversible and not associated with any inflammatory reaction. This indicated that the changes were likely to be a reactive phenomenon rather than a toxic effect. In all studies slight dose-dependent increases of liver enzyme values (e.g., ALT, AST, AP and GLDH) were observed. All changes were reversible or showed evidence for reversibility except for the thyroid activation in females. Thyroid activation is a known finding with increased liver cell metabolism.

An additional 4-week repeat-dose toxicity study in rats was conducted at up to 2000 mg/kg/day to identify a MTD. The dose of 2000 mg/kg/day (limit dose) was not tolerated while no overt signs of toxicity were seen at the next lower dose of 450 mg/kg. Treatment-related histopathology findings in multiple organs were seen at both 450 and 2000 mg/kg/day. These included alveolar foam cells (macrophages aggregates) with inflammation in the lung, hepatocellular necrosis and mononuclear infiltrates in the liver and single cell necrosis in epithelium and/or lamina propria with granulocytic infiltrates in the large intestine. The applicant considered the alveolar foam cell aggregations in the lungs, observed in previous rat studies, as associated with minimal mixed infiltrates indicating an inflammatory reaction in the area of the foamy macrophages. The applicant also proposed that this finding was likely a sequela of metabolic overload following administration of a relatively high dose (i.e. 450 mg/kg). Also, the findings observed in the large intestine (i.e. single cell necrosis with inflammatory changes) were considered secondary to the disturbed gastro-intestinal transit, following administration of relatively high doses, rather than a direct toxic effect.

In the dog, gastrointestinal symptoms were observed in all studies at dose levels of ≥ 2.5 mg/kg/day in the 4-week study, and at ≥ 3 mg/kg/day in the 13-week and 39-week studies. These signs included a dose-dependent incidence and severity of vomiting and soft and/or mucous stool with bloody admixture/diarrhoea and were accompanied by decreased body weight and reduced food consumption. The gastrointestinal symptoms had no histopathological correlate. The hepatobiliary system was identified as the main target organ in all dog studies. Increased hepatic-biliary liver enzymes and pronounced cholangitis and pericholangitis associated with inflammatory infiltrates in the liver were the main findings in the 4- and 39-week dog studies. All findings showed a trend toward reversibility or complete

reversal to normal after a recovery period of up to 12 weeks. Cardiovascular investigations performed during the repeated dose toxicity study in dogs showed no relevant effects on heart rate, arterial blood pressure, and ECG parameters including the heart rate-corrected QT-intervals.

Toxicokinetic investigations conducted within the repeat-dose toxicity studies indicated that all animals were exposed throughout the treatment period, with higher exposure in female animals (up to approximately 3-fold) than in males. Overall exposure increased with increasing tepotinib doses, although was less than dose proportional.

In summary, the identified target organs of toxicity in the repeat-dose toxicity studies were the liver/hepatobiliary system in both rat and dog. Gastrointestinal symptoms including vomiting and diarrhoea were observed in the dog with no histopathological correlate.

In a standard genotoxicity battery, neither tepotinib nor the major metabolite M506 were positive in either the Ames or the *in vitro* micronucleus assay with or without metabolic activation. Tepotinib was also negative in the *in vivo* micronucleus assay.
Carcinogenicity studies were not conducted in accordance with the ICH guideline S9 based on the current indication of advanced cancer.

In two embryo-fetal development studies, New Zealand White rabbits were dosed daily during organogenesis on gestation days (GD) 6-18 at oral doses of tepotinib of 0.5, 5, and 25 mg/kg (Study 1) or 50, 150, and 450 mg/kg (Study 2). Both studies revealed maternal toxicity (starting at a dose level of 50 mg/kg/day) and a dose dependently increased number of skeletal malformations (teratogenicity) starting at a dose level of 5 mg/kg/day. These results indicated that tepotinib has teratogenic potential and, in accordance with ICH S9 recommendations, no further embryo-fetal toxicity investigations were conducted. An increased frequency and degree (from minimal up to moderate) compared to the control animals of otherwise background findings (i.e. mineralization, tubular basophilia or dilation) were seen in the kidney of does at 50 and 150 mg/kg/day. These findings were most likely related to the described maternal conditions. There was no evidence of kidney toxicity in the repeat dose toxicity studies, including studies of chronic duration in rats and dogs, making doubtful any correlation between renal changes and tepotinib.

In line with ICH guideline S9, studies on fertility and early embryonic development and pre- and postnatal development were not conducted based on the therapeutic indication of advanced cancer. No morphological changes in male or female reproductive organs were seen in the repeat-dose toxicity studies in rats and dogs.

No toxicity studies in juvenile animals were conducted as tepotinib is not intended to be used in paediatric patients.

One major circulating human metabolite, MSC2571109A, i.e., the R-enantiomer of the chiral metabolite M506 (MSC2569775), was first identified after completion of the human mass balance trial. A retrospective analysis in repeat-dose toxicity studies in rat and dog showed that the metabolite is formed in both species, confirming that rat and dog are relevant toxicity species for human safety evaluation. Dedicated genotoxicity studies showed that MSC2571109A is not genotoxic.

Acceptance criteria for potential and specified identified impurities in the drug substance were set in agreement with recommendations from ICH M7 guideline. For all specified identified impurities with acceptance criteria above the ICH qualification thresholds, no

genotoxic activity has been identified in dedicated genotoxicity studies or published data. The specifications for these impurities are supported by the level of each impurity administered at the NOAEL in pivotal 4-week repeat-dose toxicity studies in rat.

The ultraviolet absorption bands and extinction coefficients together with *in vitro* phototoxicity testing provided initial evidence for a phototoxic potential of tepotinib. However, this was not confirmed by an *in vivo* phototoxicity study in pigmented rats after single oral administration of up to 1500 mg/kg.

