Taiwan Food and Drug Administration

Assessment Report

Trade Name：莫帕滋膜衣錠 30 毫克/
Vocabria 30 mg film-coated tablets

Active Ingredient：Cabotegravir sodium

License Number：MOHW-PI 028219

Applicant：荷商葛蘭素史克藥廠股份有限公司台灣分公司

Approval Date：110/12/24

Indication：

與 rilpivirine 錠劑併用，短期治療已達病毒學抑制效果(HIV-1 RNA <50 copies/mL)且對 cabotegravir 及 rilpivirine 不具已知或疑似抗藥性之成人的人類免疫不全病毒(HIV)-1 感染症，治療的目的為：1.在投予長效型(LA) cabotegravir 注射劑之前先進行口服導入治療，藉以評估對 cabotegravir 的耐受性。2.為錯過計劃注射 cabotegravir 注射劑時間的成人進行口服治療。

Cabotegravir tablet is indicated in combination with rilpivirine tablet, for short-term the treatment of HIV-1 infection in adults who are virologically suppressed (HIV-1 RNA<50 copies/mL) and have no known or suspected resistance to either rilpivirine or cabotegravir.
The combination of tablet form cabotegravir+rilpivirine is for:

1. **oral lead-in to assess tolerability of cabotegravir+rilpivirine prior to administration of long acting cabotegravir injection plus long acting rilpivirine injection,**
2. **oral therapy for adults who will miss planned dosing with cabotegravir injection plus rilpivirine injection.**

Background Information

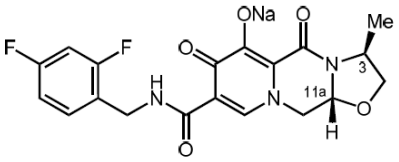
Trade Name	莫帕滋膜衣錠 30 毫克 / Vocabria 30 mg film-coated tablets
Active Ingredient(s)	Cabotegravir sodium
Applicant	荷商葛蘭素史克藥廠股份有限公司台灣分公司
Dosage Form & Strengths	膜衣錠 30mg/tablet
Indication	與 rilpivirine 錠劑併用，短期治療已達病毒學抑制效果(HIV-1 RNA <50 copies/mL)且對 cabotegravir 及 rilpivirine 不具已知或疑似抗藥性之成人的人類免疫不全病毒(HIV)-1 感染症，治療的目的為：1.在投予長效型(LA) cabotegravir 注射劑之前先進行口服導入治療，藉以評估對 cabotegravir 的耐受性。2.為錯過計劃注射 cabotegravir 注射劑時間的成人進行口服治療。 Cabotegravir tablet is indicated in combination with rilpivirine tablet, for short-term the treatment of HIV-1 infection in adults who are virologically suppressed (HIV-1 RNA<50 copies/mL) and have no known or suspected resistance to either rilpivirine or cabotegravir. The combination of tablet form cabotegravir+rilpivirine is for: 1. oral lead-in to assess tolerability of cabotegravir+rilpivirine prior to administration of long acting cabotegravir injection plus long acting rilpivirine injection, 2. oral therapy for adults who will miss planned dosing with cabotegravir injection plus rilpivirine injection.
Posology	詳見仿單
Pharmacological Category ATC Code	J05AJ04

2. Summary Report

2.1 Chemistry, Manufacturing and Controls Evaluation

2.1.1 Drug substance

The drug substance, cabotegravir sodium, is chemically designated as sodium (*3S,11aR*)-N-[(2,4-difluorophenyl)methyl]-6-hydroxy-3-methyl-5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-a]pyrido[1,2-d]pyrazine-8-carboxamide. The molecular formula and the relative molecular mass for cabotegravir sodium are $C_{19}H_{16}F_2N_3NaO_5$ and 427.33 g/mol, respectively. The chemical structure of cabotegravir sodium is shown below:



It is a white to almost white solid. The structure of cabotegravir sodium is confirmed by ^{1}H-NMR, ^{13}C-NMR, elemental analysis, mass spectroscopy, infrared spectrum and single crystal X-ray crystallography.

