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APPLICATION NUMBER:

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CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	March 11, 2011
From	Linda L. Lewis, M.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	201-152/000
Applicant	Boehringer-Ingelheim Pharmaceuticals, Inc.
Date of Submission	June 3, 2010
PDUFA Goal Date	April 3, 2011
Proprietary Name / Established (USAN) names	Viramune® XR™/nevirapine
Dosage forms / Strength	Extended-release tablets/400 mg
Proposed Indication(s)	1. For use in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults
Recommended:	***Approval***

1. Introduction

Nevirapine in both immediate-release tablet and oral suspension formulations (NVP-IR) is currently approved for use in combination with other antiretroviral drugs for the treatment of HIV-1 in patients from 2 weeks of age to adults. NVP-IR as 200 mg tablets (Viramune) was originally approved in June, 1996, the first in the class of non-nucleoside reverse transcriptase inhibitors (NNRTIs). The oral suspension (50 mg/5 mL) was subsequently approved in September, 1998, for use in pediatric patients and others who are unable to swallow tablets. Since the original approval, NVP-IR has become one of the most widely used antiretroviral drugs in the international setting, particularly in resource limited countries.

The current NDA submission contains chemistry, clinical pharmacology, clinical virology, and clinical trials data supporting a new, once daily, extended-release nevirapine 400 mg tablet (NVP-XR), which is intended to replace the original twice daily NVP-IR tablets in adult patients. The NVP-XR formulation will be marketed as Viramune XR, and is expected to provide improved dosing convenience and, thereby, improve adherence in NVP-based HIV-1 treatment regimens.

[Note: In this CDTL Review, NVP-XR refers specifically to the new 400 mg extended-release tablet under review in this NDA submission (Viramune XR), NVP-IR refers specifically to the previously approved 200 mg immediate-release tablets or oral suspension (Viramune), and nevirapine (NVP) refers to the active moiety included in all formulations.]

2. Background

Nevirapine IR has been shown to be safe and effective in multiple clinical trials over almost two decades of investigations and in broad clinical use since approval. It is indicated in combination with other antiretroviral drugs and is most often used in combination with two nucleoside reverse transcriptase inhibitors (NRTIs). The primary toxicities identified with NVP-IR use were serious rash and hepatic events, sometimes occurring together as part of a life-threatening hypersensitivity reaction. Early clinical trials with NVP-IR demonstrated that the risk of serious skin reactions can be reduced by initiating treatment with 200 mg once daily for the first 14 days, then increasing the dose to 200 mg twice daily. The NPV-IR tablet will continue to be recommended for use during the 14-day lead-in phase, followed by use of the NVP-XR once daily beginning on the fifteenth day of treatment.

Although NVP-XR was developed primarily for its once daily dosing convenience and improved adherence, the more sustained release of drug was also hoped to provide a better tolerated formulation while maintaining efficacy. Based on previous clinical trials of NVP-IR, the pharmacologic target for the NPV-XR formulation in order to achieve similar efficacy was a steady state trough concentration ($C_{min,ss}$) greater than 3000 ng/mL.

The Applicant conducted initial clinical pharmacology studies of NVP-XR in Europe and discussed product development and marketing requirements with the EMA as well as the FDA. Because the pharmacokinetic (PK) profile of the two formulations was sufficiently different, the EMA advised the Applicant to conduct a controlled clinical trial comparing NVP-XR and NVP-IR in order to determine if the PK differences were clinically relevant. This approach was acceptable to the FDA and the Applicant subsequently conducted a randomized, controlled trial in treatment-naïve HIV-1 infected adults (Study 1100.1486) and a second, supportive, "switch" trial in treatment-experienced adults who were already receiving NVP-IR in a stable regimen (Study 1100.1526). These two clinical treatment trials, along with the clinical pharmacology studies, form the basis of the current NDA submission.

During the pre-NDA discussions with the Applicant, the FDA noted that an extended-release formulation would also be of benefit to pediatric patients. (b) (4)

3. CMC/Device

At the time of this CDTL Review, there are no unresolved CMC issues. A summary of key CMC issues is included in this section.

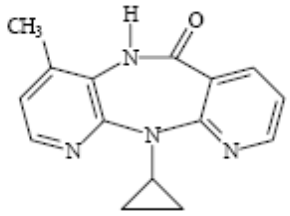
<u>General product quality considerations</u>

The NVP active moiety in NVP-XR is the same as that found in NVP-IR.

Chemical name: 5,11-Dihydro-6H-11-cyclopropyl-4-methyl-dipyrido-[3,2-b:2',3'-e][1,4] diazepin-6-one

Molecular mass: 266.3

Chemical structure:



The proposed drug product is a yellow, biconvex, oval tablet with "V04" embossed on one side and the Boehringer Ingelheim corporate logo embossed on the other side. Inactive excipients include: lactose monohydrate, hypromellose, iron oxide, and magnesium stearate. The proposed shelf life is (b) (4) when stored at room temperature (with excursions between 15-30^{o}C). Because NVP-XR is designed as an extended-release tablet with well-characterized and reproducible dissolution and resulting PK profile, it should not be broken or chewed at the time of administration.

As noted in the Chemistry Review provided by Dr. Shrikant Pagay, "The sponsor has provided sufficient information on raw material controls, manufacturing processes and process controls, and adequate specifications for assuring consistent product quality of the drug substance and drug product. The NDA also has provided sufficient stability information on the drug product to assure strength, purity, and quality of the drug product during the expiration dating period." For a detailed discussion of CMC issues, please refer to Dr. Pagay's Chemistry Review.

Facilities review/inspection

All facilities have acceptable site recommendations.