III.5 Ecotoxicity/Environmental Risk Assessment

A full Environmental Risk Assessment (ERA) was submitted with this application.

The ERA revealed that the $PEC_{SURFACEWATER}$ is below the action limit of 0.01 µg/L and, thus, no environmental fate and effect analysis in Phase II needed to be performed. However, due to a high log Dow value, a risk for the environment cannot be excluded. Therefore, the tepotinib was screened for persistence, bioaccumulation and toxicity according to the REACH guidance. As a result, environmental fate and effect studies have shown that tepotinib fulfils the criterial for persistence and toxicity, but not for bioaccumulation.

III.6 Discussion on the non-clinical aspects

The grant of a marketing authorisation is recommended.

IV CLINICAL ASPECTS

IV.1 Introduction

The following clinical studies were submitted with this application:

- 14 clinical pharmacology studies
- 2 dose response studies
- one phase 2 single-arm, open label clinical efficacy study (VISION)
- Three non-interventional studies of ‘real-world’ treatment and outcomes

All studies were conducted in line with current Good Clinical Practice (GCP).

IV. 2 Pharmacokinetics

IV.3 Pharmacodynamics

The clinical pharmacology data supporting the proposed dose were derived from 14 completed clinical studies. In these studies, a total of 588 study participants were exposed to tepotinib:

- 207 healthy participants were exposed to tepotinib monotherapy in 8 studies
- 299 patients with various advanced solid tumors were exposed to tepotinib monotherapy in 4 studies
- 64 patients with MET positive locally advanced or metastatic NSCLC were exposed to tepotinib in combination with gefitinib; these patients were harbouring an EGFR mutation and had acquired resistance to prior EGFR-TKI therapy
- 6 healthy participants and 12 patients with Child-Pugh Class A or Class B hepatic impairment were exposed to tepotinib monotherapy

Tepotinib has mean absolute bioavailability of 71.6% in the fed state and median Tmax of 8 hours. Tepotinib exposure increases in presence of food by 1.6 and 2-fold for AUC and Cmax compared to the fasted state and, therefore, tepotinib should be administered with food. In plasma, tepotinib and its major metabolite are highly protein bound (>98%) with a high volume of distribution for tepotinib during the terminal phase (573.6 L). Tepotinib is

metabolised into oxidative metabolites which account for 48% of plasma exposure. The contribution of the major circulating metabolite M506 to the overall efficacy of tepotinib is negligible. Tepotinib is excreted via faeces (85%) and urine (15%).

A 2-compartment population pharmacokinetic model with sequential zero- and first-order absorption and a first-order elimination from the central compartment was used to characterise tepotinib pharmacokinetics in plasma. Apparent clearance (CL/F) for tepotinib was estimated to be 20.4 L/h (CV%, 33.5%) and mean effective t1/2 was estimated to be 32.1 hours. Age, ethnicity, sex, body weight, and disease status had no clinically relevant influence on tepotinib pharmacokinetics. No dosage adjustment is recommended for patients with mild or moderate hepatic or renal impairment. Serum creatinine concentrations increased over time in all studies which is likely associated with tepotinib exposure. Therefore, renal function estimates that rely on serum creatinine should be interpreted with caution during tepotinib treatment.

Tepotinib is a P-gp substrate; however, it is agreed that P-gp inhibitors are not expected to alter tepotinib exposure to a clinically relevant extent. Strong P-gp inducers may have the potential to decrease tepotinib exposure and therefore they should be avoided during tepotinib treatment. Opioid analgesics and proton-pump inhibitors (PPIs) had no clinically relevant effect on tepotinib pharmacokinetics. Tepotinib can inhibit a number of transporters such as P-gp, BCRP, OCT1 and 2 and MATE, therefore monitoring of the clinical effects is recommended during coadministration with tepotinib.

The proposed dose of 500 mg tepotinib (as hydrochloride hydrate; which is equivalent to 450 mg tepotinib free base) is supported by pharmacokinetic/pharmacodynamic modelling and simulation which shows that the proposed dose would achieve ≥ 95% tumour phospho-MET inhibition in 90% or more of the population. There was a flat exposure response at the proposed dose level which is consistent with saturation of phospho-MET inhibition. Tepotinib MTD was not reached up to 1400 mg dose level and the anti-tumour activity in which the median progression-free survival (PFS) of 2.7 months, and the median overall survival (OS) of 13.5 months were determined at the recommended phase 2 dose of 500 mg once daily. Therefore, the proposed dose of 500 mg (450 mg free base) tepotinib is acceptable.

In vitro studies showed that tepotinib is a substrate of CYP3A4, CYP2C8 and P-gp and a mass balance study indicated that plasma oxidative metabolites account for 48% of total tepotinib exposure. Therefore, the effect of dual strong CYP3A4 and P-gp inhibitors on tepotinib exposure is unknown. Additionally, the effect on tepotinib exposure when P-gp, CYP3A4 and CYP2C8 are induced is also unknown.

IV.4 Clinical efficacy

The efficacy of tepotinib for the proposed indication is based on results of one Phase II single-arm, open label study (VISION).

Three non-interventional studies of ‘real-world’ treatment and outcomes of patients with NSCLC with MET alterations and amplification were included to place the VISION results in the context of data from available therapies.

Dose response studies

For monotherapy, a Phase I, open-label, dose-escalation, non-randomised first-in-human study determined a recommended phase II dose of 500 mg (equivalent to 450 mg free base) tepotinib once daily. The definition of the recommended phase II dose was based on a

nonclinical pharmacokinetic/pharmacodynamic and tumour growth model, analysis of MET inhibition in on-treatment subject biopsies, and a population pharmacokinetic model.

