CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205395Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA: 205395	Original Submission Date: March 31, 2014
Brand Name	Prezcobix
Generic Name	Darunavir/cobicistat
Reviewer	Stanley Au, Pharm.D., BCPS
Pharmacometrics Reviewer	Jeffry Florian, Ph.D.
Clinical Pharmacology Team Leader	Kellie Reynolds, Pharm.D. (acting)
OCP Division	Division of Clinical Pharmacology 4
OND Division	Division of Antiviral Products (DAVP)
Applicant	Janssen Research and Development
Formulation; strength(s)	Fixed dose combination tablet: Darunavir 800 mg/cobicistat 150 mg
Indication	Treatment of HIV-1 infection
Review Type	505 (b)(1) New Drug Application, standard review

Table of Contents

1 Executive Summary 2
1.1 Recommendation 2
1.2 Postmarketing Commitments or Requirements 3
1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings 3
2 Labeling Recommendations 5
3 Individual Trial Reviews 59
4 Pharmacometrics Review 64

1 Executive Summary

The applicant, Janssen Research and Development, submitted a New Drug Application (NDA) for a fixed dose combination tablet consisting of darunavir 800 mg and cobicistat 150 mg (formulation G006). Another applicant, Gilead Sciences, submitted the cobicistat NDA (203094) and cobicistat in combination with darunavir as single entities was evaluated as part of the cobicistat NDA. Cobicistat was approved for U.S. marketing in September 2014. The pivotal trial for the current NDA compared the relative bioavailability for darunavir and cobicistat as part of a fixed dose combination tablet compared to single entity formulations. The TMC114IFD1003 trial evaluated the relative bioavailability of the fixed dose combination tablet consisting of darunavir 800 mg and cobicistat 150 mg that is proposed for U.S. marketing (formulation G006) compared to single entity formulations of darunavir (two 400 mg tablets, formulation F030) and cobicistat (150 mg tablets). The food effect of the darunavir and cobicistat fixed dose combination tablets (formulation G006) was also evaluated as part of the TMC114IFD1003 trial.

The Clinical Pharmacology review evaluated the food effect data for the fixed dose combination tablet consisting of darunavir and cobicistat (formulation G006). Additional pertinent review issues for the TMC114IFD1003 trial include evaluating the relative bioavailability data and reviewing the inspection findings from the Office of Scientific Investigations, as well as the relevant bioanalytical information. The biopharmaceutics reviewers within the Office of New Drug Quality Assessment (ONDQA) will assess these regulatory issues. Additionally, the Division of Pharmacometrics evaluated the darunavir population pharmacokinetic data from the GS-US-216-130 trial (with darunavir and cobicistat administered as single entities) that the applicant proposes to include in the U.S. prescribing information for the darunavir/cobicistat fixed dose combination tablets (see section 4 for the Pharmacometrics review and the clinical pharmacology review for NDA 203094 for further information regarding the GS-US-216-130 trial).

The TMC114IFD1001 trial that was also included as part of NDA 205395 was not reviewed by the Office of Clinical Pharmacology. The TMC114IFD1001 trial was not conducted with the G006 formulation and instead compared two formulations of a fixed dose combination tablet consisting of darunavir 800 mg and cobicistat 150 mg (formulation G003 and formulation G004) to darunavir 800 mg and ritonavir 100 mg as single entities. The review of this trial was not necessary since cobicistat in combination with darunavir as single entities is an approved regimen in the United States for the treatment of HIV-1 infection.

1.1 Recommendation

The clinical pharmacology information submitted in the NDA supports the approval of the application.

1.2 Postmarketing Commitments or Requirements

There are no postmarketing commitments or requirements for this NDA.

1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

A) Evaluation of the food effect data from the TMC114IFD1003 trial

A food effect was observed for darunavir when administered as a fixed dose combination tablet in combination with cobicistat. When compared to fasted conditions, with high fat meals, a 70% increase in $AUC_{[0\text{-}inf]}$ and a 127% increase in C_{max} were observed when darunavir is administered as part of a fixed dose combination tablet with cobicistat The changes in darunavir exposure when administered with cobicistat as part of a fixed dose combination tablet exceeds the magnitude of the increase in C_{max} and $AUC_{(0\text{-}inf)}$ for darunavir when coadministered with ritonavir as single entity formulations with a high fat meal when compared to fasted conditions (48% increase in $AUC_{[0\text{-}inf]}$ and 59% increase in C_{max}). There was no food effect trial that was conducted for darunavir when coadministered with cobicistat as single entities.

The single entity darunavir U.S. prescribing information recommends that darunavir in combination with ritonavir should be administered with food. The same recommendation also applies for darunavir and cobicistat when coadministered as single entities. No specific darunavir exposure-safety issues have been identified for the range of darunavir exposures associated with the dosage regimens that are included in the darunavir U.S. prescribing information. A food effect was not observed for cobicistat when administered as part of a fixed dose combination tablet with darunavir. Therefore, for darunavir and cobicistat, the applicant's recommendation to administer the darunavir/cobicistat fixed dose combination tablet with food is acceptable.

B) Clinical Pharmacology revisions to the proposed U.S prescribing information for the darunavir/cobicistat fixed dose combination tablets

The Clinical Pharmacology revisions to the proposed U.S prescribing information for the darunavir/cobicistat fixed dose combination tablets that are outlined in section 2 (Labeling Recommendations) were primarily based on the information in the cobicistat U.S. prescribing information that is relevant to administration with darunavir. Please see the Clinical Pharmacology review for NDA 203094 for further information regarding the extrapolation of drug-drug interaction information for darunavir coadminstered with ritonavir to darunavir coadminstered with cobicistat. For drug-drug interactions that are not currently included in the darunavir or cobicistat U.S. prescribing information, the proposed recommendations in section 7 were based on a determination regarding the most appropriate recommendation in the absence of drug-drug interaction data for concomitant use with darunavir coadministered with cobicistat.

C) Review of the bioanalytical data for the GS-US-216-130 trial

The bioanalytical information to support the darunavir concentration data for the GS-US-216-130 trial was reviewed as part of the Clinical Pharmacology review for NDA 209094. At the time the review was finalized, the long term stability data for darunavir that was necessary for the darunavir plasma samples from the GS-US-216-130 trial was not available. The information was requested from Janssen. Based on the information that was provided, stability for darunavir was demonstrated for up to 588 days at both -20°C and -70°C in K_2EDTA anticoagulated plasma.

D) Evaluation of the relative bioavailability data from the TMC114IFD1003 trial (based on the ONDQA Biopharmaceutics review)

The applicant demonstrated that the 90% confidence were within 80-125% for the darunavir/cobicistat fixed dose combination tablets compared with the single entity darunavir and cobicistat tablets under both fed (non high fat) and fasting conditions in the TMC114IFD1003 trial.

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.