

# New Zealand Datasheet

## 1. PRODUCT NAME

VIRAMUNE 50 mg/5 mL oral suspension

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

VIRAMUNE 50 mg/5 mL oral suspension contains 10 mg nevirapine per mL (in the form of 10.35 mg/mL of nevirapine hemihydrate).

### Excipients with known effect:

Each mL of oral suspension contains 150 mg sucrose, 162 mg sorbitol, 1.8 mg of methyl hydroxybenzoate and 0.24 mg of propyl hydroxybenzoate.

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Oral suspension

White to off white homogenous suspension.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

VIRAMUNE is indicated for use in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults and children over the age of 2 months.

Resistant virus emerges rapidly and uniformly when VIRAMUNE is administered as monotherapy. Therefore, VIRAMUNE should always be administered in combination with at least two additional antiretroviral agents.

### 4.2 Dose and method of administration

#### Patients 16 years and older

The recommended dose for VIRAMUNE is 20 mL (200 mg) oral suspension 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 20 mL oral suspension twice daily, in combination with at least two additional antiretroviral agents. VIRAMUNE can be taken with or without food. For concomitantly administered nucleoside therapy, the manufacturer's recommended dosage and monitoring should be followed.

#### Paediatric Patients

The total daily dose should not exceed 400 mg of VIRAMUNE. VIRAMUNE may be dosed in paediatric patients either by body surface area (BSA) or by body weight as follows:

By BSA using the Mosteller formula the recommended oral dose for paediatric patients of all ages is 150 mg/m<sup>2</sup> once daily for two weeks followed by 150 mg/m<sup>2</sup> twice daily thereafter.

Calculation of the volume of VIRAMUNE oral suspension (50 mg/5 ml) required for paediatric dosing on a body surface basis of 150 mg/m<sup>2</sup>:

<b>BSA range (m<sup>2</sup>)</b>	<b>Volume (mL)</b>
0.08 – 0.25	2.5
0.25 – 0.42	5
0.42 – 0.58	7.5
0.58 – 0.75	10
0.75 – 0.92	12.5
0.92 – 1.08	15
1.08 – 1.25	17.5
1.25+	20

$$\sqrt{\frac{\text{Height (cm)} \times \text{Wt (kg)}}{3600}}$$

Mosteller Formula: BSA (m<sup>2</sup>) =

By weight the recommended oral dose for paediatric patients up to 8 years of age is 4 mg/kg once daily for two 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.

Calculation of the volume of VIRAMUNE oral suspension (50 mg/5 ml) required for paediatric dosing after two weeks lead-in period.

Weight Range (kg) for patients < 8 yrs of age on a body weight basis receiving 7 mg/kg.	Weight Range (kg) for patients ≥ 8 years of age on a body weight basis receiving 4 mg/kg.	Volume (ml)
1.79 – 5.36	3.13 – 9.38	2.5
5.36 – 8.93	9.38 – 15.63	5
8.93 – 12.50	15.63 – 21.88	7.5
12.50 – 16.07	21.88 – 28.12	10
16.07 – 19.64	28.12 – 34.37	12.5
19.64 – 23.21	34.37 – 40.62	15
23.21 – 26.79	40.62– 46.88	17.5
26.79+	46.88+	20

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 age.

It is important that the entire measured dose of nevirapine oral suspension is administered. This is assisted by the use of the supplied dispensing syringe. If an alternative measuring device is used (e.g. a dispensing cup or teaspoon for larger doses) the patient should ensure that the entire dose is taken by rinsing the measure with water and swallowing the rinse water.

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.

#### 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. It is strongly recommended to monitor liver function every two to three weeks in the first three months of treatment and then monthly during the next three months.

### Dosage Adjustment

VIRAMUNE must be discontinued if patients experience severe rash or a rash accompanied by constitutional findings (see section 4.4). Patients experiencing rash during the 14-day lead-in period of 200 mg/day should not have their VIRAMUNE dose increased until the rash has resolved. (see section 4.4, Information for Patients). The 200 mg once daily dosing regimen should not be continued beyond 28 days at which point an alternative antiretroviral regimen should be sought.

VIRAMUNE administration should be interrupted in patients experiencing moderate or severe liver function test abnormalities (excluding GGT), until the liver function test elevations have returned to baseline. VIRAMUNE may then be restarted at half the previous dose level. VIRAMUNE should be permanently discontinued if moderate or severe liver function test abnormalities recur (see sections 4.4 and 4.8).

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 re-administered 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 20 ml per day for adults, or 4 mg/kg/day for paediatric patients for the first 14 days (lead-in). This is followed by 20 ml twice daily for adults, and 4 or 7 mg/kg twice a day for paediatric patients depending on age.

### **4.3 Contraindications**

VIRAMUNE is contraindicated in patients with clinically significant hypersensitivity to the active ingredient or any of the excipients of the product.

VIRAMUNE should not be administered to patients with severe hepatic dysfunction (Child-Pugh C) or pre-treatment ASAT or ALAT > 5X Upper Limit of Normality (ULN) until baseline ASAT/ALAT are stabilised < 5X ULN.

VIRAMUNE should not be re-administered to patients who have required permanent discontinuation for severe rash, rash accompanied by constitutional symptoms, hypersensitivity reactions, or clinical hepatitis due to nevirapine.

VIRAMUNE should not be re-administered in patients who previously had ASAT or ALAT > 5X Upper Limit of Normality (ULN) during nevirapine therapy and had rapid recurrence of liver function abnormalities upon re-administration of nevirapine (See section 4.4).

The use of VIRAMUNE oral suspension is contraindicated in patients with rare hereditary conditions such as fructose intolerance or glucose-galactose malabsorption. The suspension contains sucrose and sorbitol (see section 4.4).

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 section 4.5).

#### 4.4 Special warnings and precautions for use

The first 18 weeks of therapy with nevirapine are a critical period, which require close monitoring of patients to disclose the potential appearance of severe and life-threatening skin reactions (including cases of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis), and 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 ( $> 250/\text{mm}^3$  in adult females and  $> 400/\text{mm}^3$  in adult males) at the initiation of VIRAMUNE therapy are associated with a greater risk of hepatic adverse events if the patient has detectable plasma HIV-1 RNA – i.e. a concentration  $\geq 50$  copies/mL – at the initiation of VIRAMUNE.

As serious and life-threatening hepatotoxicity has been observed in controlled and uncontrolled studies predominantly in patients with a plasma HIV-1 viral load of 50 copies/ml or higher, VIRAMUNE should not be initiated in adult females with CD4+ cell counts greater than 250 cells/ $\text{mm}^3$  or in adult males with CD4+ cell counts greater than 400 cells/ $\text{mm}^3$  who have a detectable plasmatic HIV-1 RNA 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 section 4.2).

##### Skin Reactions

Severe and life-threatening skin reactions, including fatal cases, have occurred in patients treated with VIRAMUNE. These have included cases of SJS, TEN, and hypersensitivity syndrome characterised by rash, constitutional findings and visceral involvement. Therefore, 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, muscle or joint aches, or general malaise), including SJS or TEN. VIRAMUNE must be permanently discontinued if any patient is experiencing hypersensitivity reactions, characterised by rash with constitutional symptoms, plus visceral involvement, such as hepatitis, eosinophilia, granulocytopenia, and renal dysfunction or signs of other visceral involvement (see section 4.8 and 4.4 - Information for patients).

Patients should be advised that the major toxicity of VIRAMUNE is rash. The lead-in period should be used as it has been found to lessen the frequency of rash. The majority of rashes associated with VIRAMUNE occur within the first six weeks of therapy therefore patients should be monitored carefully for the appearance of rash during this period. Patients should be instructed that the dose escalation is not to occur if any rash occurs during this lead-in period until the rash 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 for the first 14 days of VIRAMUNE 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, 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 (ASAT or ALAT >5 X 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 and life-threatening hepatotoxicity, including fatal fulminant hepatitis, has occurred in patients treated with VIRAMUNE. 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. Patients should be informed that hepatic reactions are a major toxicity of VIRAMUNE. Patients with signs or symptoms of hepatitis must be advised to discontinue VIRAMUNE and immediately seek medical evaluation, which should include liver function tests.

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

Increased ASAT or ALAT 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.

Female gender and higher CD4 counts at the initiation of VIRAMUNE therapy in treatment naïve patients are associated with increased risk of hepatic adverse events. In a retrospective review of predominantly patients with a plasma HIV-1 viral load of 50 copies/mL or higher, 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% versus 0.9%). An increased risk was observed in men with detectable HIV-1 RNA in plasma and CD4 counts > 400 cells/mm<sup>3</sup> (6.3% versus 1.2 % for men with CD4 counts <400 cells/mm<sup>3</sup>). This increased risk for toxicity based on CD4+ count threshold has not been detected in patients with undetectable (i.e. < 50 copies/mL) plasma viral load.

#### 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 continuing therapy.

Monitoring of hepatic 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.

With ASAT or ALAT 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 pre-treatment ASAT or ALAT > 5X ULN until baseline ASAT/ALAT are stabilised at values < 5X ULN.

