Taiwan Food and Drug Administration

Assessment Report

Trade Name：尚能嘉注射劑 / Sunlenca Injection

Active Ingredient： Lenacapavir sodium

License Number：MOHW-PI 028747

Applicant：香港商吉立亞醫藥有限公司台灣分公司

Approval Date：113.7.19

Indication：
與其他抗反轉錄病毒藥物併用，適用於治療已有廣泛治療經驗(heavily treatment-experienced)，且無法建構具抑制效果之抗病毒藥物組合的多重抗藥性第一型人類免疫缺乏病毒(HIV-1)感染症的成人病人。

In combination with other antiretroviral(s), indicated for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in heavily treatment-experienced adults with multidrug resistant HIV-1 infection failing to construct a suppressive anti-viral regimen.

Background Information

Trade Name	尚能嘉注射劑 / Sunlenca Injection
Active Ingredient(s)	Lenacapavir sodium
Applicant	香港商吉立亞醫藥有限公司台灣分公司
Dosage Form & Strengths	注射液劑 473.1mg/1.5ml
Indication	與其他抗反轉錄病毒藥物併用，適用於治療已有廣泛治療經驗(heavily treatment-experienced)，且無法建構具抑制效果之抗病毒藥物組合的多重抗藥性第一型人類免疫缺乏病毒(HIV-1)感染症的成人病人。
Posology	可採用兩種建議劑量療法的其中一種來開始 SUNLENCA 的治療，參見仿單。醫療照護人員應確認適合病人的起始療法。 SUNLENCA 口服錠劑可隨食物或不隨食物服用。
Pharmacological Category **ATC Code**	J05AX31

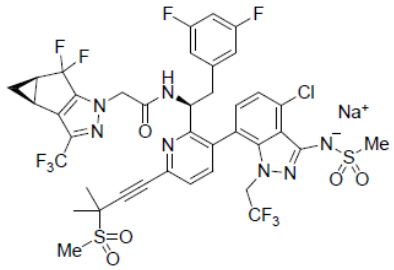
2. Summary Report

2.1 Chemistry, Manufacturing and Controls Evaluation

2.1.1 Drug substance

Lenacapavir sodium

The drug substance, lenacapavir sodium, is chemically designated as sodium (4-chloro-7-(2-((*S*)-1-(2-((3b*S*,4a*R*)-5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1*H*-cyclopropa[3,4]cyclopenta[1,2-*c*]pyrazol-1-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)-6-(3-methyl-3-(methylsulfonyl)but-1-yn-1-yl)pyridin-3-yl)-1-(2,2,2-trifluoroethyl)-1*H*-indazol-3-yl)(methylsulfonyl)amide and has the following structure:



It is a light yellow to yellow solid. The molecular formula and the relative molecular mass for lenacapavir sodium are $C_{39}H_{31}ClF_{10}N_7NaO_5S_2$ and 990.3, respectively.
Adequate information of characterization of the drug substance has been provided. The molecular structure of lenacapavir sodium has been confirmed by IR spectrum, nuclear magnetic resonance (NMR) spectroscopy and mass spectrum. Stereochemistry is determined by single crystal X-ray diffraction analysis.

Adequate specification has been presented for the drug substance and the test items include appearance, identification, clarity of solution, water content, sodium content, assay, impurity content, residual solvents, organic volatile impurities, bacterial endotoxins and microbiological examination. 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 subcutaneous administration as clear, yellow to brown solution containing 463.5 mg/1.5 mL lenacapavir (equivalent to 473.1 mg/1.5 mL lenacapavir sodium). The specifications for excipients used in the solution formulation are adequate.

Adequate specification has been presented for the solution and the test items include

appearance, identification, assay, degradation product content, viscosity, volume in container, particulate matter, sterility and bacterial endotoxins. Batch analysis data from representative batches of the solution are provided and the test results are within the specifications. Analytical methods are described well and validated.

Stability studies of the solution under long term condition (30°C/75% RH) and accelerated condition (40°C/75% RH) have been carried out. Up to 36 months of long-term and 6 months of accelerated stability data are submitted. Based on available stability data, the shelf life of the solution can be granted for 36 months under the storage condition of below 30°C.