The 500 mg (450 mg free base) once daily dose was selected because it achieved MET inhibition ≥ 90% and results in sufficiently high steady state (trough) exposure levels in ≥ 90% of subjects to induce activity in tumours with varying degrees of sensitivity to MET inhibition.

A further study was carried out in an expanded cohort of subjects treated with 500 mg (450 mg free base) tepotinib once daily administered over a 21-day cycle; and no dose-limiting toxicities were observed among 12 evaluable subjects. The 500 mg (450 mg free base) once daily dose was considered to be well tolerated and within the biologically active range and was therefore chosen for the Phase 2 study (VISION).

Main Study: VISION
This was a Phase II single-arm trial to investigate tepotinib in advanced (locally advanced or metastatic) non-small cell lung cancer with MET exon 14 (METex14) skipping alterations or MET amplification.

The study has 3 cohorts:

- Cohort A (METex14 Skipping Alterations) consisted of subjects who tested positive for METex14 skipping alterations, regardless of MET amplification status.
- Cohort B (MET Amplification) consisted of subjects who tested positive for MET amplification based on liquid biopsy (LBx), and negative for METex14 skipping alterations. Enrolment into Cohort B was halted following the pre-planned interim analysis.
- Cohort C (Confirmatory part for METex14 Skipping Alterations) consists of subjects who tested positive for METex14 skipping alterations, regardless of MET amplification status. Primary analysis sets for Cohort C are defined in the same way as for Cohort A. Enrolment into Cohort C is ongoing.

Participants
Study participants had to meet the following main inclusion/exclusion criteria:

Main inclusion criteria

1. Male or female, ≥ 18 years of age
2. Measurable disease by IRC in accordance with RECIST Version 1.1
3. Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 or 1
4. Histologically or cytologically confirmed advanced (locally advanced or metastatic) NSCLC (all types including squamous and sarcomatoid)
5. Treatment naïve patients in first-line or pre-treated patients with no more than 2 lines of prior therapy
6. Subjects with MET alterations, namely METex14 skipping alterations in plasma and/or tissue, as determined by the central laboratory or by an assay with appropriate regulatory status

Main exclusion criteria
Cancer-related

1. Subjects with symptomatic brain metastases. Subjects with leptomeningeal disease
2. Any unresolved toxicity Grade 2 or more according to National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 4.03
3. Subjects with brain metastasis as the only measurable lesion

4. Subjects with characterized EGFR activating mutations that predict sensitivity to anti-EGFR therapy
5. Subjects with characterized ALK rearrangements that predict sensitivity to anti-ALK therapy

Laboratory values and organ function

6. Inadequate haematological function
7. Inadequate liver function
8. Inadequate renal function

General

9. Prior treatment with other agents targeting the HGF/c-Met pathway
10. Impaired cardiac function

Protocol and Objectives

Patients received tepotinib 500 mg (450 mg free base) once daily in cycles of 21-day duration until disease progression, withdrawal of consent, unacceptable toxicity or death.

Patients were to have tumour assessments according to RECIST 1.1 every 6 weeks following the Cycle 1, Day 1 Visit until 9 months and every 12 weeks thereafter, until disease progression, death, or withdrawal of consent.

The primary objective of VISION was to assess the efficacy of tepotinib based on objective response (OR). The primary endpoint is OR (confirmed complete response (CR) or partial response (PR)) determined according to RECIST Version 1.1, based on independent review. Subjects were identified as having an OR if they achieved either a confirmed CR or PR from first administration of study treatment to first observation of progressive disease (PD). Confirmation was required at least 4 weeks (28 days) after the tumour assessments initially indicating CR or PR.

The secondary objectives were to assess other parameters of efficacy, including duration of response (DOR), progression-free survival (PFS) and overall survival (OS), to assess tolerability and safety of tepotinib, to assess health-related quality of life (HRQoL) and to assess the pharmacokinetics of tepotinib and its metabolite(s).

Exploratory objectives were to explore a possible link between biomarkers of MET pathway activation, other relevant oncogenic pathways in plasma, serum and tumour tissue, and the activity of tepotinib, to explore the QT/QTc interval concentration relationship, and to investigate the exposure-response relationship.

All patients were required to complete 3 patient reported outcome (PRO) assessments: EuroQol Five Dimension Five Level Scale (EQ-5D-5L), European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) and European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Lung Cancer 13 (EORTC QLQLC13).
The questionnaires were to be completed every 6 weeks from Cycle 1, Day 1 until 9 months and every 12 weeks thereafter until disease progression, death or withdrawal of consent.

Study population

Only Cohort A of the VISION Study formed the basis of the efficacy evaluation.
Results for Cohort B were not included because patients in this cohort had MET amplification, not METex14 skipping alterations, and therefore did not contribute data to the proposed indication. Results for Cohort C, the cohort established to confirm the results of Cohort A, were not included because they were preliminary at the date of data cut-off.

In Cohort A, 152 patients with confirmed METex14 skipping alterations received at least 1 dose of tepotinib and were included in the safety analysis set (SAF). One patient was excluded from the Intention-to-Treat (ITT) analysis set (overall) due to 'insufficient METex14 skipping alteration data'.

In Cohort A, 52.0% of patients were male. 71.1% were White. 73.0% had an ECOG performance status grade of 1. The median age was 73.1 years (range: 41 to 94 years) and 82.2% (125 patients) were ≥ 65 years of age, including 68 patients who were ≥ 75 years old. The disease characteristics of the group were representative of patients with NSCLC. 45.4% of patients were treatment naïve. Of the 83 patients (54.6%) who had been previously treated with systemic therapy, 49 patients had had one line, 33 had 2 lines and 1 had 3 lines.