**If ASAT or ALAT increase to > 5X ULN during treatment, VIRAMUNE should be immediately stopped. If ASAT and ALAT return to baseline values and if the patient had no clinical signs or 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 200 mg/day for 14 days followed by 400 mg/day. 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), nevirapine must be permanently stopped. VIRAMUNE should not be re-administered to patients who have required permanent discontinuation for clinical hepatitis due to VIRAMUNE.**

#### Other warnings

The following events have been reported when VIRAMUNE has been used in combination with other anti-retroviral agents: pancreatitis, peripheral neuropathy and thrombocytopenia. These events are commonly associated with other anti-retroviral 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 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 associated with HIV diseases. The long-term effects of VIRAMUNE are unknown at this time. VIRAMUNE therapy has not been shown to reduce the risk of horizontal transmission of HIV-1 to others.

Although the utility of VIRAMUNE for the prevention of mother to child HIV-1 transmission has been demonstrated for women who were not receiving other antiretrovirals, extended treatment of the mother with combination antiretroviral agents prior to delivery is recommended, when feasible, to minimise HIV-1 transmission to the infant.

VIRAMUNE is extensively metabolised by the liver and nevirapine metabolites are extensively eliminated 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).

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 following each dialysis treatment would help offset the effects of dialysis on VIRAMUNE clearance. Otherwise patients with CLcr  $\geq$  20 mL/min do not require an adjustment in VIRAMUNE dosing (see section 5.2). 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 representing 50% of the recommended daily dose of VIRAMUNE oral suspension which would help offset the effects of dialysis on VIRAMUNE clearance.

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 levels of these

medications (see also section 4.5). Therefore, when postmenopausal hormone therapy is used during administration of VIRAMUNE, its therapeutic effect should be monitored.

VIRAMUNE oral suspension contains 6 g of sucrose 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 oral suspension contains 6.5 g of sorbitol per maximum recommended daily dose. Patients with the rare hereditary condition of fructose intolerance should not take this medicine.

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

#### 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 pneumonia. Autoimmune disorders (such as Graves' disease) have also been reported to occur in the setting of immune reactivation; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment. Any inflammatory symptoms should be evaluated and treatment instituted when necessary.

#### Warning on concomitant use with other drugs (for detailed description see section 4.5)

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 delavirdine, etravirine, rilpivirine, elvitegravir (in combination with cobicistat), boceprevir; if not co-administered with low dose ritonavir: fosamprenavir, saquinavir, atazanavir.

When administering VIRAMUNE as part of an antiretroviral treatment regimen, the complete product information for each therapeutic component should be consulted before initiation of treatment.

#### Information for patients

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.

**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. Any patient experiencing severe rash or a rash accompanied by constitutional symptoms such as fever, blistering, oral lesions, conjunctivitis, swelling, muscle or joint aches, or general malaise should discontinue medication and consult a physician.

Patients should be informed that liver function test abnormalities are common in patients with HIV infection. Liver function test abnormalities have occurred in patients treated with VIRAMUNE. Some of these patients developed severe or life-threatening hepatotoxicity including fatal fulminant hepatitis.

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. However, if a dose is skipped, the patient should not double the next dose.

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.

#### 4.5 Interaction with other medicines and other forms of interaction

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

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 section 5.2). Thus, if a patient has been stabilized on a dosage regimen for a drug metabolised by CYP3A or CYP2B and begins on VIRAMUNE, dosage adjustments may be necessary.

The absorption of nevirapine is not affected by food, antacids or medicinal products which are formulated with an alkaline buffering agent.

The majority of the interaction data is presented as percent changes (geometric mean) with a 95% prediction interval (95% PI).

Drugs by therapeutic areas	Interaction	Recommendations concerning co-administration
<b>Anti-infectives, Antiretrovirals, NRTIs</b>		
Didanosine 100-150 mg BID (NVP 200 mg QD x 14 days; 200 mg BID x 14 days)	Didanosine AUC ↔ Didanosine C <sub>max</sub> ↔ Didanosine C <sub>min</sub> §	No dosage adjustments are required when VIRAMUNE is taken in combination with didanosine.
Emtricitabine	Emtricitabine is not an inhibitor of human CYP 450 enzymes.	No dosage adjustments are required when VIRAMUNE is taken in combination with emtricitabine.
Abacavir	In human liver microsomes, abacavir did not inhibit cytochrome P450 isoforms.	No dosage adjustments are required when VIRAMUNE is taken in combination with abacavir.
Lamivudine 150mg BID (NVP 200mg 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.



<b>Drugs by therapeutic areas</b>	<b>Interaction</b>	<b>Recommendations concerning co-administration</b>
Stavudine 30/40mg BID, (NVP 200 mg QD x 14 days; 200 mg BID x 14 days)	Stavudine AUC ↔ Stavudine C <sub>max</sub> ↔ Stavudine C <sub>min</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 (NVP 200 mg BID)	Tenofovir levels remain unchanged. Tenofovir does not have an effect on NVP levels.	No dosage adjustments are required when VIRAMUNE is taken in combination with tenofovir.
Zalcitabine 0.125-0.25 mg TID (NVP 200 mg QD x 14 days; 200 mg BID x 14 days)	Zalcitabine AUC ↔ Zalcitabine C <sub>max</sub> ↔ Zalcitabine C <sub>min</sub> §	No dosage adjustments are required when VIRAMUNE is taken in combination with zalcitabine.
Zidovudine 100- 200 mg TID (NVP 200 mg QD x 14 days; 200 mg BID x 14 days)	Zidovudine AUC ↓24 (↓69 to ↑83) Zidovudine C <sub>max</sub> ↓26 (↓84 to ↑254)  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>NNRTIs</b>		
Efavirenz 600 mg QD (NVP 200 mg QD x 14 days; 400 mg QD x 14 days)	Efavirenz AUC ↓28 (↓34 to ↓14) <sup>a</sup> Efavirenz C <sub>max</sub> ↓12 (↓23 to ↑1) <sup>a</sup> Efavirenz C <sub>min</sub> ↓32 (↓35 to ↓19) <sup>a</sup>	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 section 4.4) 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 section 5)
Delavirdine	Interaction has not been studied.	The concomitant administration of VIRAMUNE with NNRTIs is not recommended (see also section 4.4).
Etravirine	Concomitant use of etravirine with nevirapine may cause a significant decrease in the plasma concentrations of etravirine and loss of therapeutic effect of etravirine.	The concomitant administration of VIRAMUNE with NNRTIs is not recommended (see also section 4.4).
Rilpivirine	Interaction has not been studied.	The concomitant administration of VIRAMUNE with NNRTIs is not recommended (see also section 4.4).

Drugs by therapeutic areas	Interaction	Recommendations concerning co-administration
<b>PIs</b>		
Atazanavir/ritonavir 300/100 mg QD 400/100mg QD (NVP 200 mg BID)	<p><u>Atazanavir 300/100mg:</u> Atazanavir AUC ↓42 (↓52 to ↓29)<sup>a</sup> Atazanavir C<sub>max</sub> ↓28 (↓40 to ↓14)<sup>a</sup> Atazanavir C<sub>min</sub> ↓72 (↓80 to ↓60)<sup>a</sup></p> <p><u>Atazanavir 400/100mg</u> Atazanavir AUC ↓19 (↓35 to ↑2)<sup>a</sup> Atazanavir C<sub>max</sub> ↔ Atazanavir C<sub>min</sub> ↓59 (↓73 to ↓40)<sup>a</sup> (compared to 300/100mg without NVP) Nevirapine AUC ↑25 (↑17 to ↑34)<sup>a</sup> Nevirapine C<sub>max</sub> ↑17 (↑9 to ↑25)<sup>a</sup> Nevirapine C<sub>min</sub> ↑32 (↑22 to ↑43)<sup>a</sup></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 (NVP 200mg bid)	<p>Darunavir AUC ↔ Darunavir C<sub>min</sub> ↔</p> <p>Nevirapine AUC ↑27 Nevirapine C<sub>min</sub> ↑47</p>	Darunavir/ritonavir increases the plasma concentrations of nevirapine as a result of CYP3A4 inhibition. Since this difference is not considered to be clinically relevant, the combination of darunavir co-administered with 100 mg ritonavir and VIRAMUNE can be used without dose adjustments.
Fosamprenavir 1400 mg BID (NVP 200 mg BID)	<p>Amprenavir AUC ↓33 (↓45 to ↓20)<sup>a</sup> Amprenavir C<sub>max</sub> ↓25 (↓37 to ↓11)<sup>a</sup> Amprenavir C<sub>min</sub> ↓35 (↓51 to ↓15)<sup>a</sup></p> <p>Nevirapine AUC : ↑29 (↑19 to ↑40)<sup>a</sup> Nevirapine C<sub>max</sub> : ↑25 (↑14 to ↑37)<sup>a</sup> Nevirapine C<sub>min</sub> : ↑34 (↑21 to ↑49)<sup>a</sup></p>	VIRAMUNE should not be given with fosamprenavir if not co-administered with ritonavir. (see also section 4.4)
Fosamprenavir/ritonavir 700/100 mg BID (NVP 200 mg BID)	<p>Amprenavir AUC: not significantly altered Amprenavir C<sub>max</sub> not significantly altered Amprenavir C<sub>min</sub> ↓19 (↓32 to ↓5)<sup>a</sup></p> <p>Nevirapine AUC ↑14 (↑5 to ↑24)<sup>a</sup> Nevirapine C<sub>max</sub> ↑13 (↑3 to ↑24)<sup>a</sup> Nevirapine C<sub>min</sub> ↑22 (↑10 to ↑35)<sup>a</sup></p>	No dosing adjustments are required when VIRAMUNE is co-administered with 700/100 mg of fosamprenavir/ritonavir b.i.d.
Indinavir 800 mg q8h (NVP 200 mg QD x 14 days; 200 mg BID x 14 days)	<p>Indinavir AUC ↓31 (↓64 to ↑30) Indinavir C<sub>max</sub> ↓15 (↓53 to ↑55) Indinavir C<sub>min</sub> ↓44 (↓77 to ↑39)</p> <p>No clinically relevant change in nevirapine plasma levels was found.</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

