Taiwan Food and Drug Administration

Assessment Report

Trade Name：癌剋挺膠囊 40 毫克 / Exkivity Capsules 40mg

Active Ingredient：Mobocertinib succinate

License Number： MOHW-PI-028453

Applicant：台灣武田藥品工業股份有限公司

Approval Date： 2023/05/01

Indication：
治療先前已接受過含鉑化療之 EGFR 外顯子 20 插入突變之晚期非小細胞肺癌成年病人。
本適應症係依據腫瘤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。

Treatment of adult patients with EGFR exon 20 insertion mutations–positive advanced non-small cell lung cancer (NSCLC) who have received prior platinum-based chemotherapy

This indication is approved under accelerated approval based on objective response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial.

1. Background Information

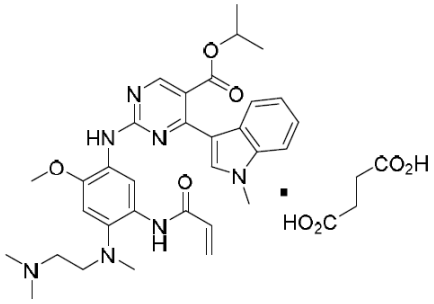
Trade Name	癌剋挺膠囊 40 毫克 / Exkivity Capsules 40mg
Active Ingredient(s)	mobocertinib succinate
Applicant	台灣武田藥品工業股份有限公司
Dosage Form & Strengths	膠囊劑 40 毫克
Indication	治療先前已接受過含鉑化療之 EGFR 外顯子 20 插入突變之晚期非小細胞肺癌成年病人。 本適應症係依據腫瘤客觀反應率及反應持續時間加速核准，此適應症仍須執行確認性試驗以證明其臨床效益。 Treatment of adult patients with EGFR exon 20 insertion mutations–positive advanced non-small cell lung cancer (NSCLC) who have received prior platinum-based chemotherapy This indication is approved under accelerated approval based on objective response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial.
Posology	每天一次 160 毫克。
Pharmacological Category **ATC Code**	L01EB10

2. Summary Report

2.1 Chemistry, Manufacturing and Controls Evaluation

2.1.1 Drug substance

The drug substance, mobocertinib succinate, is chemically designated as propan-2-yl 2-[5-(acryloylamino)-4-{[2-(dimethylamino)ethyl](methyl)amino}-2-methoxyanilino]-4-(1-methyl-1*H*-indol-3-yl)pyrimidine-5-carboxylate succinate and has the following structure:



It is a white to yellow powder. The molecular formula and the molecular weight are $C_{32}H_{39}N_7O_4$+$C_4H_6O_4$ and 703.80 g/mol, respectively.

Adequate information of characterization of the drug substance has been provided. The molecular structure of mobocertinib succinate has been confirmed by the following technologies: IR, UV, 1D/2D-^{1}H/^{13}C NMR, MS, elemental analysis, XRD, DSC and TGA. The proposed specifications and analytical methods were considered appropriate for quality control of the drug substance. Batch analyses data from commercial scale batches of the drug substance are provided and the test results are within the specifications.

2.1.2 Drug product

The drug product is provided as an immediate release capsule for oral administration. It contains 40 mg of the active ingredient, mobocertinib freebase, which equivalent to 48.06 mg of mobocertinib succinate salt. The drug substance is filled directly into size 2, white, hard gelatin capsules with imprinting, without any excipients. The information printed on the capsules including MB788 at cap and 40 mg at body, and the imprint ink color is black. The specifications for hard gelatin capsules used in the drug product is adequate.

The proposed specifications and analytical methods were considered appropriate for quality control of the drug product. Batch analyses data from commercial scale batches of the drug product are provided and the test results are within the specifications. Analytical methods are well described and validated.

Stability studies of drug product under long-term condition (30°C/70% RH) and accelerated condition (40°C/75% RH) have been carried out. Up to 24 months of long-term and 6 months of accelerated stability data are submitted. No significant chemical or physical changes are observed for the drug product, the shelf life and storage condition of drug product can be granted for 24 months under the storage condition of 30°C.

2.2 Preclinical Pharmacology/Toxicology Evaluation

2.2.1 Pharmacological Studies

In *in vitro* biochemical kinase inhibition screening assays, mobocertinib inhibited the EGFR family members and 11 EGFR variants with activating or resistance mutations. The two mobocertinib's active metabolites, AP32960 and AP32914, had similar kinase inhibitory activities to mobocertinib. In cellular assays, mobocertinib inhibited the activity of EGFR variants, including common activating mutations with or without a T790M resistance mutation, uncommon activating mutations, and exon 20 activating insertions. In a patient-derived NSCLC cell line harboring the EGFR exon 20 NPH insertion mutant, mobocertinib inhibited *in vitro* cell survival at lower concentrations than WT EGFR. Mobocertinib also inhibited EGFR-mediated signaling in NSCLC cell lines expressing common EGFR-activating mutations with or without the T790M resistance mutation.

