CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206510Orig1s000

SUMMARY REVIEW

Cross-Discipline Team Leader Review	
NDA	206510
Submission Type	505(b)(2)
Applicant	Merck Sharp & Dohme Corporation
Submission Date	April 8th, 2014
Generic Name	Raltegravir/Lamivudine
Trade Name	Dutrebis™
Dosage Form (Strength)	FDC Tablet (Raltegravir 300 mg / Lamivudine 150 mg)
Proposed Indication	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) in combination with other antiretroviral agents.
CDTL	Islam R. Younis, Ph.D.
Recommendation	Approval

1. Introduction

Raltegravir (RA) is an integrase strand transfer inhibitor that was approved in the US for the treatment of HIV-1 infection in 2007. The recommend RAL dose in adults and pediatrics weighing at least 25 Kg is 400 mg BID and it is weight based dosing for pediatric patients four weeks and older weighing at least 3 Kg to less than 25 Kg. RAL is available as 400 mg film-coated tablets, 100 mg scored and 25 mg chewable tablets, and single-use packets of 100 mg for oral suspension.

Lamivudine (3TC) is a nucleoside analog inhibitor of HIV-1 virus reverse transcriptase that was approved in the US for the treatment of HIV-1 infection in 1995. The approved 3TC dose in adults and adolescents > 16 years of age and pediatrics weighing at least 30 Kg is 300 mg daily. The approved dose in pediatrics 3 months up to 16 years of age is weight based dosing. 3TC is available as 300 mg tablets, 150 mg scored tablets, and 10 mg/mL oral solution.

2. Background

The Applicant developed a fixed dose combination (FDC) tablet containing RAL 300 mg and 3TC 150 mg. The proposed indication is 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) in combination with other antiretroviral agents (ARVs). It should be noted that the FDC contains (b) (4) newly designed formulation containing 300 mg RAL (b) (4) (b) (4).

The safety and efficacy of the RAL/3TC combination was evaluated in several clinical trials during RAL development program. 3TC was used as a component of antiretroviral backbone therapy, either selected by the investigator to optimize background ARVs or provided as part of the study, in 219 (47.4%) treatment-experienced HIV-1 patients in the two pivotal clinical trials of the RAL development program (protocols P018 and P019). Also, this combination was evaluated, with other ARVs, in two dose-ranging studies in treatment naïve and experienced patients (protocols P004 and P005), two switch studies (protocols P032 and P033) , one open label safety study (P055), and in a total of 66 pediatric patients (54%, protocol P022).

Although it is not possible to delineate the efficacy contribution or safety signals specifically attributed to the combination of RAL and 3TC in these trials, the FDC tablet provides a convenient backbone for antiretroviral therapy regimens and could improve patient compliance and satisfaction.

Based on the above, a clinical trial to evaluate the efficacy and safety of RAL/3TC FDC was not required. The Applicant is seeking approval of the current application based on the results of a single relative bioavailability (Study P253) where the pharmacokinetics of RAL and 3TC were compared following the administration of RAL 400 mg and 3TC 150 mg as single agents vs. the administration of RAL/3TC (300 mg/150mg) FDC.

3. Chemistry, Manufacturing, and Control

The NDA is recommended for approval from CMC perspective pending final recommendation for approval from the biopharmaceutics review team and the issuance of an overall acceptable recommendation from the Office of Compliance. Please refer to the CMC review by Drs. Seggel and Matecka, microbiology review by Drs. Cole and Riley, and biopharmaceutics review by Drs. Eradiri and Duan for full details.

Drug Substance:

Drug substances CMC information is considered adequate to ensure identity, strength, quality and purity of RAL and 3TC used in the manufacturing of the FDC.

The CMC reviewer did not agree with the Applicant claim that the USP monograph does not apply to (b) (4) yielded in the manufacturing process. The Applicant's proposal (b) (4) (b) (4) is considered acceptable by the DVAP pharmacology and toxicology review team and is consistent with the limits in the 3TC NDA 20564 of ~ (b) (4)% w/w. (b) (4) Variations in performance of identity testing by infrared absorption are allowed in the case of different solid state forms. Although drugs

defined in an official compendium that do not comply with the monograph requirements must be labeled accordingly in accordance with FDCA §§501(b) and 21 CFR §299.5(c), adding such wording to the current labeling is not warranted because the Applicant contacted USP to change their monograph.

