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*APPLICATION NUMBER:*

**202022Orig1s000**

**SUMMARY REVIEW**

## Decisional Review for NDA 202-022

<b>Date</b>	May 2, 2011
<b>From</b>	Debra Birnkrant, M.D.
<b>Subject</b>	Division Director's Summary Review
<b>NDA/BLA # Supp #</b>	NDA 202-022
<b>Proprietary / Established (USAN) names</b>	Rilpivirine; trade name has not been approved
<b>Dosage forms / strength</b>	25 mg tablets, once daily with food
<b>Proposed Indication(s)</b>	For use in combination with other antiretroviral agents in treatment-naive adult patients infected with HIV-1
<b>Action</b>	Approval

**1. Introduction to Review:** This Division Director's memorandum summarizes prominent features of NDA 202-022 for Tibotec, Inc.'s New Drug Application (NDA) for rilpivirine, a new molecular entity that is a diarylpyrimidine derivative belonging to the non-nucleoside reverse transcriptase inhibitor (NNRTI) drug class. This review will cover safety and efficacy in detail; other areas will be highlighted.

**2. Background/Regulatory History/Previous Actions/Foreign Regulatory Actions/Status:** Currently, there are more than 25 marketed antiretroviral products for HIV treatment. They fall into six distinct categories including nucleoside reverse transcriptase inhibitors (NRTIs), NNRTIs, protease inhibitors, fusion inhibitors, integrase strand transfer inhibitors and entry inhibitors. As there are an estimated 40,000 new cases of HIV per year in the United States and tens of millions worldwide infected with the virus, there continues to be a need for novel antiviral drugs to overcome significant treatment issues related to use in women of child-bearing potential, toxicity, resistance and adherence.

This NDA was submitted on July 23, 2010 and received a standard 10-month review because it was the fifth NNRTI in the class with a comparable adverse event profile. For similar reasons, this application was not presented before the Antiviral Products Advisory Committee.

**3. Chemistry/Manufacturing/Controls (CMC):** CMC issues have been adequately addressed. Please see primary CMC review by Drs. M. Zhou and C. Cruz, ONDQA. According to their chemistry review, there are no new impurities or degradants in the drug product other than synthesis impurities. Specifically, the potentially genotoxic impurity, (b) (4) has been shown to be adequately controlled in the drug substance process and has not been

shown to increase significantly upon storage of the drug product. Also, the dissolution method was found to be acceptable.

The reviewing chemists note that the data contained in the NDA support a shelf-life of 30 months for US use (climatic zones 1 and 2) [REDACTED] (b) (4)

The drug product is sensitive to light and the current packaging provides protection against photodegradation.

During the review of this application it was determined that the established name should be consistent with USP recommendations in terms of expressing the established name as the active moiety, rilpivirine rather than as the salt, rilpivirine HCl. Further, OSE's review of the container-closure system was found to be adequate. In addition, the DMEPA reviewer noted that there were no additional areas of needed improvement for minimization of the potential for medication errors. As of this date, agreement has not been reached on a trade name.

**4. Nonclinical Pharmacology/Toxicology:** I am in agreement with the conclusions of the thorough pharmacology/toxicology review by Drs. Mark Seaton and Hanan Ghantous that were based on toxicology studies conducted in mice, rats, rabbits, dogs and cynomolgous monkeys. Pertinent findings in animal studies were used to guide monitoring in clinical trials and included the following: 1) the primary toxicity findings were adrenal effects thought to be associated with inhibition of steroidogenesis at the level of 21-hydroxylase and 17-hydroxylase and manifested as increased serum progesterone and decreased cortisol levels 2) in a safety pharmacology study assessing the effects of rilpivirine on cardiac action potential repolarization, rilpivirine demonstrated the potential to inhibit some potassium channels at concentrations that were approximately 10X greater than clinical exposures, 3) renal effects were observed in dogs and mice, respectively at systemic exposures 25-200X greater than those seen in humans at the recommended clinical dose and included acute interstitial nephritis in two male dogs and minimal-to-moderate nephropathy in female mice, 4) dose-related thyroid effects were seen in rats that were likely to be a species-specific finding, and 5) effects on hematologic and coagulation parameters seen in toxicology studies were largely not seen in clinical trials.

