

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

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OFFICE DIRECTOR MEMO

Deputy Office Director Decisional Memo

Date	(electronic stamp)
From	John Farley, M.D.,M.P.H.
Subject	Deputy Office Director Decisional Memo
NDA #	202022
Applicant Name	Tibotec
Date of Submission	July 23, 2010
PDUFA Goal Date	May 23, 2011
Proprietary Name / Established (USAN) Name	Edurant/ Rilpivirine
Dosage Forms / Strength	25 mg tablets
Proposed Indication	In combination with other antiretroviral agents for the treatment of HIV-1 infection in treatment-naïve adult patients
Action:	Approval

Material Reviewed/Consulted	Names of discipline reviewers
OND Action Package, including:	
Medical Officer Review	Yodit Belew MD
Statistical Review	Lei Nie, Ph.D, Fraser Smith Ph.D
Pharmacology Toxicology Review	Mark Seaton Ph.D, Hanan Ghantous Ph.D, DABT, A Jacobs Ph.D
CMC Review	Maotang Zhou Ph.D, Celia Cruz Ph.D, Tien-Mien Chen Ph.D, Stephen Miller Ph.D., Terrance Ocheltree Ph.D R.Ph
Virology Review	Lisa Naeger Ph.D, Julian O’Rear Ph.D
Clinical Pharmacology Review	Stanley Au PharmD BCPS, Ruben Ayala, PharmD, Jeff Florian Ph.D, Pravin Jadhav Ph.D, Sarah Robertson, PharmD
DDMAC	Lynn Panholzer PharmD, Michelle Safarik PA-C
DSI	Antoine El-Hage Ph.D, Tejashri Purohit-Sheth MD
OSE/DMEPA	Yelena Maslov PharmD
OSE/DRISK	Sharon R Mills BSN RN CCRP
Consults	Ali Mohamadi MD, Division of Metabolism and Endocrinology Products; Melanie Blank MD, Division of Cardiovascular and Renal Products; Interdisciplinary Review Team for QT Studies
CDTL Review	Kimberly Struble PharmD
Div. Director Review	Debra Birnkrant MD

OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
DSI=Division of Scientific Investigations
CDTL=Cross-Discipline Team Leader
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management

1. Introduction

The proposed indication is the treatment of human immunodeficiency type 1 (HIV-1) infection in treatment-naïve adult patients in combination with other antiretroviral (ARV) agents.

The proposed dosing regimen is 25 mg once daily

Rilpivirine (RPV) is a diarylpyrimidine derivative which is a non-nucleoside reverse transcriptase inhibitor (NNRTI) of HIV-1. RPV binds directly to reverse transcriptase and blocks DNA polymerase activity by causing a disruption of the enzyme's catalytic site.

The proprietary name is Edurant.

The efficacy review for this NDA relies upon the results of two adequate and well-controlled phase 3 studies (C209 and C215), which are ongoing, randomized, double-blind, double-dummy, active-controlled international trials that are identical in design. The active comparator in both trials is efavirenz (EFV). The two trials differ in the background regimens: C209 included a fixed regimen of tenofovir/emtricitabine; C215 included either abacavir/lamivudine, zidovudine/lamivudine or tenofovir/emtricitabine. For this NDA submission, the primary efficacy endpoint for both phase 3 trials was defined as HIV-1 RNA <50 copies/mL at week 48.

The review team has reviewed issues pertinent to their respective disciplines with regard to the safety and efficacy of RPV for the indication proposed. For a detailed discussion of NDA 202022, the reader is referred to individual discipline specific reviews, the Cross-Discipline Team Leader Review, and the Division Director Review.

2. Background/Regulatory

RPV is a new molecular entity and there is no prior marketing experience in the U.S. or elsewhere. NNRTIs are a well-characterized class of ARV agents for the treatment of HIV-1 infection. RPV would be the fifth agent in the NNRTI drug class approved for marketing in the U.S. preceded by nevirapine, delaviridine, efavirenz and etravirine. The hallmark safety issue with the class of NNRTI agents is rash, including severe life-threatening skin reactions. Additionally, nevirapine has a Box Warning for severe life-threatening hepatic toxicity. Female gender and higher CD4⁺ cell counts at initiation of therapy are associated with an increased risk of nevirapine-associated hepatotoxicity. Efavirenz labeling includes a Warning on psychiatric symptoms and nervous system symptoms. In addition, Efavirenz is Pregnancy Category D. Development of resistance is a particular clinical management challenge with the NNRTI class. Emergence of single viral mutations can lead to loss of activity for a particular NNRTI, but often leads to cross-resistance for other drugs in the NNRTI class.