Efficacy analyses were performed in following sets:

- ITT analysis set (Overall ITT in Cohort A, n=151)
- ITT-02 Oct 2019 (ITT subset of patients who received first dose of tepotinib before 02 October 2019 - all had a follow-up of at least 9 months, n=146)
- ITT-02 Apr 2019 (ITT subset of patients who received first dose of tepotinib before 02 April 2019, all had a follow-up of at least 15 months, n=99)
- Combined analysis set for Cohorts A + C (Safety analysis set, n=255)

Results

Efficacy Results, Independent Evaluation VISION Cohort A

	Overall	1L	2L+
ITT–02 Oct 2019, N	146	65	81
ORR [a] n (%) [95% CI] [b]	66 (45.2) [37.0, 53.6]	29 (44.6) [32.3, 57.5]	37 (45.7) [34.6, 57.1]
mDOR, months [c] [95% CI] [d]	11.1 [8.4, 18.5]	10.8 [6.9, ne]	11.1 [9.5, 18.5]
DOR ≥ 6 months, n (% of responders)	49 (74.2)	21 (72.4)	28 (75.7)
mPFS, months [c] [95% CI] [d] Patients with event (PD/Death), n (%)	8.9 [8.2, 11.0] 86 (58.9)	8.5 [5.5, 11.3] 38 (58.5)	10.9 [8.2, 12.7] 48 (59.3)
mOS time [c], months [95% CI] [d] Patients with event, n (%)	17.6 [15.0, 21.0] 75 (51.4)	16.3 [9.7, 29.7] 35 (53.8)	19.7 [15.0, 21.0] 40 (49.4)
ITT–02 Apr 2019, N	99	43	56
ORR [a] n (%) [95% CI] [b]	45 (45.5) [35.4, 55.8]	19 (44.2) [29.1, 60.1]	26 (46.4) [33.0, 60.3]
mDOR, months [c] [95% CI] [d]	11.1 [8.4, 18.5]	ne [5.8, ne]	11.1 [8.4, 18.5]
DOR ≥ 6 months, n (% of responders)	34 (75.6)	14 (73.7)	20 (76.9)
mPFS, months [c] [95% CI] [d] Patients with event (PD/Death), n (%)	8.5 [6.8, 11.0] 67 (67.7)	8.0 [3.8, 11.3] 29 (67.4)	10.9 [6.7, 12.7] 38 (67.9)
mOS time [c], months [95% CI] [d] Patients with event, n (%)	17.0 [12.0, 20.4] 63 (63.6)	15.3 [8.5, 23.6] 28 (65.1)	17.1 [12.0, 21.0] 35 (62.5)

1L=first line of therapy, 2L+=second or later line of therapy, CI=confidence interval, DOR=duration of response, ITT=intention-to-treat, mDOR=median duration of response, mOS=median overall survival, mPFS=median progression-free survival, ne=not estimable, ORR=objective response rate, PD=progressive disease.

a Confirmed complete response/partial response.

b 95% exact CI using the Clopper-Pearson method.

c Product-limit (Kaplan-Meier) estimates.

d 95% CI for the median using the Brookmeyer and Crowley method.

The overall response rate (ORR), based on IRC, of the 146 patients in the main set for efficacy analyses was 45.2% (95% CI: 37.0, 53.6). ORRs were essentially the same whether patients received tepotinib as first line (44.6%) or in subsequent lines (45.7%). The ballpark response rate figure of 45% is seen across all analyses.

Response rate to tepotinib is moderate. The lower bound of the 95% confidence intervals for ORR exceed the pre-specified threshold of 20% in all analysis sets.
Tepotinib is better than currently approved therapy in the second line setting and beyond.

Duration of response (DOR) is considered durable. Median DOR was 11.1 months (95% CI: 8.4, 18.5) in the ITT-02 Oct 2019. Most of the responses to tepotinib occurred early (within 3 months of first dose). Consistent results were observed in ITT-02 Apr 2019, the subset of patients with the longest follow-up, as well as by prior treatment status.

The objective disease control rate (DCR) based on independent evaluation was 69.9% (95% CI: 61.7, 77.2) for the 146 patients in the ITT-02 Oct 2019 set.

Progression-Free Survival, Independent Evaluation, VISION Cohort A

	Overall	1L	2L+
ITT-02 Oct 2019, N	146	65	81
Patients with event, n (%)	86 (58.9)	38 (58.5)	48 (59.3)
Death	31 (21.2)	16 (24.6)	15 (18.5)
Progressive disease	55 (37.7)	22 (33.8)	33 (40.7)
mPFS [a], months [95% CI] [b]	8.9 [8.2, 11.0]	8.5 [5.5, 11.3]	10.9 [8.2, 12.7]

1L=first line of therapy, 2L+=second or later line of therapy, CI=confidence interval, ITT=intention-to-treat, mPFS=median progression-free survival.
a Product-limit (Kaplan-Meier) estimates.
b 95% CI for the median calculated using the Brookmeyer and Crowley method.

A median progression-free survival (PFS) of 8.9 months [95% CI: 8.2, 11.0] in ITT-02 Oct 2019 was observed. Similar results were observed in ITT-02 Apr 2019 (8.5 months, 95% CI: 6.8, 11.0).

Overall Survival, VISION Cohort A

	Overall	1L	2L+
ITT-02 Oct 2019, N	146	65	81
Patients with event, n (%)	75 (51.4)	35 (53.8)	40 (49.4)
mOS time [a], months [95% CI] [b]	17.6 [15.0, 21.0]	16.3 [9.7, 29.7]	19.7 [15.0, 21.0]

Source: Section 2.7.3, Table 15.
1L=first line of therapy, 2L+=second or later line of therapy, CI=confidence interval, ITT=intention-to-treat, mOS=median overall survival.
a Product-limit (Kaplan-Meier) estimates.
b 95% CI for the median calculated using the Brookmeyer and Crowley method.