Drugs by therapeutic areas	Interaction	Recommendations concerning co-administration
		<p>indinavir 1000 mg q8h with VIRAMUNE 200 mg BID will differ from that of indinavir 800 mg q8h with VIRAMUNE 200 mg BID.</p> <p>Today indinavir is generally co-administered with RTV.</p> <p>There are limited clinical data on the interaction of VIRAMUNE with indinavir/ritonavir.</p>
<p>Lopinavir/ritonavir 400/100 mg BID (NVP 200 mg BID)</p>	<p><u>In HIV positive adults:</u>  Lopinavir AUC ↓27  Lopinavir C<sub>max</sub> ↓19  Lopinavir C<sub>min</sub> ↓46</p>	<p>Although the clinical relevance of this observation has not been fully established, 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>
<p>Lopinavir/ritonavir 300/75 mg/m<sup>2</sup> BID (NVP 7 mg/kg or 4 mg/kg QD x 2 weeks; BID x 1 week)</p>	<p><u>Paediatric patients:</u>  Results from a pharmacokinetic study were consistent with the findings in adults:  Lopinavir AUC ↓22 (↓44 to ↑9)<sup>a</sup>  Lopinavir C<sub>max</sub> ↓14 (↓36 to ↑16)<sup>a</sup>  Lopinavir C<sub>min</sub> ↓55 (↓75 to ↓18)<sup>a</sup></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>
<p>Nelfinavir 750 mg TID (NVP 200 mg QD x 14 days; 200 mg BID x 14 days)</p>	<p>Nelfinavir: no clinically relevant changes in pharmacokinetic parameters after the addition of nevirapine.</p> <p>Total exposure of nelfinavir plus the AG1402 metabolite:  AUC ↓20 (↓72 to ↑128)  C<sub>max</sub> ↓12 (↓61 to ↑100)  C<sub>min</sub> ↓35 in (↓90 to ↑316)  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>
<p>Ritonavir 600 mg BID (NVP 200 mg QD x 14 days; 200 mg BID x 14 days)</p>	<p>The coadministration leads to no clinically relevant change in ritonavir or nevirapine plasma levels.  Ritonavir AUC ↔  Ritonavir C<sub>max</sub> ↔  Ritonavir C<sub>min</sub> ↔</p>	<p>No dosage adjustments are required when VIRAMUNE is taken in combination with ritonavir.</p>
<p>Saquinavir 600 mg TID (NVP 200 mg QD x 14 days; 200 mg BID x 21 days)</p>	<p>Saquinavir AUC ↓38 (↓47 to ↓11)<sup>a</sup>  Saquinavir C<sub>max</sub> ↓32 (↓44 to ↓6)<sup>a</sup>  Saquinavir C<sub>min</sub> §</p>	<p>VIRAMUNE should not be given with saquinavir if not co-administered with ritonavir. (see also section 4.4)</p>

<b>Drugs by therapeutic areas</b>	<b>Interaction</b>	<b>Recommendations concerning co-administration</b>
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 (NVP 200mg 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 clinical non-significant 20% decrease of TPV C <sub>min</sub> . No significant interaction is expected between nevirapine and tipranavir co-administered with low dose ritonavir.	No dosage adjustments are required when VIRAMUNE is taken in combination with tipranavir co-administered with ritonavir.
<b>Entry Inhibitors</b>		
Enfuvirtide	No clinically significant pharmacokinetic interactions are expected between enfuvirtide and concomitantly given medicinal products metabolised by CYP450 enzymes.	Due to the metabolic pathway of enfuvirtide no interaction is expected. Therefore no dose adjustment is recommended when co-administering enfuvirtide with VIRAMUNE.
Maraviroc 300 mg Single Dose (Nevirapine 200 mg BID)	Maraviroc AUC ↔ Maraviroc C <sub>max</sub> ↑ 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	No clinical data available	Due to the metabolic pathway of raltegravir no interaction is expected. Therefore no dose adjustment is recommended when co-administering raltegravir with VIRAMUNE.
Elvitegravir/cobicistat	Interaction has not been studied. Cobicistat, a cytochrome P450 3A inhibitor significantly inhibits hepatic enzymes, as well as other metabolic pathways. Therefore coadministration would likely result in altered plasma levels of cobicistat and VIRAMUNE.	Coadministration of VIRAMUNE with elvitegravir in combination with cobicistat is not recommended (see also section 4.4).
<b>Antivirals for Hepatitis B and C</b>		
Interferons (pegylated interferons alfa 2a and alfa 2b)	Interferons have no known effect on CYP 3A4 or 2B6. No clinically relevant drug-drug interaction is expected.	Interferons and VIRAMUNE may be co-administered without dose adjustments.

<b>Drugs by therapeutic areas</b>	<b>Interaction</b>	<b>Recommendations concerning co-administration</b>
Entecavir	Entecavir is not a substrate, inducer or an inhibitor of cytochrome P450 (CYP450) enzymes. Due to the metabolic pathway of entecavir, no clinically relevant drug-drug interaction is expected.	Entecavir and VIRAMUNE may be co-administered without dose adjustments.
Telbivudine	Telbivudine is not a substrate, inducer or inhibitor of the cytochrome P450 (CYP450) enzyme system. Due to the metabolic pathway of telbivudine, no clinically relevant drug-drug interaction is expected.	Telbivudine and VIRAMUNE may be co-administered without dose adjustments.
Adefovir	Results of in vitro studies showed a weak antagonism of nevirapine by adefovir (see also section 5), this has not been confirmed in clinical trials and reduced efficacy is not expected. Adefovir did not influence any of the common CYP isoforms known to be involved in human drug metabolism and is excreted renally. No clinically relevant drug-drug interaction is expected.	Adefovir and VIRAMUNE may be co-administered without dose adjustments.
Ribavirin	Results of in vitro studies showed a weak antagonism of nevirapine by ribavirin (see also section 5), this has not been confirmed in clinical trials and reduced efficacy is not expected. Ribavirin does not inhibit cytochrome P450 enzymes, and there is no evidence from toxicity studies that ribavirin induces liver enzymes. No clinically relevant drug-drug interaction is expected.	Ribavirin and VIRAMUNE may be co-administered without dose adjustments.
Boceprevir	Boceprevir is partly metabolized by CYP3A4/5. Co-administration of boceprevir with medicines that induce or inhibit CYP3A4/5 could increase or decrease exposure. Plasma trough concentrations of boceprevir were decreased when administered with an NNRTI with a similar metabolic pathway as nevirapine. The clinical outcome of this observed reduction of boceprevir trough concentrations has not been directly assessed.	It is not recommended to co-administer boceprevir and VIRAMUNE (see also section 4.4).

Drugs by therapeutic areas	Interaction	Recommendations concerning co-administration
Telaprevir	Telaprevir is metabolised in the liver by CYP3A and is a P-glycoprotein substrate. Other enzymes may be involved in the metabolism. Co-administration of telaprevir and medicinal products that induce CYP3A and/or P-gp may decrease telaprevir plasma concentrations. No drug-drug interaction study of telaprevir with nevirapine has been conducted, however, interaction studies of telaprevir with an NNRTI with a similar metabolic pathway as nevirapine demonstrated reduced levels of both. Results of DDI studies of telaprevir with efavirenz indicate that caution should be exercised when co-administering telaprevir with P450 inducers.	Caution should be exercised when co-administering telaprevir with nevirapine. If co-administered with VIRAMUNE, an adjustment in the telaprevir dose should be considered.
<b>Antibiotics</b>		
Clarithromycin 500 mg BID (NVP 200 mg QD x 14 days; 200 mg BID x 14 days)	<p>Clarithromycin AUC ↓31 (↓57 to ↑9)</p> <p>Clarithromycin C<sub>min</sub> ↓56 (↓92 to ↑126)</p> <p>Metabolite 14-OH clarithromycin AUC ↑42 (↓41 to ↑242)</p> <p>Metabolite 14-OH clarithromycin C<sub>max</sub> ↑47 (↓39 to ↑255)</p> <p>Nevirapine AUC ↑26</p> <p>Nevirapine C<sub>max</sub> ↑24</p> <p>Nevirapine C<sub>min</sub> ↑28</p> <p>compared to historical controls.</p>	No dose adjustment is recommended for either clarithromycin or VIRAMUNE when the two medicinal products are co-administered. Close monitoring of hepatic abnormalities is nevertheless recommended. However, alternative therapy to clarithromycin should be considered when treating a patient for mycobacterium avium-intracellulare complex, as the active metabolite is not effective in this instance.
Rifabutin 150 or 300 mg QD (NVP 200 mg QD x 14 days; 200 mg BID x 14 day)	<p>Rifabutin AUC ↑17 (↓53 to ↑191)</p> <p>Rifabutin C<sub>max</sub> ↑28 (↓44 to ↑195)</p> <p>Metabolite 25-O-desacetyl-rifabutin AUC ↑24% (↓83 to ↑787)</p> <p>Metabolite 25-O-desacetyl-rifabutin C<sub>max</sub> ↑29% (↓67 to ↑400).</p> <p>A clinically not relevant increase in the apparent clearance of nevirapine (by 9%) compared to historical pharmacokinetic data was reported.</p>	No dose adjustment is recommended when rifabutin and VIRAMUNE are co-administered. 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.