2.2 Preclinical Pharmacology/Toxicology Evaluation

2.2.1 Pharmacological Studies

Lenacapavir (LEN) is a multistage, selective inhibitor of HIV-1 capsid function that directly binds to the interface between capsid protein (p24) subunits in hexamers. Lenacapavir has been demonstrated its antiviral activity against HIV-1 isolates. Lenacapavir has no safety concerns on CNS, CV, and respiratory systems.

2.2.2 Toxicological Studies

The pivotal repeated-dose toxicity studies of lenacapavir included a 6-month study in rats and a 9-month study in dogs via subcutaneous administration. The target organ toxicities included skin reactions at the injection sites in both species and liver (bile duct degeneration and cell/bile ductile hyperplasia), gallbladder (edema and hyperplasia), kidney (tubule degeneration and dilatation), and stomach (degeneration/atrophy of mucosa) findings in dogs. The NOAELs in repeated-dose toxicology studies provided safety margins of 6~8 fold in rats and 9 fold in dogs, based on the AUC of the recommended human dose. Lenacapavir was not genotoxic and was not carcinogenic in the transgenic mouse and rats. Lenacapavir did not show any adverse effects in reproductive and developmental toxicity studies. Lenacapavir was neither a skin sensitizer nor potentially phototoxic. Lenacapavir generally generated long-lasting local effects at injection sites.

2.3 Clinical Pharmacology Evaluation

2.3.1 General Pharmacodynamics and Pharmacokinetics

The active ingredient of Sunlenca® Injection and Tablets are lenacapavir sodium (LEN sodium). The recommeded treatment regimens includes 2 options both combined with SC injections and oral tablets. The absolute bioavailability following administration of LEN tablet is low and decreases with the escalating doses due to low solubility of LEN and the active efflux of P-gp in the intestine. As the result, the increase in AUC_{inf} and C_{max} of LEN oral tablet is less than dose proportional over the dose range of 50 to 1800 mg. On the other hand, LEN is expected to be completely absorbed following SC administration. The absorption profile of SC LEN is a two-phase absorption kinetics involving delayed and first-order absorption kinetics. There would be a short initial absorption phase of LEN dissolved in the formulation, with the majority precipitated fraction forming the drug depot. Then the extended absorption leads to a prolonged T_{max} of 77 to 84 days. The C_{max} and AUC_{inf} increases proportionally between 309 and 927 mg following SC administration.

Based on the clinical trials conducted with dose regimen Option 2 and popPK modelling and simulation with dose regimen Option 1, the recommended 2 dosage regimen options present similar LEN plasma concentrations and PK parameters during the initial and maintenance dose period, indicating that the efficacy and safety profile will also likely be similar between the two options for the entire treatment duration.

LEN exposure and T_{max} are comparable following oral administration under fasted conditions or with high-/low-fat meals, supporting administration of LEN tablets with or without food. Following a single-dose of SC administration of LEN 927 mg to healthy participants, mean Vz/F values ranged between 9500 to 11,700 L, indicating extensive tissue distribution. LEN is metabolized primarily via CYP3A4 and UGT1A1. A mean 75.9% of the dose was recovered in feces, and 0.237% was recovered in urine in the clinical mass balance study. It indicated that fecal elimination is the primary elimination route of LEN and its metabolites. The median $t_{1/2}$ after oral and SC administration ranged from 10-12 days and 8-12 weeks respectively. The mean apparent clearance was 55 L/h following oral administration and 4.2 L/h following SC administration.

2.3.2 Interaction Studies

Coadministration of LEN with multiple doses of strong CYP3A/P-gp/UGT1A1 inhibitors atazanavir/cobicistat increased LEN concentrations to a larger degree

