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RESEARCH**

APPLICATION NUMBER:

206510Orig1s000

MICROBIOLOGY / VIROLOGY REVIEW(S)

January 30, 2015

This review references the incorrect NDA 203510 in the header. The review is actually related to NDA 206510.

DIVISION OF ANTIVIRAL PRODUCTS (HFD-530)

VIROLOGY REVIEW

NDA: 203-510

SDN: 001

DATE REVIEWED: 10/10/14

Applicant Name and Address: Merck Sharp & Dohme Corp.
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Rahway, NJ 07065-0900

Reviewer Name(s): Sung S. Rhee, Ph.D.

Initial Submission Dates:

Correspondence Date: April 08, 2014

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Subsequent Submissions:

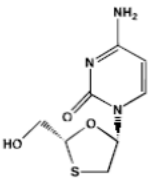
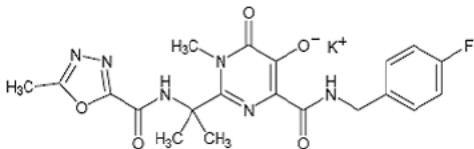
- Response to Information Request sent on June 20, 2014: July 03, 2014 (SDN 005)
- Resubmission of the revised resistance dataset, originally submitted in SDN 005, for Study Report PD001: July 18, 2014 (SDN 009)

Product Name(s): DUTREBIS tablet is a fixed-dose combination of lamivudine (150 mg) and raltegravir (300 mg). Chemical characteristics of individual components of DUTREBIS are listed below.

Proprietary: DUTREBIS™

Non-Proprietary/USAN: Lamivudine/Raltegravir FDC Tablet

Code Name/Number: LAM/RAL

Individual Component	Lamivudine (LAM)	Raltegravir (RAL)
Structure		
Chemical Name	(2R,cis)-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidin-2-one	N-[(4-Fluorophenyl)methyl]-1,6-dihydro-5-hydroxy-1-methyl-2-[1-methyl-1-[(5-methyl-1,3,4-oxadiazol-2-yl)carbonyl]amino]ethyl]-6-oxo-4-pyrimidinecarboxamide monopotassium salt
Molecular Formula	C ₈ H ₁₁ N ₃ O ₃ S	C ₂₀ H ₂₀ FKN ₆ O ₅
Molecular Weight	229.26	482.52
Drug Class	NRTI	INSTI
Supporting Document	NDA 020564	IND 69,928 & NDA 022145

Indication(s): Treatment of HIV-1 infection in combination with another antiretroviral agent in adults, adolescents (16 years of age and older), and pediatric patients (6 through

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16 years of age and weighing at least 30 kg)

Dosage Form(s): Tablet (LAM 150 mg and RAL 300 mg)

Route(s) of Administration: Oral

Recommended Dosage: One tablet taken twice daily with or without food

Dispensed: Rx X OTC (Discipline relevant)

Abbreviations: ARV, antiretroviral; BID, *bis in die* (twice a day); EC₅₀, effective concentration inhibiting viral replication by 50%; EC₉₅, effective concentration inhibiting viral replication by 95%; EFV, efavirenz; FDC, fixed-dose combination; FTC, emtricitabine; HIV-1, human immunodeficiency virus type 1; IN, integrase; INSTI, HIV-1 integrase strand transfer inhibitor; LAM, lamivudine; NDA, new drug application; NRTI, nucleos(t)ide reverse transcriptase inhibitor; QD, once daily; RAL, raltegravir; RT, reverse transcriptase; TDF, tenofovir disoproxil fumarate; VF, virologic failure

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EXECUTIVE SUMMARY

This original new drug application (NDA) is submitted for U.S. marketing approval of DUTREBIS tablets that contain a fixed-dose combination of two FDA-approved antiretrovirals (ARVs), lamivudine (LAM, 150 mg) and raltegravir (RAL, 300 mg). LAM (EPIVIR®; FDA initial approval on November 17, 1995) is an HIV-1 nucleoside reverse transcriptase inhibitor (NRTI) that consists of a dideoxy analog of cytidine. Intracellularly, LAM is phosphorylated by cellular enzymes to form LAM 5'-triphosphate that can inhibit the activity of the HIV-1 RT by competing with the natural substrate deoxycytidine 5'-triphosphate and by being incorporated into nascent viral DNA which results in chain termination. RAL (ISENTRESS®; FDA initial approval on October 12, 2007) is an HIV-1 integrase strand transfer inhibitor (INSTI) that specifically inhibits the strand transfer reaction of HIV-1 IN, and thereby prevents the covalent insertion (integration) of unintegrated linear HIV-1 DNA during the early phase of viral infection into the host cell genome necessary for the formation of the provirus. The integration of viral DNA into host chromosomal DNA is an essential step in the HIV-1 life cycle.

This 505(b)(2) NDA application, based on the relative bioavailability/bioequivalence registration strategy, contains quality and bridging safety/efficacy information to support the twice daily use of DUTREBIS tablets 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 and weighing at least 30 kg). The DUTREBIS tablet contains a new formulation of RAL (b) (4)

(b) (4) This change allowed for a lower dose, 300 mg, to be used in the fixed-dose combination product (b) (4) compared to the 400 mg in the ISENTRESS tablet.

The applicant has not conducted any nonclinical studies with DUTREBIS, or clinical Phase 2 or 3 studies of DUTREBIS in HIV-1-infected subjects, and thus **no new virology data for DUTREBIS were included in this NDA package to be reviewed**. Nonclinical and clinical virology information on LAM and RAL can be found individually in the US Prescribing Information for EPIVIR® (revised on November 18, 2011) and ISENTRESS® (revised on April 8, 2014), respectively. See also Clinical Virology reviews by Lalji Mishra, Ph.D. and Sung Rhee, Ph.D. for detailed virology descriptions of LAM and RAL, respectively. In addition, the applicant included a virology study report PD001 for longitudinal analysis of resistance development to ARVs in treatment-naïve HIV-1-infected subjects receiving a regimen containing LAM (or FTC), RAL, and TDF. Results from the analysis are summarized in Section 3 below.