Other notable issues (resolved or outstanding)

The CMC Review notes the importance of having raw materials including the drug substance meet certain quality standards in order to achieve batch reproducibility in terms of tablet hardness and porosity. These attributes are essential to achieve reproducible dissolution rate, and consequently reproducible PK profile. The Applicant's proposal for dissolution method and specifications were described by Dr. Sandra Sharp in her Biopharmaceutics Review.

The Applicant selected the proposed formulation of NVP-XR based on a PK study evaluating 4 candidate formulations with hypromellose 20%, 25%, 30% and 40% to provide different active drug release rates. Data from this study were used to develop an in vitro-in vivo correlation (IVIVC) model that explained the relationship between in vitro dissolution data and in vivo absorption data. Dr. Suarez notes in her review that the predictability of the IVIVC for the NVP-XR formulations was within acceptable limits and could be used to

support biowaiver applications. In addition, the IVIVC model accurately predicted that drug batches with dissolution profiles within the specifications would achieve equivalent in vivo drug exposure profiles.

4. Nonclinical Pharmacology/Toxicology

During the development of NVP-XR, the Applicant discussed with FDA the need for additional nonclinical studies. Because the toxicology and safety of NVP was well-characterized during the development program for NVP-IR and subsequent clinical use, no additional nonclinical pharmacology or toxicology studies were required. For a detailed description of the nonclinical studies conducted in support of NVP-IR, please refer to the Pharmacology/Toxicology Reviews for NDA 20-636 and NDA 20-933 submitted by Dr. Pritam Verma.

5. Clinical Pharmacology/Biopharmaceutics

Because NVP-XR contains the same active moiety as the previously approved NVP-IR, many of the general clinical pharmacology issues addressed in the original NDA are not described in detail in this review. The current submission contains the final study report of the clinical pharmacology study, Study 1100.1489, evaluating the bioavailability of two NVP-XR formulations at two doses compared to 400 mg of NVP-IR (2 x 200 mg tablets) in HIV-1 infected subjects. Based on the results of this study, a single XR formulation was selected for further evaluation in the clinical treatment trials Studies 1100.1486 and 1100.1526. The formulation used in Studies 1100.1486 and 1100.1526 is identical to the proposed commercial formulation. For a complete discussion of the clinical pharmacology issues presented in this submission, please refer to the Clinical Pharmacology Review conducted by Dr. Vikram Arya.

<u>General clinical pharmacology/biopharmaceutics considerations, including absorption, metabolism, half-life, food effects, bioavailability</u>

Early in the NVP-XR development program, clinical pharmacology Study 1100.1484 evaluating the sites of absorption of NVP in the gastrointestinal tract had shown that NVP was absorbed along the entire length of the gastrointestinal tract with decreasing absorption rates from jejunum to colon. This characteristic made a controlled-release formulation feasible.

The proposed formulation of NVP-XR was selected based on pharmacologic evaluation of multiple candidate formulations with different proportions of hydroxypropylmethyl-cellulose [hypromellose (20% to 40%)] (b) (4) and different doses of NVP (300 mg and 400 mg). The PK profiles of 10 different formulations were evaluated initially in healthy volunteers (Study 1100.1485) and the best candidates were further evaluated in HIV-1 infected subjects (Study 1100.1489). Study 1100.1489 evaluated the PK profiles at steady state of two formulations each in 300 and 400 mg strengths compared to the approved NVP-IR tablets. The bioavailability of the NVP-XR formulations was slightly lower than NVP-IR, with the lower peak concentrations and lower trough concentrations expected of a controlled-release

tablet given at a longer dosing interval. Relative bioavailability increased by about 20% when NVP-XR was administered with a high fat breakfast but the Applicant did not believe this degree of food effect was clinically relevant and no specific recommendations regarding food intake were included in the clinical treatment trials. After review of the PK data, the optimal formulation was determined to be the 400 mg dose (b) (4)

Drug-drug interactions

Drug-drug interactions are expected to be the same for NVP-XR as for the currently approved NVP-IR. As noted in the current Viramune label, "Nevirapine is principally metabolized by the liver via the cytochrome P450 isoenzymes, 3A and 2B6. Nevirapine is known to be an inducer of these enzymes. As a result, drugs that are metabolized by these enzyme systems may have lower than expected plasma levels when co-administered with nevirapine." These interactions are described in the Viramune package insert and will be similarly described in the Viramune XR label. No new drug-drug interaction studies were submitted with this NDA.

Pathway of elimination

As noted above, NVP-XR contains the same active drug as NVP-IR and metabolic and elimination pathways are expected to be the same. The current Viramune label states, "In subjects with renal impairment (mild, moderate or severe), there were no significant changes in the pharmacokinetics of nevirapine. Nevirapine is extensively metabolized by the liver and nevirapine metabolites are extensively eliminated by the kidney. Nevirapine metabolites may accumulate in patients receiving dialysis; however, the clinical significance of this accumulation is not known. No adjustment in nevirapine dosing is required in patients with CrCL ≥20 mL/min. In patients undergoing chronic hemodialysis, an additional 200 mg dose following each dialysis treatment is indicated." In regards to patients with hepatic impairment, the approved label states, "Because increased nevirapine levels and nevirapine accumulation may be observed in patients with serious liver disease, do not administer Viramune to patients with moderate or severe (Child-Pugh Class B or C, respectively) hepatic impairment."

Demographic interactions/special populations

Neither age nor gender are known to have an impact on absorption, distribution, metabolism, or elimination of NVP, although caution is urged in dosing geriatric patients to accommodate the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy.

Thorough QT study or other QT assessment

A thorough QT study has not been performed for either NVP-IR or NVP-XR. NVP-IR was approved for use prior to the requirement for thorough QT studies and no clinical signal for cardiac rhythm disturbances has been identified during the time since approval.

