Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Tepmetko

Active ingredients: Tepotinib

Sponsor: Merck Healthcare Pty Ltd

August 2022

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating therapeutic goods, including medicines, medical devices, and biologicals.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety, and efficacy.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to the Australian public outweigh any risks associated with the use of therapeutic goods.
- The TGA relies on the public, healthcare professionals and industry to report problems with therapeutic goods. The TGA investigates reports received to determine any necessary regulatory action.
- To report a problem with a therapeutic good, please see the information on the TGA website.

About AusPARs

- The Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission. Further information can be found in Australian Public Assessment Report (AusPAR) guidance.
- AusPARs are prepared and published by the TGA.
- AusPARs are static documents that provide information that relates to a submission at a particular point in time. The publication of an AusPAR is an important part of the transparency of the TGA's decision-making process.
- A new AusPAR may be provided to reflect changes to indications or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

List of abbreviations

Abbreviation	Meaning
ACM	Advisory Committee on Medicines
AE	Adverse event
ALK	Anaplastic lymphoma kinase
ALT	Alanine transaminase
ARTG	Australian Register of Therapeutic Goods
ASA	Australia specific annex
AST	Aspartate transaminase
AUC	Area under the concentration versus time curve
$AUC_{0\text{-inf}}$	Area under the concentration versus time curve from time zero to infinity
BIRC	Blinded independent review committee
CI	Confidence interval
CL/F	Apparent clearance
CL_{CR}	Creatinine clearance
C_{max}	Maximum concentration
CMI	Consumer Medicines Information
CR	Complete response
CV	Coefficient of variation
DLP	Data lock point
DOR	Duration of response
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal growth factor receptor
E-R	Exposure-response
FDA	Food and Drug Administration (United States of America)
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use

Abbreviation	Meaning
ILD	Interstitial lung disease
MET	Mesenchymal-epithelial transition
NCCN	National Comprehensive Cancer Network (United States of America)
NSCLC	Non-small cell lung cancer
OCE	Oncology Center of Excellence (Food and Drug Administration, (United States of America)
ORR	Overall response rate
OS	Overall survival
PD	Pharmacodynamic(s)
PD-L1	Programmed death-ligand 1
PFS	Progression free survival
PI	Product Information
PK	Pharmacokinetic(s)
PR	Partial response
PRO	Patient reported outcome
RECIST	Response evaluation criteria in solid tumours
RMP	Risk management plan
ROS1	Receptor tyrosine kinase 1
SAE	Serious adverse event
TEAE	Treatment-emergent adverse event
TGA	Therapeutic Goods Administration
TKI	Tyrosine kinase inhibitor
T_{max}	Time of maximum concentration
US(A)	United States of (America)

Product submission

Submission details

Type of submission:	New chemical entity
Product name:	Tepmetko
Active ingredient:	Tepotinib (as hydrochloride monohydrate)
Decision:	Approved for provisional registration
Date of decision:	11 January 2022
Date of entry onto ARTG:	17 January 2022
ARTG number:	370977
, *Black Triangle Scheme:*	Yes As a provisionally registered product, this medicine will remain in the Black Triangle Scheme for the duration of its provisional registration
Sponsor's name and address:	Merck Healthcare Pty Ltd Suite 1, Level 1, Building B, 11 Talavera Road, Macquarie Park, NSW 2113
Dose form:	Film coated tablet
Strength:	225 mg tepotinib (equivalent to 250 mg tepotinib hydrochloride monohydrate)
Container:	Blister pack
Pack size:	60 tablets
Approved therapeutic use:	*Tepmetko has provisional approval in Australia for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) harbouring mesenchymal-epithelial transition (MET) exon 14 skipping alterations.* *The decision to approve this indication has been made on the basis of overall response rate (ORR) and duration of response (DOR). Continued approval of this indication depends on verification and description of benefit in confirmatory trial(s).*
Route of administration:	Oral
Dosage:	Treatment should be initiated and supervised by a physician experienced in the treatment of cancer.

	The recommended dose of Tepmetko is 450 mg (two 225 mg tablets) taken orally once daily with food. Treatment should continue as long as clinical benefit is observed. When considering the use of Tepmetko (tepotinib) as a treatment for advanced NSCLC harbouring *MET exon 14* skipping alterations, the *MET exon 14* skipping status should be established prior to initiation of Tepmetko therapy. Monitoring of liver function by liver function tests (including alanine transaminase (ALT), aspartate transaminase (AST) and total bilirubin) should be conducted prior to starting, and during treatment with tepotinib. Patients should be monitored for pulmonary symptoms indicative of interstitial lung disease-like reactions during treatment. For further information regarding dosage, refer to the Product Information.
Pregnancy category:	D Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details. The use of any medicine during pregnancy requires careful consideration of both risks and benefits by the treating health professional. This must not be used as the sole basis of decision making in the use of medicines during pregnancy. The TGA does not provide advice on the use of medicines in pregnancy for specific cases. More information is available from obstetric drug information services in your State or Territory.

Product background

This AusPAR describes the submission by Merck Healthcare Pty Ltd (the sponsor) to register Tepmetko (tepotinib) 225 mg, film coated tablet for the following proposed indication:

> *The treatment of adult patients with advanced non-small cell lung cancer (NSCLC) harbouring MET tyrosine kinase receptor exon 14 (METex14) skipping alterations.*

In 2017, the age-standardised incidence rate of lung cancer was 43 per 100,000 persons in Australia. In 2021, there were estimated to be more than 13,800 new diagnoses of lung

cancer.[1,2] Lung cancer was the most common cause of cancer death in Australia in 2019 with 8,739 deaths reported.[1,2] Although the five-year relative survival for lung cancer has improved in recent years to 16.8%, the five-year survival for those with Stage IV disease remains poor at 3.2%.[3]

Non-small cell lung cancer (NSCLC) accounts for 80 to 90% of lung cancers. Mesenchymal-epithelial transition factor receptor tyrosine kinase (MET), also called c-MET or hepatocyte growth factor receptor (HGFR) is a receptor tyrosine kinase that, after binding with its ligand, hepatocyte growth factor, activates a wide range of different cellular signalling pathways, including those involved in proliferation, motility, migration and invasion.[4] MET is encoded for by the proto-oncogene *MET* and *MET* abnormalities include MET exon-14 skipping mutations (*METex14*). *METex14* mutations occur in approximately 2 to 4% of NSCLC adenocarcinoma, and 1 to 2% of patients with other NSCLC histologies.[5,6] *METex14* mutations are extremely diverse and result in aberrant splicing and exon 14 skipping. The juxtamembrane tyrosine 1003 (Y1003) negatively regulates MET by recruiting the ubiquitin ligase casitas B-lineage lymphoma (c-CBL). *METex14* mutations result in loss of the Y1003 c-CBL binding site and reduced MET degradation.[4] Patients with NSCLC harbouring *METex14* skipping alterations tend to be older (mean age around 70 years) in comparison to some other subpopulations with targetable driver mutations.

