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APPLICATION NUMBER:

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SUMMARY REVIEW

Cross-Discipline Team Leader Review

Date	December 23, 2014
From	Mary Singer, MD PhD
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	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	Fixed dose combination tablet/ 800 mg darunavir and 150 mg cobicistat
Proposed Indication(s)	Treatment of HIV-1 infection in adults in combination with other antiretroviral agents
Recommended:	*Approval*

1. Introduction

Darunavir, an HIV protease inhibitor, coadministered with ritonavir, was initially approved for treatment of HIV-1 in combination with other antiretroviral agents in June, 2006. Darunavir (Prezista) is currently available as film coated tablets (75, 150, 600, and 800 mg) and as an oral suspension for use in pediatric patients 3 years and older. In treatment-naïve and treatment-experienced adults with no darunavir resistance- associated substitutions, darunavir is dosed as 800 mg with 100 mg ritonavir once daily. In treatment-experienced adults with at least one darunavir resistance-associated substitution, the darunavir dosage is 600 mg coadministered with 100 mg ritonavir twice daily. Pediatric dosing of darunavir with ritonavir is based on weight in patients 3 years of age and older. Darunavir (Prezista) was developed by Janssen Pharmaceuticals, Inc.

Cobicistat was developed by Gilead Sciences as an alternative pharmacokinetic "booster" to ritonavir, and was approved as a single entity on September, 2014 for the indication of increasing systemic exposure of atazanavir or darunavir (once daily dosing regimen) in combination with other antiretroviral agent in treatment of HIV-1 infection. Cobicistat, like ritonavir is a strong CYP3A inhibitor, but is has no antiretroviral activity. Cobicistat was initially approved in 2012 as part of the fixed dose combination tablet, Stribild, which contains cobicistat, elvitegravir, emtricitabine, and tenofovir disoproxil fumarate for treatment of HIV-1.

2. Background

Janssen, in collaboration with Gilead, developed a fixed dose combination tablet containing darunavir 800 mg and cobicistat150 mg. The proposed indication for this fixed dose tablet is treatment of HIV-1 infection in [redacted] (b) (4) -naïve and [redacted] (b) (4) -experienced adults with no darunavir resistance associated substitutions.

The safety and efficacy of the darunavir/cobicistat fixed dose combination tablet was based on that of the individual approved products, darunavir (in combination with low dose ritonavir used to increase darunavir exposure by virtue of its CYP3A inhibitory activity) and safety and activity of cobicistat. The safety and efficacy of darunavir in combination with ritonavir was based on randomized controlled trials of darunavir/ritonavir in treatment-naïve and treatment-experienced HIV-infected adults and pediatric patients, as reviewed for NDAs 21976 and 202895. The safety and activity of cobicistat was based on a trial comparing safety and efficacy of atazanavir/cobicistat (300 mg/100 mg) to atazanavir/ritonavir (300 mg/100 mg) in treatment-naïve adults, as well as on pharmacokinetic bridging data which showed atazanavir exposures similar to that when atazanavir was coadministered with ritonavir. Cobicistat is also approved for use with darunavir (administered as single entities), based on pharmacokinetic bridging data, as reviewed for NDA 203094. For this NDA submission, the following trials were submitted as a bridge to the individual components of the FDC:

1. TMC114IFD1001: a phase one oral bioavailability study which evaluated two FDCs of DRV/Cobi (G003 and G004) compared to darunavir/ritonavir 800 mg/100 mg daily;
2. TMC114IFD1003: a phase one bioequivalence study of the selected FDC formulation compared to DRV and Cobi administered as single agents; and
3. GS-US-216-0130: a phase 3 open-label, single arm study of DRV and Cobi administered as single agents in ART-naïve or experienced HIV-infected adults.

Note that the first bioavailability trial, TMC114IFD1001, was not considered essential for this submission and was not reviewed; while TMC114IFD1003 was considered the pivotal trial for this submission. Trial TMC114IFD1003 demonstrated that the darunavir exposures achieved with darunavir/cobicistat FDC tablet were similar to those observed with darunavir coadministered with cobicistat as single entities. The single-arm, open-label GS-US-216-0130 trial was considered supportive to provide 24 week safety information for DRV 800 mg coadministered with cobicistat 150 mg.