Other notable issues (resolved or outstanding)

Measurement of trough concentrations during the clinical treatment trials supported the selection of the NVP-XR dose and formulation. A previous clinical trial conducted with NVP-IR compared the approved dose of NVP-IR 200 mg twice, NVP-IR 400 mg daily (2 x 200 mg tablets), and efavirenz 600 mg daily. The study analysis compared virologic response according to NVP trough concentrations. In this study, there was no loss of virologic response in treatment adherent subjects down to the lowest quartile of $C_{min,ss}$ values (2.3 µg/mL). Also, maintaining C_{trough} above a lower limit of 1 µg/mL resulted in no loss of virologic response. Based on these study data, a target $C_{min,ss}$ of 3 µg/mL was selected as the target PK parameter for the NVP-XR formulation.

In Study 1100.1486, all subjects had trough concentrations measured at each visit through Week 48. The geometric mean for all trough concentrations for NVP-XR from Week 4 to Week 48 was 3400 ng/mL, about 80% of the geometric mean trough concentrations obtained for NVP-IR but well above the IC90 for wild type HIV-1. In a small PK sub-study, subjects receiving NVP-XR who underwent intensive PK sampling also demonstrated lower $AUC_{0\ 24}$ compared to those receiving NVP-IR; geometric mean 75,300 ng*hr/mL compared 98,200 ng*hr/mL (ratio NVP-XR to NVP-IR, 77%). As will be described in Section 7, these lower PK parameters did not result in decreased treatment efficacy.

In Study 1100.1526, trough concentrations were measured through Week 24 of the study. This study also identified that subjects receiving NVP-XR had slightly lower C_{trough} compared to those receiving NVP-IR, 3730 ng/mL compared to 4070 ng/mL. Intensive sampling was not performed in this study and other PK parameters were not determined.

Both of the clinical treatment trials demonstrated that the PK target identified during early development of the NVP-XR formulation was achieved. Additionally, although PK parameters were lower among subjects receiving NVP-XR compared to those receiving NVP-IR, treatment efficacy was not compromised. Consequently, there are no unresolved clinical pharmacology issues related to this NDA review.

6. Clinical Microbiology

The mechanism of action of NVP as an NNRTI antiretroviral drug has been well-characterized. Similarly, the patterns of amino acid substitutions in the HIV-1 reverse transcriptase leading to resistance to NVP have been documented. Treatment failure has been associated with resistance resulting from one or more of the following substitutions: A98G, K101E, K103N, V106A/M, V108I, Y181C, Y188C/L, G190A/S, F227L, and M230L. These substitutions also confer resistance to other approved NNRTIs.

Genotypic and limited phenotypic resistance testing was performed in the clinical treatment trials of NVP-XR. In Study 1100.1486, genotypic testing was performed on baseline and on-therapy isolates from 34 and 23 subjects with virologic failure in the NVP-IR and NVP-XR arms, respectively. As noted in the Clinical Microbiology reviewer, Dr. Lalji Mishra, "Nevirapine resistance-associated substitutions developed in the on-therapy isolates of 88%

(30/34) of the subjects in the NVP-IR treatment group, and 78% (18/23) of the virologic failures subjects in the NVP-XR treatment group." The Y181C substitution was the predominant substitution emerging in on-therapy isolates from subjects with virologic failure in either treatment arm of this study. In addition, two novel substitutions for NVP resistance were identified; Y188N was identified in on-therapy isolates from one subject receiving NVP-IR and Y181I was identified in isolates from another subject receiving NVP-XR. These amino acid substitutions (Y181I and Y181C) have previously been associated with resistance to etravirine, a newer NNRTI with less cross-resistance to NVP.

Factors associated with resistance in this submission were consistent with those identified in other NVP clinical trials. Most of the subjects in Study 1100.1486 who developed resistance had HIV-1 RNA levels > 100,000 copies/mL. Subjects with lower HIV-1 RNA levels at baseline were less likely to develop resistance. As in some of the NVP-IR clinical trials, NVP trough concentration did not appear to be correlated with emergence of resistance based on C_{trough} at or near the time resistant isolates were identified.

In summary, no difference was identified in the rate or pattern of resistance-associated substitutions between subjects receiving NVP-XR and those receiving NVP-IR. For a more detailed discussion of the clinical virology aspects of the NDA submission, please refer to Dr. Mishra's Microbiology Review. At the time of this review, no unresolved microbiology issues are outstanding.

7. Clinical/Statistical- Efficacy

This NDA contains the final study reports for two clinical trials supporting the efficacy of NVP-XR in combination with other antiretroviral drugs for the treatment of HIV-1 infection. These study reports and the associated datasets were reviewed by Dr. Peter Miele, the Clinical Reviewer, and Drs. Susan Zhou (for Study 1100.1486) and Lan Zeng (for Study 1100.1526), the Statistical Reviewers. Because the two trials were different in terms of study design, patient population enrolled and timing of primary efficacy analysis, the efficacy of the two studies are described separately. For detailed discussion of the primary and secondary efficacy analyses, please refer to the Clinical Review and the Statistical Review and Evaluations. A summary of their findings related to the primary efficacy analyses is included in this secondary review.

Study 1100.1486

Study 1100.1486 (VERxVE) was a randomized, double-blind, double-dummy, active-controlled trial comparing the use of NVP-XR 400 mg once daily to NVP-IR 200 mg twice daily in combination with tenofovir DF/emtricitabine in treatment-naïve HIV-1 infected patients. Subjects were HIV-1 infected male or female adults with no prior history of antiretroviral treatment, HIV-1 RNA $\geq$ 1000 copies/mL, and calculated creatinine clearance $\geq$ 50 mL/min. In order to minimize the known risk of NVP toxicity, male subjects were required to have CD4 cell count between 50 and 400 cells/mm^3 and female subjects were required to have CD4 cell count between 50 and 250 cells/mm^3.