MET genomic alterations do not typically overlap with epidermal growth factor receptor, receptor tyrosine kinase (*ROS1*), *B-Raf* proto-oncogene and anaplastic lymphoma kinase (*ALK*) genetic variants, further reinforcing *MET* status as an oncogenic driver.[6]

Multiple case series and cohorts have now demonstrated durable overall response rates with MET-targeting tyrosine kinase inhibitors (MET-TKI's) in patients with advanced NSCLC with *METex14* mutations. In the *METex14* cohort in the PROFILE 1001 trial an overall response rate of 32% was reported with a median duration of response of 9.1 months (95% confidence interval (CI): 6.4, 12.7) and median progression-free survival of 7.3months (95% CI: 5.4, 9.1) with crizotinib.[5]

A variety of more specific MET-TKIs are under development against this target (for example, capmatinib, tepotinib, and savolitinib), with single arm Phase II trials of tepotinib or capmatinib demonstrating efficacy in patients with *METex14*-mutated NSCLC.[7,8]

In recent years, improvements in systemic therapy for advanced NSCLC, including checkpoint inhibitors with or without chemotherapy, and targeted therapies (for those with specific oncogenic driver mutations), have led to a significant reduction in mortality.**Error! Bookmark not defined.**[3] However, the prognosis in patients with a

[1] 'Lung cancer' incorporates ICD-10 (International Statistical Classification 10th revision) cancer codes of C33 (Malignant neoplasm of trachea) and C34 (Malignant neoplasm of bronchus and lung).
[2] Lung cancer statistics. See Cancer Australia for further information. Available from: https://www.canceraustralia.gov.au/cancer-types/lung-cancer/statistics Data sourced from the Australian Institute of Health and Welfare (2021) *Cancer in Australia 2021*, AIHW, Australian Government.
[3] Five years relative survival for lung cancer statistics. Data sourced from AIHW Australian Cancer Database 2016. Available from: https://ncci.canceraustralia.gov.au/outcomes/relative-survival-rate/5-year-relative-survival
[4] Organ SL, Tsao M-S. An overview of the c-MET signaling pathway. *Therapeutic Advances in Medical Oncology*. November 2011:S7-S19.
[5] National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology: Non-Small Cell Lung Cancer. Version 5.2021 – June 15, 2021. National Comprehensive Network (NCCN); 2021. Available at www.nccn.arg
[6] Metastatic Non-Small Cell Lung Cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2018 29 (suppl 4): iv192-iv237.
[7] Paik PK, Felip E, Veillon R, Sakai H, et al. Tepotinib in Non-Small-Cell Lung Cancer with *MET* Exon 14 Skipping Mutations. *N Engl J Med*. 2020 Sep 3;383(10):931-943.
[8] Wolf J, Seto T, Han JY, et al; GEOMETRY mono-1 Investigators. Capmatinib in *MET* Exon 14-Mutated or *MET*-Amplified Non-Small-Cell Lung Cancer. *N Engl J Med*. 2020 Sep 3;383(10):944-957.

dvanced NSCLC receiving therapy in the second line setting or beyond remains poor, with response rates of 6 to 20% and median PFS of 2 to 4 months associated with chemotherapy or checkpoint inhibitors.[5,6]

In patients lacking oncogenic driver mutations, first line immunotherapy with or without chemotherapy has emerged as the standard of care. [5,6] Efficacy results for immune checkpoint inhibitors in patients with *MET exon 14* skipping alterations, regardless of level of programmed death ligand 1 (PD-L1) expression, are conflicting, with overall response rates from retrospective series reported to range from 16% to 36%.[6,7,9,10,11]

For select patients with advanced NSCLC with *MET exon 14* skipping mutations, the American National Comprehensive Cancer Network guidelines recommend the use of capmatinib or tepotinib in the first line setting, or as subsequent therapy following disease progression on first line immunotherapy and/or chemotherapy.[6] Single arm Phase II trials of tepotinib or capmatinib have demonstrated clinical efficacy in NSCLC patients with *MET exon 14* mutations.[5,6,7,8]

The VISION trial (Study NCT02864992) evaluated tepotinib in patients with advanced NSCLC with a confirmed *MET exon 14* skipping mutation.[7] This showed promising results with an overall response rate of 43%, a median duration of response of 11 months, and a different safety profile of tepotinib compared to checkpoint inhibitors and/or chemotherapy. Findings from this pivotal Phase II study form the basis of this submission.

This evaluation was facilitated through Project Orbis, an initiative of the United States (US) Food and Drug Administration (FDA) Oncology Center of Excellence (OCE). Under this project, the FDA, Health Canada, Swissmedic (Switzerland) and the TGA collaboratively reviewed the submission. This evaluation process provided a framework for process alignment and management of evaluation issues in real-time across jurisdictions. Each regulator made independent decisions regarding approval (market authorisation) of the new medicine.

Regulatory status

This product is considered a new chemical entity for Australian regulatory purposes. This product received orphan drug designation on 2 July 2021 for the following indication:

The treatment of non-small cell lung cancer (NSCLC) with genetic MET alterations.

At the time the TGA considered this submission, similar submissions had been approved in Japan (on 25 March 2020), in United States of America (USA; on 3 February 2021), in Canada (on 28 May 2021), in Switzerland (on 22 June 2021) and in Great Britain (on 24 September 2021). A similar submission was under consideration in European Union and Singapore.

The following table summarises these submissions and provides the indications where approved.

[9] Sabari JK, Leonardi GC, Shu CA, et al. PD-L1 expression, tumor mutational burden, and response to immunotherapy in patients with MET exon 14 altered lung cancers. *Ann Oncol*. 2018 Oct 1;29(10):2085-2091
[10] Mazieres J, Drilon A, Lusque A, et al. Immune checkpoint inhibitors for patients with advanced lung cancer and oncogenic driver alterations: results from the IMMUNOTARGET registry. *Ann Oncol*. 2019 Aug 1;30(8):1321-1328.
[11] Drusbosky LM, Dawar R, Rodriguez E, Ikpeazu CV. Therapeutic strategies in METex14 skipping mutated non-small cell lung cancer. *J Hematol Oncol*. 2021 Aug 23;14(1):129

Table 1: International regulatory status of selected countries at the time of TGA evaluation

Region	Submission date	Status	Approved indications
Japan	November 2019	Approved on 25 March 2020	*For patients with unresectable, advanced or recurrent NSCLC with METex14 skipping alterations.*
United States of America	June 2020	Approved on 3 February 2021	*For the treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) harbouring mesenchymal-epithelial transition (MET) exon 14 skipping alterations.* *This indication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.*
Canada	July 2020	Approved on 28 May 2021	*For the treatment of adult patients with locally advanced unresectable or metastatic non-small cell lung cancer (NSCLC) harbouring mesenchymal-epithelial transition (MET) exon 14 skipping alterations. Documentation of MET tyrosine kinase receptor exon 14 (METex14) skipping alteration status based on a validated METex14 assay is required prior to treatment with TEPMETKO (see Warnings and Precautions). Efficacy in patients with NSCLC harbouring METex14 skipping alterations was based on objective response rate and duration of response in a single arm-study (see Clinical Trials).*

