

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

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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: 206-510  
Supporting document: 1  
Applicant's letter date: 3/27/2014  
CDER stamp date: 4/8/2014  
Product: Lamivudine/Raltegravir Fixed Dose Combination  
DUTREBIS  
Indication: Treatment of HIV infection  
Applicant: Merck Sharp & Dohme Corp.  
Review Division: Division of Antiviral Products  
Reviewer: Ita Yuen, PhD  
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# 1 Executive Summary

## 1.1 Introduction

Merck has submitted an NDA to support the fixed dose combination (FDC) therapy of lamivudine (3TC, EPIVIR<sup>®</sup>; nucleoside reverse transcriptase inhibitor) and raltegravir (RAL, ISENTRESS<sup>®</sup>; HIV integrase strand transfer inhibitor) for the treatment of HIV infection. Both lamivudine and raltegravir have been approved for marketing for the treatment of HIV infection. The recommended dose for lamivudine is 300 mg per day administered as a single dose or as 150 mg BID. Raltegravir is recommended to be administered at 400 mg BID.

The proposed FDC of lamivudine/raltegravir tablet contains 150 mg lamivudine and 300 mg reformulated raltegravir. The new raltegravir formulation has a (b) (4)

The approval of this FDC of lamivudine/raltegravir is based on the results from the bioequivalence study P253.

## 1.2 Brief Discussion of Nonclinical Findings

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

## 1.3 Recommendations

### 1.3.1 Approvability

There are no nonclinical pharmacology and toxicology issues that would preclude the approval of the FDC of lamivudine (150 mg BID) and raltegravir (300 mg BID).

### 1.3.2 Additional Non Clinical Recommendations

Raltegravir dose in the FDC of lamivudine/raltegravir is lower than the approved 400 mg BID for ISENTRESS<sup>®</sup>. (b) (4)  
(b) (4). Thus, no additional toxicology study is needed to support the new formulation.

### 1.3.3 Labeling

The label for the FDC of lamivudine/raltegravir 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

## Pregnancy Registry

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

### Risk Summary

There are no adequate and well-controlled studies with DUTREBIS, lamivudine, or raltegravir in pregnant women. Lamivudine caused increased early embryoletality in rabbits at exposure levels similar to those in humans. Raltegravir induced treatment-related increases in the incidence of supernumerary ribs in rats at 3-fold the exposure at the recommended human dose. DUTREBIS should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

### Clinical Considerations

#### Data

##### Human Data

Lamivudine pharmacokinetics were studied in pregnant women during 2 clinical trials conducted in South Africa. Lamivudine concentrations were generally similar in maternal, neonatal, and umbilical cord serum samples, while amniotic fluid concentrations of lamivudine were typically 2 times greater than maternal serum levels [see *Clinical Pharmacology (12.3)*]. It is not known whether risks of adverse events associated with lamivudine are altered in pregnant women compared with other HIV-1-infected patients. There have been no pharmacokinetic studies conducted with raltegravir in pregnant patients.

##### Animal Data

###### **Lamivudine**

Lamivudine is not teratogenic at oral doses up to 4000 mg/kg/day (130 times human exposures) in rats and 1000 mg/kg/day (60 times human exposures) in rabbits. Evidence of increased early embryoletality was seen in rabbits at exposure levels similar to those in humans but there was no indication of this effect in rats at exposure levels up to 35 times those in humans. Studies in pregnant rats and rabbits showed that lamivudine is transferred to the fetus through the placenta.

###### **Raltegravir**

Developmental toxicity studies were performed in rabbits (at oral doses up to 1000 mg/kg/day) and rats (at oral doses up to 600 mg/kg/day). The reproductive toxicity study in rats was performed with pre-, peri-, and postnatal evaluation. The highest doses in these studies produced systemic exposures in these species approximately 3- to 4-fold the exposure at the recommended human dose. In both rabbits and rats, no treatment-related effects on embryonic/fetal survival or fetal weights were observed. In addition, no treatment-related external, visceral, or skeletal changes were observed in rabbits. However, treatment-related increases over controls in the incidence of supernumerary ribs were seen in rats at 600 mg/kg/day (exposures 3-fold the exposure at the recommended human dose).

Placenta transfer of drug was demonstrated in both rats and rabbits. At a maternal dose of 600 mg/kg/day in rats, mean drug concentrations in fetal plasma were approximately 1.5- to 2.5-fold greater than in maternal plasma at 1 hour and 24 hours postdose, respectively. Mean drug concentrations in fetal plasma were approximately 2% of the mean maternal concentration at both 1 and 24 hours postdose at a maternal dose of 1000 mg/kg/day in rabbits.