Subjects were stratified by baseline HIV-1 RNA level (≤ 100,000 copies/mL or > 100,000 copies/mL), then randomized to receive NVP-XR or NVP-IR after a 14 day lead-in period of once daily NVP-IR. All subjects received the same once daily tenofovir DF/emtricitabine background treatment. Efficacy, safety and PK parameters were assessed at every study visit. The primary endpoint was evaluated after 48 weeks of dosing and subjects could continue assigned treatment through 144 weeks. The protocol defined primary efficacy endpoint was virologic response: two HIV-1 RNA levels < 50 copies/mL at least two weeks apart.

A total of 1626 subjects were enrolled, 1068 entered the lead-in period of dosing, and 1011 received blinded study medication and were included in the efficacy analysis; 505 received NVP-XR and 506 received NVP-IR. Of subjects initially enrolled, 558 did not actually enter the study, most due to failure to meet inclusion/exclusion criteria, and 55 discontinued study prior to randomization (i.e., during the lead-in period). Among subjects receiving randomized treatment, 82% completed 48 weeks of study. Baseline demographic and disease characteristics were similar across the two treatment arms and are summarized in Table 1 abstracted from Dr. Miele's Clinical Review.

Table 1: Subject Demographic and Baseline Characteristics (Subjects Entering Lead-In Phase) (Study 1100.1486)

Baseline characteristic	**Not randomized (N=55)**	**NVP IR 200 mg BID (N=508)**	**NVP XR 400 mg QD (N=505)**	**Total (N=1068)**
Age (years [mean])	37	38	38	38
Gender				
Male	42 (76)	433 (85)	431 (85)	906 (85)
Female	13 (24)	75 (15)	74 (15)	162 (15)
Race				
White	40 (73)	376 (74)	387 (77)	803 (75)
Black	8 (15)	113 (22)	94 (19)	215 (20)
Asian	7 (13)	13 (3)	15 (3)	35 (3)
Other [a]	0	6 (1)	9 (2)	15 (1)
Hispanic/Latino				
No	41 (75)	399 (79)	390 (77)	830 (78)
Yes	14 (25)	109 (21)	115 (23)	238 (22)
Region				
North America/Australia	14 (25)	150 (30)	141 (28)	305 (29)
Latin America	5 (9)	49 (10)	58 (11)	112 (10)
Europe	32 (58)	252 (50)	257 (51)	541 (51)
Africa	4 (7)	57 (11)	49 (10)	110 (10)
Baseline HIV-1 RNA (log_{10} copies/mL) (mean)	4.75	4.68	4.67	4.68
HIV-1 RNA stratum (copies/mL)				
≤ 100,000	35 (64)	305 (60)	311(62)	651 (61)
> 100,000	20 (36)	203 (40)	194 (38)	417 (39)

Baseline CD4 count (cells/mm^3)				
N	55	507	503	1065
Mean	226	228	230	228

Source: Clinical Review NDA 201-152

[a] Other = American Indian/Alaska native and Hawaiian/Pacific Islander

The results of Study 1100.1486 were independently confirmed by both the FDA statistical and clinical reviewers. The efficacy analysis was conducted using two different methods: time to loss of virologic response (TLOVR), the FDA's primary analysis method in the recent past, and the proportion of subjects achieving undetectable HIV-1 RNA at Week 48 (Snapshot), the current preferred analysis method. Both methods resulted in treatment response rates that were very similar and the Snapshot analysis results shown in Table 2 taken from Dr. Zhou's Statistical Review and Evaluation will be displayed in the product label. In addition, because the Roche Cobas Amplicor HIV-1 Monitor version 1.5 Ultrasensitive assay used during the clinical trials was found to have some unexpected fluctuations at low levels of HIV-1 RNA quantitation, the Applicant and the DAVP review team agreed on a re-testing procedure using the Roche Cobas TaqMan assay prior to submission of the NDA. The primary efficacy analysis was based on Amplicor-corrected assay data.

Table 2: Outcomes at Week 48 (Snapshot) - Study 1100.1486

Outcomes	**NVP IR 200 BID N=506**	**NVP XR 400 QD N=505**
Virologic Success -HIV RNA ≤ 50 copies/mL	75%	80%
Virologic Failure#	13%	11%
No Virologic Data at 48 Window		
Reasons		
Discontinued study/study drug due to AE or Death*	9%	7%
Discontinued study/study drug for Other Reasons**	3%	2%
Missing data during window but on study	<1%	-

Source: Statistical Review and Evaluation, NDA 201-152

#Includes patients who changed OBT to new class or changed OBT not permitted per protocol or due to lack of efficacy prior to Week 48, subjects who discontinued prior to Week 48 for lack or loss of efficacy and patients who are ≥ 50 copies in the 48 week window.

*Includes patients who discontinued due to AE or Death at any time point from Day 1 through the time window if this resulted in no virologic data on treatment during the specified window.

**Other includes: withdrew consent, loss to follow-up, moved etc.

The results shown in Table 2 support the non-inferiority of NVP-XR to NVP-IR in this population of treatment-naïve HIV-1 infected adults. After 48 weeks of blinded study dosing, 80.2% of subjects receiving NVP-XR compared to 75.1% of those receiving NVP-IR achieved HIV-1 RNA levels < 50 copies/mL; the difference of 4.9% with 95% CI: (-0.2%, 10.1%) was well above the pre-specified non-inferiority margin of -10%. As noted in Dr. Zhou's review, these results were robust and consistent regardless of analysis method or HIV-1 RNA assay used. In addition, the results were consistent across all subgroups evaluated (i.e., age, gender, race, ethnicity, and geographic region) adjusting for baseline HIV-1 RNA strata. In the full

study population and all subgroups, NVP-XR demonstrated numerically better treatment response although it was not statistically superior to NVP-IR.