Raltegravir is manufactured as the potassium salt according to the process documented in RAL NDA 22145. CMC information is cross-referenced to NDA 22145. Because raltegravir is introduced into the product as the potassium salt, product labeling must comply with the salt nomenclature policy and strength expressed as the free phenol (i.e., 300 mg) with a statement of equivalency to 325.8 mg potassium salt.

Drug Product:

The drug product is an immediate release film-coated (b) (4) tablet. The (b) (4) film coating is to (b) (4) The drug product is packaged in 60-count HDPE bottles with (b) (4) closures. A (b) (4) desiccant is included in each bottle (b) (4). Based on ongoing stability studies the drug product can be stored in the original container, with desiccant, at room temperature for 24 months. Long-term stability studies are being conducted at 25°C/60% RH. Studies at 30°C/75% RH, which would support use in Climatic Zone 4, have not been reported.

Manufacturing process is robust to consistently yield drug product with the required identity, strength, quality, purity, and potency. The microbiological quality of the drug product is controlled via an adequate upstream control strategy and a suitable stability testing protocol.

The dissolution acceptance criteria were not yet accepted by the biopharmaceutics review team at the time of this review because of the lack of (b) (4) dissolution data for the clinical batch at release and throughout the stability program. The deficiency was addressed by the Applicant and a final recommendation accepting the dissolution method is expected from the biopharmaceutics review team.

A final recommendation from the Office of Compliance was not issued at the time of this review. It is expected that, based on recent inspections and profile class history, the drug substance and drug product manufacturing, packaging and testing sites will have acceptable CGMP status, and approval of the application will be recommended.

4. Nonclinical Pharmacology/Toxicology

The NDA is recommended for approval from pharmacology and toxicology perspective. Please refer to the pharmacology and toxicology review by Drs. Yuen and Ghantous for full details.

No new pharmacology/toxicology studies were submitted to the NDA and there are no nonclinical pharmacology and toxicology issues that would preclude the approval of the FDC

5. Clinical Pharmacology

The NDA is recommended for approval from clinical pharmacology perspective. Please refer to the clinical pharmacology review by Drs. Chinn, Li, and Florian and biopharmaceutics review by Drs. Eradiri and Duan for full details

The pivotal trial (reviewed by the biopharmaceutics group) for this NDA was a relative bioavailability study which compared the pharmacokinetics of RAL and 3TC following the administration of RAL 400 mg and 3TC 150 mg together as single agents and the administration of RAL/3TC 300/150 mg FDC under fasted conditions. This was an open-label, single-dose, randomized, 2-treatment, 2-period, 2-sequence, crossover study in 108 healthy subjects. As shown in the Table below, similar exposures where obtained for both RAL/3TC except for RAL AUC_{inf} and concentration 12 hours pots-dose (C_{12}). The lower RAL C_{12} values are not expected to impact efficacy based on previous RAL clinical experience and PK/PD modeling and simulation provided by the Applicant. The predicted RAL C_{12} after multiple doses of the FDC are several-fold greater than the 45 nM, RAL minimum steady state C_{12} needed to maintain RAL efficacy.

Parameter	Raltegravir		Lamivudine	
	GMR	90% CI for GMR	GMR	90% CI for GMR
AUC_{0-t}	91.66	82.33-102.03	99.86	97.96-101.80
AUC_{inf}	87.85	79.49-97.09	99.69	97.91-101.50
C_{max}	103.75	89.88-119.77	102.50	98.49-106.67
C_{12}	85.87	78.62-93.79	101.82	98.95-104.77

It should be noted that the Applicant conducted another two relative bioavailability studies (P258 and P260) that were identical in design to the pivotal relative bioavailability studies with the exception of the source of the 3TC single agent (P258: European Union, P260: Canada). These studies were not reviewed.

The applicant also evaluated the effect of high-fat meal on the RAL/3TC FDC and the effect of etravirine on the pharmacokinetics of RAL. High-fat meal delayed absorption and slightly

lowered maximal concentrations of both RAL and 3TC by 23% and 21%, respectively. Overall systemic exposures (AUC) were not statistically significantly changed for RAL and 3TC and mean RAL C_{12} was increased by 20%. The study findings support the proposed recommendations to administer RAL/3TC FDC without regard to food which is also consistent with the current recommendation in the approved RAL and 3TC labels. The etravirine drug-drug interaction study did not produce significant changes in RAL exposure and therefore no dose adjustment is warranted upon the co-administration of RAL/3TC FDC and etravirine.

