AUSTRALIAN PRODUCT INFORMATION – VIRAMUNE® oral suspension and VIRAMUNE® XR (nevirapine) extended-release tablets

1 NAME OF THE MEDICINE

Nevirapine (VIRAMUNE XR extended-release tablets)

Nevirapine hemihydrate (VIRAMUNE oral suspension)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

VIRAMUNE is available as extended-release VIRAMUNE XR tablets or as a suspension for oral administration.

Each VIRAMUNE XR extended-release tablet contains 400 mg of nevirapine.

Each 5 mL of the VIRAMUNE oral suspension contains 50 mg of nevirapine (as nevirapine hemihydrate).

<u>Excipients with known effect:</u>

Each VIRAMUNE XR extended-release 400 mg tablet contains 400 mg of lactose monohydrate.

Each mL of VIRAMUNE 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 List of excipients.

3 PHARMACEUTICAL FORM

400 mg extended-release tablets	Yellow, oval, biconvex tablets. The tablets are debossed with “V04” on one side and the BI tower logo on the other side.
Oral Suspension	White to off-white suspension.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

VIRAMUNE (nevirapine) 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.

4.2 DOSE AND METHOD OF ADMINISTRATION

<u>Oral suspension</u>

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 aged 2 months 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^2 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^2 use the Mosteller formula given below.

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

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

Dose in mL = BSA (in m^2) x 15

This corresponds with a dose of 150 mg/m^2, which is to be taken once daily for two weeks (lead-in period) followed by 150 mg/m^2 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 (lead-in period) 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 especially for children 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 Section 4.4 Special Warnings and Precautions for Use, 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 experiencing 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 an oral dispensing syringe, 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 nevirapine 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 XR 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. Nevirapine 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 and monitoring should be followed.

Adult patients currently on a nevirapine immediate-release twice daily regimen

Patients already on a regimen of nevirapine 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 nevirapine 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 Section 4.4 Special Warnings and Precautions for Use, 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 nevirapine immediate-release.

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 nevirapine immediate-release tablets or oral suspension (first 14 days): All paediatric patients should initiate therapy with 150 mg/m^2 (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 nevirapine immediate-release 200 mg tablets twice daily treatment.

Maintenance dosing with VIRAMUNE XR extended-release tablets (after the lead-in): The recommended oral dose based on BSA for paediatric patients who have a BSA of ≥ 1.17 m^2 is VIRAMUNE XR extended-release 400 mg once daily.

To calculate the BSA in m^2 use the Mosteller formula given below.

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

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

The recommended weight-based paediatric dose is dependent upon the patient's age and is given in the table below 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)
25 and above	43.8 and above	400 (1 x 400 mg) once daily

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. Nevirapine 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 and monitoring should be followed.

Alternatively, VIRAMUNE immediate-release oral suspension is available for children aged over 2 months and for all BSA and weight 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 Section 4.4 Special Warnings and Precautions for Use, 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 nevirapine immediate-release.

4.3 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 > 5 x ULN during nevirapine therapy and had recurrence of liver function abnormalities upon readministration of nevirapine (see Section 4.4 Special Warnings and Precautions for Use).

VIRAMUNE XR extended-release tablets contain 400 mg lactose monohydrate per maximum recommended daily dose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

VIRAMUNE oral suspension contains 6 g sucrose and 6.7 g sorbitol per maximum recommended daily dose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take/be given this medicine.

VIRAMUNE oral suspension contains the excipients methyl hydroxybenzoate and propyl hydroxybenzoate, 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 Section 4.5 Interactions with Other Medicines and Other Forms of Interactions).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

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) 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, higher CD4+ counts (> 250/mm^3 and > 400/mm^3 if adult male); hepatitis C virus [HCV-Ab] co-infection and detectable plasma Human Immunodeficiency Virus (HIV)-1 RNA levels in treatment experienced patients at the initiation of VIRAMUNE therapy are associated with a greater risk of hepatic adverse events and rash-associated, hepatic events.

However, hepatotoxicity associated with nevirapine use can occur in both genders, all CD4+ cell counts and at any time during treatment.

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 cell/mm^3 or in adult males with CD4+ cell counts greater than 400 cells/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 Dose and Method of 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 SJS, or TEN. 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 Sections 4.4 Special Warnings and Precautions for Use, Information for Patients and 4.8 Adverse Effects (Undesirable Effects)).

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 Section 4.2 Dose and Method of 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 nevirapine 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 nevirapine 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 nevirapine immediate-release administration) has not been shown 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 Section 4.4 Special Warnings and Precautions for Use, 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.

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. Women had a three fold higher risk than men for symptomatic, often rash-associated, hepatic events (5.8% vs. 2.2%). 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^3 had a 12 fold higher risk of symptomatic hepatic adverse events compared to women with CD4+ counts <250 cells/mm^3 (11.0% vs. 0.9%). An increased risk was observed in men with detectable HIV-1 RNA in plasma and CD4+ counts >400 cells/mm^3 (6.3% vs. up to 2.3% for men with CD4+ counts <400 cells/mm^3). 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.

All patients, regardless of gender, CD4+ cell counts, or antiretroviral treatment history, should be monitored for hepatotoxicity since symptomatic hepatic adverse events have been reported at all CD4+ cell counts.

