CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 20-933
20-636/SE1-009

FINAL PRINTED LABELING

ROXANE LABS, INC.

VIRAMUNE®
(nevirapine) Tablets

VIRAMUNE®
(nevirapine) Oral Suspension

WARNING:

SEVERE AND LIFE-THREATENING SKIN REACTIONS (STEVENS-JOHNSON SYNDROME, TOXIC EPIDERMAL NECROLYSIS), INCLUDING FATAL CASES, HAVE OCCURRED IN PATIENTS TREATED WITH VIRAMUNE®. (See WARNINGS)

SEVERE AND LIFE-THREATENING HEPATOTOXICITY, INCLUDING FATAL HEPATIC NECROSIS, HAS OCCURRED IN PATIENTS TREATED WITH VIRAMUNE®. (See WARNINGS)

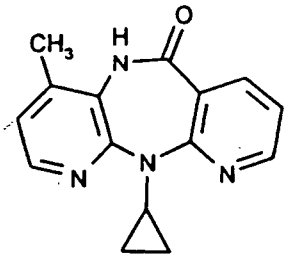
RESISTANT VIRUS EMERGES RAPIDLY AND UNIFORMLY WHEN VIRAMUNE® IS ADMINISTERED AS MONOTHERAPY. THEREFORE, VIRAMUNE® SHOULD ALWAYS BE ADMINISTERED IN COMBINATION WITH ANTIRETROVIRAL AGENTS.

DESCRIPTION: VIRAMUNE® is the brand name for nevirapine (NVP), a non-nucleoside reverse transcriptase inhibitor with activity against Human Immunodeficiency Virus Type 1 (HIV-1). Nevirapine is structurally a member of the dipyridodiazepinone chemical class of compounds.

VIRAMUNE® Tablets are for oral administration. Each tablet contains 200 mg of nevirapine and the inactive ingredients microcrystalline cellulose, lactose monohydrate, povidone, sodium starch glycolate, colloidal silicon dioxide and magnesium stearate.

VIRAMUNE® Oral Suspension is for oral administration. Each 5 mL of VIRAMUNE® suspension contains 50 mg of nevirapine (as nevirapine hemihydrate). The suspension also contains the following excipients: carbomer 934P, methylparaben, propylparaben, sorbitol, sucrose, polysorbate 80, sodium hydroxide and water.

The chemical name of nevirapine is 11-cyclopropyl-5,11-dihydro-4-methyl-6H-dipyrido[3,2-b:2',3'-][1,4] diazepin-6-one. Nevirapine is a white to off-white crystalline powder with the molecular weight of 266.3 and the molecular formula $C_{15}H_{14}N_4O$. Nevirapine has the following structural formula:



MICROBIOLOGY: ***Mechanism of Action*:** Nevirapine is a non-nucleoside reverse transcriptase inhibitor (NNRTI) of HIV-1. Nevirapine binds directly to reverse transcriptase (RT) and blocks the RNA-dependent and DNA-dependent DNA polymerase activities by causing a disruption of the enzyme's catalytic site. The activity of nevirapine does not compete with template or nucleoside triphosphates. HIV-2 RT and eukaryotic DNA polymerases (such as human DNA polymerases α, ß, γ, or δ) are not inhibited by nevirapine.

In Vitro HIV Susceptibility: The relationship between *in vitro* susceptibility of HIV-1 to nevirapine and the inhibition of HIV-1 replication in humans has not been established. The *in vitro* antiviral activity of nevirapine was measured in peripheral blood mononuclear cells, monocyte derived macrophages, and lymphoblastoid cell lines. IC_{50} values (50% inhibitory concentration) ranged from 10-100 nM against laboratory and clinical isolates of

HIV- 1. In cell culture, nevirapine demonstrated additive to synergistic activity against HIV in drug combination regimens with zidovudine (ZDV), didanosine (ddI), stavudine (d4T), lamivudine (3TC), saquinavir, and indinavir.

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

Phenotypic and genotypic changes in HIV-1 isolates from patients treated with either nevirapine (n=24) or nevirapine 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. Nevirapine+ZDV combination therapy did not alter the emergence rate of nevirapine-resistant virus or the magnitude of nevirapine resistance *in vitro*; however, a different RT mutation pattern, predominantly distributed amongst amino acid positions 103, 106, 188, and 190, was observed. In patients (6 of 14) whose baseline isolates possessed a wild type RT gene, nevirapine+ZDV combination therapy did not appear to delay emergence of ZDV-resistant RT mutations. The clinical relevance of phenotypic and genotypic changes associated with nevirapine therapy has not been established.

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

ANIMAL PHARMACOLOGY: Animal studies have shown that nevirapine is widely distributed to nearly all tissues and readily crosses the blood-brain barrier.