1. Recommendations

1.1. Recommendation and Conclusion on Approvability: Approval of this 505(b)(2) NDA application for DUTREBIS tablet (LAM 150 mg/RAL 300 mg) is recommended with respect to Clinical Virology.

1.2. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, If Approvable: None

2. Administrative**2.1. Reviewer's Signature(s)**

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Sung S. Rhee, Ph.D.
Clinical Virology Reviewer

2.2. Concurrence

HFD-530/MicroTL/J. O'Rear, Ph.D.

CC:
HFD-530/NDA # 206510
HFD-530/Division File
HFD-530/PM/M. Borbor

3. Summary of Results Described in Study Report PD001: Longitudinal Analysis of Resistance Development to ARVs

Study Report Title: Longitudinal Analysis of Antiviral Drug Resistance Development in Treatment-Naïve HIV-1 Infected Patients Receiving a Regimen Containing Raltegravir, Tenofovir Disoproxil Fumarate, and Lamivudine or Emtricitabine

Analysis Objective: To determine in what order drug resistance emerged during virologic failure, and to determine whether a different anchor drug (RAL or EFV) influences the order of resistance emergence

Materials and Methods: Subjects who experienced virologic failure (VF) in Studies 004 (Markowitz *et al.*, 2009), 021 (STARTMRK; Lennox *et al.*, 2010; Virology review N022145.734), or 071 (Eron *et al.*, 2011; Virology review I069928.1894) underwent resistance testing as specified in the study protocol. VF subjects from these 3 treatment-naïve studies whose post-baseline virus developed resistance to any component of their ARV regimens were identified, by Week 96 in Studies 004 and 021, and by Week 48 [end of study] in Study 071, to be included in this longitudinal resistance analysis. Longitudinal plasma samples of these eligible VF subjects, collected at different post-baseline time points including the sample collected at the earliest time point where viral loads exceeded 400 copies/mL (nominal cutoff value for genotypic and phenotypic resistance testing), were subjected to genotypic and phenotypic drug resistance testing (b) (4). All genotypic and phenotypic resistance data were then utilized to assess resistance for each sample. The tested virus was classified as displaying resistance to a drug (1) if genotypic resistance data showed evidence of one or more of the following substitutions associated with drug resistance:

- IN substitutions associated with RAL resistance: L74M, E92Q, F121C/Y, E138A/K, G140A/S, Y143C/H/R, Q148H/K/R, N155H, S230R
- RT substitutions associated with EFV resistance: L100I, K103N, V106A/M, V108I, Y181C/I, Y188C/H/L, G190A/E/S, P225H, M230L, P236L
- RT substitutions associated with FTC/LAM resistance: M41L, K65R, T69S(insertion complex), Q151M, M184I/V, L210W, T215F/Y, K219E/Q
- RT substitutions associated with TDF resistance: M41L, K65R, T69S(insertion complex),

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K70E, Q151M, L210W, T215F/Y, K219E/Q

or (2) if phenotypic resistance data showed a fold-increase in EC_{50} values of >3 for EFV, FTC, LAM, or RAL, or of >1.4 for TDF

The temporal order of resistance emergence for each subject's virus was assessed by placing each subject into one of 5 potential categories:

- Bin 1: Anchor drug (RAL or EFV) resistance appeared without FTC/LAM resistance
- Bin 2: Anchor drug (RAL or EFV) resistance appeared before FTC/LAM resistance
- Bin 3: Resistance to Anchor drug (RAL or EFV) and FTC/LAM appeared simultaneously
- Bin 4: Anchor drug (RAL or EFV) resistance appeared after FTC/LAM resistance
- Bin 5: FTC/LAM resistance appeared without Anchor drug (RAL or EFV) resistance

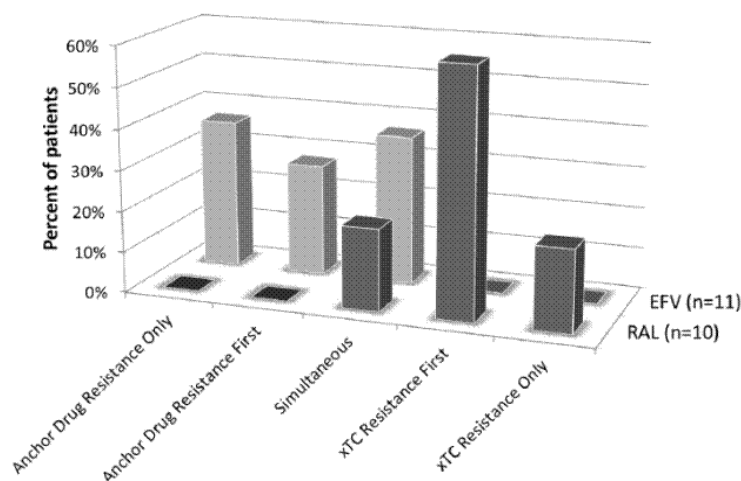
There were 3 instances where viruses were resistant to FTC at a time point where RAL resistance data were missing due to a failed test, but RAL resistance was observed at later time points. In these cases, RAL resistance was imputed to occur at the earlier time point (i.e., assigned to Bin 3 instead of Bin 4).

