PRODUCT MONOGRAPH

[Pr]VIRAMUNE®
(nevirapine)
Immediate-Release Tablets
200 mg

[Pr]VIRAMUNE® XR
(nevirapine)
Extended-Release Tablets
400 mg

ANTIRETROVIRAL AGENT

NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITOR

WITH ACTIVITY AGAINST

HUMAN IMMUNODEFICIENCY VIRUS TYPE 1 (HIV-1)

Boehringer Ingelheim (Canada) Ltd.
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For BICL use only: Tracking CCDS # 0199-17

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[Pr]Viramune®
nevirapine immediate-release tablets
[Pr]Viramune® XR
nevirapine extended-release tablets

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Oral	Immediate-Release Tablet, 200 mg	lactose
	Extended-Release Tablet, 400 mg	lactose
		For a complete listing see Dosage Forms, Composition and Packaging section.

INDICATIONS AND CLINICAL USE

VIRAMUNE or VIRAMUNE XR (nevirapine) is indicated as an alternative for:

- treatment of HIV-1 infection in combination with other antiretroviral agents.

The decision to use VIRAMUNE or VIRAMUNE XR should take into account liver and skin toxicity, potentially fatal, especially in patients with higher CD4 counts and in women (see **WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic and Skin**). Clinical trials have not established equivalence of nevirapine to protease inhibitors or to other NNRTIs.

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

Geriatrics (> 65 years of age):

Clinical studies of VIRAMUNE or VIRAMUNE XR did not include sufficient numbers of subjects aged 65 and older to determine whether elderly subjects respond differently from younger subjects. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy.

Pediatrics (< 15 years of age):

Safety and effectiveness of VIRAMUNE or VIRAMUNE XR in HIV-1 infected pediatric patients younger than 15 years of age has not been established. Nevirapine is metabolized more rapidly in pediatric patients than in adults.

CONTRAINDICATIONS

- VIRAMUNE or VIRAMUNE XR (nevirapine) is contraindicated in patients with clinically significant hypersensitivity to any of its components. For a complete listing see the **DOSAGE FORMS, COMPOSITION AND PACKAGING** sections of the Product Monograph.

- VIRAMUNE or VIRAMUNE XR should not be administered to patients with severe hepatic dysfunction or pre-treatment AST or ALT > 5X Upper Limit of Normality (ULN).

- VIRAMUNE or VIRAMUNE XR should not be readministered to patients who have been discontinued for severe rash, rash accompanied by constitutional symptoms, hypersensitivity reactions, or clinical hepatitis due to nevirapine.

- VIRAMUNE or VIRAMUNE XR should not be readministered in patients who previously had AST or ALT > 5X Upper Limit of Normality (ULN) during nevirapine therapy (see **WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic and Skin**).

- VIRAMUNE or VIRAMUNE XR should not be administered to patients with rare hereditary conditions of galactose intolerance e.g. galactosaemia, the Lapp lactase deficiency or glucose-galactose malabsorption.

- Herbal preparations containing St John's wort (*Hypericum perforatum*) must not be used while taking VIRAMUNE or VIRAMUNE XR due to the risk of potentially significant decreases of plasma concentrations and reduced clinical effects of nevirapine (see **DRUG INTERACTIONS**).

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

VIRAMUNE or VIRAMUNE XR should not be initiated in adult females, including pregnant women, with CD4+ cell counts > 250 cell/mm^3 and in adult males with CD4 cell counts> 400 cells/mm^3 unless the benefit outweighs the risk. Severe, life-threatening, and in some cases fatal hepatotoxicity, particularly in the first 18 weeks, has been reported in patients treated with VIRAMUNE. An increased risk of hepatic adverse events is associated with female gender and higher CD4 counts (see, General and Hepatic/Biliary/Pancreatic sections below).

Severe, life-threatening skin reactions, including fatal cases, have been reported with VIRAMUNE treatment, occurring almost exclusively during the first 6 weeks of therapy. These have included cases of Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and hypersensitivity syndrome characterized by rash, constitutional findings, and organ dysfunction (see ADVERSE REACTIONS, Adverse Drug Reaction Overview). Patients should be carefully monitored during the first 18 weeks of treatment. Patients developing signs or symptoms of severe skin reactions or hypersensitivity reactions (including, but not limited to, severe rash or rash accompanied by fever, general malaise, fatigue, muscle or joint aches, blisters, oral lesions, conjunctivitis, facial edema, and/or hepatitis, eosinophilia, granulocytopenia, lymphadenopathy, and renal dysfunction) must permanently discontinue VIRAMUNE or VIRAMUNE XR and seek medical evaluation immediately (see Guidelines for the MANAGEMENT OF RASH EVENTS, WARNINGS AND PRECAUTIONS and ADVERSE REACTIONS).

General

Women and patients with higher CD4 counts are at increased risk of hepatic adverse events. The first 18 weeks of therapy with VIRAMUNE or VIRAMUNE XR (nevirapine) are a critical period during which intensive monitoring of patients is required to detect potentially life-threatening hepatic events and skin reactions. The optimal frequency of monitoring during this time period has not been established, however it may be prudent to conduct clinical and laboratory monitoring more often than once per month; for example, liver function tests at baseline, prior to dose escalation and at two weeks post dose escalation. After the initial 18 week period, frequent clinical and laboratory monitoring should continue throughout treatment. 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.

Resistant virus emerges rapidly and uniformly when VIRAMUNE or VIRAMUNE XR is administered as monotherapy. Therefore, VIRAMUNE or VIRAMUNE XR should always be administered in combination with other antiretroviral agents for the treatment of HIV-1 infection.

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

When administering VIRAMUNE or VIRAMUNE XR as part of a multi-drug antiretroviral treatment regimen, the complete product information for each therapeutic component should be consulted before initiation of treatment.

Patients receiving VIRAMUNE or VIRAMUNE XR or any other antiretroviral therapy may continue to develop opportunistic infections and other complications of HIV infection, and therefore should remain under close clinical observation by physicians experienced in the treatment of patients with associated HIV diseases. VIRAMUNE or VIRAMUNE XR therapy has not been shown to reduce the risk of horizontal transmission of HIV-1 to others.

Inform patients that they may occasionally see soft remnants of VIRAMUNE XR in their stool, which sometimes resemble intact tablets. These occurrences have not been shown to affect drug levels or response.

Hepatic/Biliary/Pancreatic

Severe, life-threatening, and in some cases fatal hepatotoxicity, including fulminant and cholestatic hepatitis, hepatic necrosis and hepatic failure, have been reported in patients treated with VIRAMUNE. In some cases, patients presented with non-specific prodromal signs or symptoms of hepatitis and progressed to hepatic failure. These events are often associated with rash. Female gender and higher CD4 counts at the initiation of therapy place patients at greater risk of hepatic adverse events. Based on serious and life-threatening hepatotoxicity observed in controlled and uncontrolled studies, VIRAMUNE should not be initiated in adult females with CD4+ cell counts greater than 250 cells/mm^3, including pregnant women receiving chronic treatment for HIV infection, or in adult males with CD4+ cell counts greater than 400 cells/mm^3 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 or VIRAMUNE XR and seek medical evaluation immediately. VIRAMUNE or VIRAMUNE XR should not be restarted following severe hepatic, skin or hypersensitivity reactions.

In clinical trials, the risk of hepatic events regardless of severity was greatest in the first 6 weeks of therapy. The risk continued to be greater in the VIRAMUNE groups compared to controls through 18 weeks of treatment. However, hepatic events may occur at any time during treatment. In some cases, patients presented with non-specific, prodromal signs or symptoms of fatigue, malaise, anorexia, nausea, jaundice, liver tenderness or hepatomegaly, with or without initially abnormal serum transaminase levels. Some of these events have progressed to hepatic failure with transaminase elevation, with or without hyperbilirubinemia, prolonged partial thromboplastin time, or eosinophilia. Rash and fever accompanied some of these hepatic events. Patients with signs or symptoms of hepatitis must be advised to discontinue VIRAMUNE and immediately seek medical evaluation, which should include liver function tests.

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

Increased AST or ALT levels and/or co-infection with hepatitis B and C at the start of antiretroviral therapy are associated with a greater risk of hepatic adverse events.

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

VIRAMUNE or VIRAMUNE XR should not be administered to patients with severe hepatic dysfunction (see **CONTRAINDICATIONS**). Single dose pharmacokinetic results suggest caution should be exercised when VIRAMUNE or VIRAMUNE XR is administered to patients with moderate hepatic dysfunction. VIRAMUNE or VIRAMUNE XR is extensively metabolised by the liver and nevirapine metabolites are eliminated largely by the kidney. Increased nevirapine levels and nevirapine accumulation may be observed in patients with serious liver disease.

MANAGEMENT OF HEPATIC EVENTS WITH VIRAMUNE or VIRAMUNE XR*

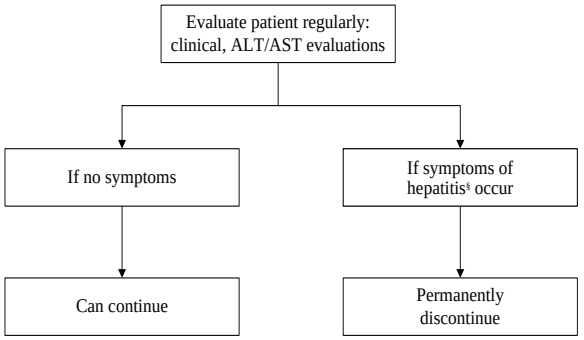
Risk Factors for Symptomatic Hepatic Events

- Elevated pretreatment ALT or AST
- HBV and/or HCV coinfection ‡
- Higher CD4+ cell count at initiation of VIRAMUNE or VIRAMUNE XR therapy
- Female gender
- **Women with CD4+ cell counts >250 cells/mm^3, including pregnant women receiving chronic treatment for HIV infection, are at considerably higher risk of hepatotoxicity, including fatal events**

Patient Management

- Counsel patients that if signs or symptoms of hepatitis,§ severe skin reactions, or hypersensitivity occur, then discontinue VIRAMUNE or VIRAMUNE XR and seek medical evaluation immediately
- Frequent clinical and laboratory monitoring is essential, especially during the first 18 weeks of treatment - extra vigilance is warranted during the first 6 weeks
- Baseline assessments should include LFTs and HBV/HCV status
- If hepatic symptoms occur:
  - Permanently discontinue VIRAMUNE or VIRAMUNE XR
  - Consider stopping all potential hepatotoxins, including concomitant antiretrovirals
  - Evaluate patient for other causes, including HBV/HCV coinfection, alcohol use, and coadministered medications
  - Continue to monitor patient until symptoms resolve
- In some cases, hepatic injury has progressed despite discontinuation of treatment

Hepatic Event Management



Other Important Information

- The 14-day lead-in period with VIRAMUNE 200 mg daily must be strictly followed||
- VIRAMUNE or VIRAMUNE XR should not be used for multiple-dose postexposure prophylaxis. Serious hepatotoxicity, including hepatic failure, has occurred in this setting

* Hepatic events include symptomatic hepatitis and/or ALT/AST >5X ULN.
‡ Risk factors associated with regimens with and without VIRAMUNE or VIRAMUNE XR.
§ Signs and symptoms of hepatitis may include anorexia, malaise, jaundice, nausea/vomiting, bilirubinemia, acholic stools, hepatomegaly, and hepatic tenderness. Other constitutional symptoms may include fever, arthralgia, fatigue, and other findings of generalized organ dysfunction. The presence of one or more of these findings does not necessarily indicate hepatitis. Diagnosis should be based on sound clinical judgment.
|| If VIRAMUNE or VIRAMUNE XR has been interrupted for >7 days, reintroduce with 200-mg once-daily lead-in dose.

Severe, life-threatening, and in some cases fatal, hepatotoxicity, including fulminant and cholestatic hepatitis, hepatic necrosis, and hepatic failure, has been reported in patients treated with VIRAMUNE. In some cases, patients presented with nonspecific prodromal signs or symptoms of hepatitis and progressed to hepatic failure. Patients with signs and symptoms of hepatitis must seek medical evaluation immediately and should be advised to discontinue VIRAMUNE or VIRAMUNE XR.

Skin

Severe, life-threatening skin reactions, including fatal cases, have been reported with VIRAMUNE treatment, occurring almost exclusively during the first 6 weeks of therapy. These have included cases of Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and hypersensitivity syndrome characterized by rash, constitutional findings, and organ dysfunction (see ADVERSE REACTIONS, Adverse Drug Reaction Overview). Patients should be carefully monitored during the first 18 weeks of treatment. Patients developing signs or symptoms of severe skin reactions or hypersensitivity reactions (including, but not limited to, severe rash or rash accompanied by fever, general malaise, fatigue, muscle or joint aches, blisters, oral lesions, conjunctivitis, facial edema, and/or hepatitis, eosinophilia, granulocytopenia, lymphadenopathy, and renal dysfunction) must permanently discontinue VIRAMUNE or VIRAMUNE XR and seek medical evaluation immediately (see Guidelines for the MANAGEMENT OF RASH EVENTS, WARNINGS AND PRECAUTIONS; Skin and ADVERSE REACTIONS, Skin and Subcutaneous Tissues). VIRAMUNE or VIRAMUNE XR should not be restarted following severe skin rash or hypersensitivity reaction (see Guideline for the MANAGEMENT OF RASH EVENTS). Some of the risk factors for developing serious cutaneous reactions include failure to follow the initial dosing of 200 mg daily during the 14-day lead-in period and delay in stopping the VIRAMUNE treatment after the onset of the initial symptoms.

Therapy with VIRAMUNE must be initiated with a 14-day lead-in period of 200 mg/day which has been shown to reduce the frequency of rash. If rash is observed during this lead-in period of 200 mg immediate-release tablet, dose escalation to 200 mg immediate-release tablet twice-daily or 400 mg extended-release tablet once daily should not occur until the rash has resolved. (see Guideline for the **MANAGEMENT OF RASH EVENTS**, and **DOSAGE AND ADMINISTRATION, Monitoring of Patients**) Patients should be monitored closely if an isolated rash of any severity occurs. The risk of development of resistance to VIRAMUNE is unknown when the 200 mg once daily dosing regimen is continued beyond 14 days.

If patients present with a suspected VIRAMUNE or VIRAMUNE XR-associated rash, liver function tests should be performed. Patients with rash-associated AST or ALT elevations should be permanently discontinued from VIRAMUNE or VIRAMUNE XR.

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

Women appear to be at higher risk than men of developing rash with VIRAMUNE or VIRAMUNE XR.

In a clinical trial, the concomitant use of prednisone (40 mg/day for the first 14 days of VIRAMUNE immediate-release administration) was associated with an increase in the incidence and severity of rash during the first 6 weeks of VIRAMUNE therapy. Therefore, the use of prednisone to prevent VIRAMUNE or VIRAMUNE XR-associated rash is not recommended.