CLINICAL PHARMACOLOGY: ***Pharmacokinetics in Adults:*** **Absorption and Bioavailability:** Nevirapine is readily absorbed (>90%) after oral administration in healthy volunteers and in adults with HIV-1 infection. Absolute bioavailability in 12 healthy adults following single-dose administration was 93 ± 9% (mean ± SD) for a 50 mg tablet and 91 ± 8% for an oral solution. Peak plasma nevirapine concentrations of 2 ± 0.4 μg/mL (7.5 μM) were attained by 4 hours following a single 200 mg dose. Following multiple doses, nevirapine peak concentrations appear to increase linearly in the dose range of 200 to 400 mg/day. Steady state trough nevirapine concentrations of 4.5 ± 1.9 μg/mL (17 ± 7 μM), (n = 242) were attained at 400 mg/day. Nevirapine tablets and suspension have been shown to be comparably bioavailable and interchangeable at doses up to 200 mg. When VIRAMUNE® (200 mg) was administered to 24 healthy adults (12 female, 12 male), 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 (AUCτ) 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. Following intravenous administration to healthy adults, the apparent volume of distribution (Vdss) of nevirapine was 1.21 ± 0.09 L/kg, suggesting that nevirapine is widely distributed in humans. Nevirapine readily crosses the placenta and is found in breast milk. (See PRECAUTIONS, *Nursing Mothers*) Nevirapine is about 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% (± 5%) of the concentrations in plasma; this ratio is approximately equal to the fraction not bound to plasma protein.

Metabolism/Elimination: *In vivo* studies in humans and *in vitro* studies with human liver microsomes have shown that nevirapine is extensively biotransformed via cytochrome P450 (oxidative) metabolism to several hydroxylated metabolites. *In vitro* studies with human liver microsomes suggest that oxidative metabolism of nevirapine is mediated primarily by cytochrome P450 isozymes from the CYP3A family, 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 given twice daily followed by a single 50 mg dose of ^{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 P450 metabolism, glucuronide conjugation, and urinary excretion of glucuronidated metabolites represent the primary route of nevirapine biotransformation and elimination in humans. Only a small fraction (<5%) of the radioactivity in urine (representing <3% of the total dose) was made up of parent compound; therefore, renal excretion plays a minor role in elimination of the parent compound.

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

Pharmacokinetics in Special Populations: **Renal/Hepatic Dysfunction:** The pharmacokinetics of nevirapine have not been evaluated in patients with either renal or hepatic dysfunction.

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 or plasma concentrations following either single- or multiple-dose administration(s).

Race: 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 Cminss = 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.

Geriatric Patients: Nevirapine pharmacokinetics in HIV-1 infected adults do not appear to change with age (range 18 – 68 years); however, nevirapine has not been extensively evaluated in patients beyond the age of 55 years.
Pediatric Patients: See PRECAUTIONS, *Pediatric Use.*

Drug Interactions: *Nucleoside Analogues:* No dosage adjustments are required when VIRAMUNE® is taken in combination with ZDV, ddI, or zalcitabine (ddC). Results from studies in HIV-1 infected patients who were administered VIRAMUNE® with different combinations of ddI or ddC, on a background of ZDV therapy, indicated that no clinically significant pharmacokinetic interactions occurred when the nucleoside analogues were administered in combination with VIRAMUNE®.

Protease Inhibitors: In the following three studies, VIRAMUNE® was given 200 mg once daily for two weeks followed by 200mg twice daily for 28 days:

Ritonavir: No dosage adjustments are required when VIRAMUNE® is taken in combination with ritonavir. Results from a 49-day study in HIV-infected patients (n=14) administered VIRAMUNE® and ritonavir (600 mg b.i.d. [using a gradual dose escalation regimen]) indicated that their coadministration did not affect ritonavir AUC or Cmax. Comparison of nevirapine pharmacokinetics from this study to historical data suggested that coadministration did not affect the pharmacokinetics of nevirapine.

Indinavir: Results from a 36-day study in HIV-infected patients (n=19) administered VIRAMUNE® and indinavir (800 mg q8h) indicated that their coadministration led to a 28% mean decrease (95% CI -39, -16) in indinavir AUC and an 11% mean decrease (95% CI -49, +59) in indinavir Cmax. The clinical significance of this interaction is not known. Comparison of nevirapine pharmacokinetics from this study to historical data suggested that coadministration did not affect the pharmacokinetics of nevirapine.

Saquinavir: Results from a 42-day study in HIV-infected patients (n=23) administered VIRAMUNE® and saquinavir (hard gelatin capsules, 600 mg t.i.d.) indicated that their coadministration led to a 24% mean decrease (95% CI -42, -1) in saquinavir AUC and a 28% mean decrease (95% CI -47, -1) in saquinavir Cmax. The clinical significance of this interaction is not known. Coadministration did not affect the pharmacokinetics of nevirapine.

In vitro: 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/sulfamethoxazole. Ketoconazole significantly inhibited the formation of nevirapine hydroxylated metabolites.