Summary of Results: The applicant has combined the resistance data from Studies 004 and 021 in this longitudinal resistance analysis, given the small number of VF subjects and the similar study design. These 2 studies were conducted in treatment-naïve subjects and compared the efficacy of RAL versus EFV, both administered with 2 background NRTIs (LAM+TDF in Study 104 and FTC+TDF in Study 021). By 96 weeks of treatment, a total of 10 and 11 VF subjects were identified as those who failed the RAL-containing and EFV-containing regimens, respectively, with resistance to any component of their ARV regimens. Resistance data of longitudinal virus samples from these subjects were included in this Analysis. The 11 RAL-treatment VF subjects had successful longitudinal IN resistance data against RAL on samples collected at 2 to 15 different post-baseline time points (median of 7) and RT resistance data against 2 background NRTIs on those collected at 3 to 15 different post-baseline time points (median of 6.5). The 10 EFV-treatment VF subjects had successful longitudinal RT resistance data against EFV and 2 background NRTIs on samples collected at 1 to 8 different post-baseline time points (median of 5). Drug resistance of each sample was determined and was placed into one of the 5 categories depending upon the order in which the virus developed resistance to each study drug as described in Materials and Methods, which was summarized in Appendix Table 1. Figure 1 (Study Report PD001, page 7) compares the temporal order of resistance for VF subjects receiving a RAL-based or EFV-based regimen.

In Studies 004 and 021 combined, resistance to FTC or LAM (FTC/LAM, denoted "xTC" in Figure 1) always emerged before RAL resistance (60%, 6/10) or simultaneously with RAL resistance (20%, 2/10); in some subjects (n=2, 20%), FTC/LAM resistance was observed without subsequent development of RAL resistance. By contrast, EFV resistance always emerged before FTC/LAM resistance (27.3%, 3/11) or simultaneously with FTC/LAM resistance (36.4%, 4/11), and in some subjects (n=4, 36.4%) EFV resistance appeared without subsequent appearance of FTC/LAM resistance. It should be noted that there is a limitation of this analysis: frequency of resistance testing was restricted to blood collection time points predetermined by the clinical protocol. The time points were typically 2 weeks apart early in the trials, later stretching to 4 and then 8 weeks apart. More frequent sampling may have revealed temporal differences in resistance emergence which may not be apparent with infrequent sampling. The

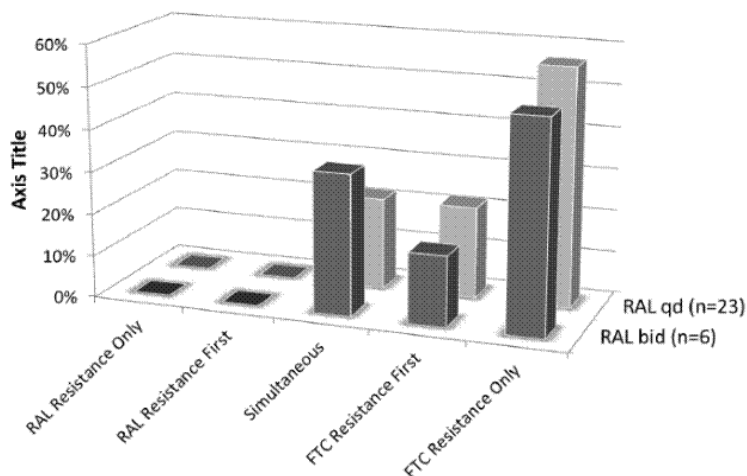
present analysis may therefore overestimate the frequency with which resistance to FTC/LAM and the anchor drug (RAL or EFV) appeared simultaneously.

Figure 1: Temporal Order of Resistance Emergence to ARVs in Studies 004 and 021 Combined



This observed pattern of FTC/LAM resistance emerging before (or simultaneously with) RAL resistance was confirmed in Study 071 (Figure 2; Study Report PD001, page 8). In Study 071 where the efficacy of RAL 400 mg BID was compared to RAL 800 mg QD, each in combination with FTC+TDF in treatment-naïve subjects, 29 subjects were identified as those having post-baseline virus resistant to one of more study drug (6 subjects in the RAL 400 mg BID arm and 23 subjects in the RAL 800 mg QD arm). These subjects had a median of 2 resistance tests (ranging from 1 to 6) each for RAL and FTC/TDF. Drug resistance of each sample was summarized in Appendix Table 1. Consistent with the findings from Studies 004 and 021, resistance to FTC appeared before RAL resistance (20.7%, 6/29) or simultaneously with RAL resistance (24.1%, 7/29). In 55.2% (16/29) of the subjects evaluated, viruses developed FTC resistance without subsequently developing RAL resistance while participating in the study. RAL resistance was never observed to appear prior to FTC resistance.

Figure 2: Temporal Order of Resistance Emergence to ARVs in Study 071



PACKAGE INSERT UPDATES: Sections 12.1 and 12.4

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Section 12.1 Mechanism of Action

DUTREBIS is a fixed-dose combination of HIV-1 antiviral drugs lamivudine and raltegravir [see *Microbiology* (12.4)].

Section 12.4 Microbiology***Mechanism of Action***

Lamivudine: Lamivudine is an HIV-1 nucleoside analogue reverse transcriptase inhibitor (NRTI). Intracellularly, lamivudine is phosphorylated to its active 5'-triphosphate metabolite, lamivudine triphosphate (3TC-TP). The principal mode of action of 3TC-TP is the inhibition of HIV-1 reverse transcriptase (RT) via DNA chain termination after incorporation of the nucleotide analogue into viral DNA.

Raltegravir: Raltegravir inhibits the (b) (4) =strand transfer activity of HIV-1 integrase (integrase strand transfer inhibitor; INSTI), an HIV-1 encoded enzyme that is required for viral replication. Inhibition of integrase prevents the covalent insertion, or integration, of unintegrated linear HIV-1 DNA into the host cell genome preventing the formation of the HIV-1 provirus. The provirus is required to direct the production of progeny virus, so inhibiting integration prevents propagation of the viral infection.