In the ITT-05 Oct 2019 analysis set, median OS was 17.6 months (95% CI: 15.0, 21.0). Median OS for the overall ITT population of 151 patients (according to the Applicant's definition) at the time of data cut-off was 17.6 months (95% CI: 15.0, 21.0) with a total of 75 deaths.

Quality of life data showed that this appeared broadly stable over time.

In subgroups with sufficient numbers, response rate was comparable to that of the overall intended population.

Supportive studies

To further substantiate the clinical activity of tepotinib, the efficacy results in the VISION study were placed in the context of:

- the outcomes of patients under prior anticancer treatments for advanced NSCLC before their entry in the VISION study (VISION pre-study anticancer therapy)
- the results from published evidence on patients with NSCLC harbouring METex14 skipping alterations who have received available therapies and did not receive any prior MET therapy
- the results of 3 recent non-interventional cohort studies on outcomes in advanced METex14 NSCLC patients treated with anti-cancer therapy describing the effectiveness of available therapies received in real-world clinical care.

Efficacy in the Pivotal VISION Study Relative to Available Therapies in Patients with Advanced NSCLC Harbouring METex14 Skipping Alterations

Population/line of therapy	VISION, Cohort A, upon therapy with tepotinib 500 mg once daily, (ITT-02 Oct 2019) [a]		Any Pre-study Anticancer Therapy for Patients Enrolled in VISION Cohort A, (Overall ITT) [b]	Literature, advanced *MET*ex14 NSCLC, available therapies [c]
	IRC (Independent Evaluation)	Investigator		
ORR, n/N (%) [95% CI]	66/146 (45.2) 37.0, [53.6]	79/146 (54.1) [45.7, 62.4]	25/81 (30.9)	4/24 (17) [6, 36] [1] 2/6 (33.3) [2] 3/13 (23.1) [2] 2/9 (22.2, first line) [6] 4/12 (33.3, first line) [7]
mDOR, months [95% CI] (min/max)	11.1 [8.4, 18.5]	12.7 [9.7, 18.3]	7.5 (1, 17)	NA
mPFS, months [95% CI] (min/max)	8.9 [8.2, 11.0]	8.6 [6.9, 11.0]	4.5 (0, 36)	1.9 [1.7, 2.7] [1] 4.0 [2.8, 14.1] [7]
mOS, months [95% CI]	17.6 [15.0, 21.0]		NA	10.9 [7.4, 16.9] [3] 8.1 [5.3, ne] [4] 6.7 5 9.5 [6.5, 23.1] [7]

CI=confidence interval, IRC=independent review committee, ITT=intention-to-treat, MET=mesenchymal-epithelial transition factor, *MET*ex14=*MET* exon 14, Max=maximum, Min=minimum, mDOR=median duration of response, mOS=median overall survival, mPFS=median progression-free survival, NA=not available, ne=not estimable, NSCLC=non-small cell lung cancer, ORR=objective response rate.

a ORR was determined as the sum of the complete response and the partial response. The 95% exact CI for the ORR was calculated using the Clopper-Pearson method. mDOR, mPFS, and mOS are product-limit (Kaplan-Meier) estimates; 95% CI using the Brookmeyer and Crowley method.

b ORR was determined as the sum of the complete response and the partial response (based on the best response across all prior drug therapies) divided by the number of patients with available data. The median presented for DOR and PFS is based on the longest value recorded across all prior drug therapies.

c ORR was determined as the sum of the complete response and the partial response. Overall survival reported for patients who have never received a MET inhibitor.

Summary of Key Effectiveness Outcome Results in Non-interventional Studies in Advanced METex14 NSCLC patients

Study	Results	1L Therapy		2L Therapy	
dynamic cohort (US)		All 1L anti-cancer n = 51	ICI n = 21	All 2L anti-cancer n = 27	ICI n = 10
	ORR, n (%) [95% CI]	18 (35.3) [22.4, 49.9]	7 (33.3) [14.6; 57.0]	5 (18.5) [6.3, 38.1]	2 (20.0) [2.5, 55.6]
	mPFS, months [95% CI]	3.06 [2.3, 5.0]	4.07 [1.5, 8.1]	4.63 [1.6, 5.7]	2.76 [0.9, 5.7]
	mOS from start of 1L, months, [95% CI], (n = 51)	10.41 [3.2, 22.7]			
multi-country chart review (US, Israel, the Netherlands, Taiwan,		All 1L anti-cancer n = 37	ICI n = 5	All 2L anti-cancer n = 17	ICI n = 6
	ORR, n (%) [95% CI]	11 (29.7) [15.9, 47.0]	1 (20.0) [0.5, 71.6]	3 (17.6) [3.8, 43.4]	0 (0.0) [0.0, 45.9]
	mPFS	NA			
	mOS from start of 1L, months, [95% CI], (n =52)	12.01 [6.8, 19.2]			
(multi-country) NIS)		Platinum-based n = 86	ICI n = 17	2L/3L Single-agent chemotherapy n = 22	2L/3L ICI n =24
	ORR, n (%) [95% CI]	22 (25.6) [16.8, 31.6]	6 (35.3) [14.2, 61.7]	3 (13.6) [2.9, 34.9]	4 (16.7) [4.7, 37.4]
	mPFS, months [95% CI]	5.1 [3.3, 6.9]	2.6 [1.0, 6.9]	2.8 [1.2, 5.0]	3.1 [1.9, 4.1]
	mOS, months [95% CI]	9.1 [7.5, 18.9]	18.4 [1.5, 18.4]	13.2 [3.0, 42.7]	11.9 [2.1, NE]

1L=first line of therapy, 2L=second line of therapy, 3L=third line of therapy, CI=confidence interval, ICI=immune checkpoint inhibitor, mOS=median overall survival, NA=not applicable, NIS=noninterventional study(ies), ORR=objective response rate, mPFS=median progression free survival, NE=not estimable.

