CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205395Orig1s000

MICROBIOLOGY / VIROLOGY REVIEW(S)

DIVISION OF ANTIVIRAL PRODUCTS (HFD-530)

VIROLOGY REVIEW

NDA: 205395 **SDN:** 000 **DATE REVIEWED:** 12/19/14

Clinical Virology Reviewer: Takashi E. Komatsu, Ph.D., RAC

NDA #: 205395 **Supporting Document Numbers:** 000

Applicant Name and Address:

Janssen Research & Development, LLC.
1125 Trenton-Harbourton Road
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Reviewer's Name: Takashi E. Komatsu, Ph.D., RAC

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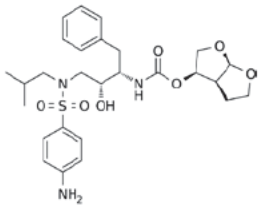
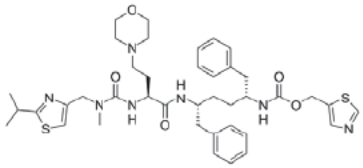
IND 62,477, IND 113198, NDA 21976, NDA 202895, NDA 203094, DMF (b) (4), DMF (b) (4), DMF (b) (4), DMF (b) (4), DMF (b) (4), DMF (b) (4), DMF 18825, DMF 25188

Product Name(s):

Proprietary: Prezcobix
Non-Proprietary/USAN: darunavir/cobicistat
Code Name/Number: DRV 800mg/COBI 150mg

Individual Component	DRV	COBI
Structure		
Chemical Name	{3-[(4-amino-benzenesulfonyl)-isobutyl-amino]-1-benzyl-2-hydroxypropyl}-carbamicacid	1,3-thiazol-5-ylmethyl[(2R,5R)-5-{[(2S)-2-[(methyl{[2-(propan-2-yl)-1,3-thiazol-4-yl]methyl}carbamoyl)amino]-

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	hexahydro-furo-[2,3-b]furan-3-ylester.ethanolate	4-(morpholin-4-yl)butanoyl]amino}-1,6-diphenylhexan-2-yl]carbamate
Molecular Formula	$C_{27}H_{37}N_3O_7S.C_2H_5OH$	$C_{40}H_{53}N_7O_5S_2$
Molecular Mass	(b) (4)	776.02
Drug Class	Protease Inhibitor	Pharmacoenhancer (No anti-HIV-1 activity)
Supporting Document	NDA 21976	NDA 203094

Indication(s): In combination with other antiretroviral agents for the treatment of human immunodeficiency virus (HIV-1) infection in:

- (b) (4) treatment (b) (4) naïve adult patients
- (b) (4)-experienced patients with no darunavir resistance-associated substitutions

Dosage Form(s): 800 mg of darunavir and 150 mg of cobicistat

Route(s) of Administration: Oral

Recommended Dosage: One tablet taken once daily with food

Dispensed: Rx _X_ **OTC** ___ **(Discipline relevant)**

Abbreviations: AAG, alpha-1-acid glycoprotein; ABC, abacavir; ADV, adefovir; APV, amprenavir; ARV, antiretroviral; ATR, Atripla; ATV, atazanavir; ATV/r, ritonavir-boosted atazanavir; AZT, zidovudine; bp, base pair; CC_{50}, 50% cytotoxic concentration; COBI, cobicistat; ddI, didanosine; DHHS, Department of Health and Human Services; DRV, darunavir; d4T, stavudine; EC_{50}, effective concentration inhibiting viral replication by 50%; EC_{90}, effective concentration inhibiting viral replication by 90%; EC_{95}, effective concentration inhibiting viral replication by 95%; EFV, efavirenz; ETR, etravirine; ETV, entecavir; FBS, fetal bovine serum; FTC, emtricitabine; HAART, highly active antiretroviral therapy; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus (including HIV-1 and -2); HIV-1, human immunodeficiency virus type 1; HIV-2, human immunodeficiency virus type 2; HS, human serum; HSA, human serum albumin; IC_{50}, 50% inhibitory concentration; IDV, indinavir; IL-2, interleukin 2; IN, HIV-1 integrase; INSTI, HIV-1 integrase strand transfer inhibitor; LAM, lamivudine; LPV, lopinavir; L-dT, telbivudine; L-FMAU, clevudine; MDR, multidrug-resistant; MOI, multiplicity of infection; MVC, maraviroc; NDA, new drug application; NFV, nelfinavir; NNRTI, HIV-1 non-nucleoside reverse transcriptase inhibitor; NR, virologic non-response; N(t)RTI, HIV-1 nucleos(t)ide reverse transcriptase inhibitor; NVP, nevirapine; PBMC, peripheral blood mononuclear cell; PCR, polymerase chain reaction; PI, HIV-1 protease inhibitor; PI/r, ritonavir-boosted HIV-1 protease inhibitor; PK, pharmacokinetics; PR, HIV-1 protease; QD, once daily; RAL, raltegravir; RBV, ribavirin; RPV, rilpivirine; RT, HIV-1 reverse transcriptase; RTE, resistance testing eligible; RTI, HIV-1 reverse transcriptase inhibitor; RTV, ritonavir; SD, standard deviation; SI, selective index; SQV, saquinavir; SR, suboptimal virologic response; TAM, thymidine analogue mutation; TDF, tenofovir disoproxil fumarate; TFV, tenofovir (active moiety of the diester prodrug TDF); TPV, tipranavir; TVD, Truvada; T-20, enfuvirtide; VF, virologic failure; VR, virologic rebound;

