Taiwan Food and Drug Administration

Assessment Report

Trade Name：
欣覓力 20 毫克膜衣錠 / Scemblix 20 mg Film-Coated Tablets
欣覓力 40 毫克膜衣錠 / Scemblix 40 mg Film-Coated Tablets

Active Ingredient：Asciminib hydrochloride

License Number：MOHW-PI-028555/ MOHW-PI-028556

Applicant： 台灣諾華股份有限公司

Approval Date： 2023.09.05
Indication：
1.治療先前曾接受兩種以上的酪胺酸激酶抑制劑治療的慢性期費城染色體陽性之慢性骨髓性白血病(Ph+ CML-CP)成年病人。

Philadelphia chromosome-positive chronic myeloid leukemia (Ph+ CML) in chronic phase (CP), previously treated with two or more tyrosine kinase inhibitors (TKIs).

2.治療慢性期費城染色體陽性且帶有 T315I 突變之慢性骨髓性白血病(Ph+ CML-CP with T315I mutation)成年病人。
Ph+ CML in CP with the T315I mutation.

Background Information

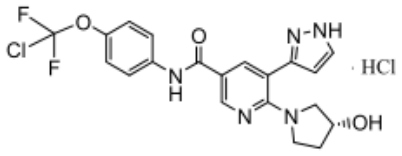
Trade Name	欣覓力 20 毫克膜衣錠 / Scemblix 20 mg Film-Coated Tablets 欣覓力 40 毫克膜衣錠 / Scemblix 40 mg Film-Coated Tablets
Active Ingredient(s)	Asciminib hydrochloride
Applicant	台灣諾華股份有限公司
Dosage Form & Strengths	膜衣錠 20 mg/ 40 mg
Indication	1.治療先前曾接受兩種以上的酪胺酸激酶抑制劑治療的慢性期費城染色體陽性之慢性骨髓性白血病(Ph+ CML-CP)成年病人。 Philadelphia chromosome-positive chronic myeloid leukemia (Ph+ CML) in chronic phase (CP), previously treated with two or more tyrosine kinase inhibitors (TKIs). 2.治療慢性期費城染色體陽性且帶有 T315I 突變之慢性骨髓性白血病(Ph+ CML-CP with T315I mutation)成年病人。 Ph+ CML in CP with the T315I mutation.
Posology	詳見仿單
Pharmacological Category **ATC Code**	L01EA06

2. Summary Report

2.1 Chemistry, Manufacturing and Controls Evaluation

2.1.1 Drug substance

The drug substance, asciminib hydrochloride, is chemically designated as *N*-[4-(Chlorodifluoromethoxy)phenyl]-6-[(3*R*)-3-hydroxypyrrolidin-1-yl]-5-(1*H*-pyrazol-3-yl) pyridine-3-carboxamide hydrogen chloride (1/1) and has the following structure:



It is a white to slightly yellow powder. The molecular formula and the molecular weight are $C_{20}H_{18}ClF_2N_5O_3 \cdot HCl$ and 486.30 g/mol, respectively.

Adequate information of characterization of the drug substance has been provided. The molecular structure of asciminib hydrochloride has been confirmed by UV spectrum, IR spectrum, nuclear magnetic resonance (NMR) spectroscopy, single-crystal X-ray diffraction and mass spectrometry. Adequate specification has been presented for the drug substance and the test items include appearance, identity, assay, enantiomer, residual solvents, loss on drying, sulphated ash, heavy metals, related substances and microbial enumeration tests. Batch analysis 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 supplied for oral use as film-coated tablets containing 20 mg and 40 mg of asciminib hydrochloride. The asciminib 20 mg film-coated tablets, with debossed "20" printed on one side and "Novartis logo" on the other side. The asciminib 40 mg film-coated tablets, with debossed "40" printed on one side and "Novartis logo" on the other side. The specifications for excipients used in the drug product formulation are adequate.

