APOSTILLE

(Convention de La Haye du 5 octobre 1961)

1. Country: *United States of America*

This public document

2. has been signed by Andrei Perlloni

3. acting in the capacity of Branch Chief, Drug Imports and Exports Compliance Branch

4. bears the seal/stamp of U.S. Department of Health and Human Services

Certified

5. at Washington, D.C.

6. the fifth of July, 2018

7. by *Assistant Authentication Officer, United States Department of State*

8. No. 18046402-4

9. Seal/Stamp:

10. Signature:

Chana M Turner

United States Food and Drug Administration

Center for Drug Evaluation and Research

10903 New Hampshire Ave, Silver Spring, MD 20993, United States of America

CDERExportCertificateProgram@fda.hhs.gov - Telephone (301) 796-4950

Certificate of a Pharmaceutical Product - Approved Drug Product

Certificate Number: **X2PB-R2UF** Certificate Issue Date: **May 29, 2018** Certificate Expiration Date: **May 28, 2020**

Importing Country: **COLOMBIA** Exporting Country: **UNITED STATES of AMERICA**

1.	Drug Trade Name, International or National non-proprietary name (as applicable) & dosage form: **VIRAMUNE®, Suspension**
1.1	Active Ingredient(s) and amount(s) per unit dose (complete quantitative composition is preferred): **nevirapine 50 MG/5 ML**
1.2	Is this product licensed to be placed on the market for use in the exporting country? **Yes**
1.3	Is this product actually on the market in the exporting country? **Yes**
2.A.1	Product license number & date of issue: **020933 09/11/1998**
2.A.2	Product license holder name & address: **Boehringer-Ingelheim Inc., 900 Ridgebury Road, P.O. Box 368, Ridgefield, CT 06877 United States of America**
2.A.3	Status of Product license holder: **Neither**
2.A.3.1	Manufacturer name & address: **West-Ward Columbus Inc., 1809 Wilson Road, Columbus, OH 43228 United States of America**
2.A.4	Is a summary basis for approval appended? **Yes**
2.A.5	Is the attached product information, complete and consonant with the license? **Yes**
2.A.6	Applicant name & address for certificate (if different from the license holder): **Boehringer-Ingelheim Inc., 900 Ridgebury Road, P.O. Box 368, Ridgefield, CT 06877 United States of America**
2.B.4	Remarks: **API Manufacturer: Zhejiang Huahai Pharmaceutica Co., Ltd., Coastal Industrial Zone, Duquiao, Linhai, Zhejiang 317016 CHINA**
3.	Does the certifying authority arrange for periodic inspection of the manufacturing plant in which the dosage form is produced? **Yes**
3.1	Periodicity of routine inspections (years): **Pursuant to section 510(h)(3) of the Federal Food, Drug & Cosmetic Act, Inspections will occur in accordance with a risk-based schedule**
3.2	Has the manufacture of this type of dosage form been inspected? **Yes**
3.3	Do the facilities and operations conform to GMPs as recommended by the WHO? (GMPs including 21 Code of Federal Regulations parts 210, 211, or ICH Q7A): **Yes, at time of inspection, site complies with FDA cGMP**
3.4	Does the information submitted by the applicant satisfy the certifying authority on all aspects of the manufacture of the product undertaken by another party? **Yes**

Andrei Perlloni

Andrei Perlloni, Branch Chief
Drug Import Export Compliance Branch
Division of Imports, Exports & Recalls
Office of Drug Security, Integrity & Response



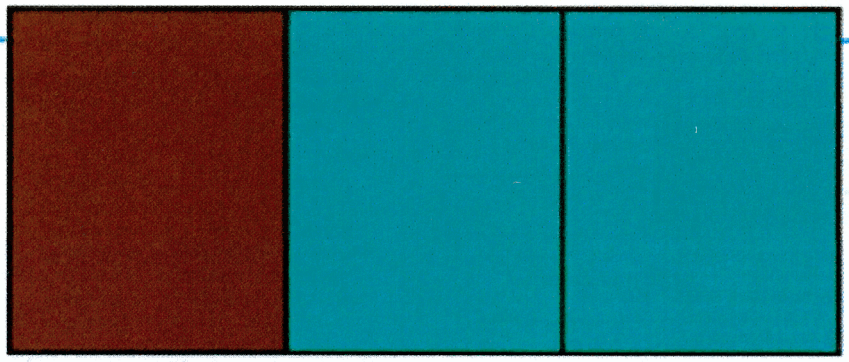
nforms to the format recommended by the World Health Organization format revised October 1, 1997 Website: www.who.int

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X2PB-R2UF

PRODUCT LABEL FOR: VIRAMUNE ORAL SUSPENSION



NDC 0597-0047-24

Pharmacist: A Medication Guide is appended to the Prescribing Information and must be dispensed with each prescription or refill.

Viramune®

(nevirapine)

Oral Suspension 50 mg/5 mL

240 mL

℞ only

Each 5 mL contains 50 mg of nevirapine as nevirapine hemihydrate.

Usual Dosage: Read accompanying prescribing information

Boehringer Ingelheim

LOT
EXP.

