OFFICE OF CLINICAL PHARMACOLOGY (OCP) MEMORANDUM

sNDA	201152
Submission Date	11 Sept 2012
Brand Name	VIRAMUNE® XR
Generic Name	Nevirapine
Primary Reviewer	Leslie Chinn, Ph.D.
Secondary Reviewer	Vikram Arya, Ph.D.
OCP Division	DCP4
OND Division	DAVP
Sponsor	Boehringer Ingelheim Pharmaceuticals, Inc.
Relevant IND	74744
Submission Type; SDN	SDN 156 [SE4 (b) (4)
Formulation; Strength	XR Tablets; 100 mg
Proposed Dosing Regimen	<u>Lead-in Period</u> • Pediatric patients (b) (4) must initiate therapy with 150 mg/m of VIRAMUNE oral suspension or with immediate-release VIRAMUNE tablets administered once daily for the first 14 days. • Pediatric patients already on a regimen of twice-daily VIRAMUNE oral suspension or immediate-release VIRAMUNE tablets can be switched to VIRAMUNE XR once daily without the 14-day lead-in period of VIRAMUNE oral suspension or immediate-release VIRAMUNE tablets. <u>After the Lead-in Period, dose by BSA:</u> BSA Range (m^2): VIRAMUNE XR tablets (mg): 0.58-0.83 200 mg once daily (2x100 mg) 0.84-1.16 300 mg once daily (3x100 mg) >1.17 400 mg once daily (1x400 mg)
Proposed Indication	(b) (4)

This memorandum documents the clinical pharmacology review of a resubmitted datasets in support of an efficacy supplement for a pediatric indication for Viramune® XR tablets. Following is a brief background on the sNDA as well as a summary of the clinical pharmacology-related findings based on the pharmacokinetic data contained in the resubmission.

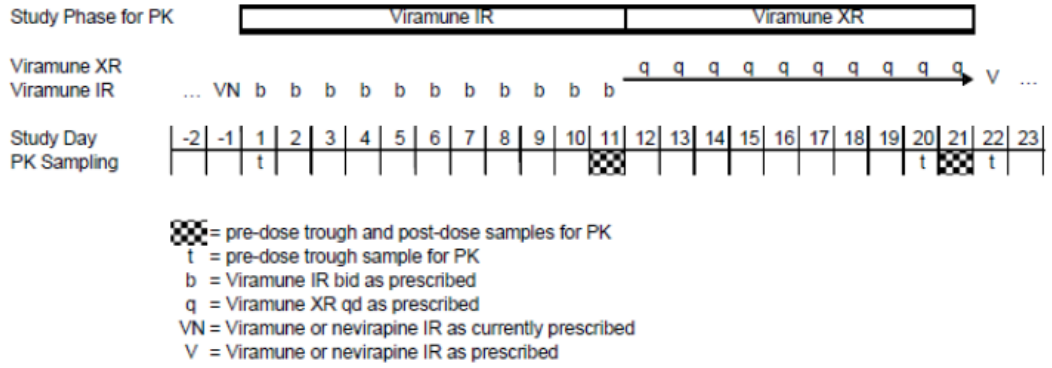
I. Background

Study reports for two clinical trials were submitted to support the approval of NDA 201154 S-004. The trials were:

1100.1517 (17 Apr to 7 Jul 2008)
The goal of this trial was to determine the single-dose pharmacokinetics of NVP XR when administered as 2x100 mg and 3x100 mg using 100 mg XR tablets in comparison to NVP IR 200 mg (1x200 mg) using 200 mg IR tablets and NVP XR 400 mg (1x400 mg) using 400 mg XR tablets to healthy adult volunteers (24 subjects per treatment group).

1100.1518 (4 Jun to 5 Feb 2010)
The goal of this trial was to characterize the steady-state pharmacokinetics of NVP XR in children between the ages of 3 and 18 years old, inclusive. The primary endpoint was dose-normalized trough drug concentration ($C_{pre,ss}$); secondary endpoints included $AUC_{tau,ss}$, $C_{min,ss}$, safety and tolerability, and efficacy (VL<50 copies/mL at Day 22).

Figure 1: Study design to compare the steady-state pharmacokinetics of Viramune® IR and NVP XR formulations (source: Study Report Figure 9.1:1)



II. Regulatory history

The approval letter for NDA 201152 (25 Mar 2011) included postmarketing commitment 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.

Although the statistical criteria to use for determining the number of subjects in each of the age groups was not agreed upon prior to initiation of the pivotal pediatric study, comparable Written Requests issued in a similar timeframe specify 6 to 12 subjects per age group, with higher numbers of subjects in younger age groups to account for greater pharmacokinetic variability.

