



Australian Government

Department of Health and Ageing  
Therapeutic Goods Administration

# Australian Public Assessment Report for Nevirapine

Proprietary Product Name: Viramune XR

Sponsor: Boehringer Ingelheim Pty Ltd

**March 2012**

**TGA** Health Safety  
Regulation

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- The Therapeutic Goods Administration (TGA) is a division of the Australian Government Department of Health and Ageing, and is responsible for regulating medicines and medical devices.
- TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website.

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- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

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# I. Introduction to Product Submission

## Submission Details

<i>Type of Submission</i>	New Dosage Form
<i>Decision:</i>	Approved
<i>Date of Decision:</i>	19 December 2011
<i>Active ingredient(s):</i>	Nevirapine
<i>Product Name(s):</i>	Viramune XR
<i>Sponsor's Name and Address:</i>	Boehringer Ingelheim Pty Ltd 78 Waterloo Road North Ryde NSW 2113
<i>Dose form(s):</i>	Modified release tablets
<i>Strength(s):</i>	50 mg, 100 mg and 400 mg
<i>Container(s):</i>	High density polyethylene (HDPE) bottle with plastic child resistant closure and induction foil seal liner (50 mg and 100 mg). Single unit polyvinyl chloride (PVC)/aluminium blisters (400 mg).
<i>Pack size(s):</i>	180: 50 mg 90: 100 mg 10 and 30: 400 mg
<i>Approved Therapeutic use:</i>	<p>Viramune (nevirapine) immediate release tablets and oral suspension in combination with antiretroviral agents is indicated for the treatment of HIV-1 infection in adults and children over the age of 2 months.</p> <p>Viramune XR (nevirapine) extended release tablets in combination with antiretroviral agents is indicated for the treatment of HIV-1 infection in adults and children over the age of three years.</p> <p>Extended release tablets are not suitable for the 14 day lead in period for patients starting nevirapine. Other nevirapine formulations, such as immediate release tablets or oral suspension should be used.</p> <p>Resistant virus emerges rapidly when Viramune is administered as monotherapy or in dual combination therapy with an antiretroviral agent. Therefore, Viramune should always be administered in combination with at least two additional antiretroviral agents.</p>
<i>Route(s) of administration:</i>	Oral
<i>Dosage:</i>	400 mg once daily for adults and 200 mg, 300 mg or 400 mg once daily for children depending on their body weight or body surface area.
<i>ARTG Number (s)</i>	176980 (400mg), 176982 (100mg), 176985 (50mg)

## Product Background

Nevirapine is a non nucleoside reverse transcriptase inhibitor (NNRTI) with activity against human immunodeficiency virus type 1 (HIV-1). Nevirapine binds directly to reverse transcriptase and blocks the RNA dependent and DNA dependent DNA polymerase activities by causing a disruption of the enzyme's catalytic site. The activity of nevirapine does not compete with template or nucleoside triphosphates. HIV-2 reverse transcriptase and eukaryotic DNA polymerases are not inhibited by nevirapine.

In Australia 29,296 people were notified with HIV up to December 2009 with 1,050 new cases in 2009. The total number of deaths in Australia from acquired immune deficiency syndrome (AIDS) totalled 6,776 to December 2009.<sup>1</sup> The World Health Organisation (WHO) estimate of the world wide prevalence in 2009 was 33.3 million cases with 2.6 million new cases for the year 2009. An estimated 30 million deaths have occurred worldwide from AIDS related illness. Death rates have been falling with the introduction of combination antiretroviral therapy and subsequently highly active antiretroviral therapy (HAART), especially in the developed world.

In the US and Europe, the target population consists of 80% men and has an average age of around 40 years. In African populations, women account for approximately 60% of estimated HIV infections. In 1992, the Center for Disease Control (CDC) published a revised classification system and case definition for AIDS which included numerous AIDS defining events comprised of opportunistic infections (candidiasis, coccidiomycosis, *Cryptococcus*, cryptosporidiosis, cytomegalovirus and cytomegalovirus retinitis, herpes simplex virus, histoplasmosis, isosporiasis, mycobacterium species and mycobacterium tuberculosis, *Pneumocystis jirovecii* (carinii) pneumonia, recurrent pneumonia, recurrent salmonella septicaemia, and cerebral toxoplasmosis), as well as other conditions (progressive multifocal leukoencephalopathy, lymphoma, Kaposi's sarcoma, invasive cervical cancer, HIV related encephalopathy, and wasting syndrome due to HIV).

Rash, fever, and pharyngitis are part of the acute HIV syndrome. Rash and other cutaneous reaction are common in HIV patients treated with antiretroviral drugs, primarily a maculopapular rash. In AIDS, mild liver disease with minimal morbidity is common. Liver function abnormalities are more common in patients co infected with hepatitis C.

Nevirapine IR (Viramune), the immediate release tablets, has been licensed for marketing in Australia for use in adults as well as paediatric patients with HIV-1 infection. This AusPAR describes the evaluation of an application from Boehringer Ingelheim Pty Ltd (the sponsor) which sought TGA's approval for registration of three strengths (50 mg, 100 mg, and 400 mg) of nevirapine XR, the extended release tablets (or modified release tablets) for the treatment of HIV-1 infection in adult and paediatric patients three years and older.

The proposed indication for Viramune XR tablets is the same as the currently approved indication for Viramune immediate release tablets and oral liquid:

*Viramune (nevirapine) in combination with antiretroviral agents is indicated for the treatment of HIV-1 infection in adults and children over the age of 2 months. Resistant virus emerges rapidly when Viramune is administered as monotherapy or in dual combination therapy with an antiretroviral agent. Therefore Viramune should always be administered in combination with at least two additional antiretroviral agents.*

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<sup>1</sup> National Centre in HIV Epidemiology and Clinical Research, HIV, viral hepatitis and sexually transmissible disease Australian Annual Surveillance report 2010  
[http://www.med.unsw.edu.au/NCHECRweb.nsf/resources/SurvRep07/\\$file/ASR2010-rev1.pdf](http://www.med.unsw.edu.au/NCHECRweb.nsf/resources/SurvRep07/$file/ASR2010-rev1.pdf) (cited 4th July 2011)

The dosage regimen varies with the age of the patient (adult or child) and whether the patient has already commenced Viramune in the immediate release form.

### **Regulatory Status**

The product received initial ARTG Registration on 9 May 1997.

A similar application has been submitted in the European Union (EU) and the application was approved 16 September 2011.

In Canada and Switzerland, only the 400 mg formulation has been approved (29 June 2011 and 29 September, respectively) and in the US, the 400 mg formulation has been approved (3 June 2010) and the application for the 100 mg formulation is under review.

### **Product Information**

The approved product information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

## **II. Quality Findings**

### **Drug Substance (active ingredient)**

Nevirapine, a NNRTI with activity against Human Immunodeficiency Virus Type 1 (HIV-1), is currently registered in Australia by Boehringer Ingelheim Pty Ltd as immediate release tablets [Viramune nevirapine 200 mg tablet bottle (AUST R 56891) and blister (AUST R 56892)], and as Viramune nevirapine (as hemihydrate) 10 mg/mL oral liquid bottle (AUST R 72099).

The present application sought to register three strengths of modified (extended) release tablets containing nevirapine 50 mg, 100 mg or 400 mg, to be administered once daily as opposed to the twice daily regime used with the immediate release tablets and oral liquid. The rate of drug release is controlled by the hypromellose excipient, which hydrates *in vivo* to form a gel from which the drug is released by erosion.

The anhydrous nevirapine drug substance is identical to that used in the Viramune immediate release tablets and the specification includes appropriate controls over the particle size distribution. The iron oxide excipient complies with USP requirements, and all other excipients (which are conventional for the dosage form) comply with Ph Eur requirements.<sup>2</sup>

### **Drug Product**

The proposed XR tablets are direct scales. The dissolution limits for the 400 mg tablet were established on the basis of a level A *in vivo/in vitro* correlation (IVIVC).<sup>3</sup> However, dissolution from the proposed 50 mg and 100 mg XR tablets is much greater than from the 400 mg XR tablets under the conditions proposed for regulatory purposes. Although there was a rank order correlation between the *in vitro* dissolution rate of these tablets and relevant pharmacokinetic (PK) parameters, a level A IVIVC could not be established for these strengths. Consequently, the limits for the 50 mg and 100 mg tablets were based solely on batch analytical and stability results.

The proposed 50 mg and 100 mg XR tablets will be packaged in HDPE bottles fitted with a polypropylene child resistant closure compliant with Therapeutic Goods Order 80, while

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<sup>2</sup> USP: United States pharmacopoeia; Ph Eur: European pharmacopoeia.

<sup>3</sup> Level A IVIVC: A correlation of this type is generally linear and represents a point-to-point relationship between *in vitro* dissolution and the *in vivo* input rate (for example, the *in vivo* dissolution of the drug from the dosage form). In a linear correlation, the *in vitro* dissolution and *in vivo* input curves may be directly superimposable or may be made to be superimposable by the use of a scaling factor. Nonlinear correlations, while uncommon, may also be appropriate.

the proposed 400 mg XR tablets will be packaged in single tablet PVC/aluminium blisters (packs of 10 or 30).

Adequate stability data have been provided to support the proposed shelf life of two years below 30°C.

### **Biopharmaceutics**

A number of biopharmaceutic studies were conducted in support of the proposed modified release tablets, using either the formulation proposed for registration or a variant thereof in which the differences are considered unlikely to be of clinical significance. The following outcomes were established:

While the proposed XR tablets given in the fasted state have a significantly lower area under the plasma concentration time curve (AUC) than the immediate release (IR) tablets, the AUC is equivalent when given with food. The proposed PI states that the bioavailability of the IR tablets is not affected by food. The significant increase in the area under the plasma concentration-time curve (AUC) when the XR tablets are given with food is noted in the PI, but this is stated to not be clinically relevant. Presumably, the latter statement is based on the observation that the minimum plasma concentration ( $C_{min}$ ) of the XR tablets given with or without food is equivalent to that of the IR tablets (Study 1100.1489).

On a dose normalised basis, the maximum plasma concentration ( $C_{max}$ ) from the 100 mg and 400 mg XR tablets is ~50% that obtained from a 200 mg IR tablet, and the 100 mg and 400 mg XR tablets are bioequivalent (on a dose normalised basis; Study 1100.1517).

Although the evaluator concluded that the proposed 50 mg XR tablet is 10-15% more bioavailable than its 100 mg XR counterpart, the 90% confidence intervals for AUC (93.0 – 132.7%, with a mean ratio of 111.1%) suggest the Study 1100.1531 was underpowered.

### **Quality Summary and Conclusions**

There were no objections in respect of chemistry, manufacturing, controls and biopharmaceutics to registration of these products.

## **III. Nonclinical Findings**

### **Nonclinical Summary and Conclusions**

There was no requirement for a nonclinical evaluation in a submission of this type.

## **IV. Clinical Findings**

### **Introduction**

To support this application, a pivotal Phase III study was conducted in adult patients infected with HIV-1. Study 1100.1486 was a non inferiority study assessing the efficacy and safety of nevirapine XR tablets given once daily compared with nevirapine IR given twice daily on a fixed background antiretroviral (ARV) regimen in treatment naïve HIV-1 infected patients. A supportive Phase III study, Study 1100.1526 assessed the efficacy and safety of nevirapine XR in patients who transitioned from nevirapine IR given twice daily to nevirapine XR given once daily.

Six pharmacokinetic studies were performed to support the application, including Study 1100.1518, a Phase I study of nevirapine XR in paediatric patients aged  $\geq 3$  to  $<18$  years to support its use in children and adolescents.

## Pharmacokinetics

### Introduction

The current immediate release (IR) formulation Viramune® is a 200 mg tablet given twice daily for adults, and as an oral suspension for paediatric use. Nevirapine IR is >90% absorbed in both tablet and oral suspension forms with linear peak concentrations in the 200 mg to 400 mg dose range. Nevirapine absorption is similar in healthy subjects and patients with HIV-1 infection and it can be absorbed throughout the gastrointestinal tract making it suitable for a controlled release formulation. The recommended dose of Viramune® is 200 mg once daily for the first 14 days, followed by 200 mg twice daily. The run in period has been shown to lessen the frequency of skin rash, a common and potentially life threatening event associated with nevirapine treatment. A controlled release formulation offers more convenience, better compliance and it might reduce the risks associated with peak drug exposure.

Oral nevirapine extended release (XR) was developed with the objective of maintaining an average steady state minimum plasma concentration of approximately 3µg/mL with once daily dosing. A series of matrix type slow release tablet formulations was developed and tested with a variety of *in vitro* dissolution methods and *in vivo* studies in dogs. Five different prototype nevirapine XR formulations were then tested in two strengths (300 mg and 400 mg) in healthy male subjects. Based on these study data, two prototypes based on a hydroxypropylmethyl cellulose polymer (KCR 20% and KCR 25%) were selected for further testing, each in 300 mg and 400 mg tablet strengths. The prototype finally selected for the clinical trial program was the nevirapine XR 400 mg KCR 25% tablet. Two additional tablet strengths, 50 mg and 100 mg, based on the same KCR 25% formulation, were developed for paediatric patients ≥3 years of age. These tablets are round (7mm and 9mm respectively) to make them easier to swallow than the larger oblong 400 mg strength (9.3 x 19.1mm).

Single dose bioavailability studies were conducted in healthy adult subjects. In paediatric patients with HIV-1, the steady state PK of nevirapine XR was compared to the IR formulation. Steady state peak and trough kinetics were also compared in adult patients with HIV-1 with different demographics and background ARV therapy, and the results were correlated with clinical and virologic responses.

*Note: Two terms are used in this AusPAR to describe the identical investigational product. Nevirapine XR is the term used in the text while nevirapine ER (extended release, the term preferred in the EU) is used in tables and figures taken from the submitted study reports.*

### Methods

#### *Pharmacokinetic data analysis*

Trial data were stored in the Oracle Clinical® (O\*<sup>C</sup>) database (Oracle Corporation, Redwood Shores, California, USA). Non compartmental PK parameters were calculated using WinNonlin™ Professional Network version 4.1 (Pharsight Corporation, Mountain View, California, USA). Maximum (peak) plasma concentration ( $C_{max}$ ) and the time to reach maximum (peak) plasma concentration following drug administration ( $t_{max}$ ) were measured by direct observation. The slope of the terminal phase ( $\lambda$ ) of the plasma concentration time profile was determined with a weighting factor of one by the method of least squares. The terminal half life ( $t_{1/2}$ ) was estimated as  $1n2/\lambda$ . AUCs were calculated using the linear up/log down algorithm. If a drug concentration was equal to or higher than the preceding concentration, the linear trapezoidal method was used. If a drug concentration was smaller than the preceding concentration, the logarithmic method was used. The area under the plasma concentration time curve at steady state over a uniform



dosing interval  $\tau$  ( $AUC_{\tau,ss}$ ) was calculated using the extrapolated or interpolated concentration at time  $t_{\tau}$  (time at the end of the dosing interval). The apparent clearance at steady state following oral multiple dose administration was calculated using the equation:  $CL/F_{ss} = \text{Dose}/AUC_{\tau,ss}$ . Concentration data identified with NOS (no sample), NOR (no valid result), NOA (not analysed), BLQ (below the limit of quantification), and NOP (no peak detectable) were ignored and not replaced by zero at any time point. Descriptive statistics of parameters were calculated only when at least two thirds of the individual parameter estimates were available. If the actual sampling time was not recorded or was missing, the planned time was used instead. PK parameters which could not be determined were identified by 'not calculated'.

### **Statistical analysis**

Statistical analyses were performed using SAS® version 8.2 (SAS Institute Inc., Cary, North Carolina, USA) on Windows XP in CARE/RAGe (Clinical Data Analysis and Reporting Environment/Report Appendix Generator), the standard Boehringer Ingelheim reporting environment.

### **Absorption**

#### **Bioavailability**

The relative bioavailability of different nevirapine XR formulations containing 300 mg or 400 mg was investigated in an open label, non randomised, parallel group Study 1100.1485 in healthy subjects. In a total of 204 subjects, 10 test formulations of nevirapine XR, with 17 subjects in each formulation group, were compared against two reference nevirapine IR formulations with 17 subjects in each group. The healthy male subjects were aged  $\geq 18$  -  $\leq 50$  years with a body mass index (BMI) range  $\geq 18.5$  -  $\leq 29.9$  kg/m<sup>2</sup>. The reference formulations were IR Viramune® given as a 1 x 200 mg tablet or as 2 x 200 mg tablets. The XR test formulations were either 300 mg or 400 mg dose strengths. The study was single dose with a 7 day observation period for safety evaluation.

The primary PK endpoints were the area under the plasma concentration-time curve from time zero to infinity ( $AUC_{0-\infty}$ ),  $C_{max}$ , and the trough concentration 24 h after the start of infusion ( $C_{24}$ ). Secondary endpoints included  $C_{max}/C_{24}$ ,  $AUC_{0-tz}$ ,  $t_{max}$ ,  $t_{1/2}$ ,  $CL/F$ ,  $V_z/F$  and  $k_a$ . Point estimations of the median intersubject ratios of  $AUC_{0-\infty}$ ,  $C_{max}$  and  $C_{24}$  with two sided 90% confidence interval (CI) were calculated using analysis of variance (ANOVA) on log transformed parameters. Safety and tolerability were assessed by vital signs, ECG, clinical laboratory tests and adverse event reporting. The bioavailability of nevirapine given as single 300 mg and 400 mg XR formulations was lower in all cases than that of nevirapine IR 400 mg given as a single dose. Plasma exposure,  $C_{max}$  and plasma concentrations at 24 h were all lower. Plasma exposure after single dose administration of the 300 mg and 400 mg XR formulations ranged from 62.1% to 87.1% for dose normalised  $AUC_{0-\infty}$  and from 51.4% to 75.5% for dose normalised  $C_{max}$  in relation to 400 mg nevirapine IR. Geometric mean  $C_{max}$  after administration of the 300 mg and 400 mg formulations ranged from 1340 to 1770 ng/mL and from 1610 to 2110 ng/mL respectively, compared with a peak level of 3130 ng/mL with nevirapine IR 400 mg. A trend towards the lowest exposures was observed with the KCR 40% and KCR 30% formulations. All nevirapine XR formulations had a median  $t_{max}$  of approximately 24 h compared with 2-3 h for the IR formulations. Exposure was linear at 24 h when approximately 80-90% of bioavailable drug was absorbed. There was a slight increase in the apparent total clearance of the drug from plasma after oral administration ( $CL/F$ ) and the apparent volume of distribution during terminal phase after non intravenous administration ( $V_z/F$ ) for all XR formulations compared to nevirapine IR, compatible with the observed lower total plasma exposure.

The bioavailability of two of the hypromellose test formulations was further investigated in Study 1100.1489, an open label, multidose and multistage, four parallel group, steady state bioavailability study of two different nevirapine XR formulations compared to steady state Viramune 200 mg BID (bis in die; twice a day), in HIV-1 infected adult patients. Trial duration was 7 weeks, including a treatment period of 22 days. Ninety-two patients entered the study; 45 were assigned to nevirapine XR KCR 25% (300 mg or 400 mg) and 47 to nevirapine XR KCR 20% (300 mg or 400 mg). Male and female HIV-1 infected patients, aged 18-60 years, with viral load  $\leq 50$  copies/mL, were treated for at least 12 weeks with a stable regimen based on Viramune 200 mg BID without protease inhibitors. Viramune 200 mg BID was administered initially for 3 days and the test products thereafter for 19 days. Patients received nevirapine XR tablets after an overnight fast of at least 10 h, or after a high fat breakfast. The primary endpoints were  $AUC_{\tau,ss}/C_{min,ss}$  and  $C_{max,ss}$ , where  $C_{min,ss}$  and  $C_{max,ss}$  are the minimum and maximum (peak) steady state plasma drug concentration during a dosage interval, respectively; and the secondary endpoints were  $C_{max,ss}/C_{min,ss}$ , the peak trough fluctuation over one dosing interval at steady state (%PTF),  $t_{max,ss}$ ,  $CL/F_{ss}$  ( $CL/F$  at steady state) and the average plasma drug concentration during multiple-dose administration ( $C_{avg}$ ). Data for the primary endpoints were analysed by ANOVA on log transformed parameters with two sided 90% CI based on the residual error from ANOVA.

While fasted, the relative bioavailability of nevirapine at steady state, administered as XR 400 mg and XR 300 mg formulations, was lower than that of nevirapine IR 200 mg BID. The geometric mean ratios (test/reference) ranged from 71% to 90.3% for dose normalised  $AUC_{\tau,ss}$  and from 63.7% to 77.0% for dose normalised  $C_{max,ss}$ . The geometric mean ratios (test/reference) for dose normalised  $C_{min,ss}$  ranged from 83.5% to 99.4% for nevirapine XR 300 mg and from 75.1% to 89.6% for nevirapine XR 400 mg formulations. The lower limits of the 90% CI for  $AUC_{\tau,ss}$ ,  $C_{max,ss}$  and  $C_{min,ss}$  were all below 100% for all nevirapine XR 300 mg and 400 mg formulations, except for the XR 300 mg KCR 25% formulation. The relative bioavailability, measured by geometric mean ratios, was marginally higher with the KCR 25% than with the KCR20% formulation. Absorption of nevirapine with all XR formulations was slow: the time to reach peak concentrations was 6-9 h compared with 1-2 h for nevirapine IR. Mean  $C_{max,ss}/C_{min,ss}$  ratios were lower for the XR formulations (1.42 to 1.60) compared with nevirapine IR (1.67 to 1.99). The mean plasma concentration ratios of all nevirapine metabolites were similar for both the IR and XR nevirapine formulations, whether given fasted or fed.

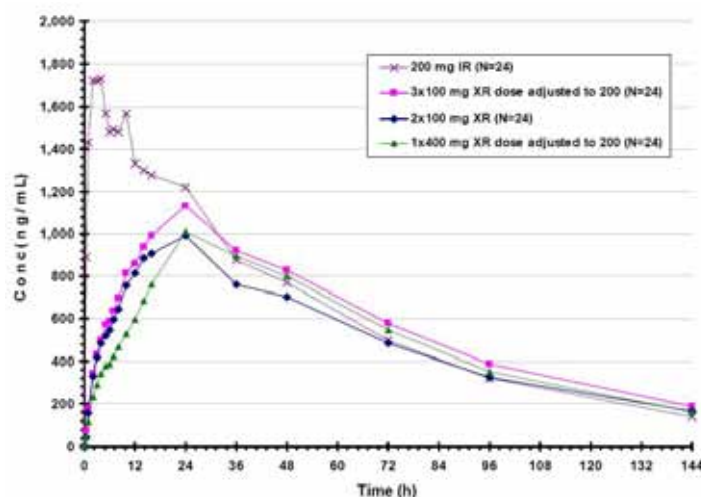
Relative bioavailability and rate of absorption tended to be lower with the nevirapine XR formulations compared with nevirapine IR and relative bioavailability was somewhat higher with the KCR 25% formulations compared with the 20% formulation.  $C_{min,ss}$ , an important determinant of long term virologic activity, was similar with the KCR 25% formulations compared with nevirapine IR. All nevirapine XR formulations were well tolerated and no virologic failures occurred. On this evidence, the nevirapine XR 400 mg KCR 25% tablet was selected for further clinical development (with 50 mg and 100 mg tablets of the same XR formulation for paediatric patients).

The objective of Study 1100.1517 was to determine the PK properties of the paediatric 100 mg XR formulation. It was an open label, non randomised, single dose, parallel group study comparing the PK properties of 200 mg (2 x 100 mg tablets once daily) and 300 mg (3 x 100 mg tablets once daily) nevirapine XR formulations with the 200 mg Viramune® tablet and with the nevirapine 400 mg XR tablet in healthy adult subjects. Twenty-four subjects in each of four groups received either nevirapine XR 200 mg, nevirapine XR 300 mg, nevirapine XR 400 mg or nevirapine IR 200 mg (Viramune®). The subjects were male, aged  $\geq 18$  -  $\leq 65$  years with BMI range  $\geq 18.5$  -  $\leq 29.9$  kg/m<sup>2</sup>. The primary criteria for evaluation were  $AUC_{0-\infty}$  and  $C_{max}$ , and the secondary endpoints included  $AUC_{0-tz}$ ,  $t_{max}$ ,

$MRT_{po}$ ,  $CL/F$ ,  $V_z/F$  and  $k_a$ . Point estimates for the ratio of test versus reference formulation for  $AUC_{0-\infty}$  and  $C_{max}$  with 90% CI were calculated after dose normalisation using ANOVA on log transformed parameters.

The 100 mg XR tablet strength, given as two or three tablets, was absorbed slowly with a median  $t_{max}$  of approximately 24 h (Figure 1) compared to median  $t_{max}$  of 2 h for the IR formulation. The absorption for the 100 mg XR tablet was marginally faster than for the 400 mg XR tablet. No dose dumping was observed in the individual PK profiles and inter subject variability was similar for all formulations. Drug exposure was approximately linear between the XR dose groups. The relative bioavailability of the 100 mg XR tablet strength was 83% (2 x 100 mg XR) and 98.5% (3 x 100 mg XR) compared to the 200 mg IR tablet. The relative bioavailability of the 100 mg XR tablet strength was 95.1% (2 x 100 mg XR) and 112.9% (3 x 100 mg XR) compared to the 400 mg XR tablet. Dose normalised  $C_{max}$  for the 100 mg tablet strength was 97.2% (2 x 100 mg XR) and 107.2% (3 x 100 mg XR) compared to the 1 x 400 mg XR tablet. The dose normalised  $C_{max}$  of the XR formulations was approximately half that of the IR reference formulation in keeping with its slow release characteristic (Figure 1).

**Figure 1: Dose adjusted geometric mean plasma concentration time profiles of nevirapine after a single dose oral administration (Study 1100.1517).**



A summary of the mean ratios of all treatments are shown in (Table 1). Nevirapine XR 200 mg can be considered equivalent to nevirapine XR 400 mg with a dose normalised  $C_{max, norm}$  ratio of 97.2% (90% CI: 82.5% to 114.5%) and dose normalised  $AUC_{0-\infty, norm}$  ratio of 95.1% (90% CI: 78.2% to 115.5%). Nevirapine XR 200 mg (2 x 100 mg XR) had less bioavailability compared with the IR formulation. The ratio for  $AUC_{0-\infty, norm}$  (area under the plasma concentration-time curve from time zero to infinity normalised for dose and weight) was 83.0% (90% CI: 68.2% to 100.9%) and the ratio for  $C_{max, norm}$  (maximum plasma concentration normalised for dose and weight) was 51.7% (90% CI: 44.1% to 60.7%). Nevirapine 300 mg (3 x 100 mg XR) can be considered equivalent to nevirapine 1 x 400 mg XR with a dose normalised  $C_{max, norm}$  ratio of 107.2% (90% CI: 96.7% to 118.8%) and  $AUC_{0-\infty, norm}$  ratio of 112.9% (90% CI: 100.3% to 127.1). Nevirapine 300 mg (3 x 100 mg XR) can be considered equivalent to nevirapine 200 mg IR (Viramune®). Dose normalised  $AUC_{0-\infty, norm}$  ratio was 98.5% (90% CI: 87.3% to 111.2%) with  $C_{max, norm}$  ratio 57.0% (90% CI: 51.8% to 62.8%).

**Table 1: Comparison of pharmacokinetic parameters of nevirapine by treatment (Study 1100.1517).**

		200 mg Nevirapine XR (N=14) Test 1		100 mg Nevirapine XR (N=14) Test 2		200 mg Nevirapine IR (VIRAMUNE®) (N=24) Reference 1		400 mg Nevirapine XR (N=14) Reference 2	
		Mean	CV [%]	Mean	CV [%]	Mean	CV [%]	Mean	CV [%]
AUC <sub>0-24</sub>	[ng.h/mL]	78200	30.1	125000	18.4	92100	24.4	155000	21.6
AUC <sub>0-24,norm</sub>	[ng.h/mL/mg]	392	30.1	428	18.4	469	24.4	389	21.6
t <sub>1/2</sub>	[h]	144 (96.0 – 170)		144 (143 – 177)		144 (95.7 – 145)		144 (143 – 145)	
AUC <sub>0-∞</sub>	[ng.h/mL]	91800	33.1	150000	24.9	105000	27.9	182000	24.3
AUC <sub>0-∞,norm</sub>	[ng.h/mL/mg]	459	33.1	514	24.9	524	27.9	456	24.3
C <sub>max</sub>	[ng/mL]	1100	29.1	1740	19.2	2030	18.9	2180	21.1
C <sub>max,norm</sub>	[ng/mL/mg]	5.50	29.1	5.30	19.2	10.2	18.9	5.44	21.1
t <sub>max</sub>	[h]	24.0 (2.00 – 24.2)		23.9 (12.1 – 24.0)		2.01 (0.500 – 10.0)		24.0 (23.8 – 47.7)	
t <sub>1/2,est</sub>	[h]	47.7	24.2	50.5	30.7	41.5	24.6	46.2	29.8
MRT <sub>0-∞</sub>	[h]	78.5	22.3	81.4	26.2	80.3	25.0	79.0	23.9
Cl <sub>T</sub>	[mL/min]	48.6	112	34.3	23.4	33.9	25.4	38.8	25.6
V <sub>d,T</sub>	[L]	198	120	144	25.7	117	20.3	153	33.8
K <sub>e</sub>	[1/h]	0.184	215	0.0975	39.8	NC	NC	0.0556	58.4

As with the 400 mg XR tablet strength, the paediatric 100 mg XR tablet, administered as one or two tablets, was absorbed more slowly than the IR formulation. However, it was absorbed slightly more quickly than the 400 mg XR formulation, presumably as the tablet size is smaller. In summary, dose normalised AUC<sub>0-∞,norm</sub> and C<sub>max,norm</sub> are comparable for the 100 mg and 400 mg XR formulations and AUC<sub>0-∞,norm</sub> are comparable between the XR and IR formulations. As expected from the design of the formulation, C<sub>max,norm</sub> for the XR formulation is approximately half that of the reference IR formulation.

### Bioequivalence

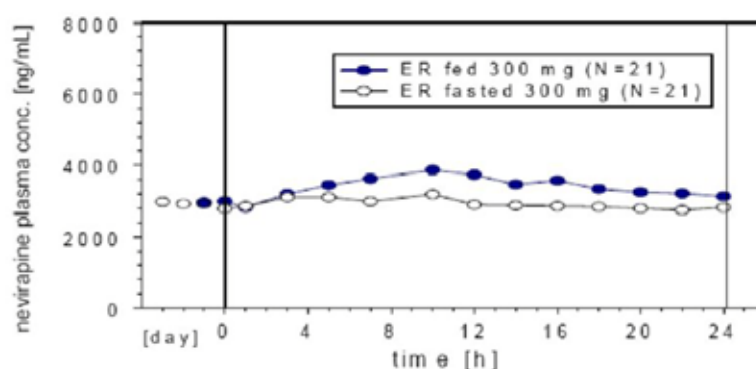
A bioequivalence Study 1100.1531 was conducted to determine the PK properties of the nevirapine XR 50 mg paediatric tablet. Nevirapine 200 mg XR was given as 4 x 50 mg XR tablets in a single dose to establish the bioequivalence of this formulation compared to 200 mg nevirapine given as 2 x 100 mg XR tablets in a single dose. This was an open label, randomised, single dose, parallel group study in healthy male subjects aged ≥21-≤50 years: 24 subjects received nevirapine XR 4 x 50 mg and 24 subjects received nevirapine XR 2 x 100 mg.

Both proposed paediatric formulations, the nevirapine XR 50 mg and 100 mg tablets, were absorbed slowly; maximum drug concentrations being reached approximately 18 h after dosing with both formulations. No dose dumping was observed and inter-subject variability was similar for both tablet strengths. Mean elimination half life of nevirapine was 47 h for both tablets. The relative bioavailability of nevirapine for the 50 mg formulation compared with the 100 mg tablet was 106.7% (90% CI: 92.8% to 122.7%) for C<sub>max</sub> and 111.1% (90% CI: 93.0% to 132.8%) for AUC<sub>0-∞</sub>. Overall absorption with the 50 mg tablet strength was slightly higher than with the 100 mg tablet with similar C<sub>max</sub> but slightly higher AUC<sub>0-∞</sub>. The primary endpoints for analysis of bioequivalence of nevirapine XR 4 x 50 mg compared with nevirapine XR 2 x 100 mg were AUC<sub>0-∞</sub> and C<sub>max</sub>. The defined limits for bioequivalence were 80% to 125%. The 90% CI were within the defined limits of bioequivalence for C<sub>max</sub> but were exceeded for AUC<sub>0-∞</sub>. Therefore, the 4 x 50 mg nevirapine XR dose was not bioequivalent to the 2 x 100 mg nevirapine XR dose. Both tablet strengths were well tolerated and the adverse event profiles for both dose formulations were similar.