The specification for the drug substance includes description, identification, solid state form, cabotegravir sodium content, sodium content, impurities, enantiomer content, diastereomer content, residual solvent, water content and particle size.

2.1.2 Drug product

The drug product is supplied for oral administration use as an immediate release tablet containing 30 mg of cabotegravir free acid (equivalent to 31.62 mg of cabotegravir sodium). All excipients are well known ingredients and suitable for proposed formulation.

The specification for the drug product includes description, identification, uniformity of dosage units, cabotegravir content, impurities, dissolution and microbial limit tests. Analytical methods are described well and validated.

Stability studies of drug product under long term conditions (5°C and 30°C/75% RH) and accelerated condition (40°C/75% RH) have been carried out.

2.2 Preclinical Pharmacology/Toxicology Evaluation

2.2.1 Pharmacological Studies

Cabotegravir, simply as CAB, is a potent and selective inhibitor of HIV Integrase Strand Transfer Inhibitor (INSTI) and inhibits the integrase catalyzed viral DNA strand transfer with IC_{50} values in the nanomolar range. CAB is a potent antiviral agent when tested in various *in vitro* assays. Additionally, the IC_{50} values of CAB for viral replication of NIH reference strains consisting of 24 strains of HIV-1 and 4 strains of HIV-2 in PBMC assays and 3 HIV-1 strains

in monocyte-derived macrophage assays were in nanomolar concentration range.

In vitro cytotoxicity studies provided a selectivity index of ≥10,000 for CAB compared with the HIV-1 antiviral potency in PBMCs. In a viral integrase susceptibility assay using the integrase coding region from 13 clinically diverse subtype B isolates, CAB demonstrated antiviral potency like that observed for laboratory strains. CAB also showed anti-HIV activity (susceptibility) equivalent to wild-type virus (fold change [FC] <5) against 22 of 25 INI-resistant mutant viruses with single mutations. No significant safety issues were identified in the nonclinical safety pharmacology studies.

2.2.2 Toxicological Studies

Repeated-dose oral toxicity studies were conducted in rats and monkeys for up to 26 weeks and 39 weeks, respectively. In addition, a 3-month repeated-dose toxicity study was conducted in rats by IM or SC. Overall, CAB was tolerated without significant adverse effects in rats and monkeys. No additional adverse effects were noted except for dose-proportional signs of redness, swelling, and inflammation following SC and IM injections. No new target organ toxicities were identified via monthly SC injection, monthly IM injection, or weekly SC injection.

The safety assessment of the parenteral route of administration for the proposed drug product is considered “bridged” to the overall oral nonclinical development program through the conduct of the definitive 13-week rat injection study. CAB was negative in *in vitro* and *in vivo* genotoxicity studies.

CAB has demonstrated no carcinogenic potential in conventional oral 2-year studies in mice and rats. No CAB-related effect on fertility was observed in male and female rats at oral doses up to 1000 mg/kg/day. Embryo-fetal toxicity studies were conducted in rats and rabbits at oral doses up to 1000 and 2000 mg/kg/day, respectively. A decrease in fetal weights at the high dose level was observed. At the mid-dose 5 mg/kg/day, maternal exposure levels were approximately 4-fold those reached in patients treated orally at 30 mg/day. In rabbits, there were no treatment-related effects on embryo-fetal development at all dose levels.

In PPND studies in rats, CAB at 1000 mg/kg/day delayed the onset of parturition, and in some rats, this delay was associated with an increased number of stillbirths and neonatal mortalities immediately after birth. There were no alterations to the growth and development of surviving offspring. When rat pups born to CAB-treated dams (1000 mg/kg/day) were cross-fostered at birth and nursed by control mothers, a similar incidence of stillbirths and neonatal mortalities was observed. There was no effect on neonatal survival of control pups nursed from birth by CAB-treated mothers, suggesting effects were related to in utero exposure, not lactational exposure. No study was conducted with the CAB-RPV combination. RPV is already marketed

in Taiwan, and animal studies have shown no effect on reproductive function and embryo-fetal development.