Region	Submission date	Status	Approved indications
Switzerland	August 2020	Approved on 22 June 2021	*For the treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) harbouring a MET tyrosine kinase receptor exon 14 (METex14) skipping mutation. Efficacy and safety of Tepmetko has not been studied in patients with additional oncogenic driver mutations including EGFR- and ALK-tumour aberrations.*
United Kingdom	February 2021	Approved on 24 September 2021	*TEPMETKO is indicated for the treatment of adult patients with advanced non-small cell lung cancer (NSCLC) harbouring mesenchymal-epithelial transition factor gene (MET) exon 14 (METex14) skipping alterations.*
Singapore	December 2020	Approved on 25 November 2021	*TEPMETKO is indicated for the treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) harbouring mesenchymal-epithelial transition factor gene (MET) exon 14 (METex14) skipping alterations.*
European Union	November 2020	Under consideration	Under consideration

The Delegate expects that the wording of conditions of registration, should approval be granted, would be aligned to that of the United States (US) Food and Drug Administration (FDA) post-marketing requirements/commitments.

The US FDA post-marketing requirements include the following:

- Post-marketing requirement 1:

  Final report submission in April 2023.

  Submit the final reports including datasets from clinical studies to confirm and further characterise the clinical benefit of tepotinib for the treatment of patients with NSCLC harboring MET exon 14 skipping alterations who are treatment-naïve and who have previously received systemic therapy, by providing a more precise estimation of the blinded independent central review assessed overall response rate and duration of response. This report will contain data from patients with NSCLC harboring MET exon 14 skipping alterations; data from at least 130 patients who are treatment naïve, after all responders have been followed for at least 12 months from the date of initial response (or until disease progression,

whichever comes first); and from at least 143 patients who have been previously treated with systemic therapy, after all responders have been followed for at least 6 months from the date of initial response (or until disease progression, whichever comes first).

- Post-marketing requirement 2:

  Final report submission in September 2022.

  Conduct a drug interaction study to evaluate the effect of itraconazole on the single dose pharmacokinetics of tepotinib to assess the magnitude of increased drug exposure and determine appropriate dosing recommendations when tepotinib is administered concomitantly with a strong CYP3A4 and P-gp inhibitors.

- Post-marketing commitment 3:

  Final report submission in July 2022.

  Conduct a drug interaction study to evaluate the effect of carbamazepine on the single dose pharmacokinetics of tepotinib to assess the magnitude of decreased drug exposure and determine appropriate dosing recommendations when tepotinib is administered concomitantly with a strong CYP3A4 inducer and moderate CYP2C8 inducer.

Product Information

The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the TGA PI/CMI search facility.

Registration timeline

The following table captures the key steps and dates for this submission.

Table 2: Timeline for Submission PM-2021-03109-1-4

Provisional review pathway

Description	Date
Designation (Orphan);[12]	2 July 2021
Determination (Provisional);[13]	2 July 2021
Submission dossier accepted and first round evaluation commenced	31 August 2021
First round evaluation completed	31 August 2021
Sponsor provides responses on questions raised in first round evaluation	31 August 2021
Second round evaluation completed	10 January 2022
Delegate's Overall benefit-risk assessment and request for Advisory Committee advice	1 November 2021
Sponsor's pre-Advisory Committee response	15 November 2021
Advisory Committee meeting	2 and 3 December 2021
Registration decision (Outcome)	11 January 2022
Completion of administrative activities and registration on the ARTG	17 January 2022
Number of working days from submission dossier acceptance to registration decision*	88

*Statutory timeframe for standard submissions is 255 working days

[12] 'Orphan drugs' are often developed to treat small and very specific patient populations who suffer from rare diseases and conditions. In order to facilitate orphan drug access to the Australian marketplace and help offset orphan drug development costs the TGA waives application and evaluation fees for prescription medicine registration applications if a related **orphan designation** is in force. A medicine may be eligible for orphan drug designation if all orphan criteria set by the TGA are met. The orphan designation application precedes the registration application and the designation is specific to the sponsor, orphan indication for which designation was granted and dosage form of the medicine.

[13] As part of the **provisional approval pathway**, the provisional registration process will allow certain medicines to be provisionally registered in the Australian Register of Therapeutic Goods (ARTG) for a limited duration. These medicines are registered on the basis of preliminary clinical data, where there is the potential for a substantial benefit to Australian patients. The TGA will re-assess risks related to the absence of evidence through data provided at a later stage, as part of the confirmatory data. Confirmatory data should confirm the relationship between outcomes predicted by the surrogate endpoint, or other preliminary data, and the clinical benefit as demonstrated by direct clinical outcomes.
The sponsor may apply to transition to full registration at any time up until the provisional registration lapse date, once they have completed the obligations outlined for the provisional registration period and complete confirmatory data on safety and efficacy are available.

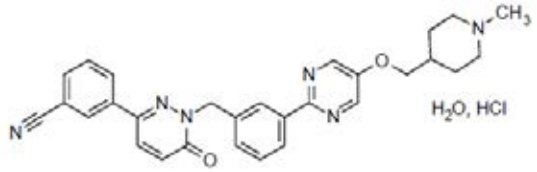
Submission overview and risk/benefit assessment

This section is a TGA summary of wording used in TGA's evaluation report, which discussed numerous aspects of overseas evaluation reports and included some information that was commercial-in-confidence.

Quality

Tepotinib is reversible type I adenosine triphosphate-competitive, small molecule inhibitor of the MET tyrosine receptor kinase. The drug substance, tepotinib hydrochloride monohydrate is shown in Figure 1. The drug substance exhibits good stability and the data submitted supports a retest period of 30 months when stored below 25 degrees celsius.

Figure 1: Chemical structure of tepotinib hydrochloride monohydrate



The drug product is a white-pink, oval, biconvex film-coated tablet, with 'M' embossed on one side and plain on the other side. Each tablet contains 250 mg of tepotinib hydrochloride monohydrate equivalent to 225 mg of tepotinib. The tablet is packaged in blister packs and are supplied in cartons of 60 tablets.

The tablets are conventionally formulated. The critical manufacturing steps are adequately controlled.

The drug product specification adequately controls the quality of the drug product. Degradation products are controlled to International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Q3B limits.[14] Dissolution limits are based on the dissolution profiles of clinical batches.

The stability data supports a shelf-life of 30 months when stored below 30 degree; no additional storage conditions are required.

There are no outstanding issues with respect to chemistry, quality control and/or bio-pharmaceutic aspects of the submission. Registration is recommended with respect to chemistry, quality control and biopharmaceutic aspects.

Nonclinical

The primary pharmacology studies support the proposed indications. The scope of the nonclinical program was generally consistent with the relevant TGA adopted guideline on the nonclinical evaluation of anticancer pharmaceuticals.[15] All pivotal safety related studies were Good Laboratory Practices (GLP) compliant.