Study 1100.1526

Study 1100.1526 (TRANxITION) was designed as a randomized, open-label, clinical trial to investigate the efficacy and safety of switching HIV-1 infected subjects who were successfully treated with a NVP-IR based regimen to NVP-XR or keeping them on their NVP-IR (2:1 ratio). All subjects remained on their stable background antiretroviral drugs (abacavir/lamivudine, zidovudine/lamivudine, or tenofovir DF/emtricitabine) and randomization was stratified by background regimen.

Subjects were eligible to enroll if they had been treated with a NVP-IR-based regimen for at least 18 weeks in combination with one of the allowed background regimens and had undetectable HIV-1 RNA in the preceding 1-4 months and at the time of screening. Safety and efficacy were assessed at each study visit. The primary efficacy analysis was performed after 24 weeks of dosing but the study continued through 48 weeks of dosing with an extension period of up to 144 weeks allowed.

A total of 499 subjects were enrolled, 445 entered the study, and 443 received randomized treatment and were analyzed for the primary endpoint (295 received NVP-XR and 148 received NVP-IR. In this study, 98% of randomized subjects completed at least 24 weeks on study. Baseline demographic and disease characteristics were similar across the two treatment arms and are summarized in Table 2 abstracted from Dr. Miele's Clinical Review.

Table 3: Subject Demographic and Baseline Characteristics (Study 1100.1526)

Baseline characteristic	Number of subjects (%)		
	NVP IR 200 mg BID (N=148)	NVP XR 400 mg QD (N=295)	Total (N=443)
Age (years [mean])	47	47	47
Gender			
Male	128 (86)	244 (83)	372 (84)
Female	20 (14)	51 (17)	71 (16)
Race			
White	134 (91)	270 (92)	404 (92)
Black	13 (9)	20 (7)	33 (7)
Asian	0	5 (2)	5 (1)
Other [a]	1 (1)	0	1 (<1)
Hispanic/Latino			
No	132 (89)	269 (91)	401 (91)
Yes	16 (11)	26 (9)	42 (9)
Region			
North America	46 (31)	98 (33)	144 (33)
Europe	102 (69)	197 (67)	299 (67)
Baseline HIV-1 RNA (copies/mL)			
< 50	136 (92)	280 (95)	416 (94)

≥ 50	12 (8)	15 (5)	27 (6)
Baseline background regimen			
Truvada®	82 (55)	158 (54)	240 (54)
Combivir®	30 (20)	63 (21)	93 (21)
Kivexa®/Epzicom™	36 (24)	74 (25)	110 (25)
Duration of previous NVP IR therapy			
< 1 year	30 (20)	52 (18)	82 (19)
1 – 3 years	44 (27)	101 (34)	145 (33)
3 – 5 years	35 (24)	75 (25)	110 (25)
> 5 years	39 (26)	67 (23)	106 (24)
Baseline CD4 count (cells/mm^3)			
N	147	295	442
Mean	567	558	561

Source: Clinical Review NDA 201-152

[a] Other = American Indian/Alaska native and Hawaiian/Pacific Islander

The results of Study 1100.1526 were also independently confirmed by both the FDA statistical and clinical reviewers. Since subjects in this study were HIV-1 undetectable at entry, the primary efficacy endpoint was continued undetectable HIV-1 RNA at Week 24 of treatment. Multiple analyses were conducted using the two analysis methods and two HIV-1 RNA quantitation assay methods. The primary efficacy endpoint results for the study, based on Amplicor-corrected assay data, abstracted from Dr. Miele's review, are displayed in Table 4.

Table 4: Outcomes at Week 24 (Snapshot) - Study 1100.1526

Outcomes	**Number of subjects (%)**		
	NVP IR 200 mg BID (N 148)	**NVP XR 400 mg QD (N 295)**	**Total (N 443)**
Virologic success	139 (94)	283 (96)	422 (95)
Virologic failure	3 (2)	5 (2)	8 (2)
No virologic data in Week 24 window	6 (4)	7 (2)	13 (3)
Discontinued study due to AE or death	0	3 (1)	3 (1)
Discontinued study for other reasons	3 (2)	4 (1)	7 (2)
Missing data during window but on study	3 (2)	0	3 (1)

Source: Clinical Review NDA 201-152

The results shown in Table 4 support the non-inferiority of switching from NVP-IR to NVP-XR in this population of treatment-experienced HIV-1 infected adults. Because these subjects were already suppressed and stable on a NVP-IR regimen, the high rates of virologic suppression after 24 weeks of continued NVP-IR or switch to NVP-XR are not surprising. As noted in Dr. Zeng's review, 95.3% of subjects receiving NVP-XR and 93.9% of those receiving NVP-IR maintained virologic suppression (HIV-1 RNA < 50 copies/mL) at Week 24, with a difference of 1.3% in favor of NVP-XR (95% CI: -3.5%, 6.1%) adjusting for the baseline background therapy. The lower bound of the treatment difference was greater than

the pre-specified noninferiority margin -12%. There was no apparent relationship between the proportion of sustained virologic responders at Week 24 and any baseline demographics or clinical characteristic.

