Taiwan Food and Drug Administration

Assessment Report

Trade Name：德邁特膜衣錠 225 毫克

TEPMETKO Film-coated Tablets 225mg

Active Ingredient：Tepotinib

License Number：MOHW-PI 028152

Applicant：台灣默克股份有限公司

Approval Date：2021/08/19

Indication：
適用於治療帶有導致間質上皮轉化因子外顯子 14 跳讀式突變 (MET exon 14 skipping mutation)的轉移性之非小細胞肺癌(NSCLC)成人病人。
[此適應症係依據客觀反應率及反應持續時間加速核准，此適應症仍須執行確認性試驗以證明其臨床效益]

Indicated for the treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) harboring mesenchymalepithelial transition (MET) exon 14 skipping alterations.
This indication is approved under accelerated approval based on objective response rate and duration of response. Confirmatory trials to demonstrate its clinical benefit is needed for continued approval for this indication.

1. Background Information

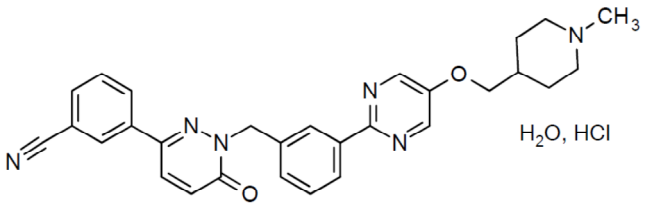
Trade Name	德邁特膜衣錠 225 毫克 / TEPMETKO Film-coated Tablets 225mg
Active Ingredient(s)	Tepotinib
Applicant	台灣默克股份有限公司
Dosage Form & Strengths	膜衣錠、225 毫克
Indication	**適用於治療帶有導致間質上皮轉化因子外顯子 14 跳讀式突變 (MET exon 14 skipping mutation)的轉移性之非小細胞肺癌(NSCLC)成人病人。** **[此適應症係依據客觀反應率及反應持續時間加速核准，此適應症仍須執行確認性試驗以證明其臨床效益]** **Indicated for the treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) harboring mesenchymalepithelial transition (MET) exon 14 skipping alterations.** **This indication is approved under accelerated approval based on objective response rate and duration of response. Further confirmatory trials to demonstrate its clinical benefit is needed for continued approval for this indication.**
Posology	詳見仿單
Pharmacological Category **ATC Code**	L01EX21

2. Summary Report

2.1 Chemistry, Manufacturing and Controls Evaluation

2.1.1 Drug substance

Tepotinib hydrochloride hydrate is used as the drug substance of TEPMETKO® film-coated tablets. Tepotinib hydrochloride hydrate has the following chemical structure:



The molecular formula and the molecular weight of the drug substance are $C_{29}H_{28}N_6O_2 \cdot HCl \cdot H_2O$ and 547.05 g/mol, respectively. It's a white to off-white powder.
The structure of tepotinib hydrochloride hydrate is confirmed by NMR spectra, mass spectrum, IR spectrum, UV spectrum, X-ray diffraction, ion-exchange chromatography, Karl Fischer titration and elemental analysis.

The specification of the drug substance includes tests for appearance, identification, identification of chloride, assay, organic impurities, water content, residual solvents, inorganic impurities, microbial limits, polymorphic form and particle size distribution.

2.1.2 Drug product

Drug product is supplied as film-coated tablets for oral administration containing 225 mg of tepotinib (equivalent to 250 mg tepotinib hydrochloride hydrate). The excipients used in the drug product formulation comply with the compendial monographs.

Adequate specification has been presented for the drug product. The test items include appearance, dimensions, identification, assay, degradation products, resistance to crushing, uniformity of dosage units, dissolution and microbial limits. Analytical methods are described and well validated.

Stability studies of the drug product under long-term condition (25±2°C/60±5%RH, 30±2°C/65±5% RH) and accelerated condition (40±2°C/75±5% RH) have been carried out.

2.2 Preclinical Pharmacology/Toxicology Evaluation

Tepotinib is a Type I, ATP competitive, reversible inhibitor of MET. In vitro, tepotinib potently inhibited MET kinase with binding IC50 values in the single-digit nanomolar range as measured in biochemical assays. In diverse kinase screens against a panel of more than 400 different recombinant kinases, tepotinib demonstrated its high selectivity for MET. Cell-based assays revealed that tepotinib inhibited either HGF-dependent or -independent MET signaling by blocking MET tyrosine kinase phosphorylation and downstream signaling in a dose-dependent matter. It also exhibited activity for inhibiting tumor cell proliferation in a dose-dependent manner, as well as the anchorage-independent growth and HGF-dependent migration in several cell lines harboring MET alteration.

In vivo, the anti-tumor activity of tepotinib was observed in many tumor models from various indications and with different mechanisms of MET activation. Oncogenic activation of MET could be used to predict the sensitivity of tumors to tepotinib in vivo. The anti-tumor activity of tepotinib was particularly pronounced in tumors with oncogenic alterations of the MET gene, such as METex14 skipping alterations or high-level MET gene amplification. Treatment of these tumors with tepotinib generally resulted in marked shrinkage or even complete regression of tumors. Data derived from unselected, patient-derived tumors confirm the results obtained with tumor cell line xenografts.