MANAGEMENT OF RASH EVENTS WITH VIRAMUNE or VIRAMUNE XR*

Patient Management

The recommended 14-day, 200-mg once-daily lead-in dose, prior to escalation to 200 mg immediate-release tablet twice daily or 400 mg extended-release tablet once daily, has been shown to reduce the frequency of rash and must be strictly followed

Do not increase the dose of VIRAMUNE or VIRAMUNE XR in the presence of rash

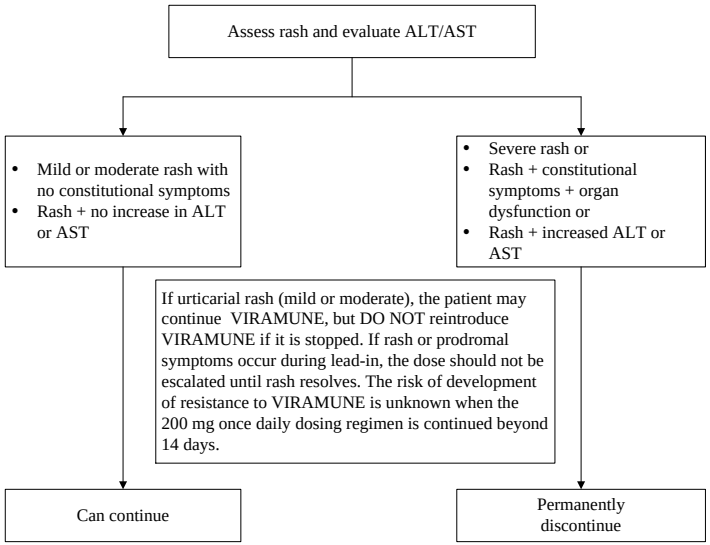
If VIRAMUNE or VIRAMUNE XR is interrupted for >7 days, reintroduce with the 14-day, 200-mg once-daily lead-in dose

It is suggested that VIRAMUNE or VIRAMUNE XR and other medications that often cause rash should not be started simultaneously

Prednisone should not be used to prevent rash. Prednisone administration during the first 2 weeks of therapy with VIRAMUNE appears to increase the incidence of rash

Antihistamines do not appear to be effective in preventing rash with VIRAMUNE or VIRAMUNE XR

Rash Management Algorithm



Definitions

• Mild or moderate rash may include:
  - Erythema
  - Diffuse erythematous or maculopapular rash

• Severe rash may include:
  - Extensive erythematous or maculopapular rash
  - Rash with moist desquamation
  - Rash with angioedema
  - Serum sickness-like reaction
  - Stevens-Johnson syndrome
  - Toxic epidermal necrolysis (TEN)

Definitions (cont'd)

• Urticaria: pruritic raised rash with welts (may be mild, moderate, or severe)
• Constitutional symptoms include fever, blistering, oral erosive lesions, conjunctivitis, facial edema, and myalgia/arthralgia

***Severe, life-threatening skin reactions, including fatal cases, have occurred in patients treated with VIRAMUNE. These have included severe cases of SJS, TEN, and hypersensitivity reactions characterized by rash, constitutional findings, and organ dysfunction. Patients developing signs and symptoms of severe skin reactions or hypersensitivity reactions must discontinue VIRAMUNE or VIRAMUNE XR as soon as possible.**

Post-Exposure Prophylaxis

VIRAMUNE or VIRAMUNE XR is not recommended for post-exposure prophylaxis. In the setting of post-exposure prophylaxis, an unapproved use, serious hepatotoxicity, including one instance of liver failure requiring transplantation, and serious skin rash including Stevens-Johnson syndrome, have been reported in HIV-uninfected individuals receiving multiple doses of VIRAMUNE in combination with other antiretroviral agents.

Carcinogenesis and Mutagenesis

In long-term carcinogenicity studies, the incidence of hepatocellular adenomas and carcinomas in mice increased at all doses in males and at the two high doses in females. In rats an increase in hepatocellular adenomas was seen in males at all doses and in females at the high dose. The systemic exposure (based on AUCs) at all doses in the two animal studies were lower than that measured in humans at the recommended daily dose.

In genetic toxicology assays, nevirapine showed no evidence of mutagenic activity in a battery of *in vitro* and *in vivo* assays including microbial assays for gene mutation (Ames test in Salmonella strains and E. coli), mammalian cell gene mutation (HGRPT) assays in Chinese hamster ovary (CHO) cell line, cytogenetic assays using a CHO cell line and mouse bone marrow micronucleus assay following oral administration. In reproductive toxicology studies, evidence of impaired fertility was seen in female rats at doses providing systemic exposure, based on AUC, approximately equivalent to that observed following a human clinical dosage of 400 mg/day.

Renal

VIRAMUNE or VIRAMUNE XR is extensively metabolised by the liver and nevirapine metabolites are eliminated largely by the kidney. In renal dysfunction, a single dose study suggested that patients with a creatinine clearance $\geq$ 20 mL/min do not require an adjustment in VIRAMUNE or VIRAMUNE XR dosing (see **DETAILED PHARMACOLOGY, Special Populations**).

Fat Redistribution

Redistribution/accumulation of body fat including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and "cushingoid appearance" have been observed in patients receiving antiretroviral therapy. The mechanism and long-term consequences of these events are currently unknown. A causal relationship has not been established.

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.

Concomitant Use with Other Drugs

VIRAMUNE or VIRAMUNE XR can alter plasma exposure of other drugs, and other drugs can alter plasma exposure of VIRAMUNE or VIRAMUNE XR. Combining the following compounds with VIRAMUNE or VIRAMUNE XR is not recommended: efavirenz, rifampicin (rifampin), ketoconazole, delavirdine, etravirine, rilpivirine, elvitegravir (in combination with cobicistat), boceprevir; if not co-administered with low dose ritonavir: fosamprenavir and saquinavir (see **DRUG INTERACTIONS**).

Birth Control Methods

Depo Medroxyprogesterone Acetate (DMPA)

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

Special Populations

Pregnant Women:
VIRAMUNE or VIRAMUNE XR should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. 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. The 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.

Severe hepatic events, including fatalities, have been reported in pregnant women receiving chronic VIRAMUNE therapy as part of combination treatment for HIV infection. Regardless of pregnancy status, women with CD4 counts >250 cells/mm^3 should not initiate VIRAMUNE or VIRAMUNE XR unless the benefit outweighs the risk. It is unclear if pregnancy augments the risk observed in non-pregnant women. (see **WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic**).

In reproductive toxicology studies, evidence of impaired fertility was seen in female rats at doses providing systemic exposure, based on AUC, approximately equivalent to that provided with the recommended clinical dose of VIRAMUNE

No human data on fertility are available.

Antiretroviral Pregnancy Registry:
To monitor maternal-fetal outcomes of pregnant women exposed to VIRAMUNE, an Antiretroviral Pregnancy Registry has been established. Physicians are encouraged to register patients by calling 1-800-258-4263.

Nursing Women:
It is currently recommended that HIV-1 infected women should not breast feed infants regardless of the use of antiretroviral agents, to avoid post-natal transmission of HIV-1.

Preliminary results from a pharmacokinetic study (ACTG 250) of 10 HIV-1-infected pregnant women who were administered a single oral dose of 100 or 200 mg VIRAMUNE at a median of 5.8 hours before delivery, indicated that nevirapine readily crosses the placenta and is found in breast milk (breast milk samples taken from 3 out of 10 mothers).

Pediatrics (< *15* years of age):
Safety and effectiveness of VIRAMUNE or VIRAMUNE XR in HIV-1-infected pediatric patients younger than 15 years of age have not been established. Nevirapine is metabolized more rapidly in pediatric patients than in adults.

Geriatrics (> 65 years of age):
Clinical studies of VIRAMUNE or VIRAMUNE XR did not include sufficient numbers of subjects aged 65 and older to determine whether elderly subjects respond differently from younger subjects. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy.

Ethnic Origin:
An evaluation of nevirapine plasma concentrations (pooled data from several clinical trials) from HIV-1-infected patients (27 Black, 24 Hispanic, 189 Caucasian) revealed no marked difference in nevirapine steady-state trough concentrations (median C_{minss}= 4.7 μg/mL Black, 3.8 μg/mL Hispanic, 4.3 μg/mL Caucasian) with long-term nevirapine treatment at 400 mg/day. However, the pharmacokinetics of nevirapine have not been evaluated specifically for the effects of ethnicity.

Monitoring and Laboratory Tests

Intensive clinical and laboratory monitoring, including liver function tests, is essential at baseline and during the first 18 weeks of treatment (see **WARNINGS AND PRECAUTIONS, General**). The optimal frequency of monitoring during this period has not been established, however it may

be prudent to conduct clinical and laboratory monitoring more often than once per month; for example, liver function tests at baseline, prior to dose escalation and at two weeks post-dose escalation. Monitoring should continue at frequent intervals thereafter, depending on the patient's clinical status. Liver function tests should be performed immediately if a patient experiences signs or symptoms suggestive of hepatitis and/or hypersensitivity reaction. Liver function tests should also be obtained for all patients who develop a rash in the first 18 weeks of treatment. Physicians and patients should be vigilant for the appearance of signs or symptoms of hepatitis, such as fatigue, malaise, anorexia, nausea, jaundice, bilirubinuria, acholic stools, liver tenderness or hepatomegaly. The diagnosis of hepatic injury should be considered in this setting, even if liver function tests are initially normal or alternative diagnoses are possible (see **WARNINGS AND PRECAUTIONS; ADVERSE REACTIONS**; and **DOSAGE AND ADMINISTRATION)**. VIRAMUNE or VIRAMUNE XR administration should be interrupted in patients experiencing moderate or severe liver function test abnormalities (> 5X ULN) (excluding GGT), until the liver function test elevations have returned to baseline. VIRAMUNE may then be restarted at the lead-in dose of one immediate-release 200 mg tablet daily for 14 days followed by one 200 mg VIRAMUNE immediate-release tablet twice daily or one 400 mg VIRAMUNE extended-release tablet once daily. Increasing the daily dose to 200 mg twice daily (400 mg/day) should be done with caution, after extended observation. If rash is observed during the lead-in period of 200 mg immediate-release tablet, dose escalation to 200 mg immediate-release tablet twice-daily or 400 mg extended-release tablet once daily should not occur until the rash has resolved (see Guideline for the **MANAGEMENT OF RASH EVENTS**, and **DOSAGE AND ADMINISTRATION**). Patients should be aware that this may not prevent serious adverse reactions. VIRAMUNE or VIRAMUNE XR should be permanently discontinued if moderate or severe liver function test abnormalities recur (see **WARNINGS AND PRECAUTIONS**).

If clinical hepatitis occurs, VIRAMUNE or VIRAMUNE XR should be permanently discontinued and not restarted after recovery. If either AST or ALT increase to > 5X ULN, VIRAMUNE or VIRAMUNE XR should be immediately stopped. VIRAMUNE or VIRAMUNE XR should not be readministered to patients who have been discontinued for severe rash, rash accompanied by constitutional symptoms, hypersensitivity reactions, or clinical hepatitis due to VIRAMUNE or VIRAMUNE XR (see Guideline for the **MANAGEMENT OF HEPATIC EVENTS**). In some cases hepatic injury progresses despite the discontinuation of treatment.

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

With AST or ALT values > 2X ULN, liver tests should be monitored more frequently.

Asymptomatic elevation of liver enzymes occurs frequently in patients infected with HIV and is not necessarily a contraindication to initiating therapy with VIRAMUNE or VIRAMUNE XR. Asymptomatic GGT elevations are not a contraindication to continuing therapy.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

The most serious adverse reactions associated with VIRAMUNE or VIRAMUNE XR (nevirapine) are clinical hepatitis/hepatic failure, Stevens-Johnson syndrome, toxic epidermal necrolysis, and hypersensitivity reactions. Clinical hepatitis/hepatic failure may be isolated or associated with signs of hypersensitivity which may include, severe rash or rash accompanied by fever, general malaise, fatigue, muscle or joint aches, blisters, oral lesions, conjunctivitis, facial edema, and/or hepatitis, eosinophilia, granulocytopenia, lymphadenopathy and renal dysfunction. Severe and life-threatening hepatic injury, and fatal fulminant hepatitis, have been reported in patients treated with VIRAMUNE. The first 18 weeks of treatment is a critical period, but such events may also occur later. 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 WARNINGS AND PRECAUTIONS Hepatic/Biliary/Pancreatic and Skin).

Hepato-Biliary

In controlled clinical trials, clinical hepatic events regardless of severity occurred in 4.0% (range 2.5% to 11.0%) of patients who received VIRAMUNE immediate-release tablets and 1.2% of patients in control groups. Transaminase elevations (ALT or AST > 5X ULN) were observed in 8.8% of patients receiving VIRAMUNE immediate-release tablets and 6.2% of patients in control groups in clinical trials. In a retrospective analysis of controlled and uncontrolled clinical trials, patients with higher CD4 counts at initiation of VIRAMUNE immediate-release tablets therapy, particularly women, were at greater risk for acute symptomatic hepatic events, including death, especially in the first six weeks of therapy.

Patients with chronic hepatitis B or C infection were at higher risk for later hepatic events (see **WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic**).

In the Phase 3 trial comparing VIRAMUNE extended release formulation to VIRAMUNE immediate release formulation in treatment naïve subjects (see **CLINICAL TRIALS,** Trial 1100.1486, VERxVE) safety data included 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 extended-release group.

In the Phase 3 trial comparing VIRAMUNE extended release formulation to VIRAMUNE immediate release formulation in treatment experienced subjects (see **CLINICAL TRIALS,** Trial 1100.1526, TRANxITION) no Grade 3 or 4 clinical hepatic events were observed in either treatment group.

Skin and Subcutaneous Tissues

The most common clinical toxicity of nevirapine is rash. In placebo-controlled trials involving 1374 patients treated with VIRAMUNE immediate-release tablets (Table 1), rash, of all grades and causality occurred in 14-20% of patients treated with VIRAMUNE. Severe or life-threatening rash occurred in approximately 2% of VIRAMUNE immediate-release tablets treated patients, almost exclusively within the first 6 weeks of therapy.

Rashes were 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. Severe and life-threatening skin reactions have occurred in patients treated with nevirapine, including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). Fatal cases of SJS, TEN and hypersensitivity reactions have been reported. Based on a denominator of 2861 nevirapine-treated clinical trial patients treated with VIRAMUNE immediate-release tablets, the overall incidence of SJS was 0.3% (9/2861).