Following review of genotoxicity studies, it was determined that rilpivirine was not genotoxic. Similarly, following review of reprotoxicity and developmental studies in animals, it was determined that rilpivirine did not demonstrate effects on fertility, fecundity, parturition or maternal behavior.

Carcinogenic potential was assessed in a two-year carcinogenicity study in rats and mice. Pertinent findings included: 1) in mice, at exposures 21X greater than human exposures at the to-be-marketed dose, hepatocellular

adenomas and combined hepatocellular adenomas/carcinomas showed a significantly significant increase; these findings, however, were thought to be species-specific and 2) in rats, rilpivirine was negative for hepatic neoplasms at exposures 3X greater than human exposures at the to-be-marketed dose.

#### **5. Clinical Pharmacology/Pharmacometrics:**

Clinical pharmacology and pharmacometrics reviews were conducted by Drs. Stanley Au, Ruben Ayala, Sarah Robertson, Jeff Florian and Pravin Jadhav. Important areas reviewed included ADME studies, one hepatic impairment study, 16 drug-drug interaction studies, and exposure-response assessments focusing on safety as in QT effects, renal effects, etc. and efficacy responses based on exposure and virologic success as well as baseline viral load. Pertinent findings are described below:

- The absorption of rilpivirine is pH dependent.
- Rilpivirine is primarily metabolized through CYP 3A with CYP 2C19 also potentially contributing to rilpivirine's metabolism; there is minimal elimination in the urine.
- Rilpivirine has the potential to inhibit P-gp; therefore the Applicant will be asked to conduct a study evaluating the inhibitory effects of rilpivirine on digoxin, a P-gp substrate.
- Rilpivirine exposure is increased with food and dosing will be recommended with meals as was done in phase 3 trials.
- The half-life of rilpivirine is approximately 50 hours and steady-state is reached between 10-15 days.
- No definitive conclusions can be made regarding whether rilpivirine pharmacokinetics are different in the elderly as only three subjects were > 65 years of age.
- No dosage adjustment is necessary for subjects with mild or moderate hepatic impairment or those who are co-infected with hepatitis B or C.
- No dose adjustment is required in subjects with mild renal impairment.

Three doses were examined in a phase 2a 7-day study, 25 mg, 75 mg and 150 mg. These same doses were examined through 48 weeks in phase 2b. The 25 mg cohort had a numerically lower response rate compared to the other doses in subjects with a higher baseline viral load and a higher response rate in subjects with viral loads less than 100,000 copies/mL at baseline. As more adverse events were seen with the 150 mg dose, Tibotec, Inc. initially chose to move forward with the 75 mg dose. However, data from the thorough QT studies demonstrating prolongation of the QT interval > 10 msec for the 75 mg dose became available prior to the initiation of phase 3 trials. The Applicant decided to study the 25 mg dose as prolongation of the QT interval at this dose was less than the threshold of regulatory concern.

Addressing exposure/response relationships for this antiviral drug, pharmacometrics reviewers determined that a lower virologic response was seen in subjects with lower rilpivirine exposures based on  $AUC_{(0-\tau)}$  and  $C_{0h}$  population PK parameters; baseline viral load was a stronger predictor of virologic success. Based on exposure/response analyses, FDA advised the Applicant to explore a 50 mg dose during drug development to improve upon trial results without compromising safety in a telephone facsimile dated 2/29/2008 in response to IND 67,699, SN203, but the Applicant declined. At this time, we are in discussions with the Applicant regarding a post marketing commitment to conduct a trial to examine the 50 mg dose in subjects with baseline viral loads greater than 100,000 copies/mL.