In vivo: ketoconazole: VIRAMUNE® and ketoconazole should not be administered concomitantly. Ketoconazole AUC and Cmax decreased by a median 63% (95% CI -95, +33) and 40% (95% CI -52, +11), respectively, in HIV-infected patients (n=22) who were given VIRAMUNE® 200 mg once daily for two weeks followed by 200 mg twice daily for two weeks along with ketoconazole 400 mg daily. (See PRECAUTIONS, *Drug Interactions*) Comparison of the pharmacokinetics from this study to historical data suggested that coadministration with ketoconazole may result in a 15 – 30% increase in nevirapine plasma concentrations. The clinical significance of this observation is not known.

Monitoring of nevirapine plasma concentrations in patients who received long-term VIRAMUNE® treatment indicate that steady-state nevirapine trough plasma concentrations were elevated in patients who received cimetidine (+21%, n=11) and macrolides (+12%, n=24), known inhibitors of CYP3A.

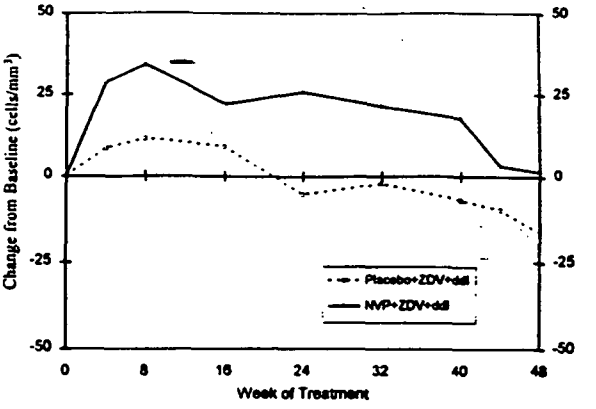
Steady-state nevirapine trough concentrations were reduced in patients who received rifabutin (-16%, n=19) and rifampin (-37%, n=3), known inducers of CYP3A. Nevirapine is an inducer of CYP3A, with maximal induction occurring within 2-4 weeks of initiating multiple-dose therapy. Other compounds that are substrates of CYP3A may have decreased plasma concentrations when co-administered with VIRAMUNE®. Therefore, careful monitoring of the therapeutic effectiveness of CYP3A-metabolized drugs is recommended when taken in combination with VIRAMUNE®. (See PRECAUTIONS, *Drug Interactions*, for recommendations regarding rifampin, rifabutin and oral contraceptives)

INDICATIONS AND USAGE: VIRAMUNE® (nevirapine) is indicated for use in combination with other antiretroviral agents for the treatment of HIV-1 infection. This indication is based on analyses of changes in surrogate endpoints. At present, there are no results from controlled clinical trials evaluating the effect of VIRAMUNE® in combination with other antiretroviral agents on the clinical progression of HIV-1 infection, such as the incidence of opportunistic infections or survival.

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

Description of Clinical Studies: **Patients with a prior history of nucleoside therapy:** ACTG 241 compared treatment with VIRAMUNE®+ZDV+ddI versus ZDV+ddI in 398 HIV-1-infected patients (median age 38 years, 74% Caucasian, 80% male) with CD4+ cell counts ≤350 cells/mm^3 (mean 153 cells/mm^3) and a mean baseline plasma HIV-1 RNA concentration of 4.59 $\log_{10}$ copies/mL (38,905 copies/mL), who had received at least 6 months of nucleoside therapy prior to enrollment (median 115 weeks). 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, 200 mg twice daily. Mean changes in CD4+ cell counts are shown in Figure 1. For 198 patients in the virology sub-study, mean HIV-1 RNA concentration changes from baseline are shown in Figure 2.

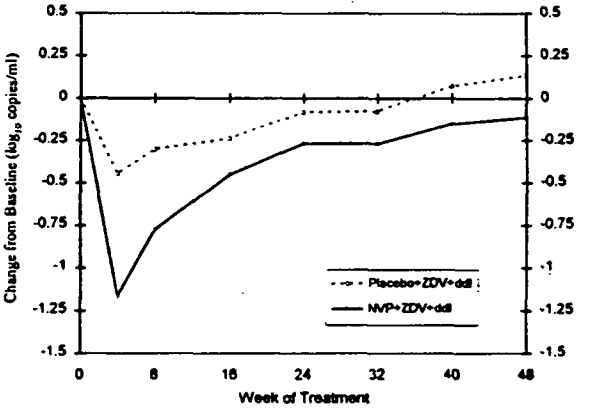
Figure 1: Mean Change From Baseline for CD4+ Cell Count (absolute number of CD4+ cells/mm^3), Trial ACTG 241



Number of patients with CD4+ cell counts at each timepoint

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

Figure 2: Mean Change From Baseline in HIV-1 RNA* Concentrations ($\log_{10}$ copies/mL), Virology Sub-study of Trial ACTG 241