Target organs of toxicity include hepatobiliary system and gastrointestinal tracts, and to a lesser extent, lungs, adrenal gland, thyroid and lymphoid system. Oedema reported in patients in clinical trials was not observed in any toxicity studies.

The selection of highest dose in the 26 week rat study was not adequate, given the relatively mild toxicity findings and low plasma drug concentrations in the study.

[14] CPMP/ICH/2738/99: ICH Q3B (R2) Impurities in new drug products. Current effective version.
[15] EMA/CHMP/ICH/646107/2008: ICH S9 Non-clinical evaluation for anticancer pharmaceuticals

Tepotinib is teratogenic in rabbits. Pregnancy category D is recommended.[16]

The application is approvable only if safety has been adequately demonstrated in clinical studies.

Clinical

This application has been submitted for review under Project Orbis. The FDA evaluation report has been reviewed as part of this submission.

Pharmacology

The proposed tepotinib dosing regimen is 500 mg tepotinib hydrochloride hydrate (equivalent to 450 mg tepotinib freebase) orally once daily with food.

The proposed dosing regimen was initially selected based on results from dose finding study where the maximum tolerated dose was not reached up to a dosage of 1400 mg daily, with dose limiting toxicities observed at dose levels of 1000 mg and 1400 mg and no dose limiting toxicities at 500 mg daily. Selection of 500 mg daily was further evaluated in additional dose selection studies, which showed an acceptable safety profile and numerically better preliminary efficacy compared to a lower dosage of 300 mg daily. In the VISION trial, no apparent exposure-response relationship was observed for safety or efficacy endpoints at a dosage of 500 mg daily.

Pharmacokinetic (PK)/pharmacodynamic (PD) modelling and simulation suggested that a dose of 500 mg once daily was sufficient to achieve sustained inhibition of phospho-MET at a level greater than 95% in more than 90% of patients with mixed solid tumours.

Tepotinib was administered immediately after breakfast in VISION trial. In the food effect study, a high fat, high calorie meal increased the mean tepotinib area under the concentration time curve from time zero to infinity ($AUC_{0\text{-}inf}$) by 1.6-fold and maximum plasma concentration (C_{max}) by 2-fold and shifted the median time of maximum plasma concentration (T_{max}) from 12 hours to 8 hours. The potential decreased exposure when tepotinib is taken without food may compromise anti-tumour activity.

Pharmacokinetics

Tepotinib exposure (as area under concentration time curve (AUC), C_{max}) increased proportionately in the range of 27 mg to 450 mg.

Median T_{max} was 8 hours (range: 6 to 12 hours).

Absolute bioavailability in the fed state in healthy people was 72% (coefficient of variation (CV) = 11%).

The apparent clearance (CL/F) of tepotinib is 23.8 L/h (87.5%) and the half-life is 32 hours following oral administration.

Tepotinib is primarily metabolised by CYP P450 isozymes CYP3A4 and CYP2C8.[17] One major circulating plasma metabolite (M506) has been identified. Following a single oral

[16] Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details.

[17] **Cytochrome P450 (CYP) enzymes:** CYPs are the major enzymes involved in drug metabolism, accounting for large part of the total metabolism. Most drugs undergo deactivation by CYPs, either directly or by facilitated excretion from the body. Also, many substances are bioactivated by CYPs to form their active compounds.

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

No clinically significant effects on tepotinib pharmacokinetics were observed based on age (18 to 89 years), race/ethnicity (White, Black, Asian, Japanese, and Hispanic), sex, body weight (35.5 to 136 kg), mild to moderate renal impairment (creatinine clearance (CL_{cr}) 30 to 89 mL/min), or mild to moderate hepatic impairment (Child-Pugh A and B).[18] The effect of severe renal impairment (CL_{cr} < 30 mL/min) and severe hepatic impairment (Child-Pugh C) on the pharmacokinetics of tepotinib has not been studied.

Metabolism and *in vitro* data suggests that tepotinib is a substrate of CYP3A4, CYP2C8 and P-gp. However, the fractions metabolised by individual major cytochrome P450 isozymes have not been reliably quantified. Confirmatory data, as part of a provisional approval, are required (see recommendations & outstanding issues below).

Recommendations and outstanding issues

Tepotinib is considered approvable from a clinical pharmacology perspective, providing the following studies are conducted as part of post-marketing requirements:

- Conduct a drug-drug interaction study to evaluate the effect of itraconazole on the single dose pharmacokinetics of tepotinib to assess the magnitude of increased drug exposure and determine appropriate dosing recommendations when tepotinib is administered concomitantly with a strong CYP3A4 and P-gp inhibitors. Design and conduct the study in accordance with the FDA Guidance;[19] 'Clinical drug interaction studies, cytochrome P450 enzyme and transporter mediated drug interactions'.
- Conduct a drug-drug interaction study to evaluate the effect of carbamazepine on the single dose pharmacokinetics of tepotinib to assess the magnitude of decreased drug exposure and determine appropriate dosing recommendations when tepotinib is administered concomitantly with a strong CYP3A4 inducer and moderate CYP2C8 inducer.

Data used for clinical evaluation

The pivotal data for efficacy come from Cohort A of the single arm VISION trial (Study MS200095-0022), which included 152 patients as of the data cut-off date of 1 July 2020 (treatment naïve: n = 69, pre-treated: n = 83).

Subsets of Cohort A were evaluated:

- 2 October 2019 cohort: 146 patients who had their first dose of tepotinib before 2 October 2019 and had at least nine months follow up at the data cut-off date

Many drugs may increase or decrease the activity of various CYP isozymes either by inducing the biosynthesis of an isozyme (enzyme induction) or by directly inhibiting the activity of the CYP (enzyme inhibition). This is a major source of adverse drug interactions, since changes in CYP enzyme activity may affect the metabolism and clearance of various drugs. Such drug interactions are especially important to take into account when using drugs of vital importance to the patient, drugs with important side-effects and drugs with small therapeutic windows, but any drug may be subject to an altered plasma concentration due to altered drug metabolism.

[18] The **Child-Pugh score** is used to assess the prognosis of chronic liver disease. The score employs five clinical measures of liver disease. Each measure is scored 1 to 3, with 3 indicating most severe derangement. Class A: 5 to 6 points, least severe liver disease, one to five year survival rate of 95%. Class B: 7 to 9 points, moderately severe liver disease, one to five year survival of 75%. Class C: 10 to 15 points, most severe liver disease, 1 to 5 year survival rate 50%.

[19] FDA guidance for industry: Clinical Drug Interaction Studies – Cytochrome P450 Enzyme – and Transporter-Mediated Drug Interactions. Available at www.FDA.com

(1 July 2020). The sponsor expected that time to response would be about three months, so that responders would have six months post-response follow up.

- 2 April 2019 cohort: 99 patients who had their first dose of tepotinib before 2 October 2019 and had at least 15 months follow up at the data cut-off date (1 July 2020). Responders would have 12 months post-response follow up.

