▼This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/reporting-problems.

AUSTRALIAN PRODUCT INFORMATION – TEPMETKO® (tepotinib (as hydrochloride monohydrate)) film-coated tablet

1 NAME OF THE MEDICINE

Tepotinib (as hydrochloride monohydrate)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

TEPMETKO is supplied as film coated tablets containing 225 mg tepotinib (equivalent to 250 mg tepotinib hydrochloride monohydrate).

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

White-pink, oval, biconvex film-coated tablet with embossment "M" on one side and plain on the other side.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

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).

4.2 DOSE AND METHOD OF ADMINISTRATION

Treatment should be initiated and supervised by a physician experienced in the treatment of cancer.

*MET*ex14 Skipping Alterations Testing

When considering the use of TEPMETKO as a treatment for advanced NSCLC harbouring *MET*ex14 skipping alterations, the *MET*ex14 skipping status should be established prior to initiation of TEPMETKO therapy. *MET*ex14 skipping status in tumour or plasma specimens should be determined using a validated or approved test. Only robust, reliable and sensitive tests for the determination of *MET*ex4 skipping status should be used.

Dosage and Method of Administration

Recommended Dose

The recommended dose of TEPMETKO is 450 mg (two 225 mg tablets) orally once daily with food. Treatment should continue as long as clinical benefit is observed.

Missed Dose

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

Dose Adjustment

Dose adjustment may be required based on individual safety and tolerability. If dose adjustment is necessary, then the recommended dose reduction of TEPMETKO is 225 mg (one tablet) orally once daily with food.

Treatment modification guidelines for the management of adverse reactions are provided hereafter:

Table 1: Recommended Treatment Modifications of TEPMETKO for the Management of Adverse Reactions

Adverse Reaction	Severity	Treatment Modification
Interstitial Lung Disease (ILD) (see Section 4.4 Special Warnings and Precautions for Use – Interstitial Lung Disease)	Any grade	Withhold TEPMETKO if ILD is suspected. Permanently discontinue TEPMETKO if ILD is confirmed.
Increased ALT and/or AST without increased total bilirubin (see Section 4.4 Special Warnings and Precautions for Use – Monitoring of Liver Function)	Grade 3	Withhold TEPMETKO until recovery to baseline ALT/AST. If recovered to baseline within 7 days, then resume TEPMETKO at the same dose; otherwise resume TEPMETKO at a reduced dose.
	Grade 4	Permanently discontinue TEPMETKO.
Increased ALT and/or AST with increased total bilirubin in the absence of cholestasis or hemolysis (see Section 4.4 Special Warnings and Precautions for Use – Monitoring of Liver Function)	ALT and/or AST greater than 3 times ULN with total bilirubin greater than 2 times ULN	Permanently discontinue TEPMETKO.

Increased total bilirubin without concurrent increased ALT and/or AST (see Section 4.4 Special Warnings and Precautions for Use – Monitoring of Liver Function)	Grade 3	Withhold TEPMETKO until recovery to baseline bilirubin. If recovered to baseline within 7 days, then resume TEPMETKO at a reduced dose; otherwise permanently discontinue.
	Grade 4	Permanently discontinue TEPMETKO.
Other adverse reactions (see Section 4.8 Adverse Effects (Undesirable Effects))	Grade 3 or higher	Reduce TEPMETKO to 225 mg until the adverse reaction recovers to ≤ Grade 2. A temporary interruption of TEPMETKO treatment for no more than 21 days can also be considered

Renal Impairment

No dose adjustment is recommended in patients with mild or moderate renal impairment (creatinine clearance 30 to 89 mL/min). The pharmacokinetics and safety of TEPMETKO in patients with severe renal impairment (creatinine clearance below 30 mL/min) have not been studied (see Section 5.2 Pharmacokinetic Properties).

Hepatic Impairment

No dose adjustment is recommended in patients with mild (Child Pugh A) or moderate (Child Pugh B) hepatic impairment. The pharmacokinetics and safety of TEPMETKO in patients with severe hepatic impairment (Child Pugh C) have not been studied (see Section 5.2 Pharmacokinetic Properties).

Elderly (> 65 years of age)

No dose adjustment is necessary in patients aged 65 years and above (see Section 5.2 Pharmacokinetic Properties).