Phase 2a functional monotherapy trials for RPV included 25mg, 50mg, 100mg, and 150mg doses. The phase 2b trial (C204) compared RPV 25mg qd, 75mg qd, 150 mg qd, with efavirenz 600 mg qd. Based on the results of the phase 2b trial, the Division and Applicant agreed that the 75 mg qd dose was appropriate for Phase 3 trials. Prior to the initiation of Phase 3 trials, results from the thorough QT study showed QTcF values for the 75 mg qd and 300 mg qd dose group above the threshold for regulatory concern. The Applicant proposed 25 mg qd as an alternate dose for Phase 3 trials. Although the Division agreed that the 25 mg qd dose was shown to be effective during the phase 2b trial, the Applicant was encouraged to include a 50 mg qd treatment dose group in a Phase 3 trial. The Applicant declined and initiated Phase 3 trials with 25 mg qd as the selected therapeutic dose.

This NDA was submitted in support of traditional approval and not accelerated approval because the clinical development included two phase 3 trials conducted for 48 weeks in duration. The Agency has granted traditional approval for HIV-1 ARV drug applications with trials conducted for at least 48 weeks.

3. Chemistry Manufacturing and Controls / Product Quality Microbiology

The CMC reviewers concluded that this NDA has provided sufficient information to assure identity, strength, purity, and quality of the drug product and recommended approval. I concur with this recommendation. There are no outstanding CMC issues.

Manufacturing site inspections have been completed. An "Acceptable" site recommendation from the Office of Compliance has been made.

The DMF was reviewed and found adequate as revised.

Based on the evaluation of the stability data, a 30 month expiry is recommended for approval in the U.S. market. The primary stability study will be continued for 36 months and extension of expiry may be established with additional data and analysis. The expiry in non-U.S. climatic zones would need to be addressed in future applications such as an application for PEPFAR use. The CMC reviewer noted that the drug substance and drug product are sensitive to light exposure, with synthesis impurities [REDACTED] (b) (4) increasing slightly under ICH confirmatory light conditions. Overall, under typical indoor lighting, the current package provides sufficient protection against photo degradation. The instruction to "Store in original bottle in order to protect from light" is included in the labeling.

The sponsor dissolution specifications as amended were deemed acceptable.

4. Non-Clinical Pharmacology Toxicology

The Pharmacology Toxicology reviewers recommended approval. I concur that there are no outstanding pharm tox issues that preclude approval.

The primary toxicity findings in nonclinical studies were adrenal effects, generally characterized by increased serum progesterone and decreased cortisol levels, observed in rats, dogs, cynomolgus monkeys, and possibly mice. The reviewers noted that these effects are thought to be associated with an inhibition of steroidogenesis at the level of cytochrome P450 21-hydroxylase (CYP21) and 17-hydroxylase. The reviewers recommended that future trials in adolescents and pre-pubertal children should include endocrine safety monitoring.

As noted in the Background Section of this review, clinical testing demonstrated a QT interval-prolongation effect of RPV at supratherapeutic doses. In follow-up nonclinical safety pharmacology studies, RPV demonstrated the potential to inhibit some potassium channels involved in cardiac action potential repolarization at concentrations approximately 10-fold greater than the clinical exposures. Given the clinical and nonclinical findings, adverse events that could be related to cardiac conduction abnormalities or to rate and rhythm disturbances were closely monitored in the Phase IIb and Phase III clinical trials.

Pregnancy Category B is recommended. Studies in animals have shown no evidence of relevant embryonic or fetal toxicity or an effect on reproductive function. In offspring from rat and rabbit dams treated with RPV during pregnancy and lactation, there were no toxicologically significant effects on developmental endpoints. The exposures at the embryo-fetal NOAELs in rats and rabbits were 15 and 70 times higher respectively than the exposure in humans at the recommended dose of 25 mg once daily. No adequate and well-controlled or pharmacokinetic studies of RPV in pregnant women have been conducted.