Secondary pharmacology studies identified no significant off-target effects for tepotinib. In vitro hERG assay showed that the IC50 value of tepotinib was approximately 24 folds higher than the unbound Cmax at MRHD. No significant effects of tepotinib on CNS, respiratory and cardiac functions had been demonstrated in the in vivo safety pharmacology studies.

GLP repeated-dose toxicity studies identified the liver/hepatobiliary system as the major target organs of toxicity in both rats and dogs. In rats, treatment-related histopathology findings in lung, liver, lymph node, and the large intestine had been noted at higher doses. Slight increases in liver enzyme values were observed in all studies conducted in rats. In dogs, increased hepatic-biliary liver enzymes and pronounced cholangitis and pericholangitis associated with inflammatory infiltrates in the liver were the main findings in the 4- and 39-week dog studies. In addition, gastrointestinal symptoms including vomiting and diarrhea accompanied by body weight decreases and reduced food consumption had been observed in all studies in dogs at doses higher than 2.5 mg/kg/day without showing the histopathological correlation. All these major findings were shown to be reversible or a trend for reversibility. It is noteworthy that the systemic exposure in these toxicology studies was generally lower than that measured in humans.

Tepotinib did not show any evidence of genotoxic activity in vitro and in vivo. No risk for impairment of fertility had been identified in the general toxicology studies with tepotinib. In two preliminary embryo-fetal development studies conducted in rabbits, tepotinib was maternal toxic and teratogenic (skeletal malformations). It is recommended that patients with reproductive potential should use effective contraception and avoid breastfeeding during treatment.

No immunotoxic potential of tepotinib could be concluded based on a weight of evidence approach. Lastly, tepotinib was shown as phototoxic in vitro, however, no phototoxic potential under the in vivo conditions was shown.

2.3 Clinical Pharmacology Evaluation

Tepotinib is a selective and potent, reversible, Type I adenosine triphosphate (ATP)-competitive small molecule inhibitor of MET. Tepotinib is indicated for the treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) harboring mesenchymal-epithelial transition (MET) exon 14 skipping alterations. The recommended dosage of tepotinib is 450 mg orally once daily with food until disease progression or unacceptable toxicity.

2.3.1 General Pharmacodynamics and Pharmacokinetics

The pharmacokinetics of tepotinib was evaluated in patients with cancer administered 450 mg once daily unless otherwise specified. At the recommended dosage, the geometric mean (coefficient of variation [CV] %) steady state C_{max} was 1,291 ng/mL (48.1%) and the AUC_{0-24h} was 27,438 ng·h/mL (51.7%). The median accumulation was 2.5-fold for C_{max} and 3.3-fold for AUC_{0-24h} after multiple daily doses of tepotinib.

The median T_{max} of tepotinib is 8 hours (range from 6 to 12 hours). The geometric mean (CV%) absolute bioavailability of TEPMETKO in the fed state was 71.6% (10.8%) in healthy subjects. The mean AUC_{0-INF} of tepotinib increased by 1.6-fold and C_{max} increased by 2-fold, following administration of a high-fat, high-calorie meal. The median T_{max} shifted from 12 hours to 8 hours.

The geometric mean (CV%) apparent volume of distribution (V_Z/F) of tepotinib is 1,038 L (24.3%). Protein binding of tepotinib is 98% and is independent of drug concentration at clinically relevant exposures. The apparent clearance (CL/F) of tepotinib is 23.8 L/h (87.5%) and the half-life is 32 hours following oral administration of tepotinib in patients with cancer.

Tepotinib is primarily metabolized by CYP3A4 and CYP2C8. One major circulating plasma metabolite (M506) has been identified. Following a single oral administration of a radiolabeled dose of 450 mg tepotinib, approximately 85% of the dose was recovered in feces (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.

2.3.2 Interaction Studies

In vitro studies demonstrated that tepotinib is a substrate of CYP3A4 and CYP2C8. Tepotinib and M506 do not inhibit CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C19, CYP2D6 or CYP2E1, and do not induce CYP1A2 or 2B6 at clinically relevant concentrations. Tepotinib and M506 also do not inhibit UGT 1A1, 1A9, 2B17, 1A3/4/6 and 2B7/15 at clinically relevant concentrations. While tepotinib is a P-gp substrate, tepotinib may inhibit intestinal BCRP at clinically relevant concentrations. But it does not inhibit bile salt export pump (BSEP), organic

anion transporter polypeptide (OATP) 1B1, B3, or organic anion transporter (OAT) 1 and 3.

Coadministration of tepotinib with dabigatran etexilate (P-gp substrate) increased dabigatran C_{max} by 40% and $AUC_{0\text{-}INF}$ by 50%. No clinically significant differences in tepotinib pharmacokinetics were observed when coadministered with multiple daily doses (40 mg daily for 5 days) of omeprazole (proton pump inhibitor) under fed conditions. Coadministration of tepotinib had no clinically significant effect on the pharmacokinetics of midazolam (sensitive CYP3A substrate).