### **8.3 Nursing Mothers**

#### **DUTREBIS**

Breastfeeding is not recommended while taking DUTREBIS. In addition, it is recommended that HIV-1-infected mothers not breastfeed their infants to avoid risking postnatal transmission of HIV-1.

#### **Lamivudine**

Lamivudine is excreted into human milk. Samples of breast milk obtained from 20 mothers receiving lamivudine monotherapy (300 mg twice daily) or combination therapy (150 mg lamivudine twice daily and 300 mg zidovudine twice daily) had measurable concentrations of lamivudine.

#### **Raltegravir**

It is not known whether raltegravir is secreted in human milk. However, raltegravir is secreted in the milk of lactating rats. Mean drug concentrations in milk were approximately 3-fold greater than those in maternal plasma at a maternal dose of 600 mg/kg/day in rats. There were no effects in rat offspring attributable to exposure of raltegravir through the milk.

### **8.4 Pediatric Use**

#### **DUTREBIS**

DUTREBIS is indicated in pediatric patients 6 through 16 years of age and weighing at least 30 kg [see *Indications and Usage (1) and Dosage and Administration (2.1)*]. DUTREBIS should not be used in children below 6 years of age or in patients weighing less than 30 kg due to weight based dosing requirements in this patient population.

## **13 NONCLINICAL TOXICOLOGY**

No animal studies have been conducted with DUTREBIS. The following data are based on findings in separate studies with the individual components of DUTREBIS (lamivudine and raltegravir).

### **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

#### **Lamivudine**

Long-term carcinogenicity studies with lamivudine in mice and rats showed no evidence of carcinogenic potential at exposures up to 10 times (mice) and 58 times (rats) those observed in humans at the recommended therapeutic dose for HIV-1 infection. Lamivudine was not active in a microbial mutagenicity screen or an *in vitro* cell transformation assay, but showed weak *in vitro* mutagenic activity in a cytogenetic assay using cultured human lymphocytes and in the mouse lymphoma assay. However, lamivudine showed no evidence of *in vivo* genotoxic activity in the rat at oral doses of up to 2,000 mg/kg, producing plasma levels of

35 to 45 times those in humans at the recommended dose for HIV-1 infection. In a study of reproductive performance, lamivudine administered to rats at doses up to 4,000 mg/kg/day, producing plasma levels 47 to 70 times those in humans, revealed no evidence of impaired fertility and no effect on the survival, growth, and development to weaning of the offspring.

### Raltegravir

Carcinogenicity studies of raltegravir in mice did not show any carcinogenic potential. At the highest dose levels, 400 mg/kg/day in females and 250 mg/kg/day in males, systemic exposure was 1.8-fold (females) or 1.2-fold (males) greater than the AUC (54  $\mu\text{M}\cdot\text{hr}$ ) at the 400-mg twice daily human dose. Treatment-related squamous cell carcinoma of nose/nasopharynx was observed in female rats dosed with 600 mg/kg/day raltegravir for 104 weeks. These tumors were possibly the result of local irritation and inflammation due to local deposition and/or aspiration of drug in the mucosa of the nose/nasopharynx during dosing. No tumors of the nose/nasopharynx were observed in rats dosed with 150 mg/kg/day (males) and 50 mg/kg/day (females) and the systemic exposure in rats was 1.7-fold (males) to 1.4-fold (females) greater than the AUC (54  $\mu\text{M}\cdot\text{hr}$ ) at the 400-mg twice daily human dose.

No evidence of mutagenicity or genotoxicity was observed in *in vitro* microbial mutagenesis (Ames) tests, *in vitro* alkaline elution assays for DNA breakage, and *in vitro* and *in vivo* chromosomal aberration studies.

No effect on fertility was seen in male and female rats at doses up to 600 mg/kg/day which resulted in a 3-fold exposure above the exposure at the recommended human dose.

## **2 Drug Information**

### **2.1 Drug**

Generic Name: Lamivudine/raltegravir 150mg/300mg (3TC/RAL) Fixed-Dose Combination (FDC)

### **2.2 Relevant INDs, NDAs, BLAs and DMFs**

IND 113,176 (3TC/RAL FDC)

NDA 20,564 (EPIVIR<sup>®</sup>, 3TC)

NDA 22,145 (ISENTRESS<sup>®</sup>, RAL)

### **2.3 Drug Formulation**

Lamivudine 150 mg plus raltegravir 300 mg FDC oral IR tablet

### **2.4 Comments on Novel Excipients**

None

### **2.5 Comments on Impurities/Degradants of Concern**

None

## **2.6 Proposed Clinical Population and Dosing Regimen**

Treatment of HIV infection with 150mg 3TC/300mg RAL FDC tablet BID

## **2.7 Regulatory Background**

3TC and RAL are both approved under their respective NDAs. All data 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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