Antiviral Activity in Cell Culture

Lamivudine: The antiviral activity of lamivudine against HIV-1 was assessed in a number of cell lines (including monocytes and fresh human peripheral blood lymphocytes) using standard susceptibility assays. EC₅₀ values (50% effective concentrations) were in the range of 0.003 to 15 µM (1 µM = 0.23 mcg/mL). HIV-1 from therapy-naïve subjects with no amino acid substitutions associated with resistance gave median EC₅₀ values of 0.429 µM (range: 0.200 to 2.007 µM) from Virco (n = 92 baseline samples from COLA40263) and 2.35 µM (1.37 to 3.68 µM) from Monogram Biosciences (n = 135 baseline samples from ESS30009). The EC₅₀ values of lamivudine against different HIV-1 clades (A-G) ranged from 0.001 to 0.120 µM, and against HIV-2 isolates from 0.003 to 0.120 µM in peripheral blood mononuclear cells. Ribavirin (50 µM) decreased the anti-HIV-1 activity of lamivudine by 3.5 fold in MT-4 cells. In HIV-1-infected MT-4 cells, lamivudine in combination with zidovudine at various ratios exhibited synergistic antiretroviral activity.

Raltegravir: Raltegravir at concentrations of 31 ± 20 nM resulted in 95% inhibition (EC₉₅) of viral spread (relative to an untreated virus-infected culture) in human T-lymphoid cell cultures infected with the cell-line adapted HIV-1 variant H9IIIB. In addition, 5 clinical isolates of HIV-1 subtype B had EC₉₅ values ranging from 9 to 19 nM in cultures of mitogen-activated human peripheral blood mononuclear cells. In a single-cycle infection assay, raltegravir inhibited infection of 23 HIV-1 isolates representing 5 non-B subtypes (A, C, D, F, and G) and 5 circulating recombinant forms (AE, AG, BF, BG, and cpx) with EC₅₀ values ranging from 5 to 12

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nM. Raltegravir also inhibited replication of an HIV-2 isolate when tested in CEMx174 cells (EC₉₅ value = 6 nM). Additive to synergistic antiretroviral activity was observed when human T-lymphoid cells infected with the H9IIIB variant of HIV-1 were incubated with raltegravir in combination with non-nucleoside reverse transcriptase inhibitors (delavirdine, efavirenz, or nevirapine); nucleoside reverse transcriptase inhibitors (abacavir, didanosine, lamivudine, stavudine, tenofovir, zalcitabine, or zidovudine); protease inhibitors (amprenavir, atazanavir, indinavir, lopinavir, nelfinavir, ritonavir, or saquinavir); or the entry inhibitor enfuvirtide.

Resistance

Lamivudine: Lamivudine-resistant variants of HIV-1 have been selected in cell culture and in subjects treated with lamivudine. Genotypic analysis showed that the resistance was due to a specific amino acid substitution in the HIV-1 reverse transcriptase at codon 184 changing the methionine to either isoleucine or valine (M184V/I).

(b) (4)

Raltegravir: The mutations observed in the HIV-1 integrase coding sequence that contributed to raltegravir resistance (evolved either in cell culture or in subjects treated with raltegravir) generally included an amino acid substitution at either Y143 (changed to C, H, or R) or Q148 (changed to H, K, or R) or N155 (changed to H) plus one or more additional substitutions (i.e., L74M, E92Q, Q95K/R, T97A, E138A/K, G140A/S, V151I, G163R, H183P, Y226C/D/F/H, S230R, and D232N). E92Q and F121C are occasionally seen in the absence of substitutions at Y143, Q148, or N155 in raltegravir-treatment failure subjects.

(b) (4)

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(b) (4)

Cross Resistance

Lamivudine: Cross-resistance has been observed among NRTIs. The M184I/V lamivudine resistance substitution confers resistance to emtricitabine. Lamivudine-resistant HIV-1 mutants were also cross-resistant to didanosine (ddI) and zalcitabine (ddC). In some subjects treated with zidovudine plus didanosine or zalcitabine, isolates resistant to multiple reverse transcriptase inhibitors, including lamivudine, have emerged.

Raltegravir: Cross-resistance has been observed among INSTIs. Amino acid substitutions in HIV-1 integrase conferring resistance to raltegravir generally also confer resistance to elvitegravir. Substitutions at amino acid Y143 confer greater reductions in susceptibility to raltegravir than to elvitegravir, and the E92Q substitution confers greater reductions in susceptibility to elvitegravir than to raltegravir. Viruses harboring a substitution at amino acid Q148, along with one or more other raltegravir resistance substitutions, may also have clinically significant resistance to dolutegravir.

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Appendix Table 1: Summary of Resistance Data Obtained from 50 Subjects Included in Longitudinal Analysis of Resistance Development to ARVs in Studies 004, 021, and 071