RPV was evaluated for carcinogenic potential by oral gavage administration to mice and rats up to 104 weeks. In rats, there were not drug related neoplasms. In mice, RPV was positive for hepatocellular neoplasms in both males and females. The Pharmacology Toxicology reviewers noted that the observed hepatocellular findings in mice may be rodent specific. At the lowest doses tested in the carcinogenicity studies, the systemic exposures (based on AUC) to RPV were 21-fold (mice) and 3-fold (rats) higher relative to those observed in humans at the recommended dose of 25 mg once daily.

RPV was negative in the *in-vitro* Ames reverse mutation assay, the *in-vitro* clastogenicity mouse lymphoma assay, and did not induce chromosomal damage in the *in-vivo* micronucleus test in mice.

5. Clinical Pharmacology/Biopharmaceutics

The overall recommendation of the Clinical Pharmacology reviewers was approval. I concur with this recommendation. They recommended that the label describe the higher virologic failure rate observed in clinical trials for those subjects with baseline viral load > 100,000 copies/mL with the 25 mg/day dose and the higher overall rate of treatment resistance and cross resistance to NNRTIs for RPV compared with EFV. This information is included in labeling. The Clinical Pharmacology reviewers recommended

that a trial evaluating the inhibitory effects of RPV on digoxin, a P-gp substrate be conducted as a PMR. This PMR is included in the Approval Letter.

Based on the potential for QT prolongation at RPV 75 mg/day and 300 mg/day, RPV 25 mg once daily was evaluated in the Phase 3 trials instead of RPV 75 mg once daily as the sponsor had originally proposed. The clinical pharmacology studies that were submitted in support of the NDA included eight in vitro studies, three trials to evaluate the effect of RPV on the QT interval (thorough QT trials), one food effect trial, one hepatic impairment trial evaluating mild and moderate hepatic impairment, one mass balance trial, and 16 drug-drug interaction trials in healthy subjects. The majority of the drug-drug interaction trials and the food effect trial were conducted at 150 mg once daily and 75 mg once daily, respectively, and extrapolation of the results to 25 mg once daily dosing was required.

The reviewers concluded that the proposed dosing regimen of 25 mg once daily is supported by pharmacokinetic studies. The formulation proposed for marketing is the same formulation that was used in the Phase 3 trials submitted. For the Phase 3 or to-be-marketed tablets, the RPV exposure at 25 mg once daily in HIV-1 infected subjects was lower (the maximum difference in RPV exposure was 50%) compared to healthy subjects. The reviewers concluded that the differences in exposure are not clinically significant and the conclusions based on the results of trials conducted in healthy subjects can be applied to HIV-1 infected subjects.

RPV exposure is increased in the presence of food. The mean RPV C_{max} and AUC(0-∞) values were decreased by 46% and 41%, respectively, under fasted conditions in comparison to RPV administered with a standard meal. The labeling recommends administration of RPV with meals. The absorption of RPV is pH-dependent. The reviewers recommended contraindication of proton-pump inhibitors and this contraindication is included in labeling.

In-vitro study results indicate that CYP 3A is the primary cytochrome P450 enzyme system responsible for RPV's metabolism with CYP 2C19 also potentially contributing to RPV's metabolism. The reviewers recommended contraindicating some CYP 3A inducers; this is included in labeling under Drug Interactions. Based on the hepatic impairment trial, no dosage adjustment was deemed necessary for subjects with mild or moderate hepatic impairment. Excretion is primarily fecal. A renal impairment trial was not conducted as part of the NDA submission. The potential changes in RPV exposure with renal impairment were evaluated based on the population PK analysis. For subjects with mild renal impairment, no dosage adjustment is necessary. No definitive conclusions could be made regarding the impact of moderate renal impairment because of the small number of available subjects. The *in-vitro* study evaluating the P-gp inhibitory effects of RPV indicated that RPV has the potential to inhibit P-gp with an IC₅₀ value for P-gp inhibition of 9.2 μM. With a 25 mg once daily dosage regimen, RPV may act as a P-gp inhibitor.

An analysis of the impact of RPV exposure on the QT interval indicates that RPV 25 mg once daily does not affect the QT interval. The exposure-response analysis demonstrated a significant linear relationship between RPV concentration and the baseline-and placebo-adjusted change in QTcF ($\Delta\Delta$ QTcF). The predicted $\Delta\Delta$ QTcF at the 25 mg/day was 4 ms (90% CI: 2-6). As noted above, the $\Delta\Delta$ QTcF at the 75 mg/day and 300 mg/day RPV C_{max} concentration was 9 ms (90% CI: 7-11) and 23 ms (90% CI: 18-27), respectively. The sponsor did not evaluate the 75 or 300 mg doses in Phase 3 trials.