Since there is no comparative study of tepotinib with standard of care, the above data look at tepotinib in the context of current 'real-world' management of patients with METex14 NSCLC from selected publications and of patients responses to prior therapy within the VISION study. These approaches do not provide robust evidence in support of tepotinib, particularly with limited numbers, but simply give an indication of how tepotinib might compare to standard of care.

It would seem that the efficacy of tepotinib is similar to chemotherapy and immunotherapy in the first line setting. However, its effect is more easily appreciated after first line given that standard systemic therapy options for advanced NSCLC in the second line setting and beyond result in low response rates and short duration of response.

Overall conclusions on clinical efficacy

This application is based on one single, open-label, non-randomised, uncontrolled clinical trial. It is therefore not possible to compare the time-to-event variables. Nevertheless, ORR is predictive of clinical benefit in NSCLC if the effect size is good and response is durable.

In patients with advanced NSCLC harbouring METex14 skipping alterations with at least 9 months of follow-up from the start of tepotinib in the VISION study (ITT-02 Oct 2019), the overall efficacy results were:
ORR (n=146): 45.2% (95% CI: 37.0, 53.6)
Median DOR (n=66): 11.1 months (95% CI: 8.4, 18.5)
Median PFS (n=146): 8.9 months (95% CI: 8.2, 11.0)
Median OS (n=146): 17.6 months (95% CI: 15.0, 21.0)

When the data were looked at by prior treatment status, ORR and DOR were very similar regardless of the line of treatment.
Overall, these results are clinically meaningful.

IV.5 Clinical safety

The safety analyses focused on the data from 255 patients in Cohorts A and C of the pivotal VISION study up to the cut-off date of 01 July 2020. These were patients with advanced NSCLC harbouring METex14 skipping alterations treated at the proposed oral dose of 500 mg (450 mg tepotinib free base) once daily.

To further characterise the safety profile of tepotinib, safety data from all 448 patients with cancer treated at the proposed dose of 500 mg (450 mg free base) once daily were pooled from the following studies:

- Ongoing pivotal VISION study (cut-off date 01 July 2020)
  - cohort A (n = 152 patients) and cohort C (n = 103 patients); NSCLC patients harbouring METex14 skipping alterations
  - cohort B (n = 24 patients); NSCLC patients with MET amplification. 2 completed Phase I single-arm studies of patients with advanced solid tumours
- Two completed Phase I single-arm studies of patients with advanced solid tumours (n= 42 patients and n= 6 patients)
- Two completed Phase II studies in patients with hepatocellular carcinoma (HCC) (n=59 patients and n=62 patients)

The median duration of tepotinib exposure for patients in Cohorts A and C was 22.3 weeks (range 0–188). About a third of patients were exposed to tepotinib for 6 months or longer.

Adverse events

All adverse events (AEs) regardless of causality were collected up to 30 days after the last dose. AEs were coded using MedDRA version 23.0 and were graded using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 or 4.03.

Overall, AEs were similar between the VISION Study and the pooled safety population.
The most common adverse events reported with an incidence of ≥ 20%, in patients treated with tepotinib were oedema, fatigue, nausea, diarrhoea, musculoskeletal pain and dyspnoea.

The most common Grade ≥3 TEAEs were oedema, pleural effusion, increased lipase, and hypoalbuminaemia.

Treatment-related Grade ≥ 3 TEAEs by PT (≥ 2% of Patients in either Dataset)

	Tepotinib 500 mg	
PT	VISION Cohorts A + C (N = 255) n (%)	POOL (N = 448) n (%)
Patients with at least one treatment-related TEAE of NCI CTCAE Grade ≥ 3	64 (25.1)	114 (25.4)
Edema peripheral	19 (7.5)	27 (6.0)
Pleural effusion	8 (3.1)	8 (1.8)
Lipase increased	7 (2.7)	16 (3.6)
Hypoalbuminemia	6 (2.4)	8 (1.8)
Alanine aminotransferase increased	5 (2.0)	8 (1.8)
Amylase increased	5 (2.0)	7 (1.6)

NCI CTCAE=National Cancer Institute - Common Terminology Criteria for Adverse Events, PT=preferred term, TEAE=treatment emergent adverse event.

Adverse events of special interest (AESI)
AESIs were interstitial lung disease, oedema, hypoalbuminaemia, increased creatinine, increased amylase and lipase, increased ALT and AST, diarrhoea and pleural effusion.

Interstitial lung disease (ILD)
ILD-like events are considered an important identified risk for tepotinib in NSCLC patients. The estimated ILD incidence in VISION Cohorts A + C is 6/255 (2.4%) patients.

Tepotinib treatment was discontinued permanently in 3 patients; and in 3 patients temporarily discontinued due to the ILD like events. In the pooled safety population of 448 patients, ILD/pneumonitis occurred in 2.2% of patients. This included one fatal event of pneumonitis, which was the only Grade 3 or higher event. Four patients (0.9%) discontinued tepotinib due to ILD/pneumonitis.

Oedema (peripheral and generalised)
In the pooled safety population of 448 patients, oedema occurred in 63% of patients (Grade 3-4 oedema 8%).