N 3 0597-0047-24 7

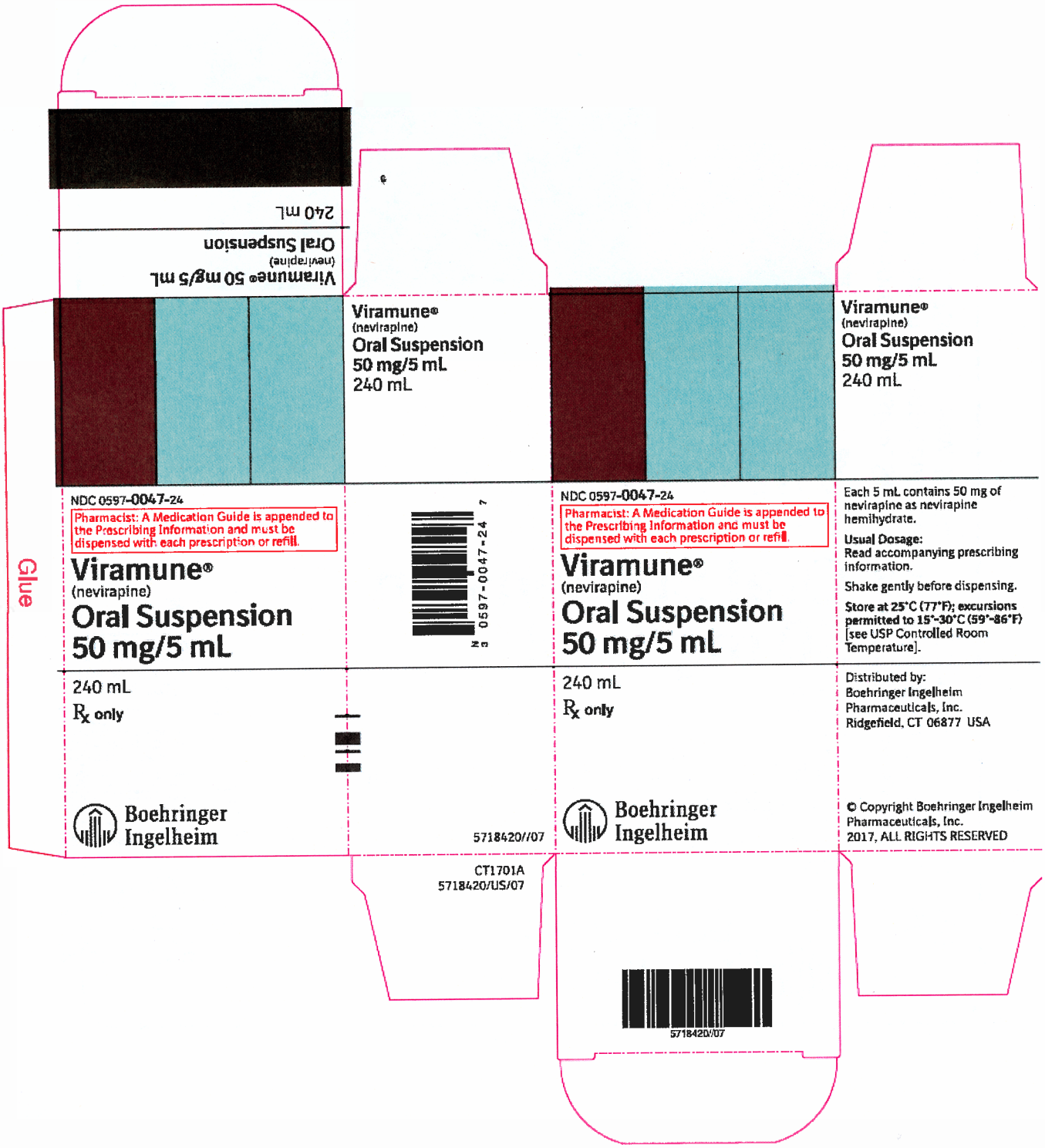
Shake gently before dispensing. **Store at 25°C (77°F); (see insert)**

Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, CT 06877 USA

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X2PB-R2UF

CARTON LABEL FOR: VIRAMUNE ORAL SUSPENSION



X2PB-R2UF

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use VIRAMUNE safely and effectively. See full prescribing information for VIRAMUNE.

VIRAMUNE® (nevirapine) tablets, for oral use
VIRAMUNE® (nevirapine) oral suspension, for oral use
Initial U.S. Approval: 1996

WARNING: LIFE-THREATENING (INCLUDING FATAL) HEPATOTOXICITY and SKIN REACTIONS

See full prescribing information for complete boxed warning.