Administration

TEPMETKO is for oral use. The tablet(s) should be taken with food and should be swallowed whole. Do not break, crush or chew the tablets.

4.3 CONTRAINDICATIONS

TEPMETKO is contraindicated in patients with known hypersensitivity to tepotinib or to any of the excipients (see Section 6.1 List of Excipients).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Assessment of METex14 skipping alterations status

Patients treated with TEPMETKO must have a confirmed *MET*ex14 skipping status based on a validated or approved test.

Interstitial lung disease

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

Patients should be monitored for pulmonary symptoms indicative of ILD-like reactions. TEPMETKO should be withheld, and patients should be promptly investigated for alternative diagnosis or specific aetiology of interstitial lung disease. TEPMETKO must be permanently discontinued if interstitial lung disease is confirmed, and the patient be treated accordingly.

Monitoring of liver function

Increases in ALT and/or AST have been reported in the VISION study in patients with advanced NSCLC harbouring *MET*ex14 skipping alterations (see Section 4.8 Adverse Effects (Undesirable Effects)), which were mostly non-serious and of low grade. ALT and/or AST increase did not lead to permanent drug discontinuation and infrequently led to temporary discontinuation or dose reduction.

Based on laboratories values, a worst-on-treatment increase of at least 1 grade was observed for 42.0% of patients for ALT and 32.9% for AST. An increase to grade 3 or higher occurred in 3.9% of patients for ALT and 2.4% of patients for AST.

Monitor liver function tests (including ALT, AST and total bilirubin) prior to the start of TEPMETKO, every 2 weeks during the first 3 months of treatment, then once a month or as clinically indicated, with more frequent testing in patients who develop increased transaminases or bilirubin. If grade 3 or higher increases occur, dose adjustment is recommended (see Section 4.2 Dose and Method of Administration – Dose Adjustment).

Embryo-fetal toxicity

TEPMETKO can cause fetal harm when administered to pregnant women. There are no available data on the use of TEPMETKO in pregnant women. However, studies in animals showed malformations (teratogenicity) (see Section 4.6 Fertility, Pregnancy and Lactation).

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

Women of childbearing potential must use effective contraception during TEPMETKO treatment and for at least 1 week after the last dose. Pregnancy testing is recommended in women of childbearing potential prior to initiating treatment with TEPMETKO.

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

Use in hepatic impairment

See Section 4.2 Dose and Method of Administration.

Use in renal impairment

See Section 4.2 Dose and Method of Administration

Use in the elderly

Of 255 patients with *MET*ex14 skipping alterations in the VISION study who received 450 mg TEPMETKO once daily, 79% were 65 years or older, and 8% were 85 years or older. No clinically important differences in safety or efficacy were observed between patients aged 65 or older and younger patients in VISION study.

Paediatric use

The safety and efficacy of TEPMETKO in paediatric patients below the age of 18 years have not been studied.

Effects on laboratory tests

Nonclinical studies suggest that tepotinib or its main metabolite inhibit the renal tubular transporter proteins organic cation transporter (OCT) 2, multidrug and toxin extrusion transporters (MATE) 2K (see Section 4.5 Interactions with Other Medicines or Other Forms of Interactions). Creatinine is a substrate of these transporters, and the observed increases in creatinine (see Section 4.8 Adverse Effects (Undesirable Effects)) may be the result of inhibition of active tubular secretion rather than actual renal injury. Renal function estimates that rely on serum creatinine (creatinine clearance or estimated glomerular filtration rate) should be interpreted with caution considering this effect.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Effects of other medicines on tepotinib

Strong CYP3A and/or P-gp inducers

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

Dual strong CYP3A inhibitors and P-gp inhibitors

The effect of strong CYP3A inhibitors or P-gp inhibitors on TEPMETKO has not been studied clinically. However, metabolism and *in vitro* data suggest concomitant use of drugs that are strong CYP3A inhibitors and P-gp inhibitors may increase tepotinib exposure, which may increase the incidence and severity of adverse reactions of TEPMETKO. Concomitant use of TEPMETKO with dual strong CYP3A inhibitors and P-gp inhibitors (e.g. ketoconazole, itraconazole) should be avoided.

Acid-reducing agents

Co-administration of omeprazole had no marked effect on the pharmacokinetic profile of tepotinib and its metabolites when administered under fed conditions.

