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APPLICATION NUMBER:

205395Orig1s000

MEDICAL REVIEW(S)

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Clinical Review

Date	December 19, 2014
From	Sarita Boyd, Pharm.D.
Subject	Clinical Review
NDA/BLA # Supplement#	NDA 205395
Applicant	Janssen
Date of Submission	March 28, 2014
PDUFA Goal Date	January 31, 2015
Proprietary Name / Established (USAN) names	Prezcobix (Darunavir/cobicistat)
Dosage forms / Strength	Tablet / 800 mg of darunavir and 150 mg of cobicistat
Proposed Indication(s)	Fixed dose combination indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults
Recommended:	Approval

1. Introduction

This review summarizes the main issues for NDA 205395, which includes Week 24 safety and efficacy data from Protocol GS-US-216-0130: *A Phase 3b, Open-Label, Single Arm Study to Evaluate the Safety and Efficacy of Cobicistat-boosted Darunavir Plus Two Fully Active Nucleoside Reverse Transcriptase Inhibitors in HIV-1 Infected, Antiretroviral Treatment-Naïve and -Experienced Adults with No Darunavir Resistance-associated Mutations.* Additionally, the review considers data from the bioavailability (BA) and pivotal bioequivalence (BE) studies, TMC114IFD1001and TMC114IFD1003, respectively.

2. Background

Darunavir (DRV) is an HIV protease inhibitor (PI) approved in combination with low-dose ritonavir (RTV), a cytochrome P450 3A (CYP3A) inhibitor that increases DRV exposure. Darunavir coadministered with ritonavir (DRV/r) and other antiretroviral agents is indicated for treatment of HIV-1 infection with two different dosage recommendations based on past treatment experience. Once daily DRV 800 mg with RTV 100 mg is recommended for treatment-naïve and -experienced adults with no DRV resistance-associated substitutions. DRV/r is not available as a fixed-dose combination (FDC) tablet.

Cobicistat (COBI) received approval on September 24, 2014 as a CYP3A inhibitor indicated to increase systemic exposure of DRV (once daily dosing regimen) or atazanavir (ATV) in combination with other antiretroviral agents for treatment of HIV-1 infection. The Applicant

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is proposing approval of a FDC product containing DRV and COBI, two currently approved drugs.

The Applicant has developed darunavir/cobicistat (DRV/co) as a FDC product in collaboration with Gilead Sciences, Inc. The bioequivalence (BE) study results are considered pivotal for approval of this application of DRV/co 800/150 mg as a FDC tablet indicated in combination with other antiretroviral agents for treatment of HIV-1 infection in adults. A clinical trial with DRV/co was not required because DRV and COBI are approved as individual drugs, and pharmacokinetic studies demonstrating bioequivalence of the FDC tablet to the approved, individual components are adequate. Efficacy and safety of DRV/co is extrapolated from DRV/r clinical trials; the link between DRV and COBI as single drugs and DRV/r was established during the COBI NDA review. This NDA includes safety and efficacy results for Protocol GS-US-216-0130 as a supportive clinical trial.

3. CMC/Device

DRV/co FDC tablets contain 800 mg of DRV (b) (4) and 150 mg of COBI (b) (4) The tablets are (b) (4)-shaped and film-coated with the color pink. The core tablet contains the following inactive ingredients: hypromellose, colloidal silicon dioxide, silicified microcrystalline cellulose, crospovidone, and magnesium stearatec. The film coating is composed of (b) (4) Pink, which contains polyvinyl alcohol-partially hydrolyzed, titanium dioxide, (b) (4), (b) (4) iron oxide red, and iron oxide black. The proposed shelf life is 24 months in all climatic zones. Please refer to the CMC Reviews by Drs. Fuqiang Liu and Krishnakali Gosh for complete details.

4. Nonclinical Pharmacology/Toxicology

Nonclinical studies were not conducted with DRV in combination with COBI. The combined use of DRV and COBI is not expected to produce clinically relevant additive or synergistic effects. Additionally, DRV and COBI are approved as single agents to use in combination for the same indication proposed in this NDA. Comprehensive nonclinical programs for single agents DRV and COBI have been conducted by the Applicant and Gilead Sciences, respectively. The nonclinical program for COBI included safety pharmacology, nonclinical pharmacokinetics, and toxicology of COBI as a single agent and in combination with ATV or elvitegravir (EVG). Please refer to the original NDA reviews for DRV and COBI as single agents for complete details.

5. Clinical Pharmacology/Biopharmaceutics

The development program for DRV/co FDC is based on comprehensive development and approval of DRV and COBI as single agents and pharmacokinetic (PK) bridging of DRV/co FDC to the single agents. Study TMC114IFD1001 evaluated relative BA of DRV with two

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different DRV/co 800/150 mg FDC formulations compared to DRV/r 800/100 mg in 36 healthy subjects following repeated once daily dosing under fed conditions. Results from this study led to selection of one of these formulations, with use of a different color coating, to move forward in development. Study TMC114IFD1003 evaluated BE of DRV with the selected DRV/co 800/150 mg FDC formulation compared to DRV 800 mg and COBI 150 mg administered as single agents in 133 subjects following single doses under fasted and fed (standard meal) conditions. Additionally, Study TMC114IFD1003 assessed the effect of a high-fat breakfast on the BA of the selected DRV/COBI FDC formulation (food effect).