Study	Arm	AN	VF week	Last week	Resistance Test Week	3TC/FTC resistance	EFV resistance	RAL resistance	TDF Resistance	ASSIGNED BIN**
PN071	RAL qd	39413	64	96	60	Yes	N/A	No	No	
PN071	RAL qd	39413	64	96	72	Yes	N/A	No	No	
PN071	RAL qd	39413	64	96	84	Yes	N/A	No Data	No	5
PN071	RAL qd	39426	60	71	60	Yes	N/A	No Data	No	
PN071	RAL qd	39426	60	71	71	No Data	N/A	No	No Data	5
PN071	RAL bid	39516	25	37	24	Yes	N/A	No	No	5
PN071	RAL qd	39601	18	18	4	Yes	N/A	No	No	
PN071	RAL qd	39601	18	18	12	Yes	N/A	Yes	No	
PN071	RAL qd	39601	18	18	16	Yes	N/A	Yes	No	4
PN071	RAL qd	40190	11	14	8	Yes	N/A	No	No	
PN071	RAL qd	40190	11	14	12	Yes	N/A	No	No	5
PN071	RAL qd	40917	11	18	8	Yes	N/A	No	No	
PN071	RAL qd	40917	11	18	12	Yes	N/A	Yes	No	4
PN071	RAL bid	40930	48	64	48	No	N/A	No	No	
PN071	RAL bid	40930	48	64	60	Yes	N/A	No	No	5
PN071	RAL bid	40932	36	72	12	No	N/A	No	No	
PN071	RAL bid	40932	36	72	60	Yes	N/A	No Data	No	
PN071	RAL bid	40932	36	72	48	Yes	N/A	Yes	No	3
PN071	RAL qd	40937	14	14	4	Yes	N/A	No	No	
PN071	RAL qd	40937	14	14	8	Yes	N/A	No	No	
PN071	RAL qd	40937	14	14	12	Yes	N/A	Yes	No	4
PN071	RAL qd	40973	24	30	24	Yes	N/A	No	No	5
PN071	RAL qd	41009	22	22	2	No	N/A	No	No	
PN071	RAL qd	41009	22	22	4	No	N/A	No	No	
PN071	RAL qd	41009	22	22	8	Yes	N/A	No	No	
PN071	RAL qd	41009	22	22	12	Yes	N/A	Yes	No	
PN071	RAL qd	41009	22	22	16	Yes	N/A	Yes	No	4
PN071	RAL bid	41022	24	24	2	No	N/A	No	No	
PN071	RAL bid	41022	24	24	4	Yes	N/A	No Data	No	
PN071	RAL bid	41022	24	24	8	Yes	N/A	No Data	No	
PN071	RAL bid	41022	24	24	12	Yes	N/A	No Data	No	
PN071	RAL bid	41022	24	24	16	Yes	N/A	No Data	No	
PN071	RAL bid	41022	24	24	24	Yes	N/A	Yes	No	3
PN071	RAL bid	41041	26	34	4	Yes	N/A	No	No	
PN071	RAL bid	41041	26	34	8	Yes	N/A	No	No	
PN071	RAL bid	41041	26	34	12	Yes	N/A	Yes	No	
PN071	RAL bid	41041	26	34	16	Yes	N/A	Yes	No	
PN071	RAL bid	41041	26	34	24	Yes	N/A	Yes	No	4
PN071	RAL qd	41053	22	57	2	No	N/A	No	No	

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Appendix Table 1-continued

Study	Arm	AN	VF week	Last week	Resistance Test Week	3TC/FTC resistance	EFV resistance	RAL resistance	TDF Resistance	ASSIGNED BIN**
PN071	RAL qd	41053	22	57	8	Yes	N/A	Yes	No	
PN071	RAL qd	41053	22	57	12	Yes	N/A	Yes	No	
PN071	RAL qd	41053	22	57	16	Yes	N/A	Yes	No	
PN071	RAL qd	41053	22	57	24	Yes	N/A	Yes	Yes	
PN071	RAL qd	41053	22	57	36	Yes	N/A	Yes	No	3
PN071	RAL qd	41067	23	38	12	Yes	N/A	No	No	
PN071	RAL qd	41067	23	38	16	Yes	N/A	No	No	
PN071	RAL qd	41067	23	38	24	Yes	N/A	No	No	
PN071	RAL qd	41067	23	38	36	No Data	N/A	No	No Data	5
PN071	RAL qd	41078	24	50	36	No	N/A	No	No	
PN071	RAL qd	41078	24	50	48	Yes	N/A	No	No	5
PN071	RAL bid	41088	6	12	4	No Data	N/A	No Data	No Data	
PN071	RAL bid	41088	6	12	8	Yes	N/A	No	No	5
PN071	RAL qd	41113	12	59	36	Yes	N/A	No	No	
PN071	RAL qd	41113	12	59	48	Yes	N/A	No	No	5
PN071	RAL qd	41116	22	22	8	Yes	N/A	No	No	
PN071	RAL qd	41116	22	22	22	Yes	N/A	No	No	5
PN071	RAL qd	41154	24	39	12	Yes	N/A	No	No	
PN071	RAL qd	41154	24	39	24	Yes	N/A	No	No	5
PN071	RAL qd	41160	15	21	15	Yes	N/A	Yes	No	
PN071	RAL qd	41160	15	21	24	Yes	N/A	Yes	No	3
PN071	RAL qd	41663	25	49	12	Yes	N/A	No	No	
PN071	RAL qd	41663	25	49	16	Yes	N/A	No	No	
PN071	RAL qd	41663	25	49	25	Yes	N/A	Yes	No	4
PN071	RAL qd	41063	11	15	2	No Data	N/A	No Data	No Data	
PN071	RAL qd	41063	11	15	4	No Data	N/A	No Data	No Data	
PN071	RAL qd	41063	11	15	8	No Data	N/A	No Data	No Data	
PN071	RAL qd	41063	11	15	11	No Data	N/A	No Data	No Data	
PN071	RAL qd	41063	11	15	15	Yes	N/A	Yes	No	3
PN071	RAL qd	40929	24	54	36	Yes	N/A	No	No	5
PN071	RAL qd	40955	48	51	48	Yes	N/A	No	No	5
PN071	RAL qd	40972	36	39	36	Yes	N/A	No	No	5
PN071	RAL qd	40983	12	12	12	Yes	N/A	No	No	5
PN071	RAL qd	40999	16	16	16	Yes	N/A	Yes	No	3
PN071	RAL qd	41012	26	26	24	Yes	N/A	Yes	No	3
PN021	RAL bid	23194	24	193	8	Yes	N/A	No	No	
PN021	RAL bid	23194	24	193	12	Yes	N/A	No Data	No	
PN021	RAL bid	23194	24	193	16	Yes	N/A	Yes	No	
PN021	RAL bid	23194	24	193	32	Yes	N/A	Yes	No	

DIVISION OF ANTIVIRAL PRODUCTS (HFD-530)