### ***Influence of food***

The influence of food was investigated in Study 1100.1489 described above. The relative bioavailability was higher when the nevirapine XR formulations were administered with food compared with when fasted (Figure 2). The test/reference ratios of  $AUC_{t,ss}$ ,  $C_{max,ss}$  and  $C_{min,ss}$  with all nevirapine XR formulations were higher under fed conditions compared with under fasted conditions. With one exception (XR 400 mg KCR 20%), the lower limits of the 90% CI were above 80% and the upper limits were below 125% for all XR formulations. The majority of lower and upper bounds of nevirapine with all XR formulations were above 100% when fed was compared with fasted.

**Figure 2: Arithmetic mean nevirapine plasma concentration time profiles after oral administration of NVP XP 300 mg KCR 25% with and without food (Study 1100.1489).**



### ***Sites of absorption in gastrointestinal tract***

A single dose, two part, open label, randomised Study 1100.1484 investigated the absorption of nevirapine when released into specific regions of the GI tract. Enterion™ capsules were filled with 50 mg nevirapine in buffer. Movement of the Enterion™ capsule through the gut was assessed by incorporating an  $^{111}\text{In}$  (1MBq) ( $^{111}\text{In}$  = the 111 isotope of indium; 1MBq = 1 megabecquerel =  $1 \times 10^6$  becquerel) marker in the radioactive tracer port of the capsule that remained in the device throughout gastrointestinal (GI) transit. To provide an outline of the anatomy of the GI tract, 30mL of water administered with the capsule contained 4 MBq of radiolabelled marker ( $^{99m}\text{Tc}$ -DTPA). Overall, the data indicated that nevirapine is absorbed throughout the gastrointestinal tract. The rate of absorption decreased from the jejunum to the descending colon. Relative bioavailability decreased in the order of oral > jejunum > ileum > ascending colon > descending colon.

### **Distribution**

The distribution of nevirapine XR was not specifically evaluated. However, this is well established with nevirapine IR (see Viramune® PI). Nevirapine is widely distributed in humans with an apparent volume of distribution of  $1.21 \pm 0.09$  L/kg. It readily crosses the placenta and is found in breast milk. Nevirapine is about 60% bound to plasma proteins. Nevirapine concentrations in CSF are approximately 40% of the plasma concentrations; approximately equal to the fraction not bound to plasma proteins.

### **Elimination**

The elimination of nevirapine XR was not specifically evaluated. However, this is well established with nevirapine IR (see Viramune® PI).

**Excretion**

Approximately 90% of a radiolabelled dose of nevirapine is found in the urine and approximately 10% excreted in the faeces. Approximately 80% of urine radioactivity consists of glucuronide conjugates of hydroxylated metabolites. The remainder of urine radioactivity is made up of other metabolites with parent drug elimination <3%.

**Metabolism**

Nevirapine is extensively metabolised via cytochrome P450 oxidative metabolism, mainly via the CYP3A family. It is also an inducer of CYP enzymes and there is an increase of approximately 1.5 to 2 fold in the apparent oral clearance of nevirapine after 2-4 weeks of dosing with 200-400 mg daily.

**Pharmacokinetics of metabolites**

Nevirapine metabolites were measured in 1100.1489. The main metabolites were measured at steady state after 3 days of treatment with nevirapine IR 200 mg BID, nevirapine XR 300 mg QD (quaque die; once a day) or nevirapine XR 400 mg QD. There were no significant differences in plasma concentration ratios between the IR and XR formulations for any metabolite.

**Dose proportionality and time dependency**

Dose proportionality for the 200 mg and 300 mg XR formulations was measured in 1100.1517 and in 1100.1485 for the various 300 mg and 400 mg pilot formulations. There was linearity in the dose range 200-400 mg. In Study 1100.1531, absorption was slightly higher with the 50 mg XR formulation compared with the 100 mg XR formulation. Linearity was not tested in a single comparator study of all XR dose strengths. However, nevirapine XR formulations exhibit the same linear kinetics as Viramune® 200 mg given once or twice daily.

Single dose studies were performed in healthy subjects. Nevirapine terminal elimination half life following single dose administration was 40-45 h and did not differ between the XR and IR formulations. Nevirapine can induce its own cytochrome P450 (CYP) metabolism via the isozymes CYP3A and CYP2B6 which leads to a 1.5 to 2 fold increase in CL/F as treatment progresses from first dose to steady state. Auto induction results in a corresponding decrease in the terminal half life of nevirapine in plasma to approximately 25-30 h after multiple dosing with 200-400 mg daily.

In 1100.1489, a multiple dose study in HIV-1 infected patients, half life could not be obtained because no washout period could be justified. Other steady state parameters from this study were compared with their corresponding single dose PK parameters from the bioavailability Study 1100.1485. CL/F increased approximately 2 fold from single dose to steady state for both IR and XR formulations with a corresponding decrease of 50% in  $AUC_{0-24,ss}$ . Accumulation of plasma concentrations would be expected because steady state half life is still over 24 h. In studies 1100.1485 and 1100.1489, there was an approximately 2 fold accumulation for  $C_{max}$  and  $C_{min}$  and an approximately 3 fold accumulation in  $AUC_{ss}$  for both IR and XR formulations. Steady state profiles show significantly higher exposure than single dose profiles. However, no further accumulation occurs with long term dosage. In Study 1100.1486, trough concentrations for both nevirapine XR 400 mg QD and nevirapine IR 200 mg BID groups were measured at Weeks 4, 6, 9, 12, 16, 24, 32, 40 and 48 in patients with HIV-1 infection after a 2 week run in period of nevirapine IR 200 mg QD. Trough concentrations were stable throughout, ranging from 76.9% to 83% XR/IR gmean%.



### Intra and interindividual variability

Intra subject variability for  $AUC_{\tau,ss}$ ,  $C_{max,ss}$  and  $C_{min,ss}$  was calculated in 1100.1486. Intra individual gCV ranged from approximately 15-30% for all the XR formulations, fed and fasted. Geometric mean (gMean) ratios were calculated using nevirapine IR 400 mg daily as the reference. For  $AUC_{\tau,ss}$ ,  $C_{max,ss}$  and  $C_{min,ss}$ , the nevirapine XR to IR ratios ranged from 70-100%.

### Pharmacokinetics in target population

Single dose PK studies using the nevirapine XR formulations were performed in healthy subjects (1100.1485, 1100.1517 and 1100.1531). No multiple dose studies were performed in healthy subjects because of the risk of nevirapine toxicity. Conversely, no single dose studies were performed in patients with HIV-1 infection but the multiple dose studies 1100.1486 and 1100.1526 compared efficacy and PK parameters of the XR and IR formulations for periods of up to 48 weeks (see below for the individual study reports). No studies directly compare the PK profiles of nevirapine XR in healthy subjects and patients with HIV-1. However, in general, there appear to be no significant differences in PK profiles between the healthy and target patient groups.

### Special populations

#### Children

An open label, multiple dose, cross over Study 1100.1518 evaluated the steady state PK parameters of nevirapine extended release tablets in HIV-1 infected children, with an optional extension phase.

#### Methods

This Phase I trial was designed to establish the steady state kinetics of nevirapine XR in children and adolescent patients, aged  $\geq 3$  to  $<18$  years, with HIV-1 infection. Before screening, the patients were treated for at least 18 weeks with a nevirapine IR based regimen and were required to have an undetectable viral load. Patients were stratified according to age (3 to  $<6$  years, 6 to  $<12$  years and 12 to  $<18$  years). It was planned to recruit approximately 75 patients with 25 in each age group. At least the first 12 patients entered into the 3 to  $<6$  years old age group, and the first 10 patients in the other age groups were to perform post dose saliva and plasma PK sampling to determine a full nevirapine profile at steady state. Following screening at baseline, children and adolescents were stratified according to age and received nevirapine IR (Viramune®) during a run-in period of a minimum of ten days. The nevirapine XR dose selected (200 mg, 300 mg or 400 mg) was based on the Viramune® IR dose corrected for body surface area (BSA) prior to enrolment as shown in Table 2.

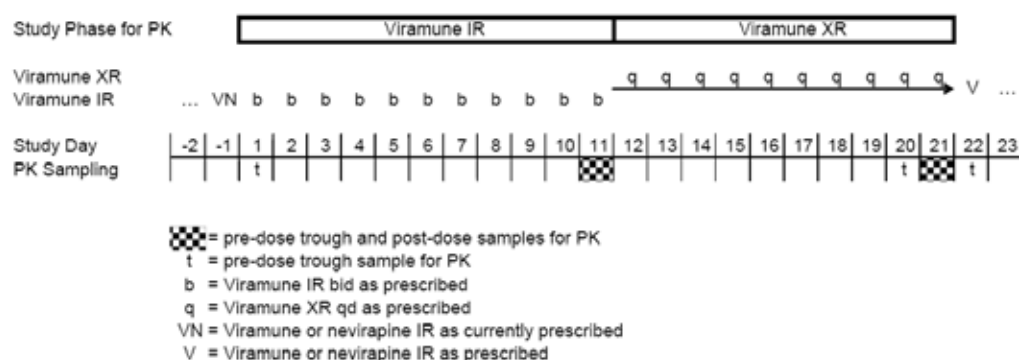
**Table 2: Selection of nevirapine XR dose (Study 1100.1518).**

Viramune® IR dose/ day calculated at Visit 2	Nevirapine XR corresponding dose at Visit 4
175mg to 249 mg /day	200 mg (2 x 100 mg nevirapine XR tablet)
250 mg to 349 mg / day	300 mg (3 x 100 mg nevirapine XR tablet)
350 mg and above	400 mg (1 x 400 mg nevirapine XR tablet)

Source data: Appendix 16.1.1.1

A PK collection for a 12 h concentration time profile was conducted on Day 11 before all patients were switched to nevirapine XR on Day 12 as shown below. All patients received nevirapine XR for 9 days before collection of a 24 h nevirapine concentration time profile on Days 21 and 22 for PK analysis (Figure 3).

**Figure 3: Experimental course followed for PK sampling following nevirapine (Viramune) dose (Study 1100.1518).**



To reduce the quantity of blood and the number of invasive interventions in paediatric patients, drug concentrations for PK analysis were measured in both plasma and saliva samples using previously published methodologies in children and adults.<sup>4</sup> In this study in children, there was a close correlation between profiles using saliva and plasma PK, and profiles plotted using only plasma measurements. For this reason, only plasma PK measurements were used to determine the primary endpoint.

### Objectives

The primary objective was to establish the PK profile at steady state of nevirapine XR in children from  $\geq 3$  to  $< 18$  years of age performed during the main part of the trial up to last visit. Secondary efficacy endpoints included the proportion of patients maintaining a viral load  $< 50$  copies/mL at Day 22; the proportion of patients maintaining a viral load  $< 400$  copies/mL at Day 22; and the change in CD4+ count between baseline and Day 22.

### Study participants

Key inclusion criteria included informed consent by a parent or guardian; HIV-1 infected males or females; treatment with a nevirapine IR based regimen for at least 18 weeks before screening; viral load  $< 50$  copies/mL; stable CD4+ count; acceptable renal and hepatic function; and able to swallow tablets. Key exclusion criteria included unstable AIDS related illness; significant concomitant illness; patients with malignant disease receiving chemotherapy; use of other investigational drugs; and concomitant HIV-1 protease inhibitor treatment.

### Treatments

Nevirapine XR was supplied as either 100 mg or 400 mg tablets. Nevirapine IR was supplied as Viramune® 200 mg tablets and oral suspension 50 mg/5mL.

### Treatment compliance and withdrawals

Patients and their guardians were counselled on the importance of not missing doses and taking doses on time. Temporary interruptions of the trial drug were strongly discouraged. A patient was to be withdrawn if consent was withdrawn; if concomitant medications which interfered with the study drug were required; no longer able to

<sup>4</sup> van Heeswijk RP, et al. Saliva as an alternative body fluid for therapeutic drug monitoring of the nonnucleoside reverse transcription inhibitor nevirapine. *Ther. Drug Monit.* 2001; 23:255-258. Rakhmanina NY, et al. Nevirapine concentration in nonstimulated saliva: an alternative to plasma sampling in children with human immunodeficiency virus infection. *Ther. Drug Monit.* 2007; 29:110-117.



participate for medical reasons; virologic failure; drug toxicity or significant adverse event; or non compliance.

#### *Outcomes and endpoints*

The primary endpoint was the morning trough (pre dose) nevirapine concentration measured during the main PK part of the study. The secondary endpoint was PK profiling to construct a drug concentration time profile for the dosing interval in 32 patients (12 patients in the 3 to <6 years old age group; 10 patients in the 6 to <12 year old age group; and 10 patients in the 12 to <18 years old age group). Secondary endpoints included the proportion of patients with viral load suppression and change in CD4+ count at Visit 7.

#### *Sample size and statistics*

This was a Phase1 study of 75 patients stratified into three groups based on age. PK parameters were reported descriptively. Two sided 90% CI for trough plasma concentrations  $C_{pre,N}$  (mean trough plasma concentrations after N doses),  $AUC_{\tau,ss}$ ,  $C_{min,ss}$  and  $C_{max,ss}$  for all patients were calculated. Dose normalised and non normalised data of  $C_{min,ss}$ ,  $AUC_{\tau,ss}$  ( $\tau = 24$  h for XR and 12 h for IR), and  $C_{max,ss}$  were reported for the 32 patients participating in the post dose PK sampling.  $C_{max,ss}/C_{min,ss}$ , %PTF,  $t_{max,ss}$ ,  $CL/F_{ss}$ , and  $C_{avg}$  were reported as descriptive statistics. Efficacy endpoints including proportion of patients with viral load <50 copies/mL, patients with viral load <400 copies/mL, and change in CD4+ count were also reported descriptively.

#### *Results*

**Recruitment:** Ninety patients were enrolled in the study and 85 received study treatment; 94.1% of patients completed Visit 7 and 5.9% were discontinued.

**Protocol deviations:** One patient took double treatment doses at Visit 4 and another took both nevirapine IR and nevirapine XR at Visits 4, 5 and 6. Both patients were excluded from the PK analysis set. One subject was entered with detectable viral load at screening and was withdrawn from the study before Visit 3.

**Compliance:** During the nevirapine IR treatment period, 96.4% of patients (80/83 patients) who had reported compliance data fell into the 80-120% compliance range. During the nevirapine XR treatment phase, there were 79 patients with compliance data and all fell within the 80-120% compliance range. The mean duration of exposure to nevirapine IR was 11.2 days with all but one patient receiving treatment for a period of at least one week. The mean duration of exposure to nevirapine XR was 10 days during the PK phase with all but one patient receiving at least one week of treatment.

**Baseline data:** Overall, 55.3% of patients were female, 92.9% were Black (enrolled in South Africa and Botswana) and 7.1% were White. The demographics between age groups were similar and the patients were distributed evenly between the three age groups.

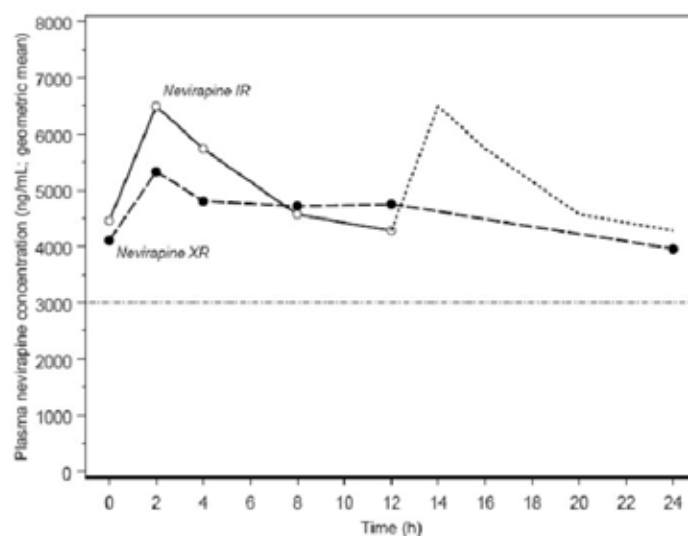
**Numbers analysed:** Eighty patients completed Visit 7; 25 patients in the 3 to <6 years age group, 24 patients in the 6 to <12 years group, and 31 patients in the 12 to <18 years group). There were 5 withdrawals, balanced between the age groups.

#### *Outcomes*

**Primary efficacy analysis:** Figure 4 shows average concentration time profiles for the IR and XR formulations. The adjusted geometric mean  $C_{pre,ss}$  (mean trough plasma concentrations at steady state) values for the XR and IR formulations, obtained from all available patients, were 4,149 ng/mL and 4,518 ng/mL respectively. The adjusted geometric mean XR/IR ratios for daily, dose normalised (primary endpoint) and non normalised  $C_{pre,ss}$  for all available patients were 91.2% and 91.8% respectively, with 90% CI for the 200 mg, 300 mg and 400 mg dose groups all within the 80% - 125% range. The

adjusted geometric mean XR/IR ratios for non-normalised  $C_{min,ss}$  and  $AUC_{\tau,ss}$  of nevirapine were 91.8% and 90.3% respectively with both of their 90% CI within the 8%-125% range. As expected,  $C_{max,ss}$  of nevirapine XR was lower than for nevirapine IR with an adjusted geometric mean XR/IR ratio of 86% for both daily dose normalised and non normalised values with the 90% CI below the 80% limit. The nevirapine XR to IR geometric mean ratios for daily dose normalised and non normalised  $C_{pre,ss}$  were similar in each age group (approximately 91%, 89% and 102% for age groups 3 to <6 years, 6 to <12 years and 12 to <18 years, respectively).

**Figure 4: Comparison of plasma nevirapine concentration time profiles for IR and XR formulations (Study 1100.1518).**



Note: The line at 3000 ng/mL indicates the target concentration for nevirapine in plasma. The broken line for Nevirapine IR from 12 to 24 h depicts the theoretical concentration time profile for the second half of a daily dose of Nevirapine IR.

**Comments:** The relative exposure and bioavailability of nevirapine XR was similar to nevirapine IR for the primary endpoint  $C_{pre,ss}$  and other key PK parameters such as  $C_{min,ss}$  and  $AUC_{\tau,ss}$ . The administration of nevirapine XR QD resulted in effective trough concentrations irrespective of whether it was given as two or three 100 mg tablets or as a single 400 mg tablet. The PK results support once daily nevirapine XR after switching from the existing nevirapine IR twice daily dosing regimen. The 50 mg XR tablet was not evaluated and the reason for this omission does not appear to have been discussed.

**Elderly:** Nevirapine XR has not been investigated in the elderly. However, nevirapine IR PK parameters in adults infected with HIV-1 do not appear to change with age in the range 19-68 years.

**Gender:** In Study 1100.1486, female patients with HIV-1 infection had approximately 20-30% higher plasma concentrations than males in both nevirapine XR and nevirapine IR treatment groups. In the multinational 2NN study of nevirapine IR in over 1200 randomised patients with HIV-1 infection, exposure in females was 13.8% higher than in males. There was no relationship to body weight, suggesting an independent gender effect.

**Weight:** In the 2NN study, a population pharmacokinetic substudy of 1077 patients showed no influence by either body weight or BMI on the clearance of nevirapine.

**Race:** In Study 1100.1486, Black patients had approximately 30% higher trough concentrations of nevirapine in both the 400 mg daily XR and IR treatment groups over 48

weeks. However, nevirapine PK in HIV-1 infected adults did not appear to change with race (Black, Hispanic or Caucasian) in pooled data from several clinical trials.

*Impaired renal function:* Nevirapine XR has not been evaluated in patients with impaired renal function. In single dose studies with nevirapine IR, PK profiles were not significantly affected by mild, moderate or severe renal impairment. Patients with end stage renal disease requiring dialysis had significantly reduced nevirapine exposure requiring supplemental dosing.

*Impaired hepatic function:* Nevirapine XR has not been evaluated in patients with hepatic impairment. The steady state pharmacokinetics of nevirapine IR 200 mg BID were studied in 46 adult patients with HIV-1 infection and mild liver fibrosis, moderate fibrosis and cirrhosis, with a median duration of therapy of 3.4 years. In general, exposure was increased in proportion to the degree of hepatic impairment and 15% of patients had trough nevirapine concentrations in excess of 9.0µg/mL.

#### ***Evaluator's overall comments on pharmacokinetics in special populations***

Nevirapine IR has been extensively studied in special populations. In keeping with the known elimination and metabolic pathways, renal impairment has an insignificant effect on steady state kinetics. Patients with creatinine clearance (CLCR)  $\geq 20$  mL/min do not require dose adjustment but renal dialysis increases drug clearance and dose supplementation may be required to maintain virologic suppression. The effects of renal impairment on drug exposure have not been studied with nevirapine XR. However, in general, exposure with nevirapine XR is less than with IR, and it is reasonable to expect that renal impairment will have no more effect on XR kinetics than is seen with the IR formulation.

Nevirapine is extensively metabolised and exposure is increased in patients with hepatic fibrosis. As in patients with severe renal impairment, in patients with hepatic impairment exposure with nevirapine XR is less than with nevirapine IR, so an increased risk of adverse reactions is no more likely if the established precautions are observed.

Age has no observable effect on nevirapine PK in adults, or in children when dosage is adjusted for BSA or age and body weight. Exposure in women is higher than in men following treatment with both the IR and XR formulations. The difference from the sponsor database suggests that this average increase is 13.8% and related to gender rather than to smaller body size. Women had increased exposure of up to 30% in the XR/IR comparator studies reviewed here and there is no obvious explanation for the disparity.

Pooled data presented in the PI suggest that exposure is similar in Blacks, Caucasians and Hispanics. Trough plasma nevirapine drug levels in Black patients (n = 80) were 30% higher than in Caucasians in Study 1100.1486 but exposure with nevirapine XR was no higher than with nevirapine IR and dosage adjustment is possibly not required.

#### **Interactions**

No specific drug interaction studies were conducted with the nevirapine XR formulation; however, precautions regarding drug interactions observed with the nevirapine IR formulation would also need to be followed with the XR formulation.

#### ***In vitro pharmacokinetic interactions***

Nevirapine is an inducer of hepatic cytochrome P450 metabolic enzymes and may result in lower plasma concentrations of other drugs which are extensively metabolised by CYP3A or CYP2B.

***In vivo pharmacokinetic interactions***

Data were obtained from numerous drug interaction studies testing nevirapine IR against other ARV, antibiotics, antifungals, antacids, contraceptives, drugs of addiction, and St John's Wort. There are numerous potential interactions with other substrates for CYP3A and CYP2B6 but these have not been investigated with the XR formulation

**Evaluator's overall comments on pharmacokinetic interactions**

There is no reason to expect drug interactions with nevirapine XR formulations to differ qualitatively from nevirapine IR. Exposure with long term nevirapine XR is less than nevirapine IR so minor quantitative differences might be expected. However, these differences are unlikely to be clinically significant and the usual precautions should be observed when prescribing concurrent medications.

**Exposure relevant for safety evaluation**

No studies of safety in relation to exposure have been conducted with nevirapine XR.

**Evaluator's overall conclusions on pharmacokinetics**

In patients with HIV-1 infection, nevirapine 400 mg XR appears to be a robust formulation that delivers nevirapine in a controlled manner by allowing the drug to be absorbed slowly throughout the GI tract. Nevirapine has a prolonged half life so any variability in the performance of a controlled release tablet is unlikely to have significant PK or clinical consequences. Peak to trough variation in plasma levels is less with the XR formulation and there is no evidence of dose dumping. Food increases nevirapine absorption by up to 20% with no increase in peak/trough variability and no dose dumping. No food restrictions are warranted.

As would be expected, the metabolism of nevirapine XR is independent of the formulation given. Exposure is approximately 20% lower with the XR formulation than with the IR tablet but trough plasma levels at steady state are still in the range expected to provide sustained virologic suppression. All the prototype formulations had similar PK profiles and the final formulation chosen was used in the subsequent bioequivalence comparisons of the 50 mg and 100 mg XR tablets and for the 400 mg XR tablet used in the Phase III studies.

Bioequivalence of the 100 mg XR compared with the 400 mg XR tablet was established in healthy adults. Dose normalised exposure with the 50 mg XR tablet was somewhat higher than the 100 mg XR tablet and not equivalent when evaluated in healthy adults. The formulations used in the bioequivalence were used in the Phase III studies and are the same as those proposed for marketing.

In the present studies, the bioavailability of nevirapine in the XR and IR groups was approximately 20-30% higher in women (independent of body weight) and in Blacks. However, in pooled studies from the sponsor's data base, this increase in exposure appears to be less pronounced in both groups. There is no obvious explanation for this disparity but the findings may not be clinically relevant because the same observation occurred with the XR and IR formulations.

Nevirapine XR has not been tested in patients with renal or hepatic impairment. However, exposure is less with nevirapine XR than IR and there is no indication for formal investigation in these patient groups. Age in adults does not appear to influence the PK profile of nevirapine XR or IR. In children aged  $\geq 3$  to  $< 18$  years old, exposure was slightly higher than in adults. However nevirapine XR had similar relative bioavailability to nevirapine IR with similar trough plasma concentrations at steady state.

## Pharmacodynamics

### Introduction

The therapeutic efficacy of nevirapine depends on HIV-1 viral suppression which must be sustained with long term treatment to prevent viral breakthrough and emergent viral resistant variants. The pharmacodynamic (PD) properties of nevirapine XR are assumed to be the same as those of nevirapine IR, with the therapeutic efficacy of the XR formulation dependent on its PK properties.

### Mechanism of action

Nevirapine is a NNRTI of HIV-1 with no activity against HIV-2. It blocks RNA dependent and DNA dependent DNA polymerase activity by disrupting the catalytic site of the enzyme. Nevirapine exhibits additive activity against HIV-1 in combination with several protease inhibitors with additive to synergistic effects in combination with NRTIs. Genotypic and phenotypic resistance to nevirapine develops quickly when it is used as monotherapy but highly active ARV combination therapies delay the development of clinical antiretroviral drug resistance.

### Primary pharmacology

The pharmacology of nevirapine XR is the same as that of nevirapine IR. It is a NNRTI to be used in combination with other ARV in the treatment of HIV-1 infection.

### Secondary pharmacology

Viramune® is associated with an increase in high density lipoprotein (HDL) and an improvement in the total to HDL cholesterol ratio. In 1100.1486, HDL rose from baseline by 32% and 27% after 48 weeks treatment with nevirapine IR and XR respectively. The significance of this observation is unknown; however, it is not clinically relevant in the context of long term treatment of HIV-1 infection.

### Relationship between plasma concentration and effect

The primary therapeutic objective of ARV is sustained virologic suppression. In Study 1100.1486, the effect of trough nevirapine concentrations on virologic response was evaluated using gMean trough levels for each patient from Week 4 to Week 48. Using gMean trough level, there was no effect on the proportion of virologic responders when trough concentrations were above 1µg/mL. Patients with trough levels in the range 1 to <2µg/mL had similar response rates to patients with trough levels ≥2µg/mL.

The same relationships were observed when response was compared to minimum trough nevirapine levels and this effect was independent of race, gender or region. For nevirapine XR, the tenth percentile trough concentrations were all above 1.8µg/mL, a concentration at least 13.4 fold higher than that required to inhibit 90% of viral replication of wild type virus. In 1100.1526, the effect of trough concentration on sustained virologic response was determined at Week 24 using gMean trough levels, defined as the mean of all available trough levels between Weeks 2-24. No trough effect was observed with either treatment group for gMean trough or minimum steady state trough levels. There were no race or gender interactions.

In summary, in 1100.1486 and 1100.1526, no concentration effect was observed for efficacy for nevirapine XR 400 mg QD or nevirapine IR 200 mg BID for trough concentrations ≥1µg/mL. This suggests that that no efficacy benefit would be gained with further dose increases. In Study 1100.1486, 36/86 (41.9%) of patients did not develop nevirapine drug resistance and the frequency was the same in the nevirapine XR and IR groups. In the 50/86 patients who developed nevirapine resistance, there were no

differences between the treatment groups and the mutations were those described in the current Viramune® label.

### **Evaluator's overall conclusions on pharmacodynamics**

The PD properties of nevirapine XR can be assumed to be similar to those of nevirapine IR. The bioavailability of nevirapine XR 400 mg QD is only 80% of nevirapine 200 mg BID at steady state so a proportional reduction in efficacy might be anticipated. However, there were no differences between the XR and IR groups in sustained virologic suppression in treatment naive patients over 48 weeks or in treatment experienced patients over 24 weeks. Patterns of emergent drug resistance were also similar in both groups. The available evidence suggests that the key determinant of virologic response is trough plasma nevirapine levels. These must be sustained above 1µg/mL and this was well exceeded in nearly all patients in both XR and IR nevirapine treatment groups in both long term studies.

### **Efficacy**

#### **Introduction**

Clinical efficacy for the nevirapine XR development program was based on two Phase III studies in adult patients with HIV-1 infection. Study 1100.1486 compared the efficacy of nevirapine XR 400 mg QD versus nevirapine IR 200 mg BID on a fixed background of ARV after 48 weeks of treatment. Study 1100.1526 assessed the effect of switching HIV-1 infected patients from nevirapine IR 200 mg BID to nevirapine XR 400 mg QD for a 24 week treatment period. The efficacy measures in both studies were similar to those used in published clinical trials to assess the efficacy of ARV regimens in HIV-1 infected patients.

The key primary endpoint for both studies was a sustained virologic response, defined as two consecutive measurements of viral load <50 copies/mL HIV-1 RNA at least two weeks apart. A virologic rebound was defined as two consecutive measurements >50 copies/mL, at least two weeks apart. The key secondary endpoint was time to loss of virologic response. Other secondary endpoints included sustained virologic response (lower limit of quantitation (LLOQ) = 400 copies/mL); death; permanent discontinuation of the study drug; and introducing a new drug to the ARV regimen.

Three Phase I PK studies were conducted to support the paediatric indication, one in children (1100.1518) and two in healthy adult volunteers (1100.1531 and 1100.1517). The adult and paediatric development programs are outlined in Figure 5.

#### **Pivotal studies**

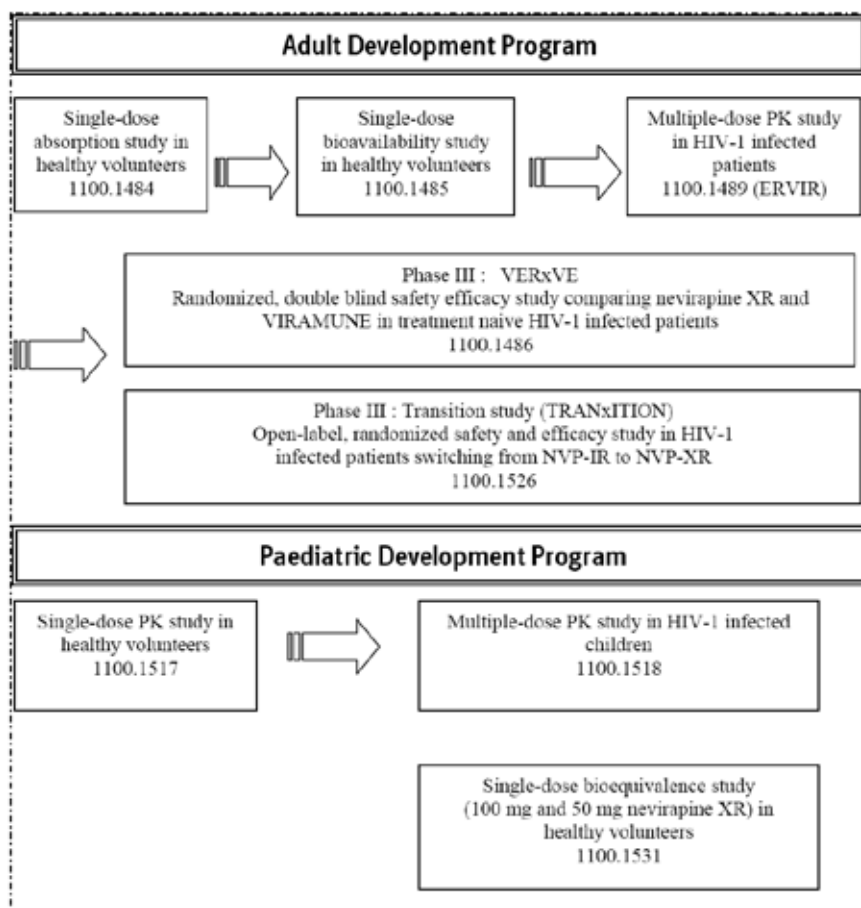
There was only one pivotal Study 1100.1486 which was a randomised, double blind, double dummy, parallel group, active controlled trial to evaluate the antiviral efficacy of 400 mg QD neVirapine Extended Release formulation in comparison to 200 mg BID neVirapine immediate release in combination with Truvada® in antiretroviral therapy naïve HIV-1 infected patients (VERxVE).