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

TABLE 1: RISK OF RASH (%) IN ADULT PLACEBO CONTROLLED TRIALS [1] – REGARDLESS OF CAUSALITY

		VIRAMUNE IR	**Placebo**
		n=1374 %	n=1331 %
Through 6 weeks of treatment[2]			
Rash events of all grades[3]		14.8	5.9
Grade 1	Erythema, pruritus	8.5	4.2
Grade 2	Diffuse maculopapular rash, dry desquamation	4.8	1.6
Grade 3 or 4	Grade 3: vesiculation, moist desquamation, ulceration; Grade 4: erythema multiforme, Stevens Johnson syndrome, toxic epidermal necrolysis, necrosis requiring surgery, exfoliative dermatitis	1.5	0.1
Through 52 weeks of treatment[2]			
Rash events of all grades[3]		24.0	14.9
Grade 1	See above	15.5	10.8
Grade 2	See above	7.1	3.9
3 or Grade 4	See above	1.7	0.2
Proportion of Patients who Discontinued Treatment Due to Rash		4.3	1.2

1 Trials 1037, 1038, 1046 and 1090
2 % based on Kaplan-Meier probability estimates
3 NCI grading system

In the Phase 3 trial comparing VIRAMUNE extended release formulation to VIRAMUNE immediate release formulation in treatment naïve subjects (see **CLINICAL TRIALS,** Trial

1100.1486, VERxVE) 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 extended-release groups respectively during the randomization 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® immediate-release treatment.

In the Phase 3 trial comparing VIRAMUNE extended-release formulation to VIRAMUNE immediate-release formulation in treatment experienced subjects (see **CLINICAL TRIALS,** Trial 1100.1526, TRANxITION) no Grade 3 or 4 rash was observed in either treatment group.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Adverse Reactions in Controlled Clinical Trials

No new adverse drug reactions from those previously known to be associated with VIRAMUNE immediate release tablets have been observed in clinical studies comparing the immediate-release and extended-release formulations.

Treatment related, adverse experiences of moderate or severe intensity observed in >2% of patients receiving VIRAMUNE immediate-release tablets in placebo-controlled trials are shown in Table 2.

TABLE 2: PERCENTAGE OF PATIENTS WITH MODERATE OR SEVERE DRUG RELATED REACTIONS IN ADULT PLACEBO-CONTROLLED TRIALS

	Trial 1090[1]		**Trials 1037, 1038, 1046[2]**	
	VIRAMUNE IR (n=1121)	Placebo (n=1128)	VIRAMUNE IR (n=253)	Placebo (n=203)
Median Exposure (weeks)	58	52	28	28
Any adverse reaction	14.5%	11.1%	31.6%	13.3%
Rash	5.1	1.8	6.7	1.5
Abnormal LFTs	1.2	0.9	6.7	1.5
Nausea	0.5	1.1	8.7	3.9
Granulocytopenia	1.8	2.8	0.4	0

Headache	0.7	0.4	3.6	0.5
Fatigue	0.2	0.3	4.7	3.9
Diarrhea	0.2	0.8	2.0	0.5
Abdominal pain	0.1	0.4	2.0	0
Myalgia	0.2	0	1.2	2.0

[1] Background therapy included 3TC for all patients and combinations of NRTIs and PIs. Patients had CD4+ counts <200 cells/mm^3.

[2] Background therapy included ZDV and ZDV+ddI; VIRAMUNE monotherapy was administered in some patients. Patients had CD4+ >200 cells/mm^3.

Abnormal Hematologic and Clinical Chemistry Findings

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 the most frequent. Cases of jaundice have been reported. Cases of hepatitis, severe and life-threatening hepatotoxicity, and fatal fulminant hepatitis, have been reported in patients treated with nevirapine.

Liver function test abnormalities (AST, ALT) were observed more frequently in patients receiving VIRAMUNE immediate-release tablets than in controls (Table 3). Asymptomatic elevations in GGT occur frequently but are not a contraindication to continue VIRAMUNE immediate-release tablets therapy in the absence of elevations in other liver function tests. Other laboratory abnormalities (bilirubin, anemia, neutropenia, thrombocytopenia) were observed with similar frequencies in clinical trials comparing VIRAMUNE immediate-release tablets and control regimens (Table 3).

TABLE 3: PERCENTAGE OF ADULT PATIENTS WITH MARKED LABORATORY ABNORMALITIES

	Trial 1090[1]		**Trials 1037, 1038, 1046[2]**	
	VIRAMUNE IR	Placebo	VIRAMUNE IR	Placebo
Laboratory Abnormality Hematology	n=1121	n=1128	n=253	n=203
Hemoglobin 80 g/L	3.2%	4.1%	0%	0%
Platelets <50 x 10^9/L	1.3	1	0.4	1.5
Neutrophils < 750 x 10^6/L	13.3	13.5	3.6	1
Blood Chemistry				
AST >250 U/L	3.7	2.5	7.6	1.5
ALT >250 U/L	5.3	4.4	14	4
Bilirubin > 42.5 μm/L	1.7	2.2	1.7	1.5

[1] Background therapy included 3TC for all patients and combinations of NRTIs and PIs. Patients had CD4+ counts <200 cells/mm^3.

[2] Background therapy included ZDV and ZDV+ddI; VIRAMUNE monotherapy was administered in some patients. Patients had CD4+ ≥200 cells/mm^3.

Because clinical hepatitis has been reported in VIRAMUNE immediate-release tablets treated patients, intensive clinical and laboratory monitoring, including liver function tests, is essential at

baseline and during the first 18 weeks of treatment. Monitoring should continue at frequent intervals thereafter, depending on the patient's clinical status (see **WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic)**.

Post-Market Adverse Drug Reactions

In addition to the adverse events identified during clinical trials, the following events have been reported with the use of VIRAMUNE in clinical practice:

Body as a Whole: fever, somnolence, drug withdrawal (see **WARNINGS AND PRECAUTIONS; DRUG INTERACTIONS**), redistribution/accumulation of body fat (see **WARNINGS AND PRECAUTIONS, Fat Redistribution**).

Gastrointestinal: vomiting

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

Hematology: anemia (more commonly observed in children), 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 reactions with rash associated with constitutional findings such as fever, blistering, oral lesions, conjunctivitis, facial edema, muscle or joint aches, general malaise or significant hepatic abnormalities (see **WARNINGS AND PRECAUTIONS, Skin**) plus one or more of the following: hepatitis, eosinophilia, granulocytopenia and/or renal dysfunction have been reported with the use of VIRAMUNE.

Apart from rash and abnormal LFTs, the most frequently reported adverse events related to VIRAMUNE therapy across all clinical trials were nausea, fatigue, fever, headache, vomiting, diarrhea, abdominal pain and myalgia. In very rare instances, cases of anaemia and neutropenia may be associated with VIRAMUNE or VIRAMUNE XR therapy. Arthralgia has been reported as a stand-alone event in rare instances in patients receiving VIRAMUNE containing regimens.

The following events have also been reported when VIRAMUNE has been used in combination with other anti-retroviral agents: pancreatitis, peripheral neuropathy and thrombocytopenia. These events are commonly associated with other anti-retroviral agents and may be expected to occur when VIRAMUNE or VIRAMUNE XR is used in combination with other agents.

In summary the list of side effects, which can be expected with VIRAMUNE or VIRAMUNE XR treatment, includes:

Blood and lymphatic system disorders

Granulocytopenia, anaemia

Immune system disorders

Drug reaction with eosinophilia and systemic symptoms, anaphylactic reaction, hypersensitivity (characterised by rash associated with constitutional symptoms such as fever, arthalgia, myalgia and lymphadenopathy plus one or more of the following: hepatitis, eosinophilia, granulocytopenia, renal dysfunction or other visceral involvement has also been reported. Also including anaphylactic reaction, angioedema, urticaria)

Nervous system disorders

Headache

Gastrointestinal disorders

Diarrhoea, abdominal pain, nausea, vomiting

Hepatobiliary disorders

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

Skin and subcutaneous tissue disorders

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

Musculoskeletal and connective tissue disorders

Arthralgia, myalgia

General disorders and administration site conditions

Pyrexia, fatigue

Investigations

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

DRUG INTERACTIONS

Serious Drug Interactions

- St. John's Wort is contraindicated
- Efavirenz is not recommended
- Fosamprenavir is not recommended
- Rifampicin is not recommended
- Ketoconazole is not recommended
- See Table 4 for drugs that may need a dose adjustment

Overview

Cytochrome P450

Nevirapine induces hepatic cytochrome P450 metabolic isoenzymes 3A4 and 2B6. Co-administration of VIRAMUNE or VIRAMUNE XR and drugs primarily metabolized by CYP3A4 or CYP2B6 may result in decreased plasma concentrations of these drugs and attenuate their therapeutic effects.

Nevirapine does not appear to affect the plasma concentrations of drugs that are substrates of other CYP450 enzyme systems, such as 1A2, 2D6, 2A6, 2E1, 2C9 or 2C19.

Table 4 contains the results of drug interaction studies performed with VIRAMUNE and other drugs likely to be co-administered. Alterations in dose or regimen may also be recommended based on these drug interaction studies conducted in HIV-1 seropositive subjects unless otherwise indicated.

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

Drug-Drug Interactions

TABLE 4: Established and Other Potential Significant Drug Interactions; Alteration in Dose or Regimen May Be Recommended Based on Drug interaction Studies or Predicted Interactions.

Concomitant Drug Class: Drug Name	Effect on Concentration of Nevirapine or Concomitant Drug	Clinical Comment
ANTI-INFECTIVES		
Antiretrovirals		
NRTIs		
Didanosine	↔ didanosine	In one crossover study, nevirapine had no effect on the steady-state pharmacokinetics of ddI (n=18).

Concomitant Drug Class: Drug Name	Effect on Concentration of Nevirapine or Concomitant Drug	Clinical Comment
		No significant effect on didanosine PK parameters seen. Didanosine and VIRAMUNE can be used without dose adjustments.
Emtricitabine		Emtricitabine is not an inhibitor of human CYP 450 enzymes. No dosage adjustments are required when VIRAMUNE® is taken in combination with emtricitabine.
Abacavir		In human liver microsomes, abacavir did not inhibit cytochrome P450 isoforms. No dosage adjustments are required when VIRAMUNE® is taken in combination with abacavir.
Lamivudine	↔ lamivudine	A population pharmacokinetic study of 90 patients assigned to receive lamivudine with VIRAMUNE or placebo revealed no changes to lamivudine apparent clearance and volume of distribution, suggesting no induction effect of VIRAMUNE on lamivudine clearance. Lamivudine and VIRAMUNE can be used without dose adjustments.
Stavudine	↔ nevirapine ↔stavudine	Results from a 36 day study in HIV infected patients administered VIRAMUNE, nelfinavir and stavudine showed no statistically significant changes in the AUC or C_{max} of stavudine. Nevirapine: compared to historical controls, levels appeared to be unchanged. Stavudine and VIRAMUNE can be used without dose adjustments.
Tenofovir	↔ nevirapine ↔ tenofovir	Tenofovir plasma levels remain unchanged when co-administered with nevirapine. Tenofovir does not have an effect on nevirapine plasma levels. Tenofovir and VIRAMUNE can be used without dose adjustments.
Zalcitabine[c]	↔ zalcitabine	In one crossover study, nevirapine had no effect on the steady-state pharmacokinetics of ddC (n=6). Zalcitabine and VIRAMUNE can be used without dose adjustments.
Zidovudine	↔ nevirapine ↓ zidovudine	Zidovudine had no effect on the pharmacokinetics of nevirapine. No significant effect on zidovudine PK parameters is seen. Zidovudine and VIRAMUNE can be used without dose adjustments.
NNRTIs		
Efavirenz	↓ efavirenz	It is not recommended to co-administer efavirenz and VIRAMUNE because of the EFV pharmacokinetic changes and the higher risk for side effects associated with their co-administration. Moreover this co-administration does not improve efficacy over either NNRTI alone. There has been no determination of appropriate doses for the safe and effective use of this combination.
Delavirdine		Interaction has not been studied. The concomitant administration of VIRAMUNE® with NNRTIs is not recommended (see also**WARNINGS AND PRECAUTIONS, Concomitant Use with Other Drugs**).
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.

Concomitant Drug Class: Drug Name	Effect on Concentration of Nevirapine or Concomitant Drug	Clinical Comment
		The concomitant administration of VIRAMUNE® with NNRTIs is not recommended (see also**WARNINGS AND PRECAUTIONS, Concomitant Use with Other Drugs**).
Rilpivirine		Interaction has not been studied. The concomitant administration of VIRAMUNE® with NNRTIs is not recommended (see also**WARNINGS AND PRECAUTIONS, Concomitant Use with Other Drugs**).
PIs		
Darunavir / ritonavir	↑ nevirapine ↑darunavir	No significant effect on darunavir PK parameters is seen when administered concomitantly with nevirapine. Exposure to nevirapine increased when administered in combination with darunavir and ritonavir. Darunavir and VIRAMUNE can be used without dose adjustments.
Fosamprenavir	↑ nevirapine ↓ amprenavir	It is not recommended to co-administer fosamprenavir and VIRAMUNE if fosamprenavir is not co-administered with ritonavir.
Fosamprenavir / ritonavir	↑ nevirapine ↓ amprenavir	No significant alteration of plasma pharmacokinetic parameters of amprenavir. Plasma trough concentrations of nevirapine were increased. Fosamprenavir/ritonavir and VIRAMUNE can be used without dose adjustments.
Indinavir	↔ nevirapine ↓ indinavir	Results from a clinical trial with HIV infected patients administered nevirapine and indinavir indicated that their co-administration leads to a decrease in indinavir AUC and C_{min}. There was no significant change in nevirapine plasma levels. 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. No clinically relevant change in nevirapine plasma levels was found.
Lopinavir / ritonavir	Adult patients: ↓ lopinavir	In HIV positive adults, nevirapine used in combination with lopinavir/ritonavir 400/100 mg (3 capsules) twice daily resulted in a decline in the mean lopinavir AUC and C_{min}. Although the clinical relevance of this observation has not been fully established, an increase in the dose of lopinavir/ritonavir to 533/133 mg (4 capsules) twice daily with food is recommended in combination with VIRAMUNE. Dose adjustment of VIRAMUNE is not required when co-administered with lopinavir.
Lopinavir[a] / ritonavir	Paediatric patients: ↓ lopinavir	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[d], particularly for patients in whom reduced susceptibility to lopinavir/ritonavir is suspected. Results from a pharmacokinetic study in paediatric patients were consistent with the findings in adults. During nevirapine co-administration, mean lopinavir AUC and C_{min}decreased. In children 6