There are some minor differences in the numbers because a small number of patients recruited to Cohort A (< 4) did not have metastatic disease or did not have *METexon14* skipping on verification.

Patients with *METexon14* skipping NSCLC had also been enrolled to Cohort C of the VISION trial (n = 103). However, the duration of follow up for this cohort was limited at the time of submission of the dossier. Data from Cohort C will contribute to the confirmatory data for the provisional approval.

Cohort B of VISION trial consisted of 24 patients with advanced/metastatic MET amplification NSCLC and were included in the pooled safety population.

Supportive safety data included results from four additional studies:

- Study EMR-001 (n = 42);
- Study EMR-003 (n = 6);
- Study EMR-004 (n = 59), and
- Study EMR-005 (n = 62).

The pooled safety population used to inform the information in the PI includes a total of 448 patients (from Cohorts A, B, and C of the VISION trial and the four additional studies above). Safety results were also reported for the 255 patients with *METexon14* skipping NSCLC, who received tepotinib in the VISION trial.

Efficacy

VISION trial (Study MS200095-0022)

The VISION trial is a Phase II, single arm, open label, ongoing study:

- Cohort A (*METexon14* skipping) provides the efficacy data for this application,
- Cohort B (MET amplified disease) (tested negative for *METexon14* skipping),
- Cohort C (*METexon14* skipping) will contribute to the confirmatory the data.

The study was conducted at 128 study centres in 11 countries: Belgium, France, Germany, Israel, Italy, Japan, Poland, South Korea, Spain, Taiwan, The Netherlands, and 27 study centres in the USA. There were no study sites in Australia.

Diagnostic criteria

From 13 September 2016 to 1 January 2020, a total of 6708 patients were pre-screened for *MET* alterations; 169 patients (2.5%) with *METexon14* skipping mutations were subsequently screened for inclusion. Of these patients, 152 were treated with tepotinib (treatment naïve: n = 69, pre-treated: n = 83).

The data cut-off was 1 July 2020. At this time:

- enrolment into Cohort-A was complete,
- enrolment into Cohort-C was ongoing.

Patients in Cohort A constituted the efficacy cohort. Patients in Cohorts A and C formed the basis of the safety evaluation. Safety results from Cohort B and four other early phase studies in solid tumours were included in the pooled safety analysis.

Key inclusion/exclusion criteria

- Histologically or cytologically confirmed locally advanced/metastatic NSCLC (all types including squamous and sarcomatoid);
- *METexon14* skipping alteration (by either tissue or liquid biopsy);
- 18 years and above;
- Eastern Cooperative Oncology Group (ECOG) performance status[20] of 0 or 1;
- Measurable disease by response evaluation criteria in solid tumours (RECIST);[21] version 1.1;
- Either treatment naïve (for first line therapy) or pre-treated with no more than two lines of prior therapy, and
- Patients with brain metastases whose condition was neurologically stable and whose glucocorticoid dose was being tapered were eligible to participate, as were patients with untreated asymptomatic brain metastases measuring 1 cm or less in the longest diameter.

Study intervention

Patients were treated with 450 mg tepotinib orally once daily (from two 250 mg Tepmetko (tepotinib hydrochloride monohydrate tablets, each delivering 225 mg tepotinib).

Treatment was continuous, until disease progression, consent withdrawal or discontinuation due to adverse events.

Primary endpoint:

- overall response rate (confirmed complete response or partial response): blinded independent review committee (BIRC) determined according to RECIST 1.1.

Patients could be evaluated for an objective response if they had undergone at least two post-baseline assessments or had discontinued participation for any reason.

Secondary endpoints include:

- investigator assessed overall response rate;
- BIRC- and investigator-assessed duration of response;

[20] **ECOG Performance Status:** The Eastern Cooperative Oncology Group (ECOG) has developed criteria used by doctors and researchers to assess how a patient's disease is progressing, assess how the disease affects the daily living abilities of the patient, and determine appropriate treatment and prognosis. The following are used:

0 - Fully active, able to carry on all pre-disease performance without restriction

1- Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, for example, light house work, office work

2 - Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours

3 - Capable of only limited self-care, confined to bed or chair more than 50% of waking hours

4 - Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair

5 – Dead

[21] The Response Evaluation Criteria in Solid Tumors (RECIST) is a voluntary, international standard using unified, easily applicable criteria for measuring tumor response using X-ray, CT and MRI.

- BIRC- and investigator-assessed progression-free survival;
- overall survival;
- patient-reported outcomes;
- treatment-emergent adverse events;
- abnormal clinical laboratory tests; and
- pharmacokinetics.

Statistical analysis plan

No formal statistical hypotheses were tested. The data were analysed in a descriptive manner. According to the protocol, the primary efficacy analysis was conducted when the target enrolment population of at least 60 patients in both the liquid biopsy and tissue-biopsy subgroups had undergone at least nine months of follow up (efficacy population). Three analysis groups were defined to independently assess findings in the liquid biopsy group, the tissue biopsy group, and the combined group (either biopsy method).

For the primary endpoint of BICR overall response rate, the study aimed for a point estimate in the range of 40% to 50% and the lower limit of the exact 95% confidence interval (CI) of greater than 20% in each of the analysis groups (liquid biopsy, tissue biopsy, combined).

Diagnostic testing

Determination of patients' *METexon14* skipping alteration was done prospectively on all patients during the pre-screening period.[7] *MET exon 14* skipping was tested centrally from either:

- circulating tumour DNA collected from plasma (liquid biopsy) using next-generation sequencing panel Guardant360 (73 gene) (n = 66), or
- RNA collected from tumour tissue (tissue biopsy) using oncomine focus assay (52 gene) (n = 60).

Contemporaneous testing with both methodologies was not a requirement for enrolment, and only 27 of 152 patients in Cohort-A had both tests.

A total of 153 patients were tested. There were minor differences in numbers because a small number of patients (< 4) did not have metastatic disease or turned out not to have a *METexon14* skipping alteration. There were also differences in datasets (2 April 2019, and 2 October 2019 cohorts) because of differing lengths of follow up (see description of populations under *Data used for clinical evaluation*, above).

Patient disposition

Of the 146 patients in the 2 October 2019 Cohort (at least nine months follow up), as at 1 July 2020 data cut-off:

- Discontinued treatment due to progressive disease (or death) (75 patients, 51%)
- Adverse event (24 patients, 16%)
- Consent withdrawal (5 patients, 3%)
- Other reasons (3 patients, 2%)
- Protocol noncompliance (one patient, 1%)
- Ongoing treatment (27 patients, 19%).

Baseline characteristics

Baseline characteristics were as follows:

- Male: 52%
- Age (years, median): 73.1 (range: 41, 94)
- Asian: 25%
- Smoking history: 52%
- Histology:
  - adeno: 86%,
  - squamous: 9%,
  - other: 5% (includes sarcomatoid and adenosquamous)
- ECOG performance status 0: 27%, ECOG performance status 1: 73%;[20]
- Brain metastases: 9.9%.

Primary endpoint results

There were no complete responses.