#### **Methods**

Eligible patients were randomised to receive 400 mg QD nevirapine XR or 200 mg BID nevirapine IR, after a 14 day lead in period in which all the patients were to receive 200 mg QD nevirapine IR formulation. Background ARV therapy was Truvada® (emtricitabine and tenofovir disoproxil fumarate) QD in both treatment groups. Treatment duration for the primary endpoint was 48 weeks with an extension through 144 weeks. Efficacy, safety, and PK parameters were evaluated at each study visit. An optional PK substudy included intensive PK blood collection on Day 28.



**Figure 5: Adult and paediatric development programs including nevirapine pharmacokinetic trials.**



### Objectives

The primary objective of this study was to evaluate the efficacy of 400 mg QD nevirapine XR formulation versus 200 mg BID nevirapine IR in ARV therapy naïve HIV-1 infected patients after 48 weeks of treatment. Secondary objectives were to compare the safety and PK of nevirapine XR and nevirapine IR.

### Study participants

The study was multicentre study with sites located in Europe, North and South America, Africa and Australia. The study was conducted in antiretroviral treatment naïve HIV-1 infected males and females  $\geq 18$  years of age. Male patients had CD4+ counts  $>50$  -  $<400$  cells/ $\mu$ L and female patients had CD4+ counts  $>50$  -  $<250$  cells/ $\mu$ L. All patients were required to have an HIV-1 viral load  $\geq 1,000$  copies/mL and a Karnofsky score  $>70$ . Baseline HIV-1 genotypic screening was performed and patients with documented resistance to NNRTIs or either one of the components of Truvada® (emtricitabine or tenofovir disoproxil fumarate) or lamivudine (3TC) were excluded.

### Treatments

After completion of a 14 day lead in period with nevirapine IR 200 mg QD, patients were randomised by viral load stratification and assigned to one of the double blind, double dummy treatments shown in Table 3.

**Table 3: Treatment groups implemented in nevirapine trial 1100.1486.**

Group A: Nevirapine XR (400 mg QD)	Nevirapine XR 400 mg QD + placebo nevirapine IR BID at Day 15 through Week 48 + TRUVADA QD (Emtricitabine 200 mg + Tenofovir DF 300 mg)
Group B: Nevirapine IR (200 mg BID)	Nevirapine IR 200 mg BID + placebo nevirapine XR QD at Day 15 through Week 48 + TRUVADA QD (Emtricitabine 200 mg + Tenofovir DF 300 mg)

***Treatment compliance and withdrawals***

Monitoring of compliance and treatment adherence with study medication and Truvada® (tablet count and study start and stop dates) was performed and recorded in the electronic clinical record form (e-CRF). Non compliance was defined as adherence <80% or >120% at any study visit. The investigator could remove patients from the study for non compliance with visits. Patients could also be considered for withdrawal from the study and appropriate therapy initiated if VL ≥500 copies/mL was detected at two consecutive visits after the patient had achieved an undetectable viral load (<50 copies/mL) in any previous measurement. Patients could also be withdrawn if consent was withdrawn; if they were required to take interfering concomitant medication; or if they were unable to continue for reasons such as surgery or adverse events. Patients who were enrolled and did not fulfil the inclusion/exclusion criteria were replaced. Patients who discontinued from the trial after randomisation and intake of at least one dose of study drug were not replaced. Temporary interruptions of the trial drug were strongly discouraged and patients were counselled on the importance of drug compliance.

***Outcomes/endpoints***

The primary endpoint was virologic response by Week 48; this was defined as viral load (VL) <50 copies/mL prior to Week 48 and without subsequent virologic rebound, or change of ARV therapy prior to Week 48. A virologic rebound was defined as two consecutive measurements of VL ≥500 copies/mL, at least two weeks apart, after the measurement of VL <50 copies/mL. If the first VL ≥500 copies/mL occurred at Week 48 and this was the first sequential VL value ≥500 copies/mL following virologic response, then another measurement at least two weeks later was required to confirm whether virologic rebound had occurred.

A change of ARV therapy was defined as either a permanent discontinuation of study drug, nevirapine XR or IR, addition of new ARV drugs, or alterations in background therapy.

Secondary efficacy endpoints included: (a) time to loss of virologic response, defined as the time between the start of lead in period and the last VL <50 copies/mL in a patient who initially had virologic response prior to Week 48, but subsequently demonstrated virologic rebound prior to the time when the last enrolled patient is on treatment for 48 weeks. Patients who do not achieve VL <50 copies/mL by Week 48 were defined as having either:

- (a) a time of loss of virologic response of zero;
- (b) virologic response by Week 48 as defined by VL <400 copies/mL prior to Week 48 and without subsequent virologic rebound or change of ARV therapy prior to Week 48;
- (c) time to virologic response, defined as the time between the start of lead in period and the first viral load <50 copies/mL prior to the time when the last enrolled patient is on treatment for 48 weeks;
- (d) time to new AIDS or AIDS related progression event or death;



- (e) change from baseline in VL and CD4+ cell count at each visit; or
- (f) genotypic resistance associated with virologic failure.

### **Sample size**

Planned enrolment was 1250 patients.

### **Randomisation and blinding**

Patients and investigators were blind to the randomised treatment. The active treatments and placebo were matched to maintain the double blind for the QD or BID active treatment regimens. Patients were randomised 1:1 after stratification by baseline viral load ( $\leq 100,000$  copies/mL or  $> 100,000$  copies/mL).

### **Statistical methods**

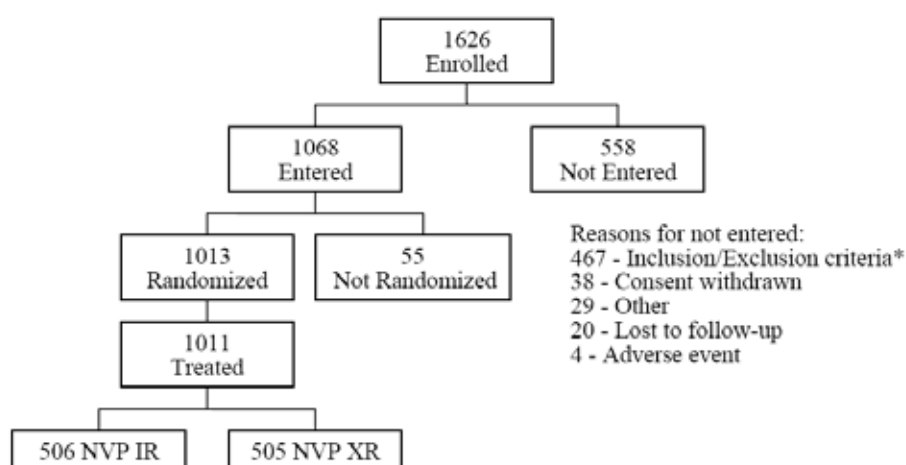
The study had 90% power to demonstrate non inferiority of nevirapine XR formulation to nevirapine IR formulation within a 10% margin, defined by the proportion of virologic response by Week 48. Outcome differences within the 10% NI margin are generally not considered to be clinically significant by clinical experts. Non inferiority of XR to IR with regard to efficacy was to be established if the lower bound of the CI was greater than -10%. The planned sample size  $n = 479$  per group had at least 90% of power to claim non inferiority with one sided  $\alpha = 0.025$ , assuming that the expected difference in proportions was zero and the virologic response proportion in both groups was 65%.

### **Results:**

#### *Recruitment*

A summary of recruitment is shown in Figure 6. A total of 1626 patients were enrolled into the study and 1068 of these were entered into the two week open label nevirapine IR 200 mg QD run in period. A total of 558 patients were not entered because they did not meet eligibility criteria. The most common reasons were 213 patients with CD4+ counts out of the permitted range; 108 patients with active hepatitis B or C; 67 with clinically significant abnormal laboratory values; 57 who were resistant to NNRTIs; and 37 with low HIV-1 viral load.

**Figure 6: Enrollment of patients in nevirapine trial 1100.1486**



Overall, 409 (80.8%) of patients in the nevirapine IR group and 421 (83.4%) of patients in the nevirapine XR group completed the Week 48 visit. There were four deaths during the treatment period. The most common reasons for discontinuation in both groups were adverse events and lack of efficacy (virologic failure). Withdrawals due to poor compliance

were few and similar in each group (nine (1.8%) in the nevirapine IR group and six (1.2%) in the nevirapine XR group).

### ***Conduct of the study***

#### *Protocol deviations*

All patients who received at least one dose of blinded treatment were included in the full analysis. A total of 45 patients were excluded from the per protocol analysis because of significant protocol violations. The most common reasons were CD4+ counts outside of eligibility at screening and poor adherence to study treatment.

#### *Baseline data*

The median age in both groups was approximately 37 years; approximately 85% were male and approximately 75% were White with similar baseline demographics in both nevirapine treatment groups. The baseline disease characteristics were also similar in each group.

#### *Numbers analysed*

A total of 1013 patients were treated with blinded medications. Of these, 1011 patients were analysed for the primary endpoint; 506 patients received nevirapine IR and 505 received nevirapine XR. Overall, 409 (80.8%) patients in the nevirapine IR group and 421 (83.4%) patients in the nevirapine XR group completed Week 48. The most common reasons for discontinuation were adverse events unrelated to their underlying disease and lack of efficacy. Three subjects in the nevirapine IR and one subject in the nevirapine XR group prematurely discontinued for death or events leading to death.

### ***Outcomes:***

#### *Primary efficacy endpoint*

The primary efficacy endpoint was virologic response at 48 weeks using LLOQ = 50 copies/mL. When adjusted for baseline HIV-1 viral load stratum, there was a difference in virologic response of 4.9% (95% CI: -0.1% to 10%) in favour of nevirapine XR. Since the pre specified non inferiority margin was -10%, the lower bound of -0.1% confirmed non inferiority of nevirapine XR to nevirapine IR ( $p < 0.001$ ). The lower bound also showed that the superiority of nevirapine XR to nevirapine IR was only marginally missed. The overall sustained virologic response was 75.9% for nevirapine IR and 81% for nevirapine XR. Virologic failure occurred in 5.9% of the nevirapine IR group and in 3.2% of the nevirapine XR group.

#### *Secondary efficacy endpoints*

The hazard of losing of virologic response was 80% for nevirapine XR compared with nevirapine IR (hazard ratio 0.80, 95% CI: 0.63 to 1.02, NS). Sustained virologic response at Week 24 was approximately 2% higher in the nevirapine XR group than in the nevirapine IR group. All other virologic endpoints marginally favoured nevirapine XR with non inferiority compared with nevirapine IR. CD4+ counts rose sharply in the first eight weeks and were sustained in both groups. At Week 48, the mean increase in CD4+ count was 192 cells for nevirapine XR and 181 cells for nevirapine IR. The time to new AIDS or AIDS related progression event or death was similar in both groups for the first six weeks but diverged thereafter: the hazard was 57% (95% CI: 28% to 116%) in the nevirapine XR group compared with nevirapine IR. Treatment emergent resistance occurred in 54 patients in the nevirapine IR group and in 32 patients in the nevirapine XR group. Emergence of resistance mutations to nevirapine alone was seen in 8.1% (7/86) patients overall.

### *Pharmacokinetic results*

The effect of trough level on sustained virologic response at Week 48 was investigated using all available mean steady state troughs from Week 4 to Week 48 for each patient. There appeared to be no relationship between virologic response and trough level above 1000 ng/mL. The relative bioavailability of nevirapine based on the geometric mean ratio was 76.7% for AUC<sub>0-24,ss</sub> and 82.7% for C<sub>min,ss</sub>. As expected for an XR formulation, C<sub>max</sub> was 31% lower for nevirapine XR compared with nevirapine IR. Peak to trough variations were 37.5% lower with the XR formulation but inter-patient variability was similar in both groups.

### *Ancillary analyses*

Age, gender, ethnicity and region had no influence on virologic response rates at 48 weeks with either treatment. However, exposure was approximately 20-30% higher in women than in men and in Blacks compared with Whites with both formulations.

**Comments:** In adult patients with HIV-1 infection, nevirapine XR 400 mg QD demonstrated non inferiority to nevirapine IR 200 mg BID for suppression of viral load. A trend towards superior efficacy was seen with nevirapine XR compared with nevirapine IR. After 48 weeks of treatment, 4.9% more patients responded to the XR formulation (95% CI: -0.1% to 10%). The non inferiority (NI) and possible efficacy benefit in favour of the XR formulation was not influenced by age, gender or ethnicity. Exposure was less with the XR formulation but peak to trough variability was lower. There appeared to be no relationship between virologic response and nevirapine trough levels. Non significant trends in favour of the XR formulation were also demonstrated for secondary efficacy endpoints including rise in CD4+ counts and time to new AIDS progression, events or death. Treatment emergent resistance to nevirapine also appeared to be less with the XR formulation.

### **Clinical studies in special populations**

In Study 1100.1518 conducted in HIV infected children, an ancillary analyses of viral suppression was conducted in 98.7% (78/79 patients) of patients had viral load <50 copies/mL at Day 22, Visit 7. No patients met the criterion for virologic failure (two consecutive measurements of viral load >50 copies/mL. These data are considered supportive as the study design and duration but are not acceptable as an efficacy study.

### **Supportive studies**

#### ***Study 1100.1526***

This was an open label, Phase IIb, randomised, parallel group study to assess the efficacy and safety of switching HIV-1 infected patients successfully treated with Nevirapine IR based regimen to Nevirapine XR 400 mg QD or remaining on Nevirapine IR 200 mg BID based regimen (TRANxITION).

#### ***Methods***

This study evaluated the efficacy and safety of switching treatment experienced, HIV-1 infected patients, who were already receiving nevirapine 200 mg BID and who were virologically suppressed for a minimum of 18 weeks, to treatment with nevirapine XR 400 mg QD. The primary analysis was performed at Week 24 with a secondary analysis at Week 48. Eligible patients were stratified according to three background treatment regimens: Truvada® (FTC + TDF), Combivir® (AZT + 3TC) or Kivexa® + Epzicom® (3TC + ABC). Within each stratum, patients were randomised 2:1 to continue on the BID nevirapine 200 mg IR formulation or to switch to QD nevirapine 400 mg XR. The study was designed to be open label to mimic the clinical situation when a single daily dose of

nevirapine XR would be used. This advantage would have been lost using a double blind, double dummy BID regimen. The proportion of patients with virologic response in the nevirapine IR group was assumed to be approximately 90% following 18 weeks of sustained virologic response with the same nevirapine IR and background treatments. Morning trough (pre dose) sample were collected for PK assessment between Visits 2 and 9 inclusive.

### *Objectives*

The primary efficacy objective of this study was to demonstrate the efficacy of a nevirapine XR based regimen for HIV-1 infected patients who received a nevirapine IR based regimen for at least 18 prior weeks before randomised therapy. The secondary objective of the study was to assess the safety and tolerance of nevirapine.

### *Study participants*

The study was conducted at 39 centres in France, Germany, the United Kingdom and the United States. Key inclusion criteria for inclusion were adult males or females aged  $\geq 18$  years who were receiving nevirapine IR and background fixed dose ARV combinations and had an undetectable HIV-1 viral load in the preceding 18 weeks. Baseline laboratory values were required to be clinically acceptable but CD4+ counts were not used to exclude patients.

### *Treatments*

After screening, patients were randomly allocated to one of the groups shown in Table 4.

**Table 4: Allocation groups for patients after screening (Study 1100.1526).**

Group A: NVP XR (400 mg QD)	NVP XR 400 mg QD + previous background therapy
Group B: NVP IR (200 mg BID)	NVP IR 200 mg BID + previous background therapy

### *Treatment compliance and withdrawals*

Patients were to be withdrawn for withdrawal of consent, poor protocol compliance, poor visit compliance, taking of prohibited medications, or an inability to continue for medical reasons. All patients were counselled about the importance of drug compliance and temporary interruptions were discouraged. Compliance was recorded by tablet count at each visit. Cumulative compliance was calculated by averaging the percentage compliance at each visit, and weighting it by the corresponding time interval.

### *Outcomes and endpoints*

The primary efficacy endpoint was a sustained virologic response using LLOQ = 50 copies/mL at Week 24. Secondary efficacy endpoints included proportion of sustained virologic response (viral load <400 copies/mL); time to loss of virologic response; change in CD4+ cell count at each visit; genotypic resistance associated with virologic failure; and various PK endpoints including trough plasma concentrations at steady state.

### *Sample size and statistics*

The primary efficacy analysis was the test of non inferiority of the nevirapine XR formulation compared to nevirapine IR with a non inferiority margin of -12%. Outcome differences within the 12% margin were considered to be not clinically significant by

expert clinicians and HA although this criterion was later tightened (before database lock) to the more stringent 10%. A 95% CI for the difference in the proportions of virologic response between nevirapine XR and nevirapine IR groups was constructed using Cochran's statistic, stratified by background therapy, and with continuity correction for the variance. Non inferiority of the XR formulation to the IR formulation was established if the lower bound of the CI was greater than -12%. Relative bioavailability and minimum and geometric mean steady state trough concentrations were determined.

#### *Randomisation and blinding*

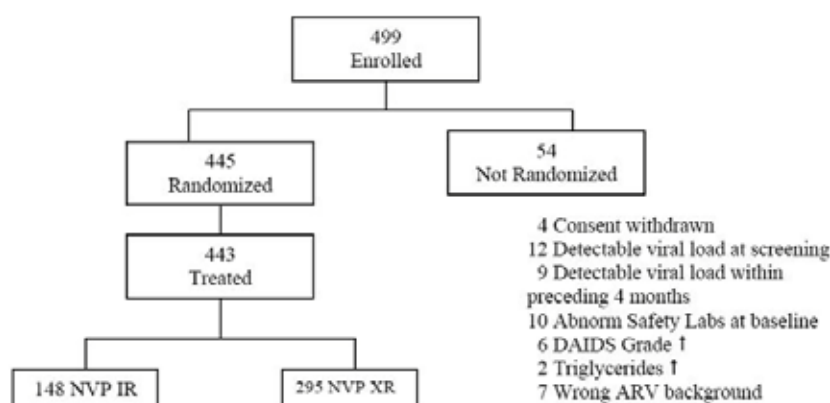
The trial was open label. Treatment assignment was by a central randomisation process in a 2:1 ratio for nevirapine XR:nevirapine IR. Eligible patients were stratified by background treatment and randomly assigned by IVRS to nevirapine XR or nevirapine IR.

### **Results**

#### *Recruitment*

A total of 499 patients were enrolled and 445 were randomized to either continue on nevirapine IR 200 mg BID or to switch to nevirapine XR 400 mg QD in a 1:2 ratio. Overall, 433 patients received at least one dose of study drug; 148 patients were randomized to the nevirapine IR group and 295 to the nevirapine XR group. A total of 54 patients did not meet eligibility criteria, mainly due to inadequate virologic control or to significant laboratory abnormalities (see Figure 7).

**Figure 7: Disposition of study patient population (Study 1100.1526).**



#### *Protocol violations*

Three randomised subjects (one in the nevirapine IR group and two in the nevirapine XR group) were excluded from the per protocol analysis but were included in the full analysis.

#### *Baseline data*

The demographics in each group were similar: 84% of patients were male; mean age was 47.4 years (55.8% in the 41-56 years age group and 6.3% ≥65 years); 91.2% were White and 7.4% were Black. The demographics were similar in both nevirapine treatment groups.

*Numbers analysed*

Overall, 148 patients in the nevirapine IR group and 295 patients in the nevirapine XR group completed Week 24. Three (2.0%) patients in the nevirapine IR group and seven (2.4%) in the nevirapine XR group discontinued study drug, mostly because of adverse events.

*Primary efficacy endpoint*

A virologic response was observed in 93.6% of patients receiving nevirapine XR and 92.6% who received nevirapine IR, a 1% difference in favour of nevirapine XR (95% CI: -4.3% to 6.2%). The lower bound of the difference was greater than -12%, demonstrating non inferiority of nevirapine XR to nevirapine IR. In the PK profile analysis, the ratio of the trough of nevirapine XR 400 mg QD to that of nevirapine IR was 89.7%. The incidence of virologic failures was similar in each group, 5.4% with nevirapine IR, and 4.1% with nevirapine XR.

*Secondary efficacy endpoints*

Overall, 94.6% of the patients in the IR group and 96.6% of the patients in the XR group achieved viral load suppression <400 copies/mL at 24 weeks. The difference in favour of nevirapine XR was 2% and the lower bound of the 95% CI was -2.5%. There was no significant difference in time to loss of virologic response. Mean CD4+ cell counts rose by 32.5 cells at Week 24 in the nevirapine IR group, and by 39.8 cells in the nevirapine XR group.

*Ancillary analyses*

Mean exposure was 32 weeks in both treatment groups. The primary efficacy endpoint was not influenced by age, gender or race. Five patients in the nevirapine IR group who received background Epzicom®/Kivexa® had virologic failure by definition but three of these were for missing observations. With this possible exception, there appeared to be no clinically significant interaction between nevirapine and background therapy. There was also no relationship between outcome and baseline CD4+, viral load and HIV-1 CDC disease staging.

The mean trough nevirapine concentrations were all above 3,000 ng/mL and were stable over the 24 week treatment period for the nevirapine IR and nevirapine XR groups. The nevirapine XR trough concentrations were approximately 10% lower than for nevirapine IR and showed slightly greater variability. The tenth percentile trough concentrations were above 2,000ng/mL for nevirapine IR and approximately 2,000 ng/mL for nevirapine XR.

**Comments:** The primary efficacy endpoint of non inferiority of nevirapine XR 400 mg QD compared with nevirapine IR 200 mg BID was met with a 1% virologic response rate benefit in favour of the XR formulation. There were also marginal benefits in favour of the XR formulation for other efficacy endpoints including time to virologic response, CD4+ counts and disease progression. The efficacy results support the switching of patients successfully treated with nevirapine 200 mg IR BID to nevirapine 400 mg XR QD.

**Evaluator's overall conclusions on clinical efficacy**

In Study 1100.1486 conducted in ARV-naïve HIV-1 infected adult patients, nevirapine XR 400 mg QD was non inferior to nevirapine IR 200 mg BID for the primary endpoint of sustained virologic response. The lower bound of the CI interval was -0.1%, significantly higher than the pre specified limit of -10% and superiority was almost demonstrated. Similar efficacy was also demonstrated for other efficacy endpoints including rise in CD4+ cell counts, disease progression and treatment emergent drug resistance. The nevirapine



XR formulation demonstrated the desired extended release characteristics with less peak to trough variability compared with the IR formulation, making it suitable for once daily dosing. Bioavailability of the XR formulation was approximately 75% lower than the IR formulation, but trough drug levels were adequate to provide sustained suppression of viral load.

In Study 1100.1526, adult patients with HIV-1 infection were switched from nevirapine IR to nevirapine XR. Sustained virologic response was seen with both treatments with a 1% benefit in favour of nevirapine XR. Non inferiority was again demonstrated. Other endpoints including time to virologic response, changes in CD4+ cell counts, and disease progression were also similar with the IR and XR formulations. Steady state trough concentrations of nevirapine XR 400 mg QD were approximately 90% of nevirapine IR 200 mg BID but non inferior efficacy confirmed that trough levels delivered adequate viral load suppression.

Non inferior efficacy results in both studies, with marginal benefits in favour of nevirapine XR, confirm that nevirapine XR delivers adequate exposure to ensure sustained virologic response in adult patients with HIV-1 infection.

The efficacy of the XR formulation was not tested in the paediatric Phase I Study 1100.1518 but there were no cases of virologic failure. However, when doses were adjusted for body surface area, exposure over a ten day treatment period was similar to adults treated for up to 48 weeks. Exposures were also similar in the stratified age groups from 3 to 18 years. The results of this Phase I study were encouraging but adequately designed, long term efficacy studies of nevirapine XR are still required in children.

## **Safety**

### **Introduction**

Nevirapine is a NNRTI of HIV-1 virus. The adverse event profile of nevirapine IR has been well described since it first received marketing approval in 1996. Expected adverse events listed in the current labelling include skin rash (including Steven-Johnson syndrome), hypersensitivity syndrome (rash with constitutional symptoms such as fever, arthralgia, myalgia, lymphadenopathy, hepatitis, eosinophilia and renal dysfunction), abnormal LFTs, jaundice and hepatitis (including fulminant hepatitis), headache, fatigue, fever, nausea, vomiting, diarrhoea, abdominal pain, myalgia, arthralgia, neutropaenia, anaemia and allergic reactions.

Safety data are presented for two Phase III studies. Study 1100.1486 was a double blind, randomised, parallel group comparison of nevirapine XR and nevirapine IR in treatment naive HIV-1 infected adult patients. Study 1100.1526 was a supportive, open label, randomised, parallel group study measuring the effects of switching adult patients with HIV-1 infection from nevirapine IR to nevirapine XR. Safety data are also obtained in five Phase I studies in adult patients (1100.1484, 1100.1485, 1100.1517, 1100.1489 and 1100.1531) and from one study in HIV-1 infected children (1100.1518). In the single dose PK studies, there were no deaths, two SAE (serious adverse events) and two discontinuations due to AE (adverse events). AE considered by the investigator to be drug related were generally mild to moderate and there was only one rash (with nevirapine IR). Safety data from these studies are not considered further.

Eight hundred and ninety-two (892) adults and 83 children with HIV-1 infection received at least one dose of nevirapine XR. In the Phase III studies, 423 treatment naive adult patients with HIV-1 received nevirapine XR for at least 48 weeks. Two hundred and eighty-nine (289) treatment experienced adults with HIV-1 infection received nevirapine

XR for at least 24 weeks. In all cases, the patients received the final nevirapine XR formulation proposed for marketing.

### **Patient exposure**

In the pivotal, double blind Study 1100.1486, 506 patients received at least one dose of nevirapine IR and 505 patients received at least one dose of nevirapine XR. The mean number of weeks of exposure (including the extension phase) was similar in both groups (60.3 weeks for nevirapine IR and 61.5 weeks for nevirapine XR). A total of 410 (81%) patients in the nevirapine IR group and 423 (83.8%) patients in the nevirapine XR group received treatment for  $\geq 48$  weeks. In the supportive, open label Study 1100.1526, 443 patients were randomised and received study drug; 148 in the nevirapine IR group and 295 in the nevirapine XR group. Overall, 98% of each treatment group received study treatment for at least 24 weeks. In Study 1100.1518, the Phase I study in children, 90 patients were enrolled and 85 patients received at least one dose of nevirapine XR at Visit 2; 94.1% of patients were exposed for between 7-14 days and all 85 patients were included in the safety analysis. In the five Phase I studies in adults, a total of 467 healthy, male subjects were exposed to various doses of nevirapine, ranging from 50 mg to 400 mg.

### **Adverse events (AE)**

In the pivotal Phase III Study 1100.1486, in treatment naïve adult patients with HIV-1 infection, 55 of 1068 patients discontinued nevirapine 200 mg IR once daily during the run in period, due mainly to skin rash. Compared with nevirapine IR, the incidence of the following was slightly lower in the nevirapine XR group: the proportion of subjects with any AE (87.7% versus 89.3%, respectively); AE considered to be drug related by the investigator (19.8% versus 24.3%); patients with AE leading to treatment discontinuation (6.3% versus 8.9%); and patients with DAIDS (Division of AIDS, NIH<sup>5</sup>) Severity Grade 3 or 4 AE (14.5% versus 18%). The most frequent AE are shown in Table 5. Twenty-five events were reported in more than 3% of patients overall, mostly related to upper respiratory tract infections. Ten of the 25 events were AE known to be associated with nevirapine including rash, nausea, vomiting, gastroenteritis and abdominal pain. During the randomised treatment period, the majority of patients in both treatment groups had mild to moderate AE. Overall, the frequency of AE was similar in the nevirapine IR and XR groups.

In Study 1100.1526, during the 24 week treatment period, there was a higher frequency of patients in the nevirapine XR group than in the nevirapine IR group with any AE (75.6% versus 60.1% respectively). However, the rate of patients with AE of DAIDS Grade severity 3 or 4 was similar in the nevirapine XR and IR groups (3.7% and 4.1%, respectively). AE defined by the investigator as drug related were reported in more patients in the nevirapine XR group compared with the IR group (11.9% versus 2.0%, respectively).

In Study 1100.1518, 85 patients were entered into the nevirapine IR period and 83 patients were entered into the nevirapine XR period (two were excluded for poor compliance). Twenty-four (28.2%) patients had at least one AE during the run in period: the majority were mild, only two were moderate with no significant differences between age groups. Thirty-nine patients (47%) experienced at least one AE during the nevirapine XR treatment period. Of these patients, 30 (36.1%) experienced DAIDS Grade 1 events; 8 (9.6%) experienced DAIDS Grade 2 events; and one patient experienced a DAIDS Grade 3 event. There were no DAIDS Grade 4 events, SAE or AE leading to study drug discontinuation in this period.

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<sup>5</sup> <http://www.niaid.nih.gov/about/organization/daids/Pages/default.aspx>



**Table 5: Preferred term adverse events reported in >3% patients overall (Study 1100.1486).**

Preferred term	NVP IR 200 mg BID N (%)	NVP XR 400 mg QD N (%)	Total N (%)
Number of patients	506 (100)	505 (100)	1011 (100)
Nasopharyngitis	83 (16.4)	90 (17.8)	173 (17.1)
Diarrhoea	62 (12.3)	62 (12.3)	124 (12.3)
Upper respiratory tract infection	54 (10.7)	51 (10.1)	105 (10.4)
Rash <sup>1</sup>	48 (9.5)	53 (10.5)	101 (10.0)
Headache	59 (11.7)	39 (7.7)	98 (9.7)
Nausea	50 (9.9)	30 (5.9)	80 (7.9)
Bronchitis	31 (6.1)	36 (7.1)	67 (6.6)
Cough	33 (6.5)	23 (4.6)	56 (5.5)
Vomiting	31 (6.1)	23 (4.6)	54 (5.3)
Gastroenteritis	24 (4.7)	25 (5.0)	49 (4.8)
Fatigue	24 (4.7)	24 (4.8)	48 (4.7)
Back Pain	23 (4.5)	25 (5.0)	48 (4.7)
Influenza	25 (4.9)	20 (4.0)	45 (4.5)
Arthralgia	25 (4.9)	19 (3.8)	44 (4.4)
Hypertension	23 (4.5)	21 (4.2)	44 (4.4)
Abdominal pain	22 (4.3)	18 (3.6)	40 (4.0)
Depression	23 (4.5)	15 (3.0)	38 (3.8)
Insomnia	22 (4.3)	15 (3.0)	37 (3.7)
Pyrexia	21 (4.2)	14 (2.8)	35 (3.5)
Anogenital warts	15 (3.0)	19 (3.8)	34 (3.4)
Oropharyngeal pain	14 (2.8)	19 (3.8)	33 (3.3)
Sinusitis	17 (3.4)	16 (3.2)	33 (3.3)
Myalgia	16 (3.2)	17 (3.4)	33 (3.3)
Pharyngitis	16 (3.2)	16 (3.2)	32 (3.2)
Herpes Zoster	15 (3.0)	16 (3.2)	31 (3.1)

<sup>1</sup> Preferred term Rash included all types of rashes, regardless of drug-relatedness.

Percentages are calculated using total number of patients per treatment as the denominator.

### Serious adverse events and deaths

In the pivotal Study 1100.1486, there were four deaths in the run in period, five deaths in the randomisation period and one death after the treatment period. Of the six deaths after randomisation, five occurred in the nevirapine IR group and one in the nevirapine XR group. The deaths were attributed to cardiac events or infections and none were considered to be drug related. A total of 20 (1.9%) patients experienced SAE during the nevirapine 200 mg once daily run in period. Eleven patients discontinued the study while nine were randomised and received study treatment. Rash was the most common SAE in the non-randomised group, occurring in five (9.1%) patients, two of whom developed Stevens-Johnson syndrome during the treatment period. SAE were reported in 11.5% of the nevirapine XR group and 10.7% in the nevirapine IR group. The most frequently reported SAE were pneumonia, depression and Kaposi's sarcoma, each reported in five patients, two in the nevirapine XR group and three in the nevirapine IR group. In general, the frequency of individual SAE was similar in each nevirapine treatment group.

In Study 1100.1526, a total of 21 patients had SAE with 17 (5.8%) in the nevirapine XR group and four (2.7%) in the nevirapine IR group. Of these cases, 19/21 were considered to be SAE because they led to hospitalisation but none of the events were considered causally related to treatment by the investigator. No deaths or SAE were recorded in the paediatric Study 1100.1518.