- **Fatal and non-fatal hepatotoxicity have been reported in patients taking VIRAMUNE. Discontinue immediately if clinical hepatitis or transaminase elevations combined with rash or other systemic symptoms occur. Do not restart VIRAMUNE after recovery. (5.1)**
- **Fatal and non-fatal skin reactions, including Stevens-Johnson syndrome, toxic epidermal necrolysis, and hypersensitivity reactions, have been reported. Discontinue immediately if severe skin reactions, hypersensitivity reactions, or any rash with systemic symptoms occur. Check transaminase levels immediately for all patients who develop a rash in the first 18 weeks of treatment. Do not restart VIRAMUNE after recovery. (5.2)**
- **Monitoring during the first 18 weeks of therapy is essential. Extra vigilance is warranted during the first 6 weeks of therapy, which is the period of greatest risk of these events. (5.1, 5.2)**

----------INDICATIONS AND USAGE----------

- VIRAMUNE is an NNRTI indicated in combination with other antiretroviral agents for the treatment of human immunodeficiency virus (HIV-1) infection in adults and pediatric patients 15 days and older. (1)

Limitations of Use:

Based on serious and life -threatening hepatotoxicity observed in controlled and uncontrolled trials, VIRAMUNE is not recommended to be initiated unless the benefit outweighs the risk, in:

- adult females with $CD4^+$ cell counts greater than 250 cells/mm3
- adult males with $CD4^+$ cell counts greater than 400 cells/mm3 (1, 5.1)

----------DOSAGE AND ADMINISTRATION----------

- The 14 day lead in period must be strictly followed; it has been demonstrated to reduce the frequency of rash (2.4, 5.2)
- If any patient experiences rash during the 14-day lead-in period, do not increase dose until the rash has resolved. Do not continue the lead-in dosing regimen beyond 28 days. (2.4)
- If dosing is interrupted for greater than 7 days, restart 14-day lead-in dosing. (2.4)

	Adults (≥16 yrs)	**Pediatric Patients*** (≥15 days)
First 14 days	200 mg once daily	150 mg/m^2 once daily
After 14 days	200 mg twice daily	150 mg/m^2 twice daily

*Total daily dose should not exceed 400 mg for any patient.

----------DOSAGE FORMS AND STRENGTHS----------

- 200 mg tablets (3)
- 50 mg per 5 mL oral suspension (3)

----------CONTRAINDICATIONS----------

- Patients with moderate or severe (Child-Pugh Class B or C, respectively) hepatic impairment. (4, 5.1, 8.7)
- Use as part of occupational and non-occupational post-exposure prophylaxis (PEP) regimens, an unapproved use. (4, 5.1)

----------WARNINGS AND PRECAUTIONS----------

- Monitor patients for immune reconstitution syndrome and fat redistribution. (5.5, 5.6)

----------ADVERSE REACTIONS----------

- The most common adverse reaction is rash. In adults the incidence of rash is 15% versus 6% with placebo, with Grade 3/4 rash occurring in 2% of subjects. (6.1)
- In pediatric subjects the incidence of rash (all causality) was 21%. (6.2)

To report SUSPECTED ADVERSE REACTIONS, contact Boehringer Ingelheim Pharmaceuticals, Inc. at (800) 542-6257 or (800) 459-9906 TTY, or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

Co-administration of VIRAMUNE can alter the concentrations of other drugs and other drugs may alter the concentration of nevirapine. The potential for drug interactions must be considered prior to and during therapy. (5.4, 7, 12.3)

----------USE IN SPECIFIC POPULATIONS----------

- Lactation: Women infected with HIV-1 should be instructed not to breastfeed due to the potential for HIV-1 transmission. (8.2)
- No dose adjustment is required for patients with renal impairment with a creatinine clearance greater than or equal to 20 mL per min. Patients on dialysis receive an additional dose of 200 mg following each dialysis treatment. (2.4, 8.6)
- Monitor patients with hepatic fibrosis or cirrhosis carefully for evidence of drug induced toxicity. Do not administer VIRAMUNE to patients with Child-Pugh B or C. (5.1, 8.7)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 3/2017

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FULL PRESCRIBING INFORMATION

WARNING: LIFE-THREATENING (INCLUDING FATAL) HEPATOTOXICITY and SKIN REACTIONS

HEPATOTOXICITY:

Severe, life-threatening, and in some cases fatal hepatotoxicity, particularly in the first 18 weeks, has 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 $CD4^+$ cell counts at initiation of therapy place patients at increased risk; women with $CD4^+$ cell counts greater than 250 cells/mm^3, including pregnant women receiving VIRAMUNE in combination with other antiretrovirals for the treatment of HIV-1 infection, are at the greatest risk. However, hepatotoxicity associated with VIRAMUNE use can occur in both genders, all $CD4^+$ cell counts and at any time during treatment. Hepatic failure has also been reported in patients without HIV taking VIRAMUNE for post-exposure prophylaxis (PEP). Use of VIRAMUNE for occupational and non-occupational PEP is contraindicated *[see Contraindications (4)]*. Patients with signs or symptoms of hepatitis, or with increased transaminases combined with rash or other systemic symptoms, must discontinue VIRAMUNE and seek medical evaluation immediately *[see Warnings and Precautions (5.1)]*.

SKIN REACTIONS:

Severe, life-threatening skin reactions, including fatal cases, have occurred in patients treated with VIRAMUNE. These have included cases of Stevens-Johnson syndrome, toxic epidermal necrolysis, and hypersensitivity reactions characterized by rash, constitutional findings, and organ dysfunction. Patients developing signs or symptoms of severe skin reactions or hypersensitivity reactions must discontinue VIRAMUNE and seek medical evaluation immediately. Transaminase levels should be checked immediately for all patients who develop a rash in the first 18 weeks of treatment. The 14-day lead-in period with VIRAMUNE 200 mg daily dosing has been observed to decrease the incidence of rash and must be followed *[see Warnings and Precautions (5.2)]*.