Labeling advises that caution should be given to co-administering drugs that have the potential to cause Torsade-de-Pointes. Labeling also addresses metabolism of rilpivirine as members of the following classes of drugs are contraindicated: anticonvulsants, proton pump inhibitors, certain antimycobacterials, more than a single dose of systemic dexamethasone and St. John's wort. Also see section 12, Clinical Pharmacology in the package insert.

**6. Clinical Microbiology:** Please see extensive review by Dr. Lisa Naeger. Dr. Naeger noted that the following amino acid substitutions emerged in resistance selection experiments: L100I, K101E/P, V106I/A, V108I, E138K/G/Q/R, V179F/I, V189I, G190E, H221Y, F227C, and M230I/L. Per the Clinical Microbiology review, rilpivirine had a less than 2.5 fold reduction in susceptibility against a majority of a panel of HIV-1 mutant laboratory strains with one NNRTI resistance-associated substitution including K103N.

In the phase 3 trials, 209 and 215, in naïve subjects, an interesting trend was observed. Pooled response rates were similar based on an ITT analysis where 83% of subjects randomized to receive rilpivirine achieved HIV RNA less than 50 copies/mL, the primary endpoint, compared to 80% of subjects randomized to the efavirenz control arms. However, when examining reasons for failure, more subjects receiving rilpivirine failed due to virologic failure while more subjects randomized to the control failed for adverse events. This discrepancy was further highlighted when examining outcomes based on baseline viral loads. For those with baseline viral loads greater than 100,000 copies/mL, virologic failure rates were 21.7% for the pooled rilpivirine arms compared to 12.5% for those on the pooled control arms. Of those failing virologically, 41% in the pooled rilpivirine arms had genotypic and phenotypic resistance to rilpivirine compared to 25% of the virologic failures in the pooled control arms who had genotypic and phenotypic resistance to efavirenz. Further, resistance to background nucleoside regimens was also greater in the rilpivirine arms as compared to efavirenz, 48% versus 15%, respectively.

Emergent post-baseline resistance data are available from 75 subjects in the pooled rilpivirine arms and 37 subjects in the efavirenz control arms from the phase 3 naïve trials. Dr. Naeger's review assessed the following treatment-emergent NNRTI substitutions and NRTI substitutions that also appear in labeling:

**Emergent NNRTI Substitutions in Virologic Failures: Rilpivirine versus Efavirenz**

<b>V90I</b>	12% (9/75), 0
<b>K101E/P/T</b>	19% (14/75), 3% (1/37)
<b>K103N</b>	0, 32% (12/37)
<b>E138K/G</b>	36% (27/75), 0
<b>E138K+ M184I</b>	
	27% (20/75), 0
<b>V179I/D/L</b>	5% (4/75), 3% (1/37)
<b>Y181C/I</b>	9% (7/75), 0
<b>V189I</b>	8% (6/75), 3% (1/37)
<b>H221Y</b>	8% (6/75), 0

**Emergent NRTI Substitutions in Virologic Failures: Rilpivirine versus Efavirenz**

<b>M184I or V</b>	53% (40/75), 22% (8/37)
<b>K65R/N</b>	9% (7/75), 5% (2/37)

As also noted in the Clinical Microbiology review, cross-resistance to efavirenz, etravirine and/or nevirapine is likely after virologic failure with a rilpivirine-based regimen.

- 7. Clinical Efficacy/Statistical:** Please see reviews by Dr. Yodit Belew and Lei Nie and CDTL memorandum by Dr. Kim Struble. Efficacy and safety were based primarily on two ongoing phase 3 studies, 209 and 215 conducted in the naïve population that were supported by a phase 2b trial, C204. The phase 3 trials were identically designed randomized, double-blind, double-dummy, active-controlled multicenter trials except for the nucleoside background regimen. In trial 209, tenofovir (TDF) and emtricitabine (FTC) were used as the background whereas in trial 215, the nucleoside background was determined at the discretion of the investigator who could select from three background regimens: TDF/FTC, abacavir/lamivudine (ABC/3TC), or zidovudine (AZT)/3TC. Stratification was based on screening viral load.