3. CMC/Device

The drug product, Prezcobix, is an immediate release film-coated tablet consisting of a fixed dose combination (FDC) of 800 mg equivalent of darunavir (b) (4) and 150 mg equivalent of cobicistat (b) (4) The tablets are oval shaped, debossed and film-coated with a pink color. The darunavir/cobicistat 800 mg/150 mg tablets are packaged in 120 mL, white, high density polyethylene (HDPE) bottles. Each bottle contains 30 tablets and is capped (b) (4) . A shelf life of 24 months is granted for all climatic zones for drug product packaged in the proposed commercial container closure system.

The Drug Master Files (DMFs) for the darunavir and cobicistat drug substances are adequate. The Drug Master Files (DMF 25188 and DMF 18825) for the cobicistat on silicon dioxide and darunavir ethanolate drug substances supporting this NDA are adequate. Information on characterization of impurities for darunavir and cobicistat drug substances is included in the respective DMFs, and no new impurities were observed in the 800/150 mg darunavir/cobicistat film-coated tablets. Information provided for NDA 205395 regarding drug product manufacturing, raw materials controls and specifications, analytical methods, and drug product stability is adequate to support the quality of the drug product through its shelf-life of 24 months.

All requested inspections of manufacturing sites for drug product and drug substance have been completed and the overall recommendation from the Office of Compliance is "Acceptable" for establishment evaluation. The Product Quality Microbiology Review by Dr. Erika Pfeiler recommends approval; and from a CMC perspective, the NDA has provided adequate information to assure the identity, strength, purity and quality of the drug product,

and is recommended for approval. For full details, see CMC review by Fuqiang Liu, Ph.D. and Stephen Miller, Ph.D.

4. Nonclinical Pharmacology/Toxicology

No new pharmacology/toxicology studies were submitted to the NDA and there have been no new safety concerns based on non-clinical studies identified with darunavir or cobicistat.

5. Clinical Pharmacology/Biopharmaceutics

Because the efficacy and safety of darunavir has been established as a single entity in combination with ritonavir for treatment of HIV-1 (see NDAs 21976 for 202895 for Prezista tablet and oral suspension, respectively), a clinical trial to evaluate the efficacy and safety of FDC darunavir/cobicistat tablet was not required; and the efficacy and safety of this new combination product relies on that previously established for darunavir, and on the safety and activity of cobicistat along with the pharmacokinetic bridging data discussed above. Cobicistat, a CYP3A inhibitor with no intrinsic antiviral activity was approved as a single entity as a pharmaco-enhancer for the HIV protease inhibitors, atazanavir and darunavir (NDA 203094, approved September 2014) and as part of the FDC Stribild (elvitegravir, cobicistat, emtricitabine, and tenofovir disoproxil fumarate (NDA 203100, approved 2012).

The pivotal trial for this NDA, TMC114IFD1003 (1003), compared the relative bioavailability of darunavir and cobicistat administered as part of the FDC tablet to single entity formulations of daruanvir (two 400 mg tablets) and cobicistat (150 mg tablets). This trial also evaluated the food effect data for the darunavir/cobicistat FDC tablet. The Clinical Pharmacology review evaluated the food effect data; while the Biopharmaceutics review evaluated the relative bioavailability data, the inspections findings by the Office of Scientific Investigations (OSI), as well as the relevant bioanalytical information. The Biopharmaceutics review also evaluated drug product dissolution method development and acceptance criteria as well as drug product formulation development and dissolution quality risks. For full details, please see Clinical Pharmacology review by Drs. Stanley Au and Kellie Reynolds, in the Office of Clinical Pharmacology; and the Biopharmaceutics review by Drs. Minerva Hughes and Angelica Dorantes, in the Office of New Drug Quality Assessment.

In brief, the 90% confidence intervals for darunavir exposure were within 80-125% for the FDC tablet compared to the single entity tablets of darunavir and cobicistat in trial 1003, as noted in the Biopharmaceutics review. The dissolution methods and acceptance criteria were considered acceptable by the Biopharmaceutics reviewers for product quality control. The Office of Scientific Investigation (OSI) was consulted to inspect the clinical and bioanalytical sites used for trial 1003 and found all clinical and analytical study data acceptable. The Biopharmaceutics reviewers have recommended approval of this NDA for the darunavir/cobicistat FDC tablet.

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