MONITORING FOR HEPATOTOXICITY AND SKIN REACTIONS:

Patients must be monitored intensively during the first 18 weeks of therapy with VIRAMUNE to detect potentially life-threatening hepatotoxicity or skin reactions. Extra vigilance is warranted during the first 6 weeks of therapy, which is the period of greatest risk of these events. Do not restart VIRAMUNE following clinical hepatitis, or transaminase elevations combined with rash or other systemic symptoms, or following severe skin rash or hypersensitivity reactions. In some cases, hepatic injury has progressed despite discontinuation of treatment.

1 INDICATIONS AND USAGE

VIRAMUNE is indicated in combination with other antiretroviral agents for the treatment of human immunodeficiency virus (HIV-1) infection in adults and pediatric patients 15 days and older *[see Clinical Studies (14.1, 14.2)]*.

Limitations of Use:

Based on serious and life-threatening hepatotoxicity observed in controlled and uncontrolled trials, VIRAMUNE is not recommended to be initiated, unless the benefit outweighs the risk, in:

- adult females with $CD4^+$ cell counts greater than 250 cells/mm^3 or
- adult males with $CD4^+$ cell counts greater than 400 cells/mm^3 *[see Warnings and Precautions (5.1)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Adult Patients

The recommended dose for VIRAMUNE is one 200 mg tablet daily for the first 14 days, followed by one 200 mg tablet twice daily, in combination with other antiretroviral agents. The 14-day lead-in period with VIRAMUNE 200 mg daily dosing must be strictly followed as the lead-in period has been observed to decrease the incidence of rash *[see Dosage and Administration (2.4) and Warnings and Precautions (5.2)]*. If rash persists beyond the 14-day lead-in period, do not dose escalate to 200 mg twice daily. The 200 mg once daily dosing regimen should not be continued beyond 28 days, at which point, an alternative regimen should be sought. For concomitantly administered antiretroviral therapy, the manufacturer's recommended dosage and monitoring should be followed.

2.2 Pediatric Patients

The recommended oral dose for pediatric patients 15 days and older is 150 mg/m^2 once daily for 14 days followed by 150 mg/m^2 twice daily thereafter. The total daily dose should not exceed 400 mg for any patient.

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

Table 1 Calculation of the Volume of VIRAMUNE Oral Suspension (50 mg per 5 mL) Required for Pediatric Dosing Based on Body Surface and a Dose of 150 mg/m^2

BSA range (m^2)	Volume (mL)
0.06 – 0.12	1.25
0.12 – 0.25	2.5
0.25 – 0.42	5
0.42 – 0.58	7.5
0.58 – 0.75	10
0.75 – 0.92	12.5
0.92 – 1.08	15
1.08 – 1.25	17.5
1.25+	20

VIRAMUNE suspension should be shaken gently prior to administration. It is important to administer the entire measured dose of suspension by using 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 water and the rinse should also be administered to the patient.

2.3 Monitoring of Patients

Intensive clinical and laboratory monitoring, including liver enzyme tests, is essential at baseline and during the first 18 weeks of treatment with VIRAMUNE. The optimal frequency of monitoring during this period has not been established. Some experts recommend clinical and laboratory monitoring more often than once per month, and in particular, would include monitoring of liver enzyme 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 VIRAMUNE treatment *[see Warnings and Precautions (5)]*. In some cases, hepatic injury has progressed despite discontinuation of treatment.

2.4 Dosage Adjustment

Patients with Rash

Discontinue VIRAMUNE if a patient experiences severe rash or any rash accompanied by constitutional findings *[see Warnings and Precautions (5.2)]*. Do not increase VIRAMUNE dose if a patient experiences mild to moderate rash without constitutional symptoms during the 14-day lead-in period of 200 mg/day (150 mg/m^2/day in pediatric patients) until the rash has resolved *[see Warnings and Precautions (5.2)]*. The total duration of the once daily lead-in dosing period should not exceed 28 days at which point an alternative regimen should be sought.

Patients with Hepatic Events

If a clinical (symptomatic) hepatic event occurs, permanently discontinue VIRAMUNE. Do not restart VIRAMUNE after recovery *[see Warnings and Precautions (5.1)]*.

Patients with Dose Interruption

For patients who interrupt VIRAMUNE dosing for more than 7 days, restart the recommended dosing, using one 200 mg tablet daily (150 mg/m^2/day in pediatric patients) for the first 14 days (lead-in) followed by one 200 mg tablet twice daily (150 mg/m^2 twice daily for pediatric patients).

Patients with Renal Impairment

Patients with CrCL greater than or equal to 20 mL per min do not require an adjustment in VIRAMUNE dosing. The pharmacokinetics of nevirapine have not been evaluated in patients with CrCL less than 20 mL per min. An additional 200 mg dose of VIRAMUNE following each dialysis treatment is indicated in patients requiring dialysis. Nevirapine metabolites may accumulate in patients receiving dialysis; however, the clinical significance of this accumulation is not known *[see Clinical Pharmacology (12.3)]*.