8. Safety

The safety profile of NVP-IR has been well characterized during drug development and during clinical use and the safety profile of NVP-XR was not expected to be significantly different. The safety of the NVP-XR formulation in HIV-1 infected has been evaluated in 800 subjects receiving NVP-XR in the clinical treatment trials. Given the previous regulatory experience with NVP, this safety database was considered adequate to assess the possibility of a different safety profile for the NVP-XR product compared to the NVP-IR product. No new safety signals for NVP-XR were identified in the two clinical trials submitted or in the earlier clinical pharmacology studies. A full description of the safety review can be found in Dr. Miele's Clinical Review but a summary of major findings will be included in this review.

Overall, 10 deaths were reported during the clinical treatment trials reported in this submission, all in Study 1100.1486. Six of these deaths occurred after the screening period when subjects were receiving study medications; five received NVP-IR and one received NVP-XR. Causes of death included tuberculous meningitis, pulmonary hypertension with respiratory failure, pneumonia and encephalitis, myocardial infarction, hypertension and arteriosclerosis, and thermal burns and wound sepsis. None of the deaths were considered related to study drugs.

Serious adverse events (SAEs) were documented in both of the clinical trials. Among the 1068 subjects who entered the 14-day lead-in period of Study 1100.1486, 20 subjects developed an SAE before reaching the randomized part of the study. The most frequent categories of SAEs in this period were infections/infestations (n 7) and skin and subcutaneous tissue (n 7). SAEs occurred in 112 of the 1011 (11%) subjects who received randomized treatment in Study 1100.1486, 54 (11%) subjects receiving NVP-IR and 58 (12%) subjects receiving NVP-XR. The most frequently reported SAEs were pneumonia, depression and Kaposi's sarcoma, each observed in 5 subjects. SAEs in the organ systems Hepatobiliary Disorders (n 9) and Skin and Subcutaneous Tissue Disorders (n 7) were documented in small numbers and evenly distributed between the two treatment groups, however, 3 subjects in the NVP-IR arm experienced Stevens-Johnson syndrome (SJS) compared to none in the NVP-XR arm. Among the 443 subject who were randomized and received study drug in Study 1100.1526, 21 (5%) subjects experienced SAEs. In this study, SAEs occurred twice as frequently in subjects receiving NVP-XR (n 17 [6%]) than in those receiving NVP-IR (n 4 [3%]). None of the SAEs in this study were serious rash or hepatic events and none were considered treatment-related.

Subjects in Study 1100.1486 were more likely than those in Study 1100.1526 to discontinue study drug during the randomized study period. In Study 1100.1486, 77 (8%) of 1011 treated subjects discontinued study drug due to AEs (n 45 [9%] receiving NVP-IR, n 32 [6%] receiving NVP- XR). The most common AEs leading to study drug discontinuation were rash

(including SJS), increased transaminases, hepatoxicity, and nausea. Because the numbers for specific AEs were small, it was not possible to demonstrate a significant difference between the treatment arms for any AE. Because subjects in Study 1100.1526 were already known to tolerate NVP-IR, it is not surprising that rates of discontinuation in this study were very low (n 3), all in the NVP-XR arm. Overall, discontinuations in these two clinical trials are similar in nature to those documented in earlier clinical trials of NVP-IR.

The general AE profile of NVP-XR compared to NVP-IR was evaluated using the pooled data from the two clinical treatment trials after randomization (i.e., excluding the lead-in period of Study 1100.1486). While the studies were of different designs and durations, the randomized nature of the studies and similar management across arms in each study allowed comparison of reported AEs. Overall, the most common AEs regardless of severity or relationship to study drug were nasopharyngitis, diarrhea, URI, rash, headache, bronchitis, fatigue and nausea. As shown in Table 5 from Dr. Miele's Clinical Review, no differences in common AEs were noted between the arms in the pooled data.

Table 5: Adverse Events Occurring in ≥ 5% Subjects, Pooled Data (Study 1100.1486 and 1100.1526)

Adverse event	Number of subjects (%)		
	NVP IR 200mg BID (N=654)	NVP XR 400mg QD (N=800)	Total (N=1454)
Nasopharyngitis	97 (15)	117 (15)	214 (15)
Diarrhea	67 (10)	88 (11)	155 (11)
Upper respiratory tract infection	56 (9)	68 (9)	124 (9)
Rash	50 (8)	55 (7)	105 (7)
Headache	62 (9)	52 (7)	114 (8)
Bronchitis	40 (6)	49 (6)	89 (6)
Fatigue	28 (4)	39 (5)	67 (5)
Nausea	51 (8)	38 (5)	89 (6)
Back pain	29 (4)	37 (5)	66 (5)
Cough	38 (6)	34 (4)	72 (5)
Hypertension	30 (5)	32 (4)	62 (4)
Vomiting	31 (5)	26 (3)	57 (4)

Source: Clinical Review NDA 201-152

More subtle, potential differences between the two formulations are suggested when more severe, drug-related AEs are examined in Study 1100.1486, in which subjects received the same lead-in period drug followed by randomization to either NVP-XR or NVP-IR (see Table 6, from the Clinical Review). The trial was not powered to show a statistical difference in any AE, however, numerically greater numbers of subjects receiving NVP-IR experienced a Grade 2 or greater AE considered possibly drug-related. In spite of selecting subjects thought to be at lower risk of NVP toxicity based on CD4 cell counts, three subjects receiving NVP-IR developed SJS compared to none receiving NVP-XR and 18 subjects receiving NVP-IR developed a Grade 2 or greater hepatobiliary AE compared to nine receiving NVP-XR.

