Taiwan Food and Drug Administration

Assessment Report

Trade Name：吉他韋膜衣錠 / BIKTARVY Tablets

Active Ingredient：bictegravir/emtricitabine/tenofovir alafenamide

License Number：MOHW-PI 027570

Applicant：香港商吉立亞醫藥有限公司台灣分公司

Approval Date：2019/01/07

Indication：BIKTARVY 適用於治療感染第一型人類免疫缺乏病毒（HIV-1）且尚未對嵌入酶抑制劑類藥品、emtricitabine 或 tenofovir 產生抗藥性突變的成人患者。
For the treatment of adults infected with human immunodeficiency virus-1 (HIV-1) without evidence of viral resistance to the integrase inhibitor class, emtricitabine or tenofovir

1. Background Information

Trade Name	吉他韋膜衣錠 / BIKTARVY; Tablets
Active Ingredient(s)	bictegravir/emtricitabine/tenofovir alafenamide
Applicant	香港商吉立亞醫藥有限公司台灣分公司
Dosage Form & Strengths	膜衣錠 50/200/25
Indication	BIKTARVY 適用於治療感染第一型人類免疫缺乏病毒（HIV-1）且尚未對嵌入酶抑制劑類藥品、emtricitabine 或 tenofovir 產生抗藥性突變的成人患者。 For the treatment of adults infected with human immunodeficiency virus-1 (HIV-1) without evidence of viral resistance to the integrase inhibitor class, emtricitabine or tenofovir
Posology	BIKTARVY 的建議劑量為每日一次隨食物或不隨食物口服一錠。(詳見仿單) One tablet taken once daily with or without food.
Pharmacological Category **ATC Code**	J05AR20

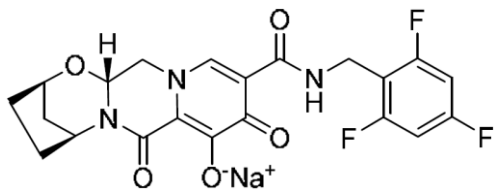
2. Summary Report

2.1 Chemistry, Manufacturing and Controls Evaluation

2.1.1 Drug substance

The fixed-dose combination drug product, Biktavry tablets, contains bictegravir (BIC) sodium, emtricitabine (FTC) and tenofovir alafenamide (TAF) fumarate as drug substances. This section focuses on the information of the only new chemical entity, bictegravir sodium.

The drug substance, bictegravir sodium, is chemically designated as sodium (2*R*,5*S*,13a*R*)-7,9-dioxo-10-[(2,4,6-trifluorobenzyl)carbamoyl]-2,3,4,5, 7,9,13,13a-octahydro-2,5-methanopyrido[1',2':4,5]pyrazino[2,1-b][1,3] oxazepin-8-olate. It has the following structure:



It is an off-white to yellow solid. The molecular formula and the molecular weight are $C_{21}H_{17}F_3N_3NaO_5$ and 471.4, respectively. BIC sodium has 3 chiral centers and is produced as a single stereoisomer. It is slightly hygroscopic. Only one polymorphic form of BIC sodium is identified.

Adequate information of characterization has been provided. The structure of BIC sodium is confirmed by nuclear magnetic resonance spectroscopy, mass spectrometry, infrared spectroscopy, ultraviolet spectroscopy, elemental analysis, and X-ray crystallography. Solid-state properties are built with data generated by X-ray powder diffraction, thermogravimetric analysis, differential scanning calorimetry, and dynamic vapor sorption.

The specification includes tests for appearance, identification, clarity of solution, water content, sodium content, impurity content, assay, residual solvents, organic volatile impurities, enantiomeric purity and particle size.

2.1.2 Drug product

Biktarvy is a tablet containing 50 mg of bictegravir, 200 mg of emtricitabine, and 25 mg of tenofovir alafenamide. The primary packaging is a white HDPE bottle. All excipients are well known ingredients and suitable for the formulation. During the manufacturing process development, optimal process operations were defined and process parameters were established.

Adequate release specification has been presented for the Biktarvy tablets and the test items include appearance, identification, water content, assay, degradation product content, uniformity of dosage units, dissolution and microbiological examination. Analytical methods are described well and validated.

Stability studies of drug product under long term condition (30°C/75% RH) and accelerated condition (40°C/75% RH) have been carried out. The results met the specification.

2.2 Preclinical Pharmacology/Toxicology Evaluation

Biktarvy is a fixed dose combination of antiretroviral drugs bictegravir (BIC), emtricitabine (FTC), and tenofovir alafenamide (TAF). The combination of FTC and TAF (DESCOVY®, 衛部藥輸字第 027274 號) has been approved in Taiwan in 2017. This summary focuses on the nonclinical safety and efficacy of BIC, and the nonclinical safety of BIC in combination with FTC and TAF.