Within Cohorts A and C of VISION (n=255), oedema occurred in 70% of patients (n=178) (Grade 3-4 oedema 9%).

Median time to onset of any-grade oedema was 7.86 weeks and the median time to resolution was approximately 469 days; 29 (11.4%) patients with oedema fully recovered. In some patients, oedema may last a long time.

Oedema led to interruption of tepotinib dosing in 23% of patients, dose reduction in 19% of patients, and permanent discontinuation of tepotinib in 5%. The incidence of oedema as serious adverse reaction was 4%.

Hypoalbuminaemia
TEAEs of hypoalbuminemia were very common in VISION Cohorts A + C (61 [23.9%] patients). 5.5% were Grade ≥3.

Hypoalbuminemia appeared to be long-lasting but did not lead to permanent treatment discontinuation. Dose reductions (2 patients, 0.8%) and temporary discontinuations (3 patients, 1.2%) were infrequent.

The incidence of hypoalbuminemia in the pooled population (n=448) was 22% (Grade 3 to 4 hypoalbuminemia 4.2%).

Increased creatinine
Based on laboratory assessment, increase in creatinine from baseline were reported in 52.9% of patients. Grade 3 occurred in one patient (0.4%).

Increased amylase and lipase
TEAEs of amylase and lipase increases were generally asymptomatic and there were no reports of pancreatitis.

The incidence of amylase increased was 8.6% and of lipase increased 7.1% in VISION Cohorts A + C: two events of lipase increase were serious (0.8%) and none for amylase increase. No event of lipase increase and amylase increase led to permanent treatment discontinuation or dose reduction.

Increased ALT /AST
In VISION Cohorts A + C, 29 (11.4%) and 19 (7.5%) patients had TEAEs of ALT increased and AST increased, respectively. Ten (3.9%) and 6 (2.4%) patients had increases to Grade ≥ 3 ALT and AST, respectively.

ALT and/or AST increase did not lead to permanent study drug discontinuation, and infrequently led to temporary discontinuation in 9 (3.5%) or dose reduction in 2 (0.8%). Median time to first onset for ALT and/or AST increase of any grade was 6.14 weeks and the median time to resolution was 35.0 days. Events resolved in 25 of 31 patients.

Increased ALT/AST occurred in 13% of patients in the pooled population (n=448). Grade 3 or 4 increased ALT/AST occurred in 4.2% of patients; the median time-to onset of Grade 3 or higher increased ALT/AST was 30 days (range 1 to 178).

Diarrhoea
Diarrhoea occurred in 27% of patients in VISION Cohorts A and C. Grade 3 – 4 diarrhoea occurred in 0.4% of patients and permanent discontinuation due to diarrhoea occurred in 1 (0.4%) patient.

Pleural effusion
Pleural effusion occurred in 13% of patients (n=34) in VISION Cohorts A and C. Grades 3 to 4 pleural effusion occurred in 5% of patients (n=13).
Pleural effusion was categorized as a serious adverse event in 7% of patients (n=17) and led to permanent discontinuation of tepotinib in 2% of patients (n=5). Dosage interruptions and dose reductions due to pleural effusion occurred in 4.3% and 2.7% of patients, respectively.

Serious adverse events (SAEs)
Serious adverse events occurred in 45% of the 255 patients in Cohorts A and C of VISION. SAEs in ≥ 2% of patients included pleural effusion (7%), pneumonia (5%), oedema (3.9%), dyspnoea (3.9%), general physical health deterioration (3.5%), pulmonary embolism (2%) and musculoskeletal pain (2%).

Most deaths were due to disease progression and general physical health deterioration or associated with respiratory disorders as expected for patients with NSCLC.

Deaths occurred in 87 (34%, 87/255) patients. 30 patients (12%) died within 30 days of their last dose. Most were due to disease progression. Death within 30 days of last dose of study drug (excluding deaths due to disease progression) was reported in 14 patients in Cohorts A and C of VISION.

Fatal adverse reactions occurred in one patient due to pneumonitis (within 30 days of the last treatment dose), one patient due to hepatic failure (after 30 days of the last treatment dose), and one patient due to dyspnea from fluid overload (within 30 days of the last treatment dose). Deaths were due to either progression of disease or underlying disease/comorbidities.

Laboratory findings
Common Grade 3 – 4 laboratory abnormalities were decreased lymphocytes, hypoalbuminaemia, hyponatraemia and increased amylase.

Effect of Age
The median age of the 90-day safety update population (n=255) enrolled in VISION Cohorts

A and C was 72 years, with 79% of patients 65 years or older and 43% of patients 75 years or older.

The incidences of Grade 3-4 AEs, SAEs, and AEs leading to dose interruption, dose reduction and treatment discontinuation were higher in the subgroup of patients ≥ 75 years old. The majority of Grade 3-4 AEs in both subgroups were Grade 3 events.

On-treatment QT Prolongation Findings
There was no clinically relevant prolongation of the QTc interval.

Adverse events leading to dose reduction and treatment interruption
Dose reductions due to an adverse event occurred in 30% of patients in Cohorts A and C of VISION. The most common reasons (in > 2% of patients) included oedema, pleural effusion, and increased blood creatinine.

Dose interruptions due to adverse events occurred in 44% of patients who received tepotinib in Cohorts A and C, 44% in all patients in the VISION Study and 39% in the all pooled population. The most common reasons (in >2% of patients) in Cohorts A and C of VISION included oedema, increased blood creatinine, pleural effusion, and pneumonia.

Adverse events leading to discontinuation of tepotinib occurred in 20% of patients in Cohorts A + C of VISION; the most common reasons were (> 1%) were oedema (5%), pleural effusion (2%), dyspnoea (1.6%), general health deterioration (1.6%) and pneumonitis (1.2%).

