Taiwan Food and Drug Administration

Assessment Report

Trade Name：洛滿舒膜衣錠 120 毫克/
LUMAKRAS Film-coated Tablets 120 mg

Active Ingredient：sotorasib

License Number： MOHW-PI 028291

Applicant：台灣安進藥品有限公司

Approval Date： 2022/5/3

Indication：
適用於治療曾接受過至少一次全身性療法，且帶有 KRAS G12C 突變之局部晚期或轉移性非小細胞肺癌(NSCLC)成年病人。
此適應症係依據腫瘤整體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。

LUMAKRAS is indicated for the treatment of adult patients with KRAS G12C-mutated locally advanced or metastatic non-small cell lung cancer (NSCLC) who have received at least one prior systemic therapy.

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 a confirmatory trial(s).

Background Information

Trade Name	洛滿舒膜衣錠 120 毫克 / LUMAKRAS Film-coated Tablets 120 mg
Active Ingredient(s)	sotorasib
Applicant	台灣安進藥品有限公司
Dosage Form & Strengths	Film-coated Tablets 120 mg
Indication	適用於治療曾接受過至少一次全身性療法，且帶有 KRAS G12C 突變之局部晚期或轉移性非小細胞肺癌 (NSCLC) 成年病人。 此適應症係依據腫瘤整體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。 LUMAKRAS is indicated for the treatment of adult patients with KRAS G12C-mutated locally advanced or metastatic non-small cell lung cancer (NSCLC) who have received at least one prior systemic therapy. 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 a confirmatory trial(s).
Posology	LUMAKRAS 的建議劑量為每日一次口服 960 mg (八顆 120 mg 藥錠) 直到疾病惡化或無法接受毒性為止。
Pharmacological Category **ATC Code**	L01XX73

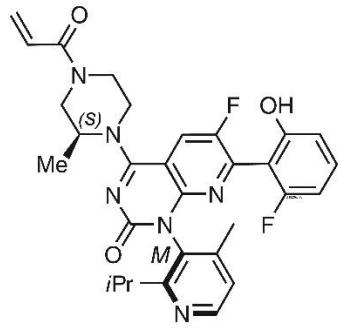
Summary Report

2.1 Chemistry, Manufacturing and Controls Evaluation

2.1.1 Drug substance

The drug substance, sotorasib, is chemically designated as 6-fluoro-7-(2-fluoro-6-hydroxyphenyl)-(1*M*)-1-[4-methyl-2-(propan-2-yl)pyridin-3-yl]-4-[(2*S*)-2-methyl-4-(prop-2-

enoyl)piperazin-1-yl]pyrido[2,3-*d*]pyrimidin-2(1*H*)-one and has the following structure:



It is a white to off-white to yellow to light brown powder. The molecular formula and the molecular weight are $C_{30}H_{30}F_2N_6O_3$ and 560.6 g/mol, respectively.

Adequate information of characterization of the drug substance has been provided. The molecular structure of sotorasib has been confirmed by elemental analysis, NMR, MS, UV/Vis, FTIR and single crystal X-ray diffraction.

The drug substance specification includes tests for description, identification, assay, organic impurities, chiral impurities, residual solvents, residue on ignition, elemental impurities and trifluoroacetic acid content.

2.1.2 Drug product

Drug product is supplied as immediate-release tablets for oral use containing 120 mg sotorasib. The excipients used in the drug product formulation comply with the compendial monographs.

The drug product specification includes tests for description, identification, assay, organic impurities, content uniformity, dissolution, water content and microbial limits. Analytical methods are well-described and validated. Stability studies of the drug product under long term condition (30°C/65% RH) and accelerated condition (40°C/75% RH) have been carried out.