Table 3: VISION trial Blinded independent review committee overall response rate results for all of Cohort A (n = 152), for the data cut-off 1 July 2020

	Treatment naïve (n = 69)	Previously treated (n = 83)
Blinded independent central review overall response rate, % (95% confidence intervals)	43% (32%, 56%)	43% (33%, 55%)
Median duration of response	11 months	11 months
Patients with duration of response ≥ 6 months, %	67%	75%
Patients with duration of response ≥ 9 months, %	30%	50%

Overall response rates and durations of response were similar all of Cohort A (n = 152) and in the subsets of Cohort A: 2 October 2019 cohort (nine months follow up, n = 146) and 2 April 2019 cohort (15 months follow up, n = 99) and for platinum-naïve versus prior platinum and treatment-naïve versus previously treated.

The BICR overall response rate was also similar across the liquid biopsy versus the tissue biopsy groups. For those patients with at least 9 months follow up, as at the 1 January 2020 cut-off, the BICR overall response rate in the liquid biopsy group (n = 66) was 49% (36%, 61%). The corresponding percentage in the tissue biopsy group (n = 60) was 50% (39%, 63%).

Most of the responses to tepotinib occurred early (within three months of the first dose).[7]

Investigator assessed overall response rate were slightly higher than BICR overall response rate, supportive of the primary analysis per BICR assessment.

Secondary endpoint results

As per regulatory guideline,[22] time to event endpoints, such progression-free survival and overall survival, are difficult to interpret in single arm trials, given the lack of internal contemporaneous controls. For completeness, the median progression-free survival was 8 to 9 months, the median overall survival was about 17 months (although this is based on small numbers). These results for progression-free survival and overall survival have not been used for regulatory decision making.

Safety

The pooled safety population comprised 448 patients with solid tumours enrolled in five open label, single arm studies receiving tepotinib as monotherapy at a dose of 450 mg once daily. Among the 448 patients, 32% were exposed for six months or longer, and 12% were exposed for longer than 12 months. The results discussed below relate to both the pooled safety population as well as for the 255 patients with *METexon14* skipping NSCLC, who received tepotinib in VISION trial (Cohorts A plus C).

Deaths

At data cutoff date of 1 January 2020, four patients in the pooled safety population died due to treatment-emergent adverse events (TEAEs) that were considered to be treatment related. Among the deaths in the VISION trial Cohort A plus C, three were considered to be due to an adverse reaction (one from fatal acute hepatic failure, one from acute respiratory failure and one due to dyspnoea from fluid overload).

Serious adverse events

At least one serious adverse event (SAE) was reported for 44.2% of patients in the VISION trial Cohorts A plus C, and 43.7% in the pooled population. The most common serious adverse events in the VISION trial Cohorts A plus C were pleural effusion (7.2%), pneumonia (4.4%) and disease progression (4.4%). Serious adverse events assessed as treatment related as per investigator in ≥ 2% of patients were pleural effusion (2.8%), generalised oedema (2.2%) and peripheral oedema (2.2%).

Discontinuation due to adverse effects

Permanent discontinuation due to an adverse reaction occurred in 21% of patients. This was most frequently due to peripheral oedema (5%), pleural effusion (2%), dyspnoea (1.6%), general health deterioration (1.6%), and pneumonitis (1.2%).

Dose interruption/reduction due to adverse effects

Dosage interruptions due to an adverse reaction occurred in 44.2% of patients in the VISION trial Cohort A plus C and 37.3% in the pooled safety population. This was most frequently due to peripheral oedema (23%), increased blood creatinine (6%), pleural effusion (4.3%), increased alanine transaminase (ALT) (3.1%), and pneumonia (2.4%).

Dose reductions due to an adverse reaction occurred in 30% of patients in VISION trial Cohort A plus C. This was most frequently due to peripheral oedema (19%), pleural effusion (2.7%), and increased blood creatinine (2.7%).

Adverse event of special interest: interstitial lung disease

Interstitial lung disease (ILD)/pneumonitis occurred in 2.2% of patients in the pooled safety population and was fatal in one patient; four patients (0.9%) discontinued tepotinib due to ILD/pneumonitis.

[22] FDA guidance for industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics. Available at www.FDA.com

The incidence of ILD/pneumonitis in patients in the VISION trial Cohorts A plus C was 3.1%.

Laboratory findings

The most common Grade 3/4 laboratory abnormalities in patients in the VISION trial Cohorts A plus C were decreased lymphocytes (11%), decreased albumin (9%), decreased sodium (8%), increased gamma-glutamyltransferase (GGT; 5%), increased amylase (4.6%), increased ALT (4.1%), increased aspartate transaminase (AST) (2.5%), and decreased haemoglobin (2%).

Aspartate transaminase/alanine aminotransferase

Increased ALT/AST occurred in 13% of patients in the pooled population; Grade 3 or 4 increases occurred in 4.2%. A fatal adverse reaction of hepatic failure occurred in one patient (0.2%). Three patients (0.7%) discontinued tepotinib due to increased ALT/AST. The median time to onset of Grade 3 or higher increased ALT/AST was 30 days (range 1 to 178).

Electrocardiogram

Exposure QTc;[23] modelling showed no clinically relevant prolongation of the QTc interval.

Risk management plan

The summary of safety concerns and their associated risk monitoring and mitigation strategies are summarised in Table 4. Further information regarding the TGA's risk management approach can be found in risk management plans for medicines and biologicals and the TGA's risk management approach.

The sponsor has submitted Core-risk management plan (RMP) version 3.0 (dated 10 May 2021; data lock point (DLP) 1 July 2020) and Australia specific annex (ASA) version 2.1 (dated 27 July 2021) in support of this application. The most recently evaluated Core RMP was version 3.0 (dated 10 May 2021; DLP 1 July 2020) and ASA version 2.0 (dated 17 May 2021) which was submitted in support of application.

Table 4: Summary of safety concerns

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine	Additional	Routine	Additional
Important identified risks	Interstitial lung disease	ü**	–	ü	–
Important potential risks	Pleural effusion	ü	–	ü	–
	Severe Hepatotoxicity	ü	–	ü	–
	QT interval prolongation	ü	–	ü	–

[23] The **QT interval** is the time from the start of the QRS wave complex to the end of the corresponding T wave. It approximates to the time taken for ventricular depolarisation and repolarisation, that is to say, the period of ventricular systole from ventricular isovolumetric contraction to isovolumetric relaxation.
The **corrected QT interval** (**QTc**) estimates the QT interval at a standard heart rate. This allows comparison of QT values over time at different heart rates and improves detection of patients at increased risk of arrhythmias.

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine	Additional	Routine	Additional
Missing information	Use of tepotinib with strong CYP3A4 and P-gp inhibitors†.	ü	ü††	ü	–
	Use of tepotinib with strong CYP3A4 inducers and moderate CYP2C8 inducers	ü	ü††	ü	–

†† Phase I Pharmacokinetic Studies (planned); ** Follow up questionnaire

The summary of safety concerns was considered to be acceptable and there have been no changes.