VIROLOGY REVIEW

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DATE REVIEWED: 10/10/14

Appendix Table 1-continued

Study	Arm	AN	VF week	Last week	Resistance Test Week	3TC/FTC resistance	EFV resistance	RAL resistance	TDF Resistance	ASSIGNED BIN**
PN021	RAL bid	23194	24	193	40	Yes	N/A	Yes	No	
PN021	RAL bid	23194	24	193	43	Yes	N/A	Yes	No	
PN021	RAL bid	23194	24	193	48	Yes	N/A	Yes	No	
PN021	RAL bid	23194	24	193	60	Yes	N/A	Yes	No	
PN021	RAL bid	23194	24	193	72	Yes	N/A	Yes	No	
PN021	RAL bid	23194	24	193	84	Yes	N/A	Yes	No	
PN021	RAL bid	23194	24	193	97	Yes	N/A	Yes	No	
PN021	RAL bid	23194	24	193	109	Yes	N/A	Yes	No	
PN021	RAL bid	23194	24	193	122	Yes	N/A	Yes	No	
PN021	RAL bid	23194	24	193	134	Yes	N/A	Yes	No	4
PN021	RAL bid	23261	17	28	2	No	N/A	No	No	
PN021	RAL bid	23261	17	28	4	Yes	N/A	No	No	
PN021	RAL bid	23261	17	28	8	Yes	N/A	Yes	No	
PN021	RAL bid	23261	17	28	12	Yes	N/A	Yes	No	
PN021	RAL bid	23261	17	28	17	Yes	N/A	Yes	No	4
PN021	RAL bid	23236	60	73	60	Yes	N/A	No	No	
PN021	RAL bid	23236	60	73	64	Yes	N/A	Yes	No	
PN021	RAL bid	23236	60	73	72	Yes	N/A	Yes	No	4
PN021	RAL bid	23304	12	14	2	Yes	N/A	No	No	
PN021	RAL bid	23304	12	14	8	Yes	N/A	Yes	No	
PN021	RAL bid	23304	12	14	12	Yes	N/A	Yes	No	4
PN021	RAL bid	20094	24	37	31	Yes	N/A	No Data	No	
PN021	RAL bid	20094	24	37	33	No Data	N/A	Yes	No Data	
PN021	RAL bid	20094	24	37	35	Yes	N/A	No Data	No	
PN021	RAL bid	20094	24	37	37	Yes	N/A	No	No	3
PN021	RAL bid	20082	23	141	23	Yes	N/A	No	No	
PN021	RAL bid	20082	23	141	31	Yes	N/A	No	No	
PN021	RAL bid	20082	23	141	40	Yes	N/A	No	No	
PN021	RAL bid	20082	23	141	48	Yes	N/A	No	No	
PN021	RAL bid	20082	23	141	59	No	N/A	No	No	
PN021	RAL bid	20082	23	141	72	Yes	N/A	No	No	
PN021	RAL bid	20082	23	141	85	Yes	N/A	No	No	
PN021	RAL bid	20082	23	141	97	Yes	N/A	No	No	5
PN021	EFV	20105	60	204	60	No Data	No Data	N/A	No Data	
PN021	EFV	20105	60	204	72	No	Yes	N/A	No	
PN021	EFV	20105	60	204	85	No	Yes	N/A	No	1
PN021	EFV	23209	77	91	77	No	Yes	N/A	No	
PN021	EFV	23209	77	91	84	Yes	Yes	N/A	No	
PN021	EFV	23209	77	91	91	Yes	Yes	N/A	Yes	2

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Appendix Table 1-continued

Study	Arm	AN	VF week	Last week	Resistance Test Week	3TC/FTC resistance	EFV resistance	RAL resistance	TDF Resistance	ASSIGNED BIN**
PN021	EFV	23408	60	64	64	Yes	Yes	N/A	No	3
PN021	EFV	23500	40	74	40	Yes	Yes	N/A	No	
PN021	EFV	23500	40	74	48	Yes	Yes	N/A	No	
PN021	EFV	23500	40	74	60	Yes	Yes	N/A	No	
PN021	EFV	23500	40	74	72	Yes	Yes	N/A	No	3
PN021	EFV	21597	24	62	31	No	Yes	N/A	No	
PN021	EFV	21597	24	62	34	No	Yes	N/A	No	
PN021	EFV	21597	24	62	40	No	Yes	N/A	No	
PN021	EFV	21597	24	62	48	No	Yes	N/A	No	
PN021	EFV	21597	24	62	62	No	Yes	N/A	No	1
PN021	EFV	23189	72	145	76	No	Yes	N/A	No	
PN021	EFV	23189	72	145	85	Yes	Yes	N/A	No	
PN021	EFV	23189	72	145	88	Yes	Yes	N/A	No	
PN021	EFV	23189	72	145	97	Yes	Yes	N/A	No	
PN021	EFV	23189	72	145	110	Yes	Yes	N/A	No	
PN021	EFV	23189	72	145	122	Yes	Yes	N/A	No	
PN021	EFV	23189	72	145	125	Yes	Yes	N/A	No	
PN021	EFV	23189	72	145	133	Yes	Yes	N/A	No	2
PN021	EFV	23252	28	29	2	No	No	N/A	No	
PN021	EFV	23252	28	29	4	No	No	N/A	No	
PN021	EFV	23252	28	29	8	No	Yes	N/A	No	
PN021	EFV	23252	28	29	12	No	Yes	N/A	No	
PN021	EFV	23252	28	29	16	No	Yes	N/A	No	
PN021	EFV	23252	28	29	24	No	Yes	N/A	No	
PN021	EFV	23252	28	29	25	No Data	No Data	N/A	No Data	
PN021	EFV	23252	28	29	28	No	Yes	N/A	No	1
PN021	EFV	23294	23	245	23	No	Yes	N/A	No	
PN021	EFV	23294	23	245	26	No	Yes	N/A	No	
PN021	EFV	23294	23	245	72	Yes	No	N/A	No	
PN021	EFV	23294	23	245	84	No	Yes	N/A	No	
PN021	EFV	23294	23	245	97	No Data	No Data	N/A	No Data	
PN021	EFV	23294	23	245	110	No	Yes	N/A	No	2
PN021	EFV	23324	13	25	2	No Data	No Data	N/A	No Data	
PN021	EFV	23324	13	25	4	No	No	N/A	No	
PN021	EFV	23324	13	25	8	No Data	No Data	N/A	No Data	
PN021	EFV	23324	13	25	12	No	Yes	N/A	No	
PN021	EFV	23324	13	25	25	No Data	No Data	N/A	No Data	1
PN004	RAL bid	345	6	12	2	No	N/A	No	No	
PN004	RAL bid	345	6	12	4	Yes	N/A	Yes	No	

