Taiwan Food and Drug Administration

Assessment Report

Trade Name：Rukobia 600mg prolonged-release tablets

Active Ingredient：Fostemsavir

License Number：MOHW-PI 028062

Applicant：荷商葛蘭素史克藥廠股份有限公司台灣分公司

Approval Date：2021/04/06

Indication：
RUKOBIA 合併其他抗反轉錄病毒藥物，適用於治療已有廣泛治療經驗(heavily treatment-experienced)且具多重抗藥性之第一型人類免疫不全病毒(HIV-1)感染症的成人病人，且因抗藥性、無法耐受或安全的考量而致目前之抗反轉錄病毒療法失敗。

RUKOBIA, in combination with other antiretroviral(s), is 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 their current antiretroviral regimen due to resistance, intolerance, or safety considerations.

Background Information

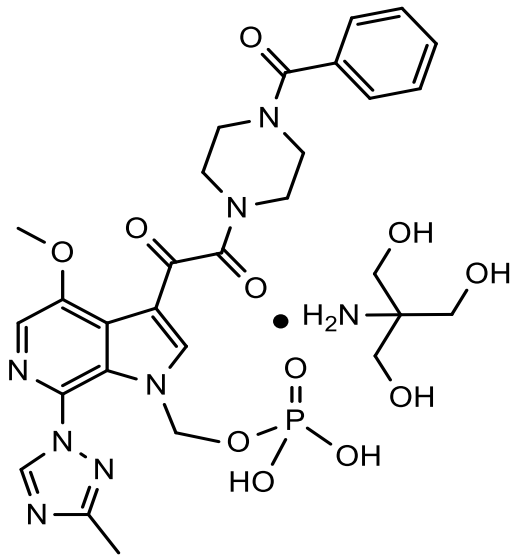
Trade Name	羅克霸持續性藥效錠 600 毫克 / Rukobia 600mg prolonged-release tablets
Active Ingredient(s)	Fostemsavir
Applicant	荷商葛蘭素史克藥廠股份有限公司台灣分公司
Dosage Form & Strengths	持續性藥效錠 prolonged-release tablets/ 600mg
Indication	RUKOBIA 合併其他抗反轉錄病毒藥物，適用於治療已有廣泛治療經驗(heavily treatment-experienced)且具多重抗藥性之第一型人類免疫不全病毒(HIV-1)感染症的成人病人，且因抗藥性、無法耐受或安全的考量而致目前之抗反轉錄病毒療法失敗。 RUKOBIA, in combination with other antiretroviral(s), is 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 their current antiretroviral regimen due to resistance, intolerance, or safety considerations.
Posology	RUKOBIA 的建議劑量為每日兩次，每次口服一顆 600 毫克錠劑，可隨食物或不隨食物服用。錠劑應整顆吞服，不可咀嚼、研碎或剝開錠劑。 The recommended dosage of RUKOBIA is one 600-mg tablet taken orally twice daily with or without food. Swallow tablets whole. Do not chew, crush, or split tablets
Pharmacological Category ATC Code	J05AX29

2. Summary Report

2.1 Chemistry, Manufacturing and Controls Evaluation

2.1.1 Drug substance

The drug substance, fostemsavir tromethamine, is chemically designated as (3-((4-benzoyl-1-piperazinyl)(oxo)acetyl)-4-methoxy-7-(3-methyl-1*H*-1,2,4-triazol-1-yl)-1*H*-pyrrolo[2,3-c]pyridin-1-yl)methyl dihydrogen phosphate, 2-amino-2-(hydroxymethyl)-1,3-propanediol (1:1). The empirical formula is $C_{25}H_{26}N_7O_8P \cdot C_4H_{11}NO_3$. The molecular weight is 704.6 g/mol. It has the following structural formula:



It is a white to almost white powder. The structure of fostemsavir tromethamine is confirmed by elemental analysis, IR spectrum, ^{1}H-NMR, ^{13}C-NMR, mass spectrum, Raman spectrum, and X-ray crystallography. The specification for the drug substance includes tests for description, identification, residual solvents, water content, residue on ignition, drug-related impurities, and assay.