Effects of tepotinib on other medicines

P-gp substrates

Tepotinib is an inhibitor of P-gp *in vitro*. Tepotinib can inhibit the transport of sensitive substrates of P-gp. Multiple administrations of TEPMETKO 450 mg orally once daily had a mild effect on the pharmacokinetics of the sensitive P-gp substrate dabigatran etexilate, increasing its AUC_t by approximately 50% and C_{max} by approximately 40%. Monitoring of the clinical effects of P-gp-dependent substances with a narrow therapeutic index (e.g. digoxin) is recommended during co-administration with TEPMETKO.

BCRP substrates

Tepotinib is an inhibitor of BCRP *in vitro*. Tepotinib can inhibit the transport of sensitive substrates of the breast cancer resistance protein (BCRP). Monitoring of the clinical effects of sensitive BCRP substrates is recommended during co-administration with TEPMETKO.

Other transporters

Tepotinib or its major circulating metabolite inhibited OCT2 and MATE2K *in vitro* at clinically relevant concentrations.

Based on *in vitro* data, tepotinib or its metabolite may have the potential to increase the AUC of co-administered metformin in humans through inhibition of metformin's renal excretion mediated via OCT2 and MATE2K. Monitoring of the clinical effects of metformin is recommended during co-administration with TEPMETKO.

CYP 450 substrates

Multiple administrations of TEPMETKO 450 mg orally once daily had no clinically relevant effect on the PK of the sensitive CYP3A substrate midazolam. Based on *in vitro* data, neither tepotinib nor its major circulating metabolite present a perpetrator for other cytochrome P450 enzymes.

UGT substrates

In vitro data do not predict clinically relevant effects on UGT substrates.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

No human data on the effect of TEPMETKO on fertility are available. No specific studies with tepotinib have been conducted in animals to evaluate the effect on fertility. No morphological changes in male or female reproductive organs were seen in the repeat-dose toxicity studies in rats and dogs, except for reduced secretion in seminal vesicles of male rats in a 4-week repeat dose toxicity study at 450 mg/kg/day (comparable to human clinical exposure based on AUC).

Use in pregnancy – Pregnancy Category D

There are no clinical data on the use of TEPMETKO in pregnant women. Studies in animals have shown teratogenicity (including malformations). Based on the mechanism of action and findings in animals TEPMETKO can cause fetal harm when administered to pregnant women. TEPMETKO must not be used during pregnancy. Women of childbearing potential or male patients with female partners of childbearing potential should be advised of the potential risk to a fetus (see Section 4.4 Special Warnings and Precautions for Use).

A dose-dependent increase in malformed fetuses (hyperextension of limbs and malrotation of limbs along with concomitant misshapen scapula and/or malpositioned clavicle and/or calcaneous and/or talus) was observed after oral administration of tepotinib to pregnant rabbits at ≥ 5mg/kg/day (approximately 0.003 times the human exposure based on AUC).

Use in lactation

There are no data regarding the secretion of tepotinib or its metabolites in human milk or its effects on the breast-fed infant or milk production. Breast-feeding should be discontinued during treatment with TEPMETKO.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

TEPMETKO may have minor influence on the ability to drive and use machines, as during treatment with tepotinib, fatigue and asthenia have been reported.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Clinical Trial Experience

The safety profile of TEPMETKO reflects exposure to tepotinib in 448 patients with various solid tumours enrolled in five open-label, single-arm studies, in which patients received tepotinib as a single agent at a dose of 450 mg once daily. This includes 255 patients with advanced NSCLC harbouring *MET*ex14 skipping alterations included in the main clinical study (VISION). The median duration of exposure in this study was 22.3 weeks (range 0 to 188 weeks).

The data described below reflect exposure to TEPMETKO 450 mg once daily in 255 patients with advanced NSCLC harbouring *MET*ex14 skipping alterations.

Serious treatment emergent adverse events (TEAEs) occurred in 45.1% of patients who received TEPMETKO. Serious TEAEs in ≥ 2% of patients included pleural effusion (6.7%), pneumonia (4.7%), dyspnoea (3.9%), general health deterioration (3.5%), peripheral oedema (2.4%), generalised oedema (2.0%) and pulmonary embolism (2.0%).