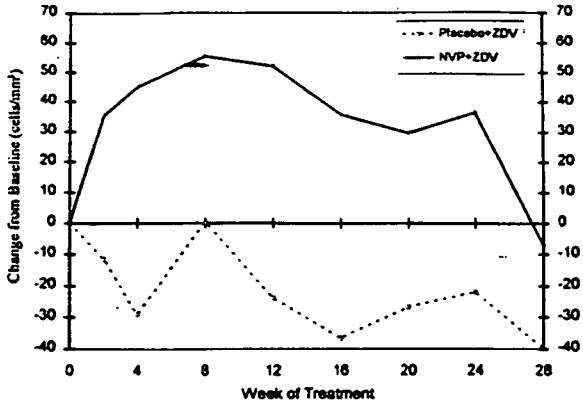
Number of patients with HIV-1 RNA data at each timepoint

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

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

Trial BI 1037 compared treatment with VIRAMUNE®+ZDV versus ZDV in 60 HIV-1-infected patients (median age 33 years, 70% Caucasian, 93% male) with CD4+ cell counts between 200 and 500 cells/mm^3 (mean 373 cells/mm^3) and a mean baseline plasma HIV-1 RNA concentration of 4.24 $\log_{10}$ copies/mL (17,378 copies/mL), who had received between 3 and 24 months of prior ZDV therapy (median 35 weeks). Treatment doses were VIRAMUNE® 200 mg daily for 2 weeks, followed by 200 mg twice daily, or placebo; ZDV, 500 - 600 mg/day. Mean changes in CD4+ cell counts are shown in Figure 3. Mean HIV-1 RNA concentration changes from baseline are shown in Figure 4.

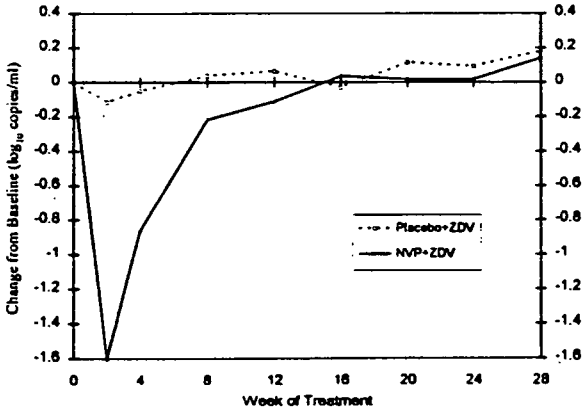
Figure 3: Mean Change From Baseline for CD4+ Cell Count (absolute number of CD4+ cells/mm^3), Trial BI 1037



Number of patients with CD4+ cell counts at each timepoint

	Baseline	Week 8	Week 16	20-28 Weeks
NVP+ZDV	30	28	26	26
Placebo+ZDV	30	30	28	29

Figure 4: Mean Change From Baseline in HIV-1 RNA Concentrations (log_{10} copies/mL), Trial BI 1037



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

	Baseline	Week 8	Week 16	20-28 Weeks
NVP+ZDV	30	27	26	26
Placebo+ZDV	30	29	28	29

Patients without a history of prior antiretroviral therapy:
BI Trial 1046 compared treatment with VIRAMUNE®+ZDV+ddI versus VIRAMUNE®+ZDV versus ZDV+ddI in 151 HIV-1-infected patients (median age 36 years, 94% Caucasian, 93% male) with CD4+ cell counts of 200 – 600 cells/mm^3 (mean 376 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. Changes in CD4+ cell counts at 24 weeks: mean levels of CD4+ cell counts in those randomized to VIRAMUNE® +ZDV+ddI and ZDV+ddI remained significantly above baseline; however there was no significant difference between these arms. Changes in HIV-1 viral RNA at 24 weeks: there was no significant difference as measured by mean changes in plasma viral RNA between those randomized to VIRAMUNE® +ZDV+ddI and ZDV+ddI. However, the proportion of patients whose HIV-1 RNA decreased below the limit of detection (400 copies/mL) was significantly

greater for the VIRAMUNE®+ZDV+ddI group (27/36 or 75%), when compared to the ZDV+ddI group (18/39 or 46%) or the VIRAMUNE®+ZDV group (0/28 or 0%); the clinical significance of this finding is unknown.

CONTRAINDICATIONS: VIRAMUNE® is contraindicated in patients with clinically significant hypersensitivity to any of the components contained in the tablet or the oral suspension.