Demographics and baseline characteristics were well balanced between arms and studies. These characteristics along with design similarities allowed for pooling of the phase 3 trials. Of note, in this naïve population,

approximately 50% of subjects had baseline viral loads greater than 100,000.copies/mL. With pooling, 80% of subjects used a TDF/FTC background compared to approximately 15 % who used AZT/3TC and 5% who used ABC/3TC. Efficacy was based on pooled analyses of trials 209 and 215 and 1,368 subjects were evaluated: 686 randomized to receive rilpivirine in combination with two NRTIs and 682 randomized to receive efavirenz with two NRTIs. The trials were powered for non-inferiority with a margin of 12%, the largest difference that would be clinically acceptable. The snapshot method, an assessment based on the proportion of subjects responding at week 48, was used for the primary analysis of the primary endpoint, that is < 50 copies of HIV RNA at 48 weeks.

Results demonstrated non-inferiority based on the primary endpoint, HIV RNA < 50 copies/ml at week 48. Comparing virologic outcomes of rilpivirine plus two NRTIs to efavirenz plus two NRTIs, 83% achieved an HIV RNA viral load less than 50 copies/mL versus 80%, respectively. Examining the primary endpoint by baseline viral load, for those subjects with less than 100,000 copies/mL, 89% versus 83% achieved HIV RNA less than 50 copies/mL (rilpivirine versus efavirenz) whereas for those subjects with greater than 500,000 copies/mL at baseline, 65% versus 73% achieved HIV RNA less than 50 copies/mL (rilpivirine versus efavirenz). Examining virologic failure by baseline viral load two situations emerged. Overall, as baseline plasma viral load increased so did virologic failure, but virologic failure was greater in subjects receiving rilpivirine as compared to efavirenz. Specifically, virologic failure in those subjects with a baseline viral load of less than 100,000 copies/mL was 5% in each of the rilpivirine and efavirenz arms. Twenty percent of subjects randomized to rilpivirine failed compared to 11% of subjects randomized to receive efavirenz if baseline viral loads were between 100,000 to 500,000 copies/mL. Lastly, for those subjects with a baseline viral load of greater than 500,000 copies/mL, 29% versus 17% (rilpivirine versus efavirenz) experienced virologic failure.

With failure comes resistance. As outlined above 41% of the virologic failures in the pooled rilpivirine arms had genotypic and phenotypic resistance to rilpivirine compared to 25% of the virologic failures in the pooled control arms who had genotypic and phenotypic resistance to efavirenz. Further, overall resistance to background nucleoside regimens was also greater in the rilpivirine arms as compared to efavirenz, 48% versus 15%, respectively with M184I/V and K65R/N emerging more frequently in rilpivirine virologic failures compared to those failing efavirenz.

Immunologic benefit was seen with rilpivirine- and efavirenz-containing regimens. Change from baseline in CD4 count was as follows: subjects

receiving rilpivirine experienced a change from baseline in CD4 count of 192 cells/mm<sup>3</sup> compared to 176 cells/mm<sup>3</sup> for efavirenz-treated subjects.

To address the issues of higher rates of virologic failure and resistance, FDA requested that the Applicant study the 50 mg dose of rilpivirine in subjects with higher baseline viral loads to attempt to improve virologic outcomes as a post-marketing commitment. To date the Applicant has not agreed to this proposal. However, the labeling reflects these findings prominently in the Indications and Usage, Microbiology and Clinical Studies sections.

- 8. Safety:** Similar to the efficacy analyses, data were pooled from the phase 3 studies for the main safety analysis. During phase 3 trials a dose of 25 mg of rilpivirine was used whereas during phase 2b, higher doses were examined, up to 150 mg. During phase 2b and phase 3 trials, 965 subjects received rilpivirine. Forty-eight week safety data were reviewed from the phase 3 trials and 192 week safety data were also reviewed from phase 2b, but were not pooled.