Permanent discontinuation due to TEAEs occurred in 20.4% of patients who received TEPMETKO. Common TEAEs (> 1.0%) leading to permanent discontinuation of TEPMETKO were peripheral oedema (3.5%), pleural effusion (2.0%), general health deterioration (1.6%), dyspnoea (1.6%), genital oedema (1.2%) and pneumonitis (1.2%).

Dosage interruptions due to TEAEs occurred in 43.9% of patients who received TEPMETKO. TEAEs which required dosage interruption in > 2% of patients who received TEPMETKO included peripheral oedema (16.9%), generalised oedema (3.1%), oedema (2.7%), increased blood creatinine (6.3%), pleural effusion (4.3%), increased ALT (3.1%) and pneumonia (2.4%).

TEAEs leading to treatment dose reduction occurred in 29.8% of patients who received TEPMETKO. The most frequent TEAEs (> 2.0%) leading to treatment dose reduction included

peripheral oedema (14.1%), increased blood creatinine (2.7%), pleural effusion (2.7%), generalised oedema (2.4%) and oedema (2.4%).

Table 2 summarises the incidence of adverse reactions that occurred in patients with NSCLC harbouring *MET*ex14 skipping alterations in VISION study.

The adverse drug reactions are listed by System Organ Class (SOC) and frequency categories, defined using the following conventions: very common (≥ 1/10), common (≥ 1/100 to <1/10), uncommon (≥1/1000 to <1/100), rare (≥1/10,000 to <1/1,000), and very rare (<1/10,000).

Table 2: Adverse Reactions in ≥ 1% Patients with NSCLC Harboring *MET*ex14 Skipping Alterations in the VISION Study

System organ class (SOC) Adverse reaction	TEPMETKO N=255	
	All grades n (%) Frequency category	Grade ≥ 3 n (%) Frequency category
Gastrointestinal disorders		
Diarrhoea	67 (26.3) Very common	1 (0.4) Uncommon
Nausea	68 (26.7) Very common	2 (0.8) Uncommon
Vomiting	33 (12.9) Very common	3 (1.2) Common
Abdominal pain[f]	42 (16.5) Very common	2 (0.8) Uncommon
Constipation	40 (15.7) Very common	0 (0) -
General disorders and administration site conditions		
Oedema[a]	176 (69.0) Very common	21 (8.2) Common
Generalised oedema	13 (5.1) Common	5 (2.0) Common
Fatigue/Asthenia	70 (27.5) Very common	4 (1.6) Common
Hepatobiliary disorders		
Increase in alanine aminotransferase (ALT)	29 (11.4) Very common	8 (3.1) Common
Increase in aspartate aminotransferase (AST)	19 (7.5) Common	3 (1.2) Common
Investigations		
Increase in creatinine[b]	66 (25.9) Very common	1 (0.4) Uncommon
Increase in amylase[c]	22 (8.6) Common	8 (3.1) Common
Increase in lipase	18 (7.1) Common	9 (3.5) Common
Metabolism and nutrition disorders		
Hypoalbuminemia[d]	61 (23.9) Very common	14 (5.5) Common
Respiratory, thoracic and mediastinal disorders		
Interstitial Lung Disease (ILD)[e]	6 (2.4) Common	1 (0.4) Uncommon

[a] includes terms oedema peripheral, oedema, oedema genital, face oedema, localised oedema, periorbital oedema, peripheral swelling, scrotal oedema
[b] includes terms blood creatinine increased, hypercreatinaemia

[c] amylase increased, hyperamylasemia
[d] includes terms hypoalbuminemia, blood albumin decreased
[e] includes terms interstitial lung disease, pneumonitis, acute respiratory failure
[f] includes abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper, gastrointestinal pain and hepatic pain

Reporting suspected adverse effects
Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Tepotinib is a Type I adenosine triphosphate (ATP)-competitive small molecule inhibitor of MET. Tepotinib inhibits HGF-dependent and independent MET phosphorylation and MET-dependent downstream signalling including the phosphatidylinositol 3-kinase/protein kinase B and mitogen-activated protein kinase/extracellular-signal regulated kinase pathways in a dose-dependent manner.

Clinical trials

The efficacy of TEPMETKO was evaluated in a single-arm, open-label, multicenter study (VISION) in adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) harbouring *MET*ex14 skipping alterations (MS200095-0022).