2.1.2 Drug product

The drug product is a film-coated, prolonged-release tablet for oral administration. Each tablet contains 600 mg of fostemsavir (equivalent to 725 mg fostemsavir tromethamine). All excipients are well known ingredients and suitable for proposed formulation. The specification for the drug product includes appearance, identification, assay, impurities, uniformity of dosage units, dissolution, and microbial limit 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 Preclinical Pharmacology/Toxicology Evaluation

2.2.1 Pharmacological Studies

Fostemsavir is a drug for treating human immunodeficiency virus type 1 (HIV-1) infection in heavily treatment-experienced (HTE) adult patients who demonstrate continuing HIV-1

replication despite ongoing antiretroviral therapy and unable to construct a viable regimen due to multidrug resistance, intolerance, or safety considerations. Fostemsavir is a methyl phosphate prodrug of the active moiety temsavir. Temsavir prevents viral entry by binding to the viral envelope gp120 and interfering with virus attachment to the host CD4 receptor.

Because temsavir binds directly to the virus and not a host cell receptor, the traditional nonclinical pharmacology studies were replaced with clinical virology studies. Both fostemsavir and temsavir have minimal cytotoxicity on human cell lines and PBMCs. The safety pharmacology studies indicated that fostemsavir-related CNS effects presented at overtly toxic or intolerable doses. Fostemsavir exhibited no significant effect on the respiratory system but presented the potential of QT interval prolongation.

2.2.2 Toxicological Studies

In the pivotal repeated-dose toxicity studies, the primary target organs were testis, kidney, adrenal glands in rats, and liver in dogs. Both the data from the pivotal toxicity study and FEED study indicated that fostemsavir has the potential to affect male sexual function at higher exposure (>100 times the maximum recommended human dose). Fostemsavir did not exhibit teratogenic effects but might cause pup mortality through the lactation exposure at higher exposure.

The *in vitro* and *in vivo* genotoxicity studies presented negative results. Fostemsavir did not exhibit carcinogenicity in mice and rats. In addition, fostemsavir had the potential to cause skin sensitization and eye irritation. The clinical studies supported the selection of the clinical dose and dosing frequency.

2.3 Clinical Pharmacology Evaluation

2.3.1 General Pharmacodynamics and Pharmacokinetics

Rukobia is a prolonged-release tablet for the treatment of adults with multidrug resistant HIV-1 infection. The drug substance of Rukobia is fostemsavir, which is the prodrug of temsavir. The recommended dose is 600 mg of fostemsavir twice daily with or without food. The absolute bioavailability of temsavir was 26.9%. Following oral administration, the T_{max} of fostemsavir was reached at 2 hour, and food delayed the time to 4 hour (standard meal) or 6.5 hour (high-fat meal). The exposure (C_{max} and AUC_{tau}) of fostemsavir was slightly greater than dose proportional over the range of 600 mg to 1800 mg, and the pharmacokinetics of temsavir following administration of fostemsavir are similar between healthy and HIV-1–infected subjects. The V_{ss} of temsavir following IV administration was 29.5 L. The human plasma protein binding was 88.4%.

Metabolism was the major route of elimination, containing hydrolysis (esterases; 36.1% of oral

dose), oxidation (CYP3A4; 21.2% of oral dose), other non-CYP3A4-mediated pathway and glucuronidation (UGT; <1% of oral dose). Following oral administration, 51% of dose excreted in urine (unchanged drug: 1.9%), and 33% of dose excreted in feces (unchanged drug: 1.9%). Plasma fostemsavir $T_{1/2}$ following administration was approximately 9 ~ 11 hours.