Routine and additional pharmacovigilance activities have been proposed. Two additional post market studies requested by the FDA are included in the Australian RMP which is acceptable.

Routine risk minimisation activities only are acceptable as tepotinib is given orally under specialist supervision.

Wording for conditions of registration

Any changes to which the sponsor has agreed should be included in a revised RMP and ASA. However, irrespective of whether or not they are included in the currently available version of the RMP document, the agreed changes become part of the risk management system.

The suggested wording is:

> *The Tepmetko Core-Risk Management Plan (RMP) (version 3.0 dated 10 May 2021; DLP 1 July 2020) and Australian Specific Annex version 2.1 (dated 27 July 2021) included with submission PM-2021-03109-1-4, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.*
>
> *An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of periodic safety update reports (PSURs).*
>
> *Unless agreed separately between the supplier who is the recipient of the approval and the TGA, the first report must be submitted to TGA no later than 15 calendar months after the date of the approval letter. The subsequent reports must be submitted no less frequently than annually from the date of the first submitted report until the period covered by such reports is not less than three years from the date of the approval letter, or the entire period of provisional registration, whichever is longer.*
>
> *The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on good pharmacovigilance practices (GVP) Module VII-periodic safety update report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration. Each report must have been prepared within ninety calendar days of the data lock point for that report.*

As Tepmetko is being considered for a provisional registration it should be included in the Black Triangle Scheme as a condition of registration. The following wording is recommended for the condition of registration:

> *Tepmetko (tepotinib) is to be included in the Black Triangle Scheme. The PI and Consumer Medicines Information (CMI) for Tepmetko must include the black triangle symbol and mandatory accompanying text for the products entire period of provisional registration.*

As Tepmetko is being considered for a provisional registration the following wording regarding confirmatory trial data is recommended for the condition of registration:

> *Confirmatory trial data (as identified in the sponsor's plan to submit comprehensive clinical data on the safety and efficacy of the medicine before the end of the 6 years that would start on the day that registration would commence) must be provided.*
>
> *Specifically, the sponsor must conduct studies as described in the clinical study plan in version 2.1 (dated 27 July 2021) of the Australia-Specific Annex. The following study report(s) should be submitted to TGA:*
>
> – *Study MS200095-0022, VISION trial, by date 1 November 2027*

Risk-benefit analysis

Delegate's considerations

Metastatic non-small cell lung cancer NSCLC is a life-threatening disease with poor survival; 2 to 4% of patients with NSCLC have tumours that harbour *METexon14* skipping mutations. Such patients tend to be older (mean age around 70 years) in comparison to some other subpopulations with targetable driver mutations. *MET* genomic alterations do not typically overlap with epidermal growth factor, ROS1, BRAF and ALK genetic variants, further reinforcing MET status as an oncogenic driver. There is only limited data regarding the response rate of checkpoint inhibitors and/or platinum-based chemotherapy for patients with NSCLC tumours with *METexon14* skipping alterations, with no strong evidence to suggest that this significantly differs from the response rate in the general population of patients with NSCLC.

There is no approved specific targeted therapy in Australia for patients with NSCLC whose tumours harbour *METexon14* skipping alterations. The standard of care for such patients (that is NSCLC with no targetable driver mutation) includes platinum-based chemotherapy and/or an immune checkpoint inhibitor in the first line setting. Overall response rates for programmed death-ligand 1 (PD-L1) inhibitor and platinum-based chemotherapy combination have been reported to range from 40 to 58%, with median duration of response ranging from 7 to 11 months. Approved second line options in Australia include immune checkpoint inhibitors (if not previously given), or chemotherapy (for example, docetaxel or gemcitabine); these are associated with response rates of 6 to 20% and median duration of response of 4 to 9 months.

Proposed indication

The sponsor proposes to register a new therapeutic entity for the following indication:

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

The proposed dose is 450 mg tepotinib (corresponding to 500 mg of tepotinib hydrochloride hydrate) taken orally, once daily.

Benefits

The sponsor has provided adequate evidence of effectiveness to support provisional approval of tepotinib for the treatment of adult patients with locally advanced or metastatic NSCLC whose tumours harbour *METexon14* skipping alterations. The

recommendation for provisional approval is supported by results from the pivotal VISION trial (Study MS200095-0022), a multicentre, non-randomised, open label, multicohort study in patients with NSCLC with *MET* mutation and/or amplification. In treatment-naïve patients (n = 69), confirmed overall response rate per BIRC was 43% (95% CI: 32, 56) with a median duration of response of 10.8 months (95% CI: 6.9, not evaluable). In patients who had received previous treatment, confirmed overall response rate per BIRC was 43% (95% CI: 33, 55) with a median duration of response of 11.1 months (95% CI: 9.5, 18.5).

Indirect comparison in the second line/subsequent setting indicates that the overall response rate and duration of response observed with tepotinib is reasonably likely to predict clinical benefit over available second line (or subsequent) treatment options.

In the treatment naïve population, indirect comparison suggests that the observed overall response rate for tepotinib is not higher than that for the standard of care (anti-PD L1 antibody and platinum-based chemotherapy), although the efficacy of checkpoint inhibitor and chemotherapy combinations in patients with NSCLC with *METexon14* skipping mutations remains unclear at present. The differing toxicity profile and convenience of oral administration makes tepotinib a reasonable treatment option in the first line setting. When considered in this context, the overall response rate and duration of response for tepotinib could be considered to likely predict clinical benefit over existing treatments.

Documentation of *MET tyrosine receptor exon 14* skipping alteration status based on a valid *METexon14* assay is required prior to treatment with tepotinib and should be outlined in the PI.

Uncertainties

No direct head-to-head comparison of tepotinib with standard treatment in either the first line or subsequent setting, has been performed, limiting the ability to more accurately evaluate benefits and risks. The potential for bias with single arm studies is well known.

The number of patients in the pivotal study was small, and the duration of follow up is limited for both treatment naïve and previously treated patients in the primary efficacy analysis population. Although the current data is considered to be adequate to support provisional approval, confirmatory data is required. The sponsor is planning to submit final study reports including datasets from clinical studies to confirm and further characterise the clinical benefit of tepotinib for the treatment of patients with NSCLC harbouring *METexon14* skipping alterations by providing a more precise estimation of the blinded independent central review-assessed overall response rate and duration of response.

Risks

The safety database included 448 patients with solid tumours who were treated with tepotinib 450 mg once daily, (including 255 patients with NSCLC with *METexon14* skipping alterations) as part of the VISION trial. The most common adverse events (AEs) were oedema, fatigue, nausea, diarrhoea, musculoskeletal pain and dyspnoea. 20% of patients permanently discontinued tepotinib due to AEs (with these AEs most frequently including oedema, pleural effusion, dyspnoea, general health deterioration and pneumonitis). 44% of patients required dose interruption for AEs; 30% required dose reductions due to AEs.