The study included patients with measurable disease according to response evaluation criteria in solid tumours (RECIST 1.1) and an Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1. Patients were to have histologically or cytologically confirmed advanced NSCLC (all types including squamous and sarcomatoid) and were either treatment-naïve or had progressed on up to 2 lines prior systemic therapies. Neurologically stable patients with central nervous system metastases were permitted. Patients with epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) activating alterations were excluded. Before entering the study, eligible patients were required to have confirmed *MET*ex14 skipping alterations status by next-generation sequencing assay using tissue and/or liquid biopsy samples.

Up to 01 July 2020 cutoff, a total of 146 patients in VISION Cohort A had received treatment with tepotinib. Patients had a median age of 73 years (range 41 to 94), 48% were female and 52% male. The majority of patients were Caucasians (70%), followed by Asian patients (26%) and were never (42%) or former smokers (50%). Most patients were ≥ 65 years of age (82%) and 45% of patients were ≥ 75 years of age. The majority of patients had stage IV disease (98%) and 87% had adenocarcinoma histology. Ten percent of the patients had stable brain

metastases. Patients received TEPMETKO as first-line (45%) or second- or later line (55%) therapy.

Patients received 450 mg TEPMETKO once daily until disease progression or unacceptable toxicity.

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

The efficacy analyses focused on 146 patients with at least 9 months of follow-up from the start of treatment (N = 146; referred as the ITT population) (see Table 3). For the patients with an objective response, all patients had ≥ 6 months follow-up from onset of response or event (progressive disease or death) or discontinued treatment < 6 months after onset of response, and 84.8% had ≥ 12 months follow-up from onset of response or event or discontinued treatment < 12 months after onset of response.

Table 3 Clinical Outcomes in the VISION Study by IRC Assessment in ITT Population

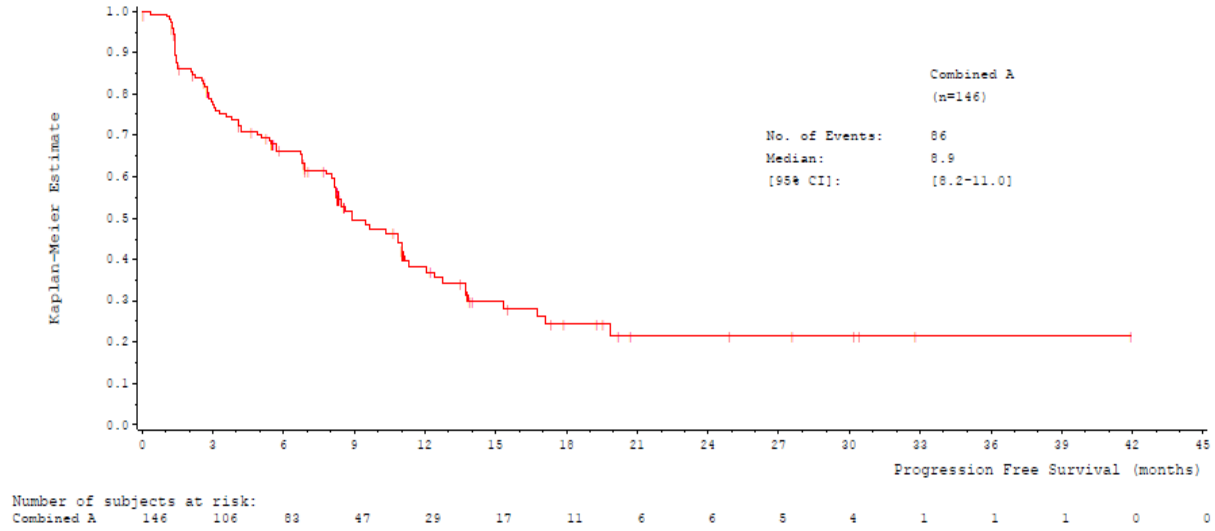
Efficacy parameter	**ITT N = 146**
Objective response rate, % [95% CI]	45.2 [37.0, 53.6]
Median duration of response, months[a] [95% CI]	11.1 [8.4, 18.5]
Duration of response	
≥ 6 months, % of responders	74.2
≥ 9 months, % of responders	43.9
≥ 12 months, % of responders	21.2
Median progression-free survival, months[a] [95% CI]	8.9 [8.2, 11.0]
Median overall survival time, months[a] [95% CI]	17.6 [15.0, 21.0]