3 DOSAGE FORMS AND STRENGTHS

Tablets: 200 mg, white, oval, biconvex, tablets embossed with 54 193 on one side
Oral suspension: 50 mg per 5 mL, white to off-white oral suspension

4 CONTRAINDICATIONS

VIRAMUNE is contraindicated:

- in patients with moderate or severe (Child-Pugh Class B or C, respectively) hepatic impairment *[see Warnings and Precautions (5.1) and Use in Specific Populations (8.7)]*.
- for use as part of occupational and non-occupational post-exposure prophylaxis (PEP) regimens *[see Warnings and Precautions (5.1)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Hepatotoxicity and Hepatic Impairment

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 controlled clinical trials, symptomatic hepatic events regardless of severity occurred in 4% (range 0% to 11%) of subjects who received VIRAMUNE and 1% of subjects in control groups.

The risk of symptomatic 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, subjects 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. Rash was observed in approximately half of the subjects with symptomatic hepatic adverse events. Fever and flu-like symptoms accompanied some of these hepatic events. Some events, particularly those with rash and other symptoms, have progressed to hepatic failure with transaminase elevation, with or without hyperbilirubinemia, hepatic encephalopathy, prolonged partial thromboplastin time, or eosinophilia. Rhabdomyolysis has been observed in some patients experiencing skin and/or liver reactions associated with VIRAMUNE use. Hepatitis/hepatic failure may be associated with signs of hypersensitivity which can include severe rash or rash accompanied by fever, general malaise, fatigue, muscle or joint aches, blisters, oral lesions, conjunctivitis, facial edema, eosinophilia, granulocytopenia, lymphadenopathy, or renal dysfunction. Patients with signs or symptoms of hepatitis must be advised to discontinue VIRAMUNE and immediately seek medical evaluation, which should include liver enzyme tests.

The first 18 weeks of therapy with VIRAMUNE are a critical period during which intensive clinical and laboratory monitoring of patients is required to detect potentially life-threatening hepatic events. The optimal frequency of monitoring during this time period has not been established. Some experts recommend clinical and laboratory monitoring more often than once per month, and in particular, include monitoring of liver enzyme 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 VIRAMUNE treatment.

Transaminases should be checked immediately if a patient experiences signs or symptoms suggestive of hepatitis and/or hypersensitivity reaction. Transaminases should also be checked immediately 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 hepatotoxicity should be considered in this setting, even if transaminases are initially normal or alternative diagnoses are possible *[see Dosage and Administration (2.3)]*.

...cal hepatitis or transaminase elevations combined with rash or other systemic symptoms occur, permanently discontinue VIRAMUNE. Do not restart ...INE after recovery. In some cases, hepatic injury progresses despite discontinuation of treatment.

...reatest risk of hepatic events, including potentially fatal events, are women with high CD4$^+$ cell counts. In general, during the first 6 weeks of ...ave a 3-fold higher risk than men for symptomatic, often rash-associated, hepatic events (6% versus 2%), and patients with higher CD4$^+$ cell counts ...INE therapy are at higher risk for symptomatic hepatic events with VIRAMUNE. In a retrospective review, women with CD4$^+$ cell counts ... had a 12-fold higher risk of symptomatic hepatic adverse events compared to women with CD4$^+$ cell counts less than 250 cells/mm^3 (11% ... was observed in men with CD4$^+$ cell counts greater than 400 cells/mm^3 (6% versus 1% for men with CD4$^+$ cell counts less than 400 ... regardless of gender, CD4$^+$ cell count, or antiretroviral treatment history, should be monitored for hepatotoxicity since symptomatic ...orted at all CD4$^+$ cell counts. Co-infection with hepatitis B or C and/or increased transaminase elevations at the start of therapy

...VIRAMUNE. During the initial phase of ...o indolent or residual opportunistic infections ...may necessitate further evaluation and treatment. ...d to occur in the setting of immune reconstitution ...peripheral wasting, facial wasting, brea... long-term consequences of these e...

with VIRAMUNE are associated with a greater risk of later symptomatic events (6 weeks or more after starting VIRAMUNE) and asymptomatic increases in AST or ALT.

In addition, serious hepatotoxicity (including liver failure requiring transplantation in one instance) has been reported in HIV-1 uninfected individuals receiving multiple doses of VIRAMUNE in the setting of post-exposure prophylaxis (PEP), an unapproved use. Use of VIRAMUNE for occupational and non-occupational PEP is contraindicated *[see Contraindications (4)]*.

Increased nevirapine trough concentrations have been observed in some patients with hepatic fibrosis or cirrhosis. Therefore, carefully monitor patients with either hepatic fibrosis or cirrhosis for evidence of drug-induced toxicity. Do not administer nevirapine to patients with moderate or severe (Child-Pugh Class B or C, respectively) hepatic impairment *[see Contraindications (4), Use in Specific Populations (8.7), and Clinical Pharmacology (12.3)]*.