2.3 Clinical Pharmacology Evaluation

2.3.1 General Pharmacodynamics and Pharmacokinetics

Cabotegravir is rapidly absorbed following oral administration, with median T_{max} at 3 hours post dose for tablet formulation. With once daily dosing, pharmacokinetic steady-state is achieved by 7 days. Cabotegravir may be administered with or without food. Food increased the extent of absorption of cabotegravir. Bioavailability of cabotegravir is independent of meal content: high fat meals increased cabotegravir $AUC_{(0-\infty)}$ by 14% and increased C_{max} by 14% relative to fasted conditions. These increases are not clinically significant. The absolute bioavailability of cabotegravir has not been established.

Cabotegravir pharmacokinetics is similar between healthy and HIV-infected subjects. The PK variability of cabotegravir is moderate. In Phase I studies in healthy subjects, between-subject CV% for AUC, C_{max}, and C_{tau} ranged from 26 to 34% across healthy subject studies and 28 to 56% across HIV-1 infected subject studies. Within-subject variability (CV%) is lower than between-subject variability.

Cabotegravir is highly bound (>99%) to human plasma proteins, based on *in vitro* data. Following administration of oral tablets, the mean apparent oral volume of distribution (V_z/F) in plasma was 12.3 L. In humans, the estimate of plasma cabotegravir V_c/F was 5.27 L and V_p/F was 2.43 L. These volume estimates, along with the assumption of high bioavailability, suggest some distribution of cabotegravir to the extracellular space.

Cabotegravir is present in the female and male genital tract. Median cervical and vaginal tissue:plasma ratios ranged from 0.16 to 0.28 and median rectal tissue:plasma ratios were ≤0.08 following a single 400 mg intramuscular injection (IM) at 4, 8, and 12 weeks after dosing. Cabotegravir is present in cerebrospinal fluid (CSF). In HIV-infected subjects receiving a regimen of cabotegravir injection plus rilpivirine injection, the cabotegravir CSF to plasma concentration ratio [median (range)] (n=16) was 0.003 (range: 0.002 to 0.004) one week following a steady-state long acting cabotegravir (Q4W or Q8W) injection. Consistent with therapeutic cabotegravir concentrations in the CSF, CSF HIV-1 RNA (n=16) was <50 c/mL in 100% and <2 c/mL in 15/16 (94%) of subjects. At the same time point, plasma HIV-1 RNA (n=18) was <50 c/mL in 100% and <2 c/mL in 12/18 (66.7%) of subjects.

Cabotegravir is primarily metabolized by UGT1A1 with a minor UGT1A9 component. Cabotegravir is the predominant circulating compound in plasma, representing > 90% of plasma total radiocarbon. Following oral administration in humans, cabotegravir is primarily

eliminated through metabolism; renal elimination of unchanged cabotegravir is low (<1% of the dose). Forty-seven percent of the total oral dose is excreted as unchanged cabotegravir in the feces. Twenty-seven percent of the total oral dose is excreted in the urine, primarily as a glucuronide metabolite (75% of urine radioactivity, 20% of total dose).

Cabotegravir has a mean terminal half-life of 41 h and an apparent clearance (CL/F) of 0.21L per hour.

2.3.2 Interaction Studies

Given the pathways of metabolism and elimination of CAB are independent of formulation and route of administration, and because plasma CAB concentrations achieved with the CAB LA Q8W or Q4W regimen are within the range of concentrations achieved with oral CAB 10 mg to 30 mg once daily, results from oral DDI studies can be used to inform the recommendations for CAB LA, when used with RPV LA.

CAB is contraindicated with the UGT1A1 inducers rifampicin, rifapentine, carbamazepine, oxcarbazepine, phenobarbital, and phenytoin due to potential for loss of therapeutic effect and development of resistance. CAB LA is contraindicated with rifabutin because rifabutin may decrease CAB plasma concentrations. There is not a significant drug interaction between CAB and RPV, the 2 components of the regimen. No dose adjustments are needed for CAB when co-administered with UGT or CYP inhibitors. Antacids containing polyvalent cations must be administered at least 2 hours before or 4 hours after oral CAB.