2.2.1 Pharmacological Studies

BIC is an integrase strand transfer inhibitor (INSTI) which inhibits the strand transfer activity of HIV-1 integrase, an HIV-1 encoded enzyme that is required for viral replication. Antiviral activity of BIC against HIV-1 has been demonstrated in T cell lines as well as primary T cells and macrophages. BIC displayed its antiviral activity across multiple HIV clinical isolates. Further studies showed that BIC inhibits HIV-1 integrase enzymatic activity and decreases HIV-1 integration in a T-cell line. BIC exhibited antiviral activity against examined clinical isolate HIV-1 clones containing INSTI resistance as well as other drug resistance mutations. Compared to another INSTI, elvitegravir, BIC had high barriers to resistance.

Weak cytotoxicity of BIC toward T cell lines, primary T cells and macrophages, and in non-target cell lines and primary cells was observed. No selective antiviral activity of BIC was observed against the examined non-HIV viruses. No significant effects of BIC on safety endpoints in regard to respiratory and central nervous system in rats, and cardiovascular system in monkeys as well as in vitro hERG assay, were observed up to the highest dose examined.

2.2.2 Toxicological Studies

In a rat 26-week repeat-dose toxicology study, no adverse changes were noted up to the highest dose examined. In a monkey 39-week repeat-dose toxicology study, increased alanine aminotransferase and gamma glutamyltransferase, and hepatobiliary changes in both dosing and recovery stage were observed in the highest dosing group; the middle dose was determined as the NOAEL of this study.

All 3 segments of the reproductive and developmental toxicology studies in rats revealed no significant changes in BIC-treated animals up to the highest dose examined. On the other hand, an embryo-fetal developmental toxicity study in rabbits showed maternal toxicity in the highest dosing group; the middle dose was determined as the NOAEL of this study.

BIC was considered non-genotoxic based on the bacterial reverse mutation assay, in vitro mammalian chromosome aberration test and in vivo rat bone marrow micronucleus assay. No carcinogenicity of BIC was observed in rats and in a rasH2 transgenic mouse model up to the highest dose examined.

An in vivo repeat-dose study on skin in pigmented rats demonstrated no phototoxicity of BIC up to the highest dose examined. No specific immunotoxicity studies were

conducted with BIC; there were no findings in the repeat-dose toxicity studies with BIC to indicate an immunological concern. Several potential and specified impurities were adequately evaluated by the bacterial reverse mutation assay and repeat-dose toxicology studies. Based on the mechanism of action and the toxicity profiles of individual agents, it is acceptable that there is no toxicology study conducted with BIC in combination with FTC and TAF.

2.3 Clinical Pharmacology Evaluation

2.3.1 General Pharmacodynamics and Pharmacokinetics

Biktarvy fixed-dose combination (FDC) tablet contains three drug substances, bictegravir (BIC) 50 mg, emtricitabine (FTC, F) 200 mg and tenofovir alafenamide (TAF) 25 mg. The FDC combination product is indicated for the treatment of HIV-1 infection in adults with no known mutations associated with resistance to the individual components of BIC/FTC/TAF. The recommended dosage of Biktarvy is one tablet taken orally once daily with or without food.

As the FTC and TAF have been already on the market and only BIC belongs to new chemical entity, the following description will focus on PK characteristic of BIC. The T_{max} was reached rapidly (2.0-4.0 hours). The exposure of bictegravir, emtricitabine and tenofovir (TFV) were not notably affected each other when combination usage, thus the fixed combination was feasible. BIC had high plasma protein binding rate (99.75%) and the blood/plasma ratio was 0.64. CYP3A and UGT1A1 were the mainly metabolized enzymes, and they were considered to play an approximately equal role in the clearance of BIC. The mass balance study showed that BIC was recovered from feces (60.3%) and urine (35.0%). Many metabolites were detected in urine and feces, and metabolism was the major clearance pathway for BIC in humans. Based on population PK analysis, the BIC terminal elimination half-life was 17.3 hours..

2.3.2 Interaction Studies

BIC was OCT2 and MATE1 inhibitor, thus co-administered OCT2 and MATE1 substrate with Biktarvy may increase their plasma concentration. Strong CYP3A and UGT1A1 inducer or inhibitor may significant decrease or elevate the BIC exposure; therefore, the co-administration with Biktarvy and aforementioned class drug was not recommended. Medications or oral supplements containing polyvalent cations (e.g., Mg, Al, Ca and Fe) may decrease the exposure of BIC, please referred to the labeling to see the detailed alternative regimen.

2.3.3 Special Populations

The renal impairment study showed that severe renal dysfunction did not significantly

alter the BIC PK. However, the FTC exposure had significant increase in severe renal impairment patients, thus Biktarvy (B/F/TAF) was administered without dose adjustment in patients with Clcr ≥ 30 mL/min, but not recommended in patients with renal impairment < Clcr 30 mL/min. Based on hepatic impairment study, moderate hepatic impairment did not have a clinically meaningful effect on the PK of BIC. Therefore, no dosage adjustment of Biktarvy is recommended in patients with mild (Child- Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment. Biktarvy is not recommended in patients with severe hepatic impairment.