5.2 Skin Reactions

Severe and life-threatening skin reactions, including fatal cases, have been reported, occurring most frequently during the first 6 weeks of therapy. These have included cases of Stevens-Johnson syndrome, toxic epidermal necrolysis, and hypersensitivity reactions characterized by rash, constitutional findings, and organ dysfunction including hepatic failure. Rhabdomyolysis has been observed in some patients experiencing skin and/or liver reactions associated with VIRAMUNE use. In controlled clinical trials, Grade 3 and 4 rashes were reported during the first 6 weeks in 2% of VIRAMUNE recipients compared to less than 1% of placebo subjects.

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 and seek medical evaluation immediately. Do not restart VIRAMUNE following severe skin rash, skin rash combined with increased transaminases or other symptoms, or hypersensitivity reaction.

The first 18 weeks of therapy with VIRAMUNE are a critical period during which intensive clinical and laboratory monitoring of patients is required to detect potentially life-threatening skin reactions. The optimal frequency of monitoring during this time period has not been established. Some experts recommend clinical and laboratory monitoring more often than once per month, and in particular, include monitoring of liver enzyme 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 VIRAMUNE treatment. In addition, the 14-day lead-in period with VIRAMUNE 200 mg daily dosing has been demonstrated to reduce the frequency of rash *[see Dosage and Administration (2.1)]*.

If patients present with a suspected VIRAMUNE-associated rash, measure transaminases immediately. Permanently discontinue VIRAMUNE in patients with rash-associated transaminase elevations *[see Warnings and Precautions (5.1)]*.

Therapy with VIRAMUNE must be initiated with a 14-day lead-in period of 200 mg per day (150 mg/m^2 per day in pediatric patients), which has been shown to reduce the frequency of rash. Discontinue VIRAMUNE if a patient experiences severe rash or any rash accompanied by constitutional findings. Do not increase VIRAMUNE dose to a patient experiencing a mild to moderate rash without constitutional symptoms during the 14-day lead-in period of 200 mg per day (150 mg/m^2/day in pediatric patients) until the rash has resolved. The total duration of the once-daily lead-in dosing period must not exceed 28 days at which point an alternative regimen should be sought *[see Dosage and Administration (2.4)]*. Patients must be monitored closely if isolated rash of any severity occurs. Delay in stopping VIRAMUNE treatment after the onset of rash may result in a more serious reaction.

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

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

5.3 Resistance

VIRAMUNE must not be used as a single agent to treat HIV-1 or added on as a sole agent to a failing regimen. 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 VIRAMUNE, the long half-life of nevirapine should be taken into account; if antiretrovirals with shorter half-lives than VIRAMUNE are stopped concurrently, low plasma concentrations of nevirapine alone may persist for a week or longer and virus resistance may subsequently develop *[see Microbiology (12.4)]*.

5.4 Drug Interactions

See Table 4 for listings of established and potential drug interactions *[see Drug Interactions (7)]*.

Concomitant use of St. John's wort (*Hypericum perforatum*) or St. John's wort-containing products and VIRAMUNE is not recommended. Co-administration of St. John's wort with non-nucleoside reverse transcriptase inhibitors (NNRTIs), including VIRAMUNE, is expected to substantially 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. Co-administration of VIRAMUNE and efavirenz is not recommended as this combination has been associated with an increase in adverse reactions and no improvement in efficacy.

5.5 Immune Reconstitution Syndrome

Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including VIRAMUNE. During the initial phase of combination antiretroviral treatment, patients whose immune system responds may develop an inflammatory response to indolent or residual opportunistic infections (such as *Mycobacterium avium* infection, cytomegalovirus, *Pneumocystis jiroveci* pneumonia, or tuberculosis), which may necessitate further evaluation and treatment.

Autoimmune disorders (such as Graves' disease, polymyositis, and Guillain-Barré syndrome) have also been reported to occur in the setting of immune reconstitution, however, the time to onset is more variable, and can occur many months after initiation of treatment.

5.6 Fat Redistribution

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

6 ADVERSE REACTIONS

6.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Clinical Trial Experience in Adult Patients

The most serious adverse reactions associated with VIRAMUNE are hepatitis, hepatic failure, Stevens-Johnson syndrome, toxic epidermal necrolysis, and hypersensitivity reactions. 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, eosinophilia, granulocytopenia, lymphadenopathy, or renal dysfunction *[see Boxed Warning and Warnings and Precautions (5.1, 5.2)]*.

Hepatic Reaction

In controlled clinical trials, symptomatic hepatic events regardless of severity occurred in 4% (range 0% to 11%) of subjects who received VIRAMUNE and 1% of subjects in control groups. Female gender and higher $CD4^+$ cell counts (greater than 250 cells/mm^3 in women and greater than 400 cells/mm^3 in men) place patients at increased risk of these events *[see Boxed Warning and Warnings and Precautions (5.1)]*.

Asymptomatic transaminase elevations (AST or ALT greater than 5X ULN) were observed in 6% (range 0% to 9%) of subjects who received VIRAMUNE and 6% of subjects in control groups. Co-infection with hepatitis B or C and/or increased transaminase elevations at the start of therapy with VIRAMUNE are associated with a greater risk of later symptomatic events (6 weeks or more after starting VIRAMUNE) and asymptomatic increases in AST or ALT.

Liver enzyme abnormalities (AST, ALT, GGT) were observed more frequently in subjects receiving VIRAMUNE than in controls (see Table 3).