The clinical pharmacology review team concluded that the RAL/3TC FDC tablet is expected to be safe and effective in pediatric patients greater than 6 years of age and weighing at least 30 kg because:

1. The predicted RAL C_{12} of the FDC tablets is higher than the average exposure achieved by RAL single agent in children 6-12 years and therefore efficacy is not expected to be compromised.
2. The predicted RAL Cmax of the FDC is lower than Cmax observed in pediatric patients 6 to 18 years of age following the administration of RAL single agent.

Inspections of the three clinical and bioanalytical sites for Study P253 was requested and conducted. The Office of Scientific Investigations (OSI) Bioequivalence Establishment Inspection Report dated on 12/19/2014 determined that one of the three sites is acceptable. The inspection results of the other sites (the clinical site and on bioanalytical laboratory) were not yet finalized at the time of writing this memo. However, the final recommendation of the OSI is expected to clear the remaining sites.

6. Clinical Microbiology

The NDA is recommended for approval from clinical virology perspective. Please refer to the clinical virology review by Drs. Rhee and O'Rear for full details.

The Applicant did not conduct any new virology studies with the RAL/3TC FDC. The applicant submitted a virology study report (Report PD001) for longitudinal analysis of resistance development to ARVs in treatment-naïve HIV-1-infected subjects receiving a regimen containing 3TC (or emtricitabine (FTC)), RAL, and tenofovir disoproxil fumarate (TDF). The report results indicated that 3TC/FTC resistance emerges before or simultaneously with RAL resistance.

7. Clinical Efficacy and Safety

The NDA is recommended for approval from clinical perspective. Please refer to the clinical review by Drs. Boyd and Sherwat for full details.

The applicant did not conduct any new clinical efficacy trials to support this application. The approval of this application is based on the pivotal BE study (see clinical pharmacology). There were no new safety concerns observed for the RAL/COBI combination in the pivotal BE study.

8. Advisory Committee Meeting

An Advisory Committee meeting was not held for this application.

9. Pediatrics

There are no pediatric data in the application. The proposed indication of the FDC includes pediatrics patients older than 6 years of age and weighing > 30 kg which is consistent with the recommended dose of RAL and 3TC singles agents in this population. The Applicant submitted Initial Pediatric Study for RAL/3TC FDC to the Agency requesting partial waiver request for pediatrics < 6 years of age and between 6 and 16 years of age weighing < 30 Kg because the drug does not represent a meaningful therapeutic benefit over existing therapies and that the FDC does not have the flexibility needed for weight based dosing in this population. The proposal was approved by the FDA Pediatric Research Committee on 01/07/2015.

10. Other Relevant Regulatory Issues

Financial disclosures for the pivotal bioequivalence trial were reviewed by the CDTL. All investigators reported having no disclosed financial interests/arrangements. Financial disclosure information does not affect the approvability of this application.

11. Labeling

The proposed proprietary name DUTREBIS for RAL/3TC FDC was considered acceptable by DMEPA and DAVP. The following labeling changes were implemented:

1. The removal of [redacted] (b) (4) because the Applicant had no specific data to support the statement. Such statement should be reserved for cases where there is an identified or predicted concern, such as for modified-release products. The Applicant agreed to remove this information from labeling.
2. Removal of RAL and 3TC clinical trial information throughout the label [redacted] (b) (4) .

3. Table (b) (4) of section 7 containing clinical recommendations regarding drug-drug interactions was updated [redacted (b) (4)];
4. Removal of the [redacted (b) (4)] The patient labeling review team concurs with this recommendation.

12. Recommendations/Risk Benefit Assessment

12.1 Recommended Regulatory Action: Approval

12.2 Risk Benefit Assessment: The risk-benefit profile of RAL/3TC FDC is acceptable based on the assessment of the review team. Because RAL/3TC FDC combination produced comparable exposure to the RAL/3TC single agents when given together, the risks and benefits of the RAL/3TC FDC is considered similar to those of the RAL/3TC single agents administered together. Efficacy and safety of RAL/3TC combination as single agents was established previously in clinical trials in HIV-1 patients.

12.3 Recommendation for Postmarketing Risk Evaluation and Management Strategies: None

12.4 Recommendation for other Postmarketing Requirements and Commitments: A PMR will be issued for pediatric studies under the Pediatric Research Equity Act (PREA) and consistent with the Agreed Initial Pediatric Study Plan.

12.5 Recommended Comments to Applicant: None

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/s/

ISLAM R YOUNIS
01/18/2015