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 nevirapine 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 nevirapine 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 Section 4.3 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 nevirapine immediate-release tablets following each dialysis treatment would help offset the effects of dialysis on VIRAMUNE clearance. Otherwise patients with $CL_{cr} \geq 20$ mL/min do not require an adjustment in VIRAMUNE dosing (see Section 5.2 Pharmacokinetic Properties: 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 nevirapine immediate-release tablets representing 50% of the recommended daily dose of VIRAMUNE oral suspension or nevirapine 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 Section 4.5 Interactions with Other Medicines and Other Forms of Interactions). 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 protease inhibitors (PIs) and lipoatrophy and nucleoside reverse transcriptase inhibitors (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.

Occasionally, the inactive ingredients of VIRAMUNE XR extended-release tablets will be eliminated in the faeces as soft, hydrated remnants which may resemble intact tablets. These occurrences have not been shown to affect drug levels or response.

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.

Use in the elderly

See Section 4.2 Dose and Method of Administration.

Paediatric use

See Section 4.2 Dose and Method of Administration.

Effects on laboratory tests

No data available.

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

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

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, etravirine, rilpivirine, elvitegravir (in combination with cobicistat); 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 Section 5.2 - Pharmacokinetic Properties). 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**
ANTI-INFECTIVES		
Antiretrovirals		
Nucleoside reverse transcriptase inhibitors (NRTIs)		
Didanosine 100-150 mg BID	Didanosine AUC ↔ Didanosine C_{min} § Didanosine C_{max} ↔	No dosage adjustments are required when VIRAMUNE is taken in combination with didanosine.
Emtricitabine	*In vitro*, emtricitabine was not an inhibitor of human CYP 1A2, 2A6, 2B6, 2C9, 2C19, 2D6 or 3A4 enzymes.	No dosage adjustments are required when VIRAMUNE is taken in combination with emtricitabine.
Abacavir	*In vitro*, abacavir did not inhibit CYP 3A4, 2C9 or 2D6.	No dosage adjustments are required when VIRAMUNE is taken in combination with abacavir.
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 30/40 mg BID	Stavudine AUC ↔ Stavudine C_{min} § Stavudine C_{max} ↔ 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_{min} § Zalcitabine C_{max} ↔	No dosage adjustments are required when VIRAMUNE is taken in combination with zalcitabine.
Zidovudine 100-200 mg TID	Zidovudine AUC ↓28 (↓40 to ↓4) Zidovudine C_{max} ↓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.

Medicinal products by therapeutic areas	Interaction	Recommendations concerning co-administration
Non-nucleoside reverse transcriptase inhibitors (NNRTIs)		
Efavirenz 600 mg QD	Efavirenz AUC ↓28 (↓34 to ↓14) Efavirenz Cmin ↓32 (↓35 to ↓19) Efavirenz Cmax ↓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 Warning on concomitant use with other medicines). 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 in vitro (see also Section 5.1 Pharmacodynamic Properties - Microbiology).
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 *Warning on concomitant use with other medicines*).
Rilpivirine	Interaction has not been studied.	The concomitant administration of VIRAMUNE with NNRTIs is not recommended (see also *Warning on concomitant use with other medicines*).
Protease Inhibitors (PIs)		
Atazanavir/ritonavir 300/100 mg QD 400/100 mg QD	<u>Atazanavir/r 300/100 mg:</u> Atazanavir/r AUC ↓42 (↓52 to ↓29) Atazanavir/r C_{min} ↓72 (↓80 to ↓60) Atazanavir/r C_{max} ↓28 (↓40 to ↓14) <u>Atazanavir/r 400/100 mg:</u> Atazanavir/r AUC ↓19 (↓35 to↑2) Atazanavir/r C_{min} ↓59 (↓73 to ↓40) Atazanavir/r C_{max} ↔ (compared to 300/100 mg without nevirapine) Nevirapine AUC ↑25 (↑17 to ↑34) Nevirapine C_{min} ↑32 (↑22 to ↑43) Nevirapine C_{max} ↑17 (↑9 to ↑25)	If given in combination with VIRAMUNE, atazanavir should be dosed with 400 mg co-administered with low dose ritonavir 100 mg.
Darunavir/ ritonavir 400/100 mg BID	Darunavir AUC ↑24 (↓3 to ↑57) Darunavir C_{min} ↔ Darunavir C_{max} ↑40 (↑14 to ↑73) Nevirapine AUC ↑27 (↑12 to ↑44) Nevirapine C_{min} ↑47 (↑20 to ↑82) Nevirapine C_{max} ↑18 (↑2 to ↑37)	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.