2.3.2 Interaction Studies

Temsavir was a substrate of CYP3A, P-glycoprotein, and breast cancer resistance protein (BCRP). Also, temsavir was an inhibitor of BCRP and OATP1B1/OATP1B3. According the DDI study, strong CYP3A inducers significantly decreased the exposure of temsavir, thus, coadministration of fostemsavir with drugs that are strong CYP3A inducers was contraindicated. There was no clinically significant effect on the plasma concentrations of temsavir when fostemsavir is co-administered with drugs that are moderate CYP3A inducers, strong CYP3A inhibitors, and P-gp and/or BCRP inhibitors.

2.3.3 Special Populations

Age and gender had no significant impact on PK of temsavir. However, data were limited in subjects aged 65 years or older. No dose adjustment was required in patients with renal impairment and patients with hepatic impairment.

2.4 Clinical Efficacy and Safety Evaluation

2.4.1 Efficacy Results

Study 205888 was reviewed to evaluate the efficacy of fostemsavir 600 mg prolonged-release tablets, in combination with other antiretroviral agents, indicated for the treatment of heavily treatment-experienced (HTE) adults with multidrug resistant HIV-1 infection for whom it is otherwise not possible to construct a suppressive anti-viral regimen due to resistance, intolerance or safety considerations.

Study 205888 was a 2-cohort Phase 3 study: randomized cohort and non-randomized cohort. The randomized cohort provided the primary evidence of efficacy for the proposed indication. For the randomized cohort, subjects must have ≤ 2 classes with at least 1 but no more than 2 fully-active ARVs remaining which can be effectively combined to form a viable new regimen. Subjects without any remaining fully active approved antiretroviral (ARV) may be enrolled in the non-randomized Cohort.

In the randomized cohort, subjects continued their failing ARV regimen and were randomized 3:1 to add fostemsavir 600 mg BID or placebo for 8 days. After Day 8, subjects received open-label fostemsavir 600 mg BID in combination with optimized background therapy (OBT) for at least 96 weeks. The primary efficacy endpoint was the adjusted mean change in log10 HIV-1 RNA (c/mL) of fostemsavir relative to placebo from Day 1 (Baseline) to Day 8. The primary

efficacy analysis was performed using a one-way ANCOVA in the randomized cohort ITT-E Population. The ITT-E Population consisted of all subjects who received at least one dose of study treatment.

A total of 272 subjects were assigned to the randomized cohort (69 in placebo group, 203 in fostemsavir group) and 99 subjects were assigned to the non-randomized cohort. In the primary efficacy analysis, the adjusted mean decline in HIV-1 RNA at Day 8 was 0.791 log10 c/mL for the fostemsavir group versus 0.166 log10 c/mL for placebo. Superiority was demonstrated in the primary efficacy analysis because the 95% CI for the mean difference between the two treatment groups excluded zero and the p-value was statistically significant (difference=-0.625, 95% CI=[-0.810, -0.441], p <0.0001).

2.4.2 Safety Results

The primary safety database generated from the Phase 3 Study 205888 in heavily treatment experienced (HTE) subjects, along with supportive data from the Phase 2b Study 205889 in generally treatment-experienced subjects. A total of 553 subjects (Study 205888 [n=370]; Study 205889 [n=183]) received at least 1 dose of fostemsavir≥1200 mg per-day. The median duration of exposure for participants in the fostemsavir Safety Cohort (those participants in the Phase 2b and Phase 3 studies that received at least one dose of FTR at ≥1200 mg/day) was 116.71 weeks. The most commonly reported AEs in the safety cohort were: diarrhea (20%), nausea (14%), upper respiratory tract infection, nasopharyngitis and headache (13% each). Most drug-related events were Grade 1 or 2 in severity.