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

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

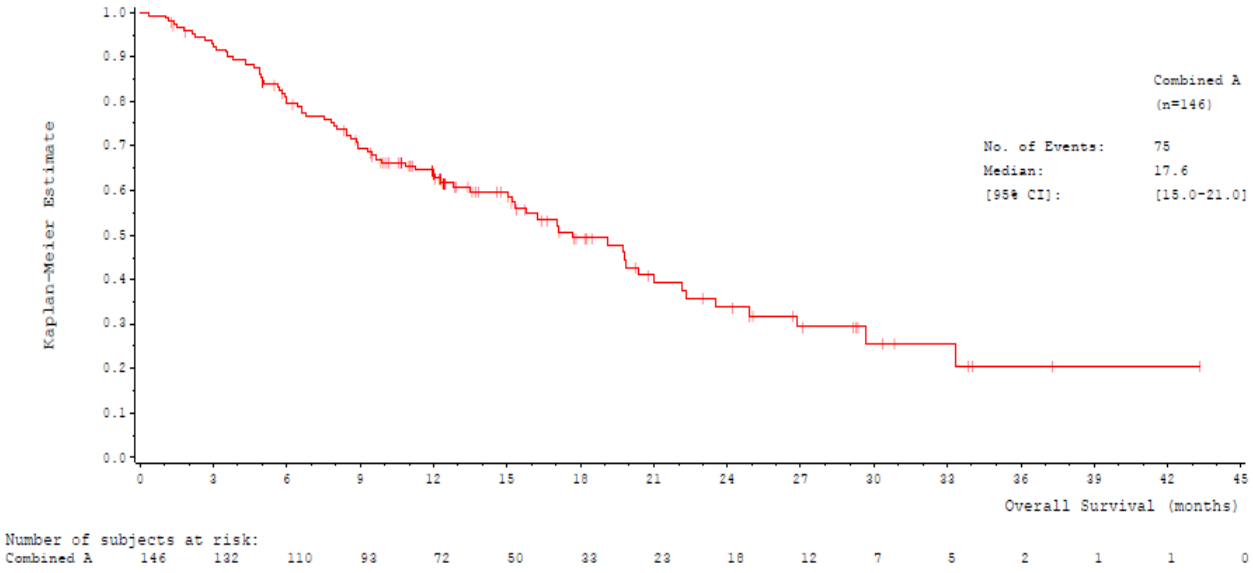
The Kaplan-Meier curves for Progression-free Survival (PFS) and Overall Survival (OS) are shown in Figure 1 and 2, respectively.

Figure 1 **Kaplan-Meier Curve Showing Progression-free Survival, Independent Evaluation, VISION – ITT population**



CI = confidence interval, ITT = intention-to-treat

Figure 2 **Kaplan-Meier Curve Showing Overall Survival, Independent Evaluation, VISION – ITT population**



CI = confidence interval, ITT = intention-to-treat

Data from patients with at least 15 months of follow-up from the start of treatment (N=99) showed similar results with ORR of 45.5% (95% CI: 35.4, 55.8), PFS (median of 8.5 months [95% CI: 6.8, 11.0]) and OS (median of 17.0 months [95% CI: 12.0, 20.4].

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

5.2 PHARMACOKINETIC PROPERTIES

Absorption

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

The presence of food (standard high-fat, high-calorie breakfast) increased the AUC of tepotinib by about 1.6 fold and C_{max} by 2 fold.

Distribution

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

Metabolism

Metabolism is not the major route of elimination. No metabolic pathway accounted for more than 25% of tepotinib elimination in humans. Only one major circulating plasma metabolite (MSC2571109A) has been identified. There is only a minor contribution of the major circulating metabolite to the overall efficacy of tepotinib in humans.

Excretion

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

Tepotinib is mainly excreted via the faeces (approximately 85% total recovery of radioactivity), with urinary excretion being a minor excretion pathway. After a single oral administration of a radiolabelled dose of 450 mg tepotinib, the unchanged tepotinib represented 45% and 7% of the total radioactivity in faeces and urine, respectively. The major circulating metabolite accounted for only about 3% of the total radioactivity in the faeces.