(321% increase in AUC_{inf} and 560% increase in C_{max}) than coadministration with cobicistat and darunavir/cobicistat, the strong CYP3A/P-gp inhibitors (128% and 94% increase respectively in AUC_{inf}). Voriconazole, which is only a strong CYP3A inhibitor, increased LEN exposure much less than the drugs inhibiting 2 more metabolism pathways of LEN (41% increase in AUC_{inf}). Based on limited exposure-response relationship for safety of LEN, drug interactions of LEN with strong CYP3A inhibitors and CYP3A/P-gp inhibitors are not considered to be clinically significant. However, when all 3 pathways (CYP3A/P-gp/UGT1A1) are inhibited, a significantly larger increase in exposure is observed. Therefore, strong inhibitors of CYP3A, P-gp and UGT1A1 together are not recommended with LEN. Rifampin, as strong inducers of CYP3A/P-gp/UGT1A1, decreased LEN AUC_{inf} by 84%, increasing the risks of therapeutic effect loss and resistance. Therefore, strong inducers of CYP3A/P-gp/UGT1A1 are contraindicated with LEN. There are no restrictions for use of LEN with gastric acid-reducing agents.

LEN appeared to inhibit tenofovir alafenamide and rosuvastatin, the substrates of P-gp and BCRP transporter. However, these interactions are unlikely to be clinically meaningful. Additionally, there were no changes in the exposures of the OATP substrate (pitavastatin) after co-administered with LEN. Thus, LEN does not inhibit OATP transporters. Overall, substrates of P-gp, BCRP, and OATP can be co-administered with LEN. On the other hand, LEN is considered a moderate inhibitor of CYP3A. Caution is advised if LEN is co-administered with sensitive CYP3A substrates that have a narrow therapeutic index.

2.3.3 Special Populations

Based on PopPK analysis of LEN, the clinically relevant differences due to age, gender, race/ethnicity or weight on the PK of LEN were not identified.

Following a single dose of oral LEN 300 mg, LEN C_{max} and AUC_{inf} in participants with severe renal impairment (CLcr 15 to 29 mL/min) increased 162% and 84% respectively compared with healthy controls. Based on limited exposure-response relationship for safety of LEN and the tolerance study in healthy participants, these observed increases in LEN exposure are not deemed clinically meaningful. No dose adjustment is recommended in patients with mild to severe renal impairment. LEN has not been studied in patients with end-stage renal disease. As the unbound fractions of LEN in the severe renal impairment participants were high (> 98.5%), dialysis is not expected to alter exposures to LEN.

Following a single dose of oral LEN 300 mg, LEN C_{max} and AUC_{inf} in participants with moderate hepatic impairment (Child-Pugh B) increased 161% and 47% respectively compared with healthy controls. Based on limited exposure-response relationship for safety of LEN and the tolerance study in healthy participants, these observed increases in LEN exposure are not deemed clinically meaningful. No dose adjustment is recommended in patients with mild or moderate hepatic impairment. LEN has not been studied in patients with severe hepatic impairment.

2.4 Clinical Efficacy and Safety Evaluation

2.4.1 Efficacy Results

In this submission, the Sponsor provided Study GS-US-200-4625 to support the efficacy of SUNLENCA® Injection for the claimed indication. The major design features and results of this study were summarized as follows:

- ***Study GS-US-200-4625:***

This is a Phase 2/3, global, randomized, placebo-controlled multicenter study of Lenacapavir (LEN) together with an optimized background regimen (OBR) in PWH with multidrug resistance (MDR) (to ≥ 2 antiretroviral (ARV) medications from each of ≥ 3 of the 4 main classes) and who are failing their current regimen (defined as plasma HIV-1 RNA ≥ 400 copies/mL).

Once eligibility had been confirmed and availability of OBR was confirmed, participants were enrolled to either of the 2 cohorts as following:

- Cohort 1: Randomized in a 2:1 ratio to receive oral LEN or placebo for 14 days starting on Day 1, while they continued their existing regimen

OR

- Cohort 2: Enrolled to receive oral LEN together with an OBR

The primary efficacy endpoint was the proportion of participants in Cohort 1 achieving a reduction in HIV-1 RNA of ≥ 0.5 log10 copies/mL from baseline at the end of the Functional Monotherapy Period.

Results showed that a significantly greater percentage of participants receiving LEN had a reduction in HIV-1 RNA of ≥ 0.5 log10 copies/mL from baseline at the end of the Functional Monotherapy Period compared to those receiving placebo (Proportional Difference = 70.8%, 95% CI:34.9%, 90.0%; p-value < 0.0001).

2.4.2 Safety Results

Safety database included three datasets: Study GS-US-200-4625 (main study), Study GS-US-200-4334, and "Pooled Studies GS-US-200-4538 and GS-US-200-5709".