Table 6: Drug-related Moderate or Severe (Toxicity Grade ≥ 2) Adverse Events during Randomized Phase (Study 1100.1486)

DAIDS Grade 2-4 adverse events (by SOC/ADR/PT)[a]	Number of subjects (%)		
	NVP IR 200 mg BID (N=506)	NVP XR 400 mg QD (N=505)	Total (N=1011)
Number with AEs	66 (13)	54 (11)	120 (12)
Skin and subcutaneous tissue disorders	20 (4)	21(4)	41(4)
Rash	15 (3)	17 (3)	32 (3)
Rash	12 (2)	16 (3)	28 (3)
Rash maculo-papular	2 (<1)	0	2 (<1)
Erythema nodosum	1 (<1)	0	1 (<1)
Rash erythematous	1 (<1)	0	1 (<1)
Rash papular	1 (<1)	0	1 (<1)
Skin reaction	0	1 (<1)	1 (<1)
Stevens-Johnson syndrome	3 (1)	0	3 (<1)
Dermatitis allergic	0	1 (<1)	1 (<1)
DRESS syndrome[b]	0	1 (<1)	1 (<1)
Investigations	29 (6)	24 (5)	53 (5)
Liver Function Test Abnormal	18 (4)	15 (3)	33 (3)
Alanine aminotransferase increased	6 (1)	6 (1)	12 (1)
Transaminases increased	6 (1)	5 (1)	11 (1)
Aspartate aminotransferase increased	3 (1)	5 (1)	8 (1)
Gamma-glutamyltransferase increased	3 (1)	2 (<1)	5 (1)
Liver function test abnormal	3 (1)	0	3 (<1)
Hepatic enzyme increase	2 (<1)	1 (<1)	3 (<1)
Hypertransaminasemia	1 (<1)	0	1 (<1)
Hepatobiliary disorders	18 (4)	9 (2)	27 (3)
Hepatitis	17 (3)	9 (2)	26 (3)
Hepatitis	6 (1)	4 (1)	10 (1)
Hepatotoxicity	6 (1)	2 (<1)	8 (1)
Hepatitis acute	2 (<1)	1 (<1)	3 (<1)
Hepatitis toxic	1(<1)	1 (<1)	2 (<1)
Liver disorder	2 (<1)	0	2 (<1)
Hepatic failure	0	1 (<1)	1 (<1)
Jaundice	1(<1)	0	1(<1)
Gastrointestinal disorders	13 (3)	4 (1)	17 (2)
Nausea	5 (1)	1 (<1)	6 (1)
Metabolism and nutrition disorders	2 (<1)	4 (1)	6 (1)
Musculoskeletal and connective tissue disorders	3 (1)	2 (<1)	5 (1)
Nervous system disorders	4 (1)	5 (1)	9 (1)
Headache	3 (1)	3 (1)	6 (1)

Source: Clinical Review NDA 201-152

[a] SOC=system organ class; ADR=adverse drug reaction (BI term); PT=preferred term

[b] DRESS=drug rash with eosinophilia and systemic systems

Serious rash and hepatic events were the AEs of most concern evaluated in the current submission, as these have previously been associated with NVP use. Most of the rash events

occurred either during the lead-in period or early during the randomized part of the Study 1100.1486 and no difference was identified in overall frequency of rash between the two treatment arms. Severe or life-threatening rash was reported infrequently but occurred more often in the NVP-IR arm (n 7) compared to the NVP-XR arm (n 3). Subjects in the NVP-IR group were more likely to have a hepatic event than subjects in the NVP-XR group. Subjects in the NVP-IR group were more likely to experience any hepatic event (n 46 [9%] receiving NVP-IR, n 27 [5%] receiving NVP-XR), develop symptoms of hepatitis (n 12 [2%] NVP-IR, n 8 [1%] NVP-XR), or develop non-specific symptoms which could be associated with a hepatic event (n 20 [4%] NVP-IR, n 10 [2%] NVP-XR).

As noted in Dr. Miele's safety review of Study 1100.1486, women appeared to be at greater risk of any AE if receiving the NVP-IR formulation. Women were more likely than men to experience a rash event. Women were twice as likely as men to have a hepatic event and were more likely to have a symptomatic hepatic AE if receiving NVP-IR. These findings are consistent with the known safety profile of NVP-IR in women but the proportion of women in this clinical trial is really too small to draw any firm conclusions regarding differences between the two formulations.

Clinically relevant laboratory abnormalities occurred relatively infrequently in the clinical treatment studies and evaluation of laboratory abnormalities revealed few differences between the two treatment groups. In Study 1100.1486, 6% of subjects receiving NVP-IR developed Grade 3 or 4 ALT elevations compared to 5% receiving NVP-XR and Grade 3 or 4 AST elevations occurred with similar frequency (4%) in both arms. Grade 2 or greater neutropenia occurred in 10% of subjects receiving NVP-IR compared to 7% of those receiving NVP-XR. Overall, changes in laboratory values from baseline were generally similar across the treatment arms and no new laboratory signals were identified.

Thus, the overall safety profile of NVP-XR was assessed to be no worse than the currently approved NVP-IR in terms of clinical events and laboratory monitoring and there was some evidence of slightly better tolerability. No new safety issues were identified during the clinical trials submitted and there are no unresolved safety concerns related to this NDA submission.

9. Advisory Committee Meeting

Because NVP-IR has been widely used since approval in 1996 and the safety profile, resistance patterns, and treatment efficacy are well-characterized and no new issues relevant to the NVP-XR formulation were identified, an Advisory Committee meeting was not convened.