<b>Drugs by therapeutic areas</b>	<b>Interaction</b>	<b>Recommendations concerning co-administration</b>
Rifampicin 600 mg QD (NVP 200 mg QD x 14 days; 200 mg BID x 14 days)	Rifampicin $C_{max}$ and AUC: no significant change.  Nevirapine AUC ↓58 Nevirapine $C_{max}$ ↓50 Nevirapine $C_{min}$ ↓68 compared to historical data.	VIRAMUNE and rifampicin should not be used in combination. Limited clinical data exist with a dose adjustment for VIRAMUNE when co-administered with Rifampicin. (see also section 4.4) Physicians needing to treat patients co-infected with tuberculosis and using a VIRAMUNE containing regimen may consider use of rifabutin instead.
<b>Antifungals</b>		
Fluconazole 200 mg QD (NVP 200 mg QD x 14 days; 200 mg BID x 14 days)	Fluconazole AUC ↔ Fluconazole $C_{max}$ ↔ Fluconazole $C_{min}$ ↔  Nevirapine exposure: ↑100% compared with historical data where nevirapine was administered alone.	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.
Itraconazole 200 mg QD (NVP 200 mg QD)	Itraconazole AUC ↓61 Itraconazole $C_{max}$ ↓38 Itraconazole $C_{min}$ ↓87  There was no significant difference in nevirapine pharmacokinetic parameters.	A dose adjustment for itraconazole should be considered when these two agents are administered concomitantly.
Ketoconazole 400 mg QD (NVP 200 mg QD x 14 days; 200 mg BID x 14 days)	Ketoconazole AUC ↓72 (↓95 to ↑101) Ketoconazole $C_{max}$ ↓44 (↓86 to ↑158)  Nevirapine plasma levels: ↑15-28% compared to historical controls.	Ketoconazole and VIRAMUNE should not be given concomitantly. (see also section 4.4)
<b>Antacids</b>		
Cimetidine	Nevirapine $C_{min}$ ↑ 7	The limited data suggest no dose adjustment when Cimetidine is co-administered with VIRAMUNE.
<b>Antithrombotics</b>		
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.	The net effect of the interaction may change during the first weeks of co-administration or upon discontinuation of VIRAMUNE, and close monitoring of anticoagulation levels is therefore warranted.

Drugs by therapeutic areas	Interaction	Recommendations concerning co-administration
<b>Contraceptives</b>		
Depo-medroxy-progesterone acetate (DMPA) 150 mg every 3 months (NVP 200 mg QD x 14 days; 200 mg BID x 14 days)	DMPA AUC ↔ DMPA C <sub>max</sub> ↔ DMPA C <sub>min</sub> ↔  Nevirapine AUC ↑20 Nevirapine C <sub>max</sub> ↑20	No dose adjustment is necessary when DMPA and VIRAMUNE are co-administered. VIRAMUNE co-administration did not alter the ovulation suppression effects of DMPA.
Ethinyl estradiol (EE) 0.035 mg and Norethindrone (NET) 1.0 mg (single dose)  (NVP 200 mg QD x 14 days; 200 mg BID x 14 days)	EE AUC ↓20 (↓57 to ↑52) EE C <sub>max</sub> ↔ EE C <sub>min</sub> §  NET AUC ↓19 (↓50 to ↑30) NET C <sub>max</sub> ↓16 (↓49 to ↑37) NET C <sub>min</sub> §	Oral hormonal contraceptives should not be used as the sole method of contraception in women taking VIRAMUNE. (see also section 4.4). 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.
<b>Analgesics/Opioids</b>		
Methadone Individual Patient Dosing (NVP 200 mg QD x 14 days; 200 mg BID ≥ 7 days)	Methadone AUC ↓65 (↓82 to ↓32) Methadone C <sub>max</sub> ↓50 (↓67 to ↓25)	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.
<b>Herbal products</b>		
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 Johns'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 section 4.3)

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

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

<sup>a</sup> data presented as geometric mean with a 90% prediction interval (90% PI).

#### Other Information

In vitro studies using human liver microsomes indicated that the formation of nevirapine hydroxylated metabolites was not affected by the presence of dapson, rifabutin, rifampicin and trimethoprim/sulfamethoxazole. Ketoconazole and erythromycin significantly inhibited the formation of nevirapine hydroxylated metabolites. Clinical studies have not been performed.



## 4.6 Fertility, pregnancy and lactation

### Pregnancy

A fair amount of data (584 first trimester and 1044 second/third trimester exposures according to the Antiretroviral Pregnancy Registry as of 31 July 2007 on pregnant women indicate no malformative or foeto/ neonatal toxicity.

The use of VIRAMUNE during pregnancy, if deemed necessary, may be considered.

No observable teratogenicity was detected in reproductive studies performed in pregnant rats and rabbits. In rats, a significant decrease in fetal body weight occurred at doses providing systemic exposure approximately 50% higher, based on AUC, than that seen at the recommended human clinical dose. The maternal and development no-observable-effect level dosages in rats and rabbits produced systemic exposures approximately equivalent to or approximately 50% higher, respectively, than those seen at the recommended daily human dose, based on AUC.

There have been no adequate and well controlled studies of VIRAMUNE in pregnant women. The US Antiretroviral Pregnancy Registry, which has been surveying pregnancy outcomes since January 1989, suggests that there is no signal apparent for birth defects related to VIRAMUNE. While the Registry population exposed and monitored to date is not sufficient to detect an increase in the risk of relatively rare defects, for VIRAMUNE sufficient numbers of first trimester exposures have been monitored to detect at least a 2-fold increase in risk of overall birth defects. These findings should provide some assurance in counselling patients.

VIRAMUNE for the prevention of mother to child transmission of HIV-1 has been demonstrated to be safe and effective when given as part of a regimen that includes a single 200 mg oral dose to mothers during labour followed by a single 2 mg/kg dose to the infant within 72 hours after birth.

*Pregnant Women:* In HIV-1-infected women in labour, the half-life of VIRAMUNE after a single oral 200 mg dose is prolonged (60-70 hours) and oral clearance is highly variable ( $2.1 \pm 1.5$  l/h), consistent with the physiological stresses of labour (studies PACTG 250 [n=17] and HIVNET 006 [n=21]). Nevirapine readily crosses the placenta such that the administration of a 200 mg dose to the mothers resulted in cord concentrations above 100 ng/ml and a cord blood-to-maternal blood ratio of  $0.84 \pm 0.19$  (n=36; range 0.37-1.22).

As hepatotoxicity is more frequent in women with CD4+ cell counts above 250 cells/mm<sup>3</sup> with detectable HIV-1 RNA in plasma (50 or more copies/mL), these conditions should be taken in consideration on therapeutic decision (see section 4.4). There is not enough evidence to substantiate that the absence of an increased risk for toxicity seen in pre-treated women initiating VIRAMUNE with an undetectable viral load (less than 50 copies/mL of HIV-1 in plasma) and CD4+ cell counts above 250 cells/mm<sup>3</sup> also applies to pregnant women. All the randomised studies addressing this issue specifically excluded pregnant women, and pregnant women were under-represented in cohort studies as well as in meta-analyses.

*Neonates:* In neonates receiving a 2 mg/kg oral dose of VIRAMUNE suspension within 72 hours after birth, born to HIV-1-infected women administered a single 200 mg dose during labour, the geometric mean half-life of nevirapine was 47 hours (n=36). Plasma levels were maintained above 100 ng/mL for the first week of life (studies PACTG 250 and HIVNET 006).

### Breastfeeding

It is recommended that HIV-infected mothers not breast-feed their infants to avoid risking postnatal transmission of HIV. Results from 2 pharmacokinetic studies (ACTG 250 and HIVNET 006) have shown that VIRAMUNE readily crosses the placenta and is found in breast milk. In study ACTG 250, breast milk samples collected in 3 of 10 HIV-1-infected pregnant women after administration of a single oral dose of 100 mg or 200 mg VIRAMUNE (at a median of 5.8 hours before delivery), demonstrated a median ratio of the concentration of VIRAMUNE in breast milk to that in maternal

serum of 76% (54-104%). Results from study HIVNET 006 (n=20) indicate a median breast milk to maternal plasma concentration of 60.5% (25-122%), after a single oral 200 mg VIRAMUNE dose.

Consistent with the recommendation that HIV-infected mothers not breast-feed their infants to avoid risking postnatal transmission of HIV, mothers should discontinue breastfeeding if they are receiving VIRAMUNE.

#### 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 provided with the recommended clinical dose of VIRAMUNE.

No human data on fertility are available.

### **4.7 Effects on ability to drive and use machines**

There are no specific studies about the ability to drive vehicles and use machinery. However, patients should be advised that they may experience undesirable effects such as fatigue during treatment with VIRAMUNE. Therefore, caution should be recommended when driving a car or operating machinery. If patients experience fatigue they should avoid potentially hazardous tasks such as driving or operating machinery.