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EXECUTIVE SUMMARY

This application was submitted in support of a new drug application (NDA) for Prezcobix fixed dose combination (FDC) tablets containing the approved HIV-1 protease inhibitor (PI) darunavir (DRV; NDA 21976, approved 6/23/06) and the pharmacokinetic enhancer cobicistat (COBI) (darunavir/cobicistat 800mg/150mg). The proposed indication for the Prezcobix tablet is treatment of human immunodeficiency virus (HIV-1) infection in combination with other antiretroviral agents in: (b) (4) treatment-naïve adult patients and (b) (4)-experienced patients with no darunavir resistance-associated substitutions. This NDA package includes clinical data from two Phase 1 studies (TMC114IFD1001 – a phase 1 oral bioavailability study investigating two FDC formulation concepts of DRV/COBI (b) (4) and TMC114IFD1003 – a phase 1 bioequivalence study of the selected FDC formulation compared to DRV and COBI coadministered as single agents) and one Phase 3 study (GS-US-216-0130 – a phase 3b open label, single arm study in ART-naïve or – experienced HIV-1 infected adults with plasma HIV 1 RNA levels ≥500 copies/mL).

Soon after the introduction of protease inhibitors, it was recognized that coadministration of the approved HIV-1 protease inhibitor ritonavir (RTV) with other PIs improves the pharmacokinetics of the approved PI, increasing the serum half life and thereby permitting a more constant exposure to the PI (i.e. reducing C_{max} and increasing C_{min}). RTV was found to be an inhibitor of the CYP3A enzymes involved in the metabolism of PIs. Currently, RTV-boosted HIV-1 PI regimens are a standard of care. However, RTV boosting is limited to PIs in protease inhibitor naïve individuals as absence of a PI could lead to selection of PI resistance-associated substitutions. RTV boosting of PIs has generated a renewed interest in PK principles and their clinical implications.

Cobicistat is structurally similar to ritonavir and was designed to be a specific inhibitor of CYP3A without HIV-1 protease inhibitory activity. Enzyme inactivation studies have demonstrated that COBI is an efficient inactivator of human hepatic microsomal CYP3A activity, with enzyme kinetic parameters (K_i and k_{inact}) comparable to those of ritonavir.

Darunavir, in combination with low-dose RTV as a pharmacokinetic enhancer and other approved ARVs, is approved for the treatment of HIV-1 infection (NDA 21976 approved on 6/23/06). DRV/r is currently indicated for (b) (4)-naïve and (b) (4)-experienced adults, as well as (b) (4)-experienced pediatric patients (b) (4) years of age and older.

1. Recommendations

1.1. Recommendation and Conclusion on Approvability:

Approval is recommended with respect to Clinical Virology of this original NDA for Prezcobix tablet (DRV 800mg/COBI 150mg), once daily, as a treatment of human immunodeficiency virus (HIV-1) infection in combination with other (b) (4) agents in: (1) (b) (4) treatment (b) (4) naïve adult patients and (2) (b) (4)-experienced patients with no darunavir resistance-associated substitutions.

1.2. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, If Approvable:

2. Summary of OND Virology Assessments

2.1. Nonclinical Virology

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