The dates and nature of correspondences between the Division and the Applicant regarding the current supplemental application (S-004) are listed below:

- *22 Jun 2012 – Complete Response letter sent to the Applicant*

  Please assemble and perform statistical analysis on the revised pharmacokinetic datasets, taking the following items into consideration:

  a. Exclude the original and repeat analysis data for all analytical runs containing QCs that failed acceptance criteria according to Agency's "*Guidance for Industry-Bioanalytical Method Validation"* including the following four runs:

     - AY1_100125_QP1_SE
     - AY1_100202_QP1_LM
     - AY1_100118_QP1_LM2
     - AY1_100113_QP2_LM

  b. Exclude the repeat analysis data for all samples which passed during initial runs, including the following runs:

     - AY1_100118_QP1_SE2
     - AY1_100115_QP1_SE2
     - QY1_100118_QP1_LM
     - AY1_100121_QP2_LM
     - AY1_100121_QP1_SE
     - QY1_100118_QP1_SE

  Please follow the "*Guidance for Industry – Bioanalytical Method Validation"* for determination of analytical run acceptability. Use the concentrations from the initial runs for PK evaluation.

- *31 July 2012 – Resubmission of summary pharmacokinetic data by the Applicant, including analytical runs "accepted by exception" (i.e. runs in which sample concentrations were "bracketed" by acceptable QCs or calibration curves, even though either the low QC samples or the LLOQ or ULOQ samples failed)*

(b) (4)

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11 Sept 2012 – Resubmission of revised pharmacokinetic data by the Applicant; revised data sets were deemed acceptable by the OSI reviewer for further review.

(b) (4)

III. Analysis of resubmission (SDN 156)

The dataset contained within the resubmission was negatively impacted by the removal of concentration data as specified by the Bioanalytical Guidance. The Applicant included an analysis of trough concentrations by age group (summarized in Table 1).

Table 1. NVP trough concentrations ($C_{pre,ss}$) by formulation and by age group, as calculated by the Applicant (source: Table 11.5.2.2.3:1 in 1100.1518 CSR and Tables 4.13-4.15 in resubmission)

	NVP XR		NVP IR		Resubmission		Orig	Adult
Age Group	N	gMean	N	gMean	Ratio	gCV (%)	Ratio	Ratio
3 to <6	4	4866.7	4	5697.1	85.42	12.0	96.67	
6 to <12	10	3743.0	13	4359.0	85.87	26.5	83.53	82.69
12 to <18	5	6555.7	6	5571.7	80.27	24.0	91.19	

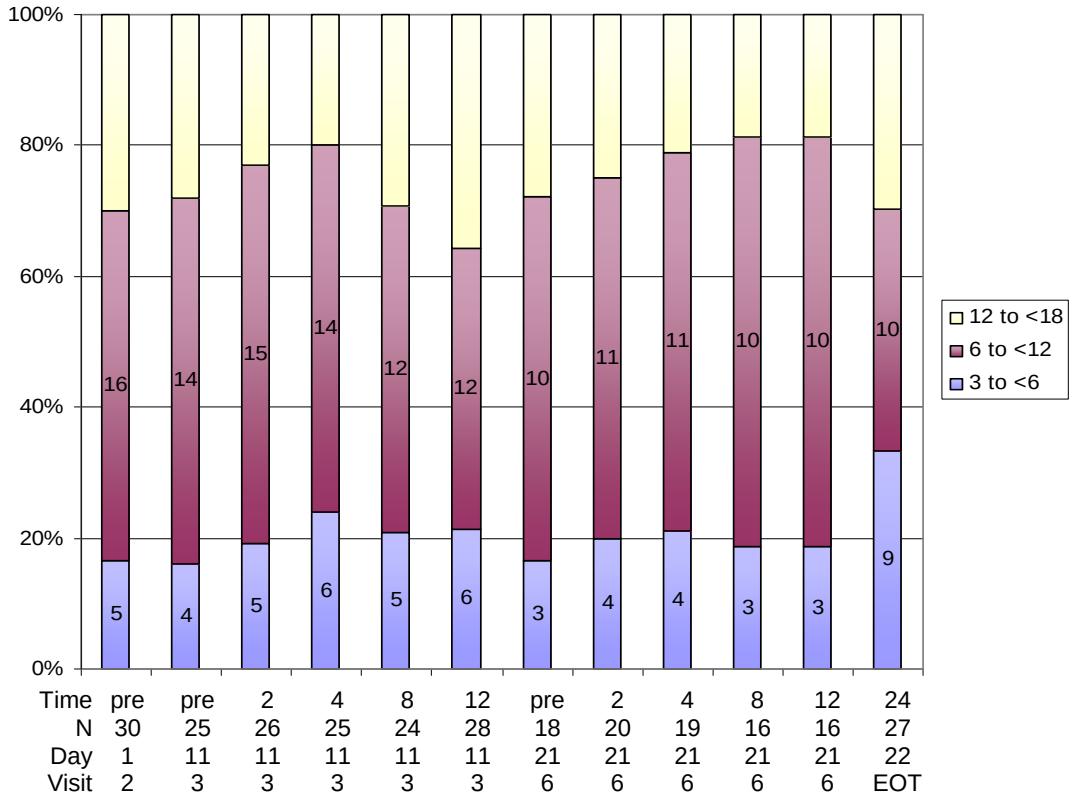
However, the Applicant did not calculate exposure (AUC, C_{max}) by age group. As approval of the pediatric indication is contingent upon accurate characterization of the pharmacokinetics of NVP, the number of subjects in each age group with sufficient concentration-time data was determined (Table 2).