### **4.8 Undesirable effects**

#### Summary of the safety profile

##### Adults

Apart from rash and abnormal Liver Function Tests (LFT), the most frequent adverse events related to VIRAMUNE therapy across all clinical trials were nausea, fatigue, fever, headache, vomiting, diarrhoea, abdominal pain and myalgia. In very rare instances 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 post-marketing experience has shown that the most serious adverse events are SJS, TEN, serious hepatitis/hepatic failure and hypersensitivity syndrome, 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 first 18 weeks of treatment is a critical period which requires close monitoring (see section 4.4).**

#### *Skin and subcutaneous tissue*

The most common clinical toxicity of VIRAMUNE is rash. Severe or life-threatening skin reactions occur with a frequency of approximately 2% (see Table 1). These include Stevens-Johnson syndrome (SJS) and, rarely, toxic epidermal necrolysis (TEN) which occur almost exclusively within the first six weeks of therapy. Based on a denominator of 2861 nevirapine-treated clinical trial patients, the overall incidence of SJS was 0.3% (9/2861).

Rashes occur alone or in the context of a hypersensitivity syndrome characterised by rash with constitutional symptoms such as fever, arthralgia, myalgia and lymphadenopathy plus visceral involvement, such as hepatitis, eosinophilia, granulocytopenia and renal dysfunction. Fatal cases of SJS, TEN and hypersensitivity syndrome have been reported.

**Table 1: Risk of Rash (%) in Adult Placebo Controlled Trials <sup>1,2</sup> through 52 weeks of treatment <sup>3</sup> – Regardless of Causality**

	<b>VIRAMUNE</b>	<b>Placebo</b>
	n=1374 %	n=1331 %
Rash events of all grades <sup>4</sup>	24.0	14.9
Grade 3 or 4 <sup>4</sup>	1.7	0.2

<sup>1</sup> Trial 1090: Background therapy included 3TC for all patients and combinations of NRTIs and PIs

<sup>2</sup> Trials 1037, 1038 and 1046: Background therapy included AZT and AZT+ddl; Viramune<sup>®</sup> monotherapy was administered in some patients

<sup>3</sup> % based on Kaplan-Meier probability estimates

<sup>4</sup> NCI grading system

Rashes are usually mild to moderate, maculopapular erythematous cutaneous eruptions, with or without pruritus, located on the trunk, face and extremities. Allergic reactions (including anaphylaxis, angio-oedema and urticaria) have been reported. The majority of rashes of any severity occur 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 prolonged-release 400 mg once daily. All patients received tenofovir + emtricitabine as background therapy. Safety data included all the patient visits up to the point in time when the last patient completed 144 weeks in the trial. This also includes safety data for patient visits in the post-week 144 open label extension (which patients in either treatment group who completed the 144 week blinded phase could enter). 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. Severe rash occurred in 1.4% and 0.2% of the VIRAMUNE immediate-release and VIRAMUNE prolonged-release groups respectively during the randomised phase. No life-threatening (Grade 4) rash events considered related to Viramune were reported during the randomised phase of this study. Six cases of Stevens-Johnson Syndrome were reported in the trial, all but one 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 prolonged-release 400 mg once daily (n=295) or remain on their VIRAMUNE immediate-release treatment (n=148) 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 including ALAT, ASAT, GGT, total bilirubin and alkaline phosphatase. Asymptomatic elevations of GGT levels are most frequent. Cases of jaundice have been reported. Cases of hepatitis, severe and life-threatening hepatotoxicity, and fulminant hepatitis, have been reported in patients treated with VIRAMUNE. In clinical trials, the risk of clinical hepatic events with VIRAMUNE at 1 year was approximately 2-fold that of placebo.

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 prolonged-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 study week 144. 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 2.4% in the VIRAMUNE immediate-release group and 1.6% in the VIRAMUNE prolonged-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 was associated with a greater risk of hepatic adverse events for both VIRAMUNE and control groups. The risk of hepatic events at 1 year of VIRAMUNE treatment was less than 2% among patients who were hepatitis B and/or C negative. 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 section 4.4).

Clinical hepatitis may be isolated or associated with rash and/or additional constitutional symptoms.

For liver function test monitoring see section 4.4.

#### Paediatric Patients

Safety has been assessed in 361 HIV-1-infected paediatric patients between the ages of 3 days to 19 years. The majority of these patients received VIRAMUNE in combination with AZT or ddl, or AZT + ddl 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 a 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 in these studies experienced SJS 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.

#### *Prevention of Vertical Transmission:*

The safety of VIRAMUNE when administered as a single 200 mg dose (two doses in one study) to HIV-infected pregnant women at the onset of labour, and a single 2 mg/kg dose (6 mg in one study) of VIRAMUNE suspension administered to the infant within the first 72 hours of life, has been assessed in over 950 mother-infant pairs in randomized, controlled clinical trials. Infant follow-up ranged from 6 weeks to 18 months after receipt of a single dose. Similar low rates of adverse events were observed in the VIRAMUNE and control groups in these studies. No mothers or infants experienced serious rash or hepatic events that were considered to be related to VIRAMUNE.

#### Summary of adverse reactions

In summary the list of side effects which can be expected with VIRAMUNE treatment include:

##### *Blood and lymphatic system disorders*

Granulocytopenia, anaemia

##### *Immune system disorders*

Drug reaction with eosinophilia and systemic symptoms, anaphylactic reaction, hypersensitivity (including anaphylactic reaction, angioedema, urticaria)

#### *Nervous system disorders*

Headache

#### *Gastrointestinal disorders*

Diarrhoea, abdominal pain, nausea, vomiting

#### *Hepatobiliary disorders*

Hepatitis (including severe and life threatening hepatotoxicity), hepatitis fulminant (which may be fatal), jaundice

#### *Skin and subcutaneous tissue disorders*

Rash, Stevens-Johnson Syndrome/toxic epidermal necrolysis (which may be fatal), angioedema, urticaria

#### *Musculoskeletal and connective tissue disorders*

Arthralgia, myalgia

#### *General disorders and administration site conditions*

Pyrexia, fatigue

#### *Investigations*

Liver function test abnormal (alanine aminotransferase increased; transaminases increased; aspartate aminotransferase increased; gamma-glutamyltransferase increased; hepatic enzyme increased; hypertransaminasaemia), blood phosphorus decreased, blood pressure increased.

#### Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions <https://nzphvc.otago.ac.nz/reporting/>.

### **4.9 Overdose**

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

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

## **5. PHARMACOLOGICAL PROPERTIES**

### **5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: Antivirals for systemic use, non-nucleoside reverse transcriptase inhibitors, ATC code J05AG01.

#### 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, which in the general population would be considered to be associated with a lower cardiovascular risk. 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.

#### 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. In recent studies using human cord blood lymphocytes and human embryonic kidney 293 cells, EC50 values (50% inhibitory concentration) ranged from 14-302 nM against laboratory and clinical isolates of HIV-1.

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 (median EC50 value of 63 nM). Nevirapine had no antiviral activity *in vitro* against isolates from group O HIV-1 and 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. Nevirapine exhibited additive to synergistic anti-HIV-1 activity in combination with the protease inhibitors amprenavir, atazanavir, indinavir, lopinavir, nelfinavir, saquinavir and tipranavir, and the NRTIs abacavir, didanosine, emtricitabine, lamivudine, stavudine, tenofovir and zidovudine. The anti-HIV-1 activity of nevirapine was antagonized 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-1 RT gene Y181C and/or V106A 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 (n = 24) or VIRAMUNE and 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 ddl (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 + ddl 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.

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 ddl. 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 etravirine-containing regimen may be used subsequently.

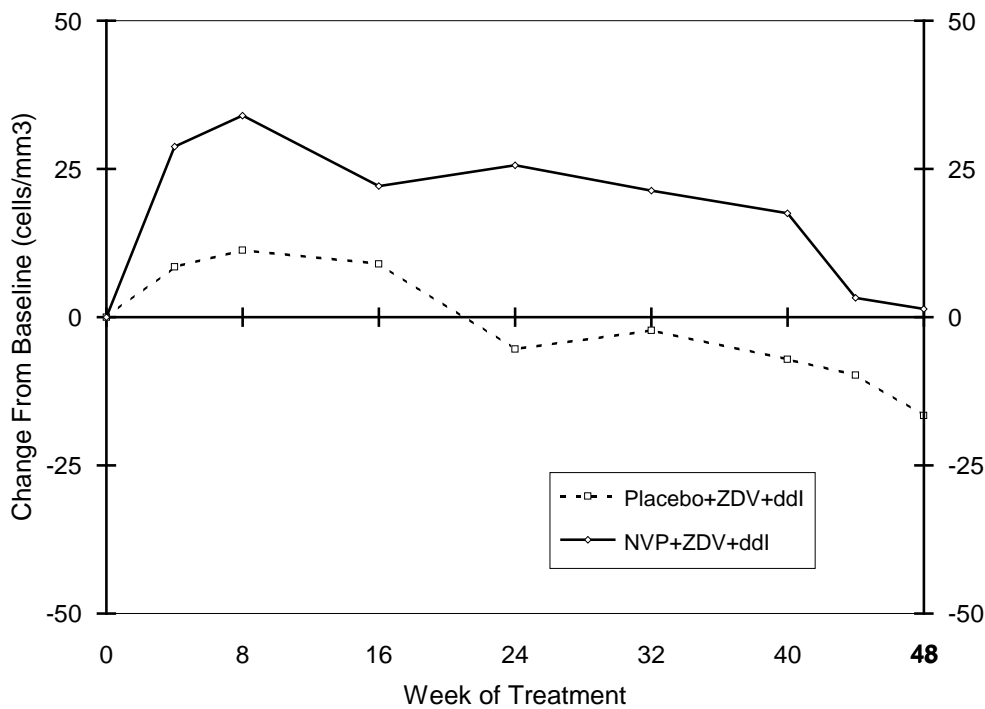
Nevirapine must not be used as a single agent to treat HIV or added on as a sole agent to a failing regimen. As with all other non-nucleoside reverse transcriptase inhibitors, resistant virus emerges rapidly when nevirapine is administered as monotherapy. The choice of new antiretroviral agents to be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

Clinical efficacy and safety

*Patients with a prior history of nucleoside therapy*

ACTG 241 compared treatment with VIRAMUNE+ AZT + ddl versus AZT + ddl in 398 HIV-1-infected patients (median age 38 years, 74% Caucasian, 80% male) with CD4+ cell counts <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; ddl, 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 1), % CD4+, quantitative PBMC microculture and plasma viral DNA (Figure 2). Favourable responses to triple therapy with VIRAMUNE were seen at all CD4+ count levels.