Dr. Belew's analyses confirmed the Applicant's analyses that overall treatment-related adverse events were lower in the rilpivirine group as compared to the efavirenz group. Comments highlight NNRTI class events; clinical assessment of abnormalities seen in non-clinical studies of rilpivirine and laboratory abnormalities.

Dr. Belew's review addresses the principal NNRTI-related adverse events during the phase 3 trials, namely psychiatric disorders and rash, known drug class events. These class events of at least grade 2 severity occurred with a lower or similar rate as compared to efavirenz. Depression however occurred at a slightly higher rate in the rilpivirine group compared to efavirenz, 3% versus 2%, respectively.

Rash, a known class effect of NNRTIs was seen at a lower incidence in the rilpivirine group compared to efavirenz. Under the section in labeling related to common adverse drug reactions, the rate of rash from the pooled studies is 3% for rilpivirine and 11% for efavirenz. Most rash events were grade 1 or 2 and discontinuation due to rash was lower in the rilpivirine group compared to the efavirenz group; most subjects were treated through the rash. Finally, no exposure-response was observed for rash.

Adrenal suppression was noted in non-clinical studies and subjects underwent monitoring in the clinical trials with measurement of basal cortisol levels and evaluation of the pituitary-adrenal axis using an ACTH stimulation test. Although cortisol levels and responses were mildly

diminished on the rilpivirine arm compared to efavirenz, there were no serious adverse events related to adrenal suppression and no related treatment discontinuations. At week 48 mean values for basal and ACTH-stimulated cortisol were within the normal range. A consult was obtained from the Division of Metabolic and Endocrine Products (DMEP) during the drug development process and for this NDA review. DMEP reviewers concluded that differences seen were minimal and likely clinically insignificant. The package insert describes adrenal function under section 6.

Overall the incidence of hepatic events was 5.5% in the rilpivirine treated subjects compared to 6.6% in the efavirenz group. Most of these events were grade 1 or 2. There were no Hy's Law cases in the database. There appeared to be an imbalance in biliary events in the rilpivirine group compared to efavirenz. A total of 8 (1.2%) of subjects in the rilpivirine group experienced the following: cholecystitis, cholelithiasis, or biliary colic. In comparison, only two subjects in the efavirenz group experienced findings related to the biliary system. Biliary related adverse events are included in the package insert in the section of less common adverse drug reactions.

Renal effects were seen in non-clinical studies. Acute interstitial nephritis was seen in two male dogs and in mice, renal findings were limited to minimal to moderate nephropathy in female animals. At the time of NDA review, consultation was obtained from the Division of Cardiorenal Products.

Focusing on emergent laboratory events in the clinical trials, increased serum creatinine concentrations were seen in the rilpivirine group and not in the efavirenz group. Elevated serum creatinine was seen regardless of the nucleoside backbone. Most of the increases occurred in the first few weeks and then plateaued. The mean change from baseline was 0.19 mg/dL (range 0-0.70 mg/dL). Changes in serum creatinine were greater for those with normal baseline creatinine values compared to those subjects with elevated baseline values. Other pertinent details include the following:

- The effect of rilpivirine appears to diminish over a 4-week follow-up period however subjects still had elevated values compared to baseline with a mean increase of 0.09 mg/dL at the end of the trial that decreased to 0.04 mg/dL at follow-up week 4.
- Estimated GFR by cystatin C did not reveal a decrease in GFR.
- Exposure-response analyses did not show a trend in changes in GFR based on rilpivirine exposure.

- No accompanying changes in BUN were seen.

A likely explanation for the increased creatinine may be related to the impact on the tubular secretion of creatinine given the above findings. Eleven subjects receiving other drugs known to inhibit tubular secretion, e.g. cimetidine and trimethoprim were identified. In those subjects the mean maximum decrease in creatinine clearance was less than the overall population lending support to this hypothesis, but not completely ruling out frank nephrotoxicity. Notably, there were two cases of glomerular nephritis in the rilpivirine group; these cases are listed in the package insert.