### Laboratory findings

In Study 1100.1486, 74 treatment naive patients had a hepatic event; 22 of them were symptomatic, commonly with anorexia, jaundice and vomiting. Of the 74 patients with hepatic events, 47 discontinued from the study. Hepatic events were more common in the nevirapine IR group (9.1%) compared with the nevirapine XR group (5.5%). Patients who

were randomised to nevirapine IR were 71% (OR = 1.71, 95% CI: 1.05 – 2.79) more likely to have a hepatic event than patients who were randomized to nevirapine XR. There was a similar effect size in symptomatic patients. In Study 1100.1526, involving a population of treatment experienced patients (nearly half of whom had received nevirapine treatment for at least 3 years), no patient had a hepatic event attributed to study drug although eleven patients had co-infection with hepatitis B or C.

Median changes in laboratory values in Study 1100.1486, from baseline to last visit, are shown in Table 6. The changes, including liver function tests, were generally small and similar in both nevirapine IR and XR groups. DAIDS Severity Grade 3 or 4 abnormalities were similar in both nevirapine treatment groups. The largest difference between treatment groups was for ALT (alanine transaminase): 36 (7.1%) patients in the nevirapine IR group had a Grade 3 or 4 event compared with 24 (4.8%) in the nevirapine XR group. Median changes in laboratory values, including liver function tests (LFTs), were also small in Study 1100.1526 with no clinically significant difference between the nevirapine IR and XR groups. In the paediatric Study 1100.1518, there were few changes in laboratory values (including LFTs) from baseline.

**Table 6: Median changes from baseline in laboratory values to last value on treatment for selected analytes (Study 1100.1486).**

	Median Difference from Baseline			
	NVP IR		NVP XR	
	N <sup>1</sup>	Median Change	N	Median Change
<b>Haematology</b>				
Neutrophils (cells/mm <sup>3</sup> )	496	280	498	430
Hemoglobin (g/dL)	500	0.4	503	0.5
Haematocrit (%)	499	1.0	502	1.0
Platelets (cells/mm <sup>3</sup> )	488	26,000	495	28,000
<b>Enzymes</b>				
ALT (U/L)	502	3	503	3
AST (U/L)	502	-1	502	-1
GGT(U/L)	504	28	505	23
Amylase (U/L)	503	-4	505	-5
Lipase (U/L)	503	-1	505	0
CPK (U/L)	502	30	504	34
Alkaline phosphatase (U/L)	504	23	505	20
<b>Substrates</b>				
Triglycerides (mg/dL)	503	-8	505	-7
Cholesterol (mg/dL)	503	18	505	21
LDL (mg/dL)	496	7	494	10
HDL (mg/dL)	503	11	502	10
Bilirubin, total (mg/dL)	502	-0.1	504	-0.1
Glucose (mg/dL)	502	3	503	4
Creatinine (mg/dL)	504	0	505	0

<sup>1</sup> Number of patients with a baseline and at least one on-treatment value reported.

### Safety in special populations

Limited safety data were obtained in children in Study 1100.1518. Thirty-nine patients (47%) experienced at least one AE during nevirapine XR treatment: 30 patients (36.1%) experienced DAIDS Grade 1 events; 8 patients experienced DAIDS Grade 2 events; and one patient (1.2%) experienced a DAIDS Grade 3 event. There were no DAIDS Grade 4 events, SAEs or AEs leading to discontinuation of study treatment.

Overall, AE profiles were similar in children compared with adult males and females although limited patient numbers and treatment duration in children make comparisons difficult. In Study 1100.1486, more women (94.7%) than men (88.4%) in the nevirapine IR group experienced an AE. However, the reverse trend was observed in the nevirapine XR group, 81% in females compared with 88.9% in males. Among women, a 13.6% greater

proportion reported AE with nevirapine IR compared with nevirapine XR. The frequency of drug related rashes was similar between men and women in the run in period, whereas in the randomised period, women experienced more drug related rashes, particularly in the nevirapine IR group. Women were approximately twice as likely to have any category of hepatic event as men although this gender effect was seen only in the nevirapine IR group. Similar trends for race and region as in the overall AE summary were seen for randomised patients. However, Black patients had a slightly higher frequency of AEs in the nevirapine XR group (87.2%) compared to the nevirapine IR group (82.3%). Hepatic events were similar among races and no significant differences in AE profiles or hepatic events were identified between regions. In Study 1100.1526, the AE rates observed in subgroups defined by gender, race or background treatment were generally consistent with those observed in the overall study population.

### **Safety related to drug-drug interactions and other interactions**

No new drug interaction studies were conducted with nevirapine XR. All contra indications which apply to nevirapine IR are assumed to apply to nevirapine XR. There is no clinically relevant food interaction with either formulation of nevirapine.

### **Nevirapine XR remnants in stools**

There were six patients in Study 1100.1486 with self reported nevirapine XR remnants in stools and nine subjects in Study 1100.1526. Incomplete dissolution of the matrix tablet formulation during gut transit might lead to incomplete drug absorption. However, mean trough nevirapine concentrations were acceptable in all these patients and all met their primary endpoints after 48 and 24 weeks, respectively.

### **Discontinuation due to Adverse Events**

In Study 1100.1486, 45 patients discontinued treatment during the run in period due to AEs, mainly rash (45.5%) and pyrexia (18.2%). Two patients discontinued treatment because of Stevens-Johnson syndrome. During the randomised period, a total of 77 (7.6%) patients discontinued treatment due to AE; skin rash (2.8%) and hepatic events (2.3%) were the most common events. Slightly more patients discontinued study medication due to an AE in the nevirapine IR group than in the nevirapine XR group (8.9% versus 6.3%, respectively). The most common event leading to discontinuation of study drug during the randomised period was rash (12 [2.4%] patients in the nevirapine IR group and nine [1.8%] in the nevirapine XR group). In the nevirapine IR group, eight patients were withdrawn due to hepatitis and five patients in the nevirapine XR group. In Study 1100.1526, only three patients were withdrawn due to AE, all in the nevirapine XR group. Skin rash occurred in one patient.

### **Evaluator's overall conclusions on clinical safety**

Overall, the two Phase III studies did not demonstrate any new or unexpected safety issues for nevirapine IR or XR and the side effect profile did not differ significantly from the profile of nevirapine IR in the current marketed labelling. Most AEs leading to study drug discontinuation occurred in the first 6-8 weeks of treatment. Known AEs of special interest include rash and hepatic events and rash was the most common reason for discontinuation of treatment in the double blind study in treatment naive patients. Hepatic events were also common, slightly more so in patients who received nevirapine IR compared with nevirapine XR. The frequency of AE in other categories, and events leading to study drug discontinuation, were also slightly but consistently less in patients who received nevirapine XR compared with nevirapine IR. There were no deaths attributed to the study drug.

AE leading to discontinuation were infrequent in the run in period of the open label study. This would be expected in a patient population half of whom had received previous nevirapine treatment for over three years. More patients who were switched from nevirapine IR treatment to nevirapine XR reported AEs, mostly mild, and significantly more AEs were considered drug related by the investigator. However, the frequency of more severe AE (DAIDS Severity Grade 3 or 4) was similar in the nevirapine XR group (3.7%) and the nevirapine IR group (4.1%). There is no obvious reason for this disparity between the two studies although it is possible that reporting was biased by the open label design in the switch study.

There were no deaths and no discontinuations due to an AE in the Phase I multiple dose, crossover study in children. Children were able to swallow the XR formulation easily and there was no evidence that the safety profile of nevirapine XR in children was significantly different from adults when dosage was adjusted for BSA. AE were reported in more women than men. Whether this difference warrants dose reduction is debatable but the decision should probably be left to treating clinicians. AEs were slightly more common in Blacks than in Whites but the difference was not clinically significant.

### **List of Questions**

During 2010, the TGA began to change the way applications were evaluated. As part of this change, after an initial evaluation, a List of Questions to the sponsor is generated.

### **Pharmacokinetics**

The paediatric nevirapine XR 50 mg tablet was not equivalent to the XR 100 mg tablet when tested in healthy adults (relative bioavailability was approximately 10% higher with the 50 mg tablet, possibly related to smaller tablet size). In the Phase I Study 1100.1518 in children with HIV-1 infection, it appears that nevirapine XR was supplied as either 100 mg or 400 mg tablets. Can the sponsors justify not testing the 50 mg XR tablet in the intended target population?

### **Safety**

Can the sponsors explain the higher exposures in women and Blacks with the IR and XR formulations compared with previously published studies? Would the risk/benefit equation in these groups be improved with a lower dose of nevirapine XR, for example, 300 mg QD? Only 1.7% of adult subjects, and none of the children, exposed to nevirapine XR were Asian. Is there a pharmacovigilance plan for nevirapine XR in Asian populations?

### **Product Information / Consumer Medicine Information**

There was a question on the Product Information but such questions are beyond the scope of this AusPAR.

### **Clinical Summary and Conclusions**

#### **Clinical aspects**

##### ***Pharmacokinetics***

Absorption of nevirapine was found to occur from all sites in the GI tract making it suitable for a matrix controlled release formulation. Compared to nevirapine IR, the relative bioavailability of nevirapine XR was similar in the proximal GI tract and less in the distal GI tract, the latter possibly contributing to the lower overall relative bioavailability of the XR formulation. The bioavailabilities of ten XR formulations were tested, either 300 mg or 400 mg as a single dose, with varying concentrations of hypromellose using cross linked polymer technology. *In vivo* PK profiles were then compared with *in vitro* dissolution rates and an accurate correlation between the two was established. The relative bioavailabilities

of the different formulations (based on  $AUC_{0-\infty}$ ,  $C_{max}$  and  $C_{24}$ ) were similar and all were lower compared to nevirapine IR 2 x 200 mg. Peak to trough variability was less with the XR formulations compared with nevirapine IR and trough concentrations were consistently higher than 1 µg/mL.

The best candidate prototype selected for full development was the 400 mg tablet with 25% cross polymerisation. The same technology was then used to manufacture 50 mg and 100 mg tablet strengths for paediatric use. Exposure was 11% higher with 4 x 50 mg tablets compared to 2 x 200 mg tablets but this is unlikely to be clinically significant. Exposure measured by  $AUC_{0-\infty}$  and  $C_{max}$  was proportional for the 300 mg and 400 mg XR tablet strengths and approximately 80% of the IR formulation. The bioavailability of the 50 mg and 100 mg XR tablets was higher (possibly due to the smaller tablet sizes) but similar to the IR formulation. In summary, based on the PK profiles, all the XR formulations given once daily (with the possible exception of the 50 mg tablet) are suitable replacements for the corresponding IR formulation given twice daily in both adults and children.

### **Pharmacodynamics**

The primary PD endpoint in the two Phase III studies was virologic suppression for nevirapine XR given in combination with other ARV medication.

In adults, nevirapine XR 400 mg QD was compared with nevirapine IR 200 mg BID in:

- (a) treatment naive patients with HIV-1 infection in Study 1100.1486 and
- (b) treatment experienced patients with HIV-1 who were switched from treatment with nevirapine IR to nevirapine XR in Study 1100.1526.

Nevirapine XR was tested in children aged  $\geq 3$  to  $<18$  years in the Phase I Study 1100.1518.

There was sustained virologic suppression in all studies detailed in the summary of clinical efficacy immediately below. No effect of nevirapine trough levels was observed on the proportion of virologic responders when the gMean of all available nevirapine trough levels at steady state was calculated. In Study 1100.1486, the gMean trough concentration was above 3.3 µg/mL and stable throughout the 48 week observation period for both nevirapine XR and IR formulations, with similar results for minimum trough concentrations. Virologic response was sustained above the target concentration of 3 µg/mL even though treatment with nevirapine XR was associated with lower drug exposure measured by AUC and  $C_{max}$ . For nevirapine XR, the tenth centile trough concentrations were all above 1.8 µg/mL, a concentration at least 13 fold higher than the  $IC_{90}$  for wild type virus. Moreover, there was no relationship between virologic suppression and exposure as long as trough concentrations were above 1 µg/mL.

There were no significant interactions between minimum steady state concentrations and race, gender or region. In the studies submitted, resistance testing was performed in 86 patients and the observed mutations were those to be expected with nevirapine therapy. No difference in resistance related to nevirapine IR compared with nevirapine XR was observed.

In summary, treatment with nevirapine XR 400 mg QD caused sustained virologic suppression even though overall exposure was lower than in patients receiving nevirapine IR 200 mg BID. Trough concentrations with nevirapine XR were consistently higher by at least an order of magnitude than the concentration where 90% of the maximal observed effect is obtained ( $IC_{90}$ ) of wild type virus.

### ***Clinical efficacy***

Clinical efficacy was determined primarily in a pivotal Phase III Study 1100.1486. This was a large, double dummy, double blind, parallel group, randomised, study of nevirapine XR 400 mg QD versus nevirapine IR 200 mg BID for 48 weeks in treatment naive adult patients infected with HIV-1. The primary endpoint was virologic response at Weeks 48, defined as viral load <50 copies/mL. Other endpoints included time to loss of virologic response; time to AIDS related disease progression; changes from baseline in VL and CD4+ count; and genotypic resistance associated with virologic failure.

Patients were randomised 1:1 after stratification according to baseline viral load. The study had 90% power to demonstrate non inferiority of the nevirapine XR formulation compared with nevirapine IR within a 10% margin. A total of 1013 patients received blinded, randomised treatment and more than 80% in each treatment group completed the 48 week study period.

At 48 weeks, there was difference in virologic response (defined as <50 copies/mL) of 4.9% (95% CI: -0.1% to 10%) in favour of nevirapine XR. Since the pre specified non inferiority margin was -10%, the lower bound of -0.1% confirmed the non inferiority of nevirapine XR to nevirapine IR ( $p < 0.001$ ). The lower bound showed that superiority of nevirapine XR to nevirapine IR was only narrowly missed. Sustained virologic response was 75.9% for nevirapine IR and 81% for nevirapine XR. Virologic failure occurred more frequently in the nevirapine IR group compared with the nevirapine XR group (5.9% versus 3.2%, respectively). Secondary endpoints were similar with non-inferiority between the treatment groups or trends in favour of nevirapine XR. Age, gender, ethnicity and region had no influence on virologic response rates.

Exposure was less with the nevirapine XR formulation and peak to trough variability was also less. However, there appeared to be no relationship between virologic response and nevirapine trough levels.

The supportive Study 1100.1526 was an open label, randomised, parallel group, Phase III study to assess the efficacy of switching patients from nevirapine IR 200 mg BID to nevirapine XR 4QD over 24 weeks. The study was conducted in treatment experienced adult patients infected with HIV-1, at least half of whom had received nevirapine IR treatment for at least three years before the start of the study. The study was designed to be open label to mimic the clinical situation when a single daily dose of nevirapine would be used. As in the double blind study, the primary endpoint was sustained virologic response, <50 copies/mL at 24 weeks. Secondary endpoints included time to loss of virologic response; change in CD4+ cell count from baseline at each visit; and genotypic resistance associated with virologic failure.

Patients were randomised in a 2:1 ratio for nevirapine XR:nevirapine IR. The primary efficacy analysis was the test of non inferiority of the nevirapine XR formulation compared to nevirapine IR with a margin of -12%, changed before database lock to a more stringent -10%. 445 patients were randomised to either continue on nevirapine 200 mg BID or to switch to nevirapine 400 mg QD. A total of 148 patients in the nevirapine IR group and 295 patients in the nevirapine XR group completed Week 24.

A sustained virologic response was seen in 93.6% of patients receiving nevirapine XR and 92.6% of patients who received nevirapine IR, a 1% difference in favour of nevirapine XR (95% CI: -4.3% to 6.2%). The lower bound of the difference was greater than -12% (and the more stringent -10% lower bound) confirming the non inferiority of nevirapine XR compared with nevirapine IR. Virologic failures were 5.4% in the nevirapine IR group and 4.1% in the nevirapine XR group. The primary endpoint was not influenced by age, gender



or race. Secondary endpoints showed little or no differences between the IR and XR formulations.

The efficacy of nevirapine XR was not tested in the paediatric study Phase I Study 1100.1518. However, with doses adjusted for BSA, exposure over ten days was similar to adults treated for 48 weeks and there were no cases of virologic failure. Efficacy was not established in children so there is no evidence to support an indication in these patients.

In summary, the non inferiority of nevirapine XR compared with nevirapine IR was confirmed convincingly in two Phase III studies in adult patients with HIV-1 infection. There were also minor but consistent trends in favour of nevirapine XR for most efficacy endpoints. The results were similar in treatment naive and treatment experienced patients and they were not influenced by age, gender or race.

### ***Clinical safety***

Nevirapine IR was given marketing approval in 1996 and the adverse event profile is well understood. Expected AEs include rash (including Stevens-Johnson syndrome), with or without constitutional symptoms such as pyrexia, arthralgia, myalgia, hepatitis and eosinophilia; abnormal LFTs with jaundice and hepatitis; headache; nausea, vomiting and diarrhoea; anaemia and neutropaenia. The adverse event profiles recorded in the pivotal and supportive Phase III studies did not differ from those recorded in the current marketing labelling for nevirapine IR. Skin rash and hepatitis were the most common reasons for discontinuation of study treatment.

In the randomised period of the double blind, pivotal Study 1100.1486, there were slightly fewer patients in the nevirapine XR group than the nevirapine IR group with any AE (87.7% versus 89.3%); AE considered to be drug related by the investigator (19.8% versus 24.3%); AE leading to treatment discontinuation (6.3% versus 8.9%); and patients with AE of DAIDS Severity Grade 3 or 4 (14.5% versus 18%). In the open label study in treatment experienced patients Study 1100.1526, the trend in favour of nevirapine XR was reversed. AE were experienced more frequently in the nevirapine XR group than in the nevirapine IR group (75.6% versus 60.1%, respectively). AE considered to be drug related by the investigator were also more common in the nevirapine XR group than in the nevirapine IR group (11.9% versus 2.0%, respectively). However, the rate of AEs of DAIDS Severity Grade 3 or 4 was similar in the nevirapine XR and IR groups (3.7% versus 4.1% respectively).

In Study 1100.1486, a total of 20 (1.9%) patients developed SAE during the run in period on nevirapine IR 200 mg QD. Rash was the most common event and Stevens-Johnson syndrome occurred in two patients. In the randomised treatment period, a SAE were reported in 11.5% of the nevirapine XR group and in 10.7% of the nevirapine IR group, the most common being pneumonia, depression and Kaposi's sarcoma. In general, the pattern of SAEs was similar in both treatment groups. In the open label Study 1100.1526, SAE were reported in 5.8% of patients in the nevirapine XR group and in 2.7% in the nevirapine IR group. However, none of the SAEs were considered to be drug related by the investigator.

Hepatic events occurred commonly in treatment naive patients in the randomisation period of Study 1100.1486. Hepatic events were more common in the nevirapine IR group (9.1%) compared with the nevirapine XR group (5.5%). Patients who were randomised to nevirapine IR were 71% (OR = 1.71, 95% CI 1.05-2.79) more likely to have a hepatic event than patients who were randomised to nevirapine XR. There was a similar effect size in symptomatic patients. In Study 1100.1526, a population of treatment experienced patients (nearly half of whom had received nevirapine treatment for at least three years), no

patient had a hepatic event attributed to study drug (although eleven patients had co infection with hepatitis B or C). Changes in other laboratory parameters were usually minor with no clinically relevant differences between the nevirapine IR and XR groups.

There were no deaths and no discontinuations due to AEs in the Phase I multiple dose, cross over, PK study in children with HIV-1 infection. Children were able to swallow the XR formulation easily and there was no evidence that the safety profile of nevirapine XR in children was significantly different from adults when dosage was adjusted for BSA. In the adult Phase III studies, AE were reported in more women than men and in slightly more Blacks than Whites. In the nevirapine IR group, hepatitis occurred more frequently in women than in men. However, there were no significant gender differences in the incidence of hepatitis in the nevirapine XR group.

Overall, the safety profile of nevirapine XR was similar to nevirapine IR with no new or unexpected findings in either adults or children. AE of all descriptions in the double blind, adult Phase III study were somewhat less common in the nevirapine XR group compared with the IR group. This finding is compatible with the reduced nevirapine exposure seen with the XR formulation. In the open label adult study, significantly more AEs and SAEs were observed with the XR formulation although the frequency of moderate to severe AEs was similar in both groups. There is no obvious explanation for this disparity other than patient and investigator bias against a new investigational product introduced by the open label design.

Most study drug discontinuations due to an AE occurred with nevirapine IR in the run in period of the double blind study. Most were related to rash and hepatitis, both known to be associated with nevirapine treatment. However, discontinuation rates were similar in the randomised period of the double blind study and unlikely to have biased the study results and conclusions.

## **Benefit risk assessment**

### ***Benefits***

Several published studies in HIV-1 infection have shown that successful long-term treatment relies on the potency of the drug combination and on compliance with treatment. The efficacy of nevirapine IR has been established in numerous studies since it was first marketed in 1996 and its safety profile is well understood. The aim of the nevirapine XR program was to provide once daily administration while maintaining adequate trough concentrations and safety. The final XR formulation selected for the clinical trial program aimed to provide reduced nevirapine exposure, with a lower  $C_{max}$  while maintaining  $C_{min}$  levels adequate to maintain virologic control. The target PK profile in adults was a median trough drug concentration of 3 µg/mL at steady state (more than 15 fold higher than IC95 for wild type HIV-1 virus) with reduced peak/trough variability.

The XR formulation met its PK objectives and demonstrated non inferior efficacy compared with the IR formulation ( $p < 0.001$ ) for a variety of endpoints, while safety appeared to be comparable. The selected 400 mg QD nevirapine XR formulation achieved steady state trough concentrations of approximately 3 µg/mL (2.8 µg/mL fasted; 3.0 µg/mL fed) in a PK study with higher mean trough concentrations in the two Phase III studies 1100.1486 and 1100.1526 (3.3 µg/mL and 3.4 µg/mL, respectively). In Study 1100.1486, 4.9% more patients achieved sustained virologic control at Week 48 with the XR formulation (95% CI: -0.1% to 10%), the lower bound indicating a trend towards superior efficacy in favour of nevirapine XR. The lack of virologic failure confirms adequate exposure to nevirapine even though total exposure was somewhat lower with the XR formulation.



The nevirapine XR formulation appeared to be well tolerated in children and no patients suffered loss of virologic control. Exposure was similar to the adult population with mean trough nevirapine levels above 3 µg/mL in all age groups.

The advantage of the once daily formulation is added convenience, leading potentially to greater compliance, improved virologic control and better clinical disease outcomes.

### ***Risks***

There was no evidence of dose dumping with the XR formulation and nevirapine trough concentrations at steady state were in the predicted range with low peak/trough variability. Tablet 'ghosts' were observed in stools from some patients but trough nevirapine levels were in the therapeutic range in all patients with no evidence of loss of virologic control.

The AE profile observed in these studies was consistent with the current labelling and no new events were identified. Safety outcomes were similar in both XR and IR groups, with a slight benefit in favour of nevirapine XR for most categories of AE in the double blind Study 1100.1486. This trend applied to both rash and hepatitis, the most clinically significant AE of special interest. The opposite trend was observed in the open label Study 1100.1526 in which more AE were reported in the nevirapine XR group compared with the nevirapine IR group. This disparity is of concern but patient and investigator bias introduced by the open label study is the most plausible explanation for the following reasons: the double blind Study 1100.1486 was robustly designed and the AE data were clear and internally consistent; total nevirapine exposure and peak/trough variability are lower with the XR formulation; moderate to severe AE event rates in Study 1100.1526 were similar in the XR and IR groups; and laboratory abnormalities were similar in both treatment groups in both Phase III studies.

A similar AE pattern was observed in the paediatric Study 1100.1518 with more frequent AE in the nevirapine XR group (47%) compared with the nevirapine IR group (28.2%). However, the patient numbers in this study were small and AE numbers in the XR group were driven by an excess of infections considered unrelated to the study drug. There is extensive experience with nevirapine IR in paediatric patients but exposure to the XR formulation was only 7-14 days in the PK phase, with only small numbers entered into the optional extension phase. There is no reason to question the efficacy and safety of the XR formulation in children but larger clinical studies and post marketing surveillance are required.

### ***Balance***

The initial treatment of HIV-1 infection should include a combination of three drugs; two nucleoside/nucleotide reverse transcriptase inhibitors, and a third drug which may be either a non nucleoside reverse transcriptase inhibitor (NNRTI) or a protease inhibitor. Nevirapine is an effective NNRTI as part of triple combination therapy and efficacy is dependent on sustained virologic suppression and adherence to treatment. Adherence to treatment is promoted by good tolerability and by once daily dosing.

Nevirapine XR given once daily was formulated to give less exposure than nevirapine IR with reduced  $C_{max}$  and less peak/trough variability. However, in the Phase III studies, trough drug levels at steady state were consistently high enough to ensure sustained virologic suppression at least equal to that of the IR formulation. This was achieved in adults and children when dosage was adjusted for BSA or body weight. There were no treatment emergent differences in genotypic resistance between the XR and IR formulation groups. Changes in CD4+ cell count and indices of HIV-1 disease progression were also similar with trends in favour of the XR formulation.

There is little reason to doubt the long term safety and efficacy of nevirapine XR tablets in children although AEs were reported more frequently in children treated with nevirapine XR compared with nevirapine IR. The PK profile of the 100 mg XR tablet is satisfactory in children. However, there appears to be little rationale for the 50 mg tablet and the 100 mg tablet should be tested in a properly designed safety and efficacy study.

The most significant risks associated with nevirapine IR treatment are rash and hepatic events, both of which may be life threatening or fatal. Both occur most frequently in the first six weeks of therapy in treatment naive patients and the risk can be mitigated by introducing nevirapine IR at low dose for a period of two weeks. There was an excess of non serious AE in the open label, switch study, but there were no cases of drug related rash or hepatitis in these patients with previous long term exposure to nevirapine. In treatment naive patients, AEs including rash and hepatitis were no more frequent in patients who received nevirapine XR than nevirapine IR after the initial run in period. The safety profile of nevirapine in other respects was similar to nevirapine IR.

Nevirapine XR is non inferior to nevirapine IR with marginal trends in favour of nevirapine XR in relation to efficacy, while the safety profiles of both formulations are similar. The slight overall trend in favour of nevirapine XR is achieved with once daily dosage and reduced drug exposure compared with nevirapine IR. Increased compliance with the once daily XR formulation (assumed but not proven in these studies) is the most likely therapeutic benefit in patients with HIV-1 infection.

The Phase I study in children demonstrated satisfactory PK profiles in children of all ages when dosage was adjusted for body weight. The 100 mg XR tablet was easily swallowed and compliance was satisfactory. However, efficacy, safety and tolerability must be confirmed in a properly designed, long term treatment study in children with HIV-1 infection.

### **Conclusions**

The overall risk balance of nevirapine XR given once daily is positive for use in combination with antiretroviral treatment of HIV-1 infection in adults (but not children). Due to lack of adequate evidence, approval for children cannot be granted at this stage.

The decisive factor is increased compliance (assumed but not proven) with long term antiretroviral therapy. It is recommended that nevirapine XR, in combination with at least two other antiretroviral agents, be approved as an alternative to nevirapine IR for the treatment of HIV-1 infection in adults.

## **V. Pharmacovigilance Findings**

### **Risk Management Plan**

The sponsor submitted a Risk Management Plan (RMP) which was reviewed by the TGA's Office of Product Review (OPR).

### **Safety Specification**

The sponsor stated that there are two important identified risks:

- Skin rash, including severe or life threatening skin reactions such as Stevens-Johnson syndrome and toxic epidermal necrolysis; and
- Severe and life threatening hepatotoxicity including fatal fulminant hepatitis.

The sponsor stated that safety concerns categories of 'Important potential risks' and 'Important missing information' are not applicable.

The OPR reviewer noted that in the clinical evaluation report it is commented that: *However, efficacy, safety and tolerability must be confirmed in a properly designed, long term treatment study in children with HIV-1 infection and Due to lack of adequate evidence, approval for children cannot be granted at this stage.*

Considering these comments, together with the concerns outlined regarding the recommended dosage regimen calculated on the basis of bodyweight and age for children, it was recommended to the sponsor that 'Safety in the paediatric population' be included in the RMP as 'Important Missing Information' for the current formulation.

Pharmacovigilance and risk minimisation activities for this safety concern will therefore also be required.

### **Pharmacovigilance Plan**

The sponsor outlined the pharmacovigilance plan which involved routine pharmacovigilance for the two important identified risks.<sup>6</sup>

The sponsor's proposal for routine pharmacovigilance was considered adequate for these risks. These risks are already well documented with previous pharmacovigilance activities, and the routine processes should continue as outlined with the additional requirement for the sponsor to submit PSUR (Periodic Safety Update Reports) as this is a change of formulation.

In their consideration of skin reactions and hepatotoxicity from clinical trial data, it is noted that 50% more women than men develop these reactions. The increased likelihood of these reactions in women is noted in the PI in the precautions section relating to both rash and hepatic toxicity for the IR only preparation, therefore it is recognised that routine risk minimisation activities are already in place for this safety concern. The sponsor was requested to provide specific reference to adverse events in women in the PSUR.

An updated RMP will be required if the sponsor identifies new or amplified safety concerns with the use of nevirapine in the XR form, or additional pharmacovigilance activities are planned or undertaken.

### **Risk Minimisation Activities**

The sponsor has described skin rash and severe and life threatening hepatotoxicity (including fulminant hepatitis), have been identified as the only important identified risk.

The sponsor states that for both these risks the current knowledge has been adequately taken up for inclusion in the product labelling, in particular the Australian PI.

### **Summary of Recommendations**

It was recommended to the sponsor that 'Safety in the paediatric population' be included in the RMP as 'Important Missing Information' for the current formulation.

Pharmacovigilance and risk minimisation activities for this safety concern will therefore also be required.

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<sup>6</sup> Routine pharmacovigilance practices involve the following activities:

- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labeling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

The OPR reviewer also made some recommendation with respect to the PI but these are beyond the scope of this AusPAR.

Additional safety concerns regarding drug-drug interactions, development of drug resistance, use of this product in patients with renal failure and hepatic impairment, and the additional risk of adverse events when nevirapine is prescribed to women, are already addressed by the sponsor both in terms of routine pharmacovigilance and risk minimisation. No modification of this document is required around these considerations; however the sponsor is requested to provide specific reference to these additional Ongoing Safety Concerns in the PSURs. It is suggested that these safety concerns should be considered for inclusion in any RMP update. Furthermore, an updated RMP will be required if the sponsor identifies new or amplified safety concerns with the use of nevirapine in the XR form, or additional pharmacovigilance or risk minimisation activities are planned or undertaken for the above safety concerns.

## **VI. Overall Conclusion and Risk/Benefit Assessment**

The submission was summarised in the following Delegate's overview and recommendations:

### **Quality**

The evaluator concluded that approval was recommended from quality and biopharmaceutic perspectives, subject to the sponsor providing an assurance that the TGA will be notified immediately in the event of any unexpected trends or batch failures becoming apparent during ongoing or future long term stability trials of the extended release tablets.

### **Nonclinical**

There was no requirement for a nonclinical evaluation in a submission of this type.

### **Clinical**

#### **Pharmacokinetics**

Six pharmacokinetic studies (Studies 1100.1484, 1100.1485, 1100.1489, 1100.1517, 1100.1518, 1100.1531) were submitted to support this application. These studies evaluated the PK profiles, including bioavailability/bioequivalence, of various formulations and different doses of nevirapine XR in healthy volunteers (single dose studies) and in HIV patients (multiple dose studies). Only two were multidose studies, one (Study 1100.1518) in paediatric HIV patients and one in adult HIV patients. The other four studies were single dose studies in healthy adults.

Study 1100.1484 found that the absorption of nevirapine XR occurred from all sites in the GI tract. Study 1100.1485 assessed the bioavailabilities of 10 XR formulations when administered as a single dose of either 300 mg or 400 mg with varying concentrations of hypromellose. The relative bioavailabilities of the different XR formulations (based on  $AUC_{0-\infty}$ ,  $C_{max}$  and  $C_{24}$ ) were similar and all were lower compared to nevirapine IR. All XR formulations had a median  $T_{max}$  of about 24 h compared with 2-3 h for the IR formulation.

Study 1100.1489 evaluated the bioavailabilities of two of the hypromellose XR formulations, nevirapine XR KCR 25% and nevirapine XR KCR 20%. This was a multidose study in adult HIV patients. The relative bioavailability and rate of absorption were found to be lower with the XR formulations compared with IR formulation, and was somewhat higher with the KCR 25% formulation. The KCR 25% XR formulation was selected as the final formulation for a full development.