2.2 Preclinical Pharmacology/Toxicology Evaluation

2.2.1 Pharmacological Studies

AMG 510 inhibited SOS1-catalyzed nucleotide exchange of recombinant mutant $KRAS^{G12C/C118A}$, but did not appreciably inhibit wildtype $KRAS^{C118A}$. AMG 510 inhibited basal ERK1/2 phosphorylation in the KRAS *p.G12C* cell lines, but had no inhibitory effect in cell lines with no KRAS *p.G12C* mutation. Besides, AMG 510 reduced viability only in cell lines harboring the *p.G12C* mutation. The combination of AMG 510 with the pan-ErbB kinase inhibitor, the SHP2 inhibitor, or MEK inhibitors resulted in highly synergistic tumor cell killing in NCI-H358 and NCI-H2122 cells. In vivo pharmacodynamic analyses demonstrated that AMG 510 covalently modified $KRAS^{G12C}$, inhibited KRAS signaling, and induced apoptosis

and accumulation of active EGFR in KRAS *p.G12C* tumor xenografts. AMG 510 profoundly inhibited the growth of tumors harboring the KRAS *p.G12C* mutation but had no effect on tumors lacking the mutation. AMG 510 was effective in combination with numerous agents, including chemotherapy and the inhibitors of MAPK and PD-1. AMG 510 established an anti-tumor immune memory through the recognition of shared antigens in mice bearing syngeneic mouse $KRAS^{G12C}$ tumor cell lines. Treatment of $KRAS^{G12C}$ tumor-bearing mice with AMG 510 was associated with a pro-inflammatory tumor microenvironment. Regarding safety pharmacology, AMG 510 showed no effects in an hERG testing and cardiovascular, CNS and respiratory studies.

2.2.2 Toxicological Studies

AMG 510 was evaluated in rat and dog repeated-dose toxicology studies for up to 3 months. In rats, renal tubular epithelial degeneration/necrosis, increased spleen weight, increased leukocytes, and decreased red blood cell mass were observed. Renal tubular injury could partially reverse during the recovery period, except a few tubules were surrounded by fibroplasia. The STD_{10} was 180 mg/kg/day in the 3-month repeated-dose toxicology study, and the exposure was approximately 1.7 times the human AUC at the clinical dose of 960 mg. In the dog 3-month repeated dose toxicity study, the liver was a common target (centrilobular hepatocellular hypertrophy was observed). Thyroid atrophy and hepatocellular glycogen increase were observed at high-dose treatment. The HNSTD was considered in 1000 mg/kg/day, and the exposure was approximately 0.4 times the human AUC at the clinical dose of 960 mg. AMG 510 did not have significant adverse developmental effects or affect embryo-fetal survival up to the high dose in rats. Lower fetal body weights and a reduction in the number of ossified metacarpals in fetuses were only observed at high dose AMG 510 in rabbits. No carcinogenicity studies have been conducted since AMG 510 is used in advanced cancer. AMG 510 has no significant genotoxic risk and phototoxic potential. No local irritant effect was observed in the digestive tract.

2.3 Clinical Pharmacology Evaluation

2.3.1 General Pharmacodynamics and Pharmacokinetics

Following oral administration, the time to maximum concentration was observed at 1-hour post-dose. Sotorasib exhibited non-linear and time-dependent PK over the dose range of 180 mg to 960 mg once daily with similar systemic exposure (i.e., $AUC_{0\text{-}24h}$ and C_{max}) across doses at steady-state. Steady state was reached within 22 days. No accumulation was observed after repeat dosing with a mean accumulation ratio of 0.56. When 960 mg sotorasib was administered with a high-fat, high-calorie meal in patients, $AUC_{0\text{-}24h}$ increased by 25% compared to fasted conditions. Sotorasib systemic exposure was comparable between film-coated tablets and film-coated tablets pre-dispersed in water administered under fasted conditions.

In vitro unbound fraction of sotorasib to human plasma proteins was 0.086 to 0.15 at concentrations of 0.25 to 25 μM. In the phase 1/2 study (Study 20170543), a mean steady-state apparent clearance and apparent V_d of 32.5 L/hr and 367 L were observed, respectively. The main metabolic pathways of sotorasib are non-enzymatic conjugation and oxidative metabolism with CYP3As. After a single dose of radiolabeled sotorasib, the primary route of excretion was in the feces, accounting for a geometric mean of 74% of the dose (53% unchanged), with urine accounting for 6% (1% unchanged). The sotorasib mean terminal elimination half-life is 5 hours in subjects with advanced NSCLC.

