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RESEARCH**

APPLICATION NUMBER:

206510Orig1s000

MEDICAL REVIEW(S)

Clinical Review

Date	December 30, 2014
From	Sarita Boyd, Pharm.D.
Subject	Clinical Review
NDA/BLA #	NDA 206510
Supplement#	
Applicant	Merck
Date of Submission	April 8, 2014
PDUFA Goal Date	February 6, 2015
Proprietary Name / Established (USAN) names	Dutrebis (lamivudine/raltegravir)
Dosage forms / Strength	Tablet / 150 mg of lamivudine and 300 mg of raltegravir
Proposed Indication(s)	Fixed dose combination indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults, adolescents (16 years of age and older), and pediatric patients (6 through 16 years of age weighing at least 30 kg)
Recommended:	Approval

1. Background

The Applicant is proposing approval of a fixed-dose combination (FDC) tablet containing lamivudine and raltegravir, two approved drugs. Lamivudine, a nucleoside reverse transcriptase inhibitor (NRTI), and raltegravir, an integrase strand transfer inhibitor (INSTI), are individually indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection. The development program for the lamivudine/raltegravir FDC is based on comprehensive development and approval of lamivudine and raltegravir as single agents and pharmacokinetic (PK) bridging of the FDC to the single agents. The bioavailability (BA)/bioequivalence (BE) trial P253 is pivotal for approval of this application of lamivudine/raltegravir 150/300 mg as an FDC tablet indicated in combination with other antiretroviral agents for treatment of HIV-1 infection.

2. CMC

The selected dosage form of the lamivudine/raltegravir FDC is an immediate-release solid oral (b) (4) tablet with a film coat. Because the formulation of raltegravir as a single agent is not favorable for use in FDC forms, a new tablet formulation was developed and used for the lamivudine/raltegravir FDC. The new formulation differs from the original formulation (b) (4)

(b) (4) Due to improved bioavailability, each FDC tablet contains 300 mg of raltegravir, (b) (4) Each tablet also contains 150 mg of lamivudine and the following inactive ingredients: hypromellose, croscarmellose

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sodium, lactose monohydrate, silicon dioxide, magnesium stearate, and microcrystalline cellulose. The coating agent (b) (4) is composed of hypromellose, lactose monohydrate, triacetin, yellow iron oxide, FD&C Blue #2, and titanium dioxide. The proposed shelf life is 24 months from the date of manufacture. Please refer to the CMC review by Dr. James Vidra for complete details.

3. Clinical Pharmacology/Biopharmaceutics

The reformulation of raltegravir for the lamivudine/raltegravir FDC tablet allows for (b) (4)

(b) (4). Trial P253 compared BE of lamivudine 150 mg and raltegravir 300 mg in the FDC tablet to the single, approved agents raltegravir 400 mg (Isentress) and U.S.-sourced lamivudine 150 mg (Epivir), respectively, when administered as a *single dose* in 108 healthy subjects under fasted conditions. Lamivudine exposures were within the limits of all pre-specified BE criteria. While raltegravir area under the concentration-time curve (AUC_{inf}) and maximum plasma concentration (C_{max}) were within the pre-specified limits for BE, the lower bound of the 90% CI for the plasma trough concentration (C_{trough}) was slightly below (0.78) the pre-specified bound (0.80).

To assess raltegravir C_{trough} differences with the FDC that fell outside the standard “no effect” bounds, modeling and simulation analyses as well as historical PK data associated with clinical efficacy and safety were used. Dr. Fang Li’s modeling results show the predicted mean *steady-state* C_{trough} level with raltegravir (300 mg twice daily) in the FDC (232 nM) is lower than that observed with Isentress 400 mg twice daily (257 nM); but it is substantially higher than that observed with Isentress 800 mg once daily (40 nM), which failed from an efficacy standpoint in Trial P071. Furthermore, historical exposure-response data for efficacy predict that achieved raltegravir exposure with the FDC will be effective. Overall, historical data and modeling and simulation results show that the slightly lower C_{trough} levels in Trial P253 are not clinically significant.

Modeling and simulation analyses were also used to determine appropriateness of the lamivudine/raltegravir FDC tablet in the proposed pediatric population (≥ 16 years of age and > 6 years to < 16 years of age weighing at least 30 kg). Although C_{trough} levels are predicted to be higher than historically approved exposures, they are within the safe range previously observed with approved dosages for pediatric patients.