Medicinal products by therapeutic areas	Interaction	Recommendations concerning co-administration
Fosamprenavir 1400 mg BID	Amprenavir AUC ↓33 (↓45 to ↓20) Amprenavir C_{min} ↓35 (↓51 to ↓15) Amprenavir C_{max} ↓25 (↓37 to ↓11) Nevirapine AUC ↑29 (↑19 to ↑40) Nevirapine C_{min} ↑34 (↑21 to ↑49) Nevirapine C_{max} ↑25 (↑14 to ↑37)	VIRAMUNE should not be given with fosamprenavir if not co-administered with ritonavir. (see also *Warning on concomitant use with other medicines*).
Fosamprenavir/ ritonavir 700/100 mg BID	Amprenavir AUC ↓11 (↓23 to ↑3) Amprenavir C_{min} ↓19 (↓31 to ↓4) Amprenavir C_{max} ↔ Nevirapine AUC ↑14 (↑5 to ↑24) Nevirapine C_{min} ↑22 (↑10 to ↑35) Nevirapine C_{max} ↑13 (↑3 to ↑24)	No dosing adjustments are required when VIRAMUNE is co-administered with 700/100 mg of fosamprenavir/ritonavir BID.
Indinavir 800 mg Q8H	Indinavir AUC ↓31 (↓39 to ↓22) Indinavir C_{min} ↓44 (↓53 to ↓33) Indinavir C_{max} ↓15 (↓24 to ↓4) No clinically relevant change in nevirapine plasma levels was found.	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.
Lopinavir/ritonavir (capsules) 400/100 mg BID	<u>In HIV positive adults</u>: Lopinavir AUC ↓27 Lopinavir C_{min} ↓46 Lopinavir C_{max} ↓19	An increase in the dose of lopinavir/ritonavir to 533/133 mg (4 capsules) twice daily with food is recommended in combination with VIRAMUNE**.**
Lopinavir/ritonavir (oral solution) 300/75 mg/m^2 BID	<u>Paediatric patients</u>: Lopinavir AUC ↓22 (↓44 to 9↑) Lopinavir Cmin ↓55 (↓75 to ↓18) Lopinavir Cmax ↓14 (↓36 to ↑16)	For children, increase of the dose of lopinavir/ritonavir to 300/75 mg/m^2 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.
Nelfinavir 750 mg TID	Nelfinavir: AUC ↔ C_{max} ↔ Total exposure of nelfinavir plus	No dosage adjustments are required when VIRAMUNE is taken in combination with nelfinavir.

Medicinal products by therapeutic areas	Interaction	Recommendations concerning co-administration
	the AG1402 metabolite: AUC ↓20 (↓72 to ↑128) C_{min} ↓35 (↓90 to ↑316) C_{max} ↓12 (↓61 to ↑100) Nevirapine: compared to historical controls, levels appeared to be unchanged.	
Ritonavir 600 mg BID	Nevirapine AUC ↔ Nevirapine C_{max} ↔ Ritonavir AUC ↔ Ritonavir C_{min} ↔ Ritonavir C_{max} ↔	No dosage adjustments are required when VIRAMUNE is taken in combination with ritonavir.
Saquinavir 600 mg TID	Saquinavir AUC ↓38 (↓47 to ↓11) Saquinavir C_{min} § Saquinavir C_{max} ↓32 (↓44 to ↓6)	VIRAMUNE should not be given with saquinavir if not co-administered with ritonavir (see also *Warning on concomitant use with other medicines*).
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_{min}.	No dosage adjustments are required when VIRAMUNE is taken in combination with tipranavir co-administered with ritonavir.
Entry Inhibitors		
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_{min} § Maraviroc C_{max} ↑ 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.
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.
Elvitegravir/cobicistat	Interaction has not been studied. Cobicistat, a cytochrome P450	Coadministration of VIRAMUNE with elvitegravir in combination with

Medicinal products by therapeutic areas	Interaction	Recommendations concerning co-administration
	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.	cobicistat is not recommended (see also *Warning on concomitant use with other medicines*).
ANTIVIRALS FOR HEPATITIES B AND C		
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	*In vitro*, telbivudine was not a substrate or inhibitor of the cytochrome P450 (CYP450) enzyme system (CYP1A2, 2C9, 2C19, 2D6, 2E1 or 3A4). Telbivudine did not induce CYP450 enzymes in animal. 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 an *in vitro* study showed an additive or no interaction effect of nevirapine with adefovir (see also Section 5 Pharmacological properties), this has not been confirmed in clinical trials and reduced efficacy is not expected. Adefovir did not inhibit and is not a substrate of common CYP isoforms, such as CYP1A2, CYP2C9, CYP2C19, CYP2D6 and CYP3A4.	Adefovir and VIRAMUNE may be co-administered without dose adjustments.
ANTIBIOTICS		
Clarithromycin 500 mg BID	Clarithromycin AUC ↓31 (↓38 to ↓24) Clarithromycin C_{min} ↓56 (↓70 to ↓36) Clarithromycin C_{max} ↓23 (↓31 to ↓14) Metabolite 14-OH clarithromycin AUC ↑42 (↑16 to ↑73) Metabolite 14-OH clarithromycin C_{max} ↑47 (↑21 to ↑80) Nevirapine AUC ↑26 Nevirapine C_{min} ↑28 Nevirapine C_{max} ↑24 compared to historical controls	Clarithromycin exposure was significantly decreased, 14-OH metabolite exposure increased. Because the clarithromycin active metabolite has reduced activity against *Mycobacterium aviumintracellulare 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.
Rifabutin 150 or 300 mg QD	Rifabutin AUC ↑17 (↓2 to ↑40) Rifabutin C_{max} ↑28 (↑9 to ↑51)	No dose adjustment is recommended when rifabutin and VIRAMUNE are co-