Concomitant Drug Class: Drug Name	Effect on Concentration of Nevirapine or Concomitant Drug	Clinical Comment
		months to 12 years of age, consideration should be given to increasing the dose of lopinavir/ritonavir to 13/3.25 mg/kg for those 7 to < 15 kg; 11/2.75 mg/kg for those 15 to 45 kg; and up to a maximum dose of 533/133 mg for those > 45 kg twice daily when used in combination with nevirapine, particularly for patients in whom reduced susceptibility to lopinavir/ritonavir is suspected.
Nelfinavir	↔ nevirapine ↓nelfinavir C_{min} ↓ nelfinavir-M8 metabolite	Results from a 28 day study in HIV infected patients administered VIRAMUNE, nelfinavir showed no statistically significant changes in nelfinavir pharmacokinetic parameters after the addition of VIRAMUNE. Compared to historical controls VIRAMUNE levels appeared to be unchanged. The major metabolite of nelfinavir (M8) which has comparable activity to the parent compound, however, has a decrease in AUC, C_{max} and C_{min}. The appropriate dose for nelfinavir in combination with nevirapine, with respect to safety and efficacy, has not been established. Nelfinavir and VIRAMUNE can be used without dose adjustments.
Ritonavir	↔ nevirapine ↔ ritonavir	Results from a clinical trial with HIV infected patients administered nevirapine and ritonavir indicated that their co-administration leads to no significant change in ritonavir or nevirapine plasma concentrations. Ritonavir and VIRAMUNE can be used without dose adjustments.
Saquinavir	↔ nevirapine ↓saquinavir	Results from a clinical trial with HIV infected patients administered nevirapine and saquinavir hard gelatine capsule indicated that their co-administration leads to a mean reduction in saquinavir AUC and no significant change in nevirapine plasma levels. This decrease is not thought to be clinically significant and no dose adjustments of saquinavir or nevirapine are recommended. The safety and efficacy of the combination of nevirapine and saquinavir/ritonavir have not been established.
Tipranavir / ritonavir	↓nevirapine ↓tipranavir	No specific drug-drug interaction study has been performed. The limited data available from a phase IIa study in HIV-infected patients have shown a clinical non significant 20% decrease of TPV C_{min}. No significant effect on tipranavir and VIRAMUNE PK parameters is expected. Tipranavir and VIRAMUNE can be used without dose adjustments.
Entry Inhibitors		
Enfuvirtide	↔ nevirapine ↔ enfuvirtide	No clinically significant pharmacokinetic interactions are expected between enfuvirtide and concomitantly given medicinal products metabolised by CYP450 enzymes. No significant effect on enfurtivide and VIRAMUNE PK parameters is expected. Enfuvirtide and VIRAMUNE can be used without dose adjustments.
Maraviroc	↑ maraviroc	Nevirapine concentrations not measured, no effect is expected. No significant effect on maraviroc and VIRAMUNE PK parameters is expected. The combination of maraviroc and VIRAMUNE, lamivudine and tenofovir can he administered without dose adjustment.
Integrase Inhibitors		
Raltegravir	↔ nevirapine	No clinical data available. Due to the metabolic pathway of raltegravir

Concomitant Drug Class: Drug Name	Effect on Concentration of Nevirapine or Concomitant Drug	Clinical Comment
	↔ raltegravir	no interaction is expected. No significant effect on raltegravir and VIRAMUNE PK parameters is expected. Raltegravir and VIRAMUNE can be used without dose adjustments.
Elvitegravir/ cobicistat		Interaction has not been studied. Cobicistat, a cytochrome P450 3A inhibitor significantly inhibits hepatic enzymes, as well as other metabolic pathways. Therefore coadministration would likely result in altered plasma levels of cobicistat and Viramune. Coadministration of VIRAMUNE® with elvitegravir in combination with cobicistat is not recommended (see also**WARNINGS AND PRECAUTIONS, Concomitant Use with Other Drugs**).
Antivirals for Hepatities B and C		
Interferons (pegylated interferons alfa 2a and alfa 2b)		Interferons have no known effect on CYP 3A4 or 2B6. No clinically relevant drug-drug interaction is expected. Interferons and VIRAMUNE® may be co-administered without dose adjustments.
Entecavir		Entecavir is not a substrate, inducer or an inhibitor of cytochrome P450 (CYP450) enzymes. Due to the metabolic pathway of entecavir, no clinically relevant drug-drug interaction is expected. Entecavir and VIRAMUNE® may be co-administered without dose adjustments.
Telbivudine		Telbivudine is not a substrate, inducer or inhibitor of the cytochrome P450 (CYP450) enzyme system. Due to the metabolic pathway of telbivudine, no clinically relevant drug-drug interaction is expected. Telbivudine and VIRAMUNE® may be co-administered without dose adjustments
Adefovir		Results of *in vitro* studies showed a weak antagonism of nevirapine by adefovir (see also Pharmacological properties), this has not been confirmed in clinical trials and reduced efficacy is not expected. Adefovir did not influence any of the common CYP isoforms know to be involved in human drug metabolism and is excreted renally. No clinically relevant drug-drug interaction is expected. Adefovir and VIRAMUNE® may be co-administered without dose adjustments.
Ribavirin		Results of *in vitro* studies showed a weak antagonism of nevirapine by ribavirin (see also Pharmacological properties), this has not been confirmed in clinical trials and reduced efficacy is not expected. Ribavirin does not inhibit cytochrome P450 enzymes, and there is no evidence from toxicity studies that ribavirin induces liver enzymes. No clinically relevant drug-drug interaction is expected. Ribavirin and VIRAMUNE® may be co-administered without dose adjustments.
Boceprevir		Boceprevir is partly metabolized by CYP3A4/5. Co-administration of boceprevir with medicines that induce or inhibit CYP3A4/5 could

Concomitant Drug Class: Drug Name	Effect on Concentration of Nevirapine or Concomitant Drug	Clinical Comment
		increase or decrease exposure. Plasma trough concentrations of boceprevir were decreased when administered with an NNRTI with a similar metabolic pathway as nevirapine. The clinical outcome of this observed reduction of boceprevir trough concentrations has not been directly assessed. It is not recommended to co-administer boceprevir and VIRAMUNE® (see also**WARNINGS AND PRECAUTIONS, Concomitant Use with Other Drugs**).
Telaprevir		Telaprevir is metabolised in the liver by CYP3A and is a P-glycoprotein substrate. Other enzymes may be involved in the metabolism. Co-administration of telaprevir and medicinal products that induce CYP3A and/or P-gp may decrease telaprevir plasma concentrations. No drug-drug interaction study of telaprevir with nevirapine has been conducted, however, interaction studies of telaprevir with an NNRTI with a similar metabolic pathway as nevirapine demonstrated reduced levels of both. Results of DDI studies of telaprevir with efavirenz indicate that caution should be exercised when co-administering telaprevir with P450 inducers. Caution should be exercised when co-administering telaprevir with nevirapine. If co-administered with VIRAMUNE®, an adjustment in the telaprevir dose should be considered.
Antibiotics		
Clarithromycin	↑ nevirapine ↓ clarithromycin ↑ clarithromycin - 14-OH Metabolite	Results of a VIRAMUNE-clarithromycin drug-drug interaction study resulted in a significant reduction in clarithromycin AUC, C_{max} and C_{min} but a significant increase in AUC and C_{max} of the active metabolite 14-OH clarithromycin. There was a significant increase in the nevirapine C_{min} and a non-significant increase in nevirapine AUC and C_{max}. Alternatives to clarithromycin, such as azithromycin should be considered. Close monitoring of hepatic abnormalities is recommended.
Rifabutin	↔ nevirapine ↑ rifabutin ↑ Metabolite 25-O-desacetylrifabutin	In an open label pharmacokinetic study the concomitant administration of rifabutin following full induction with nevirapine resulted in an increase in the steady-state AUC, C_{max}, and C_{min} of rifabutin. There was also an increase in the 25-O-desacetyl-rifabutin metabolite exposure in extent and rate. Due to the high intersubject variability some patients may experience large increases in rifabutin exposure and may be at higher risk for rifabutin toxicity. Therefore, caution should be used in concomitant administration. A clinically not relevant increase in the apparent clearance of nevirapine (by 9%) compared to historical pharmacokinetic data was reported. Rifabutin and VIRAMUNE can be used without dose adjustments.
Rifampicin (Rifampin)	↓ nevirapine ↔ rifampicin	It is not recommended to co-administer rifampicin and VIRAMUNE. Limited clinical data exist with a dose adjustment for VIRAMUNE when co-administered with rifampicin. Physicians needing to treat patients co-infected with tuberculosis and using a VIRAMUNE containing regimen may consider use of rifabutin instead. (see **WARNINGS AND PRECAUTIONS**).
Antifungals		

Concomitant Drug Class: Drug Name	Effect on Concentration of Nevirapine or Concomitant Drug	Clinical Comment
Fluconazole	↑ nevirapine ↔ fluconazole	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. Fluconazole may only be added to a stable nevirapine containing regimen when the benefits clearly outweigh the risks. There was no clinically relevant effect of nevirapine on fluconazole.
Itraconazole	↔ nevirapine ↓ itraconazole	There was no significant difference in nevirapine pharmacokinetic parameters. A dose adjustment for itraconazole should be considered when these two agents are administered concomitantly; however, a higher dosage of itraconazole might have an inhibitory effect on nevirapine plasma concentration.
Ketoconazole	↑ nevirapine ↓ ketoconazole	Administration of nevirapine with ketoconazole resulted in a significant reduction in ketoconazole AUC and C_{max}. In the same study, ketoconazole administration resulted in an increase in the plasma levels of nevirapine compared to historical controls. It is not recommended to co-administer ketoconazole and VIRAMUNE. A dose adjustment for ketoconazole should be considered when these two agents are administered concomitantly.
ANTACIDS		
Cimetidine	nevirapine C_{min} ↑	The median nevirapine trough for patients on cimetidine was 7% higher than the control group. The limited data suggest no dose adjustment when cimetidine is co-administered with VIRAMUNE.
ANTITHROMBOTICS		
Warfarin	↑ or ↓ warfarin	The interaction between nevirapine and the antithrombotic agent warfarin is complex with the potential for both increases and decreases in coagulation time when used concomitantly. The net effect of the interaction may change during the first weeks of co-administration, during the re-establishment of therapeutic effect only after dose adjustment, or upon discontinuation of VIRAMUNE. Close monitoring of anticoagulation levels is therefore warranted.
CONTRACEPTIVES		
Depo-medroxyprogesterone acetate (DMPA)	↑ nevirapine ↔ DMPA	No significant effect on DMPA and VIRAMUNE PK parameters is seen. DMPA and VIRAMUNE can be used without dose adjustments. VIRAMUNE co-administration did not alter the ovulation suppression effects of DMPA as measured by progesterone levels.
Ethinyl estradiol (EE) / Norethindrone (NET)	↓ethinyl estradiol (EE) ↓ norethindrone (NET)	Oral hormonal contraceptives should not be used as the sole method of contraception in women taking VIRAMUNE. 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.
ANALGESICS/OPIOIDS		

Concomitant Drug Class: Drug Name	Effect on Concentration of Nevirapine or Concomitant Drug	Clinical Comment
Methadone	↓ methadone	Results from a study with HIV-infected patients in the presence of nevirapine, steady state plasma methadone concentrations have been shown to be reduced at Cmax and in extent of methadone exposure (AUC). 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	↓ nevirapine	Concomitant use of VIRAMUNE and St. John's wort (*Hypericum perforatum*) or St. John's wort-containing products is not recommended. Co-administration of non-nucleoside reverse transcriptase inhibitors including VIRAMUNE, with St. John's wort is expected to decrease NNRTI concentrations and may result in sub-optimal levels of VIRAMUNE and lead to loss of virologic response and possible resistance to VIRAMUNE or to the class of NNRTIs. This is due to induction of drug metabolism enzymes and/or transport proteins by St Johns Wort. If a 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.

§ = C_{min} below detectable level of the assay
↑ = Increase, ↓ = Decrease, ↔ = No Effect
[a] Pediatric subjects ranging in age from 6 months to 12 years
[b] Parallel group design; n for VIRAMUNE +lopinavir/ritonavir, n for lopinavir/ritonavir alone
[c] Discontinued in Canada
[d] VIRAMUNE is not approved in Canada for use in paediatric patient population

The effects of Nevirapine on the pharmacokinetics of co-administered drugs and the co-administered drugs on Nevirapine are summarized in Tables 5and 6, respectively. This data is based on the results of drug interaction studies conducted in HIV-1 seropositive subjects unless otherwise indicated.

TABLE 5: Drug Interactions: Pharmacokinetic Parameters for Nevirapine in the Presence of Co-administered Drug (see Table 4 For Recommended Alterations in Dose or Regimen)

Co-administered Drug	Dose of Co-administered Drug	Dose Regimen of VIRAMUNE	n	Ratio Change of Nevirapine Pharmacokinetic Parameters (90% CI) No effect = 1.00		
ANTI-INFECTIVES				AUC	C_{max}	C_{min}

Antiretrovirals						
PIs						
Darunavir/ritonavir[b]	400/100 mg BID	200 mg BID	8	1.27 (1.12-1.44)	1.18 (1.02-1.37)	1.47 (1.20-1.82)
Fosamprenavir	1400 mg BID	200 mg BID	17	1.29 (1.19-1.40)	1.25 (1.14-1.37)	1.34 (1.21-1.49)
Fosamprenavir/ Ritonavir	700/100 mg BID	200 mg BID	17	1.14 (1.05-1.24)	1.13 (1.03-1.24)	1.22 (1.10-1.35)
Antibiotics						
Clarithromycin[a]	500 mg BID	200 mg daily x 14 days; 200 mg BID x 14 days	15	1.26	1.24	1.28
Rifampin[a]	600 mg daily	200 mg daily x 14 days; 200 mg BID x 14 days	14	0.42	0.50	0.32
Antifungals						
Itraconazole[b]	200 mg daily	200 mg daily	12	1.02[†] (1.00-1.06)	1.05[†] (1.04-1.06)	1.14 (1.08-1.27)[†]
CONTRACEPTIVES						
Depo-medroxy-progesterone acetate (DMPA)	150 mg every 3 months	200 mg daily x 14 days; 200 mg BID x 14 days)	16	1.17 (1.03-1.33)	1.19 (1.05-1.33)	--

↑ = Increase, ↓ = Decrease

[†] = Mean ratio measured at 95% Confidence Interval

[a] For information regarding clinical recommendations see Table 4

[b] Studies reported from healthy subjects

TABLE 6: Drug Interactions: Pharmacokinetic Parameters for Co-administered Drug in the Presence of Nevirapine (see Table 4 For Recommended Alterations in Dose or Regimen)