Only three subjects >65 years of age were included as part of the data analysis for the Phase 3 trials, and no definitive conclusions could be made regarding whether RPV pharmacokinetics are different between elderly and younger patients.

6. Clinical Virology

The Clinical Virology reviewer recommended approval with labeling recommendations regarding the higher rate of virologic failure among RPV treated subjects with viral load > 100,000 copies/mL at the start of therapy, the observed virologic failure rate in RPV treated subjects conferred a higher rate of overall treatment resistance and cross-resistance to the NNRTI class compared to EFV treated subjects, and more subjects treated with RPV developed lamivudine/emtricitabine associated resistance compared to EFV treated subjects. These recommendations are reflected in labeling, and I concur with these recommendations.

In the pooled resistance analysis from the Phase 3 trials, the emergence of resistance was greater in the RPV arms compared to the EFV arms in both trials. In an as-treated analysis of the combined trials, 41% (38/92) of the virologic failures in the RPV arms developed evidence of genotypic and phenotypic RPV resistance compared to 25% (15/60) of the virologic failures in the EFV arms who developed EFV resistance. Resistance to a background drug occurred in 48% (44/92) of the virologic failures in the RPV arms compared to 15% (9/60) in the EFV arms. Emerging NNRTI substitutions in the RPV virologic failures were V90I, K101E/P/T, E138K/G, V179I/L Y181I/C, V189I, H221Y, F227C/L and M230L which were associated with a RPV phenotypic fold change range of 2.6 - 621.

Cross-resistance to the other NNRTIs, particularly etravirine, was more likely in phase 3 trials after virologic failure with a RPV-containing regimen compared with a EFV-containing regimen. Of the 38 virologic failures in the RPV arms with evidence of RPV resistance from the pooled analysis of the Phase 3 clinical trials, 89% (n=34) were resistant to etravirine and EFV, and 63% (n=24) were resistant to nevirapine. In the EFV arms, none of the 15 EFV-resistant virologic failures were resistant to etravirine at failure.

7. Clinical/Statistical Efficacy

The Clinical Reviewer, Statistical Reviewers, CDTL and Division Director recommended approval. I concur with these recommendations.

The efficacy of RPV was evaluated in HIV-1 infected, treatment naïve adults in two Phase 3 trials with supportive information from the Phase 2b trial. In these trials, EFV was used as the active comparator. The Phase 3 trials were identical in study design except for the background regimen. Therefore, the review team concluded that pooled analysis could be conducted. In trial C209, only tenofovir (TDF) + emtricitabine (FTC) were allowed for construction of the background regimen. In trail C215, three options were available: TDF/FTC, zidovudine (AZT)/lamivudine (3TC), or abacavir (ABC)/3TC. Most (60%) subjects in C215 received TDF/FTC; 30% received AZT/3TC, and 10% received ABC/3TC. Both trials were stratified by baseline viral load (</> 100,000 and </> 500,000). Stratification by background regimen was also included for trial C215. The total duration of the Phase 3 trials is planned for a minimum of 96 weeks. The ITT population included 1,368 subjects, 686 of whom received RPV and 682 of whom received EFV. At baseline, median time since diagnosis of HIV was 1.4 years, median viral load was 5.0 log₁₀ copies/ml, and median CD4 cell count was 263.0 cells/μl. A higher proportion of subjects in the EFV arms (11.4% vs. 4.7%) had no virologic data at the week 48 window. This was primarily due to a higher proportion of subjects in the EFV arms who discontinued due to adverse event or death (7.2% vs. 2.2%).