WARNINGS: Severe and life-threatening skin reactions have occurred in patients treated with VIRAMUNE®, including Stevens-Johnson syndrome and toxic epidermal necrolysis. Fatal cases of toxic epidermal necrolysis have been reported. VIRAMUNE® must be discontinued in patients developing a severe rash or a rash accompanied by constitutional symptoms such as fever, blistering, oral lesions, conjunctivitis, swelling, muscle or joint aches, or general malaise. (See PRECAUTIONS, *Information for Patients*; ADVERSE REACTIONS) VIRAMUNE® therapy must be initiated with a 14-day lead-in period of 200 mg/day (4 mg/kg/day in pediatric patients), which has been shown to reduce the frequency of rash. If rash is observed during this lead-in period, dose escalation should not occur until the rash has resolved. (See DOSAGE AND ADMINISTRATION)

Severe or life-threatening hepatotoxicity, including fatal fulminant hepatitis (transaminase elevations, with or without hyperbilirubinemia, prolonged partial thromboplastin time, or eosinophilia), has occurred in patients treated with VIRAMUNE®. Some of these cases began in the first few weeks of therapy and some were accompanied by rash. VIRAMUNE® administration should be interrupted in patients experiencing moderate or severe ALT or AST abnormalities until these return to baseline values. VIRAMUNE® should be permanently discontinued if liver function abnormalities recur upon readministration. Monitoring of ALT and AST is strongly recommended, especially during the first six months of VIRAMUNE® treatment. (See PRECAUTIONS, *Information for Patients*; ADVERSE REACTIONS; DOSAGE AND ADMINISTRATION)

PRECAUTIONS: ***General:*** Nevirapine is extensively metabolized by the liver and nevirapine metabolites are extensively eliminated by the kidney. However, the pharmacokinetics of nevirapine have not been evaluated in patients with either hepatic or renal dysfunction. Therefore, VIRAMUNE® should be used with caution in these patient populations.

The duration of clinical benefit from antiretroviral therapy may be limited. Patients receiving VIRAMUNE® or any other antiretroviral therapy may continue to develop opportunistic infections and other complications of HIV infection, and therefore should remain under close clinical observation by physicians experienced in the treatment of patients with associated HIV diseases.

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

Drug Interactions: The induction of CYP3A by nevirapine may result in lower plasma concentrations of other concomitantly administered drugs that are extensively metabolized by CYP3A. (See CLINICAL PHARMACOLOGY) Thus, if a patient has been stabilized on a dosage regimen for a drug metabolized by CYP3A, and begins treatment with VIRAMUNE®, dose adjustments may be necessary.

Rifampin/Rifabutin: There are insufficient data to assess whether dose adjustments are necessary when nevirapine and rifampin or rifabutin are coadministered. Therefore, these drugs should only be used in combination if clearly indicated and with careful monitoring.

Ketoconazole: VIRAMUNE® and ketoconazole should not be administered concomitantly. Coadministration of nevirapine and ketoconazole resulted in a significant reduction in ketoconazole plasma concentrations. (See CLINICAL PHARMACOLOGY, Drug Interactions)

Oral Contraceptives: There are no clinical data on the effects of nevirapine on the pharmacokinetics of oral contraceptives. Nevirapine may decrease plasma concentrations of oral contraceptives (also other hormonal contraceptives); therefore, these drugs should not be administered concomitantly with VIRAMUNE®.

Information for Patients: **Patients should be instructed that the major toxicity of VIRAMUNE® is rash and should be advised to promptly notify their physician of any rash.** The majority of rashes associated with

VIRAMUNE® occur within the first 6 weeks of initiation of therapy. Patients should be instructed that if any rash occurs during the two-week lead-in period, the VIRAMUNE® dose should not be escalated until the rash resolves. Any patient experiencing severe rash or a rash accompanied by constitutional symptoms such as fever, blistering, oral lesions, conjunctivitis, swelling, muscle or joint aches, or general malaise should immediately discontinue medication and consult a physician.

Patients should be instructed that abnormal liver function tests and cases of clinical hepatitis, including fatal fulminant hepatitis, have been reported with VIRAMUNE®. Liver function tests should be monitored, especially during the first six months of therapy. VIRAMUNE® administration should be interrupted in patients experiencing moderate or severe liver function test abnormalities, until liver function tests return to baseline values; VIRAMUNE® should be permanently discontinued if liver function abnormalities recur upon readministration. Patients should be instructed to consult their physicians immediately should symptoms of hepatitis occur.

Oral contraceptives and other hormonal methods of birth control should not be used as a method of contraception in women taking VIRAMUNE®. (See PRECAUTIONS, *Drug Interactions*)

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

VIRAMUNE® is not a cure for HIV-1 infection; patients may continue to experience illnesses associated with advanced HIV-1 infection, including opportunistic infections. Treatment with VIRAMUNE® has not been shown to reduce the incidence or frequency of such illnesses; patients should be advised to remain under the care of a physician when using VIRAMUNE®.

Patients should be informed to take VIRAMUNE® every day as prescribed. Patients should not alter the dose without consulting their doctor. If a dose is missed, patients should take the next dose as soon as possible. However, if a dose is skipped, the patient should not double the next dose. Patients should be advised to report to their doctor the use of any other medications.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term carcinogenicity studies of nevirapine in animals are currently in progress. In genetic toxicology assays, nevirapine showed no evidence of mutagenic or clastogenic activity in a battery of *in vitro* and *in vivo* assays including microbial assays for gene mutation (Ames: Salmonella strains and *E. coli*), mammalian cell gene mutation assays (CHO/HGPRT), cytogenetic assays using a Chinese hamster ovary cell line and a mouse bone marrow micronucleus assay following oral administration. In reproductive toxicology studies, evidence of impaired fertility was seen in female rats at doses providing systemic exposure, based on AUC, approximately equivalent to that provided with the recommended clinical dose of VIRAMUNE®.