In *in vivo* pharmacology, daily oral administration of mobocertinib led to tumor growth inhibition in immunocompromised mice implanted with tumor cells harboring EGFR mutations, with increased efficacy associated with increased plasma concentrations of mobocertinib and its active metabolite. Mobocertinib also exhibited *in vivo* anti-tumor activity in four HER2-driven tumor models. In safety pharmacology, mobocertinib and its metabolites showed a low potential for QT prolongation *in vitro*, and *in vivo* assessments in dogs did not demonstrate any cardiac electrophysiologic effects.

2.2.2 Toxicological Studies

The toxicity profile of mobocertinib was evaluated in rats and dogs in GLP-compliant studies for up to 3 months. The main toxicities associated with mobocertinib administration were similar between rats and dogs and included changes in the gastrointestinal tract, reproductive system, hematological system, and the epithelium in multiple organs, such as the skin and oral cavity. Dogs were generally more sensitive to mobocertinib than rats. Other findings in rats included salivary gland acinar atrophy and exacerbation of chronic progressive nephropathy in the kidneys of males. The NOAEL was 10 mg/kg in males and 5 mg/kg in females. In dogs, treatment with 1 mg/kg mobocertinib (approximately 0.7 times the human exposure at the 160 mg clinical dose) was not tolerated in males, with oral cavity ulceration leading to early euthanasia. Additional ocular findings in 4-week toxicology studies included decreased corneal epithelial thickness in rats and sclera injection, partial or complete closure of the eye, and corneal epithelial atrophy in dogs.

In a rat embryo-fetal development study, once daily oral administration of 10 mg/kg mobocertinib (approximately 1.7 times the clinical AUC at the 160 mg human dose) to pregnant rats during the period of organogenesis resulted in increasing post-implantation/early resorptions and decreasing fetal weight. These findings were accompanied by maternal toxicity characterized by a decrease in food consumption and body weight throughout the dosing period. As per ICH S9, no carcinogenicity studies have been conducted since mobocertinib is indicated

for advanced cancer. Besides, mobocertinib has no significant genotoxic or phototoxic risk.

2.3 Clinical Pharmacology Evaluation

2.3.1 General Pharmacodynamics and Pharmacokinetics

Mobocertinib is a kinase inhibitor and is intended to treat adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with EGFR exon 20 insertion mutations. The oral absolute bioavailability is 36.7%. Over the dose range of 5 to 180 mg once daily (QD), mobocertinib and combined molar AUC_{24} of mobocertinib, AP32960 and AP32914 increased in a dose-proportional manner. Following 160 mg mobocertinib QD, the T_{max} of mobocertinib reached approximately at 4 ~ 6 hours, and $T_{1/2}$ was 12.6 or 19.9 hours (17.6 hours based on pop-PK analysis). No accumulation was seen at 160 mg QD dose. The exposure of mobocertinib did not have significant difference under high-fat meal or low-fat meal, compared to those under fasted condition. Thus, mobocertinib can be administered with or without food.

Mobocertinib and its active metabolites were highly plasma protein bound (mobocertinib: 99.3%; AP32960: 99.5%; AP32914: 98.6%), regardless of concentration (0.5 ~ 5.0 μM). The geometric mean apparent volume of distribution at steady-state for mobocertinib was 3510 L. Mobocertinib was primarily metabolized by CYP3A4/5 (93.5%) and produced several metabolites (including two active metabolites: AP32960 and AP32914). The metabolite to mobocertinib ratio (M/P ratio) for AP32960 and AP32914 were 62% and 7%, respectively. Mass balance study showed that feces route was the main excretion pathway, urine route was minor [76% of the dose was recovered in feces and 4% was recovere in urine]. This may be due to mobocertinib's high bile excretion. The apparent oral clearance of mobocertinib was 108 L/h based on the population PK analysis.

2.3.2 Interaction Studies

Coadministration of mobocertinib with strong or moderate CYP3A inhibitors significantly increased mobocertinib plasma concentrations. Also, coadministration with strong or moderate CYP3A inducers significantly decreased mobocertinib plasma concentration. Thus, avoid concomitant use of these drugs with mobocertinib. Mobocertinib may decrease plasma concentrations of CYP3A substrates; thus, avoid concomitant use of hormonal contraceptives or other CYP3A substrates where minimal concentration changes may lead to serious therapeutic failures.