The primary efficacy endpoint for the Phase 3 trials was defined as HIV-1 RNA <50 copies/mL (virologic success) at Week 48 for this NDA submission. The FDA’s snapshot algorithm was utilized for calculating the primary endpoint. A 12% non-inferiority margin justification was submitted by the applicant, and the non-inferiority margin justification was acceptable to the Clinical and Statistical Reviewers. RPV was non-inferior to EFV, regardless of background regimen. The proportions of subjects in the Phase 3 trials at week 48 with viral load <50 copies/mL in the RPV and EFV groups were 83% and 80%, respectively. For Trial C209, the corresponding 95% confidence interval of the proportion difference between the RPV group and the EFV group was (-5.1%, 6.4%). For Trial C215, the corresponding 95% confidence interval of the proportion difference between the RPV group and the EFV group is (-1.7%, 10.2%). Virologic success was similar regardless of gender and race. More RPV treated subjects than EFV treated subjects experienced virologic failure (12.8% vs 8.4%). Pooled response to treatment for pooled Trials C209 and C215 is shown in Table 1 below:

Table 1: Subjects Response to Treatment, FDA Snapshot Results, Pooled Trials C209 and C215 (Source: Statistical Review)

Virologic Outcome at Week 48	Pooled Trials C209 and C215	
	RPV N=686	EFV N=682
Virologic success, HIV-1 RNA <50 copies/ml	566 (82.5%)	547 (80.2%)
Virologic failure	88 (12.8%)	57 (8.4%)
No virologic data at Week 48 window	23 (4.7%)	78 (11.4%)
Discontinued due to AE or death	15 (2.2%)	49 (7.2%)

For subjects participating in the Phase 2b C204 trial who received RPV 25 mg qd, 96 week efficacy data is available. The proportion with virologic success (HIV-1 RNA <50

copies/mL) at week 96 was 71/93 (76.3%) for the RPV arm and 63/89 (70.8%) for the EFV arm. The findings are similar for virologic success at weeks 144 and weeks 196. However, the subjects originally randomized to RPV 25 mg qd had been switched to 75 mg qd RPV between weeks 96 and 144 in this trial as this was the original trial design.

Virologic failure with RPV was associated with higher baseline HIV-1 RNA. The virologic success rate was similar between RPV and EFV regardless of baseline viral load strata. However, the virologic failure rate for subjects with higher baseline viral load (HIV-1 RNA >100,000 copies/mL) was higher than the rate observed in subjects with baseline HIV-1 RNA ≤ 100,000 copies/mL. See Table 2 below:

Table 2: Virologic Failure Rate at a Week 48 by Baseline Viral Load, Trials C209 and C215 (Source: Statistical Review)

	RPV (N=686)		EFV (N=682)	
	N	Proportion of Subjects with HIV-1 RNA > 50 copies/ml at Week 48 (%) n	N	Proportion of Subjects with HIV-1 RNA > 50 copies/ml at Week 48 (%) n
Baseline Plasma Viral Load (copies/ml), Snapshot Algorithm				
≤ 100,000 (p=.86) ¹	368	5.2% (19/368)	330	5.5% (18/330)
> 100,000 (p=.002) ¹	318	21.7% (69/318)	352	12.5% (44/352)

¹p is the statistical significance level (p value) calculated using a chi-square test for the difference between RPV and EFV in each subgroup.

Exposure appears to be a factor in achieving suppression, particularly for subjects with baseline HIV-1 RNA >100,000 copies/mL. An exposure response relationship between rilpivirine C_{0h} and AUC and virologic success (HIV-1 RNA < 50 copies/mL) was seen. Analyses found that, for subjects with baseline HIV-1 RNA >100,000 copies/mL, an increase in exposure may result in a greater percentage increase in patients achieving virologic success; alternatively, subjects with baseline HIV-1 RNA ≤ 100,000 copies/mL may attain less benefit from an exposure increase. The CDTL and Division Director recommended the sponsor consider evaluating a higher dose of RPV in patients with baseline HIV RNA > 100,000 copies/mL post-marketing. The sponsor declined a PMC to conduct such a trial. Conditions that may result in decreased RPV exposure (dosing without food, co-administration of drugs that lower gastric pH) should be avoided. This is included in the labeling.

There were differences in the emergence of resistance and cross-resistance, with emergence of resistance greater in the RPV group compared to the EFV group. Cross-resistance to other NNRTIs, particularly etravirine, was more common among virologic failures in the RPV group as well as resistance to other antiretroviral drugs in the regimen. See the Clinical Virology section of this review above.

8. Safety

The Clinical Reviewer, CDTL, and Division Director recommended approval. I concur with these recommendations.