Adequate specification has been presented for the drug product and the test items includes appearance, identity, assay, purity, uniformity of dosage units, dissolution and microbial enumeration tests. Batch analysis data from commercial scale batches of the drug product are provided and the test results are within the specifications. Analytical methods are described well and validated.

Stability studies of drug product under long-term condition (25°C/60% RH and 30°C/75% RH) and accelerated condition (40°C/75% RH) have been carried out. Up to 12 months of long-term and 6 months of accelerated stability data are submitted. The statistical poolability of the data for drug product is evaluated, too. 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 vitro pharmacodynamic studies revealed that asciminib inhibited the ABL1 kinase and the proliferation of BCR-ABL1+ CMLs with IC_{50} values in the low nanomolar range but had no effect on ABL-negative or BCR-ABL1 kinase-negative cells. *In vivo* studies showed that asciminib exhibited antitumor activities against different CML models of xenografted human-derived tumors. In secondary pharmacological studies, asciminib inhibited some off-targets with IC_{50} values over 3.3 μM, but compared to the free exposure achieved in patients at 40mg BID, the calculated safty margins are > 60 for all targets.

Safety pharmacology studies showed that asciminib had no notable effects on neurological and respiratory systems. Regarding cardiovascular functions, asciminib did not affect ECG parameters in dogs and monkeys but increased the heart rate and decreased the blood pressure in dogs only at doses higher than the clinical dose.

2.2.2 Toxicological Studies

Asciminib (QD, PO) was evaluated in GLP-compliant toxicity studies for up to 26 weeks in rats and 39 weeks in monkeys. Toxicity findings of asciminib included changes in the hematopoietic system, adrenal gland, Harderian gland, and gastrointestinal tract, liver toxicity, and decreased body weight and food consumption. The HNSTD was 50 mg/kg/day in monkeys, and the STD_{10} was 200 mg/kg in rats, providing margins of 2.7 and 2.6 based on AUC, respectively. Toxicity findings in rats and monkeys were partially recovered after a 4-week recovery period. Notably, pancreas toxicity was noted only in dogs, and the genomic data indicated that asciminib induced an indirect cytotoxic effect on the pancreas.

Asciminib was not genotoxic but induced embryo-fetal toxicity. Women of childbearing potential are advised to implement contraception while receiving asciminib. In 2-year rat carcinogenicity study, no asciminib-related neoplastic or hyperplastic findings were observed. In accordance with ICH S9 guidance, the absence of PPND studies is considered acceptable since the intended clinical use and target patient population. Asciminib was phototoxic in vitro and in vivo. At the NOAEL, exposure based on

Cmax in plasma was 15- or 6- or 2-fold higher than the exposure in patients on 40 mg twice daily or 80 mg once daily, or 200 mg twice daily, respectively.

2.3 Clinical Pharmacology Evaluation

2.3.1 General Pharmacodynamics and Pharmacokinetics

Asciminib was rapidly absorbed with a median time to reach maximum plasma concentration (T_{max}) of 2 to 3 hours. Asciminib steady-state exposure (AUC and C_{max}) increased slightly more than dose proportional across the dose range of 10 to 200 mg administered once or twice daily. Steady state was reached by Day 3. There was no clinically relevant difference in the PK of healthy subjects compared to patients with cancer. Food decreases the bioavailability of asciminib. Following low-fat and high-fat meal, AUC_{inf} was decreased by 30% and 62.3%, respectively.

The apparent volume of distribution (V_z/F) based on Pop PK analysis and human ADME study were ~111 L. The fraction of asciminib bound to plasma proteins in vitro was high (97.3%) and independent of plasma concentration. In blood, asciminib was mainly distributed to plasma with a low fraction in red blood cells (0.58). The major metabolizing enzymes of asciminib were CYP3A4 (36.0%), UGT2B7 (13.3%) and UGT2B17 (7.8%). No major plasma metabolite was observed (<10% of total drug related AUC) *in vivo*. Asciminib and its metabolites are almost exclusively excreted in the feces (80%) after oral administration. In feces, asciminib was the major component, accounting for 56.7% of the administered radioactive dose. Excretion via the urine is minor (11%), with only a small fraction of the dose being excreted as unchanged asciminib (2.5%).