Medicinal products by therapeutic areas	Interaction	Recommendations concerning co-administration
	Metabolite 25-O-desacetylrifabutin AUC ↑24 (↓16 to ↑84) Metabolite 25-O-desacetylrifabutin C_{max} ↑29 (↓2 to ↑68) A clinically not relevant increase in the apparent clearance of nevirapine (by 9%) compared to historical pharmacokinetic data was reported.	administered. Due to the high inter subject 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.
Rifampicin 600 mg QD	Rifampicin AUC ↔ Rifampicin C_{max} ↔ Nevirapine AUC ↓58 Nevirapine C_{min} ↓68 Nevirapine C_{max} ↓50 compared to historical controls	It is not recommended to co-administer rifampicin and VIRAMUNE. Physicians needing to treat patients co-infected with tuberculosis and using a VIRAMUNE containing regimen may consider co-administration of rifabutin instead.
ANTIFUNGALS		
Fluconazole 200 mg QD	Fluconazole AUC ↔ Fluconazole C_{min} ↔ Fluconazole C_{max} ↔ 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	Itraconazole AUC ↓61 Itraconazole C_{min} ↓87 Itraconazole C_{max} ↓38 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	Ketoconazole AUC ↓72 (↓80 to ↓60) Ketoconazole C_{min} § Ketoconazole C_{max} ↓44 (↓58 to ↓27) Nevirapine plasma levels: ↑15-28% compared to historical controls.	Ketoconazole and VIRAMUNE should not be given concomitantly (see also *Warning on concomitant use with other medicines*).
ANTACIDS		
Cimetidine	Cimetidine: no significant effect on cimetidine PK parameters is seen. Nevirapine C_{min} ↑7	The limited data suggest no dose adjustment when Cimetidine is co-administered with VIRAMUNE.

Medicinal products by therapeutic areas	Interaction	Recommendations concerning co-administration
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_{min} ↔ DMPA C_{max} ↔ Nevirapine AUC ↑20 Nevirapine C_{max} ↑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_{min} § EE C_{max} ↔	Oral hormonal contraceptives should not be used as the sole method of contraception in women taking VIRAMUNE (see also Section 4.4 Special Warnings and Precautions for Use, Information for patients). 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_{min} § NET C_{max} ↓16 (↓27 to ↓3)	
ANALGESICS/OPIOIDS		
Methadone Individual Patient Dosing	Methadone AUC ↓60 (↓69 to ↓49) Methadone C_{min} § Methadone C_{max} ↓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 (*Hypericum perforatum*). 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 Section 4.3 Contraindications).

§ = C_{min} 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, lidocaine (lignocaine)); ciclosporin; 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 1 Potential drug interactions

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

4.6 FERTILITY, PREGNANCY AND LACTATION

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.

No human data on fertility are available.

Use in Pregnancy (Category B3)

Data from the Antiretroviral Pregnancy Registry (1171 first trimester and 1529 second/third trimester exposures to nevirapine as of June 2021) on pregnant women indicate no increased malformative or foeto/neonatal toxicity.

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

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 maternally toxic 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. 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 1.5-fold increase in risk of overall birth defects. These findings should provide some assurance in counselling patients.

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^3 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 Special Warnings and Precautions for Use). Severe hepatic events, including fatalities, have been reported in pregnant women receiving chronic nevirapine therapy as part of combination treatment of HIV-1 infection. Regardless of pregnancy status, women with CD4+ cell counts greater than 250 cells/mm^3 should not initiate nevirapine unless the benefit outweighs the risk.

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 Section 4.4 Special Warnings and Precautions for Use).

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.

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 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at http://www.tga.gov.au/reporting-problems.

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 (≥1/10); common (≥1/100, <1/10); uncommon (≥1/1,000, <1/100); rare (≥1/10,000, <1/1,000); very rare (<1/10,000).

System Organ Class	Very Common	Common	Uncommon	Rare
Blood and lymphatic system disorders		granulocytopenia	anaemia	
Immune system disorders		hypersensitivity (including anaphylactic reaction, angioedema, urticaria)	drug reaction with eosinophilia and systemic symptoms anaphylactic reaction	
Nervous system disorders		headache		
Gastrointestinal disorders		nausea vomiting abdominal pain diarrhoea		
Hepatobiliary disorders		hepatitis (1.2 %) (including severe and life-threatening hepatotoxicity) liver function tests abnormal	jaundice	liver failure / fulminant hepatitis (which may be fatal)
Skin and subcutaneous tissue disorders	rash		Stevens-Johnson syndrome (0.3 %) toxic epidermal necrolysis (which may be fatal) urticaria angio-oedema	
Musculoskeletal and connective tissue disorders		myalgia	arthralgia	
General disorders and administration site conditions		fatigue pyrexia	fever	
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	

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. 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 XR extended-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 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^3 for women and <400 cells/mm^3 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 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 AST or ALT 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 Section 4.4 Special Warnings and Precautions for Use). 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^2 once daily for two weeks followed by 120 mg/m^2 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.

4.9 OVERDOSE

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

There is no known antidote for VIRAMUNE overdosage. 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.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Non-nucleoside reverse transcriptase inhibitor, 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 α, β, γ, or δ) 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_{50} 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 ≥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-naive individuals receiving various combinations of these agents was examined in a double blind controlled randomised trial (INCAS study). In this study, antiretroviral naive subjects with CD4+ cells counts of 200-600/mm^3 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_{50} 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_{50}, 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 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.