Trial P254 assessed the effect of a high-fat meal on the PK of lamivudine and raltegravir when administered as a FDC. Results demonstrate it is appropriate to administer the FDC tablet without regard to food, which is consistent with the individual components.

Overall, Trial P253 combined with historical data and modeling analyses for raltegravir showed clinically acceptable exposures of lamivudine and raltegravir when administered as a FDC compared to single agents. Please refer to the Biopharmaceutics Review by Dr. Okpo Eradri and the Clinical Pharmacology Reviews by Drs. Leslie Chinn and Fang Li for complete details.

4. Clinical Efficacy and Safety

Safety and efficacy of lamivudine/raltegravir FDC is bridged to that of the individual components by demonstrating similar plasma drug exposures of lamivudine and raltegravir with the FDC tablet compared to the individual components. No new safety and efficacy trials involving lamivudine and raltegravir were reviewed for this application, but supportive data for coadministration is available from previous trials. During the Applicant's raltegravir development program, the Phase 2 trial P004 (Part II) consisted of 240 weeks of treatment with raltegravir (4 doses for 48 weeks, followed by 400 mg twice daily) versus efavirenz, each in combination with lamivudine and tenofovir, in HIV-infected treatment-naïve subjects. Results from this trial were similar to results from other clinical trials assessing raltegravir in combination with other antiretroviral drugs and support coadministration of lamivudine and raltegravir; a total of 160 subjects received lamivudine and raltegravir in Trial P004.

Lamivudine/raltegravir FDC has not been studied in HIV-infected subjects. Limited safety data from PK trials conducted in healthy subjects did not generate any new safety concerns.

5. Pediatrics

The dosage recommendation for lamivudine/raltegravir FDC is the same for adults, adolescents ≥ 16 years of age, and pediatric patients 6 to 16 years of age and weighing ≥ 30 kg. These recommendations represent the combined recommendations from lamivudine and raltegravir as single agents. Although raltegravir exposures (C_{trough}) with the FDC (300 mg twice daily) are predicted to be higher than with Isentress (400 mg twice daily), they fall within the previously established safe range as discussed in Section 3 of this review.

The Applicant submitted the Agreed Initial Pediatric Study Plan for lamivudine/raltegravir FDC; the Agency previously agreed with the Applicant's planned waiver request. The Applicant submitted a partial waiver request for children < 6 years of age and 6 to 16 years of age weighing < 30 kg because in these age groups, the drug does not represent a meaningful therapeutic benefit over existing therapies and is not likely to be used by a substantial number of patients. Furthermore, the dosing for the individual components in these patients requires flexibility based on age and weight which cannot be reasonably accommodated with a FDC. The waiver request will be reviewed by the Pediatric Review Committee (PeRC) on January 7, 2015.

6. Labeling

Overall, lamivudine and raltegravir

(b) (4)

Instead, the FDC label refers to the labels of the individual components.

Additional major revisions proposed to the Applicant are as follows:

U.S. Package Insert (USPI)

INDICATION AND USAGE

- Simplification as follows, “DUTREBIS is indicated in combination with other antiretroviral agents for treatment of human immunodeficiency virus (HIV-1) infection.”

DOSAGE AND ADMINISTRATION

- Consolidation of adult and pediatric recommendations because the dosage recommendation is the same for both patient populations.
- Deletion of the statement “DUTREBIS (b) (4)

(b) (4)

ADVERSE REACTIONS

- Inclusion of only the adverse reactions from the HIGHLIGHTS section of the Epivir (lamivudine) and Isentress (raltegravir) labels.

U.S. Patient Package Insert (USPPI)

- (b) (4)

7. Recommendations/Risk Benefit Assessment

I recommend approval of lamivudine/raltegravir 150/300 mg tablet, a fixed-dose NRTI and INSTI, in combination with other antiretroviral agents for the treatment of HIV-1 infection. The recommendation is based on the clinically similar lamivudine and raltegravir exposures with the FDC tablet compared to the approved single-agent products for the same indication. The BE/BA trial results, historical exposure-response data, and modeling analyses show the risk benefit assessment is favorable and similar to that of the individual, approved components.

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/s/

SARITA D BOYD
12/30/2014

ADAM I SHERWAT
12/30/2014