2.3.2 Interaction Studies

The asciminib AUC_{inf} and C_{max} increased by 36% and 19%, respectively, following coadministration of a single asciminib dose of 40 mg with a strong CYP3A4 inhibitor (clarithromycin). The strong CYP3A4 inducer rifampicin decreased asciminib AUC_{inf} by 14.9%. Co-administration of multiple doses of an itraconazole oral solution containing hydroxypropyl-β-cyclodextrin at a total of 8 g per dose with a 40 mg dose of asciminib decreased asciminib AUC_{inf} by 40.2% in healthy subjects. No clinically significant differences in the PK of asciminib were observed when coadministered with rabeprazole (acid-reducing agent) and quinidine (P-gp inhibitor).

Asciminib was identified as *in vitro* inducer of CYP1A2 and CYP3A4 and as reversible inhibitor of CYP3A4, CYP2C8, CYP2C9 and UGT1A1. A clinical DDI study with the sensitive substrates midazolam (CYP3A4), warfarin (CYP2C9) and repaglinide

(CYP2C8) evaluated interaction potential of asciminib with those CYPs. The midazolam AUC_{inf} and C_{max} increased by 28% and 11%, respectively, following coadministration with asciminib 40 mg twice daily. The S-warfarin AUC_{inf} and C_{max} increased by 52% and 4%, respectively, following coadministration with asciminib at 80 mg once daily and 314% and 7%, respectively, at 200 mg twice daily based on PBPK simulations. The repaglinide (substrate of CYP2C8, CYP3A4, and OATP1B) AUC_{inf} and C_{max} increased by 8% and 14%, respectively, following coadministration of repaglinide with asciminib 40 mg twice daily.

2.3.3 Special Populations

From the results of Pop PK analysis, there was no clinically meaningful difference in asciminib exposures based on age, gender, ethnicity, and body weight.

A renal impairment study (Study A2105) was conducted to evaluate the PK of asciminib in subjects with severe renal impairment (based on eGFR) in comparison to matching healthy subjects. A similar C_{max} and 56% higher asciminib AUC_{inf} in the severe renal impairment cohort compared to the normal renal function cohort was observed. The exposure changes in patients with severe renal impairment are not considered clinically meaningful.

A hepatic impairment study (Study A2103) was conducted to evaluate the PK of asciminib in subjects with mild, moderate, and severe hepatic impairment (based on Child-Pugh) in comparison to matching healthy subjects. Asciminib AUC_{inf} was increased by 22%, 3% and 66% in subjects with mild, moderate and severe hepatic impairment, respectively, compared to subjects with normal hepatic function, following oral administration of a single 40 mg dose of asciminib.

2.4 Clinical Efficacy and Safety Evaluation

2.4.1 Efficacy Results

The clinical program of asciminib includes a Phase I study (ABL001X2101 [Study X2101]), data cut-off date of 02-Apr-2020, and a Phase 3 study (Study ABL001A2301[Study A2301], data cut-off date of 25-May-2020 and 06-Oct-2021).

As the pivotal study, Study A2301 is a Phase III, multi-center, active-controlled, open-label, 2:1 randomized study of oral asciminib (40 mg BID) versus bosutinib (500 mg QD) in patients with Ph+ CML-CP, previously treated with at least 2 TKIs (i.e. imatinib, nilotinib, dasatinib, radotinib or ponatinib). Patient with known presence of the T315I or V299L mutation would be excluded. The primary and key secondary