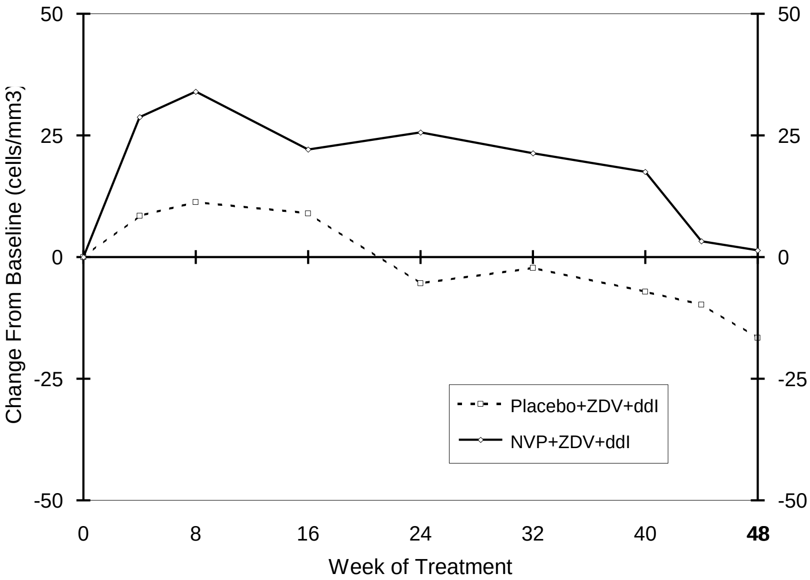
Clinical trials

VIRAMUNE immediate-release tablets

<u>Patients with a prior history of nucleoside therapy</u>

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^3 (mean 153 cells/mm^3) and a mean baseline plasma HIV-1 RNA concentration of 4.59 $\log_{10}$ 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 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.

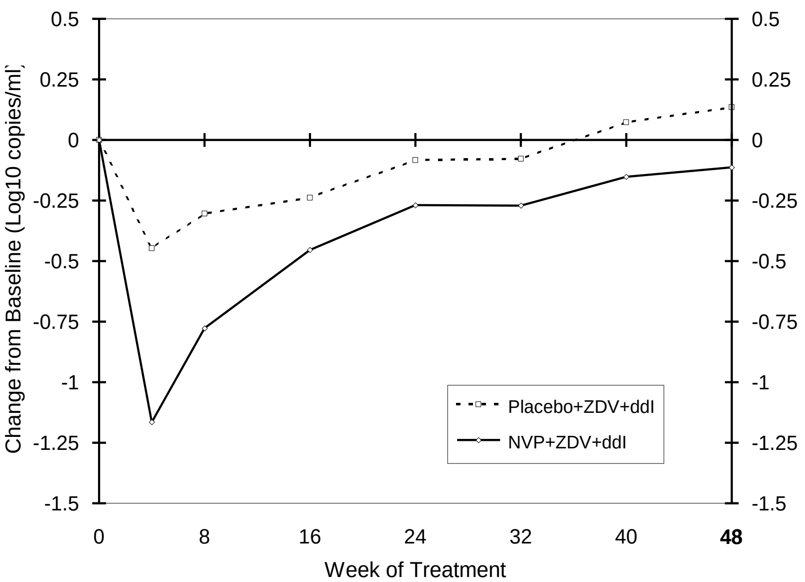
Figure 1: Mean Change from Baseline for CD4+ Cell Count (absolute number of CD4+ cells/mm^3), Trial ACTG 241



Number of patients with CD4+ cell counts at each timepoint

	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 2: Mean Change from Baseline in HIV-1 RNA Concentrations (Log_{10} copies/mL), Virology Sub-study of Trial ACTG 241



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

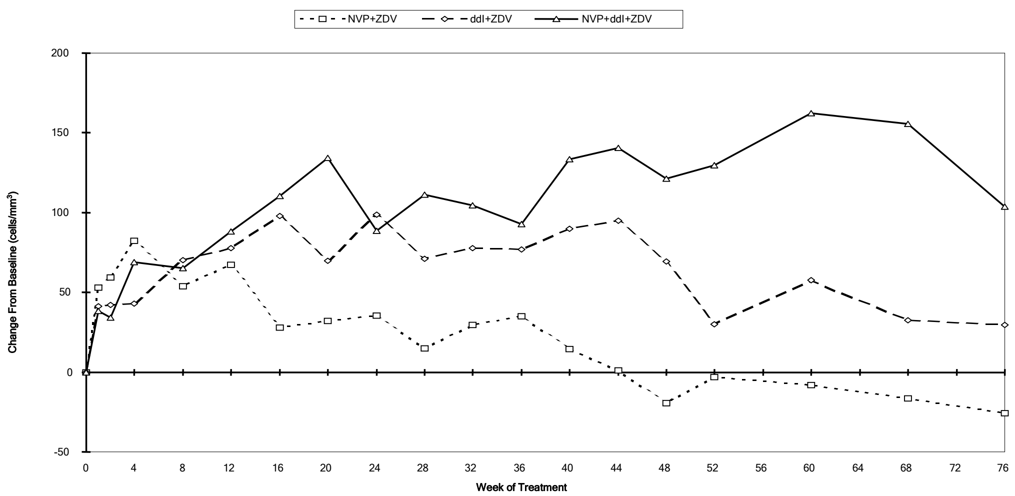
	Baseline	Week 16	Week 32	40-48 Weeks
NVP+AZT+ddI	95	84	75	74
Placebo+AZT+ddI (ZDV=AZT)	93	82	75	75

Clinical Endpoint Trial: ACTG 193a was a placebo controlled trial which compared treatment with VIRAMUNE + AZT + ddI versus AZT + ddI, as well as studying AZT + ddC and AZT alternating with ddI monthly, in 1298 HIV-1-infected patients (mean age 37 years, 51% Caucasian, 87% male) with CD4+ cell counts <50 cells/mm^3 (mean 25 cells/mm^3). 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; ddI 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 + ddI treatment group as compared to the AZT + ddI 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 +ddI treatment group as compared to 54 weeks in the AZT + ddI 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 ddI (57 weeks) groups.