In the fostemsavir safety cohort, the most common drug-related AEs were nausea (7%), diarrhea (4%), headache (3%), fatigue (2%), dyspepsia (2%), vomiting (2%), somnolence (1%), insomnia (1%), blood creatinine increased (1%), dizziness (1%), and immune reconstitution inflammatory syndrome (IRIS) (1%). Frequency of Adverse Drug Reactions (causally-related adverse events) of ECG QT prolongation in the Safety Cohort was <1% (2/553). Overall, the frequency of AEs of QT prolongation (regardless of causality) was 1% (7/553). Notably, no ventricular tachyarrhythmias were observed.

The majority of SAEs and fatalities related to complications of AIDS and acute infection. Only one fatal case was considered related to study medication: Immune reconstitution inflammatory syndrome (IRIS) related to recurrent atypical mycobacterial infection.

2.5 Bridging Study Evaluation

The PK parameters in Asian healthy subjects or HIV-1 infected patients presented inconsistently trend (higher or lower than non-Asian healthy subjects or HIV-1 infected patients). This may be due to limited enrolled subjects and body weight (BW) influence. Fostemsavir is hydrolyzed to

temsavir (the active moiety of fostemsavir) primarily by alkaline phosphatase in the intestines. Following absorption, temsavir metabolism is predominantly catalyzed by CYP3A4 and unidentified hydrolytic enzyme(s). Given the multiple enzymes involved in fostemsavir/temsavir clearance and the shallow exposure-response relationship demonstrated during the FTR functional monotherapy phase of the Phase 3 study (205888), conducted in the target HTE population, the ethnic difference in pharmacokinetics between Asian and non-Asian individuals is expected to be minor. However, fostemsavir is a novel first-in-class anti-HIV-1 infection drug, more data needed to be collected.

In the Phase 2b/3 studies, there were 4 subjects of Asian ancestry, including 2 subjects (enrolled from Taiwan and USA) with HTE MDR HIV-1 from Phase 3 Study 205888, and 2 subjects (enrolled from South Africa) with generally treatment-experienced HIV-1 from Phase 2b Study 205889. All the 4 subjects received FTR≧1200mg/day.

Two subjects of Asian ancestry, living with HTE MDR HIV-1 infection and advanced AIDS (baseline CD4 count <20 cells/μL), were included in the FTR Phase 3 study (205888) as part of the Randomized Cohort. Both participants were randomized to the blinded-fostemsavir arm for the eight-day functional monotherapy phase of the study. One of two subjects had a clinically meaningful reduction (>0.5 log10) in baseline HIV-1 RNA at Day 8. Notably, the participant that did not achieve virologic response during the short-term double-blind period had HIV-1 AE subtype, which has demonstrated reduced susceptibility to temsavir (the active moiety of FTR) in the limited number of subtype AE clinical isolates evaluated to date. However, at the Week 96 timepoint, both subjects of Asian ancestry had achieved virologic suppression (HIV-1 RNA <40 c/mL) by Snapshot Analysis on a regimen of open-label FTR (600 mg BID) plus an optimized background therapy. All four subjects of Asian ancestry were included for safety evaluation for ethnic sensitivity. Of note, the 2 subjects from Phase 2b study were not HTE patients, and their FTR dose was more than the proposed dosing regimen. All the AEs reported by the 4 subjects of Asian ancestry were mild in severity (mostly Grade 1), and was generally consistent with the common AEs reported in the FTR Safety Cohort.

There was no obvious ethnic difference based on the limited Asian data. Considered the unmet status for HTE MDR HIV-1 subjects, the bridging study is suggested to be waived. The sponsor was required to collect post-marketing safety and effectiveness data to further detect possible safety signal and resistant profile in Asian.

2.6 Conclusion

Submitted dossiers for CMC, pharmacology/toxicology, PK/PD were adequate and acceptable. This NDA is recommended to be approved. The approval indication is “RUKOBIA, in combination with other antiretroviral(s), is 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 their current antiretroviral regimen due to resistance, intolerance, or safety considerations."

3. Post-Marketing Requirements

To collect post-marketing safety and effectiveness data in Taiwan to further detect possible safety signal, and resistant profile if available.