Overall, Study TMC114IFD1003 showed acceptable BE of DRV/co FDC compared to the single agents under fasted and fed (standard meal) conditions. Although the study formulation (white) differs from the commercial formulation (pink) in its color coating, the change does not impact the BE study results per the Biopharmaceutics Reviewer, Dr. Minerva Hughes, because the film coating is nonfunctional.

A high-fat meal (vs. fasting) increased the area under the concentration time curve (AUC) and maximum plasma concentration (C_{max}) for DRV by 70% and 127%, respectively, with the FDC. However, absolute DRV C_{max} values overlap for DRV/co FDC administered with either a standard meal (i.e., recommended administration) or a high fat meal. DRV AUCs observed or estimated in the original DRV NDA (with RTV) were comparable or higher than those observed in the DRV/co FDC food effect study. In the original NDA for DRV/r once daily dosing, there were no apparent relationships between DRV exposures and maximum changes in laboratory parameters or occurrence of adverse events (AEs). Therefore, the increased DRV exposures occurring when DRV/co is coadministered with a high fat meal are not expected to be clinically relevant.

Please refer to the Biopharmaceutics Review by Dr. Minerva Hughes and the Clinical Pharmacology Review by Dr. Stanley Au for complete details.

6. Clinical Microbiology

Study GS-US-216-0130 provides supportive virology data for the use of DRV and COBI as single agents in treatment-naïve and -experienced subjects with no DRV resistance-associated substitutions, which are bridged to the FDC via the pivotal, BE study. In the Week 24 analysis of Study GS-US-216-0130, 10 of 313 subjects who received at least 1 dose of study drug (DRV/co) met the criteria for resistance test analysis. One treatment-experienced subject developed a DRV resistance-associated substitution, I84I/V, and one treatment-naïve subject developed a secondary PI substitution, I93I/L. Phenotypic resistance to DRV or other PIs was not seen in either of these subjects or in any other subjects. One treatment-experienced subject developed 2 reverse transcriptase (RT) substitutions, L74I/L and P225H/P, which are associated with resistance to abacavir and didanosine and to efavirenz, respectively. M184I/V was present at baseline and on treatment in this subject. Of note, the subject's background regimen in the study included emtricitabine, tenofovir, and zidovudine. Although interpretation of results is relatively limited in an open-label, single arm trial with Week 24

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results, the low rate of resistance development with DRV/co is consistent with that observed for DRV/r in the same population. Please refer to the Clinical Virology review by Dr. Takashi Komatsu for complete details.

7. Clinical Efficacy

Efficacy Summary

Study GS-US-216-0130 is an ongoing Phase 3b, open-label, single arm, multicenter study evaluating the safety and efficacy of DRV/co (as single agents) coadministered with 2 fully active NRTIs in HIV-1 infected, antiretroviral treatment-naïve (n=295) and treatment-experienced (n=18) adults with no DRV resistance-associated mutations. At baseline, the median age of subjects was 35 years, 11% were female, 40% were non-white, 42% had HIV-1 RNA >100,000 copies/mL, and 19% had CD4+ cell count <200 cells/mm^3. At 24 weeks, 82% of subjects treated with darunavir and cobicistat plus two nucleoside reverse transcriptase inhibitors achieved HIV RNA <50 copies/mL. Although interpretation of clinical efficacy in a single-arm trial is somewhat limited, the results provide support that DRV and COBI have adequate antiviral activity.

7.1 Indication

The proposed indication for DRV/co 800/150 mg FDC is for use in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults. The recommended patient population includes treatment-naïve and -experienced patients with no DRV resistance-associated substitutions, which is the same for DRV/co administered as single agents (see approved prescribing information for TYBOST [cobicistat]) and DRV/r 800/100 mg once daily regimen (see approved prescribing information for PREZISTA [darunavir]).

7.1.1 Methods

The indication is based on clinical pharmacology data from Studies TMC114IFD1001 and TMC114IFD1003, which compared BA and BE of DRV/co FDC to DRV/r and DRV/co as single agents, respectively. See Section 5 for discussion of these studies.

There are no clinical efficacy data with the DRV/co administered as the FDC formulation. Study GS-US-216-0130 provides supportive clinical data for DRV/co administered as single agents, (b) (4).
The efficacy review includes Week 24 data analysis of GS-US-216-0130 using JReview.

7.1.2 Demographics

The full analysis set includes 313 HIV-infected subjects who received at least 1 dose of DRV/co. The majority of subjects were treatment-naïve (n=295) vs. treatment-experienced

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