Because of the low DDI liability for CAB as perpetrators, there are no comedications that require dose adjustment when given together with CAB and there are no DDI limitations to the antiretroviral regimens that can be given after discontinuation of CAB. CAB did not significantly change ethinyl estradiol and levonorgestrel plasma concentrations to a clinically relevant extent. No dose adjustment of oral contraceptives is necessary.

2.3.3 Special Populations

Population pharmacokinetic analyses revealed no clinically relevant effect of gender or BMI on the exposure of cabotegravir, therefore no dose adjustment is required on the basis of gender or BMI. Population pharmacokinetic analysis of cabotegravir revealed no clinically relevant effect of age on cabotegravir exposure. Pharmacokinetic data for cabotegravir in subjects of >65 years old are limited.

No clinically important pharmacokinetic differences between subjects with severe renal impairment (CrCL <30 mL/min and not on dialysis) and matching healthy subjects were observed. No dosage adjustment is necessary for patients with mild to severe renal impairment

(not on dialysis). Cabotegravir has not been studied in patients on dialysis.

No clinically important pharmacokinetic differences between subjects with moderate hepatic impairment and matching healthy subjects were observed. No dosage adjustment is necessary for patients with mild to moderate hepatic impairment (Child-Pugh Score A or B). The effect of severe hepatic impairment (Child-Pugh Score C) on the pharmacokinetics of cabotegravir has not been studied.

2.4 Clinical Efficacy and Safety Evaluation

2.4.1 Efficacy Results

Cabotegravir tablet is used as oral lead-in prior to administration of cabotegravir injection. The efficacy of CAB tablet was supported with the dossier of whole IM CAB + RPV regimen.

Two Phase 3 pivotal studies (201584 and 201585) and one Phase 3b supportive study (207966) were reviewed to evaluate the efficacy of cabotegravir for the claimed indication.

Study 201584 was designed to demonstrate non-inferior antiviral activity of switching to cabotegravir + rilpivirine Q4W (CAB+RPV group) after an Induction Phase of ABC/DTG/3TC compared with remaining on CAR (Abacavir sulfate /Dolutegravir /Lamivudine [ABC/DTG/3TC]) in HIV-1, ART-naïve adult subjects. Study 201585 was designed to demonstrate non-inferior antiviral activity of switching to CAB + RPV Q4W compared with remaining on CAR in HIV-1 infected ART- experienced subjects. Following the screen period, HIV-1 infected patients who were on a stable ARV regimen containing 2 NRTIs plus an INI, NNRTI, or a PI were eligible to enter the 52-week maintenance phase.

In study 201584, virologic failure rate was 2.1% in the CAB + RPV Q4W group and 2.5% in the CAR group in the ITT population. In 201585, virologic failure rate was 1.6% in the CAB + RPV Q4W group and 1.0% in the CAR group in the ITT population. Within each of the individual studies 201584 and 201585, non-inferiority of CAB+ RPV to CAR in the proportion of subjects having plasma HIV-1 RNA ≥50 c/mL at Week 48 using the Snapshot algorithm was achieved because the upper bound of the 95% CI for the adjusted treatment difference below 6%. The adjusted treatment difference (95% CI) between CAB + RPV and CAR in the ITT-E Population was -0.4 (-2.8, 2.1) for Study 201584 and 0.6 (-1.2, 2.5) for Study 201585. Results for the PP population were similar to those for the ITT-E Population in both studies. In the pooled analysis of Studies 201584 and 201585 using a pre-specified non-inferiority margin of -4%, once-monthly CAB + RPV is non-inferior to CAR in maintaining virologic suppression in HIV-1 infected subjects, with <2% of subjects having plasma HIV-1 RNA ≥ 50 c/mL at Week 48 per the Snapshot algorithm (adjusted difference 0.2 [-1.4, 1.7]).