<u>Patients who are antiretroviral naive</u>

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^3 (mean 375 cells/mm^3) and a mean baseline plasma HIV-1 RNA concentration of 4.41 $\log_{10}$ 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%) (Figures 3-5). The clinical significance of this finding is unknown.

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

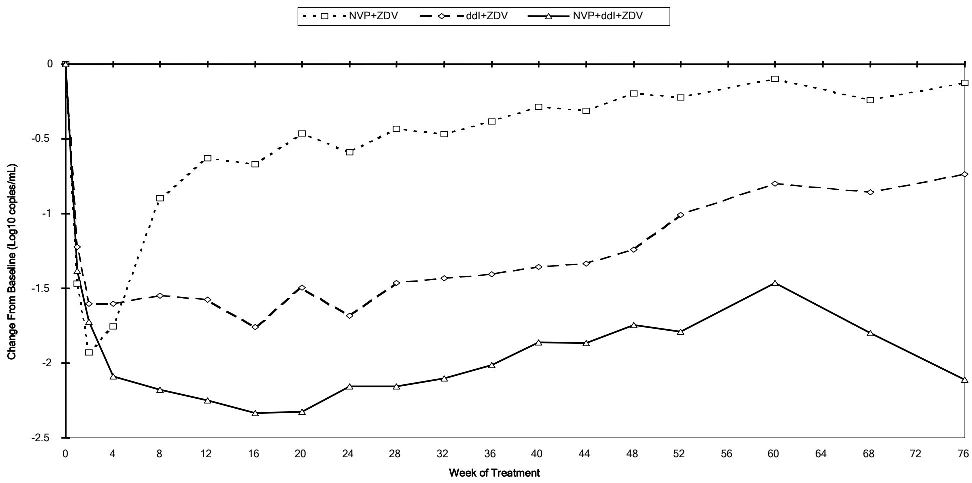


Number of patients with CD4+ cell counts at each timepoint

	Baseline	Week 16	Week 32	Week 52	Week 76
NVP+AZT+ddI	51	41	40	38	15
Placebo+AZT+ddI	52	38	35	33	12
NVP+AZT+Placebo	47	35	27	26	15

(ZDV=AZT)

Figure 4: Mean Change from Baseline in HIV-1 RNA Concentrations (Log_{10} copies/mL), Trial BI 1046

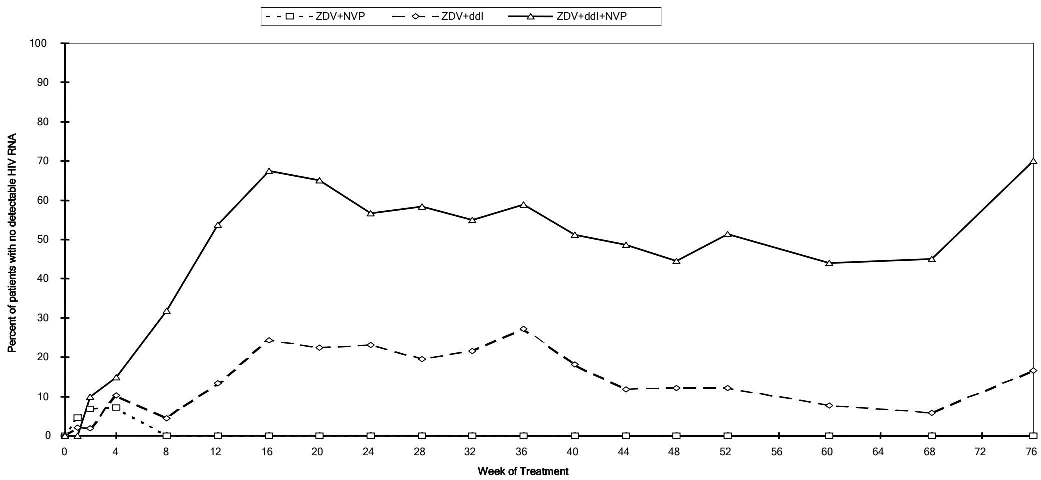


Number of patients with HIV-1 RNA data at each timepoint

	Baseline	Week 16	Week 32	Week 52	Week 76
NVP+ZDV+ddI	51	40	40	37	10
Placebo+ZDV+ddI	51	37	37	33	6
NVP+ZDV+Placebo	46	35	26	25	6

(ZDV=AZT)

Figure 5: 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

	Baseline	Week 16	Week 32	Week 52	Week 76
NVP+ZDV+ddI	51	40	40	37	10
Placebo+ZDV+ddI	51	37	37	33	6
NVP+ZDV+Placebo	46	35	26	25	6

(ZDV=AZT)

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 (≤100,000 copies/mL and >100,000 copies/mL). Selected demographic and baseline disease characteristics are displayed in Table 2.