Pregnancy: Pregnancy Category C: No observable teratogenicity was detected in reproductive studies performed in pregnant rats and rabbits. In rats, a significant decrease in fetal body weight occurred at doses providing systemic exposure approximately 50% higher, based on AUC, than that seen at the recommended human clinical dose. The maternal and developmental no-observable-effect level dosages in rats and rabbits produced systemic exposures approximately equivalent to or approximately 50% higher, respectively, than those seen at the recommended daily human dose, based on AUC. There are no adequate and well-controlled studies in pregnant women. VIRAMUNE® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

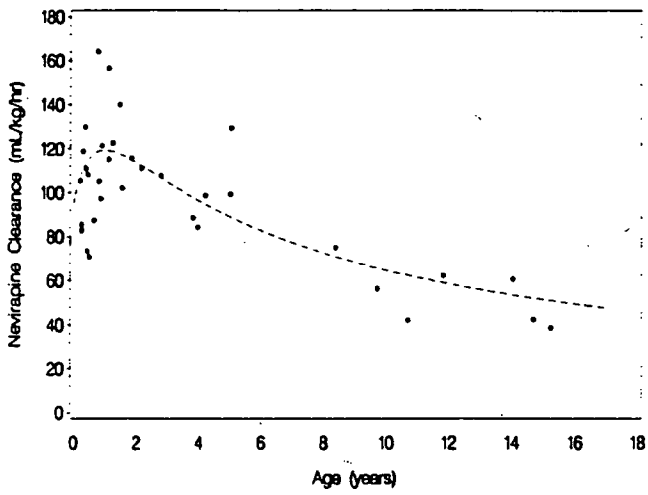
Nursing Mothers: Preliminary results from an ongoing pharmacokinetic study (ACTG 250) of 10 HIV-1-infected pregnant women who were administered a single oral dose of 100 or 200 mg VIRAMUNE® at a median of 5.8 hours before delivery, indicate that nevirapine readily crosses the placenta and is found in breast milk. Consistent with the recommendation by the U.S. Public Health Service Centers for Disease Control and Prevention that HIV-infected mothers not breast-feed their infants to avoid risking postnatal transmission of HIV, mothers should discontinue nursing if they are receiving VIRAMUNE®.

Pediatric Use: The pharmacokinetics of nevirapine have been studied in two open-label studies in children with HIV-1 infection. In one study (BI 853; ACTG 165), nine HIV-1-infected children ranging in age from 9 months to 14 years were administered a single dose (7.5 mg, 30 mg, or 120 mg per m^2; n=3 per dose) of nevirapine suspension

after an overnight fast. The mean nevirapine apparent clearance adjusted for body weight was greater in children compared to adults.

In a multiple dose study (BI 882; ACTG 180), nevirapine suspension or tablets (240 or 400 mg/m^2/day) were administered as monotherapy or in combination with ZDV or ZDV+ddI to 37 HIV-1-infected pediatric patients with the following demographics: male (54%), racial minority groups (73%), median age of 11 months (range: 2 months-15 years). The majority of these patients received 120 mg/m^2/day of nevirapine for approximately 4 weeks followed by 120 mg/m^2/b.i.d. (patients > 9 years of age) or 200 mg/m^2/b.i.d. (patients ≤ 9 years of age). Nevirapine apparent clearance adjusted for body weight reached maximum values by age 1 to 2 years and then decreased with increasing age. Nevirapine apparent clearance adjusted for body weight was at least two-fold greater in children younger than 8 years compared to adults. The relationship between nevirapine clearance with long term drug administration and age is shown in Figure 5. The pediatric dosing regimens were selected in order to achieve steady-state plasma concentrations in pediatric patients that approximate those in adults. (See DOSAGE AND ADMINISTRATION, *Pediatric Patients*)

Figure 5: Nevirapine Apparent Clearance (mL/kg/hr) in Pediatric Patients



Evaluation of the pharmacokinetics of nevirapine in neonates is ongoing.
Safety was assessed in trial BI 882 in which patients were followed for a mean duration of 33.9 months (range: 6.8 months to 5.3 years, including long-term follow-up in 29 of these patients in trial BI 892). The most frequently reported adverse events related to VIRAMUNE® in pediatric patients were similar to those observed in adults, with the exception of granulocytopenia which was more commonly observed in children. Serious adverse events were assessed in ACTG 245, a double-blind, placebo controlled trial of VIRAMUNE® (n = 305) in which pediatric patients received combination treatment with VIRAMUNE®. In this trial two patients were reported to experience Stevens-Johnson syndrome or Stevens-Johnson/toxic epidermal necrolysis transition syndrome. Cases of allergic reaction, including one case of anaphylaxis, were also reported. The evaluation of the antiviral activity of VIRAMUNE® in pediatric patients is ongoing..