Table 2. Numbers of subjects with Viramune® IR and XR plasma concentrations in the original analysis and resubmission (source: 1100.1518 CSR and Recalculated Nevirapine Concentrations, SDN 156)

	Original		Resubmission	
Age Group	IR (N)	XR (N)	IR (N)	XR (N)
3 to <6	16	16	5	3
6 to <12	16	15	11	11
12 to <18	17	14	5	3

The numbers of subjects contributing concentration data to the exposure parameters are shown in Figure 2. The size of the data set was similar across all the time points for NVP XR and IR.

Figure 2. Accepted nevirapine plasma concentrations from Study 1100.1518, by visit and age. Subjects received NVP IR BID on Days 1-11 (dosed by BSA or BW) and XR QD on Days 12-21 (dose based on IR dose at study entry).



IV. Labeling changes (SDN 156)

Labeling changes proposed by the Applicant were discussed in the Office of Clinical Pharmacology review filed in DARRTS on 25 May 2012. In the resubmission, additional edits were made by the Division for consideration by the Applicant. These edits include changing the proposed indication to "[c]ombination antiretroviral treatment of HIV-1 infection in children 6 to <18 years of age" (b) (4) as well as recalculating the pediatric pharmacokinetic parameters described in Section 12.3 of the label, as shown below.

The Applicant did not include subjects 10196 and 10197 in the calculation of the pharmacokinetic parameters due to insufficient data. After exclusion of the pharmacokinetic data from subjects 10196 and 10197, the Applicant's calculations demonstrated that nevirapine pharmacokinetics were similar following administration of Viramune® XR and IR, with XR:IR geometric mean ratios and 90% confidence intervals for $C_{min,ss}$ and AUC_{ss} falling within the no-effect bounds of 80 to 125%. In the opinion of this reviewer, the exclusion of pharmacokinetic data from subjects 10196 and 10197 did not significantly impact the overall conclusions from the study.

V. Conclusion

Following a review of the revised plasma concentration dataset contained in SDN 156, the pharmacokinetic data appear to support approval of the use of Viramune® XR tablets in pediatric patients who are six years of age or older.

While the number of subjects over the age of 12 was limited, the pharmacokinetic properties of NVP are expected to be similar between adolescents and adults. This is further supported by the

unanimous recommendation of the Pharmaceutical Science and Clinical Pharmacology Advisory Committee that "dose(s) for the adolescent (>12 years) population [may] be derived using adult data without the need for a PK study" in March 2012 (http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AdvisoryCommitteeforPharmaceuticalScienceandClinicalPharmacology/UCM306989.pdf). In addition, the total daily dose of NVP (400 mg) administered as either NVP XR (1x400 mg XR) or NVP IR (2x200 mg IR) is expected to be similar between adults and pediatric patients 12 to less than 18 years of age. Hence, there is sufficient information to support the approval of Viramune® XR in patients 12 to less than 18 years of age.

The number of subjects in the 6 to less than 12 year old age group was sufficient to calculate the pharmacokinetic parameters of NVP after administration of NVP IR and NVP XR and account for pharmacokinetic variability (N=11 in both the IR and XR treatment groups). The NVP XR:IR geometric mean ratios for $C_{min,ss}$ and AUC_{ss} were 97% and 94%, respectively, with associated 90% confidence intervals between 80 and 125%. Further, the relative bioavailability of NVP XR in comparison to NVP IR was similar in adult and pediatric patients. The aforementioned information supports the approval of Viramune® XR in patients 6 to less than 12 years of age.

(b) (4)

Based on the available clinical pharmacology information, approval of Viramune® XR 100 and 400 mg tablets as part of a combination antiretroviral treatment of HIV-1 infection in children 6 to less than 18 years of age is recommended.

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/s/

LESLIE W CHINN
11/08/2012

VIKRAM ARYA
11/08/2012