Table 2: Demographic and Baseline Disease Characteristics in Study 1100.1486

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

[a] Includes 2 patients who were randomised but never received blinded medication.
[b] Includes American Indians/Alaska native and Hawaiian/Pacific islander.

Table 3 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 3: Outcomes at Week 48 in Study 1100.1486[a]

	VIRAMUNE immediate-release N=506	**VIRAMUNE XR extended-release N=505**
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%

	VIRAMUNE immediate-release N=506	VIRAMUNE XR extended-release N=505
Discontinued study drug prior to Week 48	18.2%	15.8%
Death	0.6%	0.2%
Adverse events	8.3%	6.3%
Other[b]	9.3%	9.4%

[a]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.
[b]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^3 and 197 cells/mm^3 for the groups receiving VIRAMUNE immediate-release and VIRAMUNE XR extended-release respectively.

Table 4 shows outcomes at 48 weeks in Trial 1100.1486 based on baseline viral load.

Table 4: Outcomes at 48 weeks in Study 1100.1486 by Baseline Viral Load[a]

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

[a]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.
[b]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 5.

Table 5: 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[1] N=406	Baseline (mean) N=505	Week 48 (mean) N=419	Percent Change[1] 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

[1]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.

5.2 PHARMACOKINETIC PROPERTIES

Pharmacokinetics in Adult Patients (immediate-release)

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±9% (mean±SD) for a 50 mg tablet and 91±8% for an oral solution. Peak plasma nevirapine concentrations of 2±0.4 microgram/mL (7.5 μM) 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±1.9 microgram/mL (17±7 μM), (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_{dss}) of nevirapine was 1.21±0.09 L/kg, suggesting that nevirapine is widely distributed in humans. Nevirapine readily crosses the placenta and is found in breast milk (see Section 4.6 Fertility, Pregnancy and Lactation, Use in Pregnancy). 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% (±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}C-nevirapine, approximately 91.4%±10.5% of the radiolabelled dose was recovered, with urine (81.3%±11.1%) representing the primary route of excretion compared to faeces (10.1%±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 $AUC_{0-24,ss}$ and $C_{min,ss}$ measured after 19 days of fasted dosing of VIRAMUNE XR extended-release 400 mg once daily were approximately 80% and 90%, respectively, of the $AUC_{0-24,ss}$ and $C_{min,ss}$ measured when patients were dosed with VIRAMUNE immediate-release 200 mg twice daily. The geometric mean nevirapine $C_{min,ss}$ was 2770 ng/mL.

When VIRAMUNE XR extended-release was dosed with a high fat meal, the nevirapine $AUC_{0-24,ss}$ and $C_{min,ss}$ were approximately 94% and 98%, respectively, of the $AUC_{0-24,ss}$ and $C_{min,ss}$ 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 which may resemble intact tablets. These occurrences have not been shown to affect drug levels or response.

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 (7.5 mg, 30 mg or 120 mg per m^2; 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$\pm$10.2 hours.

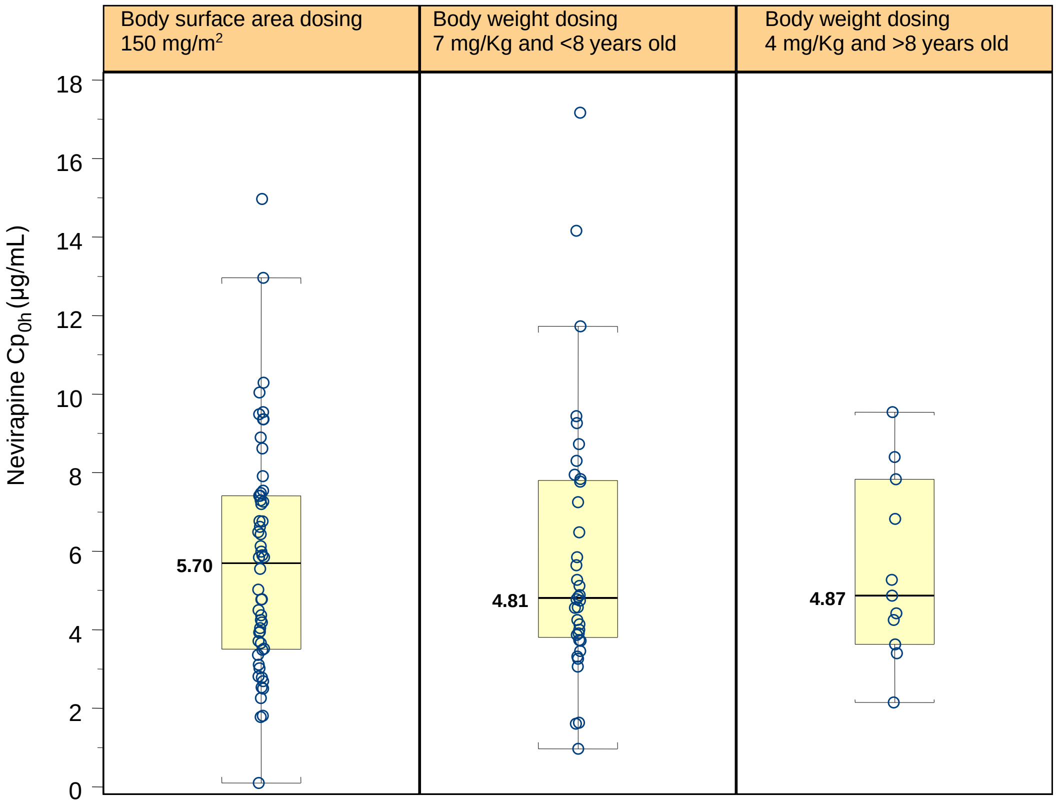
In a second multiple dose study, VIRAMUNE suspension or tablets (240 to 400 mg/m^2/day) were administered as monotherapy or in combination with AZT or AZT and ddI to 37 HIV-1-infected children with the following demographics: male (54%), racial minority groups (73%), median age of 11 months (range: 2 months – 15 years). These patients received 120 mg/m^2/day of nevirapine for approximately 4 weeks followed by 120 mg/m^2/twice a day (patients >9 years of age) or 200 mg/m^2/twice a day (patients $\leq$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^2 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^2 once daily for two weeks followed by 150 mg/m^2 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 6: 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 6: 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_{max} (microgram/mL)	Geometric mean (Mean±SD) Clearance (L/h/m²)
≥ 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 body surface area based (150 mg/m²) nevirapine dosing is effective in treating antiretroviral naive paediatric patients.