Table 1 summarizes the marked laboratory abnormalities occurring in pediatric patients in Trial BI 882 and in follow-up Trial BI 892.

Table 1: Number of Pediatric Patients (%) with Marked Laboratory Abnormalities in Trials BI 882 and BI 892 Combined.

	No. (%) of Patients n=37
Hematology	
Decreased Hg (<8.0 g/dL)	7 (19)
Decreased platelets (<50,000/mm^3)	4 (11)
Decreased neutrophils (<750/mm^3)	14 (38)
Increased MCV (>100 F/L)	13 (35)
Blood Chemistry	
Increased ALT (>250 U/L)	4 (11)
Increased AST (>250 U/L)	5 (14)
Increased GGT (>450 U/L)	4 (11)
Increased total bilirubin (>2.5 mg/dL)	1 (3)
Increased alkaline phosphatase (>2x ULN)	19 (51)
Increased amylase (>2x ULN)	6 (16)

ADVERSE REACTIONS: ***Adults:*** The most frequently reported adverse events related to VIRAMUNE® therapy were rash, fever, nausea, headache, and abnormal liver function tests.

The major clinical toxicity of VIRAMUNE® is rash, with VIRAMUNE®-attributable rash occurring in 17% of patients in combination regimens in Phase II/III controlled studies. Thirty-seven percent of patients treated with VIRAMUNE® experienced rash compared with 20% of patients treated in control groups of either ZDV+ddI or ZDV alone (Table 2). Severe or life-threatening rash occurred in 7.6% of VIRAMUNE®-treated patients compared with 1.2% of patients treated in the control groups.

Rashes are usually mild to moderate, maculopapular erythematous cutaneous eruptions, with or without pruritus, located on the trunk, face and extremities. The majority of severe rashes occurred within the first 28 days of treatment; 25% of the patients with severe rashes required hospitalization; and one patient required surgical intervention. All patients recovered. Overall, 7% of patients discontinued VIRAMUNE® due to rash.

Table 2: Percentage of Patients with Rashes in Adult Controlled Trials[a]

	ACTG 241[b]		BI 1037		BI 1011		COMBINED DATA	
	NVP+ZDV +ddI	ZDV+ddI	NVP+ZDV	ZDV	NVP+ZDV	ZDV	NVP	CONTROL
n	197	201	30	30	25	24	252	255
Rash events of all Grades and all causality	39.6%	23.9%	26.7%	6.7%	32.0%	4.2%	37.3%	20.0%
Grade 3 or 4 rash events: all causality	8.1%	1.5%	3.3%	0%	8.0%	0%	7.6%	1.2%

a At recommended dose of one 200 mg tablet daily for the first 14 days followed by one 200 mg tablet twice daily

b Trial ACTG 241 was designed to report Grade 3/4 (severe or life-threatening) events; except for several pre-specified events including rash for which all grades are reported

Table 3 lists treatment-related clinical adverse events that occurred in patients receiving VIRAMUNE® in ACTG 241 and in Trials BI 1037 and BI 1011.

Table 3: Comparative Incidence of Selected Drug-Related Events in Adult Controlled Trials

	ACTG 241		Trial BI 1037 and BI 1011	
	Grade 3/4 events		All severities	
	NVP+ZDV+ddI	ZDV+ddI	NVP+ZDV	ZDV alone
Number of patients	197	201	55	30
Overall incidence of related adverse events	31%	23%	42%	33%
Rash	8	2	20	3
Fever	3	3	11	3
Nausea	5	4	9	3
Headache	3	3	11	0
Diarrhea	2	2	0	0
Abdominal pain	1	2	2	0
Ulcerative stomatitis	0	0	4	0
Peripheral neuropathy	0	2	0	0
Paraesthesia	1	0	2	0
Myalgia	1	0	2	7
Hepatitis	1	0	4	0

Laboratory Abnormalities: Table 4 summarizes marked laboratory abnormalities occurring in three controlled studies.

Table 4: Percentage of Adult Patients with Marked Laboratory Abnormalities

	Data combined for controlled trials ACTG 241, BI 1037 & BI 1011	
	VIRAMUNE® n=252	Control n=255
Hematology		
Decreased Hg (<8.0 g/dL)	1.2%	2.0%
Decreased platelets (<50,000/mm^3)	0.8	0.8
Decreased neutrophils (<750/mm^3)	11.1	10.2
Blood chemistry		
Increased ALT (>250 U/L)	3.4	3.5
Increased AST (>250 U/L)	2.0	2.4
Increased GGT (>450 U/L)	2.4	1.2
Increased total bilirubin (>2.5 mg/dL)	0.4	1.2

Asymptomatic elevations in GGT levels are more frequent in VIRAMUNE® recipients than in controls. Because clinical hepatitis has been reported in VIRAMUNE®-treated patients, monitoring of ALT (SGPT) and AST (SGOT) is strongly recommended, especially during the first six months of VIRAMUNE® treatment. (See WARNINGS)

Pediatric Patients: The most frequently reported adverse events related to VIRAMUNE® in pediatric patients were similar to those observed in adults, with the exception of granulocytopenia which was more commonly observed in children (See PRECAUTIONS: *Pediatric Use.*) The safety profile of VIRAMUNE® in neonates has not been established.