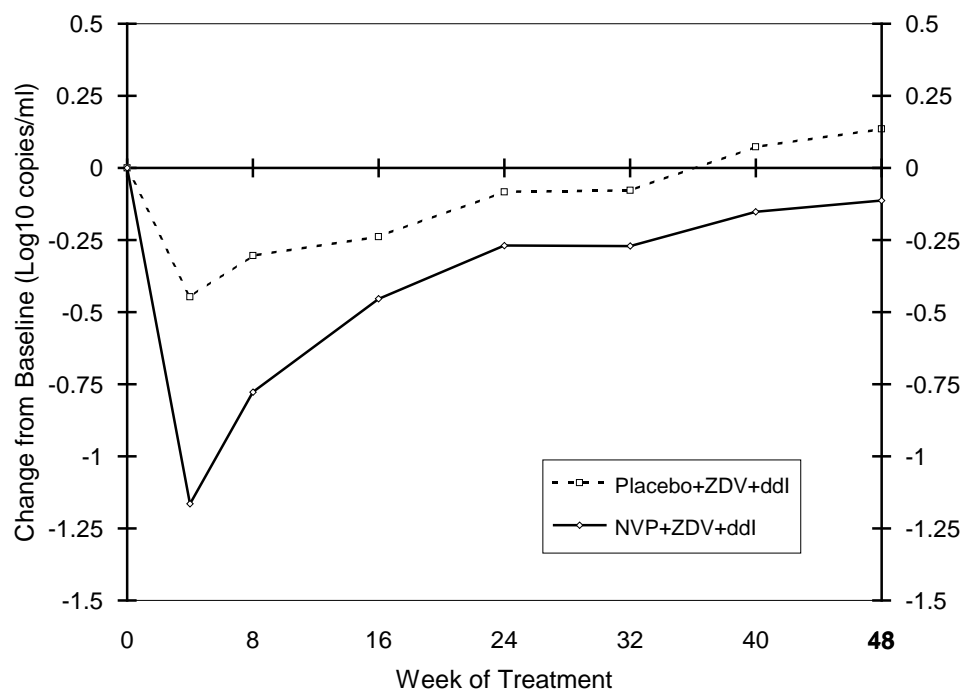
**Figure 1:** Mean Change from Baseline for CD4+ Cell Count (absolute number of CD4+ cells/mm<sup>3</sup>), Trial ACTG 241



	Number of patients with CD4 cell counts at each timepoint			
	<u>Baseline</u>	<u>Week 16</u>	<u>Week 32</u>	<u>40-48 Weeks</u>
NVP+AZT+ddl	196	177	157	161
Placebo+AZT+ ddl (ZDV=AZT)	196	176	160	167



**Figure 2:** Mean Change from Baseline in HIV-1 RNA\* Concentrations (Log<sub>10</sub> copies/ml), Virology Sub-study of Trial ACTG 241

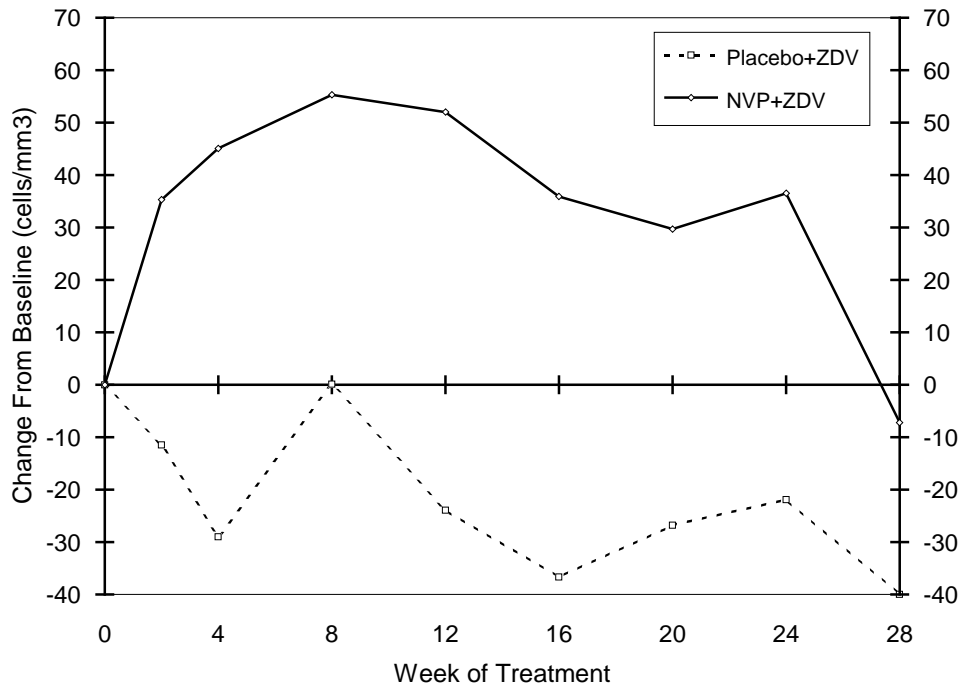


	Number of patients with HIV-1 RNA data at each timepoint			
	<u>Baseline</u>	<u>Week 16</u>	<u>Week 32</u>	<u>Weeks 40-48</u>
NVP+AZT+ddl	95	84	75	74
Placebo+AZT +ddl (ZDV=AZT)	93	82	75	75

\*the clinical significance of changes in serum viral RNA measurements during treatment with VIRAMUNE has not been established

Trial BI 1037 compared treatment with VIRAMUNE+ AZT versus AZT in 60 HIV-1-infected patients (median age 33 years, 70% Caucasian, 93% male) with CD4+ cell counts between 200 and 500 cells/mm<sup>3</sup> (mean 373 cells/mm<sup>3</sup>) and a mean baseline plasma HIV-1 RNA concentration of 4.24 log<sub>10</sub> copies/ml (17,378 copies/mL), who had received between 3 and 24 months of prior AZT therapy (median 35 weeks). Treatment doses were VIRAMUNE 200 mg daily for 2 weeks, followed by 200 mg twice daily, or placebo; AZT, 500-600 mg/day. Mean changes in CD4+ cell counts are shown in Figure 3. Mean HIV-1 RNA concentration changes from baseline are shown in Figure 4. The improvement was statistically significant at weeks, 2, 4 and 8.

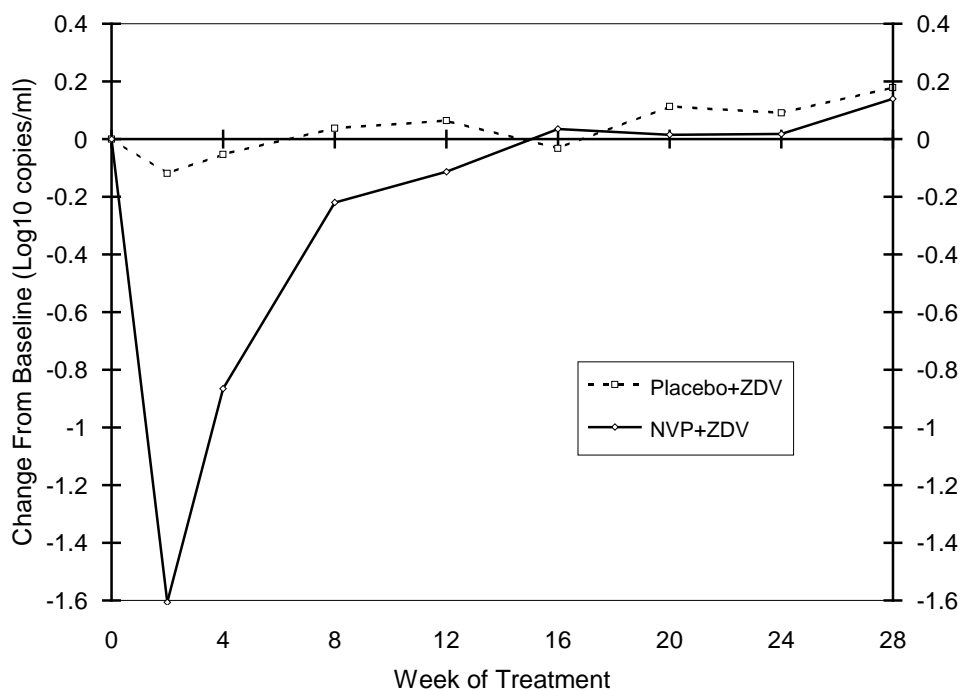
**Figure 3:** Mean Change from Baseline for CD4+ Cell Count (absolute number of CD4+ cells/mm<sup>3</sup>), Trial BI 1037