Although tepotinib can cause severe toxicities, information in the Warnings and Precautions and Dosage and Administration sections of the PI should be able to address these safety issues adequately. Interstitial lung disease/pneumonitis and hepatotoxicity are considered significant and serious enough to warrant inclusion in the Warnings and Precautions of the PI.

Uncertainties

As discussed above, the single arm study design of the VISION trial precludes the direct comparison of safety/toxicity profile of tepotinib with standard of care. The number of patients in the VISION trial was relatively small, limiting the ability to fully characterise rare AEs.

The assessment of unexpected serious of risk of increased drug exposure when tepotinib is administered concomitantly with strong CYP3A4 and P-gp inhibitors, and strong CYP3A4/moderate CYP2C8 inducers, remains insufficient. The corresponding post marketing requirement/commitments aim to address this issue (see Regulatory status, and Risk management plan section).

Benefit-risk balance

Overall, the benefit-risk assessment for tepotinib is favourable with respect to supporting provisional registration. The overall response rate and duration of response from the VISION trial, are considered to be clinically meaningful and reasonably likely to predict clinical benefit in the proposed population. Although tepotinib can cause serious toxicities, the safety profile demonstrated is acceptable when considered in the context of a life-threatening disease (that is advanced NSCLC), and the lack of available targeted therapy options in Australia for the intended patient population at present.

The study design limits interpretation of survival; although available evidence supports provisional approval, further data is required in order to confirm clinical benefit. The sponsor will be required to submit final reports of post-marketing requirement studies (see Regulatory status, and Risk management plan sections). These are as aligned with FDA post-marketing requirements.

Proposed action

The benefit risk assessment for tepotinib is considered to be favourable to support provisional registration.

> *Provisional approval of tepotinib for the intended population is therefore recommended for the indication as follows: 'for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) harbouring mesenchymal-epithelial transition (MET) exon 14 skipping alterations. The decision to approve this indication has been made on the basis of overall response rate (ORR) and duration of response (DOR). Continued approval of this indication depends on verification and description of benefit in confirmatory trials'.*

Advisory Committee considerations

The Advisory Committee on Medicines (ACM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following.

Specific advice to the Delegate

The ACM advised the following in response to the Delegate's specific request for advice:

1. ***Are the clinical findings from the VISION trial (Study MS200095-0022) adequate to support the use of tepotinib in the proposed population in the first-line treatment setting?***

The ACM agreed that the overall response rate and duration of response observed in the treatment naïve group within the VISION study is adequate to support the use of tepotinib in first line therapy for adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) harbouring *METexon 14* skipping alterations.

The ACM noted that the availability of Tepmetko would allow an oral tyrosine kinase inhibitors to be available prior to chemoimmunotherapy which would provide another treatment option to patients and clinicians.

2. Are the clinical findings from VISION trial (Study MS200095-0022) adequate to support the use of tepotinib in the proposed population in the second-line/subsequent treatment settings?

The ACM agreed that the overall response rate and duration of response observed in the pre-treated group within the VISION trial is adequate to support the use of tepotinib as second line/subsequent therapy for adult patients with locally advanced or metastatic NSCLC harbouring *MET exon 14* skipping alterations.

The ACM noted the important of providing patients and clinicians with additional efficacious options at multiple treatment lines.

3. Other advice

The ACM noted that this is a provisional application and advised that the confirmatory studies should be provided once available.

The ACM commented that NSCLC harbouring *MET exon 14* skipping alterations is a rare subtype of cancer and acknowledged the potential challenges with randomised controlled studies. The ACM noted that this is of particular consideration for NSCLC harbouring *METexon14* skipping mutations as many DNA-based next-generation sequencing panels currently used in Australia do not identify these *MET* mutations.

Conclusion

The ACM considered this product to have an overall positive benefit-risk profile for the provisional indication:

> *For the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) harbouring mesenchymal-epithelial transition (MET) exon 14 skipping alterations.*
>
> *The decision to approve this indication has been made on the basis of overall response rate (ORR) and duration of response (DOR). Continued approval of this indication depends on verification and description of benefit in confirmatory trials.*

Outcome

Based on a review of quality, safety, and efficacy, the TGA approved the registration of Tepmetko (tepotinib) 225 mg, film coated tablet, blister pack, indicated for:

> *Tepmetko has provisional approval in Australia for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) harbouring mesenchymal-epithelial transition (MET) exon 14 skipping alterations.*
>
> *The decision to approve this indication has been made on the basis of overall response rate (ORR) and duration of response (DOR). Continued approval of this indication depends on verification and description of benefit in confirmatory trial(s).*

Specific conditions of registration applying to these goods

- Tepmetko (tepotinib) is to be included in the Black Triangle Scheme. The PI and CMI for Tepmetko must include the black triangle symbol and mandatory accompanying text for the products entire period of provisional registration.

- Confirmatory trial data (as identified in the sponsor's plan to submit comprehensive clinical data on the safety and efficacy of the medicine before the end of the 6 years that would start on the day that registration would commence) must be provided.

  Specifically, the sponsor must conduct studies as described in the clinical study plan inversion 2.1 (dated 27 July 2021) of the Australia specific annex. The following study report should be submitted to TGA:

  – Study MS200095-0022, VISION [trial], by date 1 November 2027.

  Further guidance for sponsors is available on the TGA website.

- The Tepmetko Core-Risk Management Plan (RMP) (version 3.0 dated 10 May 2021; DLP 1 July 2020) and Australian Specific Annex version 2.1 (dated 27 July 2021) included with submission PM-2021-03109-1-4, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

  An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of periodic safety update reports (PSURs).

  Unless agreed separately between the supplier who is the recipient of the approval and the TGA, the first report must be submitted to TGA no later than 15 calendar months after the date of the approval letter. The subsequent reports must be submitted no less frequently than annually from the date of the first submitted report until the period covered by such reports is not less than three years from the date of the approval letter, or the entire period of provisional registration, whichever is longer.

  The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on good pharmacovigilance practices (GVP) Module VII-periodic safety update report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration. Each report must have been prepared within ninety calendar days of the data lock point for that report.

- Submit final reports including datasets from clinical studies to confirm and further characterise the clinical benefit of tepotinib for the treatment of patients with non-small cell lung cancer (NSCLC) harboring *MET exon 14* skipping alterations who are treatment-naïve and who have previously received systemic therapy, by providing a more precise estimation of the blinded independent central review-assessed overall response rate and duration of response.
- Conduct a drug interaction study to evaluate the effect of itraconazole on the single dose pharmacokinetics of tepotinib to assess the magnitude of increased drug exposure and determine appropriate dosing recommendations when tepotinib is administered concomitantly with a strong CYP3A4 and P-gp inhibitors.
- Conduct a drug interaction study to evaluate the effect of carbamazepine on the single dose pharmacokinetics of tepotinib to assess the magnitude of decreased drug exposure and determine appropriate dosing recommendations when tepotinib is administered concomitantly with a strong CYP3A4 inducer and moderate CYP2C8 inducer.

Attachment 1. Product Information

The PI for Tepmetko approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA PI/CMI search facility.

Therapeutic Goods Administration

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