2.3.2 Interaction Studies

Interactions of sotorasib as perpetrator and as victim with other medications were assessed in several clinical drug-drug interaction studies. Coadministration of repeat doses of omeprazole (PPI) with a single dose of sotorasib decreased sotorasib C_{max} by 65% and AUC by 57% under fed conditions, and decreased sotorasib C_{max} by 57% and AUC by 42% under fasted conditions. Coadministration of a single dose of famotidine (H_2 receptor antagonist) given 10 hours prior to and 2 hours after a single dose of sotorasib under fed conditions decreased sotorasib C_{max} by 35% and AUC by 38%. Coadministration of repeat doses of rifampin (a strong CYP3A4 inducer) with a single dose of sotorasib decreased sotorasib C_{max} by 35% and AUC by 51%.

No clinically meaningful effect on the exposure of sotorasib was observed following coadministration of sotorasib with itraconazole (a combined strong CYP3A4 and P-gp inhibitor) and a single dose of rifampin (an OATP1B1/1B3 inhibitor), or metformin (a MATE1/MATE2-K substrate). Coadministration of sotorasib with midazolam (a sensitive CYP3A4 substrate) decreased midazolam C_{max} by 48% and AUC by 53%. Coadministration of sotorasib with digoxin (a P-gp substrate) increased digoxin C_{max} by 91% and AUC by 21%.

2.3.3 Special Populations

The influence of intrinsic factors on the PK of sotorasib were investigated using population PK analysis. No clinically meaningful differences in the PK of sotorasib were observed based on age (28 to 86 years), sex, race (White, Black and Asian), body weight (36.8 to 157.9 kg), line of therapy, and ECOG PS (0, 1). Subjects with renal impairment (normal [n=199], mild [n=255], and moderate [n=37] based on eGFR) and hepatic impairment (normal [n=413], mild [n=83], and moderate [n=3] based on NCI criteria) did not show significant effects on sotorasib CL_{ss}. Sotorasib PK has not been studied in subjects with moderate to severe hepatic impairment and subjects with severe renal impairment.

2.4 Clinical Efficacy and Safety Evaluation

2.4.1 Efficacy Results

Study 20170543 is an ongoing phase 1/2, open-label, single-group study evaluating sotorasib in the treatment of subjects with KRAS p.G12C-mutated solid tumors. The efficacy of the proposed indication was based on results from 126 subjects with KRAS p.G12C-mutated advanced NSCLC who received 960 mg QD at the pivotal phase 2 portion of Study 20170543. Of the 126 subjects with NSCLC, 81.7% were white and 50% were men. The median (range) age was 63.5 (37, 80) years. Most subjects had non-squamous NSCLC (99.2%) and stage IV disease at screening (96.0%). Regarding prior anticancer therapy, 42.9% received 1 prior line, 34.9% received 2 prior lines, 22.2% received 3 prior lines, and no subject received 4 or more. A total of 113 subjects (89.7%) received prior platinum-based chemotherapy and 115 subjects (91.3%) received prior anti-PD-1/PD-L1 immunotherapy therapy. A total of 102 subjects (81.0%) had received and progressed on treatment with both checkpoint inhibitors and platinum-based therapy.

Based on blinded independent central review using RECIST 1.1(data cutoff date of 01 September 2020), the ORR among 123 subjects with NSCLC in the phase 2 portion of Study 20170543 was 37.4% (95% CI: 28.8, 46.6). Median duration of response (DOR) was 8.4 months (95% CI: 6.9, 8.4). The median follow-up time for PFS was 8.3 months (range: 0.3 to 11.5+). Median PFS was 6.7 months (95% CI: 4.9, 8.1); Median OS was 12.0 months (95% CI: 9.5, not estimable). Among the subjects who had prior treatment with both platinum-based chemotherapy and anti-PD-1 or anti-PD-L1, ORR was 32.3% (95% CI: 23.3, 42.5) and median DOR was not estimable (95% CI: 6.9 months, not estimable).

2.4.2 Safety Results

The analysis of the safety profile of sotorasib was primarily based on the pooled monotherapy at 960mg QD data from ongoing Study 20170543. Safety data was compared between populations with different cancers of NSCLC (190 subjects), CRC(87 subjects), and other tumor type(62 subjects). Subjects with NSCLC were less heavily pretreated. Regardless of tumor type, the median relative dose intensity of sotorasib monotherapy was 100% (Q1, Q3:96.34, 100.00). More dose changes were reported in subjects with NSCLC. The most frequently reported reason for dose change was adverse event. Adverse events leading to dose reduction or interruption of sotorasib were reported in 35.3% of subjects with NSCLC.