Study 1100.1489 also showed that the peak/trough variation in plasma levels is less with the XR formulation compared with IR formulation. There is no evidence of dose dumping. Food increases nevirapine XR absorption by up to 20% with no increase in peak/trough variability and no dose dumping. No food restrictions are considered as warranted. The steady state geometric mean (gMean) of trough levels with the XR formulation was 2770 ng/mL when patients were fasted and was 3030 ng/mL when food were allowed. These trough levels were all in the range expected to provide sustained virologic suppression. The metabolism of nevirapine XR is independent of the formulation.

The 50 mg and 100 mg nevirapine XR tablets are manufactured using the same technology as that for the final 400 mg XR formulation. This final formulation was used in the studies testing the bioequivalence between 50 mg, 100 mg and 400 mg XR tablets. This final formulation is the formulation used in the Phase III studies and the formulation proposed for marketing.

Bioequivalence between the 100 mg XR and the 400 mg XR tablet was established in a single dose parallel group study in healthy adults (Study 1100.1517). In another single dose parallel group study in healthy adults (Study 1100.1531), the exposure with 4 x 50 mg XR tablets (200 mg) was found to be 11% higher than that with 2 x 100 mg XR tablets (200 mg). The 50 mg XR tablet does not appear to be equivalent to the 100 mg XR tablet in Study 1100.1531; this may be attributable to the small sample size.

### ***Paediatrics PK study***

Study 1100.1518 evaluated the steady state PK profile of nevirapine XR in HIV-1 infected subjects aged  $\geq 3$  to  $<18$  years. The primary endpoint was the morning trough (pre dose  $C_{pre,ss}$ ) nevirapine concentration measured during the main PK part of the study.

The PK analysis shows that the adjusted geometric mean  $C_{pre,ss}$  values for the XR and IR formulations, obtained from all available patients, were 4149 ng/mL and 4518 ng/mL, respectively. The adjusted geometric mean XR/IR ratios for daily dose normalised (primary endpoint) and non normalised  $C_{pre,ss}$  from all available patients were 91.2% and 91.8%, respectively, with 90% CI for the 200 mg, 300 mg and 400 mg dose groups all within the 80-125% range. The adjusted geometric mean XR/IR ratios for non normalised  $C_{min,ss}$  and  $AUC_{r,ss}$  of nevirapine were 91.8% and 90.3%, respectively, with both of their 90% CI within the 80-125% range. As expected,  $C_{max,ss}$  of nevirapine XR was lower than for nevirapine IR with an adjusted geometric mean XR/IR ratio of 86% for both daily dose normalised and non normalised values with the 90% CI below the 80% limit. The nevirapine XR to IR geometric mean ratios for daily dose normalised and non normalised  $C_{pre,ss}$  were similar in each age group.

Overall, once daily of nevirapine XR resulted in adequate trough concentrations irrespective of whether it was given as two or three of the 100 mg tablets or as a single 400 mg tablet. The 50 mg XR tablet was not evaluated in this study.

### **Pharmacodynamics**

The relationship between drug concentration and antiviral effect measured by sustained virological response (SVR) were assessed in the pivotal, supportive and some PK studies. No effect of trough levels on SVR was observed when the gMean of nevirapine trough levels was calculated. In the pivotal study (Study 1100.1486), the gMean trough level was above 3.3  $\mu\text{g/mL}$  and was stable throughout the 48 week for both XR and IR formulations. Virologic response was sustained above the target concentration of 3  $\mu\text{g/mL}$ , even though treatment with nevirapine XR was associated with lower drug exposure compared to IR formulation. For nevirapine XR, the tenth centile trough levels were all above 1.8  $\mu\text{g/mL}$ , a concentration at least 13 fold higher than the  $IC_{90}$  for wild type virus. Moreover, there was

no relationship between virologic suppression and exposure as long as trough concentrations were above 1 µg/mL. In the studies submitted, resistance testing was performed in 86 patients and the observed mutations were those to be expected with nevirapine therapy. No difference in resistance between nevirapine IR and nevirapine XR was observed.

## **Clinical efficacy**

### ***Pivotal study (Study 1100.1486)***

One pivotal Phase III study, Study 1100.1486, was submitted. This was a large, double dummy, double blind, parallel group, randomised study conducted in treatment naive adult patients infected with HIV-1. It was a non inferiority study comparing the efficacy/safety of nevirapine XR 400 mg QD with nevirapine IR 200 mg BID, both on a fixed background ARV regimen (tenofovir + emtricitabine). The primary endpoint was SVR by Week 48, defined as viral load (VL) <50 copies/mL prior to Week 48 and without subsequent virologic rebound, or change of ARV therapy prior to Week 48. Other endpoints included time to loss of virologic response; time to AIDS related disease progression; changes from baseline in viral load and CD4+ count; and genotypic resistance associated with virologic failure.

The 48 weeks efficacy analysis was conducted in all patients who were randomised and received at least one dose of blinded medicinal product. The efficacy analysis showed that at 48 weeks, there was difference in SVR of 4.9% (95% CI: -0.1% to 10%) in favour of nevirapine XR. Since the pre specified non inferiority margin was -10%, the lower bound of -0.1% confirmed the non inferiority of nevirapine XR to nevirapine IR ( $p < 0.001$ ). The SVR was 75.9% for nevirapine IR and 81% for nevirapine XR. Virologic failure occurred more frequently in the nevirapine IR group compared with the nevirapine XR group (5.9% versus 3.2%, respectively). Secondary endpoints were similar with non inferiority between the treatment groups or trends in favour of nevirapine XR. At Week 48, mean change from baseline in CD4+ cell count was 184 cells/mm<sup>3</sup> and 197 cells/mm<sup>3</sup> for the groups receiving nevirapine IR and nevirapine XR respectively. Age, gender, ethnicity and region had no influence on virologic response rates.

### ***Supportive study (Study 1100.1526)***

Study 1100.1526 was an open label randomised parallel group Phase III study. The study assessed the efficacy and safety of nevirapine XR in patients who transitioned from nevirapine IR 200 mg BID to nevirapine XR 400 mg QD. The open label design was to mimic the clinical situation when a single daily dose of nevirapine XR would be used. The primary endpoint was SVR <50 copies/mL at 24 weeks. Secondary endpoints included time to loss of virologic response; change in CD4+ cell count from baseline at each visit; and genotypic resistance associated with virologic failure.

The study was conducted in treatment experienced adult HIV patients, at least half of whom had received nevirapine IR for at least three years before the start of the study. The study subjects were randomised in a 2:1 ratio to nevirapine XR or nevirapine IR. The primary efficacy analysis was the test of non inferiority of the nevirapine XR compared to nevirapine IR with a margin of -12%, which was changed before database lock to a more stringent -10%. A total of 445 patients were randomised to either continue on nevirapine 200 mg BID or to switch to nevirapine 400 mg QD, and 148 patients in the nevirapine IR group and 295 patients in the nevirapine XR group completed Week 24.

At 24 weeks after randomisation, a SVR was achieved in 93.6% of patients who received nevirapine XR and 92.6% of patients who received nevirapine IR, a 1% difference in favour of nevirapine XR (95% CI, -4.3% to 6.2%). The lower bound of the difference was



greater than -12% (and the more stringent -10%) confirming the non inferiority of nevirapine XR compared with nevirapine IR. Virologic failures were 5.4% in the nevirapine IR group and 4.1% in the nevirapine XR group. The primary endpoint was not influenced by age, gender or race. Secondary endpoints showed little or no differences between nevirapine IR and XR groups.

### ***Clinical safety***

The AE profile of nevirapine XR observed in the pivotal and supportive adult Phase III studies was similar to the AE profile of nevirapine IR with no new or unexpected findings. Skin rash and hepatitis were the most common reasons for discontinuation of study treatment. The AEs in the pivotal study were somewhat less common in the nevirapine XR group compared with the IR group, and this finding is compatible with the reduced nevirapine exposure seen with the XR formulation. In the supportive adult Phase III study, significantly more AEs and SAEs were observed with the XR formulation although the frequency of moderate to severe AEs was similar in both groups. This disparity is of concern, but patient and investigator bias introduced by the open label study is considered as the most plausible explanation. Most study drug discontinuations due to AEs occurred with nevirapine IR in the run in period of the double blind study. Most were related to rash and hepatitis which are known to be associated with nevirapine treatment. However, discontinuation rates were similar in the randomised period of the double blind study and unlikely to have biased the study results and conclusions.

In the adult Phase III studies, AEs were reported in more women than men and in slightly more Blacks than Whites. In the nevirapine IR group, hepatitis occurred more frequently in women than in men. However, there were no significant gender differences in the incidence of hepatitis in the nevirapine XR group.

In the Phase I paediatric PK study (1100.1518), 85 patients entered into the ten days nevirapine IR run in period and 83 patients entered into the ten days nevirapine XR treatment period (two were excluded for poor compliance). Twenty-four (28.2%) patients had at least one AE during the nevirapine IR run in period: the majority was mild, only two were moderate with no significant differences between age groups. Thirty-nine patients (47%) experienced at least one AE during the nevirapine XR treatment period, and of these patients, 30 (36.1%) experienced DAIDS Severity Grade 1 events; 8 (9.6%) experienced DAIDS Severity Grade 2 events; and one patient experienced a DAIDS Severity Grade 3 event. There were no Severity Grade 4 events, no SAE or AE leading to study drug discontinuation in XR treatment period. Children were able to swallow the XR formulation easily.

### **Risk Management Plan**

The submitted RMP was reviewed by the Office of Product Review (OPR). The OPR evaluator agreed that the important identified risks include severe skin reactions and severe hepatotoxicity. The sponsor's proposal for routine pharmacovigilance was considered adequate for these identified risks. The routine pharmacovigilance processes should continue with the additional requirement for the sponsor to submit PSURs as Nevirapine XR is a new dosage form.

### **Risk-Benefit Analysis**

#### **Delegate Considerations**

Nevirapine XR 400 mg QD achieved steady state trough levels of approximately 3 µg/mL in a PK study, and slightly higher mean trough concentrations were observed in the two Phase III studies (3.3 µg/mL in Study 1100.1486 and 3.4 µg/mL in Study 1100.1526). The non inferiority of nevirapine XR compared with nevirapine IR in terms of sustained



virologic response was confirmed in two Phase III studies in adult patients with HIV-1 infection. There were also minor but consistent trends in favour of nevirapine XR for most secondary efficacy endpoints. The results were similar in treatment naive and treatment experienced patients and they were not influenced by age, gender or race. The safety profile of nevirapine XR appeared to be comparable with nevirapine IR.

In the paediatric PK study (Study 1100.1518), when the doses were adjusted for BSA, the drug exposure to nevirapine XR over ten days in these children was similar to that observed in the adult patients with mean trough nevirapine levels above 3 µg/mL. The AE pattern was similar between XR and IR treatment with more frequent AE in the nevirapine XR group (47%) compared with the nevirapine IR group (28.2%). However, this study had a small subject number and short study duration, and AE numbers in the XR group were driven by an excess of infections considered unrelated to the study drug.

The clinical evaluator recommended approval of nevirapine XR tablets for the adult HIV indication. With regards to the paediatric indication, the clinical evaluator considered that the efficacy and safety of the XR tablets have not been assessed in a properly designed long term study in HIV infected children; therefore, approval should not be granted for paediatric indication. The clinical evaluator also questioned the necessity of 50 mg XR tablets.

The sponsor argued that the paediatric development strategy is consistent with the TGA adopted program. The sponsor's paediatric program was developed under the assumption that safety and efficacy in children could reasonably be derived from adult studies given comparable PK exposure in adults and children. The comparable PK exposure in adults and children was shown to be true based on the results from the pivotal study (1100.1486), supportive study (1100.1526), and paediatric PK study (1100.1518) (Table 7). The mean trough concentration in children treated with nevirapine XR (Study 1100.1518) is similar to the efficacious and safe exposure levels demonstrated in adult patients who were treated with nevirapine XR (Study 1100.1486) and in adult patients who were switching to nevirapine XR from a nevirapine IR (Study 1100.1526). Given the comparable plasma levels, nevirapine XR is expected to exert the same efficacy in children as in adults because virus susceptibility to the drug does not differ in these two patient populations.

**Table 7: Nevirapine exposure in Studies 1100.1518, 1100.1486 and 1100.1526.**

	<b>1100.1518</b>	<b>1100.1486</b>	<b>1100.1526</b>
	N = 78	N = 448	N = 264
<b>g Mean Trough</b>	4,160 ng/mL	3.354 ng/mL	3.492 ng/mL

With regards to the 50 mg XR tablets, the sponsor explained that the company initially developed a 100 mg XR tablet for use in children three years and older. During discussions with the European Health Authorities regarding the Paediatric Investigational Plan for the XR tablets, the Paediatric Committee emphasised the medical need for a 50 mg XR tablet that could be used as an alternative in children who are unable to swallow the slightly larger 100 mg XR tablet.

The 50 mg XR tablets were therefore developed at a later stage and thus were not available for assessment when Study 1100.1518 commenced. The sponsor noted that children in Study 1100.1518 experienced minimal difficulty swallowing the 100 mg XR tablets and as such, the 100 mg XR tablets should be considered the primary paediatric strength, with the 50 mg XR tablets providing a slightly smaller alternative for children experiencing difficulties swallowing the 100 mg XR tablets.

The Delegate accepted the sponsor's arguments that the paediatric development approach is consistent with the EMEA guideline. The Delegate was of the view that a close safety monitoring in paediatric patients is required if Nevirapine XR is to be registered for use in paediatric HIV patients because:

- (1) Nevirapine XR is a new dosage form (extended release);
- (2) efficacy and safety of this dosage form in paediatric subjects have not been assessed in a longer term clinical study; and
- (3) higher rates of non SAE with Nevirapine XR (47%) than with Nevirapine IR (28.2%) were observed in Phase I paediatric PK study (Study 1100.1518).

The Delegate noted that as a postmarketing commitment to the FDA, the sponsor agreed to conduct a multiple dose pharmacokinetic and safety study of nevirapine extended release tablets, in combination with other antiretroviral agents, in HIV infected paediatric 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. The sponsor should also submit this study to the TGA once the study report become available.

The Delegate considered that the availability of 50 mg XR tablets would benefit a small number of children who may experience difficulties swallowing the 100 mg XR tablets.

ACPM advice was requested, specifically with the following two issues:

1. The approval of nevirapine XR for the treatment of HIV infection in paediatric patients over 3 years old based on the comparable drug exposure between the paediatric and adult HIV patients
2. The registration of the 50 mg XR tablet as an alternative for children experiencing difficulties swallowing the 100 mg XR tablets

Based on the above discussions, and pending advice from the ACPM, the Delegate was of the view that nevirapine XR, in combination with other antiretroviral agents, may be approved as an alternative to nevirapine IR for the treatment of HIV-1 infection in adults and children over the age of three years. The indications for Nevirapine XR tablets (400 mg, 100 mg, and 50 mg) should be as follows:

*Viramune XR in combination with antiretroviral agents is indicated for the treatment of HIV-1 infection in adults and children over the age of three years.*

The recommended dose for adults is 400 mg once daily. The recommended doses for children are 200 mg, 300 mg or 400 mg once daily depending on their body weight or body surface area. Conditions of registration should include:

- Submission of the study report of the 24 weeks paediatric PK/safety study
- Submission of any safety studies/information relating to nevirapine XR
- Implementation of the RMP with an emphasis on the postmarketing safety monitoring of Nevirapine XR in paediatric patients

### **Response from Sponsor**

The sponsor was in agreement with the Delegate's proposed action to register Viramune XR nevirapine extended release tablets as an alternative to Viramune nevirapine immediate release tablets and oral suspension for the treatment of HIV-1 infections in adults and children over the age of three years. The indication for Viramune XR tablets (400 mg, 100 mg and 50 mg) should be as follows:

*Viramune XR (nevirapine) extended-release tablets in combination with antiretroviral agents is indicated for the treatment of HIV-1 infection in adults and children over the age of three years.*

The sponsor also agreed with the Delegate's recommended dose for adults, that is, 400 mg once daily, and for children, that is, 200 mg, 300 mg or 400 mg once daily, depending on their body weight or body surface area.

### **Advisory Committee Considerations**

The Advisory Committee on Prescription Medicines (ACPM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

#### ***Efficacy***

The ACPM agreed with the Delegate that the submission demonstrates clinically relevant efficacy. Use in children is supported based on long term experience with the IR formulation of this product in children and the limited findings of Study 1100.1518. The ACPM advised that more paediatric data is needed.

#### ***Safety***

The ACPM agreed with the Delegate that there were no new safety signals identified in the studies; however, while the committee was doubtful of the proportion of three year olds capable of swallowing a tablet, it was supportive of the smaller, 50 mg XR tablet being available. More data are required for confirmation of its utility and especially of safety.

#### ***Indication***

The ACPM considered this product to have a positive benefit risk profile for the indication of:

*Viramune XR in combination with other antiretroviral agents is indicated for the treatment of HIV-1 infection in adults and children over the age of three years.*

*Extended-release tablets are not suitable for the 14 days lead-in phase for patients starting nevirapine. Other nevirapine formulations, such as immediate-release tablets or oral suspension should be used.*

The ACPM also made a recommendation concerning the PI and the Consumer Medicines Information (CMI) but this is beyond the scope of this AusPAR.

#### ***Conditions of Registration***

The ACPM agreed with the conditions proposed by the Delegate.

The ACPM further advised that the implementation by the sponsor of the recommendations to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided for Viramune XR 50 mg, 100 mg and 400 mg tablets would support the safe and effective use of this product.

#### **Outcome**

Based on a review of quality, safety and efficacy, TGA approved the registration of Viramune XR containing nevirapine 400 mg, 100 mg and 50 mg extended release tablets and approve the amendments to the product information for Viramune containing nevirapine 200 mg tablets and 10 mg/mL oral liquid.

The full indications are now:

*Viramune (nevirapine) immediate-release tablets and oral suspension in combination with antiretroviral agents is indicated for the treatment of HIV-1 infection in adults and children over the age of 2 months.*

*Viramune XR (nevirapine) extended-release tablets in combination with antiretroviral agents is indicated for the treatment of HIV-1 infection in adults and children over the age of three years.*

*Extended-release tablets are not suitable for the 14 day lead-in period for patients starting nevirapine. Other nevirapine formulations, such as immediate-release tablets or oral suspension should be used.*

*Resistant virus emerges rapidly when Viramune is administered as monotherapy or in dual combination therapy with an antiretroviral agent. Therefore, Viramune should always be administered in combination with at least two additional antiretroviral agents.*

## **Attachment 1. Product Information**

The following Product Information was approved at the time this AusPAR was published. For the current Product Information please refer to the TGA website at [www.tga.gov.au](http://www.tga.gov.au).

## **Therapeutic Goods Administration**

PO Box 100 Woden ACT 2606 Australia

Email: [info@tga.gov.au](mailto:info@tga.gov.au) Phone: 1800 020 653 Fax: 02 6232 8605

**[www.tga.gov.au](http://www.tga.gov.au)**

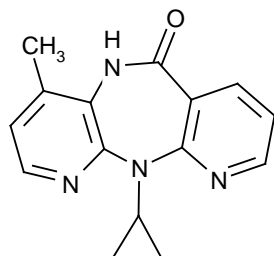
Reference/Publication #

**VIRAMUNE® Tablets**  
**VIRAMUNE® XR Extended-Release Tablets**  
**VIRAMUNE® Oral Suspension**  
**(Nevirapine)**

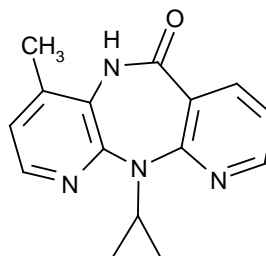
**NAME OF THE DRUG**

Viramune contains the active ingredient nevirapine. In the solid state, nevirapine can exist in either an anhydrous form (the actual active moiety, used for production of Viramune tablets), or a hemihydrate pseudopolymorph (used in Viramune oral suspension).

Nevirapine has the following structural formula:



*Nevirapine*



.½H<sub>2</sub>O

*Nevirapine hemihydrate*

**DESCRIPTION**

Nevirapine is a non-nucleoside reverse transcriptase inhibitor with activity against Human Immunodeficiency Virus Type 1 (HIV-1).

The chemical name of nevirapine is 11-cyclopropyl-5,11-dihydro-4-methyl-6H-dipyrido[3,2-b:2',3'-e][1,4]diazepin-6-one. Nevirapine is a white to off-white crystalline powder with the molecular weight of 266.3 and the molecular formula C<sub>15</sub>H<sub>14</sub>N<sub>4</sub>O. The Chemical Abstracts Service Registration number is 129618-40-2.

The chemical name of nevirapine hemihydrate is 11-cyclopropyl-5,11-dihydro-4-methyl-6H-dipyrido[3,2-b:2',3'-e][1,4]diazepin-6-one hemihydrate. Nevirapine hemihydrate is a white to off-white crystalline powder with a molecular weight of 275.3 and molecular formula of C<sub>15</sub>H<sub>14</sub>N<sub>4</sub>O.½H<sub>2</sub>O.

Viramune is available as immediate-release Viramune tablets, extended-release Viramune XR tablets or as a suspension for oral administration.

Each Viramune immediate-release tablet contains 200 mg of nevirapine and the inactive ingredients microcrystalline cellulose, lactose, povidone, sodium starch glycolate, colloidal anhydrous silica and magnesium stearate.

Each Viramune XR extended-release tablet contains either 400 mg, 100 mg or 50 mg of nevirapine and the inactive ingredients lactose, hypromellose, iron oxide yellow CI77492 and magnesium stearate.

Each 5 mL of the oral suspension contains 50 mg of nevirapine (as nevirapine hemihydrate) and the inactive ingredients carbomer 934P, methyl hydroxybenzoate, propyl hydroxybenzoate, polysorbate 80, sucrose, sorbitol solution (70%) (non-crystallising), sodium hydroxide and purified water.



### Mechanism of Action

Nevirapine is a non-nucleoside reverse transcriptase inhibitor (NNRTI) of HIV-1. Nevirapine binds directly to reverse transcriptase (RT) and blocks the RNA-dependent and DNA-dependent DNA polymerase activities by causing a disruption of the enzyme's catalytic site. The activity of nevirapine does not compete with template or nucleoside triphosphates. HIV-2 RT and eukaryotic DNA polymerases (such as human DNA polymerases  $\alpha$ ,  $\beta$ ,  $\gamma$ , or  $\delta$ ) are not inhibited by nevirapine.

In clinical studies, Viramune has been associated with an increase in HDL-cholesterol and an overall improvement in the total to HDL-cholesterol ratio. However, in the absence of specific studies with Viramune on modifying the cardiovascular risk in HIV infected patients, the clinical impact of these findings is not known. The selection of antiretroviral drugs must be guided primarily by their antiviral efficacy.

### Microbiology

#### *In Vitro* HIV Susceptibility

The *in vitro* antiviral activity of nevirapine has been measured in a variety of cell lines including peripheral blood mononuclear cells, monocyte derived macrophages, and lymphoblastoid cell lines. Nevirapine exhibited antiviral activity *in vitro* against group M HIV-1 isolates from clades A, B, C, D, F, G, and H, and circulating recombinant forms (CRF), CRF01\_AE, CRF02\_AG and CRF12\_BF in assays with human embryonic kidney 293 cells (median IC<sub>50</sub> value of 63 nM; range, 14-302 nM). Nevirapine had no significant antiviral activity *in vitro* against isolates from group O HIV-1 and no activity against HIV-2.

Nevirapine in combination with efavirenz exhibited a strong antagonistic anti-HIV-1 activity *in vitro* and was additive to antagonistic with the protease inhibitor ritonavir or the fusion inhibitor enfuvirtide in C8166 cells. Nevirapine exhibited predominantly additive anti-HIV-1 activity in combination with the protease inhibitors amprenavir, atazanavir, indinavir, lopinavir, nelfinavir, saquinavir and tipranavir, and additive to synergistic anti-HIV-1 activity with the NRTIs abacavir, didanosine, emtricitabine, lamivudine, stavudine, tenofovir and zidovudine. The anti-HIV-1 activity of nevirapine was antagonised by the anti-HBV drug adefovir and by the anti-HCV drug ribavirin *in vitro*.

### Resistance

HIV isolates with reduced susceptibility (100-250-fold) to nevirapine emerge *in vitro*. Genotypic analysis showed mutations in the HIV RT gene at amino acid positions 181 and/or 106 depending upon the virus strain and cell line employed. Time to emergence of nevirapine resistance *in vitro* was not altered when selection included nevirapine in combination with several other NNRTIs.

Phenotypic and genotypic changes in HIV-1 isolates from patients treated with either Viramune immediate-release (n=24) or Viramune immediate-release+AZT (n=14) were monitored in Phase I/II trials over 1 to  $\geq 12$  weeks. After 1 week of Viramune monotherapy, isolates from 3/3 patients had decreased susceptibility to nevirapine *in vitro*; one or more of the RT mutations at amino acid positions 103, 106, 108, 181, 188 and 190 were detected in some patients as early as 2 weeks after therapy initiation. By week eight of Viramune monotherapy, 100% of the patients tested (n=24) had HIV isolates with a  $>100$ -fold decrease in susceptibility to nevirapine *in vitro* compared to baseline, and had one or more of the nevirapine-associated RT resistance mutations; 19 of 24 patients (80%) had isolates with a position 181 mutation regardless of dose. Viramune+AZT combination therapy did not alter the emergence rate of nevirapine-resistant virus or the magnitude of nevirapine resistance *in vitro*; however, a different RT mutation pattern, predominantly distributed amongst amino acid positions 103, 106, 188, and 190, was observed. In patients (6 of 14) whose baseline isolates possessed a wild type RT gene, Viramune+AZT combination therapy

did not appear to delay emergence of AZT-resistant RT mutations. The development of genotypic and phenotypic resistance to Viramune / ddI / AZT as a function of virologic response to therapy in a group of drug-naïve individuals receiving various combinations of these agents was examined in a double blind controlled randomised trial (INCAS study). In this study, antiretroviral naïve subjects with CD4 cells counts of 200-600/mm<sup>3</sup> were treated with either Viramune + AZT (N=46), AZT + ddI (N=51) or Viramune + AZT + ddI (N=51) and followed for 52 weeks or longer on therapy. Virologic evaluations were performed at baseline, six months and 12 months. The phenotypic resistance test performed required a minimum of 1000 copies/mL HIV RNA in order to be able to amplify the virus. Of the three study groups, 16, 19 and 28 patients respectively had evaluable baseline isolates and subsequently remained in the study for at least 24 weeks. At baseline, there were five cases of phenotypic resistance to nevirapine; the IC<sub>50</sub> values were 5 to 6.5-fold increased in three and >100 fold in two. At 24 weeks, all available isolates recoverable from patients receiving Viramune were resistant to this agent, while 18/21 (86%) patients carried such isolates at 30-60 weeks. In 16 subjects viral suppression was below the limits of detection (<20 copies/mL = 14, <400 copies/mL = 2). Assuming that suppression below <20 copies/mL implies Viramune susceptibility of the virus, 45% (17/38) of patients had virus measured or imputed to be susceptible to Viramune. All 11 subjects receiving Viramune + AZT who were tested for phenotypic resistance were resistant to Viramune by six months. Over the entire period of observation, one case of ddI (5%) resistance was seen. AZT (19%) resistance emerged as more frequent after 30-60 weeks, especially in patients receiving double combination therapy. Based on the increase in IC<sub>50</sub>, AZT resistance appeared lower in the Viramune + AZT + ddI group than the other treatment groups.

With respect to Viramune resistance, all isolates that were sequenced carried at least one mutation associated with resistance, the most common single changes being K103N and Y181C. In summary, the use of highly active drug therapies is associated with a delay in the development of antiretroviral drug resistance. The genotypic correlates of phenotypic Viramune resistance were identified in 12 plasma isolates from 11 triple therapy patients. Treatment-emergent, Viramune resistance-associated mutations were:

Mutation	Frequency
K101E	2
K103N	8
V106A	2
Y181C	5
G190A	6

Combinations of mutations were observed in nine of the 12 patients. These data from INCAS illustrate that the use of highly active drug therapies is associated with a delay in the development of antiretroviral drug resistance.

Genotypic analysis was performed on isolates from 86 antiretroviral naïve patients who discontinued the VERxVE study (1100.1486) after experiencing virologic failure (rebound, partial response) or due to an adverse event or who had transient increase in viral load during the course of the study. The analysis of these samples of patients receiving Viramune immediate-release twice daily or Viramune XR extended-release once daily in combination with tenofovir and emtricitabine showed that isolates from 50 patients contained resistance mutations expected with a nevirapine-based regimen. Of these 50 patients, 28 developed resistance to efavirenz and 39 developed resistance to etravirine (the most frequently emergent resistance mutation being Y181C). There were no differences based on the formulation taken (immediate-release twice daily or extended-release once daily).

The observed mutations at failure were those expected with a nevirapine-based regimen. Two new substitutions on codons previously associated with nevirapine resistance were observed: one patient with Y181I in the Viramune XR extended-release group and one patient with Y188N in the Viramune immediate-release group; resistance to nevirapine was confirmed by phenotype.

The clinical relevance of phenotypic and genotypic changes associated with Viramune therapy has not been established.

## **Cross-Resistance**

Rapid emergence of HIV strains which are cross-resistant to NNRTIs has been observed *in vitro*. Data on cross-resistance between the NNRTI nevirapine and nucleoside analogue RT inhibitors are very limited. In four patients, AZT-resistant isolates tested *in vitro* retained susceptibility to nevirapine and in six patients, nevirapine-resistant isolates were susceptible to AZT and ddI. Cross-resistance between nevirapine and HIV protease inhibitors is unlikely because the enzyme targets involved are different.

Cross-resistance to delavirdine and efavirenz is expected after virologic failure with nevirapine. Depending on resistance testing results, an efavirenz-containing regimen may be used subsequently.

Nevirapine must not be used as a single agent to treat HIV or added on as a sole agent to a failing regimen. As with all other non-nucleoside reverse transcriptase inhibitors, resistant virus emerges rapidly when nevirapine is administered as monotherapy. The choice of new antiretroviral agents to be used in combination with nevirapine should take into consideration the potential for cross resistance.

When discontinuing an antiretroviral regimen containing nevirapine, the long half-life of nevirapine should be taken into account; if antiretrovirals with shorter half-lives than nevirapine are stopped concurrently, low plasma concentrations of nevirapine alone may persist for a week or longer and virus resistance may subsequently develop.

## **Pharmacokinetics**

### **Pharmacokinetics in Adult Patients (immediate-release tablets)**

#### **Absorption and Bioavailability**

Nevirapine is readily absorbed (>90%) after oral administration in healthy volunteers and in adults with HIV-1 infection. Absolute bioavailability in 12 healthy adults following single-dose administration was  $93 \pm 9\%$  (mean $\pm$ SD) for a 50 mg tablet and  $91 \pm 8\%$  for an oral solution. Peak plasma nevirapine concentrations of  $2 \pm 0.4$  microgram/mL ( $7.5 \mu\text{M}$ ) were attained by 4 hours following a single 200 mg dose. Following multiple doses, nevirapine peak concentrations appear to increase linearly in the dose range of 200 to 400 mg/day. Steady state trough nevirapine concentrations of  $4.5 \pm 1.9$  microgram/mL ( $17 \pm 7 \mu\text{M}$ ), (n=242) were attained at 400 mg/day.

The absorption of nevirapine is not affected by food, antacids or medicinal products that are formulated with an alkaline buffering agent (e.g. didanosine).

#### **Distribution**

Nevirapine is highly lipophilic and is essentially nonionised at physiologic pH. Following intravenous administration in healthy adults, the apparent volume of distribution ( $V_{\text{dss}}$ ) of nevirapine was  $1.21 \pm 0.09$  L/kg, suggesting that nevirapine is widely distributed in humans. Nevirapine readily crosses the placenta and is found in breast milk (see Use in Pregnancy under PRECAUTIONS). Nevirapine is about 60% bound to plasma proteins in the plasma concentration range of 1-10 microgram/mL. Nevirapine concentrations in human cerebrospinal fluid (n=6) were 45% ( $\pm 5\%$ ) of the concentrations in plasma; this ratio is approximately equal to the fraction not bound to plasma protein.