The long-term (≥ 48 Weeks) safety of RPV was evaluated in HIV-1 infected, treatment naïve adults in two Phase 3 trials (C209 and C215) described above. The 192 week data from Phase 2b trial C204 also provided supportive data for the evaluation of the safety of RPV. The number of subjects randomized to RPV was 346 (C209), 340 (C215), and 279 (C204: 93 subjects 25 mg qd, 95 subjects 75 mg qd, 91 subjects 150 mg qd) – a total of 965 subjects. At the time of safety reporting cut-off for this NDA, 89% of subjects in the Phase 3 trials were dosed for a minimum of 48 weeks and 66% of subjects in the Phase 2b trial were dosed for a minimum of 192 weeks.

In the pooled Phase 3 analyses, 5 subjects (1 in the RPV group and 4 in the EFV group) died during the 48 week treatment period. The cause of death for the RPV treated subject was listed as bronchopneumonia. None of the adverse events leading to deaths were considered related to study drug. Overall, fewer subjects treated with RPV discontinued due to adverse events (2% vs. 4%).

The incidence of ‘skin disorders’ leading to discontinuation was higher in the EFV group, (0.3% RPV vs. 1.8% EFV). Considering treatment-emergent AEs with a severity grade of 2 or higher occurring in at least 2% of subjects, rash was reported in 3% of RPV treated subjects and in 11% of subjects treated with EFV.

In addition to rash, the principal treatment-related, grade 2 and above adverse events identified during the Phase 3 trials were psychiatric disorders (depression, insomnia, abnormal dreams). With exception of depression, these adverse events occurred with either similar or lower incidence in the RPV group compared to EFV group: insomnia (3% vs. 3%), abnormal dreams (1% vs. 4%). The incidence of depression was 4% and 3% in the RPV and EFV groups, respectively. There were 2 suicide attempts in the RPV group and 0 in the EFV group. Suicidal ideation was reported in 1 RPV treated subject and 3 EFV treated subjects. The Clinical Reviewer recommended information regarding depressive disorders be included in the RPV labeling. This information is included under Warnings and Precautions and described in Adverse Reactions.

The clinical laboratory results demonstrated a small increase in serum creatinine over time, an observation only seen in the RPV group. A small mean increase in serum creatinine was observed in the RPV treated subjects (mean change of 0.09 mg/dL at Week 48). Most of the increase occurred during the first 2 to 4 weeks of treatment. The increase appeared to be reversible with cessation of treatment, although return to baseline was not complete during a 4 week follow-up period post cessation of treatment. 5% of RPV subjects experienced a Grade 1 creatinine toxicity compared with <1% of EFV subjects. Grade 2 toxicity was <1% in both groups and Grade 3 toxicity was 0 in both groups. In subjects who entered the trial with mild or moderate renal impairment, the serum creatinine increase observed was similar to that seen in subjects with normal renal function. To assess the possible effect of RPV on the GFR, cystatin C was added to the safety biochemistry laboratory assessments of trial C215. According to the Applicant,

there was an increase in eGFR (estimation of GFR by cystatin) at Week 2 and at Week 24 in both the RPV and EFV treatment groups, indicating that there was not evidence of RPV-induced nephrotoxicity. A consult from the Division of Cardiovascular and Renal Products was obtained. The consultant concluded that the eGFR results were difficult to interpret and that a potential effect of RPV on GFR cannot be excluded. The review team concluded that renal monitoring is a part of routine HIV care, and that additional monitoring is not warranted. I agree with this conclusion. The clinical trial findings regarding the observed increase in serum creatinine are described in labeling.

Another significant laboratory finding included asymptomatic hyperbilirubinemia. Most cases were mild (grade 1) and were due to an increase in indirect bilirubin. While 2 subjects treated with RPV met the laboratory criteria for Hy's Law, they had abnormal baseline laboratory results and/or co-infection with hepatitis C.

An exposure-response relationship was not demonstrated for either the increase in serum creatinine or the hyperbilirubinemia.

Adrenal suppression was identified early in the pre-clinical developmental stage. During the Phase 3 clinical trials, no adverse report of adrenal insufficiency was reported. However, a small (-13.1nmol/L) mean decrease in basal cortisol levels and an attenuated cortisol response to ACTH stimulation was observed in 3% of subjects treated with RPV. A consult was obtained from the Division of Metabolism and Endocrinology Products. The consultant concluded that these observations should be described in the Adverse Reactions section of labeling, and this information has been included.