"Study GS-US-200-4625"

In interim analysis (IA) at Week 52, the median duration for Cohorts 1 and 2 was 484 days and 317 days, respectively. During the Functional Monotherapy Period for Cohort 1, the percentages of participants who experienced AEs were 37.5% in LEN group and 25.0% in placebo group. Nausea was the only AE reported in more than one participant (LEN 12.5% vs placebo 0). No deaths, serious adverse events (SAEs), AEs leading to discontinuation of study drug, or Grade 3 or higher AEs were reported during this period.

The percentage of participants who received LEN in all Cohorts 1 and 2 who experienced AEs was 93.1% (67 of 72 participants). Adverse events reported in over 10% of 72 participants were injection site reactions (swelling, pain, erythema, nodule and induration), followed by diarrhea, nausea and COVID-19. Grade 3 or higher AEs were all injection site reactions. A total of eight patients (11.1%) were reported SAEs by Week 52, and only COVID-19 was reported for more than one participant (2 participants). One participant in Cohort 2 died with anal cancer on Study Day 90. None of these SAEs led to discontinuation of study drug or were considered related to study drug.

"Study GS-US-200-4334" and "Pooled Studies"

The median duration of exposure to *Study GS-US-200-4334*, 157 participants, was 66.3 weeks in the LEN total group by Week 54 analysis. LEN regimen of all combination groups in Study GS-US-200-4334 was the same with the regimen in Study GS-US-200-4625. Oral daily Biktarvy® (BVY) was used as a comparator. The percentages of participants who experienced AEs were 87.9% in LEN total group while 8.3% (13/157) participants experienced Grade 3 or higher AEs. Adverse events reported in over 10% of 72 participants were injection site reactions (erythema, swelling, pain, nodule), followed by headache and nausea. The frequency of injection site reactions, headache and nausea in LEN total group was higher than in BVY group. None of AEs of Grade 3 or higher were reported for more than 1 participant. No deaths were reported by Week 54. Serious AEs were reported for 6.4% (10/157 participants) in the LEN total group, and 5 of 10 were categorized to System Organ Class "Infections and infestations". None of SAEs were reported for more than 1 participant. All were considered not related to the study drugs.

A total of 55 participants received at least 1 dose of study drug in “Pooled Studies” with median duration of 135 days. The percentages of participants who experienced AEs were 92.7% in LEN group (N=55) and 85.0% in placebo group (N=20).

In the pooled analysis, the 3 most commonly reported AEs (> 5% of participants) in each treatment group were all injection site reactions. Grade 3 or higher AEs were reported one in each group. In LEN group, tibia fracture was reported as the only Grade 3 or higher AE and the only one SAE. There were no deaths.

2.5 Bridging Study Evaluation

PK parameters comparison between Asian and bnon-Asian were not be provided, but instead of the plasma concentrations of the two groups at different time points. Although the drug concentrations in 15 Asians tend to be higher and most Asians were from Thailand, the geometric mean ratio for Asian versus White were almost 100%, indicating the similarity between the two groups. The 90% CIs of the plasma concentrations can also be expected to have no clinical significance.

Clinical evaluation of ethnic difference was based on Study GS-US-200-4625. A total of 15 Asian participants were enrolled from sites in Thailand (11 participants), Taiwan (1 participant), Japan (2 participants), and Canada (1 participant), and only 2 Asians were randomized to LEN group of Cohort 1. The percentage of HIV-1 RNA less than 50 copies/mL at Weeks 26 was 100% of the total 15 Asians, while it was 76.8% (43/56) in non-Asian subgroup. The safety profile was generally comparable between Asians and Non-Asians, regarding the limited participants. Most commonly reported AEs in Asians were injection site reactions and followed by nausea, COVID-19, and diarrhea.

Based on available data, clinical impact of ethnic difference was considered minimal.

2.6 Conclusion

The overall benefit risk balance of Sunlenca® Injection is favorable in combination with other antiretroviral(s), for the treatment of heavily treatment-experienced adults with multidrug resistant HIV-1 infection for whom it is not possible to construct a suppressive anti-viral regimen.

3. Post-Marketing Requirements

Nil.