Dosing of nevirapine at 150 mg/m² BID (after a two-week lead in at 150 mg/m² 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 $C_{min,ss}$ and AUC_{ss} with 90% confidence intervals within 80% - 125%; the ratio for $C_{max,ss}$ 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 <6 years, 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.

Occasionally, the inactive ingredients of VIRAMUNE XR extended-release tablets will be eliminated in the faeces as soft, hydrated remnants which may resemble intact tablets. These occurrences have not been shown to affect drug levels or response.

Special Populations

<u>Renal dysfunction</u>

The single-dose pharmacokinetics of VIRAMUNE immediate-release have been compared in 23 subjects with either mild ($50 \leq CL_{cr} < 80$ mL/min), moderate ($30 \leq CL_{cr} < 50$ mL/min) or severe renal dysfunction (CL_{cr} < 30 mL/min), renal impairment or end-stage renal disease (ESRD) requiring dialysis, and 8 subjects with normal renal function (CL_{cr} > 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 7. 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 7: Geometric means and 95% confidence intervals for nevirapine pharmacokinetic parameters

Parameter	Population	mild fibrosis § Gmean / CI	moderate fibrosis Gmean / CI	cirrhosis Gmean / CI
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 Section 4.4 Special Warnings and Precautions for Use).

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 sub study 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.

5.3 PRECLINICAL SAFETY DATA

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).

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

Each VIRAMUNE XR extended-release tablet contains the inactive ingredients lactose monohydrate, hypromellose, iron oxide yellow CI77492 and magnesium stearate.

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

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

400 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.

6.5 NATURE AND CONTENTS OF CONTAINER

400 mg extended-release tablets	Polyvinyl chloride (PVC)/aluminium foil push through blister units. Blister pack: 10*, 30 tablets.
Oral Suspension	High density polyethylene (HDPE) bottle with a plastic child-resistant cap. Each bottle contains 240 mL of oral suspension.

* Not currently distributed in Australia.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

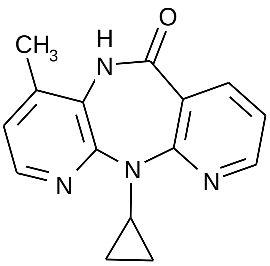
In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

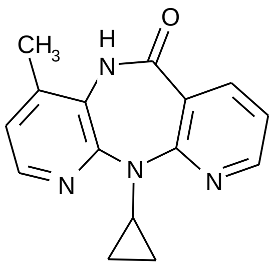
VIRAMUNE contains the active ingredient nevirapine. In the solid state, nevirapine can exist in either an anhydrous form (the actual active moiety, used for production of VIRAMUNE tablets), or a hemihydrate pseudopolymorph (used in VIRAMUNE oral suspension).

Chemical structure

Nevirapine base and hemihydrate have the following structural formulae:



Nevirapine



$.\frac{1}{2}H_2O$

Nevirapine hemihydrate

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 $C_{15}H_{14}N_4O$.

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 $C_{15}H_{14}N_4O.\frac{1}{2}H_2O$.

CAS number

129618-40-2 (nevirapine) and 220988-26-1 (nevirapine hemihydrate).

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 – Prescription Only Medicine

8 SPONSOR

Boehringer Ingelheim Pty Limited
ABN 52 000 452 308
78 Waterloo Road
North Ryde NSW 2113
www.boehringer-ingelheim.com.au

9 DATE OF FIRST APPROVAL

VIRAMUNE nevirapine (as hemihydrate) 10mg/mL oral liquid bottle	2 August 2000
VIRAMUNE XR nevirapine 400mg extended-release tablet blister pack	4 January 2012

10 DATE OF REVISION

04 September 2024

SUMMARY TABLE OF CHANGES

Section changed	**Summary of new information**
4.5	Correction of typographical error