Taiwan Food and Drug Administration

Assessment Report

Trade Name：泰芮塔 150 毫克膜衣錠 / Tabrecta 150mg Film-Coated Tablets ；泰芮塔 200 毫克膜衣錠/Tabrecta 200mg Film-Coated Tablets

Active Ingredient：Capmatinib hydrochloride(Anhydrous)

License Number：MOHW-PI 028096 ；MOHW-PI 028097

Applicant：台灣諾華股份有限公司

Approval Date： 2021/6/9

Indication：

治療轉移性非小細胞肺癌(NSCLC)的成人病人，其腫瘤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)。此適應症係依據腫瘤整體反應率(ORR)及反應持續時間(DOR)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) whose tumors have a mutation that leads to mesenchymal-epithelial transition (MET) exon 14 skipping.

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 trial(s)

Background Information

Trade Name	泰芮塔 150 毫克膜衣錠 / Tabrecta 150mg Film-Coated Tablets ； 泰芮塔 200 毫克膜衣錠 / Tabrecta 200mg Film-Coated Tablets
Active Ingredient(s)	Capmatinib hydrochloride(Anhydrous)
Applicant	台灣諾華股份有限公司
Dosage Form & Strengths	116 膜衣錠 176.55 mg ；235.40 mg
Indication	治療轉移性非小細胞肺癌(NSCLC)的成人病人，其腫瘤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)。 此適應症係依據腫瘤整體反應率(ORR)及反應持續時間(DOR)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) whose tumors have a mutation that leads to mesenchymal-epithelial transition (MET) exon 14 skipping. 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 trial(s).
Posology	400 mg orally twice daily with or without food.
Pharmacological Category **ATC Code**	L01EX17

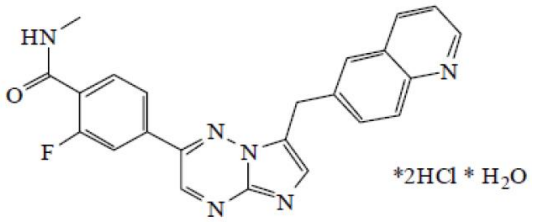
2. Summary Report

2.1 Chemistry, Manufacturing and Controls Evaluation

2.1.1 Drug substance

The drug substance, capmatinib hydrochloride, is chemically designated as 2-fluoro-*N*-methyl-4-[7-(quinolin-6-ylmethyl)imidazo[1,2*b*][1,2,4]triazin-2-yl]benzamide—

hydrogen chloride—water (1/2/1). The molecular formula and the relative molecular mass for capmatinib hydrochloride are $C_{23}H_{21}Cl_2FN_6O_2$ and 503.36 g/mol, respectively. It has the following chemical structural:



It is a yellow powder. The structure of capmatinib hydrochloride is confirmed by elemental analysis, IR spectrum, ^{1}H-NMR, ^{13}C-NMR, high resolution mass spectrum (HR-MS), UV/Vis spectrum and single crystal X-ray diffraction. The specification for the drug substance includes tests for appearance, particle size, identity, purity, microbiology and assay.

2.1.2 Drug product

The drug product is supplied for oral use as ovaloid, curved film-coated tablets containing 150 mg or 200 mg capmatinib (equivalent to 176.55 mg or 235.40 mg respectively of capmatinib hydrochloride anhydrous). All excipients are well known ingredients and suitable for proposed formulation. The specification for the drug product includes appearance, identity, assay, purity, uniformity of dosage units, dissolution and microbial enumeration tests. Analytical methods are described well and validated. Stability studies of drug product under long term conditions (25°C/60% RH and 30°C/75% RH) and accelerated condition (40°C/75% RH) have been carried out.

2.2 Non-clinical Pharmacology/Toxicology Evaluation

Capmatinib is an oral selective, potent inhibitor of the MET receptor tyrosine kinase. *In vitro*, capmatinib inhibited MET with an IC_{50} value in the sub-nanomolar range measured in biochemical assays. Cell-based assays revealed that capmatinib inhibited phosphorylation of MET and the downstream signaling proteins and the proliferation, survival, and migration of the cells with IC_{50} values in the sub-nanomolar to single-digit nanomolar range. Capmatinib was a highly selective MET kinase inhibitor with a selectivity factor of approximately more than 1000-fold compared to panels of other kinases or mutants. Capmatinib treatment led to marked or partial growth inhibition effects in human cancer cell lines with strong MET overexpression mediated by high-level MET gene amplification and cell lines expressing both MET and HGF, respectively. In the tested lung cancer PDX models with MET exon 14 skipping mutation or MET overexpression with or without amplification, capmatinib treatment resulted in tumor regression.

