

**CENTER FOR DRUG EVALUATION AND
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APPLICATION NUMBER:

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PHARMACOLOGY REVIEW(S)

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

PHARMACOLOGY/TOXICOLOGY NDA/BLA REVIEW AND EVALUATION

Application number: 205-395

Supporting document/s:	Supporting Document	Sponsor Submission Date	CDER Received Date
	1	3/31/14	3/31/14

Product: Darunavir/Cobicistat Fixed Dose Combination
(DRV-COBI FDC)

Indication: Treatment of HIV infection

Applicant: Janssen Products LP

Review Division: Division of Antiviral Products

Reviewer(s): Peyton Myers, PhD

Supervisor/Team Leader: Hanan Ghantous, Ph.D., DABT

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Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 205-395 are owned by Janssen Products or are data for which Janssen Products has obtained a written right of reference. Any information or data necessary for approval of NDA 205-395 that Janssen Products does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of NDA 205-395.

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1 Executive Summary

1.1 Introduction

Janssen Products has submitted an NDA to support the fixed dose combination (FDA) therapy of darunavir (DRV, prezista®, TMC114; HIV-1 protease inhibitor) and cobicistat (COBI or GS-9350; CYP450 3A enzyme inhibitor) for the treatment of HIV infection. The proposed clinical dose regimen includes 800 mg/day DRV + 150 mg/day COBI.

There are approved NDAs for DRV which indicate that DRV must be co-administered with ritonavir (also a CYP3A inhibitor). This will be the first FDC for DRV and COBI.

1.2 Brief Discussion of Nonclinical Findings

No new studies were submitted. All nonclinical studies were included in the individual drug product NDAs.

1.3 Recommendations

1.3.1 Approvability

There are no nonclinical pharmacology and toxicology issues which would preclude the approval of the FDC of DRV(800 mg/day)+COBI(150 mg/day)

1.3.2 Additional Non Clinical Recommendations

None.

1.3.3 Labeling

The label for the FDC of DRV+COBI is merged from the single drug product NDA labels. The merged label is acceptable.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C: PREZCOBIX should be used during pregnancy only if the potential benefit justifies the potential risk.

No adequate and well controlled studies have been conducted in pregnant women using darunavir, cobicistat, or PREZCOBIX.

Antiretroviral Pregnancy Registry: To monitor maternal fetal outcomes of pregnant women exposed to PREZCOBIX, an Antiretroviral Pregnancy Registry has been established. Physicians are encouraged to register patients by calling 1 800 258 4263.

Animal Data:

Cobicistat: Studies in animals have shown no evidence of teratogenicity or an effect on reproductive function. In offspring from rat and rabbit dams treated with cobicistat during pregnancy, there were no toxicologically significant effects on developmental endpoints. The exposures at the embryo fetal No Observed Adverse Effects Levels (NOAELs) in rats and rabbits were respectively 1.4 and 3.3 times higher than the exposure in humans at the recommended daily dose of 150 mg.

Darunavir: Reproduction studies conducted with darunavir showed no embryotoxicity or teratogenicity in mice and rats in the presence or absence of ritonavir as well as in rabbits with darunavir alone. In these studies, darunavir exposures (based on AUC) were higher in rats (3 fold), whereas in mice and rabbits, exposures were lower (less than 1 fold) compared to those obtained in humans at the recommended clinical dose of darunavir (b) (4) with ritonavir. In the rat pre and postnatal development study, a reduction in pup body weight gain was observed with darunavir alone or (b) (4) with ritonavir during lactation. This was due to exposure of pups to drug substances via the milk. Sexual development, fertility and mating performance of offspring were not affected by maternal treatment with darunavir alone or (b) (4) with ritonavir. The maximal plasma exposures achieved in rats were approximately 50% of those obtained in humans at the recommended clinical dose boosted with ritonavir.

In the juvenile toxicity study where rats were directly dosed with darunavir, deaths occurred from post natal day 5 through 11 at plasma exposure levels ranging from 0.1 to 1.0 of the human exposure levels. In a 4 week rat toxicology study, when dosing was initiated on post natal day 23 (the human equivalent of 2 to 3 years of age), no deaths were observed with a plasma exposure (in combination with ritonavir) of 0.1 of the human plasma exposure levels.

8.3 Nursing Mothers

The Centers for Disease Control and Prevention recommend that HIV infected mothers in the United States not breastfeed their infants to avoid risking postnatal transmission of HIV. Although it is not known whether darunavir or cobicistat are secreted in human milk, darunavir and cobicistat are secreted into the milk of lactating rats. Because of both the potential for HIV transmission and the potential for serious adverse reactions in nursing infants, instruct mothers not to breastfeed.

8.4 Pediatric Use

Safety, effectiveness, and pharmacokinetics of PREZCOBIX in pediatric patients less than 18 years of age have not been established. Darunavir, and thus

PREZCOBIX is not recommended in pediatric patients below 3 years of age in view of toxicity and mortality observed in juvenile rats dosed with darunavir [see Nonclinical Toxicology (13.2)].

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis and Mutagenesis

Darunavir: Darunavir was evaluated for carcinogenic potential by oral gavage administration to mice and rats up to 104 weeks. Daily doses of 150, 450 and 1000 mg/kg were administered to mice and doses of 50, 150 and 500 mg/kg (b) (4) administered to rats. A dose related increase in the incidence of hepatocellular adenomas and carcinomas (b) (4) observed in males and females of both species (b) (4) an increase in thyroid follicular cell adenomas in male rats. The observed hepatocellular findings in rodents are considered to be of limited relevance to humans. Repeated administration of darunavir to rats caused hepatic microsomal enzyme induction and increased thyroid hormone elimination, which predispose rats, but not humans, to thyroid neoplasms. At the highest tested doses, the systemic exposures to darunavir (based on AUC) were between 0.4 and 0.7 fold (mice) and 0.7 and 1 fold (rats), (b) (4) observed in humans at the recommended therapeutic doses (b) (4)

Darunavir was not mutagenic or genotoxic in a battery of in vitro and in vivo assays including bacterial reserve mutation (Ames), chromosomal aberration in human lymphocytes and in vivo micronucleus test in mice.