The incidence of adverse events for subjects with NSCLC (98.4%) was comparable to the incidence for subjects with CRC (95.4%), slightly higher than subjects with other tumor type (88.7%). Grade≥ 3 and serious adverse events were reported more among subjects with NSCLC with the incidences of 60.0% and 52.1%, respectively. The most frequently reported (≥ 5% of subjects) grade≥ 3 adverse events in subjects with NSCLC treated at 960 mg once-daily by preferred term were increased ALT (7.9%), increased AST (6.8%), pneumonia (6.8%), diarrhea (5.3%), and pleural effusion (5.3%). The most frequently reported (≥ 2% of subjects) serious adverse events in subjects with NSCLC by preferred term were pneumonia (7.4%),

NSCLC(4.7%), pleural effusion (4.7%), respiratory failure (3.7%), back pain (2.6%), and metastatic lung cancer (2.1%). The types of grade ≥ 3 and serious adverse events observed were generally similar across these cancer types.

Grade≥ 3 hepatotoxicity adverse events of interest were reported for 30 subjects (15.8%) with NSCLC treated at 960 mg once-daily. Among them, 9 subjects (4.7%) were serious. No fatal hepatotoxicity adverse events of interest were reported. None of the cases of hepatotoxicity adverse events consistent with Hy's Law.

The incidence of adverse events was generally similar across subgroups of age or sex.

2.5 Bridging Study Evaluation

In subjects with KRAS p.G12C-mutated advanced solid tumors following oral administration of 960 mg sotorasib daily (Study 20170543), Asian subjects (N=20) had 15%~30% lower mean Cmax and 24% lower mean AUC0-24h relative to Non-Asian subjects. The population PK analysis included sotorasib PK data from 344 subjects with a total of 48 East Asians patients from Japan and Korea. Post-hoc estimates of the PK parameters following single-dose of sotorasib and following 960mg QD doses at steady-state showed the differences in PK exposures (Cmax,1dose, AUCinf,1dose, Cmax,ss and AUCtau,ss) were <16% between East Asian and Western Caucasian. The reason for numerically lower mean exposure in Asian subjects is unknown. However, the exposure difference is within the inter-subject variability for sotorasib PK parameters, suggesting the difference may not be statistically significant. Overall, race is not considered a sensitive factor on sotorasib PK.

A total of 24 Asian subjects with NSCLC received monotherapy 960mg QD in Study 20170543, including Phase 1(6 subjects) and Phase 2(18 subjects) parts. The ORR among Asian subjects was 29.2% (95% CI: 12.6, 51.1). The proportion of subjects with SD was comparable between these Asian participants(45.8%) and overall Phase 2 NSCLC population(44.4%). Median DOR was not estimable.

Subgroup analysis of Phase 2 part of Study 20170543 revealed the ORR (41.6%) in White (101 subjects) was higher than the ORR (16.7%) in Asians (18 subjects) by race. The safety profile of the limited number of Asian subjects with NSCLC was generally comparable to the overall population.

Race is not considered a sensitive factor on sotorasib PK. The efficacy of sotorasib monotherapy for NSCLC in Asians is uncertain. However, it is recommended to waive the bridging study considering the rare incidence of KRAS G12C-mutated NSCLC in Asians and the unmet medical need for the advanced disease status.

2.6 Conclusion

Submitted dossiers for CMC, pharmacology/toxicology, PK/PD were adequate and acceptable. The efficacy of sotorasib was demonstrated by durable ORR in adult patients with KRAS G12C-mutated locally advanced or metastatic non-small cell lung cancer (NSCLC) who have received at least one prior systemic therapy. For NSCLC, ORR is considered a potential surrogate endpoint which is reasonably likely to predict a clinical benefit. 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.

In conclusion, the overall benefit/risk ratio is favorable to support **accelerated approval** of the claimed indications.

3. Post-Marketing Requirements

1. Submit final report of Hepatic Impairment study (Study 20200362), Drug interaction study (Study 20200426) after study completion.
2. Submit final report of Study 20190147 to support the ethnic difference evaluation.
3. Submit final report of confirmatory trial Study 20190009 after completion.
4. Provide drug consumption data and estimate drug demand in Taiwan during the 5 years after approval to fulfill the requirement of Rare and Severe Disease Designation.