2.3.3 Special Populations

No clinically meaningful differences in the pharmacokinetics of mobocertinib were observed based on age (18 to 86 years), gender, body weight (37.3 to 132 kg), mild to moderate renal impairment (CrCL: 26.3 to 251 mL/min and eGFR: 33.6 to 304 mL/min/1.73 m2 by MDRD)

and mild hepatic impairment (total bilirubin ≤ULN and AST or ALT >ULN or total bilirubin >1-1.5 times ULN and any AST or ALT by NCI-ODWG). Thus, no dose adjustment was required based on aforementioned intrinsic factors. The effect of severe renal impairment and moderate to severe hepatic impairment on mobocertinib pharmacokinetics is unknown. The impact of them can be acquired by two ongoing organ impairment studies (TAK-788-1007 and TAK-788-1008).

2.4 Clinical Efficacy and Safety Evaluation

2.4.1 Efficacy Results

The pivotal study supporting the indication of mobocertinib was AP32788-15-101 study, a phase 1/2, open-label, single-arm, multicenter, 3-part study enrolling previously-treated advanced NSCLC patients. Antitumor activity was assessed in 114 patients with NSCLC with EGFR exon 20 insertion mutations who had previously been treated with platinum-based chemotherapy and received mobocerinib 160mg QD. Among these participants, mean age was 59.6 years old. 42 patients (36.8%) were >=55 years old. 75 patients (65.8%) were female and 66 patients (57.8%) were Asian. 113 patients (99.1%) were stage IV and one patient was stage IIIB. One patient was large cell lung cancer and one patient was SCC, while all the remaining patients were adenocarcinoma. The primary efficacy endpoint was confirmed ORR by IRC. All efficacy endpoints result by IRC were summarized in the following table.

Tumor Response	n (%)	95%CI
Confirmed ORR	32 (28.1)	20.06, 37.26
Confirmed DCR	89 (78.1)	69.35, 85.28
Time to Event(months)	median	95%CI
DOR	15.77	7.39, 19.35
PFS	7.29	5.52, 9.23
OS	20.17	14.88, 25.26

Compared to clinical outcomes in patients with advanced NSCLC with EGFR exon 20 insertion mutations before the era of targeted therapy approval for this mutation collected from a retrospective observational cohort study, the available result from AP32788-15-101 study demonstrated benefit potential.

2.4.2 Safety Results

For the 114 patients, TEAEs were experienced by all. The most common TEAEs (>30% of patients) included diarrhea (93%), rash (47%), decreased appetite (45%), vomiting (43%), nausea (40%), paronychia (39%), blood creatinine increased (35%), anemia (34%), and dry skin (33%). The most common Grade ≥3 AEs (≥5% of the study population) included diarrhea (24%); ECG QT prolonged (8%); hypertension (7%); anemia (6%); and nausea, amylase

increased, and dyspnea(5% each). SAEs were reported by half patients. The most common SAEs included diarrhea (8%), dyspnea (7%), and vomiting (6%). One death, an SAE of cardiac failure, was deemed related to study drug. The other 14 deaths were associated with the underlying disease. These frequency and severity of the reported AEs with mobocertinib have been characterized and are consistent with the class of EGFR TKIs.

Identified risks were QTc interval prolongation and Torsades de Pointes, interstitial lung disease (ILD)/pneumonitis, cardiac toxicity, and diarrhea, which were included in the Warnings and Precautions section of the proposed label. ECG QT prolonged occurred more frequently among Asian patients compared with non-Asian patients. Therefore, risk manage plan for QTc interval prolongation was required in Taiwan.

2.5 Bridging Study Evaluation

According to the cross-study comparison and pop-PK analysis, the exposure difference between East-Asian subjects and global population were < 28%. Considering the PK characteristic of mobocertinib, and no significant exposure-response relationship for efficacy or safety; thus, the ethnic difference was considered negligible and no additional bridging study was required from PK perspective.

In AP32788-15-101 study, only Part 3 had Asian sites and all the Asian sites were located at East Asian. Among 96 subjects at Part 3, 57 were East Asians. The subgroup analyses revealed similar cORR by IRC between races (Asian vs. Non-Asian) or regions (Asia Pacific vs North America). The safety profile between Asian and non-Asian subgroups were similar, without newly identified risks in Asians. However, more participants in Asian subgroup experienced rash, pruritis, blood creatinine increased and anemia than in non-Asian population. ECG QT prolonged occurred more frequently among Asian patients compared with non-Asian patients. Ethnic difference with clinical impact was not observed.

2.6 Conclusion

This multidisciplinary review recommends approval for Exkivity Capsules 40mg (mobocertinib succinate) for the indication of treatment for adult patients with EGFR exon 20 insertion mutations–positive metastatic NSCLC who have received prior platinum-based chemotherapy.

3. Post-Marketing Requirements

- Submit final report of confirmatory TAK-788-3001 study after study completion.
- Submit final report of TAK-788-1007 and TAK-788-1008 studies. Meanwhile provide the label recommendation on dose adjustment for patients with renal and hepatic impairment.