## **Metabolism/Elimination**

*In vivo* studies in humans and *in vitro* studies with human liver microsomes have shown that nevirapine is extensively biotransformed via cytochrome P450 (oxidative) metabolism to several hydroxylated metabolites. *In vitro* studies with human liver microsomes suggest that oxidative metabolism of nevirapine is mediated primarily by cytochrome P450 isoenzymes from the CYP3A family, although other isoenzymes may have a secondary role. In a mass balance/excretion study in eight healthy male volunteers dosed to steady state with nevirapine 200 mg twice daily followed by a single 50 mg dose of  $^{14}\text{C}$ -nevirapine, approximately  $91.4\% \pm 10.5\%$  of the radiolabelled dose was recovered, with urine ( $81.3\% \pm 11.1\%$ ) representing the primary route of excretion compared to faeces ( $10.1\% \pm 1.5\%$ ). Greater than 80% of the radioactivity in urine was made up of glucuronide conjugates of hydroxylated metabolites. Thus cytochrome P450 metabolism, glucuronide conjugation, and urinary excretion of glucuronidated metabolites represent the primary route of nevirapine biotransformation and elimination in humans. Only a small fraction ( $<5\%$ ) of the radioactivity in urine (representing  $<3\%$  of the total dose) was made up of parent compound; therefore, renal excretion of nevirapine plays a minor role in elimination of the parent compound.

Nevirapine has been shown to be an inducer of hepatic cytochrome P450 metabolic enzymes. The pharmacokinetics of autoinduction are characterised by an approximately 1.5 to 2 fold increase in the apparent oral clearance of nevirapine as treatment continues from a single dose to two-to-four weeks of dosing with 200-400 mg/day. Autoinduction also results in a corresponding decrease in the terminal phase half-life of nevirapine in plasma from approximately 45 hours (single dose) to approximately 25-30 hours following multiple dosing with 200-400 mg/day.

## **Adults**

Nevirapine pharmacokinetics in HIV-1 infected adults do not appear to change with age (range 19-68 years).

### **Pharmacokinetics in Adult Patients (extended-release tablets)**

The pharmacokinetics of nevirapine have been studied in a single dose study (Trial 1100.1485) of Viramune XR extended-release in 17 healthy volunteers. The relative bioavailability of nevirapine when dosed as one 400 mg Viramune XR extended-release tablet, relative to two 200 mg Viramune immediate-release tablets, was approximately 75%. The mean peak plasma concentration of nevirapine was 2060 ng/mL measured at a mean 24.5 hours after administration of 400 mg Viramune XR extended-release.

The pharmacokinetics of Viramune XR extended-release have also been studied in a multiple dose pharmacokinetics study (Trial 1100.1489) in 24 HIV-1 infected patients who switched from chronic Viramune immediate-release therapy to Viramune XR extended-release. The nevirapine  $\text{AUC}_{0-24,\text{ss}}$  and  $\text{C}_{\text{min,ss}}$  measured after 19 days of fasted dosing of Viramune XR extended-release 400 mg once daily were approximately 80% and 90%, respectively, of the  $\text{AUC}_{0-24,\text{ss}}$  and  $\text{C}_{\text{min,ss}}$  measured when patients were dosed with Viramune immediate-release 200 mg twice daily. The geometric mean nevirapine  $\text{C}_{\text{min,ss}}$  was 2770 ng/mL.

When Viramune XR extended-release was dosed with a high fat meal, the nevirapine  $\text{AUC}_{0-24,\text{ss}}$  and  $\text{C}_{\text{min,ss}}$  were approximately 94% and 98%, respectively, of the  $\text{AUC}_{0-24,\text{ss}}$  and  $\text{C}_{\text{min,ss}}$  measured when patients were dosed with Viramune immediate-release tablets. The difference in nevirapine pharmacokinetics observed when Viramune XR extended-release tablets are dosed under fasted or fed conditions is not considered clinically relevant. Viramune XR extended-release tablets can be taken with or without food.

The effects of gender on the pharmacokinetics of Viramune XR extended-release have been investigated in Trial 1100.1486. Female patients tend to have higher (approximately 20-30%) trough concentrations in both Viramune XR extended-release and Viramune immediate-release treatment groups.

Nevirapine pharmacokinetics in HIV-1 infected adults do not appear to change with age (range 18-68 years). Black patients (n=80/group) in Trial 1100.1486 showed approximately 30% higher trough concentrations than Caucasian patients (250-325 patients/group) in both the Viramune immediate-release and Viramune XR extended-release treatment groups over 48 weeks of treatment at 400 mg/day.

Viramune XR extended-release has not been evaluated in subjects with hepatic impairment or renal dysfunction.

Occasionally, the inactive ingredients of Viramune XR extended-release tablets will be eliminated in the faeces as soft, hydrated remnants.

### **Pharmacokinetics in Children (immediate-release tablets and oral suspension)**

The pharmacokinetics of nevirapine in children have been studied in two open-label studies in children with HIV-1 infection. In one study, nine HIV-infected children ranging in age from 9 months to 14 years were administered a single dose (7.5mg, 30mg or 120mg per m<sup>2</sup>; n=3 per dose) of Viramune suspension after an overnight fast. Nevirapine AUC and peak concentration increased in proportion with dose. Following absorption nevirapine mean plasma concentrations declined log linearly with time. Nevirapine terminal phase half-life following a single dose was 30.6±10.2 hours.

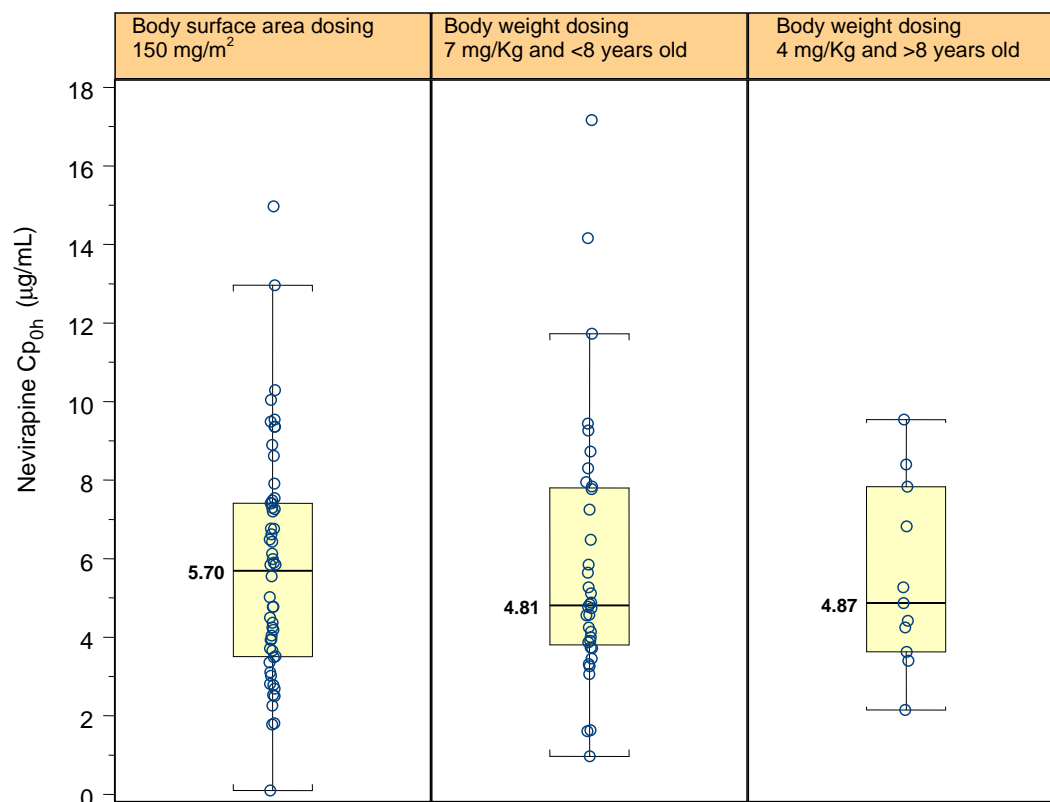
In a second multiple dose study, Viramune suspension or tablets (240 to 400 mg/m<sup>2</sup>/day) were administered as monotherapy or in combination with AZT or AZT and ddI to 37 HIV-1-infected children with the following demographics: male (54%), racial minority groups (73%), median age of 11 months (range: 2 months – 15 years). These patients received 120 mg/m<sup>2</sup>/day of nevirapine for approximately 4 weeks followed by 120 mg/m<sup>2</sup>/twice a day (patients >9 years of age) or 200 mg/m<sup>2</sup>/twice a day (patients ≤9 years of age). Nevirapine clearance adjusted for body weight reached maximum values by age 1 to 2 years and then decreased with increasing age. Nevirapine apparent clearance adjusted for body weight was approximately two-fold greater in children younger than 8 years compared to adults. Nevirapine half-life for the study group as a whole after dosing to steady state was 25.9±9.6 hours. With long term administration, the mean values for nevirapine terminal half-life changed with age as follows: 2 months to 1 year (32 hours), 1 to 4 years (21 hours), 4 to 8 years (18 hours), greater than 8 years (28 hours).

Further data concerning the pharmacokinetics of nevirapine in antiretroviral naïve HIV-1 positive paediatric patients have been derived from a 48 week, open-label, multi-centre trial conducted in South Africa. The aims of the study included evaluation of steady state pharmacokinetic parameters of nevirapine 150 mg/m<sup>2</sup> after 4 weeks treatment.

Patients aged 3 months to 16 years were stratified into the four groups based on age. The first 10 patients in each age group received nevirapine doses based on body surface area (BSA). Subsequently patients were randomised 2:1 to receive nevirapine doses determined by BSA or by weight + age. A total of 123 patients were enrolled, 66 were included in the group receiving the nevirapine dose based on BSA.

A dose regimen of 150 mg/m<sup>2</sup> once daily for two weeks followed by 150 mg/m<sup>2</sup> twice daily for one month resulted in mean trough nevirapine concentration of 5.7 microgram/mL. Dosing regimens based on body weight + age produced steady-state plasma concentrations of 4 - 6 microgram/mL.

Figure 1: Median trough nevirapine concentrations observed using the BSA algorithm (n=56 patients).



Note: The box plot identifies the median (line within the box) and quartiles (top and bottom limit) that correspond to the 25th and 75th percentiles connected to whiskers that are drawn to the nearest value not beyond a standard span (1.5 x interquartile range) from the quartiles; points beyond this value (outliers) are drawn individually.

Pharmacokinetic data on patients in this study demonstrated that clearance of nevirapine increased with increasing age.

Table 1: Evaluation of the part of the BSA dosing group by Age, which underwent more intensive PK investigation

Age range	n	Geometric mean (Mean±SD) AUC (microgram•h/mL)	Geometric mean (Mean±SD) C <sub>max</sub> (microgram/mL)	Geometric mean (Mean±SD) Clearance (L/h/m <sup>2</sup> )
≥ 3 m to < 2 y	8	92.6 (97.3±37.2)	9.06 (9.39±2.96)	1.62 (1.69±0.45)
≥ 2 y to < 7 y	11	84.1 (85.8±18.5)	8.55 (8.78±2.14)	1.78 (1.82±0.38)
≥ 7 y to < 12 y	9	52.7 (62.0±26.6)	5.80 (6.15±2.38)	2.62 (2.79±0.97)
≥ 12 y	5	57.1 (69.1±43.8)	5.89 (6.71±3.67)	2.59 (3.19±2.32)

Compared to adults, individual plasma nevirapine concentrations in the paediatric age range were more variable, particularly for patients less than three months of age.



The results of the 48-week analysis of the South African study confirmed that the the body surface area based (150 mg/m<sup>2</sup>) nevirapine dosing is effective in treating antiretroviral naive paediatric patients.

Dosing of nevirapine at 150 mg/m<sup>2</sup> BID (after a two-week lead in at 150 mg/m<sup>2</sup> QD) produced geometric mean or mean trough nevirapine concentrations between 4-6 microgram/mL (as targeted from adult data).

The consolidated analysis of Paediatric AIDS Clinical Trials Group (PACTG) protocols 245, 356, 366, 377, and 403 allowed for the evaluation of paediatric patients less than 3 months of age (n=17) enrolled in these PACTG studies.

The plasma nevirapine concentrations observed were within the range observed in adults and the remainder of the paediatric population, but were more variable between patients, particularly in the second month of age.

### **Pharmacokinetics in Children (extended-release tablets)**

The pharmacokinetics of Viramune extended-release was assessed in Trial 1100.1518. Eighty-five patients 3 to <18 years received weight or body surface area dose-adjusted Viramune immediate-release for a minimum of 18 weeks and then were switched to Viramune XR extended-release tablets (2 x 100 mg, 3 x 100 mg or 1 x 400 mg once daily) in combination with other antiretrovirals for 10 days. The observed geometric mean ratios of Viramune XR extended-release to Viramune XR immediate-release were ~ 90% for C<sub>min,ss</sub> and AUC<sub>ss</sub> with 90% confidence intervals within 80% - 125%; the ratio for C<sub>max,ss</sub> was lower and consistent with a once daily extended-release dosage form. Geometric mean steady-state plasma Viramune XR extended-release pre-dose trough concentrations were 3,880 ng/mL, 3,310 ng/mL and 5,350 ng/mL in age groups 3 to <6years, 6 to <12 years, and 12 to <18 years of age, respectively. Overall, the exposure in children was similar to that observed in adults receiving Viramune XR extended-release in Trial 1100.1486.

In single-dose, parallel group bioavailability studies (Trials 1100.1517 and 1100.1531), the Viramune XR extended-release 50 and 100 mg tablets exhibited extended release characteristics of extended absorption and lower maximal concentrations, similar to the findings when a 400 mg extended-release tablet was compared to the Viramune immediate-release 200 mg tablet. Dividing a 200 mg total dose into four 50 mg doses rather than two 100 mg doses produced a 7 – 11% greater overall absorption, but with comparable drug release rates. The observed pharmacokinetic difference between the 50 mg and 100 mg Viramune XR extended-release tablets is not clinically relevant, and the 50 mg extended-release tablet can be used as an alternative to the slightly larger 100 mg tablet.

Occasionally, the inactive ingredients of Viramune XR extended-release tablets will be eliminated in the faeces as soft, hydrated remnants.

### **Special Populations**

#### **Renal dysfunction**

The single-dose pharmacokinetics of Viramune immediate-release have been compared in 23 subjects with either mild (50 ≤ CL<sub>cr</sub> < 80 mL/min), moderate (30 ≤ CL<sub>cr</sub> < 50 mL/min) or severe renal dysfunction (CL<sub>cr</sub> < 30 mL/min), renal impairment or end-stage renal disease (ESRD) requiring dialysis, and 8 subjects with normal renal function (CL<sub>cr</sub> > 80 mL/min). Renal impairment (mild, moderate and severe) resulted in no significant change in the pharmacokinetics of nevirapine. However, subjects with ESRD requiring dialysis exhibited a 43.5% reduction in Viramune AUC (94.9±28.8 microg.h/mL versus 168.1±38.1 microg.h/mL) and reduction in nevirapine half life (28.2±8.5 h versus 66.3±19.9 h) compared to normal volunteers over a one-week exposure period. There was also accumulation of nevirapine hydroxy-metabolites in plasma. The results suggest that supplementing Viramune therapy with an additional 200 mg dose of Viramune immediate-release tablets following each dialysis treatment would help offset the effects

of dialysis on nevirapine clearance. Otherwise patients with  $CL_{cr} \geq 20$  mL/min do not require an adjustment in Viramune dosing. Viramune XR extended-release tablets have not been studied in patients with renal dysfunction.

### Hepatic impairment

Patients with hepatic impairment should be monitored carefully for evidence of drug induced toxicity. Patients with hepatic impairment associated with ascites may be at risk of accumulating nevirapine with resultant increase in AUC.

A steady state study was conducted comparing 46 adult patients with liver fibrosis. Three groups were studied: Mild fibrosis n=17 participants with Ishak Score 1-2; Moderate fibrosis, n=20 participants with Ishak Score 3-4; Cirrhosis, n=9 participants with Ishak Score 5-6 and Child Pugh A. The patients studied received antiretroviral therapy including Viramune 200 mg twice-daily immediate-release tablets for at least 6 weeks prior to pharmacokinetic sampling. The median duration of therapy was 3.4 years.

Results of the pharmacokinetic analyses are summarised in Table 2. Approximately 15% of the patients with hepatic fibrosis had nevirapine trough concentrations above 9.0 micrograms/mL with no correlation between grade of fibrosis and higher plasma concentration.

In this study, the multiple dose pharmacokinetic disposition of nevirapine and the five oxidative metabolites were not altered compared to the established pharmacokinetics in patients.

Table 2: Geometric means and 95% confidence intervals for nevirapine pharmacokinetic parameters

<b>Parameter</b>	<b>Population</b>	<b>mild fibrosis § Gmean / CI</b>	<b>moderate fibrosis Gmean / CI</b>	<b>cirrhosis Gmean / CI</b>
$C_{minSS}$ (ng/mL)	n=46	4583 [3351, 6268]	6021 [4786, 7574]	5854 [ 4337, 7901]
$AUC_{SS(t)}$ (h•µg/mL)	n=46	55.0 [40,75]	72.3 [57, 91]	70.2 [52, 95]
$C_{maxSS}$ (ng/mL)	intensive only (n=33)	7117 [5146, 9844]	7087 [5679, 8846]	7262 [5163, 10215]

§ without patients 131 and 301

population: all = troughs on all patients, intensive = additional samples drawn at 1, 2, and 4 hours

In a single dose pharmacokinetic study of 200 mg Viramune immediate-release tablets in HIV-negative patients with mild and moderate hepatic impairment (Child-Pugh A, n=6; Child-Pugh B, n=4), a significant increase in the AUC of nevirapine was observed in one Child-Pugh B patient with ascites suggesting that patients with worsening hepatic function and ascites may be at risk of accumulating nevirapine in the systemic circulation. Because nevirapine induces its own metabolism with multiple dosing, this single dose study may not reflect the impact of hepatic impairment on multiple dose pharmacokinetics (see PRECAUTIONS).

Viramune XR extended-release has not been evaluated in subjects with hepatic impairment.

## Gender and ethnic background

In the multinational 2NN study, a population pharmacokinetic substudy of 1077 patients was performed that included 391 females. Female patients showed a 13.8% lower clearance of nevirapine than did male patients. This difference is not considered clinically relevant. Since neither body weight nor Body Mass Index (BMI) had influence on the clearance of nevirapine, the effect of gender cannot be explained by body size.

Nevirapine pharmacokinetics in HIV-1 infected adults do not appear to change with race (Black, Hispanic or Caucasian). This information is derived from an evaluation of pooled data derived from several clinical trials.

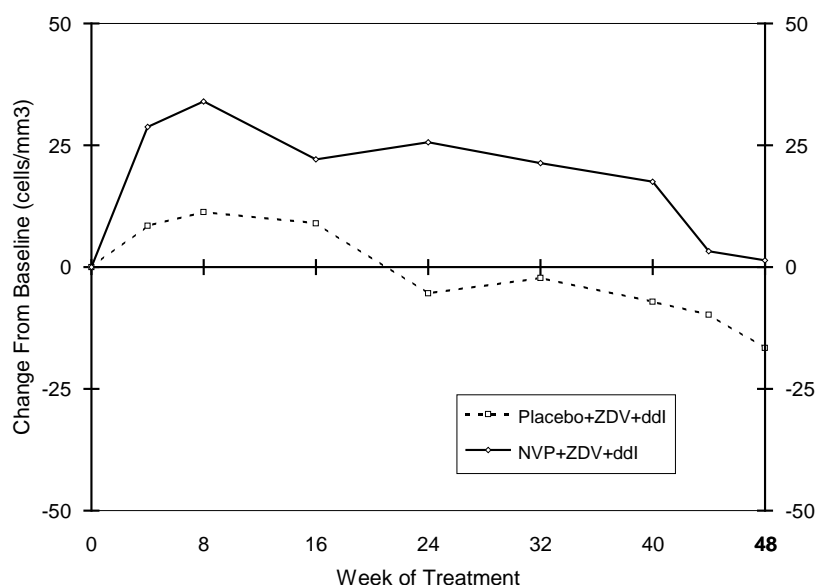
## CLINICAL TRIALS

### **Viramune immediate-release tablets**

#### Patients with a prior history of nucleoside therapy

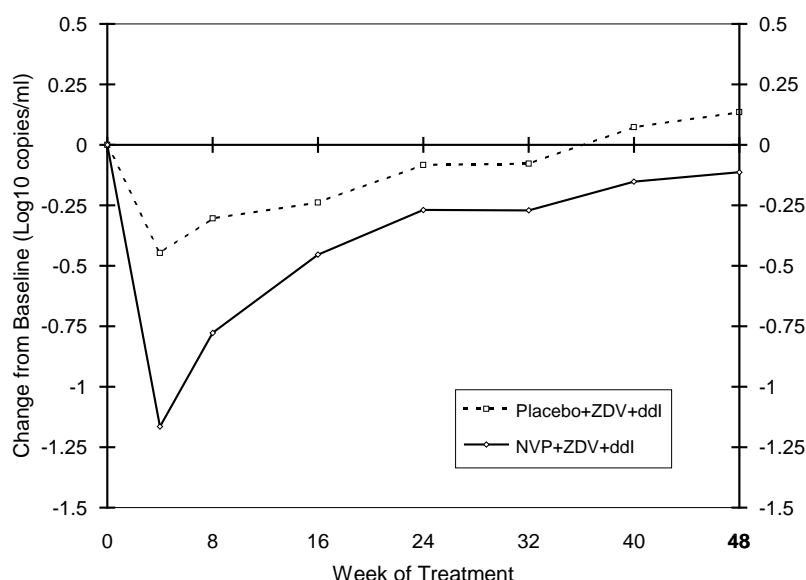
ACTG 241 compared treatment with Viramune + AZT + ddI versus AZT + ddI in 398 HIV-1-infected patients (median age 38 years, 74% Caucasian, 80% male) with CD4+ cell counts  $\leq 350$  cells/mm<sup>3</sup> (mean 153 cells/mm<sup>3</sup>) and a mean baseline plasma HIV-1 RNA concentration of 4.59 log<sub>10</sub> copies/mL (38,905 copies/mL), who had received at least 6 months of nucleoside therapy prior to enrolment (median 115 weeks). Treatment doses were Viramune, 200 mg daily for two weeks, followed by 200 mg twice daily, or placebo; AZT, 200 mg three times daily; ddI, 200 mg twice daily. A significant benefit of triple therapy with Viramune compared to double therapy was observed throughout a 48 week treatment period in terms of CD4+ cell count (Figure 2), % CD4+, quantitative PBMC microculture and plasma viral DNA (Figure 3). Favourable responses to triple therapy with Viramune were seen at all CD4+ count levels.

Figure 2: Mean Change from Baseline for CD4+ Cell Count (absolute number of CD4+ cells/mm<sup>3</sup>), Trial ACTG 241



	Baseline	Week 16	Week 32	40-48 Weeks
NVP+AZT+ddI	196	177	157	161
Placebo+AZT+ddI (ZDV=AZT)	196	176	160	167

Figure 3: Mean Change from Baseline in HIV-1 RNA Concentrations (Log<sub>10</sub> copies/mL), Virology Sub-study of Trial ACTG 241



	Number of patients with HIV-1 RNA data at each timepoint			
	<u>Baseline</u>	<u>Week 16</u>	<u>Week 32</u>	<u>40-48 Weeks</u>
NVP+AZT+ddl	95	84	75	74
Placebo+AZT+ddl (ZDV=AZT)	93	82	75	75

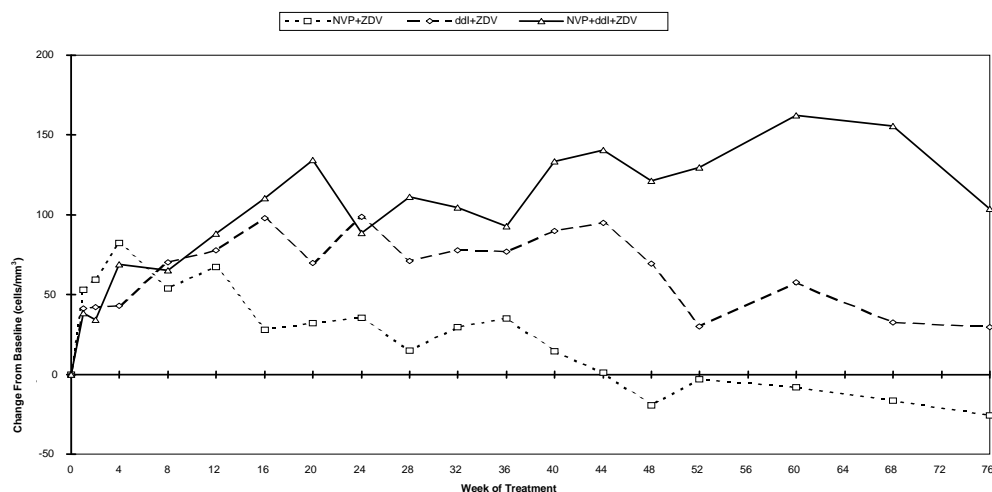
**Clinical Endpoint Trial:** ACTG 193a was a placebo controlled trial which compared treatment with Viramune + AZT + ddl versus AZT + ddl, as well as studying AZT + ddC and AZT alternating with ddl monthly, in 1298 HIV-1-infected patients (mean age 37 years, 51% Caucasian, 87% male) with CD4+ cell counts <50 cells/mm<sup>3</sup> (mean 25 cells/mm<sup>3</sup>). Eighty-four percent (84%) of patients had received nucleoside therapy prior to enrolment (median 15 months). Treatment doses were Viramune 200 mg daily for two weeks, followed by 200 mg twice daily, or placebo; AZT 200 mg three times daily; ddC 0.75 mg three times daily; ddl 200 mg twice daily (or 125 mg twice daily for patients weighing less than 60 kg). The median time to HIV progression event or death was significantly delayed in the Viramune + AZT + ddl treatment group as compared to the AZT + ddl group (82 weeks versus 62 weeks, p=0.013). Mortality was similar for the two groups throughout the trial (112 versus 114, respectively, p=0.126). Patients with prior nucleoside experience had a median time to HIV progression event or death of 79 weeks for the Viramune + AZT +ddl treatment group as compared to 54 weeks in the AZT + ddl treatment group (p=0.004). The results for patients who were nucleoside naive were not statistically significant (p=0.333). The median time to HIV progression event or death was shorter for AZT + ddC (53 weeks) and alternating AZT and ddl (57 weeks) groups.

#### Patients who are antiretroviral naive

BI Trial 1046 compared treatment with Viramune + AZT + ddl versus Viramune + AZT versus AZT + ddl in 151 HIV-1-infected patients (median age 37 years, 94% Caucasian, 93% male) with CD4+ cell counts of 200-600 cells/mm<sup>3</sup> (mean 375 cells/mm<sup>3</sup>) and a mean baseline plasma HIV-1 RNA concentration of 4.41 log<sub>10</sub> copies/mL (25,704 copies/mL). Treatment doses were Viramune, 200 mg daily for two weeks, followed by 200 mg twice daily, or placebo; AZT, 200 mg three times daily; ddl, 125 or 200 mg twice daily. Changes in CD4+ cell counts at 52 weeks: mean levels of CD4+ cell counts in those randomised to Viramune + AZT + ddl and AZT + ddl remained significantly above baseline; the Viramune + AZT + ddl group was significantly improved compared to the AZT + ddl group. Changes in HIV-1 viral RNA at 52 weeks: there was a significantly better response in the Viramune + AZT + ddl group than the AZT + ddl group as measured by mean changes in plasma viral RNA. The proportion of patients whose HIV-1 RNA was decreased to below the limit of detection (20 copies/mL) for every timepoint from 40 to 52 weeks was significantly greater in the Viramune + AZT + ddl group (18/40 or 45%), when compared to the AZT + ddl group (2/36 or 6%)

or the Viramune + AZT group (0/28 or 0%) (Figures 4-6). The clinical significance of this finding is unknown.

Figure 4: Mean Change from Baseline for CD4+ Cell Count (absolute number of CD4+ cells/mm<sup>3</sup>), Trial BI 1046

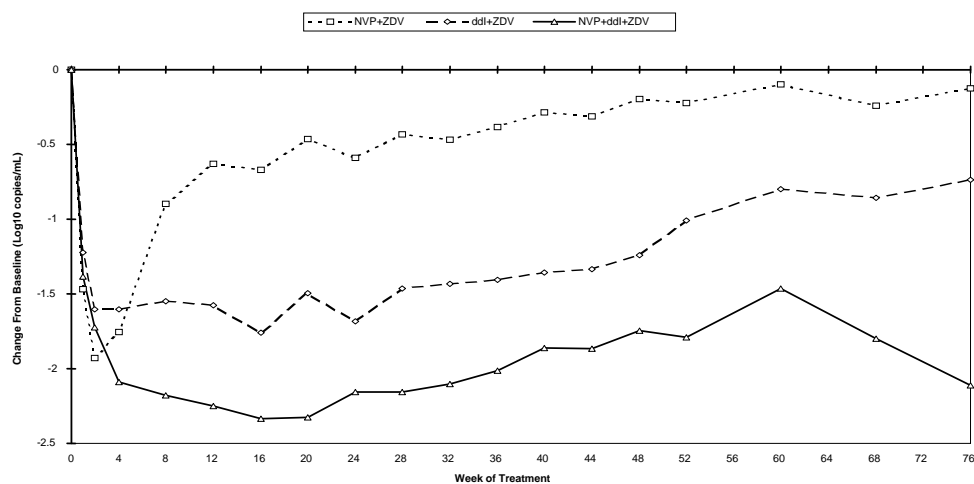


Number of patients with CD4 cell counts at each timepoint

	<u>Baseline</u>	<u>Week 16</u>	<u>Week 32</u>	<u>Week 52</u>	<u>Week 76</u>
NVP+AZT+ddl	51	41	40	38	15
Placebo+AZT+ddl	52	38	35	33	12
NVP+AZT+Placebo	47	35	27	26	15

(ZDV=AZT)

Figure 5: Mean Change from Baseline in HIV-1 RNA Concentrations (Log<sub>10</sub> copies/mL), Trial BI 1046

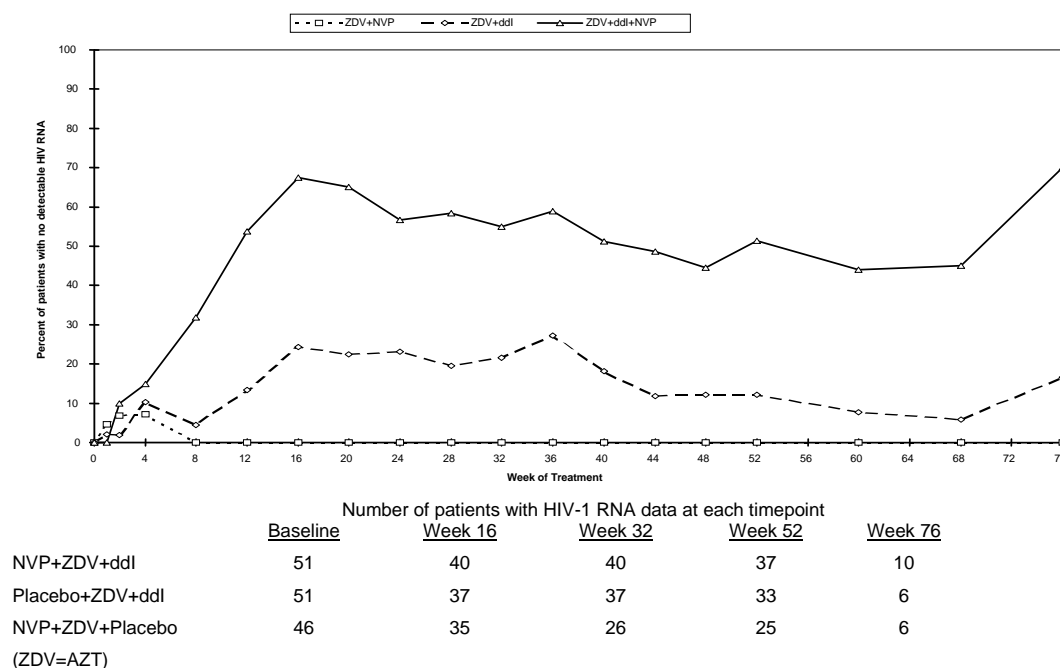


Number of patients with HIV-1 RNA data at each timepoint

	<u>Baseline</u>	<u>Week 16</u>	<u>Week 32</u>	<u>Week 52</u>	<u>Week 76</u>
NVP+ZDV+ddl	51	40	40	37	10
Placebo+ZDV+ddl	51	37	37	33	6
NVP+ZDV+Placebo	46	35	26	25	6

(ZDV=AZT)

Figure 6: Percent of Patients with HIV RNA Below the Limit of Detection, Trial BI 1046



## Viramune XR extended-release tablets

The clinical efficacy of Viramune XR extended-release is based on 48-week data from an ongoing, randomised, double-blind, double-dummy Phase 3 trial (VERxVE - Study 1100.1486) in treatment-naïve patients and on 24-week data from an ongoing, randomised, open-label trial in patients who transitioned from Viramune immediate-release tablets administered twice daily to Viramune XR extended-release tablets administered once daily (TRANxITION - Study 1100.1526).