As discussed in the Clinical Pharmacology section of this review, RPV has been shown to prolong the QT interval at suprathreshold doses (75 mg qd, 300 mg qd), but a QT study at the recommended dose of 25 mg found a QTcF below the 10 ms threshold for regulatory concern. One subject randomized to RPV in the Phase 3 trials discontinued treatment due to a grade 3 AE of QTc interval prolongation. The Clinical Reviewer recommended that co-administration with drugs with a known risk of Torsade de Pointes should be addressed in labeling. This information has been included in the Warnings and Precaution and Drug Interactions sections.

The mean increase from baseline in total cholesterol, LDL and triglycerides was less for the RPV group compared to the EFV group.

The applicant did not submit a proposed REMS, and the review team concluded that the clinical data supports the proposed plan to conduct routine pharmacovigilance monitoring.

9. Advisory Committee Meeting

The applicant submitted a justification for waiver of an Advisory Committee meeting. The Division and Office Directors agreed that this NDA would not be presented at the Antiviral Products Advisory Committee. RPV is neither first-of-a-kind, first-in-class

medical product nor a medical product for a significant new indication. RPV is not a novel product or use of new technology. The review team's assessment was that the risk/benefit ratio is not controversial and risks and benefits appear similar to other approved drugs in the NNRTI class. The safety concerns appear typical for the NNRTI drug class and HIV drugs in general. The review team had not identified any significant questions or concerns about how the trials were conducted nor identified any significant differences of scientific opinion on the preliminary trial results. The efficacy and safety results and labeling have similar issues the Division has dealt with in past applications which do not require outside expertise.

10. Pediatrics

The NDA was reviewed by the PERC. Submission of pediatric studies was deferred because the product is ready for approval for use in adults and pediatric studies have not been completed.

There are two deferred required pediatric studies:

A pediatric safety and antiviral activity study of RPV with activity based on the results of virologic response over at least 24 weeks of dosing and safety monitored over 48 weeks in pediatric subjects from birth to <12 years of age.

A pediatric safety and antiviral activity study of RPV with activity based on the results of virologic response over at least 24 weeks of dosing and safety monitored over 48 weeks in pediatric subjects from 12 to <18 years of age.

11. Other Relevant Regulatory Issues

Four clinical investigator sites were inspected as well as the applicant. The DSI reviewer noted that no significant problems were detected that would adversely impact data acceptability.

There are no other unresolved relevant regulatory issues.

12. Labeling

The DMEPA reviewer found the proprietary name Edurant to be acceptable from both a promotional and safety perspective.

Labeling including Full Prescribing Information, Patient Information, and container label has been finalized in discussions with the sponsor and is attached to the Approval Letter.

13. Decision/Action/Risk Benefit Assessment

I concur with the review team that the appropriate regulatory action is approval of RPV for the proposed indication: "in combination with other antiretroviral agents for the treatment of HIV-1 infection in treatment-naïve adult patients."

The overall risk benefit assessment is favorable. Substantial evidence of efficacy was demonstrated in two adequate and well-controlled trials which showed non-inferiority to EFV for the primary efficacy endpoint of HIV-1 RNA <50 copies/mL (virologic success) at week 48 regardless of baseline viral load. As RPV is Pregnancy Category B, RPV offers an alternative to EFV to women of childbearing potential who may desire pregnancy. In addition, RPV offers an alternative to NVP for ARV naïve patients with higher CD4⁺ T cell counts. Discontinuation due to adverse reaction was less common compared with EFV. Skin adverse reactions were less common compared with EFV, while psychiatric disorder adverse reactions were similar. More RPV treated subjects with HIV-1 RNA greater than 100,000 at the start of therapy experienced virologic failure and the observed failure rate in RPV treated subjects conferred a higher rate of overall treatment resistance and NNRTI cross-resistance. This risk for patients with HIV-1 RNA greater than 100,000 at the start of therapy is described prominently in labeling.

A REMS is not recommended. Routine pharmaco-vigilance monitoring will be conducted.

The following Post-marketing Requirements are recommended in addition to required deferred pediatric studies:

Submit final study reports for Week 96 data analyses (safety, efficacy and resistance evaluation) from the ongoing Phase 3 studies TMC278-C209 and TMC278-C215.

Conduct a clinical trial in healthy subjects to evaluate the effect of RPV at steady state on the single dose pharmacokinetics of digoxin.

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/s/

JOHN J FARLEY
05/20/2011

EDWARD M COX
05/20/2011