The effective half-life for tepotinib is approximately 32 hours. After multiple daily administrations of 450 mg tepotinib, median accumulation was 2.5 fold for C_{max} and 3.3 fold for $AUC_{0\text{-}24h.}$

Special populations and conditions

A population kinetic analysis did not show any effect of age (range 18 to 89 years), race, sex, body weight, or mild to moderate renal impairment (CLcr 30 to 89 mL/min) on the pharmacokinetics of tepotinib.

<u>Patients with hepatic impairment</u>

Following a single oral dose of 450 mg TEPMETKO, the exposure was similar in healthy subjects and patients with mild hepatic impairment (Child-Pugh Class A) and was slightly lower (-13% AUC and -29% C_{max}) in patients with moderate hepatic impairment (Child-Pugh Class B) compared to healthy subjects. However, the free plasma concentrations of tepotinib were in a similar range in the healthy subjects, patients with mild hepatic impairment and in patients with moderate hepatic impairment. The pharmacokinetics of TEPMETKO have not been studied in patients with severe (Child Pugh Class C) hepatic impairment.

Patients with renal impairment

There was no clinically meaningful change in exposure in patients with mild and moderate renal impairment. Patients with severe renal impairment (creatinine clearance less than 30 mL/min) were not included in clinical trials.

Dose and time dependence

Tepotinib exposure increases dose-proportionally over the clinically relevant dose range up to 450 mg. The pharmacokinetics of tepotinib did not change with respect to time.

Cardiac electrophysiology

In the VISION study (patients with *MET*ex14 skipping alterations; n = 181), 4 patients (2.2%) experienced a QTcF prolonged to > 500 ms and 10 patients (5.5%) had a QTcF prolonged by at least 60 ms from baseline.

In an exposure-QTc analysis, the QTcF interval prolongation potential of TEPMETKO was assessed in 392 patients with various solid tumours following single or multiple daily doses of TEPMETKO ranging from 27 mg to 1,261 mg. At the recommended dose, no large mean increases in QTc (i.e. > 20 ms) were detected. A concentration-dependent increase in QTc interval was observed. The QTc effect of tepotinib at high clinical exposures has not been evaluated.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

No mutagenic or genotoxic effects of tepotinib were observed in the bacterial reverse mutation assay and mouse lymphoma assay *in vitro* and a rat micronucleus test *in vivo*.

The major circulating metabolite was also shown to be non-mutagenic in the bacterial reverse mutation assay and mouse lymphoma assay *in vitro*.

Carcinogenicity

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

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Tablet core: Mannitol, colloidal anhydrous silica, crospovidone, magnesium stearate, microcrystalline cellulose.

Film coating: Hypromellose, lactose monohydrate, macrogol 3350, triacetin, iron oxide red, titanium dioxide.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30^0C in the original package in order to protect from moisture.

6.5 NATURE AND CONTENTS OF CONTAINER

Blister foil: Multilayer composite, consisting of polyvinylchloride-polyethylene-polyvinylidenechloride-polyethylene-polyvinylchloride.

Lidding foil (child-resistant): aluminum-polyethylene terephthalate

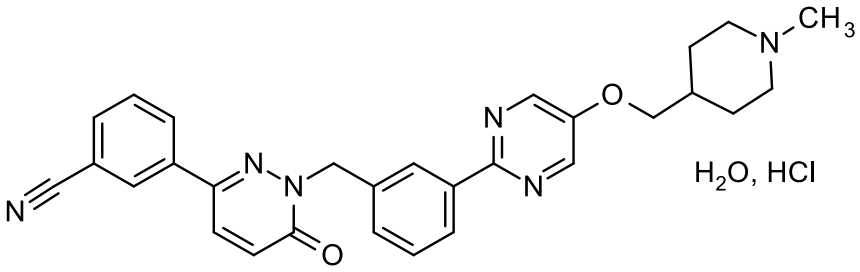
Each pack contains 6 blister foils, each containing 10 TEPMETKO tablets.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure



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

CAS number: 1100598-30-8

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 (Prescription Only Medicine)

8 SPONSOR

Merck Healthcare Pty Ltd

Suite 1, Level 1, Building B

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Macquarie Park NSW 2113

Australia

E-mail: Medinfo.australia@merckgroup.com

Phone: 1800 633 463

9 DATE OF FIRST APPROVAL

17 January 2022

10 DATE OF REVISION

N/A

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
N/A	N/A