DIVISION OF ANTIVIRAL PRODUCTS (HFD-530)

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SDN: 001

DATE REVIEWED: 10/10/14

Appendix Table 1-continued

Study	Arm	AN	VF week	Last week	Resistance Test Week	3TC/FTC resistance	EFV resistance	RAL resistance	TDF Resistance	ASSIGNED BIN**
PN004	RAL bid	345	6	12	5	Yes	N/A	Yes	No	3
PN004	RAL bid	345	6	12	6	Yes	N/A	Yes	No	
PN004	RAL bid	345	6	12	7	Yes	N/A	Yes	No	
PN004	RAL bid	345	6	12	10	No Data	N/A	Yes	No Data	
PN004	RAL bid	345	6	12	11	Yes	N/A	Yes	No	
PN004	RAL bid	345	6	12	12	Yes	N/A	Yes	No	
PN004	RAL bid	363	23	81	1	No	N/A	No	No	4
PN004	RAL bid	363	23	81	2	Yes	N/A	No	No	
PN004	RAL bid	363	23	81	8	Yes	N/A	Yes	No	
PN004	RAL bid	363	23	81	12	Yes	N/A	Yes	No	
PN004	RAL bid	363	23	81	16	Yes	N/A	Yes	No	
PN004	RAL bid	363	23	81	23	Yes	N/A	Yes	Yes	
PN004	RAL bid	363	23	81	25	Yes	N/A	Yes	Yes	
PN004	RAL bid	363	23	81	33	Yes	N/A	Yes	Yes	
PN004	RAL bid	363	23	81	40	Yes	N/A	Yes	Yes	
PN004	RAL bid	363	23	81	47	Yes	N/A	Yes	Yes	
PN004	RAL bid	363	23	81	60	Yes	N/A	Yes	Yes	
PN004	RAL bid	363	23	81	72	Yes	N/A	Yes	Yes	
PN004	RAL bid	363	23	81	79	Yes	N/A	Yes	Yes	
PN004	RAL bid	398	12	151	7	Yes	N/A	No	No	4
PN004	RAL bid	398	12	151	12	Yes	N/A	No	No	
PN004	RAL bid	398	12	151	13	Yes	N/A	No	No	
PN004	RAL bid	398	12	151	15	Yes	N/A	No	No	
PN004	RAL bid	398	12	151	24	Yes	N/A	No	No	
PN004	RAL bid	398	12	151	32	Yes	N/A	No	No	
PN004	RAL bid	398	12	151	40	Yes	N/A	No	No	
PN004	RAL bid	398	12	151	49	Yes	N/A	No	No	
PN004	RAL bid	398	12	151	61	Yes	N/A	No	No	
PN004	RAL bid	398	12	151	87	Yes	N/A	Yes	No	
PN004	RAL bid	398	12	151	97	Yes	N/A	Yes	No	
PN004	RAL bid	398	12	151	109	Yes	N/A	Yes	No	
PN004	RAL bid	398	12	151	122	Yes	N/A	Yes	No	
PN004	RAL bid	398	12	151	134	Yes	N/A	Yes	No	
PN004	RAL bid	398	12	151	151	Yes	N/A	Yes	No	
PN004	RAL bid	399	7	12	2	No	N/A	No	No	
PN004	RAL bid	399	7	12	4	No	N/A	No	No	
PN004	RAL bid	399	7	12	7	Yes	N/A	No	No	
PN004	RAL bid	399	7	12	9	Yes	N/A	No	No	
PN004	RAL bid	399	7	12	10	Yes	N/A	No	No	

DIVISION OF ANTIVIRAL PRODUCTS (HFD-530)

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Appendix Table 1-continued

Study	Arm	AN	VF week	Last week	Resistance Test Week	3TC/FTC resistance	EFV resistance	RAL resistance	TDF Resistance	ASSIGNED BIN**
PN004	RAL bid	399	7	12	12	Yes	N/A	No	No	5
PN004	EFV	118	8	80	4	Yes	Yes	N/A	Yes	3
PN004	EFV	118	8	80	8	Yes	Yes	N/A	Yes	
PN004	EFV	118	8	80	12	Yes	Yes	N/A	Yes	
PN004	EFV	118	8	80	16	Yes	Yes	N/A	Yes	
PN004	EFV	118	8	80	24	Yes	Yes	N/A	Yes	
PN004	EFV	311	60	108	48	Yes	Yes	N/A	No	3
PN004	EFV	311	60	108	60	Yes	Yes	N/A	No	
PN004	EFV	311	60	108	62	Yes	Yes	N/A	No	
PN004	EFV	311	60	108	72	Yes	Yes	N/A	No	
PN004	EFV	311	60	108	84	Yes	Yes	N/A	No	
PN004	EFV	311	60	108	96	Yes	Yes	N/A	No	
PN004	EFV	311	60	108	108	Yes	Yes	N/A	No	

Source: Study Report PD001, Appendix Table 1, pages 11-16

Bin assignment refers to which category each subject was placed in as described in the Materials and Methods section.