### Treatment-naïve patients

VERxVE (Study 1100.1486) is a Phase 3 study in which treatment-naïve patients received Viramune immediate-release 200 mg once daily for 14 days and then were randomised to receive either Viramune immediate-release 200 mg twice daily or Viramune XR extended-release 400 mg once daily. All patients received tenofovir + emtricitabine as background therapy. Randomisation was stratified by screening HIV-1 RNA level  $\leq 100,000$  copies/mL and  $>100,000$  copies/mL. Selected demographic and baseline disease characteristics are displayed in Table 3.



Table 3: Demographic and Baseline Disease Characteristics in Study 1100.1486

	<b>VIRAMUNE immediate-release N=508<sup>a</sup></b>	<b>VIRAMUNE XR extended-release N=505</b>
<b>Gender</b>		
Male	85%	85%
Female	15%	15%
<b>Race</b>		
White	74%	77%
Black	22%	19%
Asian	3%	3%
Other <sup>b</sup>	1%	2%
<b>Region</b>		
North America	30%	28%
Europe	50%	51%
Latin America	10%	12%
Africa	11%	10%
<b>Baseline Plasma HIV-1 RNA (log<sub>10</sub> copies/mL)</b>		
Mean (SD)	4.7 (0.6)	4.7 (0.7)
≤100,000	66%	67%
>100,000	34%	33%
<b>Baseline CD4+ count (cells/mm<sup>3</sup>)</b>		
Mean (SD)	228 (86)	230 (81)
<b>HIV-1 subtype</b>		
B	71%	75%
Non-B	29%	24%

<sup>a</sup> Includes 2 patients who were randomised but never received blinded medication.

<sup>b</sup> Includes American Indians/Alaska native and Hawaiian/Pacific islander.

Table 4 describes week 48 outcomes in the VERxVE study (1100.1486). These outcomes include all patients who were randomised after the 14 day lead-in with Viramune immediate-release and received at least one dose of blinded study medication.

Table 4: Outcomes at Week 48 in Study 1100.1486<sup>a</sup>

	<b>VIRAMUNE immediate-release N=506</b>	<b>VIRAMUNE XR extended-release N=505</b>
Virologic Responder (HIV-1 RNA <50 copies/mL)	75.9%	81.0%
Virologic failure	5.9%	3.2%
Never suppressed through Week 48	2.6%	1.0%
Rebound	3.4%	2.2%
Discontinued study drug prior to Week 48	18.2%	15.8%
Death	0.6%	0.2%
Adverse events	8.3%	6.3%
Other <sup>b</sup>	9.3%	9.4%

<sup>a</sup>Includes patients who received at least one dose of blinded study medication after randomisation. Patients who discontinued treatment during the lead-in period are excluded.

<sup>b</sup>Includes lost to follow-up, consent withdrawn, noncompliance, lack of efficacy, pregnancy, and other.

At week 48, mean change from baseline in CD4+ cell count was 184 cells/mm<sup>3</sup> and 197 cells/mm<sup>3</sup> for the groups receiving Viramune immediate-release and Viramune XR extended-release respectively.

Table 5 shows outcomes at 48 weeks in Trial 1100.1486 based on baseline viral load.

Table 5: Outcomes at 48 weeks in Study 1100.1486 by Baseline Viral Load<sup>a</sup>

	<b>Number with response/total number (%)</b>		<b>Difference in % (95% CI)</b>
	<b>VIRAMUNE immediate-release</b>	<b>VIRAMUNE XR extended-release</b>	
Baseline HIV-1 viral load stratum (copies/mL)			
- ≤ 100,000	240/303 (79.2%)	267/311 (85.0%)	6.6 (0.7, 12.6)
- >100,000	144/203 (70.9%)	142/194 (73.2%)	2.3 (-6.6, 11.1)
<b>Total</b>	<b>384/506 (75.9%)</b>	<b>409/505 (81.0%)</b>	<b>4.9 (-0.1, 10.0)<sup>b</sup></b>

<sup>a</sup>Includes patients who received at least one dose of blinded study medication after randomisation. Patients who discontinued treatment during the lead-in period are excluded.

<sup>b</sup>Based on Cochran's statistic with continuity correction for the variance calculation

## Lipids. Change from Baseline

Changes from baseline in fasting lipids are shown in Table 6.

Table 6: Summary of lipid laboratory values at baseline (screening) and Week 48 - Study 1100.1486

	VIRAMUNE immediate-release			VIRAMUNE XR extended-release		
	Baseline (mean) N=503	Week 48 (mean) N=407	Percent Change <sup>1</sup> N=406	Baseline (mean) N=505	Week 48 (mean) N=419	Percent Change <sup>1</sup> N=419
LDL (mg/dL)	98.8	110.0	+9	98.3	109.5	+7
HDL (mg/dL)	38.8	52.2	+32	39.0	50.0	+27
Total cholesterol (mg/dL)	163.8	186.5	+13	163.2	183.8	+11
Total cholesterol/HDL	4.4	3.8	-14	4.4	3.9	-12
Triglycerides (mg/dL)	131.2	124.5	-9	132.8	127.5	-7

<sup>1</sup>Percent change is the median of within-patient changes from baseline for patients with both baseline and Week 48 values and is not a simple difference of the baseline and Week 48 mean values, respectively.

## Patients switching from Viramune immediate-release to Viramune XR extended-release

TRANxITION (Study 1100.1526) is a Phase 3 study to evaluate safety and antiviral activity in patients switching from Viramune immediate-release to Viramune XR extended-release. In this open-label study, 443 patients already on an antiviral regimen containing Viramune immediate-release 200 mg twice daily with HIV-1 RNA <50 copies/mL were randomised in a 2:1 ratio to Viramune XR extended-release 400 mg once daily or Viramune immediate-release 200 mg twice daily. Approximately half of the patients had tenofovir + emtricitabine as their background therapy, with the remaining patients receiving abacavir sulfate + lamivudine or zidovudine + lamivudine. Approximately half of the patients had at least 3 years of prior exposure to Viramune immediate-release prior to entering Trial 1100.1526.

At 24 weeks after randomisation in the TRANxITION study, 92.6% and 93.6% of patients receiving Viramune immediate-release 200 mg twice daily or Viramune XR extended-release 400 mg once daily, respectively, continued to have HIV-1 RNA <50 copies/mL.

## INDICATIONS

Viramune (nevirapine) immediate-release tablets and oral suspension in combination with antiretroviral agents is indicated for the treatment of HIV-1 infection in adults and children over the age of 2 months.

Viramune XR (nevirapine) extended-release tablets in combination with antiretroviral agents is indicated for the treatment of HIV-1 infection in adults and children over the age of three years.

Extended-release tablets are not suitable for the 14 day lead-in period for patients starting nevirapine. Other nevirapine formulations, such as immediate-release tablets or oral suspension should be used.

Resistant virus emerges rapidly when Viramune is administered as monotherapy or in dual combination therapy with an antiretroviral agent. Therefore, Viramune should always be administered in combination with at least two additional antiretroviral agents.

## CONTRAINDICATIONS

Viramune is contraindicated in patients with clinically significant hypersensitivity to the active ingredient or any of the excipients in the tablet or oral suspension.

Viramune should not be administered to patients with severe hepatic dysfunction (Child-Pugh C) or pretreatment AST or ALT >5x Upper Limit of Normality (ULN) until baseline AST/ALT are stabilised (<5x ULN).

Viramune should not be readministered to:

- patients who have required permanent discontinuation for severe rash, rash accompanied by constitutional symptoms, hypersensitivity reactions, or clinical hepatitis due to nevirapine;
- patients who previously had AST or ALT > 5x ULN during nevirapine therapy and had recurrence of liver function abnormalities upon readministration of nevirapine (see PRECAUTIONS).

Viramune immediate-release tablets contain 636 mg lactose per maximum recommended daily dose. Patients with the rare hereditary conditions of galactose intolerance, galactosaemia, the Lapp-lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Viramune XR extended-release tablets contain 400 mg of lactose per maximum recommended daily dose. Patients with the rare hereditary conditions of galactose intolerance e.g. galactosaemia, should not take this medicine

Viramune suspension contains 6 g sucrose and 6.5 g sorbitol per maximum recommended daily dose. Patients with the rare hereditary conditions of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

Viramune suspension contains the excipients methyl parahydroxy benzoate and propyl parahydroxy benzoate, which may cause allergic reactions (possibly delayed).

Herbal preparations containing St John's Wort (*hypericum perforatum*) must not be used while taking Viramune due to the risk of decreased plasma concentrations and reduced clinical effects of nevirapine (see also Interactions with other Medicines).

## PRECAUTIONS

On the basis of pharmacodynamic data, Viramune should only be used with at least two other antiretroviral agents.

**The first 18 weeks of therapy with Viramune are a critical period which requires close monitoring of patients to disclose the potential appearance of severe and life-threatening skin reactions (including cases of Stevens-Johnson syndrome and toxic epidermal necrolysis) or serious hepatitis/hepatic failure. The greatest risk of hepatic events and skin reactions occurs in the first 6 weeks of therapy. However, the risk of any hepatic event continues past this period and monitoring should continue at frequent intervals. Female gender and higher CD4 counts at the initiation of therapy place patients at greater risk of hepatic adverse events.**

**Based on serious and life-threatening hepatotoxicity observed in controlled and uncontrolled studies, Viramune should not be initiated in adult females with CD4+ cell counts greater than 250 cell/mm<sup>3</sup> or in adult males with CD4+ cell counts greater than 400 cells/mm<sup>3</sup> unless the benefit outweighs the risk.**

In some cases, hepatic injury has progressed despite discontinuation of treatment. Patients developing signs or symptoms of hepatitis, severe skin reaction or hypersensitivity reactions must discontinue Viramune and seek medical evaluation immediately. Viramune should not be restarted following severe hepatic, skin or hypersensitivity reactions.

The dosage must be strictly adhered to, especially the 14-days lead-in period (see DOSAGE AND ADMINISTRATION).

### Cutaneous reactions

Severe and life-threatening skin reactions, including fatal cases, have occurred in patients treated with Viramune mainly during the first 6 weeks of therapy. These have included cases of Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and hypersensitivity reactions characterised by rash, constitutional findings and visceral involvement. Patients should be carefully monitored during the first 18 weeks of treatment. Patients should be closely monitored if an isolated rash occurs.

Viramune must be permanently discontinued in any patient experiencing severe rash or a rash accompanied by constitutional symptoms (such as fever, blistering, oral lesions, conjunctivitis, facial oedema/swelling, muscle or joint aches, or general malaise), including Stevens-Johnson syndrome, or toxic epidermal necrolysis. Viramune must be permanently discontinued in any patient experiencing hypersensitivity reactions characterised by rash with constitutional symptoms, plus visceral involvement (such as hepatitis, eosinophilia, granulocytopenia, and renal dysfunction or signs of visceral involvement) (see Information for Patients; ADVERSE REACTIONS).

Patients should be instructed that the major toxicity of Viramune is rash. The lead-in period should be used because it has been found to lessen the frequency of rash (see DOSAGE AND ADMINISTRATION). The majority of rashes associated with Viramune occur within the first 6 weeks of initiation of therapy, therefore, patients should be monitored carefully for the appearance of rash during this period.

For Viramune immediate-release, patients should be instructed that dose escalation to twice-daily dosing is not to occur if any rash occurs during the two-week lead-in dosing period, until the rash has resolved. The 200 mg once daily dosing regimen should not be continued beyond 4 weeks (28 days) at which point an alternative antiretroviral regimen should be sought.

For Viramune XR extended-release, patients should be instructed that they should not begin Viramune XR extended-release until any rash that has occurred during the 14 day lead-in period of Viramune immediate-release has resolved. The 200 mg once daily dosing regimen should not be continued beyond 28 days at which point an alternative antiretroviral regimen should be sought.

In rare instances, rhabdomyolysis has been observed in patients experiencing skin and/or liver reactions associated with Viramune use.

Concomitant prednisone use (40 mg/day for the first 14 days of Viramune immediate-release administration) has been shown not to decrease the incidence of Viramune-associated rash, and may be associated with an increase in rash during the first 6 weeks of Viramune therapy.

Risk factors for developing serious cutaneous reactions include failure to follow the initial dosing of 200 mg daily during the lead-in period. A long delay between the initial symptoms and medical consultation may increase the risk of a more serious outcome of cutaneous reactions. Women appear to be at higher risk than men of developing rash, whether receiving Viramune or non-Viramune containing therapy.

**Any patient experiencing severe rash or a rash accompanied by constitutional symptoms such as fever, blistering, oral lesions, conjunctivitis, facial oedema/swelling, muscle or joint aches, or general malaise should discontinue medication and immediately seek medical evaluation. In these patients Viramune must not be restarted.**

**If patients present with a suspected Viramune-associated rash, liver function tests should be performed. Patients with moderate to severe elevations (AST or ALT > 5x ULN) should be permanently discontinued from Viramune.**

**If a hypersensitivity reaction occurs, characterised by rash with constitutional symptoms such as fever, arthralgia, myalgia and lymphadenopathy, plus visceral involvement, such as hepatitis, eosinophilia, granulocytopenia, and renal dysfunction, Viramune should be permanently stopped and not be re-introduced.**

## **Hepatic reactions**

Severe or life-threatening hepatotoxicity, including fatal fulminant hepatitis, has occurred in patients treated with Viramune. The first 18 weeks of treatment are a critical period which requires close monitoring. The risk of hepatic events is greatest in the first 6 weeks of therapy. However, the risk continues past this period and monitoring should continue at frequent intervals throughout treatment. Patients should be informed that hepatic reactions are a major toxicity of Viramune. Patients with signs or symptoms suggestive of hepatitis must be advised to immediately seek medical evaluation, which should include liver function tests (see Information for Patients).

In rare instances, rhabdomyolysis has been observed in patients experiencing skin and/or liver reactions associated with Viramune use.

Increased AST or ALT levels >2.5 x ULN and/or co-infection with hepatitis B and/or C at the start of antiretroviral therapy is associated with greater risk of hepatic adverse events during antiretroviral therapy in general, including Viramune-containing regimens.

Women and patients with higher CD4 counts are at increased risk of hepatic adverse events. In a retrospective analysis of pooled clinical studies with Viramune immediate-release tablets, women had a three fold higher risk than men for symptomatic, often rash-associated, hepatic events (5.8% vs. 2.2%), and patients with higher CD4 counts at initiation of Viramune therapy were at higher risk for symptomatic hepatic events with Viramune. Women with CD4 counts >250 cells/mm<sup>3</sup> had a 12 fold higher risk of symptomatic hepatic adverse events compared to women with CD4 counts <250 cells/mm<sup>3</sup> (11.0% vs. 0.9%). An increased risk was observed in men with CD4 counts >400 cells/mm<sup>3</sup> (6.3% vs. up to 2.3% for men with CD4 counts <400 cells/mm<sup>3</sup>).

## **Liver monitoring**

Abnormal liver function tests have been reported with Viramune, some in the first few weeks of therapy. Asymptomatic elevations of liver enzymes are frequently described and are not necessarily a contraindication to use Viramune. Asymptomatic GGT elevations are not a contraindication to continue therapy.

Monitoring of liver function tests is strongly recommended at frequent intervals, appropriate to the patient's clinical needs, especially during the first 18 weeks of treatment. Clinical and laboratory monitoring should continue throughout Viramune treatment. Physicians and patients should be vigilant for prodromal signs or findings of hepatitis, such as anorexia, nausea, jaundice, bilirubinuria, acholic stools, hepatomegaly or liver tenderness. Patients should be instructed to seek medical attention if these occur.

For patients already on a regimen of Viramune immediate-release twice daily, who switch to Viramune XR extended-release once daily, there is no need for a change in their monitoring schedule.

With AST or ALT values >2.5 x ULN before or during treatment, liver tests should be monitored more frequently during regular clinic visits. Viramune should not be administered to patients with pretreatment AST or ALT >5 x ULN until baseline AST/ALT are stabilised at values <5 x ULN.

**If AST or ALT increase to >5 x ULN, Viramune should be immediately stopped. If AST or ALT return to baseline values and if the patient had no clinical signs/symptoms of hepatitis or constitutional symptoms or other findings suggestive of organ dysfunction, it may be possible to reintroduce Viramune, based on clinical needs and judgment, on a case by case basis. Viramune should be restarted with heightened clinical and laboratory vigilance at the starting dosage regimen of one immediate-release 200 mg tablet daily for 14 days followed by one 200 mg Viramune immediate-release tablet twice daily or one 400 mg Viramune XR extended-release tablet once daily. If liver function abnormalities rapidly recur, Viramune should be permanently discontinued.**

**If clinical hepatitis occurs, characterised by anorexia, nausea, vomiting, icterus AND laboratory findings such as moderate or severe liver function test abnormalities (excluding GGT), Viramune must be permanently stopped. Viramune should not be readministered to patients who have required permanent discontinuation for clinical hepatitis due to Viramune.**

## **Other**

The following events have also been reported when Viramune has been used in combination with other antiretroviral agents: anaemia, pancreatitis, peripheral neuropathy and thrombocytopenia. These events are commonly associated with other antiretroviral agents and may be expected to occur when Viramune is used in combination with other agents; however it is unlikely that these events are due to nevirapine treatment.

Patients receiving Viramune or any of other antiretroviral therapy may continue to develop opportunistic infections and other complications of HIV infection, and therefore should remain under close clinical observation by physicians experienced in the treatment of patients with associated HIV diseases. The long-term effects of Viramune are unknown at this time. Viramune therapy has not been shown to reduce the risk of transmission of HIV-1 to others.

Viramune is extensively metabolised by the liver and nevirapine metabolites are eliminated largely by the kidney. Pharmacokinetic results suggest caution should be exercised when Viramune is administered to patients with moderate hepatic dysfunction (Child-Pugh Class B). Viramune should not be administered to patients with severe hepatic dysfunction (Child-Pugh Class C) (see CONTRAINDICATIONS). Viramune XR extended-release has not been evaluated in subjects with hepatic impairment.

In adult patients with renal dysfunction who are undergoing dialysis pharmacokinetic results suggest that supplementing Viramune therapy with an additional 200 mg dose of Viramune immediate-release tablets following each dialysis treatment would help offset the effects of dialysis on Viramune clearance. Otherwise patients with CL<sub>Cr</sub> ≥ 20 mL/min do not require an adjustment in Viramune dosing (see Pharmacokinetics: Special Populations).

In paediatric patients with renal dysfunction who are undergoing dialysis it is recommended that following each dialysis treatment patients receive an additional dose of Viramune oral suspension or immediate-release tablets representing 50% of the recommended daily dose of Viramune oral suspension or immediate-release tablets which would help offset the effects of dialysis on Viramune clearance. Viramune XR extended-release tablets have not been studied in patients with renal dysfunction.

Hormonal methods of birth control other than DMPA should not be used as the sole method of contraception in women taking Viramune. Nevirapine may lower the plasma concentrations of these medications (see also Interactions with other Medicines). Therefore, when postmenopausal hormone therapy is used during administration of Viramune, its therapeutic effect should be monitored.

Nevirapine may be taken with other additional antiretroviral agents. Please also refer to the manufacturers' prescribing information of the antiretroviral agents for contraindications, warnings, side effects and potential drug interactions.



Combination antiretroviral therapy has been associated with the redistribution of body fat (lipodystrophy) in HIV infected patients. The long-term consequences of these events are currently unknown. Knowledge about the mechanism is incomplete. A connection between visceral lipomatosis and PIs and lipoatrophy and NRTIs has been hypothesised. A higher risk of lipodystrophy has been associated with individual factors such as older age, and with drug related factors such as longer duration of antiretroviral treatment and associated metabolic disturbances. Clinical examination should include evaluation for physical signs of fat redistribution. Consideration should be given to the measurement of fasting serum lipids and blood glucose. Lipid disorders should be managed as clinically appropriate.

### **Immune Reactivation Syndrome**

In HIV-infected patients with severe immune deficiency at the time of institution of combination antiretroviral therapy, an inflammatory reaction to asymptomatic or residual opportunistic pathogens may arise and cause serious clinical conditions, or aggravation of symptoms. Typically, such reactions have been observed within the first few weeks or months of initiation of combination antiretroviral therapy. Relevant examples are cytomegalovirus retinitis, generalised and/or focal mycobacterial infections, and *Pneumocystis carinii* pneumonia. Any inflammatory symptoms should be evaluated and treatment instituted when necessary.

### **Carcinogenicity**

In carcinogenicity studies, nevirapine was administered in the diet for two years to mice and rats at respective doses of 50, 375 and 750 mg/kg/day and 3.5, 17.5 and 35 mg/kg/day. In mice, the two higher doses were associated with increased incidences of hepatocellular adenomas and carcinomas; adenomas were also increased in low dose males. In rats, an increased incidence of hepatocellular adenomas was observed at all doses in males and at the high dose in females. Nevirapine strongly induces liver enzyme activities in mice and rats, and liver tumour induction in these species probably involves a nongenotoxic mechanism. Plasma nevirapine levels were lower than clinical levels at all doses in both species, due to more rapid drug clearance.

### **Genotoxicity**

In genetic toxicity assays, nevirapine showed no evidence of mutagenic activity (*Salmonella* strains, *E. coli* and Chinese hamster ovary cells) or clastogenic activity (Chinese hamster ovary cell *in vitro* and a mouse bone marrow micronucleus assay).

### **Effects on fertility**

In reproductive toxicology studies, evidence of impaired fertility was seen in female rats at doses providing systemic exposure, based on AUC, approximately equivalent to that observed following a human clinical dose of 400 mg/day.

### **Use in Pregnancy**

Category B3. There was no evidence for teratogenicity in reproductive studies performed in rats and rabbits treated with oral doses up to 50 and 300 mg/kg/day nevirapine. In rats a significant decrease in foetal body weight occurred at doses providing systemic exposure approximately 50% higher, based on AUC, than that seen at the recommended clinical dose. Maternal toxicity and observable effects on foetal development were not observed in the rat with a systemic exposure equivalent to that seen at the recommended human dose or in the rabbit with a systemic exposure approximately 50% higher than that seen at the recommended human dose.

There have been no adequate and well controlled studies of nevirapine in pregnant women, nor are there reports of infants born to women who conceived while receiving nevirapine chronic dosing in clinical trials. Nevirapine readily crosses the placenta.

The US Antiretroviral Pregnancy Registry, which has been surveying pregnancy outcomes since January 1989, has not found an increased risk of birth defects following first trimester exposures to nevirapine. The prevalence of birth defects after any trimester exposure to nevirapine is comparable to the prevalence observed in the general population.

Caution should be exercised when prescribing Viramune to pregnant women. As hepatotoxicity is more frequent in women with CD4 cell counts above 250 cells/mm<sup>3</sup>, these conditions should be taken in consideration on therapeutic decision (see Precautions).

Women of childbearing potential should not use oral contraceptives as the sole method for birth control, since Viramune (nevirapine) might lower the plasma concentrations of these medications (see Precautions).

### **Use in Lactation**

Nevirapine is excreted in the breast milk.

It is generally recommended that HIV-1 infected women should not breastfeed infants regardless of the use of antiretroviral agents, to avoid post-natal transmission of HIV-1.

### **Interactions with other Medicines**

The following data were generated using the Viramune immediate-release tablets but are expected to apply to all dosage forms.

Warning on concomitant use with other medicines (for detailed description see Table listed below).

Viramune can alter plasma exposure of other drugs, and other drugs can alter plasma exposure of Viramune.

Combining the following compounds with Viramune is not recommended: Efavirenz, rifampicin, ketoconazole; if not co-administered with low dose ritonavir: fosamprenavir, saquinavir, atazanavir.

Viramune has been shown to be an inducer of hepatic cytochrome P450 metabolic enzymes (CYP3A, CYP2B) and may result in lower plasma concentrations of other concomitantly administered drugs that are extensively metabolised by CYP3A or CYP2B (see Pharmacokinetics). Thus, if a patient has been stabilised on a dosage regimen for a drug metabolised by CYP3A or CYP2B and begins treatment with Viramune, dose adjustments may be necessary.

The absorption of Viramune (nevirapine) is not affected by food or antacids.

The interaction data is presented as geometric mean value with 90% confidence interval (90% CI) whenever these data were available.

Medicinal products by therapeutic areas	Interaction	Recommendations concerning co-administration
<b>ANTI-INFECTIVES</b>		
<b>Antiretrovirals</b>		
<b><i>Nucleoside reverse transcriptase inhibitors (NRTIs)</i></b>		
Didanosine 100-150 mg BID	Didanosine AUC ↔ Didanosine C <sub>min</sub> § Didanosine C <sub>max</sub> ↔	No dosage adjustments are required when Viramune is taken in combination with didanosine.
Lamivudine 150 mg BID	No changes to lamivudine apparent clearance and volume of distribution, suggesting no induction effect of nevirapine on lamivudine clearance.	No dosage adjustments are required when Viramune is taken in combination with lamivudine.
Stavudine 30/40mg BID	Stavudine AUC ↔ Stavudine C <sub>min</sub> § Stavudine C <sub>max</sub> ↔  Nevirapine: compared to historical controls, levels appeared to be unchanged.	No dosage adjustments are required when Viramune is taken in combination with stavudine.
Tenofovir 300 mg QD	Tenofovir plasma levels remain unchanged. Tenofovir does not have an effect on nevirapine levels.	No dosage adjustments are required when Viramune is taken in combination with tenofovir.
Zalcitabine 0.125-0.25 mg TID	Zalcitabine AUC ↔ Zalcitabine C <sub>min</sub> § Zalcitabine C <sub>max</sub> ↔	No dosage adjustments are required when Viramune is taken in combination with zalcitabine.
Zidovudine 100-200 mg TID	Zidovudine AUC ↓28 (↓40 to ↓4) Zalcitabine C <sub>min</sub> § Zidovudine C <sub>max</sub> ↓30 (↓51 to ↑4)  Paired data suggest that zidovudine had no effect on the pharmacokinetics of nevirapine.	No dosage adjustments are required when Viramune is taken in combination with zidovudine.
<b><i>Non-nucleoside reverse transcriptase inhibitors (NNRTIs)</i></b>		
Efavirenz 600 mg QD	Efavirenz AUC ↓28 (↓34 to ↓14) Efavirenz C <sub>min</sub> ↓32 (↓35 to ↓19) Efavirenz C <sub>max</sub> ↓12 (↓23 to ↑1)	This co-administration is not recommended since the co-administration of efavirenz and Viramune could lead to a higher risk for side effects (see also <i>Warning on concomitant use with other medicines</i> ). Moreover this co-administration does not improve efficacy over either NNRTI alone.  Viramune in combination with efavirenz exhibited a strong antagonistic anti-HIV-1 activity <i>in vitro</i> (see also <i>Pharmacology - Microbiology</i> ).

<b>Protease Inhibitors (PIs)</b>		
Atazanavir/ritonavir 300/100 mg QD 400/100mg QD	<p><u>Atazanavir/r 300/100mg:</u> Atazanavir/r AUC ↓42 (↓52 to ↓29) Atazanavir/r C<sub>min</sub> ↓72 (↓80 to ↓60) Atazanavir/r C<sub>max</sub> ↓28 (↓40 to ↓14)</p> <p><u>Atazanavir/r 400/100mg:</u> Atazanavir/r AUC ↓19 (↓35 to ↑2) Atazanavir/r C<sub>min</sub> ↓59 (↓73 to ↓40) Atazanavir/r C<sub>max</sub> ↔ (compared to 300/100mg without nevirapine)</p> <p>Nevirapine AUC ↑25 (↑17 to ↑34) Nevirapine C<sub>min</sub> ↑32 (↑22 to ↑43) Nevirapine C<sub>max</sub> ↑17 (↑9 to ↑25)</p>	If given in combination with Viramune, atazanavir should be dosed with 400mg co-administered with low dose ritonavir 100mg.
Darunavir/ritonavir 400/100 mg BID	<p>Darunavir AUC ↑24 (↓3 to ↑57) Darunavir C<sub>min</sub> ↔ Darunavir C<sub>max</sub> ↑40 (↑14 to ↑73)</p> <p>Nevirapine AUC ↑27 (↑12 to ↑44) Nevirapine C<sub>min</sub> ↑47 (↑20 to ↑82) Nevirapine C<sub>max</sub> ↑18 (↑2 to ↑37)</p>	Darunavir/ritonavir increases the plasma concentrations of nevirapine as a result of CYP3A4 inhibition. Darunavir co-administered with 100 mg ritonavir and Viramune can be used without dose adjustments.
Fosamprenavir 1400 mg BID	<p>Amprenavir AUC ↓33 (↓45 to ↓20) Amprenavir C<sub>min</sub> ↓35 (↓51 to ↓15) Amprenavir C<sub>max</sub> ↓25 (↓37 to ↓11)</p> <p>Nevirapine AUC ↑29 (↑19 to ↑40) Nevirapine C<sub>min</sub> ↑34 (↑21 to ↑49) Nevirapine C<sub>max</sub> ↑25 (↑14 to ↑37)</p>	Viramune should not be given with fosamprenavir if not co-administered with ritonavir. (see also <i>Warning on concomitant use with other medicines</i> ).
Fosamprenavir/ritonavir 700/100 mg BID	<p>Amprenavir AUC ↓11 (↓23 to ↑3) Amprenavir C<sub>min</sub> ↓19 (↓31 to ↓4) Amprenavir C<sub>max</sub> ↔</p> <p>Nevirapine AUC ↑14 (↑5 to ↑24) Nevirapine C<sub>min</sub> ↑22 (↑10 to ↑35) Nevirapine C<sub>max</sub> ↑13 (↑3 to ↑24)</p>	No dosing adjustments are required when Viramune is co-administered with 700/100 mg of fosamprenavir/ritonavir BID.