Study 207966 was designed to demonstrate the non-inferior antiviral activity of CAB + RPV every 8 weeks (Q8W) compared with CAB + RPV every 8 weeks (Q4W). In the ITT population, 1.7% of subjects in the Q8W group and 1.0% of subjects in the Q4W group reached plasma HIV-1 RNA ≧50 c/mL at Week 48. The primary analysis demonstrated that Q8W CAB LA + RPV LA was noninferior to Q4W CAB LA + RPV LA in maintaining virologic suppression in HIV-1 infected subjects at Week 48, with few subjects having plasma HIV-1 RNA ≥50 c/mL at Week 48 in either group for the ITT-E population. The upper bound of 95% CI for the adjusted treatment difference between Q8W and Q4W was 2.2%, which was less than the pre-defined non-inferiority margin of 4%. Results for the PP population were similar to those for the ITT-E Population.

2.4.2 Safety Results

The 3 most commonly reported AEs for the CABOTEGRAVIR + RPV were injection site pain, nasopharyngitis, and upper respiratory tract infection. There were more Grade 4 AEs in CAB+RPV group compared with CAR group, including HAV infection, CPK increased, lipase increased, etc. The common AEs or Grade 3-5 were similar between Q8W and Q4W groups. All deaths were considered not to be related to study drug. The most frequently reported SAE in pooled Phase III studies was HAV infection. The proportion of subjects having liver monitoring/stopping events was higher in CAB+RPV group in all studies compared to CAR group. Almost all events were related to viral hepatitis infection. The severity of hepatitis or hepatocellular injury was not related to dosage, duration or dosing interval (Q4W or Q8W IM). The status of viral hepatitis infection and liver function should be monitored during use. Although QT prolongation had been reported in previous trials of oral rilpivirine, ECG monitoring did not reveal occurrence in current CAB+RPV trials.

2.5 Bridging Study Evaluation

A cross-study comparison indicated that, following a single oral dose of CAB 30 mg, the Cmax and AUC were 4.70 μg/mL and 70.10 μg*h/mL, respectively, in Japanese, and were 2.97 μg/mL and 43.60 μg*h/mL in the West. The exposure tended to be higher (1.61-fold) in the HIV-1 infected subjects in Japan. A population pharmacokinetic analysis also presented there was a trend to higher (1.23 to 1.43-fold) CAB steady-state Cmax, AUC(0-τ) and Cτ in the North East Asia cohort (n=20) compared with the Not-North East Asia cohort (n=1627). However, since the robust relationships between CAB concentration and efficacy or safety effects have not been observed and established, and the PK/PD correlation results of Japanese were within the range of overall population, the magnitude of the difference in exposure was not considered to be clinically significant.

There were 44 East Asians participating Study 201584 and 201585. Twenty-two East Asian patients received CAB+RPV. These Asian subjects receiving CAB+RPV were slightly older

than other Asian subjects receiving CAR and Western subjects. Both East Asian subjects in CAB+RPV group and CAR group had less body weight than Western subjects. In the East Asian subgroup, none of 44 subjects had a plasma HIV-1 RNA ≥50 c/mL at Week 48. No East Asian subjects had confirmed virologic failure. Higher proportion of withdrawal was noted in East Asian Subgroup (Asian: n=3, 14%; Overall: n=51, 9%). Two subjects withdrew due to adverse events (one was due to HBV and the other was due to memory loss). Among the 15 subjects meeting the liver monitoring/stopping criteria, two are East Asian subjects. In general, there was no ethnic difference with clinical impact between Asian and other subjects.

2.6 Conclusion

Based on review of the submitted package, the review team considered Vocabria demonstrates a favorable risk-benefit profile with enough evidence to recommend regular approval for the following indication:

Vocabria tablet is indicated in combination with rilpivirine tablet for treatment of HIV-1 infection in adults who are virologically suppressed (HIV-1 RNA <50 copies/mL) and have no known or suspected resistance to either cabotegravir or rilpivirine, for use as:

-oral lead-in to assess the tolerability of cabotegravir prior to administration of cabotegravir injection.

-oral therapy for patients who will miss planned injection dosing with cabotegravir.

3. Post-Marketing Requirements

N/A