OVERDOSAGE: There is no known antidote for VIRAMUNE® overdosage. Cases of VIRAMUNE® overdose at doses ranging from 800 to 1800 mg per day for up to 15 days have been reported. Patients have experienced events including edema, erythema nodosum, fatigue, fever, headache, insomnia, nausea, pulmonary infiltrates, rash, vertigo, vomiting and weight decrease. All events subsided following discontinuation of VIRAMUNE®.

DOSAGE AND ADMINISTRATION: ***Adults:*** The recommended dose for VIRAMUNE® 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, in combination with antiretroviral agents. For concomitantly administered antiretroviral therapy, the manufacturer's recommended dosage and monitoring should be followed.

Pediatric Patients: The recommended oral dose of VIRAMUNE® for pediatric patients 2 months up to 8 years of age is 4 mg/kg once daily for the first 14 days followed by 7 mg/kg twice daily thereafter. For patients 8 years and older the recommended dose is 4 mg/kg once daily for two weeks followed by 4 mg/kg twice daily thereafter. The total daily dose should not exceed 400 mg for any patient.

VIRAMUNE® suspension should be shaken gently prior to administration. It is important to administer the entire measured dose of suspension by using an oral dosing syringe or dosing cup. An oral dosing syringe is recommended, particularly for volumes of 5 mL or less. If a dosing cup is used, it should be thoroughly rinsed with water and the rinse should also be administered to the patient.

Monitoring of Patients: Clinical chemistry tests, which include liver function tests, should be performed prior to initiating VIRAMUNE® therapy and at appropriate intervals during therapy. (See WARNINGS)

Dosage Adjustment: **VIRAMUNE® should be discontinued if patients experience severe rash or a rash accompanied by constitutional findings. (See WARNINGS) Patients experiencing rash during the 14-day lead-in period of 200 mg/day (4 mg/kg/day in pediatric patients) should not have their VIRAMUNE® dose increased until the rash has resolved. (See PRECAUTIONS, *Information for Patients*)**

VIRAMUNE® administration should be interrupted in patients experiencing moderate or severe liver function test abnormalities (excluding GGT), until the liver function test elevations have returned to baseline. VIRAMUNE® may then be restarted at 200 mg per day (or 4 mg/kg/day in pediatric patients). Increasing the daily dose to 200 mg twice daily (4 or 7 mg/kg twice daily, according to age, for pediatric patients) should be done with caution, after extended observation. VIRAMUNE® should be permanently discontinued if moderate or severe liver function test abnormalities recur. (See WARNINGS)

Patients who interrupt VIRAMUNE® dosing for more than 7 days should restart the recommended dosing, using one 200 mg tablet daily (4 mg/kg/day in pediatric patients) for the first 14 days (lead-in) followed by one 200 mg tablet twice daily (4 or 7 mg/kg twice daily, according to age, for pediatric patients).

No data are available to recommend a dosage of VIRAMUNE® in patients with hepatic dysfunction, renal insufficiency, or undergoing dialysis.

HOW SUPPLIED: VIRAMUNE® (nevirapine) Tablets, 200 mg, are white, oval, biconvex tablets, 9.3 mm 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.

VIRAMUNE® Tablets are supplied in bottles of 100 (NDC 0054-4647-25), bottles of 60 (NDC 0054-4647-21), and individually blister-sealed unit-dose cartons of 100 tablets as 10 x 10 cards (NDC 0054-8647-25).

VIRAMUNE® (nevirapine) Oral Suspension, is a white to off-white preserved suspension containing 50 mg nevirapine (as nevirapine hemihydrate) in each 5 mL. VIRAMUNE® suspension is supplied in plastic bottles with child-resistant closures containing 240 mL of suspension (NDC 0054-3905-58).

VIRAMUNE® Tablets and Oral Suspension should be stored at 15°C – 30°C (59°F – 86°F).

VIRAMUNE® Tablets

Manufactured by:
Boehringer Ingelheim Pharmaceuticals, Inc.
Ridgefield, CT 06877

Distributed by:
Roxane Laboratories, Inc
Columbus, OH 43216

VIRAMUNE® Oral Suspension

Manufactured by:
Roxane Laboratories, Inc.
Columbus, OH 43216

Distributed by:
Roxane Laboratories, Inc.
Columbus, OH 43216

R_x only

Revised 9/10/98

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