Cobicistat: In a long term carcinogenicity study in mice, no drug related increases in tumor incidence were observed at doses up to 50 and 100 mg/kg/day (males and females, respectively). Cobicistat exposures at these doses were approximately 7 (male) and 16 (females) times, respectively, the human systemic exposure at the therapeutic daily dose. In a long term carcinogenicity study of cobicistat in rats, an increased incidence of follicular cell adenomas and/or carcinomas in the thyroid gland was observed at doses of 25 and 50 mg/kg/day in males, and at 30 mg/kg/day in females. The follicular cell findings are considered to be rat specific, secondary to hepatic microsomal enzyme induction and thyroid hormone imbalance, and are not relevant for humans. At the highest doses tested in the rat carcinogenicity study, systemic exposures were approximately 2 times the human systemic exposure at the therapeutic daily dose.

Cobicistat was not genotoxic in the reverse mutation bacterial test (Ames test), mouse lymphoma or rat micronucleus assays.

Impairment of Fertility

Darunavir: No effects on fertility or early embryonic development were observed with darunavir in rats and darunavir has shown no teratogenic potential in mice or rats (in the presence or absence of ritonavir), (b) (4) rabbits.

Cobicistat: Cobicistat did not affect fertility in male or female rats at daily exposures (AUC) approximately 4 fold higher than human exposures at the recommended 150 mg daily dose.

Fertility was normal in the offspring of rats exposed daily from before birth (in utero) through sexual maturity at daily exposures (AUC) of approximately 1.2 fold higher than human exposures at the recommended 150 mg daily dose.

13.2 Animal Toxicology and/or Pharmacology

Darunavir: In juvenile rats single doses of darunavir (20 mg/kg to 160 mg/kg at ages 5-11 days) or multiple doses of darunavir (40 mg/kg to 1000 mg/kg at age 12 days) caused mortality. The mortalities were associated with convulsions in some of the animals. Within this age range exposures in plasma, liver and brain were dose and age dependent and were considerably greater than those observed in adult rats. These findings were attributed to the ontogeny of the CYP450 liver enzymes involved in the metabolism of darunavir and the immaturity of the blood brain barrier. No treatment related mortalities were noted in juvenile rats after a single dose of darunavir at 1000 mg/kg on day 26 of age or after repeat dosing at 500 mg/kg from day 23 to 50 of age. The exposures and toxicity profile in the older animals (day 23 or day 26) were comparable to those observed in adult rats. Due to uncertainties regarding the rate of development of the human blood brain barrier and liver enzymes, do not administer (b) (4) in pediatric patients below 3 years of age.

2 Drug Information

2.1 Drug

Generic Name

Darunavir/cobicistat 800mg/150mg (DRV/COBI) Fixed-Dose Combination (FDC) tablets

2.2 Relevant INDs, NDAs, BLAs and DMFs

NDA 203-100 -- COBI FDC

NDA 203-094 -- COBI

NDA 21976 -- DRV

2.3 Drug Formulation

Fixed Dose Tablets

2.4 Comments on Novel Excipients

None.

2.5 Comments on Impurities/Degradants of Concern

None.

2.6 Proposed Clinical Population and Dosing Regimen

HIV treatment with 800mg/150mg (DRV/COBI) Fixed-Dose Combination (FDC) tablets

2.7 Regulatory Background

DRV and COBI are both approved under their respective NDAs. This is the FDC tablet combination with DRV and COBI. All data for COBI and DRV are in their respective NDAs.

3 Studies Submitted

3.1 Studies Reviewed

N/A

3.2 Studies Not Reviewed

N/A

3.3 Previous Reviews Referenced

None.

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/s/

LAINÉ P MYERS
12/23/2014

HANAN N GHANTOUS
12/24/2014

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 205395 **Applicant:** Janssen Products LP **Stamp Date:** March 31, 2014

Drug Name: DRV/COBI FDC **NDA/BLA Type:** Standard (Not NME)

On **initial** overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?			N/A. No module 4 – no data to review. The review will consist entirely of a label review.
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?			N/A
3	Is the pharmacology/toxicology section legible so that substantive review can begin?			N/A
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?			N/A
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).			N/A
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant <u>submitted</u> a rationale to justify the alternative route?			N/A
7	Has the applicant <u>submitted</u> a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) <u>or</u> an explanation for any significant deviations?			N/A
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			N/A

File name: 5_Pharmacology_Toxicology Filing Checklist for NDA_BLA or Supplement
010908

**PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR
NDA/BLA or Supplement**

	Content Parameter	Yes	No	Comment
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m2 or comparative serum/plasma levels) and in accordance with 201.57?	X		Will review this section to conform with the individual drug product(s) labels.
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)			N/A
11	Has the applicant addressed any abuse potential issues in the submission?			N/A
12	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?			N/A

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? ___ Yes ___

If the NDA/BLA is not fileable from the pharmacology/toxicology perspective, state the reasons and provide comments to be sent to the Applicant.

None.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

None.

Laine Peyton Myers, PhD

April 30, 2014

Reviewing Pharmacologist

Date

Hanan Ghantous, PhD, DABT

April 30, 2014

Team Leader/Supervisor

Date

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

LAINÉ P MYERS
05/06/2014

HANAN N GHANTOUS
05/06/2014