efficacy endpoints were major molecular response (MMR) at Week 24 and MMR at Week 96. Two hundred thirty-three (233) patients with CML-CP were enrolled, and 157 were randomized to treatment with asciminib and 76 to treatment with bosutinib (full analysis set, FAS). As of the first data cut-off (25-May-2020), the two treatment arms were balanced for the demographic characteristics assessed, with exception of ethnicity and gender. When comparing efficacy of primary endpoint, MMR rate at 24 weeks, with bosutinib, superity was demonstrated for asciminib. The MMR rate at 24 weeks was 25.5% in the asciminib arm compared to 13.2% in the bosutinib arm. The treatment difference was both statistically significant, 12.2% (95% CI: 2.19, 22.30, two-sided p-value: 0.029) and approximately two-fold increase in the MMR rate between the two arms. When comparing efficacy of the key secondary endpoint, MMR rate at 96 weeks was 37.6% in the asciminib arm and 15.8% in the bosutinib arm. The risk difference was 21.7% (95% CI: 10.53, 32.59, two-sided p-value: 0.001) which was statistically significant. Sensitivity, subgroup and supportive analyses demonstrated a consistent treatment effect with the main analysis result. Therefore, it is evident for the applicant to claim the efficacy of treatment for asciminib to Ph+ CML-CP adults who were previously treated with at least 2 TKIs.

In the Study X2101, patients with Ph+ CML-CP/-AP who had prior treatment with at least 2 prior TKIs, received treatment with increasing doses of oral asciminib monotherapy (10 mg to 200 mg BID) and in combination with either nilotinib or imatinib or dasatinib. Efficacy data of patients with CML-CP harboring the T315I mutation was analyzed in a descriptive nature. A total of 45 CML-CP patients harboring the T315I mutation assigned to asciminib 200 mg twice daily monotherapy included in the T315I mutation analysis set. As of the data cut-off date, overall MMR was achieved by 22 in 45 (48.9%) patients. The MMR rates of all participants for week 24 and 48, 72 and 96 weeks were 37.8% (n=45), 34.1% (n=45), 36.1% (n=36) and 34.4% (n=32), respectively.

2.4.2 Safety Results

The safety database of asciminib monotherapy is composed of the following parts: Study A2301 (156 patients) and Study X2101 (200 patients), as well as pooled analysis data of all patients using asciminib (Pool A: 356 patients), pooled analysis data of patients using asciminib 40 mg BID (Pool C: 187 patients) and pooled analysis data of healthy volunteers from clinical pharmacology studies (Pool D: 310 adults). The median duration of exposure in Pool A was from 65.1 to 115.6 weeks from the Week 24 data cut-off to the Week 96 cut-off. A total of 70 of whom had Ph+ CML-CP harboring the T315I mutation received asciminib at various doses. Of these 70

patients, 48 received asciminib at the recommended dose of 200 mg twice daily with the median duration of exposure of 69.8 weeks.

In Study A2301 at the Week 24 data cut-off, 89.7% of the patients in the asciminib treatment group and in the bosutinib treatment group and 96.1% of the patients experienced adverse events (AEs). The frequencies of severe AEs (≥ grade 3) were lower in the asciminib treatment group (50.6%) compared to the bosutinib treatment group (60.5%). A total of 13.5% of the patients in the asciminib treatment group and in the bosutinib treatment group 18.4% of the patients experienced serious adverse events (SAEs). The most frequently occurred AEs (of ≥ 10%) regardless of study relationship by preferred terms in the asciminib treatment group include thrombocytopenia (22.4%), neutropenia (17.9%), headache (16.0%), hypertension (11.5%), diarrhea (11.5%), nausea (11.5%), fatigue (10.3%), and arthralgia (10.3%).

The frequencies of non-fatal SAEs were lower in the asciminib treatment group (13.5%) compared to the bosutinib treatment group (18.4%). The individual number of non-fatal SAEs by preferred terms in the pivotal study or Pool C was too limited to conclude on the trend. In Pool A, none of the SAEs was reported in > 2% of patients except of pleural effusion and pneumonia at the Week 24 (2.2% and 2.0% respectively) and Week 96 data cut-off (2.5% and 2.2% respectively).In the asciminib safety pool A (all patients) at the Week 24 data cut-off, there were 8 on-treatment deaths: 3 cases were due to the study indication and 5 cases were attributed to arterial embolism, ischemic stroke, cardiac arrest, completed suicide, and general physical condition deterioration.