As renal monitoring is part of routine HIV care, it is felt that additional monitoring is not warranted. The Office of Surveillance and Epidemiology was made aware of this adverse event as well as others, and will monitor post-marketing reports.

- 9. Mortality:** Adverse events leading to death fell into a few categories: infections, malignant neoplasms, nervous system disorders and respiratory failure. In the phase 3 trials, one subject in the rilpivirine group died compared to four subjects in the efavirenz group. The subject who died on the rilpivirine arm was a 45 year old male with a baseline viral load of greater than 300,000 copies /mL and a CD4 count of 48 cells/mm<sup>3</sup>. Approximately 52 days after initiating antiretroviral therapy with a rilpivirine based regimen, the subject was diagnosed with bronchopneumonia and thrombocytopenia. The investigator's assessment was that the adverse events were not related to rilpivirine. Dr. Belew's review concurs with this assessment. An additional four subjects died in the phase 2b study. None of the deaths was assessed as related to study medication.

- 10. Risk Minimization Considerations:** No particular risk minimization programs are being requested of the Applicant. A patient package insert is included to highlight and explain key findings and dosing recommendations.

Post-marketing requirements (PMRs) center on submission of data from ongoing trials, pediatric studies, and drug interaction studies. Specifically, the following PMRs and timelines have been requested:

1. 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.

The Division proposed October 2012 as the due date for the submission of the final study report.

2. Deferred pediatric study under PREA for the treatment of HIV-1 infection in pediatric subjects from 12 to <18 years of age. Conduct a pediatric safety and antiviral activity study of rilpivirine with activity based on the results of virologic response over at least 24 weeks of dosing and safety monitored over 48 weeks.

Study completion by: September 2013  
Final report submission by: June 2010

3. Deferred pediatric study under PREA for the treatment of HIV-1 infection in pediatric subjects from birth to <12 years of age. Conduct a pediatric safety and antiviral activity study of rilpivirine with activity based on the results of virologic response over at least 24 weeks of dosing and safety monitored over 48 weeks.

Protocol submission by: March 2011  
Study completion by: September 2017  
Final report submission by: January 2018

4. Digoxin Study: Conduct a clinical trial in healthy subjects to evaluate the effect of rilpivirine at steady state on the single dose pharmacokinetics of digoxin. The pharmacokinetics of digoxin when coadministered with rilpivirine (test arm) will be compared to the pharmacokinetics of digoxin by itself (reference arm). The primary digoxin pharmacokinetic parameters that will be evaluated are  $AUC_{(0-\infty)}$ ,  $AUC_{(0-t)}$ , and  $C_{max}$ .

Negotiation with Tibotec is planned for the study completion and final report submission due dates.

The following PMC is recommended. Negotiation with Tibotec is ongoing.

Conduct a trial to evaluate the virologic failure rates with rilpivirine 50 mg once daily compared to efavirenz in subjects with baseline HIV RNA > 100,000 copies/mL.

**11. Conclusions and Recommendations:** I am in agreement with the multidisciplinary review team that rilpivirine should be approved for use only in treatment naïve HIV-1 infected subjects in combination with other antiretroviral agents. This application receives a full approval because it contained long term efficacy and safety data in the naïve population. It has been demonstrated that the benefits of using rilpivirine in the indicated population exceed the risks of using rilpivirine, particularly in those with viral loads less than 100,000 copies/ml. In addition, as this drug is pregnancy category B as compared to efavirenz which is category D, it offers an alternative to women of childbearing potential who may desire pregnancy.

Labeling adequately addresses the drug's variable performance with regard to virologic failure in subjects with low and high viral loads. Post-marketing commitments, including a proposed study of a 50 mg dose of rilpivirine in subjects with higher baseline viral loads, address the concerns of the review team and consultants.

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