2.4 Clinical Efficacy and Safety Evaluation

2.4.1 Efficacy Results

The sponsor provided 2 phase III studies for the treatment-naïve HIV infected adult patients (study GS-US-380-1489 and GS-US-380-1490), along with 2 phase III studies for the treatment-experienced, virologically suppressed HIV infected adult patients (study GS-US-380-1844 and GS-US-380-1878). The treatment periods in these studies were 144 weeks, and 48-week interim reports were provided in this application.

The efficacy of B/F/TAF for treatment of HIV-1 infection in ART-naïve adults is supported by two Phase 3, randomized (1:1), double-blind, active-controlled, non-inferior studies (GS-US-380-1489 and GS-US-380-1490). In Study GS-US-380-1489, the primary analytical results showed the percentages of subjects in the FAS (n=629) with HIV-1 RNA<50 copies/mL at week 48 of B/F/TAF FDC was non-inferior to ABC/DTG/3TC (92.4% vs. 93.0%; difference: -0.6%, 95.002% CI: -4.8% to 3.6%; non-inferiority margin: -12%). In Study GS-US-380-1490, the primary analytical results showed the percentages of subjects in the FAS (n=645) with HIV-1 RNA<50 copies/mL at week 48 of B/F/TAF FDC was non-inferior to DTG+F/TAF (89.4% vs. 92.9%; difference: -3.5%, 95.002% CI: -7.9% to 1.0%; non-inferiority margin: -12%).

The efficacy of B/F/TAF for the treatment of HIV-1 infection in virologically suppressed adults is supported by two Phase 3, randomized (1:1), active-controlled, non-inferior studies (GS-US-380-1844 and GS-US-380-1878). In study GS-US-380-1844, HIV-1 RNA 1 < 50 copies/mL on a stable regimen for at least 3 consecutive months was required for the enrollments. The primary analytical results showed the percentages of subjects in the FAS (n=563) with HIV-1 RNA≥50 copies/mL at week 48 of B/F/TAF FDC was non-inferior to maintaining ABC/DTG/3TC (1.1% vs. 0.4%; difference: 0.7%, 95.002% CI: -1.0% to 2.8%; non-inferiority margin: 4%). In study GS-US-380-1878, HIV-1 RNA 1 < 50 copies/mL on a stable regimen for

at least 6 consecutive months was required for the enrollments. The primary analytical results showed the percentages of subjects in the FAS (n=577) with HIV-1 RNA≥50 copies/mL at week 48 of B/F/TAF FDC was non-inferior to maintaining baseline regimen (1.7% vs. 1.7%; difference: -0.0%, 95.002% CI: -2.5% to 2.5%; non-inferiority margin: 4%).

In summary, the efficacy of Biktarvy for treatment of HIV infection is acceptable.

2.4.2 Safety Results

In the phase II and phase III clinical trials, a total of 1511subjects have received at least 1 dose of Biktarvy. The most common adverse reactions for Biktarvy in treatment-naïve subjects were diarrhea, nausea, headache, fatigue, dizziness, and insomnia.

The safety profile in treatment-experienced, viorologically suppressed subjects was similar to the treatment naïve subjects. In study GS-US-380-1489 and GS-US-380-1490, total bilirubin abnormalities were reported in 12% of subjects treated with Biktarvy, which was higher than the active comparators. Most events were grade 1 or grade 2. No subject met Hy's Law criteria. Renal AEs and SAEs were reported for similar percentages of subjects between treatment groups in the Phase III studies. There were no reports of proximal renal tubulopathy (including Fanconi syndrome) in any treatment group. The median change of serum creatinine was also similar between treatment groups in the phase III studies.

In summary, the safety of Biktarvy for treatment of HIV infection is acceptable.

2.5 Bridging Study Evaluation

There was no significant PK difference between Japanese and Caucasian subjects (BIC C_{max}: ↑26%; BIC AUC:↑14%; data from study GS-US-380-1991) and the pop-PK analysis showed that race had no significant effect on BIC PK exposure.

The sponsor provided data of 13 treatment-naïve Asians and 63 treatment-experience Asians (mainly are Thailand female) to evaluate the efficacy and safety of Asian population. It showed comparable virological response and safety profile between Asian and non-Asian. Besides, there are no clinically relevant differences in drug exposure between Asian and non-Asian.

From both PK and clinical perspective, the ethnic difference between Asian and non-Asian is considered negligible. The waiver of bridging study is recommended.

2.6 Conclusion

Biktarvy showed a positive benefit-risk profile for the treatment of adults infected with human immunodeficiency virus-1(HIV-1) without evidence of viral resistance to the integrase inhibitor class, emtricitabine or tenofovir. Approval is recommended for this NDA.

3. Post-Marketing Requirements

(1) The sponsor should provide final CSR of study GS-US-380-1489, GS-US-380-1490, GS-US-380-1484, and GS-US-380-1478 after the completion of these studies.

(2) The sponsor should provide CSR of pediatric studies after completion.