Co-administered Drug	Dose of Co-administered Drug	Dose Regimen of VIRAMUNE	n	Ratio Change of Co-administered Drug Pharmacokinetic Parameters (90% CI) No effect = 1.00		
ANTI-INFECTIVES				AUC	Cmax	Cmin
Antiretrovirals						
NRTIs						
Didanosine	100 - 150 mg BID	200 mg daily x 14 days; 200 mg BID x 14 days	18	1.08 (0.92-1.27)	0.98 (0.79-1.21)	§
Stavudine/ Nelfinavir	30-40 mg BID 750 mg TID	200 mg daily x 14 days; 200 mg BID x 14 days	22	0.96 (0.89-1.03)	0.94 (0.86-1.03)	§
Zalcitabine[e] Zidovudine	0.125-0.25 mg TID 100-200 mg TID	200 mg daily x 14 days; 200 mg BID x 14 days	6	1.14 (0.87-1.52)	0.97 (0.75-1.25)	§
Zidovudine	100-200 mg TID	200 mg daily x 14 days; 200 mg BID x 14 days	11	0.72 (0.60-0.96)	0.70 (0.49-1.14)	§
NNRTIs						
Efavirenz[a]	600 mg daily	200 mg daily x 14 days; 400 mg daily x 14 days	17	0.72 (0.66-0.86)	0.88 (0.77-1.01)	0.68 (0.65-0.81)
PIs						
Darunavir/ritonavir[d]	400/100 mg BID	200 mg BID	8	1.24 (0.97-1.57)	1.40 (1.14-1.73)	1.02 (0.79-1.32)
Fosamprenavir	1400 mg BID	200 mg BID	17	0.67 (0.55-0.80)	0.75 (0.63-0.89)	0.65 (0.49-0.85)
Fosamprenavir/ ritonavir	700/100 mg BID	200 mg BID	17	0.89 (0.77-1.03)	0.97 (0.85-1.10)	0.81 (0.69-0.96)

Co-administered Drug	Dose of Co-administered Drug	Dose Regimen of VIRAMUNE	n	Ratio Change of Co-administered Drug Pharmacokinetic Parameters (90% CI) No effect = 1.00		
ANTI-INFECTIVES				AUC	Cmax	Cmin
Antiretrovirals						
Indinavir[a]	800 mg q8H	200 mg daily x 14 days; 200 mg BID x 14 days	19	0.69 (0.61-0.78	0.85 (0.76-0.96)	0.56 (0.47-0.67)
Lopinavir[a, b]	300/75 mg/m^2 (lopinavir/ ritonavir) [b]	7 mg/kg or 4 mg/kg daily x 2 weeks; BID x 1 week	12, 15 [c]	0.78 (0.56-1.09)	0.86 (0.64-1.16)	0.45 (0.25-0.81)
Lopinavir[a]	400/100 mg BID (lopinavir/ ritonavir)	200 mg daily x 14 days; 200 mg BID > 1 year	22, 19 [c]	0.73 (0.53-0.98)	0.81 (0.62 - 0.95)	0.54 (0.28-0.74)
Nelfinavir[a]	750 mg TID	200 mg daily x 14 days; 200 mg BID x 14 days	23	0.94 (0.78-1.14)	1.06 (0.92-1.22)	0.68 (0.50-1.05)
Nelfinavir-M8 metabolite				0.38 (0.30–0.47)	0.41 (0.32–0.52)	0.34 (0.26–0.45)
Ritonavir	600 mg BID	200 mg daily x 14 days; 200 mg BID x 14 days	18	0.92 (0.79-1.07)	0.91 (0.78-1.07)	0.93 (0.76-1.14)
Saquinavir[a]	600 mg TID	200 mg daily x 14 days; 200 mg BID x 21 days	23	0.62 (0.53-0.89)	0.68 (0.56-0.94)	§
Entry Inhibitors						
Maraviroc/ Lamivudine/ Tenofovir DF	300 mg Single Dose/ 300 mg daily/ 300 mg daily	200 mg BID	8	1.01 (0.65 -1.55)	1.54 (0.94-2.51)	§
Antibiotics						
Clarithromycin[a]	500 mg BID	200 mg daily x 14 days; 200 mg BID x 14 days	15	0.69 (0.62-0.76)	0.77 (0.69-0.86)	0.44 (0.30-0.64)
Metabolite 14-OH-clarithromycin				1.42 (1.16-1.73)	1.47 (1.21-1.80)	0 (0.68-1.49)
Rifabutin[a]	150 or 300 mg	200 mg daily x 14	19	1.17	1.28	1.07

Co-administered Drug	Dose of Co-administered Drug	Dose Regimen of VIRAMUNE	n	Ratio Change of Co-administered Drug Pharmacokinetic Parameters (90% CI) No effect = 1.00		
ANTI-INFECTIVES				AUC	Cmax	Cmin
Antiretrovirals						
	daily	days; 200 mg BID x 14 days		(0.98-1.40)	(1.09-1.51)	(0.84-1.37)
Metabolite 25-O-desacetyl-rifabutin				1.24 (0.84-1.84)	1.29 (0.98-1.68)	1.22 (0.86-1.74)
Rifampicin (Rifampin)[a]	600 mg daily	200 mg daily x 14 days; 200 mg BID x 14 days	14	1.11 (0.96-1.28)	1.06 (0.91-1.22)	§
Antifungals						
Fluconazole	200 mg daily	200 mg daily x 14 days; 200 mg BID x 14 days	19 [0]	0.94 (0.88-1.01)	0.92 (0.85-0.99)	0.93 (0.86-1.01)
Itraconazole [d]	200 mg daily [1]	200 mg daily	12	0.39[†]	0.62[†]	0.13[†]
Ketoconazole[a]	400 mg daily	200 mg daily x 14 days; 200 mg BID x 14 days	21	0.28 (0.20-0.40)	0.56 (0.42-0.73)	§
CONTRACEPTIVES						
Ethinyl estradiol (EE)[a] and	0.035 mg (as Ortho-Novum® 1/35)	200 mg daily x 14 days; 200 mg BID x 14 days	10	0.80 (0.67 - 0.97)	0.94 (0.79 - 1.12)	§
Norethindrone[a] (NET)	1 mg (as Ortho-Novum® 1/35)			0.81 (0.70 - 0.93)	0.84 (0.73 - 0.97)	§
DRUG ABUSE						
Methadone	Individual Patient Dosing	200 mg daily x 14 days; 200 mg BID ≥ 7 days	8	0.40 (0.31 - 0.51)	0.58 (0.50 - 0.67)	§

§ = C_{min} below detectable level of the assay
↑ = Increase, ↓ = Decrease, ↔ = No Effect
[†] = Mean ratio measured at 95% Confidence Interval
[a] For information regarding clinical recommendations see Table 4
[b]Pediatric subjects ranging in age from 6 months to 12 years
[c]Parallel group design; n for VIRAMUNE +lopinavir/ritonavir, n for lopinavir/ritonavir alone
[d] Studies reported from healthy subjects
[e] Discontinued in Canada

In addition to established drug interactions, there may be potential pharmacokinetic interactions between nevirapine and other drug classes that are metabolized by the cytochrome P450 system. These potential drug interactions are listed in Table 7. Although specific drug interaction studies in HIV-1 seropositive subjects have not been conducted for the classes of drugs listed in Table 7, additional clinical monitoring may be warranted when co-administering these drugs.

TABLE 7: POTENTIAL DRUG INTERACTIONS: USE WITH CAUTION, DOSE ADJUSTMENT OF CO-ADMINISTERED DRUG MAY BE NEEDED DUE TO POSSIBLE DECREASE IN CLINICAL EFFECT

Drug Class	Examples of Drugs	Clinical Comment
Antiarrhythmics	Amiodarone, disopyramide, lidocaine	Plasma concentrations may be decreased.
Anticonvulsants	Carbamazepine, clonazepam, ethosuximide	Plasma concentrations may be decreased.
Calcium channel blockers	Diltiazem, nifedipine, verapamil	Plasma concentrations may be decreased.
Cancer chemotherapy	Cyclophosphamide	Plasma concentrations may be decreased.
Ergot alkaloids	Ergotamine	Plasma concentrations may be decreased.
Immunosuppressants	Cyclosporin, tacrolimus, sirolimus	Plasma concentrations may be decreased.
Motility agents	Cisapride*	Plasma concentrations may be decreased.
Opiate agonists	Fentanyl	Plasma concentrations may be decreased.

* Cisapride is no longer marketed in Canada

Other Drugs Metabolized By CYP3A

Biotransformation of nevirapine involves extensive cytochrome P450 metabolism (CYP3A>CYP2B6) and glucuronidation with maximal induction occurring within 2-4 weeks of initiating multiple-dose therapy. Available data on the potential interaction between nevirapine and other drugs that are extensively metabolized by CYP3A are limited and preliminary; therefore, careful monitoring of the therapeutic effectiveness of CYP3A-metabolized drugs is recommended when taken in combination with nevirapine.

In Vitro Studies

Studies using human liver microsomes indicated that the formation of nevirapine hydroxylated metabolites was not affected by the presence of dapsone, rifabutin, rifampin and trimethoprim/sulphamethoxazole. Ketoconazole and erythromycin significantly inhibited the formation of nevirapine hydroxylated metabolites.

Drug-Lifestyle Interactions

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 drowsiness during treatment with VIRAMUNE or VIRAMUNE XR. Therefore, caution should be recommended when driving a car or operating machinery. If patients experience drowsiness they should avoid potentially hazardous tasks such as driving or operating machinery.

DOSAGE AND ADMINISTRATION

Dosing Considerations

- VIRAMUNE or VIRAMUNE XR should be discontinued if patients experience severe rash or a rash accompanied by constitutional findings (see **WARNINGS AND PRECAUTIONS, Serious Warnings and Precautions Box**)."
- Intensive clinical and laboratory monitoring, including liver function tests, is essential at baseline and during the first 18 weeks of treatment with VIRAMUNE or VIRAMUNE XR (see **WARNINGS AND PRECAUTIONS**, **Monitoring and Laboratory Tests**).
- VIRAMUNE or VIRAMUNE XR administration should be interrupted in patients experiencing moderate or severe liver function test abnormalities (> 5x ULN) (excluding GGT), until the liver function test elevations have returned to baseline (see **WARNINGS AND PRECAUTIONS**, **Monitoring and Laboratory Tests**).

Recommended Dose and Dosage Adjustment

Immediate-Release Tablets

The recommended dose for VIRAMUNE (nevirapine) is one 200 mg tablet 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 200 mg tablet twice daily, as part of a multi-drug antiretroviral treatment regimen. VIRAMUNE or VIRAMUNE XR can be taken with or without food. The manufacturer's recommended dosage and monitoring for the concomitantly administered antiretroviral therapy should be used.

Extended-Release Tablets

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

The VIRAMUNE extended-release tablets should not be broken or chewed. VIRAMUNE extended-release tablets can be taken with or without food. VIRAMUNE immediate-release tablets and VIRAMUNE extended-release tablets should be combined with at least two

additional antiretroviral agents. For concomitantly administered therapy, the manufacturers recommended dosage should be followed.

Patients currently on a VIRAMUNE immediate-release twice daily regimen

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

Monitoring of Patients

VIRAMUNE or VIRAMUNE XR should be discontinued if patients experience severe rash or a rash accompanied by constitutional findings (see WARNINGS AND PRECAUTIONS, Skin). Patients experiencing rash during the 14-day lead-in period of 200 mg/day of immediate-release tablets should not have their VIRAMUNE dose increased to 400 mg/day until the rash has resolved (see WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic and Skin). The risk of development of resistance to VIRAMUNE is unknown when the 200 mg once daily dosing regimen is continued beyond 14 days.

Patients with Renal Impairment
In End Stage Renal Disease (ESRD) appropriate doses of VIRAMUNE or VIRAMUNE XR with respect to safety and efficacy have not been established. Subjects with ESRD requiring dialysis exhibited a 43.5% reduction in VIRAMUNE AUC over a one week exposure period with an accumulation of nevirapine hydroxy-metabolites in plasma. An additional 200 mg dose of VIRAMUNE immediate-release tablets following each dialysis treatment is recommended in patients requiring dialysis. In renal dysfunction, a single dose study suggested that patients with a creatinine clearance $\geq$ 20 mL/min do not require an adjustment in VIRAMUNE dosing. VIRAMUNE extended-release tablets have not been studied in patients with renal dysfunction.

Patients with Hepatic Impairment
Patients with mild hepatic impairment do not require an adjustment in VIRAMUNE dosing; however, caution should be exercised when VIRAMUNE or VIRAMUNE XR is administered to patients with moderate hepatic impairment. VIRAMUNE or VIRAMUNE XR should not be administered to patients with severe hepatic dysfunction.

Patients with Lactose Intolerance
VIRAMUNE immediate-release tablets contain 636 mg of lactose per maximum recommended daily dose.

VIRAMUNE extended-release tablets contain 400 mg of lactose per maximum recommended daily dose.

Patients with rare hereditary conditions of galactose intolerance e.g. galactosaemia, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Missed Dose
Patients who miss a dose should take it as soon as they remember and then continue as before. Do not double the next dosage.

Patients who interrupt VIRAMUNE or VIRAMUNE XR dosing for more than 7 days should restart the recommended dosing, using one 200 mg tablet daily for the first 14 days (lead-in) followed by one 200 mg tablet twice daily or one 400 mg tablet once daily.

OVERDOSAGE

For the management of a suspected drug overdose, contact your regional Poison Control Centre.

There is no known antidote for VIRAMUNE or VIRAMUNE XR (nevirapine) overdosage. The use of activated charcoal may be helpful.

Cases of VIRAMUNE 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 edema, erythema nodosum, fatigue, fever, headache, insomnia, nausea, pulmonary infiltrates, rash, vertigo, vomiting, increase in transaminases, and weight decrease. All subsided following discontinuation of VIRAMUNE.

In one case, a patient accidentally ingested VIRAMUNE 1200 mg daily for three days, and then 1800 mg for a fourth day. The patient suffered fever, generalized rash, nausea, vomiting, headache, chills, and facial swelling, and was admitted to hospital for 5 days. The event resolved without sequelae.

In another case, a patient ingested 9 tablets of VIRAMUNE (1800 mg) per day for 10 days. The patient presented with rash (erythema nodosum), pulmonary infiltrate, and bilateral edema of hands and feet. He was hospitalized for 2 weeks during which time he was aggressively diuresed. The events resolved over 3 weeks.

No acute toxicities or sequelae were reported for one patient who ingested 800 mg of VIRAMUNE for one day.

ACTION AND CLINICAL PHARMACOLOGY

Absorption

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 the 50 mg tablet and 91.8% for the oral solution.

Peak plasma nevirapine concentrations of 2 ± 0.4 μg/mL are 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 μg/mL (17 ± 7 μM), (n=242) were attained at 400 mg/day.

When VIRAMUNE (200 mg) was administered to 24 healthy adults (12 male, 12 female), with either a high fat breakfast (857 kcal, 50 g fat, 53% of calories from fat) or antacid (Maalox® 30 mL), the extent of nevirapine absorption (AUC) was comparable to that observed under fasting conditions. In a separate study in HIV-1-infected patients (n=6), nevirapine steady-state systemic exposure (AUC_τ) was not significantly altered by ddI, which is formulated with an alkaline buffering agent. VIRAMUNE may be administered with or without food, antacid or ddI.