Secondary pharmacology studies indicated that capmatinib and its major metabolite CMN288 (M16) did not reveal significant off-target effects. *In vitro* hERG assay showed that the IC_{50} value of capmatinib was approximately 40 folds unbound Cmax at the therapeutic dose of 400 mg bid in humans. *In vivo* safety pharmacology studies demonstrated that capmatinib had no significant effects on CNS, respiratory and cardiac functions.

GLP repeat-dose toxicity studies in rats and monkeys identified the pancreas (rat and monkey), brain/CNS (rat), liver (monkey), and potentially kidney (monkey) as the target organs. Main effects included reversible pancreatic acinar cell vacuolation and/or apoptosis, and increased amylase or lipase in the pancreas (rats, monkeys), reversible signs of CNS toxicity and histopathological findings of white matter vacuolation in the brain (rats), a reversible subcapsular neutrophilic infiltration associated with single-cell necrosis in the liver (13-week monkeys), and histopathologic changes of deposits of amphophilic, crystalline-like material found within the renal interstitium and/or tubular lumen in the kidneys without alterations in renal function (4-week monkeys). Most of the observed effects were reversible.

Capmatinib was non-genotoxic, as demonstrated in a battery of genotoxicity studies. Embryo-fetal development studies in rats and rabbits indicated that capmatinib is toxic to fetuses and teratogenic to both species. The teratogenicity is consistent with the mechanism of action by MET inhibition. It is recommended that patients with reproductive potential should use effective contraception and avoid breastfeeding during treatment.

Lastly, capmatinib showed potential for photosensitization (phototoxicity) and weak skin irritating potential in *in vitro* and *in vivo* assays. Patients should be advised to avoid exposure to excessive sunlight/UV during treatment.

2.3 Clinical Pharmacology Evaluation

2.3.1 General Pharmacodynamics and Pharmacokinetics

The absolute bioavailability of capmatinib tablet was unknown. Tmax was reached rapidly (1~ 2 hour) in healthy subjects and in patient. The exposure of capmatinib increased approximately proportionally across the range of 200 mg ~ 400 mg. Steady state was reached by the third day following twice-daily dosing achieved with accumulation ratio of 1.39. A high-fat meal increased capmatinib AUC_{inf} by 46%, C_{max} by 15%; however, low fat meal increased capmatinib AUC_{inf} by 20%, C_{max} by 11%.

After considering the safety data from Study 2201, there was no significant higher AE incidence in with/without food cohort than fasted state Cohort. Thus, capmatinib taken with or without food was acceptable.

Co-administration with PPI (rabeprazole, QD, for 4 days) decreased capmatinib AUC by 25% and C_{max} by 38% in healthy subjects. The same trend was also seen in patient studies. Although the clinical effect on efficacy may not be relevant, it is recommended to use with caution during concomitant use of capmatinib with proton pump inhibitors, and replace with a short-acting gastric pH-altering agent (such as H2-receptor antagonists or antacids). The apparent mean volume of distribution at steady state (V_{ss}/F) was 164 L in subjects with cancer. Capmatinib was highly bound to human plasma proteins (96%) in vitro, independent of concentration. The in vitro blood-to-plasma ratio was 1.5, but decreased at higher concentrations to 0.9. Capmatinib is extensively metabolized in liver, including CYP metabolism (CYP 3A4; ~ 40~50%) and Non-CYP metabolism (~50~60%). Unchanged capmatinib was the most abundant radioactive component in plasma, and inactive M16 (CMN288) was the most abundant circulating metabolite. The total recovery was 99.7%, 77.9% of the radiolabeled material was excreted into feces and 21.8% into urine.

2.3.2 Interaction Studies

Based on several DDI studies and PBPK model, caution should be exercised during concomitant use of capmatinib with strong CYP3A inhibitors, and concomitant use of capmatinib with strong or moderate CYP3A inducers should be avoided. Caution should be exercised during concomitant use of capmatinib with CYP1A2 substrates with a narrow therapeutic index, P-gp or BCRP substrates.