Indinavir 800 mg Q8H	<p>Indinavir AUC ↓31 (↓39 to ↓22)  Indinavir C<sub>min</sub> ↓44 (↓53 to ↓33)  Indinavir C<sub>max</sub> ↓15 (↓24 to ↓4)</p> <p>No clinically relevant change in nevirapine plasma levels was found.</p>	<p>No definitive clinical conclusions have been reached regarding the potential impact of co-administration of Viramune and indinavir. A dose increase of indinavir to 1000 mg Q8H should be considered when indinavir is given with Viramune 200 mg BID; however, there are no data currently available to establish that the short term or long term antiviral activity of indinavir 1000 mg Q8H with Viramune 200 mg BID will differ from that of indinavir 800 mg Q8H with Viramune 200 mg BID. Today indinavir is generally co-administered with ritonavir. There are limited clinical data on the interaction of Viramune with indinavir/ritonavir.</p>
Lopinavir/ritonavir (capsules) 400/100 mg BID	<p><u>In HIV positive adults:</u>  Lopinavir AUC ↓27  Lopinavir C<sub>min</sub> ↓46  Lopinavir C<sub>max</sub> ↓19</p>	<p>An increase in the dose of lopinavir/ritonavir to 533/133 mg (4 capsules) twice daily with food is recommended in combination with Viramune.</p>
Lopinavir/ritonavir (oral solution) 300/75 mg/m <sup>2</sup> BID	<p><u>Paediatric patients:</u>  Lopinavir AUC ↓22 (↓44 to ↑9)  Lopinavir C<sub>min</sub> ↓55 (↓75 to ↓18)  Lopinavir C<sub>max</sub> ↓14 (↓36 to ↑16)</p>	<p>For children, increase of the dose of lopinavir/ritonavir to 300/75 mg/m<sup>2</sup> twice daily with food should be considered when used in combination with Viramune, particularly for patients in whom reduced susceptibility to lopinavir/ritonavir is suspected.</p>
Nelfinavir 750 mg TID	<p>Nelfinavir:  AUC ↔  C<sub>max</sub> ↔</p> <p>Total exposure of nelfinavir plus the AG1402 metabolite:  AUC ↓20 (↓72 to ↑128)  C<sub>min</sub> ↓35 (↓90 to ↑316)  C<sub>max</sub> ↓12 (↓61 to ↑100)</p> <p>Nevirapine: compared to historical controls, levels appeared to be unchanged.</p>	<p>No dosage adjustments are required when Viramune is taken in combination with nelfinavir.</p>
Ritonavir 600 mg BID	<p>Nevirapine AUC ↔  Nevirapine C<sub>max</sub> ↔</p> <p>Ritonavir AUC ↔  Ritonavir C<sub>min</sub> ↔  Ritonavir C<sub>max</sub> ↔</p>	<p>No dosage adjustments are required when Viramune is taken in combination with ritonavir.</p>

Saquinavir 600 mg TID	Saquinavir AUC ↓38 (↓47 to ↓11) Saquinavir C <sub>min</sub> § Saquinavir C <sub>max</sub> ↓32 (↓44 to ↓6)	Viramune should not be given with saquinavir if not co-administered with ritonavir. (see also <i>Warning on concomitant use with other medicines</i> ).
Saquinavir/ ritonavir	The limited data available with saquinavir soft gel capsule boosted with ritonavir do not suggest any clinically relevant interaction between saquinavir boosted with ritonavir and nevirapine	No dosage adjustments are required when Viramune is taken in combination with saquinavir co-administered with ritonavir.
Tipranavir/ritonavir 500/200 mg BID	No specific drug-drug interaction study has been performed. The limited data available from a phase IIa study in HIV-infected patients have shown a clinically non significant 20% decrease of tipranavir C <sub>min</sub> .	No dosage adjustments are required when Viramune is taken in combination with tipranavir co-administered with ritonavir.
<b>Entry Inhibitors</b>		
Enfuvirtide	Due to the metabolic pathway of enfuvirtide no clinically significant pharmacokinetic interactions are expected between enfuvirtide and nevirapine.	No dosage adjustment is recommended when co-administering enfuvirtide with Viramune.
Maraviroc 300 mg QD	Maraviroc AUC ↔ Maraviroc C <sub>min</sub> § Maraviroc C <sub>max</sub> ↑ 54 compared to historical controls  Nevirapine concentrations not measured, no effect is expected.	Comparison to exposure in historical controls suggests that maraviroc 300 mg twice daily and Viramune can be co-administered without dose adjustment.
<b>Integrase Inhibitors</b>		
Raltegravir 400 mg BID	No clinical data available.	Due to the metabolic pathway of raltegravir no interaction is expected. No dose adjustment is recommended when co-administering raltegravir with Viramune.
<b>Antibiotics</b>		
Clarithromycin 500 mg BID	Clarithromycin AUC ↓31 (↓38 to ↓24) Clarithromycin C <sub>min</sub> ↓56 (↓70 to ↓36) Clarithromycin C <sub>max</sub> ↓23 (↓31 to ↓14)  Metabolite 14-OH clarithromycin AUC ↑42 (↑16 to ↑73)  Metabolite 14-OH clarithromycin C <sub>max</sub> ↑47 (↑21 to ↑80)  Nevirapine AUC ↑26 Nevirapine C <sub>min</sub> ↑28 Nevirapine C <sub>max</sub> ↑24	Clarithromycin exposure was significantly decreased, 14-OH metabolite exposure increased. Because the clarithromycin active metabolite has reduced activity against <i>Mycobacterium aviumintracellulare</i> complex overall activity against the pathogen may be altered. Alternatives to clarithromycin, such as azithromycin should be considered. Close monitoring for hepatic abnormalities is recommended.

	compared to historical controls	
Rifabutin 150 or 300 mg QD	<p>Rifabutin AUC ↑17 (↓2 to ↑40) Rifabutin C<sub>max</sub> ↑28 (↑9 to ↑51)</p> <p>Metabolite 25-O-desacetyl-rifabutin AUC ↑24 (↓16 to ↑84)</p> <p>Metabolite 25-O-desacetyl-rifabutin C<sub>max</sub> ↑29 (↓2 to ↑68)</p> <p>A clinically not relevant increase in the apparent clearance of nevirapine (by 9%) compared to historical pharmacokinetic data was reported.</p>	<p>No dose adjustment is recommended when rifabutin and Viramune are co-administered.</p> <p>Due to the high intersubject variability some patients may experience large increases in rifabutin exposure and may be at higher risk for rifabutin toxicity. Therefore, caution should be used in concomitant administration.</p>
Rifampicin 600 mg QD	<p>Rifampicin AUC ↔ Rifampicin C<sub>max</sub> ↔</p> <p>Nevirapine AUC ↓58 Nevirapine C<sub>min</sub> ↓68 Nevirapine C<sub>max</sub> ↓50 compared to historical controls</p>	<p>It is not recommended to co-administer rifampicin and Viramune.</p> <p>Physicians needing to treat patients co-infected with tuberculosis and using a Viramune containing regimen may consider co-administration of rifabutin instead.</p>
<b>Antifungals</b>		
Fluconazole 200 mg QD	<p>Fluconazole AUC ↔ Fluconazole C<sub>min</sub> ↔ Fluconazole C<sub>max</sub> ↔</p> <p>Nevirapine exposure: ↑100% compared with historical data where nevirapine was administered alone.</p>	<p>Because of the risk of increased exposure to Viramune, caution should be exercised if the medicinal products are given concomitantly and patients should be monitored closely.</p>
Itraconazole 200 mg QD	<p>Itraconazole AUC ↓61 Itraconazole C<sub>min</sub> ↓87 Itraconazole C<sub>max</sub> ↓38</p> <p>There was no significant difference in nevirapine pharmacokinetic parameters.</p>	<p>A dose adjustment for itraconazole should be considered when these two agents are administered concomitantly.</p>
Ketoconazole 400 mg QD	<p>Ketoconazole AUC ↓72 (↓80 to ↓60) Ketoconazole C<sub>min</sub> § Ketoconazole C<sub>max</sub> ↓44 (↓58 to ↓27)</p> <p>Nevirapine plasma levels: ↑15-28% compared to historical controls.</p>	<p>Ketoconazole and Viramune should not be given concomitantly (see also <i>Warning on concomitant use with other medicines</i>).</p>
<b>ANTACIDS</b>		
Cimetidine	<p>Cimetidine: no significant effect on cimetidine PK parameters is seen.</p> <p>Nevirapine C<sub>min</sub> ↑7</p>	<p>The limited data suggest no dose adjustment when Cimetidine is co-administered with Viramune.</p>



ANTITHROMBOTICS		
Warfarin	The interaction between nevirapine and the antithrombotic agent warfarin is complex, with the potential for both increases and decreases in coagulation time when used concomitantly.	Close monitoring of anticoagulation levels is warranted.
CONTRACEPTIVES		
Depot-medroxy progesterone acetate (DMPA) 150 mg every 3 months	DMPA AUC ↔ DMPA C <sub>min</sub> ↔ DMPA C <sub>max</sub> ↔  Nevirapine AUC ↑20 Nevirapine C <sub>max</sub> ↑20	Viramune co-administration did not alter the ovulation suppression effects of DMPA. No dose adjustment is necessary when DMPA and Viramune are co-administered.
Ethinyl estradiol (EE) 0.035 mg	EE AUC ↓20 (↓33 to ↓3) EE C <sub>min</sub> § EE C <sub>max</sub> ↔	Oral hormonal contraceptives should not be used as the sole method of contraception in women taking Viramune (see also <i>Information for patients</i> ). Appropriate doses for hormonal contraceptives (oral or other forms of application) other than DMPA in combination with Viramune have not been established with respect to safety and efficacy.
Norethindrone (NET) 1.0 mg QD	NET AUC ↓19 (↓30 to ↓7) NET C <sub>min</sub> § NET C <sub>max</sub> ↓16 (↓27 to ↓3)	
DRUG ABUSE		
Methadone Individual Patient Dosing	Methadone AUC ↓60 (↓69 to ↓49) Methadone C <sub>min</sub> § Methadone C <sub>max</sub> ↓42 (↓50 to ↓33)	Narcotic withdrawal syndrome has been reported in patients treated with Viramune and methadone concomitantly.  Methadone-maintained patients beginning Viramune therapy should be monitored for evidence of withdrawal and methadone dose should be adjusted accordingly.
HERBAL PRODUCTS		
St John's Wort	Serum levels of nevirapine can be reduced by concomitant use of the herbal preparation St John's Wort ( <i>Hypericum perforatum</i> ). This is due to induction of drug metabolism enzymes and/or transport proteins by St Johns Wort.	Herbal preparations containing St John's Wort should not be combined with Viramune. If patient is already taking St John's Wort check nevirapine and if possible viral levels and stop St John's Wort. Nevirapine levels may increase on stopping St John's Wort. The dose of Viramune may need adjusting. The inducing effect may persist for at least 2 weeks after cessation of treatment with St John's Wort (see also Contraindications).

§ = C<sub>min</sub> below detectable level of the assay

↑ = Increase, ↓ = Decrease, ↔ = No Effect

## Other information

*In vitro* studies using human liver microsomes indicated that the formation of nevirapine hydroxylated metabolites was not affected by the presence of dapsone and trimethoprim/sulphamethoxazole. Erythromycin significantly inhibited the formation of nevirapine hydroxylated metabolites. Clinical studies have not been performed.

It should be noted that other compounds that are substrates of CYP3A and CYP2B6 might have decreased plasma concentrations when co-administered with nevirapine. The following drugs have been reported as substrates for the CYP3A isoenzyme system and might theoretically interact with nevirapine: some calcium channel blocking drugs including diltiazem and verapamil; some antiarrhythmic drugs (including disopyramide, lignocaine); cyclosporin; some imidazole antifungal agents including itraconazole; some anticonvulsant drugs (including carbamazepine); some antidepressant drugs (including fluoxetine, fluvoxamine and nefazodone); some antihistamines (loratadine); gestodene; grapefruit juice. These potential interactions have not been investigated, however the results from studies of other CYP3A inducing drugs have demonstrated a negligible effect on nevirapine.

Table 7 Potential drug interactions

<b>Examples of drugs in which plasma concentrations may be decreased by co-administration with nevirapine</b>	
<b>Drug class</b>	<b>Examples of drugs</b>
Antiarrhythmics	Amiodarone, disopyramide, lidocaine
Anticonvulsants	Carbamazepine, clonazepam, ethosuximide
Antifungals	Itraconazole
Calcium channel blockers	Diltiazem, nifedipine, verapamil
Cancer chemotherapy	Cyclophosphamide
Ergot alkaloids	Ergotamine
Immunosuppressants	Cyclosporin, tacrolimus, sirolimus
Motility agents	Cisapride
Opiate agonists	Fentanyl
<b>Examples of drugs in which plasma concentrations may be increased by co-administration with nevirapine</b>	
Antithrombotics	Warfarin Potential effect on anticoagulation. Monitoring of anticoagulation levels is recommended.

## **Information for patients**

**Patients should be instructed that the major toxicity of Viramune is rash and should be advised to promptly notify their physician of any rash.** The majority of rashes associated with Viramune occur within the first 6 weeks of initiation of therapy. Therefore, patients should be monitored carefully for the appearance of rash during this period. Patients should be instructed that dose escalation is not to occur if any rash occurs during the two-week lead-in dosing period, until the rash resolves. The 200 mg once daily dosing regimen should not be continued beyond 4 weeks (28 days) at which point an alternative regimen should be sought.

Patients should be informed that liver function test abnormalities are common in patients with HIV infection. Abnormal liver function tests and cases of clinical hepatitis have been reported with Viramune. **Patients should be instructed to consult their physicians immediately should symptoms of hepatitis occur.**

Patients should be informed that Viramune is not a cure for HIV-1 infection, and that they may continue to experience illnesses associated with advanced HIV-1 infection, including opportunistic infections. Treatment with Viramune has not been shown to reduce the incidence or frequency of

such illnesses, and patients should be advised to remain under the care of a physician when using Viramune.

Patients should be informed that the long term effects of Viramune are unknown at this time. They should also be informed that Viramune therapy has not been shown to reduce the risk of transmission of HIV-1 to others through sexual contact or blood contamination.

Viramune may interact with some drugs; therefore, patients should be advised to report to their doctor the use of any other medications.

Patients should be instructed that oral contraceptives and other hormonal methods of birth control should not be used as a method of contraception in women taking Viramune.

Patients should be informed to take Viramune every day as prescribed. Patients should not alter the dose without consulting their doctor. If a dose is missed, patients should take the next dose as soon as possible.

Patients taking Viramune suspension should be advised that if they decide to use a metric measure other than the dispensing syringe provided with the suspension, they should ensure that the entire dose is taken by rinsing the metric measure with water and swallowing the rinse water.

## ADVERSE EFFECTS

The most frequently reported adverse events related to Viramune therapy were rash, fever, nausea, headache, fatigue, somnolence, vomiting, diarrhoea, abdominal pain and myalgia. Cases of anaemia and neutropenia may be associated with Viramune therapy. Arthralgia has been reported as a stand-alone event in rare instances in patients receiving Viramune containing regimens.

The following adverse events which may be causally related to the administration of Viramune immediate-release have been reported. The frequencies estimated are based on pooled clinical trial data for events considered related to Viramune immediate-release treatment.

Frequency classes: very common ( $\geq 1/10$ ); common ( $\geq 1/100$ ,  $< 1/10$ ); uncommon ( $\geq 1/1,000$ ,  $< 1/100$ ); rare ( $\geq 1/10,000$ ,  $< 1/1,000$ ); very rare ( $< 1/10,000$ ).

### Blood and lymphatic system disorders

common: granulocytopenia,  
uncommon: anaemia

### Immune system disorders

common: hypersensitivity (including anaphylactic reaction, angioedema, urticaria)  
uncommon: drug rash with eosinophilia and systemic symptoms, anaphylactic reaction

### Nervous system disorders

common: headache

### Gastrointestinal disorders

common: nausea, vomiting, abdominal pain, diarrhoea

### Hepato-biliary disorders

common: hepatitis (1.2 %) (including severe and life-threatening hepatotoxicity), liver function tests abnormal  
uncommon: jaundice  
rare: liver failure / fulminant hepatitis (which may be fatal)

### Skin and subcutaneous tissue disorders

very common: rash

uncommon: Stevens-Johnson syndrome (0.3 %), toxic epidermal necrolysis (which may be fatal), urticaria, angio-oedema

### Musculoskeletal, connective tissue and bone disorders

common: myalgia

uncommon: arthralgia

### General disorders and administration site conditions

common: fatigue, pyrexia

uncommon: fever

### Investigations

common: liver function test abnormal (alanine aminotransferase increased; transaminases increased; aspartate aminotransferase increased; gamma-glutamyltransferase increased; hepatic enzyme increased; hypertransaminasaemia).

uncommon: blood phosphorus decreased, blood pressure increased

There are no new adverse drug reactions for Viramune XR extended-release that have not been previously identified for Viramune immediate-release tablets and oral suspension.

## **Skin and subcutaneous tissues**

The most common clinical toxicity of Viramune is rash, with Viramune attributable rash occurring in 9% of patients in combination regimens in controlled studies (Trials 1100.1037, 1100.1038, 1100.1046, 1100.1090). In these clinical trials 24% of patients treated with Viramune-containing regimen experienced rash compared with 15% of patients treated in control groups. Severe or life-threatening rash occurred in 1.7% of Viramune-treated patients compared with 0.2% of patients treated in the control groups.

Rashes are usually mild to moderate, maculopapular erythematous cutaneous eruptions, with or without pruritus, located on the trunk, face and extremities. Allergic reactions (anaphylaxis, angio-oedema and urticaria) have been reported. Rashes occur alone or in the context of hypersensitivity reactions, characterised by rash with constitutional symptoms such as fever, arthralgia, myalgia and lymphadenopathy, plus visceral involvement, such as hepatitis, eosinophilia, granulocytopenia and renal dysfunction.

Severe and life-threatening skin reactions including Stevens-Johnson syndrome (SJS) and uncommonly toxic epidermal necrolysis (TEN) have occurred in patients treated with Viramune immediate-release tablets. Fatal cases of SJS, TEN and hypersensitivity reactions have been reported. The majority of severe rashes occurred within the first 6 weeks of treatment.

In Trial 1100.1486 (VERxVE) antiretroviral-naïve patients received a lead-in dose of Viramune immediate-release 200 mg once daily for 14 days (n=1068) and then were randomised to receive either Viramune immediate-release 200 mg twice daily or Viramune XR extended-release 400 mg once daily. All patients received tenofovir + emtricitabine as background therapy. The safety data include all patient visits up to the time of the last patient's completion of the 48-week primary endpoint in the study (mean observation period 61 weeks). Severe or life-threatening rash considered related to Viramune treatment occurred in 1.1% of patients during the lead-in phase with Viramune immediate-release, and in 0.8% and 0.6% of the Viramune immediate-release and Viramune XR extended-release groups respectively during the randomisation phase. In addition, five cases of Stevens-Johnson Syndrome were reported in the trial, all of which occurred within the first 30 days of Viramune treatment.

In Study 1100.1526 (TRANxITION) patients on Viramune immediate-release 200 mg twice daily treatment for at least 18 weeks were randomised to either receive Viramune XR extended-release 400 mg once daily (n=295) or remain on their Viramune immediate-release treatment. In this study, no Grade 3 or 4 rash was observed in either treatment group.

## **Hepato-biliary**

The most frequently observed laboratory test abnormalities are elevations in liver function tests (LFTs) including ALT, AST, GGT, total bilirubin and alkaline phosphatase. Asymptomatic elevations of GGT levels are more frequent in Viramune recipients than in controls. Cases of jaundice have been reported. Cases of hepatitis, severe and life-threatening hepatotoxicity, and fatal fulminant hepatitis have occurred in patients treated with Viramune. In a large clinical trial (Trial 1100.1090), the risk of a serious hepatic event among 1121 patients receiving Viramune immediate-release for a median duration of greater than one year was 1.2% (versus 0.6% in placebo group).

In Trial 1100.1486 (VERxVE) treatment-naïve patients received a lead-in dose of Viramune 200 mg immediate-release once daily for 14 days and then were randomised to receive either Viramune immediate-release 200 mg twice daily or Viramune XR extended-release 400 mg once daily. All patients received tenofovir + emtricitabine as background therapy. Patients were enrolled with CD4+ counts <250 cells/mm<sup>3</sup> for women and <400 cells/mm<sup>3</sup> for men. Data on potential symptoms of hepatic events were prospectively collected in this trial. The safety data include all patient visits up to the time of the last patient's completion of the 48-week primary endpoint in the study (mean observation period 61 weeks). The incidence of symptomatic hepatic events during the Viramune immediate-release lead-in phase was 0.5%. After the lead-in period the incidence of symptomatic hepatic events was 2.8% in the Viramune immediate-release group and 1.6% in the Viramune XR extended-release group. Overall, there was a comparable incidence of symptomatic hepatic events among men and women enrolled in VERxVE.

In Study 1100.1526 (TRANxITION) no Grade 3 or 4 clinical hepatic events were observed in either treatment group.

Increased ASAT or ALAT levels and/or seropositivity for hepatitis B and/or C were associated with a greater risk of hepatic adverse events for both Viramune immediate-release and control groups. The best predictor of a serious hepatic event was elevated baseline liver function tests.

The first 18 weeks of treatment is a critical period which requires close monitoring. The risk of hepatic events is greatest in the first 6 weeks of therapy. However the risk continues past this period and monitoring should continue at frequent intervals throughout treatment (see PRECAUTIONS). Clinical hepatitis may be isolated or associated with rash and/or additional constitutional symptoms.

## **Postmarketing surveillance**

The postmarketing experience has shown that the most serious adverse reactions are Stevens-Johnson syndrome, toxic epidermal necrolysis, hepatitis/hepatic failure and hypersensitivity reactions, (characterised by rash with constitutional symptoms such as fever, arthralgia, myalgia and lymphadenopathy, plus visceral involvement, such as hepatitis, eosinophilia, granulocytopenia, and renal dysfunction).

The following events have been reported with the use of Viramune in clinical practice:

*Body as a Whole:* fever, somnolence, drug withdrawal, redistribution/accumulation of body fat

*Gastrointestinal:* vomiting

*Liver and Biliary:* jaundice, fulminant and cholestatic hepatitis, hepatic necrosis, hepatic failure

*Haematology:* anaemia, eosinophilia, neutropenia

*Musculoskeletal:* arthralgia

*Neurologic:* paraesthesia

*Skin and Appendages:* allergic reactions including anaphylaxis, angioedema, bullous eruptions, ulcerative stomatitis and urticaria have all been reported. In addition, hypersensitivity syndrome and hypersensitivity reactions with rash associated with constitutional findings such as fever, blistering, oral lesions, conjunctivitis, facial oedema, muscle or joint aches, general malaise, fatigue or significant hepatic abnormalities plus one or more of the following: hepatitis, eosinophilia, granulocytopenia, lymphadenopathy and/or renal dysfunction have been reported with the use of Viramune.

## Children

### Viramune immediate-release

Safety has been assessed in 361 HIV-1-infected children between the ages of 3 days to 19 years. The majority of these patients received Viramune in combination with AZT or ddI, or AZT and ddI in two studies. In an open-label trial BI 882 (ACTG 180), 37 patients were followed for a mean duration of 33.9 months (range: 6.8 months to 5.3 years, including long-term follow-up trial BI 892). In ACTG 245, a double-blind placebo controlled study, 305 patients with a mean age 7 years (range: 10 months to 19 years) received combination treatment with Viramune for at least 48 weeks at a dose of 120 mg/m<sup>2</sup> once daily for two weeks followed by 120 mg/m<sup>2</sup> twice daily thereafter. The most frequently reported adverse events related to Viramune were similar to those observed in adults, with the exception of granulocytopenia which was more commonly observed in children. Two Viramune-treated patients experienced Stevens-Johnson Syndrome or Stevens-Johnson/toxic epidermal necrolysis transition syndrome. Both patients recovered after Viramune treatment was discontinued.

In post-marketing surveillance anaemia has been more commonly observed in children.

## Monitoring of Patients

Clinical chemistry tests, which include liver function tests, should be performed prior to initiating Viramune therapy and at appropriate intervals during therapy.

## DOSAGE AND ADMINISTRATION

### Immediate release tablets and oral suspension

#### Adults 16 years and older

The recommended dose is Viramune 200 mg daily for the first 14 days (this lead-in period should be used because it has been found to lessen the frequency of rash), followed by 200 mg twice daily, in combination with at least two additional antiretroviral agents. Viramune can be taken with or without food. For concomitantly administered antiretroviral therapy, the manufacturer's recommended dosage and monitoring should be followed.

## Children and adolescents to 15 years

The total daily dose should not exceed 400 mg of Viramune.

Viramune may be dosed in paediatric patients by body surface area (BSA) where BSA is less than 1.33 m<sup>2</sup> or by body weight where body weight is less than 47 kg.

In general BSA dosing is preferred to body weight based dosing, especially for children around 8 years of age to avoid a sudden reduction of the actual dose at this stage.

To calculate the BSA in m<sup>2</sup> use the Mosteller formula given below.

$$\text{Mosteller Formula: BSA (m}^2\text{)} = \sqrt{\frac{\text{Height (cm)} \times \text{Wt (kg)}}{3600}}$$

The recommended oral dose of Viramune oral suspension (50 mg/5 mL) in mL is then calculated by multiplying the BSA in m<sup>2</sup> by a factor of 15.

$$\text{Dose in mL} = \text{BSA (in m}^2\text{)} \times 15$$

This corresponds with a dose of 150 mg/m<sup>2</sup>, which is to be taken once daily for two weeks followed by 150 mg/m<sup>2</sup> twice daily thereafter.

By weight the recommended oral dose for paediatric patients up to 8 years of age is 4 mg/kg once daily for 2 weeks followed by 7 mg/kg twice daily thereafter. For patients 8 years and older the recommended dose is 4 mg/kg once daily for two weeks followed by 4 mg/kg twice daily thereafter. A dose calculated on BSA is preferred around 8 years of age to avoid a sudden reduction of actual dose at this age.

In a subset of paediatric patients (n=17) less than 3 months of age, the plasma nevirapine concentrations observed were within the range observed in adults and the remainder of the paediatric population, but were more variable between patients, particularly in the second month of life.

## Dosage Management Considerations

Patients should be advised of the need to take Viramune every day as prescribed. If a dose is missed the patient should not double the next dose but should take the next dose as soon as possible.

Clinical chemistry tests, which include liver function tests, should be performed prior to initiating Viramune therapy and at appropriate intervals during therapy.

Viramune administration should be discontinued if patients experience severe rash or a rash accompanied by constitutional symptoms. Patients experiencing rash during the 14-day lead-in period should not have their Viramune dose increased until the rash has resolved (see PRECAUTIONS, Information for Patients). The 200 mg once daily dosing regimen should not be continued beyond 4 weeks (28 days) at which point an alternative antiretroviral regimen should be sought.

Viramune administration should be interrupted in patients experience moderate or severe liver function test abnormalities (excluding GGT) until liver function tests have returned to baseline. Viramune may then be restarted using the two week lead-in period. Viramune should be permanently discontinued if moderate or severe liver function test abnormalities recur.

If clinical hepatitis occurs, characterised by anorexia, vomiting, icterus AND laboratory findings such as moderate or severe liver function test abnormalities (excluding GGT), Viramune must be permanently stopped. Viramune should not be readministered to patients who have required permanent discontinuation for clinical hepatitis due to Viramune.



Patients who interrupt Viramune dosing for more than 7 days should restart the recommended dosing, using the recommended lead-in dose for the first 14 days followed by the recommended twice daily dose.

Patients taking Viramune suspension should be advised that if they decide to use a metric measure other than the dispensing syringe provided with the suspension, they should ensure that the entire dose is taken by rinsing the metric measure with water and swallowing the rinse water.

## **Extended-release tablets**

### Adults 16 years and older

Patients should initiate therapy with one 200 mg tablet of Viramune immediate-release once daily for the first 14 days (this lead-in period should be used because it has been found to lessen the frequency of rash), followed by one 400 mg tablet of Viramune extended-release once daily.

The Viramune XR extended-release tablets should not be broken, crushed or chewed. Viramune XR extended-release tablets can be taken with or without food. Viramune immediate-release tablets and Viramune XR extended-release tablets should be combined with at least two additional antiretroviral agents. For concomitantly administered therapy, the manufacturers recommended dosage should be followed.

### Adult patients currently on a Viramune immediate-release twice daily regimen

Patients already on a regimen of Viramune immediate-release 200 mg twice daily in combination with other antiretroviral agents can be switched to Viramune XR extended-release 400 mg once daily in combination with other antiretroviral agents without a lead-in period of Viramune immediate-release.

### Dosage Management Considerations

Patients should be advised of the need to take Viramune every day as prescribed. If a dose is missed the patient should not double the next dose but should take the next dose as soon as possible.

Clinical chemistry tests, including liver function tests, should be performed prior to initiating Viramune therapy and at appropriate intervals during therapy.

Patients experiencing rash during the 14 day lead-in period of 200 mg daily should not initiate treatment with Viramune XR extended-release 400 mg until the rash has resolved (see PRECAUTIONS, Information for Patients). The 200 mg once daily lead-in dosing regimen should not be continued beyond 28 days at which point an alternative antiretroviral regimen should be sought.

Patients who interrupt Viramune XR extended-release dosing for more than 7 days should restart the recommended dosing regimen, using the two week lead-in period of Viramune immediate-release.

There are no data on the interchangeability of 100 mg or 50 mg Viramune XR extended-release tablets compared to 400 mg extended-release tablets. Therefore no dosage recommendation can be given for the use of 100 mg or 50 mg Viramune XR extended-release tablets as a substitute for the 400 mg dose form.

### Children three years and older

The safety and efficacy of Viramune XR extended-release tablets in children aged less than 3 years has not been established.

The total daily dose at any time during treatment should not exceed 400 mg for any patient. Viramune XR extended-release tablets may be dosed based on a patient's weight or body surface

area (BSA). In general BSA dosing is preferred to body weight based dosing, especially for children around 8 years of age to avoid a sudden reduction of the actual dose at this stage.

Lead-in dosing with Viramune immediate-release tablets or oral suspension (first 14 days):

All paediatric patients should initiate therapy with 150 mg/m<sup>2</sup> (calculated using the Mosteller formula) or 4 mg/kg body weight administered once daily for the first 14 days. This lead-in period should be used because it has been found to lessen the frequency of rash. The lead-in period is not required if the patient is already on chronic Viramune oral suspension or Viramune immediate-release 200 mg tablets twice daily treatment.

Maintenance dosing with Viramune XR extended-release tablets (after the lead-in):

The recommended oral doses for paediatric patients based upon their BSA is described in the table below.

Recommended Paediatric Dosing by BSA after the Lead-in Period:

BSA range (m <sup>2</sup> )	VIRAMUNE XR extended-release tablets dose (mg)
0.58 - 0.83	200 (2 x 100 mg or 4 x 50 mg)
0.84 - 1.16	300 (3 x 100 mg or 6 x 50 mg)
≥ 1.17	400 (1 x 400 mg)

$$\text{Mosteller Formula: BSA (m}^2\text{)} = \sqrt{\frac{\text{Height (cm)} \times \text{Wt (kg)}}{3600}}$$

The recommended oral doses for paediatric patients based upon their weight are described in the table below. The recommended weight-based paediatric dose is dependent upon the patient's age, with different recommended doses for children from 3 to <8 years of age and children 8 years or older.

Weight range (kg) for patients < 8 years of age	Weight range (kg) for patients ≥ 8 years of age	VIRAMUNE XR extended-release tablets dose (mg)
12.5 - 17.8	17.9 - 31.2	200 (2 x 100 mg or 4 x 50 mg)
17.9 - 24.9	31.3 - 43.7	300 (3 x 100 mg or 6 x 50 mg)
25 and above	43.8 and above	400 (1 x 400 mg)

A dose calculated on BSA is preferred around 8 years of age to avoid a sudden reduction of actual dose at this age.

All paediatric patients should have their weight or BSA checked frequently to assess if dose adjustments are necessary.

The Viramune XR extended-release tablets should not be broken, crushed or chewed. Viramune XR extended-release tablets can be taken with or without food. Viramune immediate-release tablets and Viramune XR extended-release tablets should be combined with at least two additional antiretroviral agents. For concomitantly administered therapy, the manufacturer's recommended dosage should be followed.

Alternatively, Viramune immediate-release oral suspension is available for all age groups for twice daily administration.

## Dosage Management Considerations

Patients should be advised of the need to take Viramune every day as prescribed. If a dose is missed the patient should not double the next dose but should take the next dose as soon as possible.

Clinical chemistry tests, including liver function tests, should be performed prior to initiating Viramune therapy and at appropriate intervals during therapy.

Patients experiencing rash during the 14 day lead-in period should not initiate treatment with Viramune XR extended-release until the rash has resolved (see PRECAUTIONS, Information for Patients). The lead-in dosing regimen should not be continued beyond 28 days at which point an alternative antiretroviral regimen should be sought.

Patients who interrupt Viramune XR extended-release dosing for more than 7 days should restart the recommended dosing regimen, using the two week lead-in period of Viramune immediate-release.

## OVERDOSAGE

There is no known antidote for Viramune overdose. Cases of overdose with Viramune immediate-release at doses ranging from 800 to 6000 mg per day for up to 15 days have been reported. Patients have experienced events including oedema, erythema nodosum, fatigue, fever, headache, insomnia, nausea, pulmonary infiltrates, rash, vertigo, vomiting, increase in transaminases and weight decrease. All events subsided following discontinuation of Viramune.

For information on the management of overdose contact the Poisons Information Centre on 13 11 26 (Australia).

## PRESENTATION AND STORAGE CONDITIONS

### Presentation

200 mg immediate-release tablets	White, oval, biconvex tablets. One side is embossed with "54 193", with a single bisect line separating the "54" and "193". The opposite side has a single bisect line. Bottles: 60, 100 tablets. Blister packs: 14, 60, 100 tablets.
400 mg extended-release tablets	Yellow, oval, biconvex tablets. The tablets are embossed with "V04" on one side and the BI tower logo on the other side. Blister pack: 10, 30 tablets.
100 mg extended-release tablets	Yellow, round biconvex tablets, embossed with "V01" on one side and the BI tower logo on the other side. Bottle: 90 tablets.
50 mg extended-release tablets	Yellow, round biconvex tablets, embossed with "V5" on one side and the "BI" on the other side. Bottle: 180 tablets.
Oral Suspension	White to off-white suspension containing nevirapine 10 mg/1mL (as nevirapine hemihydrate) Bottles of 240 mL of suspension, with a 5 mL dispensing syringe and bottle-syringe adapter.

## Storage

200 mg immediate-release tablets	Bottles: Store below 30°C. Blisters: Store below 25°C.
400 mg, 100 mg, 50 mg extended-release tablets	Bottles and blisters: Store below 30°C.
Oral Suspension	Store below 30°C. Once opened the bottle should be used within 6 months.

**Not all pack sizes and presentations are being distributed in Australia.**

## NAME AND ADDRESS OF THE SPONSOR

Boehringer Ingelheim Pty Limited  
ABN 52 000 452 308  
78 Waterloo Road  
North Ryde NSW 2113

## POISON SCHEDULE OF THE MEDICINE

S4 – Prescription Only Medicine

## DATE OF APPROVAL

TGA approval date: 19 December 2011