Number of patients with CD4 cell counts at each timepoint

	<u>Baseline</u>	<u>Week 8</u>	<u>Week 16</u>	<u>Weeks 20-28</u>
NVP+AZT	30	28	26	26
Placebo+AZT (ZDV=AZT)	30	30	28	29

**Figure 4:** Median Change from Baseline in HIV-1 RNA Concentrations (Log<sub>10</sub> copies/ml), Trial BI 1037

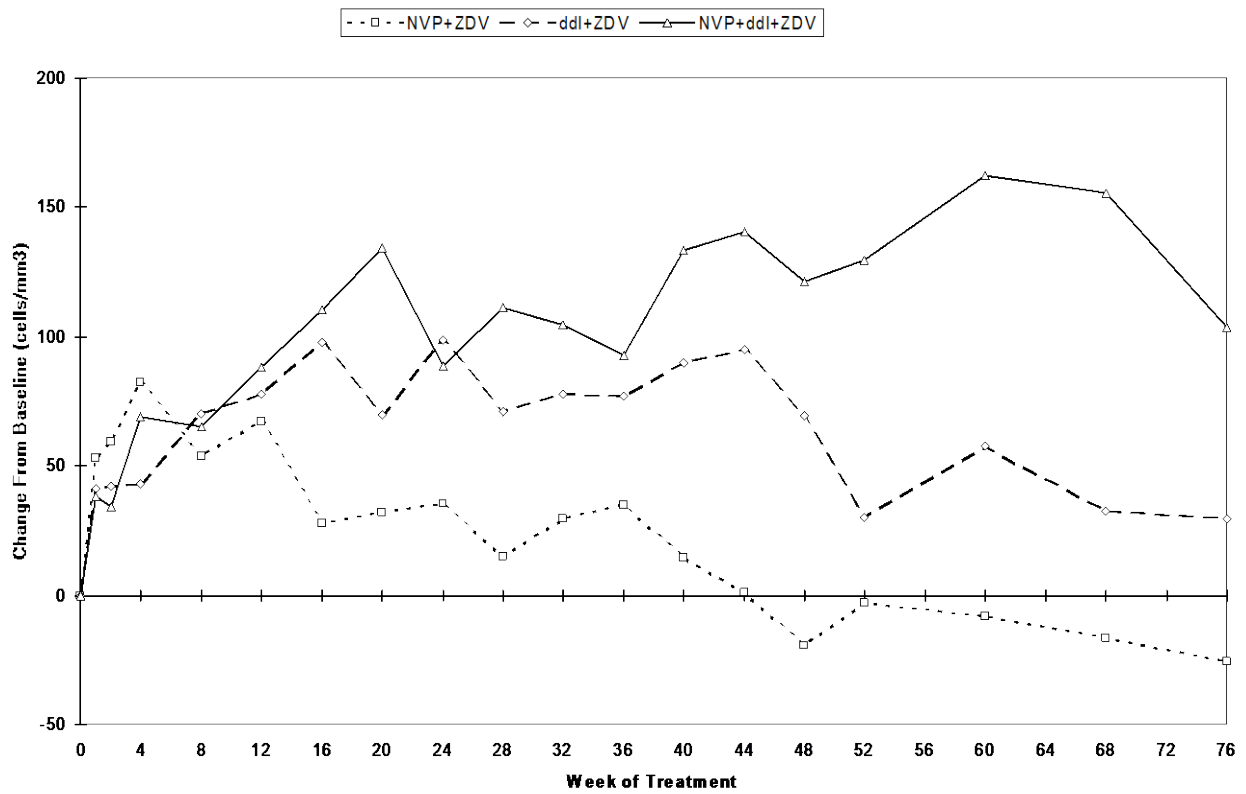


	Number of patients with HIV-1 RNA data at each timepoint			
	<u>Baseline</u>	<u>Week 8</u>	<u>Week 16</u>	<u>Weeks 20-28</u>
NVP+AZT	30	27	26	26
Placebo+AZT (ZDV=AZT)	30	29	28	29

*Patients without a history of prior antiretroviral therapy*

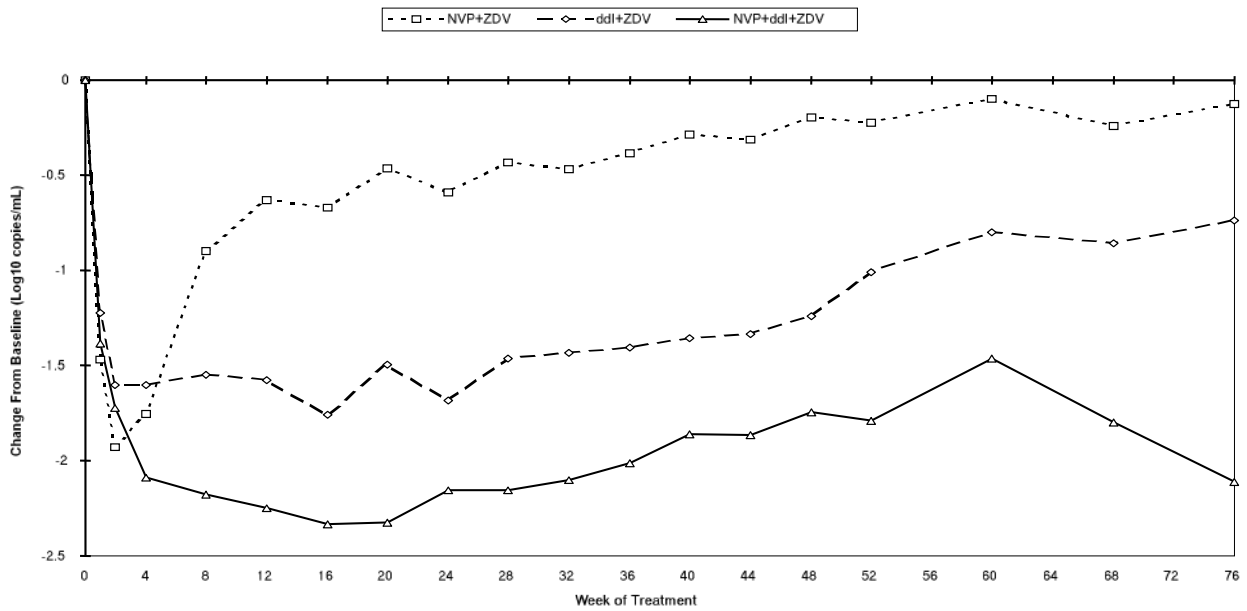
BI Trial 1046 compared treatment with VIRAMUNE+ AZT + ddI versus VIRAMUNE+ AZT versus AZT + ddI in 151 HIV-1-infected patients (median age 37 years, 94% Caucasian, 93% male) with CD4+ cell counts of 200-600 cells/mm<sup>3</sup> (mean 375 cells/mm<sup>3</sup>) and a mean baseline plasma HIV-1 RNA concentration 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; ddI, 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 + ddI and AZT + ddI remained significantly above baseline; the VIRAMUNE + AZT + ddI group was significantly improved compared to the AZT + ddI group. Changes in HIV-1 viral RNA at 52 weeks: there was a significantly better response in the VIRAMUNE + AZT + ddI group than the AZT + ddI 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 + ddI group (18/40 or 45%), when compared to the AZT + ddI group (2/36 or 6%) or the VIRAMUNE+ AZT group (0/28 or 0%); the clinical significance of this finding is unknown.