10. Pediatrics

The DAVP considered development of an extended-release formulation to be of potential public health benefit to pediatric patients. (b) (4)

[redacted]

(b) (4)

The Applicant requested a deferral of pediatric studies in patients 3 to 18 years of age and a waiver of pediatric studies in patients less than 3 years of age. Studies in pediatric patients 3 to 18 years of age are deferred because the product is ready for approval in adults and the pediatric study is not yet complete. In addition, the Applicant requested a partial waiver in younger children based on their belief that studies are impossible or highly impractical to conduct in this age group. Because DAVP believes effective treatment of HIV-1 infection represents a critical public health benefit for pediatric patients, we do not accept this rationale. However, we are waiving the pediatric study requirement for pediatric patients from birth to less than three years because the NVP-XR product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this age group and is not likely to be used in a substantial number of pediatric patients in this group. The extended-release formulation is a solid dosage form that must not be chewed or crushed at the time of dosing. Therefore, this formulation is not appropriate for younger pediatric patients unable to swallow tablets. Viramune (nevirapine) Oral Suspension is available and approved for use in children down to the age of 2 weeks and is an appropriate option in pediatric patients younger than 3 years.

A review of the requested partial waiver and deferral was completed by the Pediatric Review Committee (PeRC) on January 26, 2010 and the PeRC agreed with the DAVP plan to grant the partial waiver and deferral. The deferred pediatric study is considered a required postmarketing study under the Pediatric Research Equity Act (PREA) and will be listed in the approval letter as follows:

1741-1 Multiple-dose pharmacokinetic and safety study of nevirapine extended release tablets, in combination with other antiretroviral agents, in HIV-infected pediatric patients from 3 to < 18 years old. Study report and datasets will include safety and antiviral activity data through 24 weeks of dosing with nevirapine extended release tablets in a cohort of subjects.

Final Protocol Submission: December 2008
Final Report Submission: September 2011

In addition, the Applicant was issued a Written Request (WR) for a pediatric safety and activity trial (b) (4) but decided to decline the WR. Because the PREA study is being conducted, DAVP does not believe the WR is necessary to obtain adequate pediatric data for safe use of NVP-XR.

11. Other Relevant Regulatory Issues

At the time of this review, audits conducted by the Division of Scientific Investigation have been completed and no significant deficiencies in data integrity were identified. No issues

related to financial disclosure or Good Clinical Practice standards were identified. There are no unresolved regulatory issues.

12. Labeling

Viramune XR will have a separate label from the currently approved Viramune label but all NVP products will share a common Medication Guide. Both physician and patient labeling have been reviewed and revisions have been discussed with the Applicant and incorporated into final labeling. All major safety labeling including Warnings and Precautions, drug interaction information and resistance data from the Viramune label will be incorporated into the Viramune XR label and augmented as appropriate with information from the NVP-XR clinical treatment trials. The pertinent clinical pharmacology information related to the NVP-XR formulation and the safety and efficacy results of Studies 1100.1486 and 1100.1526 will be reported in the Viramune XR label.

The proprietary name, Viramune XR, was reviewed by Shenee' Toombs, PharmD, Safety Evaluator in the Division of Medication Error Prevention and Analysis (DMEPA). She found no potential for medication errors or promotional concerns related to the proposed product name. She also reviewed the carton and container labeling for the product and made recommendations to ensure adequate labeling.

In addition, the Medication Guide to be distributed with Viramune XR extended-release tablets, Viramune tablets, and Viramune Oral Suspension was reviewed by Safety and Patient Labeling Evaluators in the Division of Drug Marketing, Advertising, and Communications (DDMAC) and the Division of Risk Management (DRISK). Their recommendations to improve readability and completeness and to ensure consistent organization of the Medication Guide were discussed with the Applicant and these revisions were incorporated into the final patient labeling.

13. Recommendations/Risk Benefit Assessment

Recommended Regulatory Action

I agree with Dr. Miele and the other members of the review team and recommend this NDA for Viramune XR (nevirapine) extended-release tablets be approved. None of the discipline reviewers have voiced any disagreement on the approvability of the NDA.

Risk Benefit Assessment

The clinical pharmacology studies support the use of NVP-XR as a once daily component of antiretroviral treatment. The two clinical trials, Studies 1100.1486 and 1100.1526 demonstrate that NVP-XR is non-inferior to NVP-IR when used in a variety of 3-drug antiretroviral regimens in treatment-naïve and treatment-experienced subjects. In both of these studies, NVP-XR treatment resulted in numerically more subjects who achieved the primary efficacy

endpoint of undetectable HIV-1 RNA than NVP-IR. No new safety signals were identified in subjects receiving NVP-XR and the safety profile of NVP-XR was similar to that of NVP-IR. There was some evidence that some adverse events such as serious rash may be slightly less frequent with this formulation. Given the once daily dosing, NVP-XR may provide an advantage in terms of patient adherence. Overall, the risk/benefit assessment of the data submitted favor approval of NVP-XR.

Recommendation for Postmarketing Risk Evaluation and Management Strategies

No new postmarketing REMS are recommended. NVP-IR (Viramune) currently has a Medication Guide REMS and this will be carried over to NVP-XR (Viramune XR) at the time of this action. The NVP-IR and NVP-XR products will have separate package inserts describing the clinical trials conducted to support NVP-IR and NVP-XR but will share a Medication Guide as the active moiety and resulting potential risks of the products are the same. The Medication Guide has been reviewed by the Safety Evaluators in DDMAC and DRISK and has been revised according to their recommendations.

Recommendation for other Postmarketing Requirements and Commitments

In accordance with PREA requirements, the approval letter will include a postmarketing commitment for submission of deferred pediatric studies in patients 3 to 18 years of age. No other postmarketing requirements or commitments will be requested.

Recommended Comments to Applicant

No other specific comments will be conveyed to the applicant in the regulatory action letter as there are no deficiencies that need to be resolved.

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/s/

LINDA L LEWIS
03/11/2011