Overall conclusions on clinical safety
The database included 448 patients with solid tumours who were treated with tepotinib at 500 mg once daily (equivalent to 450 mg tepotinib of the free base form), including 255 patients with NSCLC harbouring METex14 skipping alterations from the VISION study.

Among the 255 patients in Cohorts A and C of VISION, permanent discontinuation of tepotinib due to adverse events occurred in 20% of patients, 44% of patients had tepotinib dosing interrupted for adverse events, and dose reductions due to adverse events occurred in 30% of patients.

The most common adverse events (incidence ≥20%) were oedema, fatigue, nausea, diarrhoea, musculoskeletal pain, and dyspnoea.

The safety issues considered significant and serious were interstitial lung disease/pneumonitis and hepatotoxicity.

There are no major safety concerns.

IV.6 Risk Management Plan (RMP)
The applicant has submitted an RMP, in accordance with the requirements of Regulation 182 of The Human Medicines Regulation 2012, as amended. In addition to routine pharmacovigilance and risk minimisation measures, the following additional pharmacovigilance activities have been proposed:

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Non-interventional study Status: Planned	The NIS will aim to describe and compare effectiveness and safety events in a cohort of advanced patients who received Tepotinib, matched with a cohort of patients who received available therapies in real-world care.	Important identified risks: • Interstitial lung disease Important potential risks: • Pleural/pericardial effusion • QTc prolongation • hepatotoxicity	Final analysis results	Q4 2027
			Final report	Q1 2028
Phase I, Open-Label, Single sequence, Cross-Over Study in Healthy Participants Status: Planned	To investigate the effect of multiple doses of Carbamazepine on single dose tepotinib PK in healthy participants.	Use of tepotinib with strong CYP3A4 and P-gp inhibitors	Final results:	Approximately Q3 2022
Phase I, Open label, Single sequence, Crossover Study in Healthy Participants Status: Planned	To investigate the effect of multiple doses of itraconazole on single dose tepotinib PK in healthy participants.	Use of tepotinib with strong CYP/P-gp inducers	Final results:	Approximately Q3 2022

This is acceptable.

IV.7 Discussion on the clinical aspects

This application is based on one single-arm open label Phase II study. The applicant has provided selected published literature on efficacy of approved therapies in the 'real world' and has given information about patients' response to treatment prior to their entry into the VISION Study if they had previously been treated.

Despite the methodological limitations, these indirect comparisons indicate that tepotinib is better (reasonable response rate and durable responses) than currently approved therapies when used in the second line setting or beyond for patients with NSCLC harbouring METex14 skipping alterations.

In the first-line setting, tepotinib's efficacy in METex14 NSCLC appears to be similar to chemotherapy and/or immunotherapy in the overall NSCLC population.

The safety profile seems acceptable though is yet to be fully characterised.
The grant of a conditional marketing authorisation is recommended for this application.

V USER CONSULTATION

A full colour mock-up of the Patient Information Leaflet (PIL) has been provided with the application in accordance with legal requirements.

The PIL has been evaluated via a user consultation study in accordance with legal requirements. The results show that the PIL meets the criteria for readability as set out in the guideline on the readability of the label and package leaflet of medicinal products for human use.

VI OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the product is acceptable. The non-clinical and clinical data submitted have shown the positive benefit/risk of this product in the treatment of adult patients with advanced non-small cell lung cancer (NSCLC) harbouring mesenchymal-epithelial transition factor gene (MET) exon 14 (METex14) skipping alterations.

TEPMETKO 225 mg film-coated tablets has been authorised with a Conditional Marketing Authorisation (CMA). The Marketing Authorisation Holder shall complete, within the stated timeframe, the following measures:

Description	Due date
Submit the final clinical study report of the VISION trial	December 2023
Submit the outcome of the non-intervention study: External control study using ENSURE data to contextualise and strengthen efficacy and safety results of tepotinib as assessed in the VISION trial	Q4 2025
Submit the outcome of the non-intervention study: Registry-based study to compare the effectiveness and safety of tepotinib to other treatment options available in Europe for patients with non-small cell lung cancer (NSCLC) harbouring MET Exon 14 skipping alterations.	Q1 2028

The Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling are satisfactory, and in line with current guidelines.

In accordance with legal requirements, the current approved GB versions of the SmPC and PIL for this product are available on the MHRA website.

Representative copies of the labels at the time of licensing are provided below.


TEPMETKO® 225 mg
film-coated tablets
60 film-coated tablets
MERCK
TW2707602
FBO_65x60x93-DF-TP
tepotinib
Oral use
Each film-coated tablet contains 225 mg tepotinib (as hydrochloride hydrate).
Contains lactose. See package leaflet for further information.
Read the package leaflet before use.
Keep out of the sight and reach of children.
Store in the original package in order to protect from moisture.
7809826007
Great Britain
4 065266 473650
POM
PLGB 11648/0291
Merck Serono Ltd., 5 New Square, Bedfont Lakes Business Park, Feltham, Middlesex, TW14 8HA, UK

TABLE OF CONTENT OF THE PAR UPDATE

Steps taken after the initial procedure with an influence on the Public Assessment Report (non-safety variations of clinical significance).

Please note that only non-safety variations of clinical significance are recorded below and in the annexes to this PAR. The assessment of safety variations where significant changes are made are recorded on the MHRA website or European Medicines Agency (EMA) website. Minor changes to the marketing authorisation are recorded in the current SmPC and/or PIL available on the MHRA website.

Application type	**Scope**	**Product information affected**	**Date of grant**	**Outcome**	**Assessment report attached Y/N**