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

/s/

SUNG S RHEE
12/11/2014

JULIAN J O REAR
12/11/2014

MEMORANDUM



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

DATE: 18 August 2014

TO: NDA 206510

FROM: Jessica G. Cole, PhD
Review Microbiologist
CDER/OPS/New Drug Microbiology Staff
(301) 796-5148

THROUGH: Bryan Riley, PhD
Microbiology Team Leader
CDER/OPS/New Drug Microbiology Staff

cc: Althea Cuff
Project Manager
CDER/OPS/ONDQA

SUBJECT: Product Quality Microbiology assessment of Microbial Limits for
Dutrebis (lamivudine/raltegravir) tablet [Submission Date: 08 April
2014]

The microbial control strategy for Dutrebis (lamivudine/raltegravir) is acceptable from a Product Quality Microbiology perspective. The applicant has proposed a waiver of microbial enumeration at release but adequate upstream controls are established. This submission is recommended for approval from the standpoint of product quality microbiology.

Dutrebis (lamivudine/raltegravir) is a film-coated tablet for oral administration. The [REDACTED] (b) (4) step has a maximum hold time of [REDACTED] (b) (4) and the applicant proposed a waiver for microbial enumeration release tests.

The formal stability batches included testing for Microbial Limits using a method consistent with USP Chapter <61> (Microbiological Examination of Non-sterile Products: Microbial Enumeration Tests) and <62> (Microbiological Examination of Non-sterile Products: Tests for Specified Microorganisms). The Microbial Limits acceptance criteria are consistent with USP Chapter <1111> (Microbiological Examination of Non-sterile Products: Acceptance Criteria for Pharmaceutical Preparations and Substances for Pharmaceutical Use).

Information request sent in the 74 day letter and summary of the 03 July 2014 response

MEMORANDUM

1. We refer to Module 3.2.P.8.1.2.5. Justify the inclusion of USP<61> but not USP<62> tests for the formal stability batches WL00047478, WL00047479, and WL00047480. USP<1111> recommends the absence of *Escherichia coli* for solid oral dosage forms and any deviations from these recommendations should be justified.

The USP<62> test for the absence of *E. coli* was included in the stability program for the registration batches and the results were acceptable at release and 12 months.

2. Confirm that the USP microbial enumeration studies were verified to be suitable for use according to the methods described in USP<61> and <62>.

The compendial methods were verified for use according to the recommendation in USP<61> and <62>.

3. Provide the maximum hold time, or a bioburden specification, (b) (4). Any extended hold times should be supported by data that demonstrate low levels of contaminating microorganisms will not proliferate to unsafe levels.

The applicant proposed a maximum holding time (b) (4). A sampling study was conducted where TAMC, TYMC, and the absence of *E. coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and *Salmonella* were evaluated at the beginning and end of the process.

Information request sent on 14 July 2014 and summary 01 August 2014 response

We refer to your 03 July 2014 response to question 6 from the filing communication regarding the holding time (b) (4). The data presented in Table 6 do not allow for an evaluation of the potential for microbial proliferation (b) (4) during the proposed (b) (4) hold time.

1. Provide the time interval between the samples collected (b) (4) for batches 1015680, 1015690, and 1015700.
2. If applicable, describe any (b) (4) steps involved in the (b) (4) preparation.
3. With the proposed absence of any routine microbial enumeration release studies the (b) (4) controls for the (b) (4) are critical to control the final bioburden in the proposed drug product. If the sample interval for batch 1015680 does not approach the proposed (b) (4) interval, then justify the proposed (b) (4) hold time. Historical data from similar products may be applicable and could be used to support the proposed (b) (4) hold time.

The applicant provided the requested intervals, which are shown in Table 1. (b) (4)

MEMORANDUM

Table 1- Results from microbial sampling (b) (4) (Sponsor Table 1 from 01 August 2014 amendment)

Sample Description	Batch Number	Time From Previous MLT Sample Taken	Results				<i>E. coli</i>
			Total aerobic average plate counts	Total aerorbic dilution factor	Total aerobic microbial count	Total combined yeast and mold	
(b) (4)	1015680	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	Absent
							Absent
	1015690						Absent
							Absent
	1015700						Absent
							Absent
							Absent
							Absent
<i>Acceptance Criteria^a: Total aerobic microbial count < (b) (4) cfu/ml</i> <i>Total combined yeast and mold < (b) (4) cfu/ml (yeasts and molds)</i> <i>Absence of E. coli</i> <i>a: Presence of Pseudomonas aeruginosa, Staphylococcus aureus and Salmonella sp were also tested and found to be absent</i>							

REVIEWER COMMENT- This study does not evaluate the potential for growth of low numbers of microorganisms potentially present (b) (4). However, the three batches evaluated contained low number of microorganisms and adequate microbial control of raw materials and routine cleaning of the equipment are likely to keep the bioburden levels low during the (b) (4) hold time. Under cGMPs, the risk to patients of excessive microbial growth and/or toxin production is low. As such, no additional information will be requested at this time.

4. You propose waiving microbial limits release testing for your drug product. This will be evaluated during the review process and after receipt of the information requested here. However, you should minimally perform microbiological testing at the initial stability time point for the annual stability batches. Provide an updated stability schedule to reflect this testing. Include the proposed limits for USP<61> and <62> test methods.

The applicant updated the annual stability program to include microbial enumeration at release. The specification was also updated to include reference to USP<61> and <62> testing to occur on stability at the initial time point. Any significant shift in microbial control would be detectable in the stability program.

MEMORANDUM

ADEQUATE

Reviewer Comments – The microbiological quality of the drug product is controlled via an adequate upstream control strategy and a suitable stability testing protocol.

END

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

/s/

JESSICA COLE
08/18/2014

BRYAN S RILEY
08/18/2014
I concur.