Distribution

Nevirapine is highly lipophilic and is essentially nonionized at physiologic pH. Animal studies have shown that nevirapine is widely distributed to nearly all tissues and readily crosses the blood-brain barrier. Following intravenous administration in healthy adults, the apparent volume of distribution (Vdss) of nevirapine was 1.21 ± 0.09 L/kg, suggesting that nevirapine also is widely distributed in humans. Nevirapine is approximately 57-61% bound to plasma proteins in the plasma concentration range of 1-10 μg/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

In vivo studies in humans and *in vitro* studies with human liver microsomes have shown that nevirapine is extensively biotransformed *via* cytochrome P-450 (oxidative) metabolism to several hydroxylated metabolites. *In vitro* studies with human liver microsomes suggest that oxidative metabolism of nevirapine is mediated primarily by cytochrome P-450 isozymes from the CYP3A4 and CYP2B6 families, although other isozymes may have a secondary role. In a mass balance/excretion study in eight healthy male volunteers dosed to steady state with nevirapine 200 mg b.i.d. followed by a single dose of 50 mg ^{14}C-nevirapine, approximately 91.4% ± 10.5% of the radiolabeled dose was recovered, with urine (81.3% ± 11.1%) representing the primary route of excretion compared to feces (10.1% ± 1.5%). Greater than 80% of the radioactivity in urine was made up of glucuronide conjugates of hydroxylated metabolites. Thus cytochrome P-450 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.

Excretion

Nevirapine is an inducer of hepatic cytochrome P450 (CYP) metabolic enzymes 3A4 and 2B6. Nevirapine induces CYP3A4 and CYP2B6 by approximately 20-25%, as indicated by

erythromycin breath test results and urine metabolites. Autoinduction of CYP3A4 and CYP2B6 mediated metabolism leads to 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.

Special Populations and Conditions

Pediatrics:
Safety and effectiveness of VIRAMUNE or VIRAMUNE XR in HIV-1 infected pediatric patients younger than 15 years of age has not been established.

Age:
Nevirapine pharmacokinetics in HIV-1-infected adult males and females do not appear to change with age (range 18-68 years); however, nevirapine has not been extensively evaluated in patients beyond the age of 65 years. Nevirapine is metabolized more rapidly in pediatric patients than in adults.

Gender:
In one Phase I study in healthy volunteers (15 females, 15 males), the weight-adjusted apparent volume of distribution (Vdss/F) of nevirapine was higher in the female subjects (1.54 L/kg) compared to the males (1.38 L/kg), suggesting that nevirapine was distributed more extensively in the female subjects. However, this difference was offset by a slightly shorter terminal-phase half-life in the females resulting in no significant gender difference in nevirapine oral clearance (24.6±7.7 mL/kg/hr in females vs. 19.9±3.9 mL/kg/hr in males after single dose) or plasma concentrations following either single- or multiple-dose administration(s).

An evaluation of nevirapine plasma concentrations (pooled data from several clinical trials) from HIV-1-infected patients (37 females, 205 males) revealed no clinically significant difference in nevirapine steady-state trough concentrations (median C_{minss} = 4.6 μg/mL females, 4.2 μg/mL males) with long-term nevirapine treatment at 400 mg/day.

Race:
The pharmacokinetics of nevirapine have not been evaluated specifically for the effects of ethnicity. However, an evaluation of nevirapine plasma concentrations (pooled data from several clinical trials) from HIV-1-infected patients (27 Black, 24 Hispanic, 189 Caucasian) revealed no marked difference in nevirapine steady-state trough concentrations (median C_{minss} = 4.7 μg/mL Black, 3.8 μg/mL Hispanic, 4.3 μg/mL Caucasian) with long-term nevirapine treatment at 400 mg/day.

Hepatic Insufficiency:
The single-dose pharmacokinetics of VIRAMUNE have been compared in 10 subjects with hepatic impairment and 8 subjects with normal hepatic function. Overall, the results suggest that mild to moderate hepatic impairment had no significant effect on the pharmacokinetics of

VIRAMUNE. However, the pharmacokinetics of VIRAMUNE in one subject with a Child-Pugh score of 8 and moderate to severe ascites suggests that patients with worsening hepatic function may be at risk of accumulating nevirapine in the systemic circulation (see **DOSAGE AND ADMINISTRATION, Patients with Hepatic Impairment**).

In a 200 mg nevirapine single dose pharmacokinetic study of HIV-negative patients with mild and moderate hepatic impairment, a significant increase in the AUC of nevirapine was observed in one patient with moderate hepatic impairment and ascites suggesting that patients with worsening hepatic function and ascites may be at risk of accumulating nevirapine in the systemic circulation.

Renal Insufficiency:
The single dose pharmacokinetics of VIRAMUNE 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 ($Cl_{cr} < 30$ 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 VIRAMUNE. Subjects with ESRD requiring dialysis exhibited a 43.5% reduction in VIRAMUNE AUC over a one week exposure period with an accumulation of nevirapine hydroxy-metabolites in plasma (see **DOSAGE AND ADMINISTRATION, Patients with Renal Impairment**).

STORAGE AND STABILITY

Solid substance stability studies have shown nevirapine bulk drug to be extremely stable. Viramune 200 mg immediate-release tablets are packaged in bottles of 60 tablets and Viramune 400 mg extended-release tablets are packaged in bottles of 30 tablets and should be stored at $15^oC – 30^oC$ ($59^oF – 86^oF$). The bottles should be kept tightly closed.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Immediate-Release Tablets

VIRAMUNE (nevirapine) 200 mg immediate-release tablets are white, oval, biconvex tablets, 9.3 x. 19.1 mm. One side is embossed with “54 193", with a single bisect separating the “54" and “193". The opposite side has a single bisect.

Each tablet contains 200 mg of nevirapine and the non-medicinal ingredients: colloidal silicon dioxide, lactose, magnesium stearate, microcrystalline cellulose, povidone, and sodium starch glycolate.

Immediate-release tablets are packaged in bottles of 60 tablets. The bottles should be kept tightly closed.

Extended-Release Tablets

VIRAMUNE XR (nevirapine) 400 mg extended-release tablets are yellow, oval, biconvex tablets, 9.3 x. 19.1 mm. One side is embossed with "V04", and the BI tower logo on the other side.

Each tablet contains 400 mg of nevirapine and the non-medicinal ingredients: lactose, hypromellose, iron oxide (E172) and magnesium stearate.

Extended-release tablets are packaged in bottles of 30 tablets. The bottles should be kept tightly closed.

PART II: SCIENTIFIC INFORMATION

Pharmaceutical Information

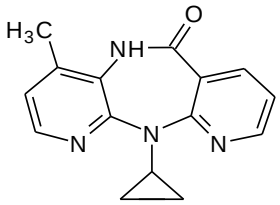
Drug Substance

DRUG SUBSTANCE

I.N.N./U.S.A.N. Name: Nevirapine

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

Structural Formula:



M.W.: 266.3

Physical Form: White to off-white crystalline powder

Solubility (mg/mL @ 25°C):

water	0.1
ethanol	5.5
methanol	8.1
chloroform	100.0
cyclohexane	0.01
hexane	0.001
40% propylene glycol/water	1.0

pKa: $pKa_1 = 2.8$; $pKa_2 = -0.4$

Partition Co-efficient: Log $K_{ow} = 1.8$

Melting Point: ~245°C

CLINICAL TRIALS

Study Demographics and trial design

Table 8: Summary of patient demographics for Viramune immediate-release formulation (1100.1090)

Study #	Trial Design	Dosage, Route of Administration and duration	Study Subjects (n=number)	Mean age (Range)	Gender
1100.1090	Randomized, double-blind, placebo-controlled, study	Study drug: nevirapine IR 200 mg BID, Oral	1121 nevirapine IR 200 mg BID, 1128 placebo	Nevirapine IR 200 mg BID: 37.7 y, 18.0 to 71.5 y Placebo: 36.7 y, 17.9 to 71.8 y	M879/F242 M902/F226

Table 9: Summary of patient demographics for Viramune immediate-release formulation (1100.1046)

Study #	Trial Design	Dosage, Route of Administration and duration	Study Subjects (n=number)	Mean age (Range)	Gender
1100.1046	Randomized, double-blind, placebo-controlled, study NVP/ZDV/ddI PBO/ZDV/ddI NVP/ZDV/PBO	Study drug: nevirapine IR 200 mg BID, Oral	NVP/ZDV/ddI: 51 PBO/ZDV/ddI: 53 NVP/ZDV/PBO: 47	NVP/ZDV/ddI: 38.0 y (22.0 to 62.0 y) PBO/ZDV/ddI: 36.4 y (21.0 to 54.0 y) NVP/ZDV/PBO: 37.8 y (25.0 to 65.0 y)	M47/F4 M50/F3 M43/F4

Table 10: Summary of patient demographics for Viramune extended-release formulation (1100.1486)

Study #	Trial Design	Dosage, Route of Administration and duration	Study Subjects (n=number)	Mean age (Range)	Gender
1100.1486	Randomized, double-blind, double dummy, parallel-group, active-control	Study drug: nevirapine XR 400 mg QD, Oral	Number of Subjects randomized 508 nevirapine IR 200 mg BID,	Nevirapine IR 200 mg BID: 37.0 y, 18 to 68 y	M433/F75

	study	Control drug: nevirapine IR, 200 mg BID, Oral	505 nevirapine XR 400 mg QD Number of Subjects at end of study (W48) 409 nevirapine IR 200 mg BID, 421nevirapine XR 400 mg QD	nevirapine XR 400 mg QD; 38.0 y, 19 to71 y	M431/F74

Table 11: Summary of patient demographics for Viramune extended-release formulation (1100.1526)

Study #	Trial Design	Dosage, Route of Administration and duration	Study Subjects (n=number)	Mean age (Range)[a]	Gender
1100.1526	Open-label, randomized, parallel-group, active-control study	Study drug: nevirapine XR 400 mg QD, Oral Control drug: nevirapine IR, 200 mg BID, Oral	Number of Subjects randomized 149 nevirapine IR 200 mg BID, 296 nevirapine XR 400 mg QD Number of Subjects at end of study (W24) 144 nevirapine IR 200 mg BID, 288 nevirapine XR 400 mg QD	Nevirapine IR 200 mg BID: 46.0 y, 27 to 71 y nevirapine XR 400 mg QD; 46.0 y, 22 to78 y	M128/F20 M244/F51

[a] For study 1100.1526, although 149 and 296 patients were randomized to the nevirapine IR and XR groups, respectively, demographic data were available for the 148 and 295 patients who received study treatment in the nevirapine IR and XR groups, respectively.

Trial BI 1090 (Patients With Advanced HIV Disease, with or without Prior Antiretroviral Treatment).

Trial BI 1090 was a placebo-controlled, double-blind, randomized trial in 2249 adult patients with <200 CD4+ cells at screening. More than 75% of patients had extensive prior treatment with monotherapy or dual therapy prior to entering the trial. Treatment in this trial reflected the pre-HAART era of standard of care. BI 1090 compared treatment with VIRAMUNE +

lamivudine versus placebo + lamivudine in NNRTI naive patients, who were also taking other background antiretroviral agents. Treatment doses were VIRAMUNE, 200 mg daily for two weeks followed by 200 mg twice daily, or placebo; lamivudine 150 mg twice daily; other antiretroviral agents were given at standard doses. The patients (median age 36.5 years, 70% Caucasian, 79% male) had advanced HIV infection, with a median baseline CD4+ cell count of 96 cells/mm^3 and a baseline HIV RNA of 4.58 log_{10} copies/mL (38,291 copies/mL). Prior to entering the trial, 45% had previously experienced an AIDS-defining clinical event. There was no maximum limit to the duration of prior antiretroviral treatment. The 24% of patients who were permanently lost to follow-up during the study are included in the intent to treat (ITT) evaluations of virologic outcome. Patients were classified as responders at 48 weeks if their viral load decreased and remained below the limit of quantification (LOQ=50 copies/mL) by 48 weeks. Patients were categorized as non-responders if they did not complete 48 weeks, changed or added additional antiretroviral therapy, or experienced an AIDS defining event prior to 48 weeks. The virologic responder rate at 48 weeks was significantly higher for VIRAMUNE patients (19%) than for placebo patients (3%).

Of the 2249 patients, 527 (23.4%) entered the trial as treatment naive or having received only ZDV prior to entering the trial. The patients had advanced HIV-infection with a median CD4+ cell count of 91 cells/mm^3 and baseline HIV RNA of 5.02 log_{10} copies/mL (105,213 copies/mL). The virologic responder rates at 48 weeks were significantly higher for the VIRAMUNE patients (40%) than the placebo patients (3%).

The change from baseline in CD4+ count through one year of therapy was significantly greater for the VIRAMUNE group compared to the placebo group for the overall study population (64 cells/mm^3 vs 22 cells/mm^3, respectively). This was also evident for patients who entered the trial as first HAART (treatment naïve or having received only ZVD); the change from baseline in CD4+ count was significantly greater for the VIRAMUNE group over placebo (85 cells/mm^3 vs 25 cells/mm^3, respectively).

Using an endpoint of the time to first new AIDS disease event or death in an intent to treat analysis in the overall study population, there was a 28% improvement in event-free survival in the VIRAMUNE group compared to the placebo group (Risk ratio: 1.28; 95% confidence interval: 1.03 to 1.58).

<u>INCAS (BI Trial 1046 – Adult Antiretroviral Naive Patients)</u>

INCAS (BI Trial 1046) compared treatment with VIRAMUNE+ZDV+ddI versus ZDV+ddI versus VIRAMUNE+ZDV in 151 HIV-1-infected patients (median age 36 years, 94% Caucasian, 93% male) with CD4+ cell counts of 200–600 cells/mm^3 (median 370 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; ZDV, 200 mg three times daily; ddI, 125 or 200 mg twice daily.

Using an intent to treat evaluation of virologic outcome, patients were classified as responders at 48 weeks if their viral load decreased and remained below LOQ (400 copies/mL) by 48 weeks. Patients were categorized as non-responders if they did not complete 48 weeks, changed or

added additional antiretroviral therapy, or experienced an AIDS defining event prior to 48 weeks. The virologic responder rates at 48 weeks were significantly higher for VIRAMUNE+ZDV+ddI patients (45%) compared to either the ZDV+ddI (19%) or VIRAMUNE+ZDV patients (0%).

CD4+ cell counts in the VIRAMUNE+ZDV+ddI group increased above baseline by a mean of 139 cells/mm^3 at one year, significantly greater than the increase of 87 cells/mm^3 in the ZDV+ddI patients. The VIRAMUNE+ZDV group mean decreased by 6 cells/mm^3 below baseline.

The clinical efficacy of VIRAMUNE 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 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 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 12.