2.3.3 Special Populations

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 (CL_{cr} 30 to 89 mL/min), or mild to moderate hepatic impairment (Child-Pugh A and B). 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.

2.4 Clinical Efficacy and Safety Evaluation

2.4.1 Efficacy Results

Study VISION is an ongoing, single-arm, open-label, Phase 2 study to evaluate the efficacy and tolerability of tepotinib in subjects with advanced non-small cell lung cancer (NSCLC) harboring *MET* exon 14 skipping alterations or *MET* amplification in either plasma samples or tissue samples of tumor biopsy. Both treatment-naïve subjects and pretreated subjects with no more than 2 lines of prior therapy were eligible. Subjects with *EGFR* activating mutations that predict sensitivity to anti-EGFR therapy or with *ALK* rearrangements that predict sensitivity to anti-ALK therapy were ineligible for this study. Nearly all subjects had metastatic disease.

Subjects were administered tepotinib 450 mg monotherapy once daily in cycles of 21-day duration and continued treatment until disease progression, death, an adverse event (AE) leading to treatment discontinuation, or withdrawal of consent.

The primary efficacy endpoint was objective response rate (ORR) assessed using Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, based on independent review. The secondary efficacy endpoint included ORR based on investigator assessment, duration of response (DOR), disease control rate, best overall response, progression free survival (PFS) and overall survival (OS).

One hundred and forty-six (146) subjects with NSCLC harboring *MET* exon 14 skipping alterations were enrolled and treated with tepotinib. Duration of follow-up was at least 9

months. There were 65 subjects treatment-naïve and 81 subjects previously treated.

Among the 65 treatment-naïve subjects, the ORR based on independent review (95% confidence interval [CI]) was 44.6% (32.3%, 57.5%). The median DOR (95% CI) was 10.8 (6.9, not evaluable) months. The median PFS (95% CI) was 8.5 (5.5, 11.3) months. The median OS (95% CI) was 16.3 (9.7, 29.7) months.

Among the 81 previously-treated subjects, the ORR based on independent review (95% CI) was 45.7% (34.6%, 57.1%). The median DOR (95% CI) was 11.1 (9.5, 18.5) months. The median PFS (95% CI) was 10.9 (8.2, 12.7) months. The median OS (95% CI) was 19.7 (15.0, 21.0) months.

2.4.2 Safety Results

A total of 255 subjects with advanced NSCLC harboring *MET* exon 14 skipping alterations received at least one dose of tepotinib in Study VISION.

The most commonly reported adverse events (AEs) were edema peripheral (60.0%), nausea (26.7%), diarrhea (26.3%), blood creatinine increased (25.1%), hypoalbuminemia (23.1%), dyspnea (18.0%), constipation (15.7%), decreased appetite (15.7%), fatigue (14.9%), pleural effusion (13.3%), vomiting (12.9%), asthenia (12.5), cough (12.2%), alanine aminotransferase (ALT) increased (11.4%), back pain (11.0%), and pneumonia (10.2%). The most common Grade ≥ 3 AEs were edema peripheral (7.8%), hypoalbuminemia (5.5%), and pleural effusion (5.1%).

The most common serious AEs (SAEs) were pleural effusion (6.7%), disease progression (4.7%), pneumonia (4.7%), dyspnea (3.9%), general physical health deterioration (3.5%), edema peripheral (2.4%), generalized edema (2.0%), and pulmonary embolism (2.0%).

The identified risks for tepotinib included interstitial lung disease, edema, creatinine increased, hypoalbuminemia, amylase and/or lipase increase, ALT and/or aspartate aminotransferase (AST) increase, diarrhea nausea, and vomiting. The potential risks for tepotinib included pleural effusion and QT prolongation. Interstitial lung disease and ALT and/or AST increase are notable events. There was one fatal case due to interstitial lung disease related to tepotinib and another fatal case considered as a drug-induced liver injury related to tepotinib.

2.5 Bridging Study Evaluation

The population PK analysis did not find ethnicity to be a statistically significant covariate on the exposure of tepotinib. No dose adjustments are recommended for patients based on their

ethnicity.

The efficacy results were generally comparable between subjects from East Asia (ORR: 47.1%) and total population (ORR: 45.0%) in Study VISION.

The safety results were also comparable between Asian subjects and Caucasian subjects. ALT and/or AST increase was noted more frequently in Asian subjects; however, the proportion of subjects with Grade ≥ 3 ALT and/or AST increase was comparable in Asian and Caucasian subjects.

2.6 Conclusion

Based on the above multidiscipline review, CDE review team recommends granting accelerated approval for tepotinib. Post-marketing confirmatory study is required to verify its clinical benefit.

3. Post-Marketing Requirements

Submit the final clinical study report of Study VISION Cohort A and Cohort C. If there are other post-marketing studies requested by United States Food and Drug Administration (US FDA), submit the clinical study reports after completion.