In the asciminib safety pool at Week 96 data cut-off, there was one additional on-treatment death compared to Week 24, which was one case due to COVID-19 pneumonia. The monitor of adverse events of special interests (AESIs) include myelosuppression, pancreatic toxicity, hypersensitivity, hepatotoxicity, hepatitis B virus reactivation, reproductive toxicity, GI toxicity, phototoxicity, QTc prolongation, cardiac failure, edema and fluid retention, ischemic heart disease and CNS conditions, and haemorrhage. At the Week 96 cut-off, the proportion of patients experiencing gastrointestinal toxicity, hepatotoxicity (laboratory events only) and hypersensitivity AESIs were substantially lower in the asciminib treatment group compared to the bosutinib treatment group (both all grades and grade ≥ 3). The AESIs which had comparable incidence (difference of < 5%) across both the treatment groups were myelosuppression (except for thrombocytopenia), pancreatic toxicity, hemorrhage, ischemic heart and CNS conditions, QTc prolongation, cardiac failure, edema and

fluid retention, and reproductive toxicity.The overall pattern of adverse events was similar in 48 patients with T315I mutations treated at 200 mg twice daily asciminib in comparison to those treated at 40 mg twice daily. The most common reported AEs (of ≥ 15%) were fatigue (29.2%), nausea (27.1%), diarrhea and lipase increase (both 20.8%), vomiting(18.8%), headache and thrombocytopenia (both 16.7%). Grade ≥ 3 events were reported in 56.3% of patients, including lipase increase (16.7%) and thrombocytopenia (14.6%). Serious adverse events occurred in 20.8% of patients who received asciminib in this cohort with the most common events of abdominal pain, pneumonia, and vomiting. One on-treatment deaths occurred in patients receiving asciminib 200 mg once daily treatment which was not suspected to be treatment-related (cardiac arrest, Day 1324). No on-treatment deaths were reported in patients with Ph+ CML-CP harboring the T315I mutation and receiving the asciminib 200 mg twice daily in Study X2101.

2.5 Bridging Study Evaluation

Study A2301 is an ongoing, randomized, open-label, active-controlled (bosutinib), multi-center Phase III study to compare the efficacy and safety of oral asciminib 40 mg b.i.d. with that of bosutinib 500 mg q.d. in patients with CML-CP, previously treated with at least 2 TKIs. On Week 2 Day 1, asciminib C_{max}, $AUC_{0\text{-}12h}$ and $AUC_{0\text{-}last}$ in Japanese patients were 37%, 15% and 26% higher compared to non-Asian patients. Study X2101 is a Phase I, multicenter, open-label, dose escalation first-in-human study. Following repetitive dosing of 200 mg b.i.d. (Cycle 2 Day 1), asciminib C_{max}, AUC_{tau}, $AUC_{0\text{-}last}$ and C_{trough} at steady state were comparable between East Asian and non-Asian patients. Based on these results, there is no clinically relevant difference in the PK of asciminib between races.

The sponsor has provided the complete clinical data package of asciminib that includes two studies conducted primarily on Caucasian populations, Study A2301 (Week 24 data cut-off) and Study X2101 (ongoing), as well as a pooled East-Asian subgroup (Japan, South Korea, Singapore). Results from limited sample size suggested that asciminib would be tolerable and possibly effective in East-Asian patients. The impact of ethnic difference might be low. Therefore, the bridging trial was waived.

CDE had encouraged the sponsor to provide the 96-weeks information of efficacy and safety in Study A2301 and the final report of Study X2101 during the NDA application stage. Dossiers provided in NDA submission fulfills this request.

2.6 Conclusion

In conclusion, the benefit-risk balance of Scemblix is favorable when administered at 40 mg twice daily in the treatment of patients with Ph+ CML-CP previously treated with two or more tyrosine kinase inhibitors. The benefit-over-risk is acceptable when administered at 200 mg twice daily in patients with Ph+ CML-CP with T315I mutations, for the reason that treatment options are limited among this population.

3. Post-Marketing Requirements

Nil