Skin Reaction

The most common clinical toxicity of VIRAMUNE is rash, which can be severe or life-threatening *[see Boxed Warning and Warnings and Precautions (5.2)]*. Rash occurs most frequently within the first 6 weeks of therapy. Rashes are usually mild to moderate, maculopapular erythematous cutaneous eruptions, with or without pruritus, located on the trunk, face and extremities. In controlled clinical trials (Trials 1037, 1038, 1046, and 1090), Grade 1 and 2 rashes were reported in 13% of subjects receiving VIRAMUNE compared to 6% receiving placebo during the first 6 weeks of therapy. Grade 3 and 4 rashes were reported in 2% of VIRAMUNE recipients compared to less than 1% of subjects receiving placebo. Women tend to be at higher risk for development of VIRAMUNE-associated rash *[see Boxed Warning and Warnings and Precautions (5.2)]*.

Treatment-related, adverse experiences of moderate or severe intensity observed in greater than 2% of subjects receiving VIRAMUNE in placebo-controlled trials are shown in Table 2.

Table 2 Percentage of Subjects with Moderate or Severe Drug-Related Events in Adult Placebo-Controlled Trials

	Trial 1090[1]		**Trials 1037, 1038, 1046[2]**	
	VIRAMUNE	**Placebo**	**VIRAMUNE**	**Placebo**
	(n=1121)	**(n=1128)**	**(n=253)**	**(n=203)**
Median exposure (weeks)	58	52	28	28
Any adverse event	15%	11%	32%	13%
Rash	5	2	7	2
Nausea	1	1	9	4
Granulocytopenia	2	3	<1	0
Headache	1	<1	4	1
Fatigue	<1	<1	5	4
Diarrhea	<1	1	2	1
Abdominal pain	<1	<1	2	0
Myalgia	<1	0	1	2

[1] Background therapy included 3TC for all subjects and combinations of NRTIs and PIs. Subjects had $CD4^+$ cell counts less than 200 cells/mm^3.

[2] Background therapy included ZDV and ZDV+ddI; VIRAMUNE monotherapy was administered in some subjects. Subjects had $CD4^+$ cell count greater than or equal to 200 cells/mm^3.

Laboratory Abnormalities

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

Table 3 Percentage of Adult Subjects with Laboratory Abnormalities

	Trial 1090[1]		Trials 1037, 1038, 1046[2]	
	VIRAMUNE	Placebo	VIRAMUNE	Placebo
Laboratory Abnormality	**(n=1121)**	**(n=1128)**	**(n=253)**	**(n=203)**
Blood Chemistry				
SGPT (ALT) >250 U/L	5	4	14	4
SGOT (AST) >250 U/L	4	3	8	2
Bilirubin >2.5 mg/dL	2	2	2	2
Hematology				
Hemoglobin <8.0 g/dL	3	4	0	0
Platelets <50,000/mm^3	1	1	<1	2
Neutrophils <750/mm^3	13	14	4	1

[1] Background therapy included 3TC for all subjects and combinations of NRTIs and PIs. Subjects had CD4$^+$ cell counts less than 200 cells/mm^3.
[2] Background therapy included ZDV and ZDV+ddI; VIRAMUNE monotherapy was administered in some subjects. Subjects had CD4$^+$ cell count greater than or equal to 200 cells/mm^3.

Clinical Trial Experience in Pediatric Patients

Adverse events were assessed in BI Trial 1100.1032 (ACTG 245), a double-blind, placebo-controlled trial of VIRAMUNE (n=305) in which pediatric subjects received combination treatment with VIRAMUNE. In this trial two subjects were reported to experience Stevens-Johnson syndrome or Stevens-Johnson/toxic epidermal necrolysis transition syndrome. Safety was also assessed in trial BI 1100.882 (ACTG 180), an open-label trial of VIRAMUNE (n=37) in which subjects 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 subjects in trial BI 1100.892). The most frequently reported adverse events related to VIRAMUNE in pediatric subjects were similar to those observed in adults, with the exception of granulocytopenia, which was more commonly observed in children receiving both zidovudine and VIRAMUNE. Cases of allergic reaction, including one case of anaphylaxis, were also reported.

The safety of VIRAMUNE was also examined in BI Trial 1100.1368, an open-label, randomized clinical trial performed in South Africa in which 123 HIV-1 infected treatment-naïve subjects between 3 months and 16 years of age received combination treatment with VIRAMUNE oral suspension, lamivudine and zidovudine for 48 weeks *[see Use In Specific Populations (8.4) and Clinical Pharmacology (12.3)]*. Rash (all causality) was reported in 21% of the subjects, 4 (3%) of whom discontinued drug due to rash. All 4 subjects experienced the rash early in the course of therapy (less than 4 weeks) and resolved upon nevirapine discontinuation. Other clinically important adverse events (all causality) include neutropenia (9%), anemia (7%), and hepatotoxicity (2%) *[see Use in Specific Populations (8.4) and Clinical Studies (14.2)]*.

Safety information on use of VIRAMUNE in combination therapy in pediatric subjects 2 weeks to less than 3 months of age was assessed in 36 subjects from the BI 1100.1222 (PACTG 356) trial. No unexpected safety findings were observed although granulocytopenia was reported more frequently in this age group compared to the older pediatric age groups and adults.