Table 12: Demographic and Baseline Disease Characteristics in Study 1100.1486

	VIRAMUNE immediate-release N=508[a]	**VIRAMUNE 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 13 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 13: Outcomes at Week 48 in Study 1100.1486[a]

	VIRAMUNE immediate-release N=506	**VIRAMUNE 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%
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® extended-release respectively. Non-inferiority of the extended-release formulation to the immediate-release formulation was observed. The lower bound of the 95% CI of the difference in virologic response proportions was greater than -10% (Table 14).

Table 14shows outcomes at 48 weeks in Trial 1100.1486 based on baseline viral load.

Table 14: Study 1100.1486 – sustained virologic response at Week 48 (LLOQ = 50 copies/mL, Amplicor-corrected, TLOVR algorithm, FAS)

Background HIV-1 viral load stratum (copies/mL)	No. with response/total No. (%)		Difference in % (95% CI)	P-value for non-inferiority test
	NVP IR 200 BID	NVP XR 400 QD		
≤100,000	240/303 (79.2)	267/311 (85.9)	6.6 (0.7, 12.6)	-
>100,000	144/203 (70.9)	142/194 (73.2)	2.3 (-6.6, 11.1)	-
Total	**384/506 (75.9)**	**409/505 (81.0)**	**4.9 (-0.1, 10.0)[a]**	**<0.0001**

[a] Based on Cochran's statistic with continuity correction for the variance calculation.

Patients switching from VIRAMUNE immediate-release to VIRAMUNE 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 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 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 extended-release 400 mg once daily, respectively, continued to have HIV-1 RNA <50 copies/mL. Non-inferiority of the extended-release formulation to the immediate-release formulation was observed. The lower bound of the 95% CI of the difference in virologic response proportions was greater than -10% (Table 15).

Table 15: Study 1100.1526 – sustained virologic response at Week 24 (LLOQ = 50 copies/mL, Amplicor-corrected, TLOVR algorithm, FAS)

Background ARV	No. of patients with response/total No. of Patients (%)		Difference in % response (95% CI)
	NVP IR 200 BID	NVP XR 400 QD	
Truvada	77/82 (93.9)	145/158 (91.8)	-2.1 (-8.9, 4.6)
Combivir	29/30 (96.7)	59/63 (93.7)	-3.0 (-11.8, 5.8)
Kivexa/Epzicom	31/36 (86.1)	72/74 (97.3)	11.2 (-0.7, 23.1)
Total	**137/148 (92.6)**	**276/295 (93.6)**	**1.0 (-4.3, 6.2)[a]**

[a] Based on Cochran's statistic with continuity correction for the variance calculation.

DETAILED PHARMACOLOGY

Mechanism of Action

VIRAMUNE or VIRAMUNE XR (nevirapine) is a highly selective, non-nucleoside reverse transcriptase inhibitor (NNRTI) of Human Immunodeficiency Virus Type 1 (HIV-1). The enzymatic activity of reverse transcriptase (RT) is required for replication of HIV. Nevirapine binds directly to RT and blocks the RNA-dependent and DNA-dependent DNA polymerase activities by causing a disruption of the enzyme's catalytic site. The inhibitory activity of nevirapine is not competitive with respect to template or nucleoside triphosphates. Reverse transcriptase from HIV-2 and eukaryotic DNA polymerases (such as human DNA polymerases α, β, γ, or δ) are not inhibited by nevirapine.

Pharmacodynamics

Nevirapine is a non-nucleoside RT inhibitor which exhibits selective antiviral activity against HIV-1. Nevirapine inhibits the replication of a wide variety of HIV-1 strains in a number of cellular assays. HIV-1 isolates exhibiting reduced susceptibility to nevirapine were selected in cell culture experiments and during *in vivo* clinical studies.

The *in vitro* antiviral activity of nevirapine has been measured in a variety of cell lines including peripheral blood mononuclear cells, monocyte derived macrophages, and lymphoblastoid cell lines. In recent studies using human cord blood lymphocytes and human embryonic kidney 293 cells, EC50 values (50% inhibitory concentration) ranged from 14->400 nM against laboratory and clinical isolates of HIV-1. Some isolates of HIV-1 group M clade A demonstrated reduced susceptibility to nevirapine *in vitro*. The antiviral activity of nevirapine against HIV-1, group M, clade E is unknown.

Nevirapine exhibited antiviral activity *in vitro* against group M HIV-1 isolates from clades A, B, C, D, F, G, and H, and circulating recombinant forms (CRF), CRF01_AE, CRF02_AG and CRF12_BF (median EC50 value of 63 nM). Nevirapine had no antiviral activity in vitro against isolates from group O HIV-1 and HIV-2. Some isolates of HIV-1 group M clade A demonstrated reduced susceptibility to nevirapine *in vitro*. The antiviral activity of nevirapine against HIV-1, group M, clade E is unknown.

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

Pharmacokinetics

The pharmacokinetics of nevirapine have been studied in nine Phase I studies and two Phase IIA studies in both HIV-1 infected adults (n=380) and healthy adult volunteers (n=119) given single doses of up to 400 mg and multiple doses of up to 600 mg/day (given q.d. or b.i.d.).

The pharmacokinetics of nevirapine are characterized by rapid and nearly complete oral absorption, an apparent volume of distribution that exceeds total body water, and a prolonged disposition phase in humans. Nevirapine is approximately 60% bound to plasma proteins in the plasma concentration range of 1-10 μg/mL. Nevirapine concentrations in human cerebrospinal fluid (n=6) were 45% of the concentration in plasma; this ratio is approximately equal to the fraction not bound to plasma protein. Nevirapine is extensively biotransformed by cytochrome P450 to several hydroxylated metabolites; *in vitro* studies suggest that this metabolism is mediated primarily by CYP3A, although other CYP isozymes may have a secondary role. The multiple dose pharmacokinetics are characterized by metabolic autoinduction of cytochrome P450 isozymes resulting in a 1.5 to 2 fold increase in nevirapine systemic clearance 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 45 hours (single dose) to approximately 25 to 30 hours with multiple dosing. The pharmacokinetics of nevirapine remain approximately linear in the dose range of 200-400 mg/day following induction.

The pharmacokinetics of nevirapine has been studied in a single dose study (Trial 1100.1485) of VIRAMUNE extended-release in 17 healthy volunteers. The relative bioavailability of nevirapine when dosed as one 400 mg VIRAMUNE extended-release tablet, relative to two 200 mg VIRAMUNE immediate-release tablets, was approximately 75%. The study demonstrated that the nevirapine extended-release formulation exhibited very slow absorption with a mean Tmax of approximately 24 hours compared to a mean Tmax of approximately 4 to 6 hours for nevirapine IR 200 mg and 400 mg, respectively.The mean peak plasma concentration of nevirapine was 2060 ng/mL measured at a mean of 24.5 hours after administration of a single dose 400 mg VIRAMUNE extended-release tablet. This is in comparison to a mean peak plasma concentration of 3150 ng/mL measured at a mean 6.35 hours after administration of a single dose of 400 mg immediate release tablets.

The pharmacokinetics of VIRAMUNE extended-release has 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 extended-release. The nevirapine $AUC_{0\text{-}24,ss}$ and $C_{min,ss}$ measured after 19 days of fasted dosing of VIRAMUNE extended-release 400 mg once daily were approximately 80% and 90%, respectively, of the $AUC_{0\text{-}24,ss}$ and $C_{min,ss}$ measured when patients were dosed with VIRAMUNE immediate-release 200 mg twice daily. The mean nevirapine $C_{min,ss}$ was 2920 ng/mL for the extended release formulation compared to 3240 ng/mL for the immediate release formulation.

When VIRAMUNE extended-release was dosed with a high fat meal, the nevirapine $AUC_{0\text{-}24,ss}$ and $C_{min,ss}$ were approximately 94% and 98%, respectively, of the $AUC_{0\text{-}24,ss}$ and $C_{min,ss}$ measured

when patients were dosed with VIRAMUNE immediate-release tablets. The difference in nevirapine pharmacokinetics observed when VIRAMUNE extended-release tablets are dosed under fasted or fed conditions is not considered clinically relevant, as long term virological efficacy depends on maintaining the C_{min} above 3000 ± 500 ng/mL threshold. Both the fed and fasted conditions met this criterion. VIRAMUNE extended-release tablets can be taken with or without food.

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

Nevirapine pharmacokinetics in HIV-1 infected adults does 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 extended-release treatment groups over 48 weeks of treatment at 400 mg/day.

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

Special Populations

Renal Impairment

The single-dose pharmacokinetics of VIRAMUNE immediate-release has been compared in 23 subjects with either mild (50 creatinine clearance < 80 ml/min), moderate (30 creatinine clearance < 50 ml/min) or severe renal dysfunction (creatinine clearance < 30 ml/min), renal impairment or end-stage renal disease (ESRD) requiring dialysis, and 8 subjects with normal renal function (creatinine clearance > 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 over a one-week exposure period. There was also accumulation of nevirapine hydroxy-metabolites in plasma. In renal dysfunction, a single-dose study suggested that patients with creatinine clearance 20 ml/min do not require an adjustment in VIRAMUNE dosing. VIRAMUNE extended-release tablets have not been studied in patients with renal dysfunction.

Hepatic Impairment

The single-dose pharmacokinetics of VIRAMUNE have been compared in 10 subjects with hepatic dysfunction and 8 subjects with normal hepatic function. Overall, the results suggest that patients with mild to moderate hepatic dysfunction, defined as Child-Pugh Classification Score ≤ 7, do not require an adjustment in VIRAMUNE dosing. However, the pharmacokinetics of VIRAMUNE in one subject with a Child-Pugh score of 8 and moderate to severe ascites suggests that patients with worsening hepatic function may be at risk of accumulating nevirapine in the systemic circulation.

In a single dose pharmacokinetic study of 200 mg VIRAMUNE immediate-release tablets in HIV-negative patients with mild and moderate hepatic impairment, a significant increase in the AUC of nevirapine was observed in one patient with moderate hepatic impairment and ascites suggesting that patients with worsening hepatic function and ascites may be at risk of accumulating nevirapine in the systemic circulation.

Therefore caution should be exercised when VIRAMUNE or VIRAMUNE XR is administered to patients with moderate hepatic dysfunction. VIRAMUNE or VIRAMUNE XR should not be administered to patients with severe hepatic dysfunction.

Special Analysis

Gender

In one Phase I study in healthy volunteers (15 females, 15 males), the weight-adjusted apparent volume of distribution (Vdss/F) of nevirapine was higher in the female subjects (1.54 L/kg) compared to the males (1.38 L/kg), (p=0.001, Wilcoxon rank sum test) suggesting that nevirapine was distributed more extensively in the female subjects. However, this difference was offset by a slightly shorter terminal-phase half-life in the females resulting in no significant gender difference in nevirapine oral clearance or plasma concentrations following either single- or multiple-dose administration(s). Furthermore, an evaluation of nevirapine plasma concentrations (pooled data from several clinical trials) from HIV-1-infected patients (37 females, 205 males) revealed no clinically significant difference in nevirapine steady-state trough concentrations (median C_{minss} = 4.6 μg/mL females, 4.2 μg/mL males) with long-term nevirapine treatment at 400 mg/day.

Age

Nevirapine pharmacokinetics in HIV-1-infected adult males and females do not appear to change with age (range 18-68 years); however, nevirapine has not been extensively evaluated in patients beyond the age of 65 years. Nevirapine is metabolized more rapidly in pediatric patients than in adults.

Ethnic Origin

An evaluation of nevirapine plasma concentrations (pooled data from several clinical trials) from HIV-1-infected patients (27 Black, 24 Hispanic, 189 Caucasian) revealed no marked difference in nevirapine steady-state trough concentrations (median C_{minss}= 4.7 μg/mL Black, 3.8 μg/mL Hispanic, 4.3 μg/mL Caucasian) with long-term nevirapine treatment at 400 mg/day. However, the pharmacokinetics of nevirapine have not been evaluated specifically for the effects of ethnicity.

VIROLOGY

Resistance

HIV isolates with reduced susceptibility (100-250 fold) to nevirapine emerge *in vitro.* Genotypic analysis showed mutations in the HIV-1 RT gene Y181C and/or V106A depending upon the virus strain and cell line employed. Time to emergence of nevirapine resistance *in vitro* was not altered when selection included nevirapine in combination with several other NRTI's.

Phenotypic or genotypic changes in HIV-1 isolates from treatment-naïve patients treated with either VIRAMUNE immediate-release (n=24) or VIRAMUNE immediate-release and ZDV (n=14) were monitored in Phase I/II trials over 1 to ≥ 12 weeks. After 1 week of nevirapine 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 nevirapine 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.

The prevalence of phenotypic drug resistance was assessed in 60 patients with a viral rebound after they received a protease inhibitor (PI) or nevirapine containing regimen. Resistance testing was done within 36 weeks of viral rebound classified as a subsequent increase to >500 copies/mL following an initial viral load decrease to <500 copies/mL or a viral rebound of ≥ 0.5 $\log_{10}$ following an initial drop of ≥ 1.0 $\log_{10}$. In total, 88.9% given nevirapine had strains with reduced susceptibility to the drug. Overall, 46 patients (76.7%) harboured a strain resistant to ≥ 1 drug of their initial PI or nevirapine containing regimen. Of 53 patients who remained on treatment at the time of the study (40 had switched to a different combination from that at baseline), 6 harboured isolates susceptible to all drugs they had ever received.

Genotypic analysis of isolates from antiretroviral naïve patients with virologic rebound (n=71) receiving nevirapine once daily (n=25) or twice daily (n=46) in combination with lamivudine and stavudine (study 2NN) for 48 weeks showed that isolates from 8/25 and 23/46 patients, respectively, contained one or more of the following NNRTI resistance-associated mutations: Y181C, K101E, G190A/S, K103N, V106A/M, V108I, Y188C/L, A98G, F227L and M230L.

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 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 extended-release group and one patient with Y188N in the VIRAMUNE immediate-release group; resistance to nevirapine was confirmed by phenotype.

Cross-Resistance

Rapid emergence of HIV strains which are cross-resistant to NNRTI's has been observed *in vitro*. Data on cross-resistance between the NNRTI nevirapine and nucleoside analogue RT inhibitors are very limited. In four patients, ZDV-resistant isolates tested *in vitro* retained susceptibility to nevirapine and in six patients, nevirapine-resistant isolates were susceptible to ZDV and ddI. One case of double resistance to ZDV and nevirapine including transmission has been reported.

Cross-resistance between nevirapine and HIV protease inhibitors is unlikely because the enzyme targets involved are different.

Cross-resistance among the currently registered NNRTIs is broad. Some genotypic resistance data indicate that in most patients failing NNRTIs, viral strains express cross-resistance to the other NNRTIs.

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.