2.3.3 Special Populations

Age, gender or body weight had no statistically significant effect on the PK of capmatinib; therefore, no dose adjustment was required. Based on population PK analysis, no significant difference in the steady state $AUC_{0\text{-}12h}$ was observed in subjects with mild or moderate renal impairment, no dose adjustment was necessary. The effect of all degree of hepatic impairment on capmatinib PK was evaluated. Severe hepatic impaired function increased capmatinib AUC_{inf} and $AUC_{inf,u}$ by 24% and 78%. Overall, no dose adjustment was required in subjects with mild, moderate, and severe hepatic impairment according the AE data.

2.4 Clinical Efficacy and Safety Evaluation

2.4.1 Efficacy Results

In this submission, one Phase II pivotal study ([CINC280A2201]) was provided to support the efficacy of capmatinib for the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC).

Study [CINC280A2201] was a Phase II, open-label, multi-center, dose-escalation pivotal study to evaluate single-agent capmatinib in MET mutated NSCLC. The primary endpoint was the overall response rate (ORR), defined as the proportion of patients with a best overall response (BOR) as complete response (CR) or partial response (PR), as assessed per RECIST 1.1 by BIRC. The key secondary endpoint was BIRC-assessed duration of response (DOR).

The BIRC-assessed ORR was 40.6% (95% CI: 28.9, 53.1) in Cohort 4 and 67.9% (95% CI: 47.6, 84.1) in Cohort 5b. As the estimated ORR was ≧ 35% and the lower 95% CI was > 25% in Cohort 4, and the estimated ORR was ≧ 55% and the lower 95% CI was > 35% in Cohort 5b. Therefore, the primary objective of this study was met for both Cohort 4 ($2^{nd}/3^{rd}$ line) and Cohort 5b (treatment-naïve) in subjects with MET-mutated NSCLC.

In addition, the estimated median DOR was 9.72 months (95% CI: 5.55, 12.98) in Cohort 4 (MET mutated, pre-treated), and the estimated median DOR was 11.14 months (95% CI: 5.55, NE) in Cohort 5b (MET mutated, treatment naïve).

2.4.2 Safety Results

Common TEAEs included peripheral edema (49.7%), nausea (44.0%), vomiting (28.1%), and increased blood creatinine (25.4%). Other less frequent AEs included pneumonitis/ILD, hepatotoxicity, renal dysfunction, CNS toxicity, pancreatitis, photosensitivity, teratogenicity, DDI with strong CYP3A4 inducers, and QTc interval prolongation.

2.5 Bridging Study Evaluation

The exposure in Asian subjects was higher than non-Asian subjects. Same trend was seen in population PK analysis. Body weight was a covariate on CL and V1. Based on the following consideration including Asian subjects with low body weight, moderate inter-subject variability, no genetic polymorphism enzyme involved in metabolism, no exposure-response relationship for efficacy, and dose adjustment when adverse effect occurred. Therefore, bridging study can be waived from PK point of view.

In clinical trial A2201, limited East Asian subjects (N=20) revealed comparable

efficacy with overall subjects; apparent higher rate of AEs were noted in 74 East Asian subjects of safety dataset. Available East Asian experience was limited. The sponsor committed to provide additional East Asian data from ongoing studies.

2.6 Conclusion

Submitted dossiers for CMC, pharmacology/toxicology, PK/PD were adequate and acceptable.

The sponsor provided preliminary clinical information of capmatinib with durable ORR to support the efficacy and safety of claimed indication for the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) whose tumors have a mutation that leads to mesenchymal-epithelial transition (MET) exon 14 skipping. For NSCLC, ORR is considered a potential surrogate endpoint which is reasonably likely to predict a clinical benefit. Moreover, only 2-4 % of NSCLC patients harboring MET exon 14 skipping mutation and there is currently no approved agent for this mutation.

The overall safety profile was acceptable and can be adequately managed by labeling and routine pharmacovigilance in the post-market setting. A risk management plan (RMP) is not required to ensure that the benefits of the drug outweigh the risks.

The overall benefit/risk ratio is favorable to support accelerated approval of the claimed indications.

3. Post-Marketing Requirements

The sponsor committed to conduct extension study of A2201 as post-marketing confirmatory trial: additional 30 treatment-experienced and 27 treatment-naive subjects will be enrolled.

The sponsor also committed to provide additional East Asian data from ongoing studies.