**Figure 5:** 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 (ZDV=AZT)	47	35	27	26	15

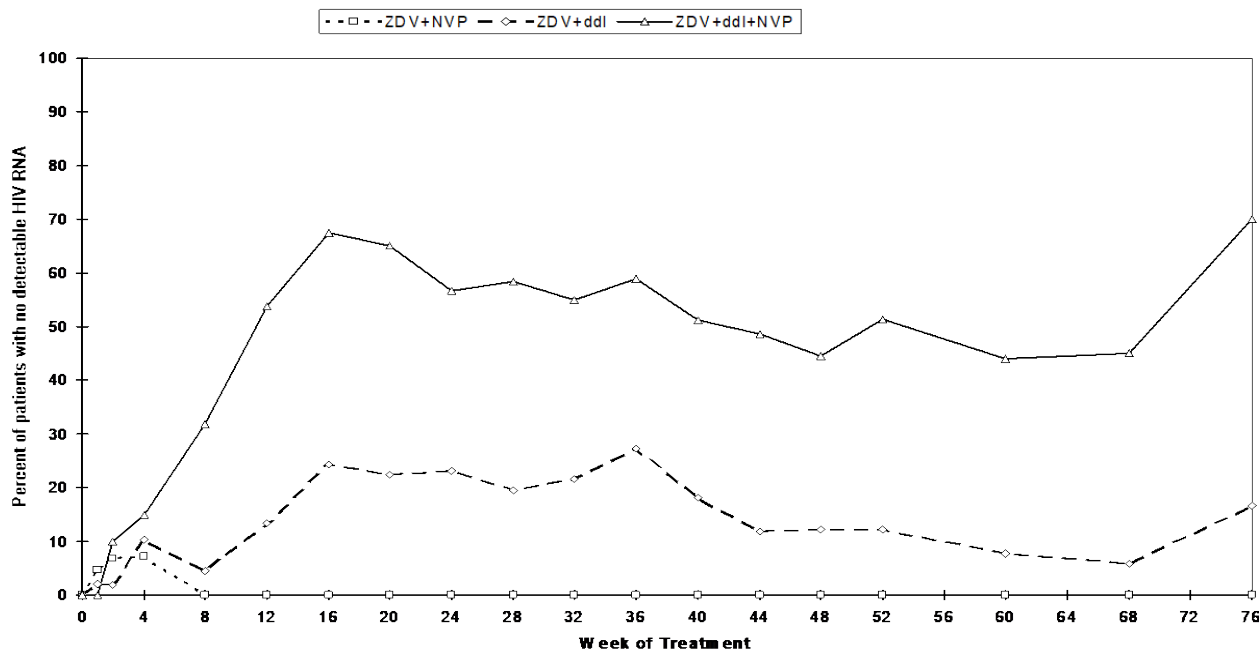
**Figure 6:** Mean Change from Baseline in HIV-1 RNA\* Concentrations (Log<sub>10</sub> copies/ml), Trial BI 1046



	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+AZT+ddl	51	40	40	37	10
Placebo+AZT+ddl	51	37	37	33	6
NVP+AZT+Placebo (ZDV=AZT)	46	35	26	25	6

\* the clinical significance of changes in serum viral RNA measurements during treatment with VIRAMUNE has not been established

**Figure 7:** Percent of Patients with HIV RNA below the Limit of Detection\*, 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+AZT+ddl	51	40	40	37	10
Placebo+AZT+ddl	51	37	37	33	6
NVP+AZT+Placebo (ZDV=AZT)	46	35	26	25	6

\* the clinical significance of viral RNA measurements during treatment with VIRAMUNE has not been established

### 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 a 11298 HIV-1- infected patients (mean age 37 years, 51% Caucasian, 87% male) with CD4 + cell counts  $\leq 50$  cells/mm<sup>3</sup> (mean 25 cells/mm<sup>3</sup>). Eighty-four per cent (84%) of patients had received nucleoside therapy prior to enrollment (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) suggest switching ddl with ddC dosing last. The median time to HIV progression event or death VIRAMUNE + AZT + ddl treatment group as compared to the AZT + ddl group (82 weeks versus 62 weeks). Mortality was similar for the two groups, throughout the trial. The median time to HIV progression event or death was shorter for AZT + ddC (53 weeks) and alternating AZT and ddl (57 weeks) group.

## 5.2 Pharmacokinetic properties

### Adult Patients

#### Absorption and Bioavailability in Adults

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  $91 \pm 8\%$  for an oral solution. Peak plasma nevirapine concentrations of  $2 \pm 0.4$  mcg/ml (7.5 mcM) 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  $4.5 \pm 1.9$  mcg/ml ( $17 \pm 7$  mcM), (n = 242) were attained at 400 mg/day.

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

#### *Distribution*

Nevirapine is highly lipophilic and is essentially nonionized at physiologic pH. Animal studies have shown that nevirapine is widely distributed to nearly all tissues and readily crosses the blood-brain barrier. Following intravenous administration in healthy adults, the apparent volume of distribution ( $V_{dss}$ ) of nevirapine was  $1.21 \pm 0.09$  l/kg, suggesting that nevirapine is also widely distributed in humans. Nevirapine readily crosses the placenta and is found in breast milk (see section 4.6). Nevirapine is about 60% bound to plasma proteins in the plasma concentration range of 1-10 mcg/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 is 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.

Gender: 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.

#### Special Populations

Nevirapine pharmacokinetics in HIV-1 infected adults does not appear to change with age (range 18-68 years) or race (Black, Hispanic, or Caucasian). This information is derived from an evaluation of pooled data derived from several clinical trials.

#### *Renal dysfunction*

The single-dose pharmacokinetics of VIRAMUNE has been compared in 23 subjects with either mild ( $50 \leq \text{CLcr} < 80$  mL/min), moderate ( $30 \leq \text{CLcr} < 50$  mL/min) or severe renal dysfunction ( $\text{CLcr} < 30$  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 VIRAMUNE. However subjects with ESRD requiring dialysis exhibited a 43.5% reduction VIRAMUNE AUC 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 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.

#### *Hepatic impairment*

A steady state study comparing 46 patients with mild (n=17; Ishak Score 1-2), moderate (n=20; Ishak Score 3-4), or severe (n=9; Ishak Score 5-6, Child-Pugh A in 8 pts., for 1 Child-Pugh score not applicable) liver fibrosis as a measure of hepatic impairment was conducted.

The patients studied were receiving antiretroviral therapy containing VIRAMUNE 200 mg twice-daily for at least 6 weeks prior to pharmacokinetic sampling, with a median duration of therapy of 3.4 years. In this study, the multiple dose pharmacokinetic disposition of nevirapine and the five oxidative metabolites were not altered.

However, approximately 15% of these patients with hepatic fibrosis had nevirapine trough concentrations above 9.000 ng/ml (2-fold the usual mean trough). Patients with hepatic impairment should be monitored carefully for evidence of drug induced toxicity.

In a 200 mg nevirapine single dose pharmacokinetic study of 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 section 4.4).

#### Paediatric Patients

Data concerning the pharmacokinetics of nevirapine have been derived from two major sources: a 48-week paediatric trial in South Africa involving 123 HIV-1 positive, antiretroviral naïve patients aged 3 months to 16 years; and a consolidated analysis of five Paediatric AIDS Clinical Trials Group (PACTG) protocols comprising 495 patients aged 14 days to 19 years.

The results of the 48-week analysis of the South African study confirmed that the 4/7 mg/kg and 150 mg/m<sup>2</sup> nevirapine dose groups were well tolerated and effective in treating antiretroviral naïve paediatric patients. A marked improvement in the CD4+ cell percent was observed through Week 48 for both dose groups. Also, both dosing regimens were effective in reducing the viral load. In this 48-week study no unexpected safety findings were observed in either dosing group.

Pharmacokinetic data on 33 patients (age range 0.77 – 13.7 years) in the intensive sampling group demonstrated that after oral intake clearance of nevirapine increased with increasing age in a manner consistent with increasing body surface area. 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 µg/ml (as targeted from adult data). In addition, the observed trough nevirapine concentrations were comparable between the two methods.

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.



## 5.3 Preclinical safety data

### Genotoxicity

In genetic toxicology assays, nevirapine showed no evidence of mutagenic or clastogenic activity in a battery of in vitro and in vivo assays including microbial assays for gene mutation (Ames: Salmonella strains and E.coli), mammalian cell gene mutation assays (CHO/HGPRT), cytogenic assays using Chinese hamster ovary cell line and a mouse bone marrow micronucleus assay following oral administration. 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 provided with recommended clinical dose of VIRAMUNE.

### 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.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Carbomer, methyl hydroxybenzoate, propyl hydroxybenzoate, sorbitol, sucrose, polysorbate 80, sodium hydroxide and purified water.

### 6.2 Incompatibilities

Not applicable

### 6.3 Shelf life

36 months

Use suspension within 6 months of opening the bottle.

### 6.4 Special precautions for storage

Keep out of reach of children

Store below 30°C.

### 6.5 Nature and contents of container

White high density polyethylene (HDPE) bottle with two piece child-resistant closure (outer shell white high density polyethylene, inner shell natural polypropylene) with a low density polyethylene (LDPE) foam liner. Each bottle contains 240 ml of oral suspension.

Clear polypropylene 5 mL dispensing syringe with silicone rubber piston seal.

Clear low density polyethylene bottle-syringe adapter.

## 6.6 Special precautions for disposal and other handling

### Instructions for Use of Suspension

The required dosage volumes should be measured emptying the enclosed dispensing syringe and adapter, as described in steps 1-5 below. The maximum volume which can be measured with the dispensing syringe is 5 ml and therefore steps 2-5 must be repeated for dosage volumes greater than 5 ml.

1. Shake the bottle gently
2. Open the bottle and insert the plastic adapter into the open bottle neck. Make sure the adapter is tightly inserted.
3. Insert the syringe into the adapter. Make sure the syringe is tightly inserted.
4. Turn the bottle upside down and gently withdraw the required amount of VIRAMUNE oral suspension.
5. The maximum volume you can withdraw is 5 ml at a time. If you require a higher dose please repeat steps 2 - 4.

## 7. MEDICINE SCHEDULE

Prescription Medicine

## 8. SPONSOR

Boehringer Ingelheim (N.Z.) Limited  
PO Box 76-216  
Manukau City  
Auckland  
NEW ZEALAND

Telephone: 0800 802 461

Facsimile 0508 774 748

## 9. DATE OF FIRST APPROVAL

2 March 2000

## 10. DATE OF REVISION OF THE TEXT

9 October 2018

## SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
All	Reformatting of Data Sheet into SPC style format
All	Deletion of the Viramune immediate-release 200mg presentation throughout
6.3	Shelf life added
6.5	Reference to immediate container added
8	Company phone and fax number updated
9	Date of first approval added