TOXICOLOGY

Acute, Subchronic and Chronic Toxicity in Laboratory Animals

Acute oral toxicity studies conducted in the mouse, rat, dog, and monkey revealed that the NOEL was 200 mg/kg, and lethality did not occur in any of these species with single PO doses ranging from 50 to 400 mg/kg. These studies indicated that the species sensitivity was (in order of decreasing sensitivity): rat > dog > mouse > monkey. Subchronic non-clinical NOELs ranged from 5 to <650 mg/kg/day, in mice, rats, and dogs. Maximum tolerated dose (MTD) ranged from 25 to 1500 mg/kg/day in the same species. Chronic studies in the rat and dog indicated that the liver and haematopoietic system are amongst the target organs, with NOELs of 5.50 mg/kg/day and MTDs of 50-200 mg/kg/day.

There was no evidence of 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 fetal body weight occurred at doses providing systemic exposure approximately 50% higher, based on AUC, than that seen at the recommended clinical dose. Maternal toxicity and observable effects on fetal 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.

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PART III: CONSUMER INFORMATION

Pr Viramune®
(nevirapine**)** Immediate ReleaseTablets

Pr Viramune® XR
(nevirapine**)** Extended ReleaseTablets

This leaflet is part III of a three-part "Product Monograph" published when VIRAMUNE or VIRAMUNE XR was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about VIRAMUNE or VIRAMUNE XR. Contact your doctor or pharmacist if you have any questions about the drug.

PLEASE READ THIS INFORMATION CAREFULLY AND COMPLETELY BEFORE YOU USE VIRAMUNE or VIRAMUNE XR EVEN IF YOU HAVE JUST REFILLED YOUR PRESCRIPTION, SINCE SOME INFORMATION MAY HAVE CHANGED. SINCE VIRAMUNE or VIRAMUNE XR IS ALWAYS TAKEN WITH OTHER DRUGS, IT IS IMPORTANT TO ALSO READ THE INFORMATION GIVEN WITH THE OTHER DRUGS BEFORE TAKING VIRAMUNE or VIRAMUNE XR. PLEASE CONSULT YOUR DOCTOR OR PHARMACIST IF YOU HAVE ANY QUESTIONS.

ABOUT THIS MEDICATION

What the medication is used for:

VIRAMUNE or VIRAMUNE XR is a medicine used to treat Human Immunodeficiency Virus (HIV) infection, the virus that causes AIDS (Acquired Immune Deficiency Syndrome).

VIRAMUNE or VIRAMUNE XR does not cure HIV or AIDS, and it is not known if it will help you live longer with HIV. People taking VIRAMUNE or VIRAMUNE XR may still get infections common in people with HIV (opportunistic infections). Therefore, it is very important that you stay under the care of your doctor.

What it does:

VIRAMUNE or VIRAMUNE XR is a type of anti-HIV medicine called a "non-nucleoside reverse transcriptase inhibitor" (NNRTI). It works by lowering the amount of HIV in the blood ("viral load"). You must take VIRAMUNE or VIRAMUNE XR with other anti-HIV medicines. When taken with other anti-HIV medicines, VIRAMUNE or VIRAMUNE XR can reduce viral load and increase the number of CD4 cells ("T cells"). CD4 cells are a type of immune helper cell in the blood. VIRAMUNE or VIRAMUNE XR may not have these effects in every patient.

VIRAMUNE or VIRAMUNE XR is not a cure for HIV infection.

When it should not be used:

- If you are allergic (hypersensitive) to nevirapine or its components (see **What the non-medicinal ingredients are**).
- If you have a severe liver problem.
- If you have rare hereditary conditions of galactosemia, galactose intolerance, glucose/galactose malabsorption, Lapp lactase deficiency, as this product contains lactose.
- If you are allergic (hypersensitive) to nevirapine or its components (See **What the non-medicinal ingredients are**) or have used VIRAMUNE or VIRAMUNE XR and had a severe rash with associated symptoms such as malaise, fatigue, muscle/joint aches, blisters, facial edema (facial swelling), oral lesions, conjunctivitis, and/or hepatitis, eosinophilia(a lot of white blood cells called eosinophils in the blood), granulocytopenia (a decrease in white blood cells called granulocytes in the blood), lymphadenopathy (swelling of the lymph nodes), and renal dysfunction (kidneys not working properly), you must permanently discontinue VIRAMUNE or VIRAMUNE XR and seek medical evaluation immediately. (See **WARNINGS AND PRECAUTIONS**)
- Do not take VIRAMUNE or VIRAMUNE XR with St. John's wort (*Hypericum perforatum*) as it will reduce VIRAMUNE or VIRAMUNE XR blood levels.

What the medicinal ingredient is:

VIRAMUNE or VIRAMUNE XR tablets contain the active ingredient nevirapine.

What the non-medicinal ingredients are:

VIRAMUNE Immediate Release Tablets:
Non-medicinal Ingredients (in alphabetical order): colloidal silicon dioxide, lactose, magnesium stearate, microcrystalline cellulose, povidone, and sodium starch glycolate.

VIRAMUNE XR Extended Release Tablets:
Non-medicinal Ingredients (in alphabetical order): hypromellose, iron oxide (E172), lactose and magnesium stearate.

What dosage forms it comes in:

VIRAMUNE (nevirapine) comes as an immediate release white tablet containing 200 mg of nevirapine or as VIRAMUNE XR (nevirapine), an extended release yellow tablet containing 400 mg of nevirapine.

WARNINGS AND PRECAUTIONS

Severe, life-threatening, and in some cases fatal liver toxicity, particularly in the first 18 weeks, has been reported in patients

treated with VIRAMUNE, including pregnant women receiving chronic VIRAMUNE therapy in conjunction with other antiretroviral medication. Female gender and higher CD4 counts at the start of therapy may increase the risk of liver problems (see SIDE EFFECTS AND WHAT TO DO ABOUT THEM).

Severe skin and allergic reactions, including fatal cases have occurred with accompanying symptoms such as severe rash with fever, fatigue, muscle/joint pain, swelling of the face, hepatitis (liver inflammation), blood and kidney problems. If this occurs discontinue VIRAMUNE or VIRAMUNE XR and contact your doctor immediately.

In rare cases liver problems have led to liver failure and can lead to a liver transplant or death. Therefore, if you develop any of the following symptoms of liver problems stop taking VIRAMUNE or VIRAMUNE XR and call your doctor right away:

- general ill feeling or "flu-like" symptoms
- yellowing skin or whites of your eyes
- tiredness
- dark urine (tea colored)
- nausea (feeling sick to your stomach)
- pale stools (bowel movements)
- lack of appetite
- pain, ache, or sensitivity to touch on your right side below your ribs

Your doctor should check you and do blood tests often to check your liver function during the first 18 weeks of therapy. Checks for liver problems should continue regularly during treatment with VIRAMUNE or VIRAMUNE XR.

Skin Reactions
Skin rash is the most common side effect of VIRAMUNE or VIRAMUNE XR. Most rashes occur in the first 6 weeks of treatment. In a small number of patients, **rash can be serious and result in death**. Therefore, **if you develop a rash with any of the following symptoms, stop using VIRAMUNE or VIRAMUNE XR and call your doctor right away:**

- general ill feeling or "flu-like" symptoms
- blisters
- fever
- mouth sores
- muscle or joint aches
- swelling of your face
- conjunctivitis (red or inflamed eyes, like "pink-eye")
- tiredness
- any symptoms of liver problems discussed above

If your doctor tells you to stop treatment with VIRAMUNE or VIRAMUNE XR because you have experienced the serious liver or skin reactions described above, never take VIRAMUNE or VIRAMUNE XR again.

These are not all the side effects of VIRAMUNE or VIRAMUNE XR. See the section **SIDE EFFECTS AND WHAT TO DO ABOUT THEM** for more information. Tell your doctor if you have any side effects from VIRAMUNE or VIRAMUNE XR.

BEFORE you use VIRAMUNE or VIRAMUNE XR talk to your doctor or pharmacist:

- If you have or have had any diseases of the liver particularly hepatitis B or C infection;
- If you are pregnant or intend to become pregnant;
- If you are a breast-feeding mother. **It is recommended that HIV infected women not breast-feed, to avoid transmission of the virus to the infant;**
- If you are taking any medications, including prescription, non-prescription, herbal or homeopathic remedies;
- If you have any allergies to foods or drugs;
- If you are undergoing dialysis.

INTERACTIONS WITH THIS MEDICATION

Drugs that may interact with VIRAMUNE or VIRAMUNE XR include:
VIRAMUNE or VIRAMUNE XR may change the effect of other medicines, and other medicines can change the effect of VIRAMUNE or VIRAMUNE XR. Tell your doctors and pharmacists about **all** medicines you take, including non-prescription medicines, vitamins and herbal supplements.

Do **not** take ketoconazole, rifampin, efavirenz, delavirdine, etravirine, rilpivirine, elvitegravir (in combination with cobicistat), or boceprevir; with VIRAMUNE or VIRAMUNE XR.

Tell your doctor if you take clarithromycin, fluconazole, methadone, rifabutin, indinavir, lopinavir/ritonavir combination, saquinavir or itraconazole.

VIRAMUNE or VIRAMUNE XR may not be right for you, or you may need careful monitoring.

You should be aware that VIRAMUNE or VIRAMUNE XR may change the effectiveness of oral contraceptives. Therefore oral contraceptives and other hormonal methods of birth control should not be used as a method of contraception in women taking VIRAMUNE or VIRAMUNE XR; other methods (barrier) must be used.

PROPER USE OF THIS MEDICATION

Usual dose:
Adult:
Follow the directions exactly as given to you by your doctor or pharmacist regarding the amount and frequency of dosing. The label will usually tell you this information as well. If you are not sure about dosing, ask your doctor or pharmacist.

VIRAMUNE Immediate Release Tablets:
As a general guide, swallow one tablet (200 mg) once a day 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 200 mg tablet twice daily as part of a multi-drug treatment program. VIRAMUNE immediate release tablets can be taken with or without food.

VIRAMUNE XR Extended Release Tablets:
Swallow one 200 mg tablet of VIRAMUNE immediate release once daily for the first 14 days 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 or chewed. VIRAMUNE XR extended release tablets can be taken with or without food.

It is important to strictly follow the once daily dose for the first 14 days. Do not start taking the 200 mg VIRAMUNE twice daily or the 400 mg VIRAMUNE XR once daily if you have any symptoms of liver problems or skin rash (see **SIDE EFFECTS AND WHAT TO DO ABOUT THEM)**. The manufacturer's recommended dosage and monitoring for the other administered anti-retroviral drugs should be followed.

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

Overdose:

In case of drug overdosage, contact a healthcare practitioner (e.g. doctor), hospital emergency department or regional Poison Control Centre, even if there are no symptoms.

Missed Dose:
If you miss a dose: If you forget to take your medicine, take it as soon as you remember. Then continue as before; do not double your next dosage.

If it is almost time for your next dose, do not take the missed dose. Instead, follow your regular dosing schedule by taking the next dose at its regular time.

If you stop taking VIRAMUNE or VIRAMUNE XR for more than 7 days, ask your doctor how much to take before you start taking it again. You may need to start with once-a-day 200 mg VIRAMUNE tablet dosing.

Avoid doing things that can spread HIV infection, as VIRAMUNE or VIRAMUNE XR does not stop you from passing HIV infection to others. Do not share needles, other injection equipment or personal items that can have blood or body fluids on them, like toothbrushes and razor blades. Always practice safe sex by using a latex or polyurethane condom to lower the chance of sexual contact with semen, vaginal secretions, or blood.

This medicine is for you. Never give it to someone else, as it may harm them even if their symptoms are the same as yours.

Take your medications exactly as prescribed by your doctor. Do not change the dose without consulting your doctor.

Do not take any other medication including prescription, non prescription, herbal or homeopathic remedies without your doctor's advice. Also, inform any other doctor, dentist or pharmacist you consult that you are taking this medication.

Keep out of reach of children.

If you have any other questions about VIRAMUNE or VIRAMUNE XR, contact your doctor or pharmacist.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

VIRAMUNE or VIRAMUNE XR can cause serious liver damage and skin reactions that can cause death. Any patients can experience such side effects, but some patients are more at risk than others. See WARNINGS AND PRECAUTIONS.

Other common side effects of VIRAMUNE or VIRAMUNE XR include nausea, fatigue, fever, headache, vomiting, diarrhea, abdominal pain, skin rash and itching, myalgia (muscle pain) and arthralgia (joint pain). This list of side effects is not complete. Ask your doctor or pharmacist for more information.

Abnormal liver function test results, decrease in red blood cells or white blood cells called granulocytes, decrease in blood phosphorus, increase in blood pressure amd hypersensitivity including severe allergic reaction with facial swelling may also occur.

If you feel unwell in any other way or have any symptoms that you do not understand, you should contact your doctor immediately.

Sleepiness can occur. Do not drive or operate machinery if you become drowsy.

Always tell your doctor or pharmacist about any undesirable effects you experience after taking VIRAMUNE or VIRAMUNE XR, even those not mentioned above.

Changes in body fat have been seen in some patients taking anti-retroviral therapy. These changes may include increased amount of fat in the upper back and neck ("buffalo hump"), breast, and around the trunk. Loss of fat from the legs, arms and face may also happen. The cause and long term health effects of these conditions are not known at this time.

Occasionally, the inactive ingredients of VIRAMUNE XR extended release tablets may be eliminated in the stool as a soft hydrated mass that looks like a whole tablet. There is no cause for alarm.

Consult your doctor immediately if you experience any symptoms as listed above, or any symptoms that you do not understand.

This is not a complete list of side effects. For any unexpected effects while taking* VIRAMUNE or VIRAMUNE XR*, contact your doctor or pharmacist.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Uncommon	Severe liver disease with symptoms such as nausea, abdominal pain, aches, tiredness, lack of appetite, dark urine, pale stools (bowel movement) , yellowing of skin and eyes, and a general ill feeling or "flu-like" symptoms.			✓
	Severe skin reactions such as rash, blistering accompanied by symptoms such as fever, muscle/joint pain, tiredness, mouth sores, swelling of the face, conjunctivitis, and a general ill feeling or "flu-like" symptoms.			✓

HOW TO STORE IT

Store VIRAMUNE or VIRAMUNE XR tablets at normal room temperature (between 15°C and 30°C). As with all medicines, keep VIRAMUNE or VIRAMUNE XR tightly closed and out of the reach of children. Do not take your medicine after the expiry date shown on the bottle.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- **Report online at www.healthcanada.gc.ca/medeffect**
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**
  Fax toll-free to 1-866-678-6789, or
  Mail to: Canada Vigilance Program
  Health Canada
  Postal Locator 0701D
  Ottawa, ON K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect

NOTE: Should you require information related to the management of side effects contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at: http://www.boehringer-ingelheim.ca or by contacting the sponsor, Boehringer Ingelheim (Canada) Ltd., at: 1-800-263-5103, ext. 84633 (Medical Information). Please visit our website to see if more up-to-date information has been posted.

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