6.2 Post-Marketing Experience

In addition to the adverse events identified during clinical trials, the following adverse reactions have been identified during post-approval use of VIRAMUNE. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Body as a Whole: fever, somnolence, drug withdrawal *[see Drug Interactions (7)]*, redistribution/accumulation of body fat *[see Warnings and Precautions (5.6)]*
Gastrointestinal: vomiting
Liver and Biliary: jaundice, fulminant and cholestatic hepatitis, hepatic necrosis, hepatic failure
Hematology: anemia, eosinophilia, neutropenia
Investigations: decreased serum phosphorus
Musculoskeletal: arthralgia, rhabdomyolysis associated with skin and/or liver reactions
Neurologic: paraesthesia
Skin and Appendages: allergic reactions including anaphylaxis, angioedema, bullous eruptions, ulcerative stomatitis and urticaria have all been reported. In addition, hypersensitivity syndrome and hypersensitivity reactions with rash associated with constitutional findings such as fever, blistering, oral lesions, conjunctivitis, facial edema, muscle or joint aches, general malaise, fatigue, or significant hepatic abnormalities, drug reaction with eosinophilia and systemic symptoms (DRESS) *[see Warnings and Precautions (5.1)]* plus one or more of the following: hepatitis, eosinophilia, granulocytopenia, lymphadenopathy, and/or renal dysfunction have been reported.

In post-marketing surveillance anemia has been more commonly observed in children although development of anemia due to concomitant medication use cannot be ruled out.

7 DRUG INTERACTIONS

Nevirapine is principally metabolized by the liver via the cytochrome P450 isoenzymes, 3A and 2B6. Nevirapine is known to be an inducer of these enzymes. As a result, drugs that are metabolized by these enzyme systems may have lower than expected plasma levels when co-administered with nevirapine.

The specific pharmacokinetic changes that occur with co-administration of nevirapine and other drugs are listed in *Clinical Pharmacology*, Table 5. Clinical c about possible dosage modifications based on established drug interactions are listed in Table 4. The data in Tables 4 and 5 are based on the results of drug trials conducted in HIV-1 seropositive subjects unless otherwise indicated. In addition to established drug interactions, there may be potential pharmacc interactions between nevirapine and other drug classes that are metabolized by the cytochrome P450 system. These potential drug interactions are a Although specific drug interaction trials in HIV-1 seropositive subjects have not been conducted for some classes of drugs listed in Table 4, addi monitoring may be warranted when co-administering these drugs.

Laboratory Abnormalities
Liver enzyme test abnormalities
GGT occur frequently but are not a contraindicatio abnormalities (bilirubin, anemia, neutropenia, thron (see Table 3).

The *in vitro* interaction between nevirapine and the antithrombotic agent warfarin is complex. As a result, when giving these drugs concomitantly, plasma warfarin levels may change with the potential for increases in coagulation time. When warfarin is co-administered with nevirapine, anticoagulation levels should be monitored frequently.

Table 4 Established and Potential Drug Interactions: Use With Caution, Alteration in Dose or Regimen May Be Needed Due to Drug Interaction
Established Drug Interactions: See Clinical Pharmacology (12.3), Table 5 for Magnitude of Interaction.

Drug Name	Effect on Concentration of Nevirapine or Concomitant Drug	Clinical Comment
HIV Antiviral Agents: Protease Inhibitors (PIs)		
Atazanavir/Ritonavir*	↓ Atazanavir ↑ Nevirapine	Do not co-administer nevirapine with atazanavir because nevirapine substantially decreases atazanavir exposure and there is a potential risk for nevirapine-associated toxicity due to increased nevirapine exposures.
Fosamprenavir*	↓Amprenavir ↑Nevirapine	Co-administration of nevirapine and fosamprenavir without ritonavir is not recommended.
Fosamprenavir/Ritonavir*	↓Amprenavir ↑Nevirapine	No dosing adjustments are required when nevirapine is co-administered with 700/100 mg of fosamprenavir/ritonavir twice daily. The combination of nevirapine administered with fosamprenavir/ritonavir once daily has not been studied.
Indinavir*	↓ Indinavir	The appropriate doses of this combination of indinavir and nevirapine with respect to efficacy and safety have not been established.
Lopinavir/Ritonavir*	↓Lopinavir	Dosing in adult patients: A dose adjustment of lopinavir/ritonavir to 500/125 mg tablets twice daily or 533/133 mg (6.5 mL) oral solution twice daily is recommended when used in combination with nevirapine. Neither lopinavir/ritonavir tablets nor oral solution should be administered once daily in combination with nevirapine. Dosing in pediatric patients: Please refer to the Kaletra® prescribing information for dosing recommendations based on body surface area and body weight. Neither lopinavir/ritonavir tablets nor oral solution should be administered once daily in combination with nevirapine.
Nelfinavir*	↓Nelfinavir M8 Metabolite ↓Nelfinavir C_{min}	The appropriate doses of the combination of nevirapine and nelfinavir with respect to safety and efficacy have not been established.
Saquinavir/ritonavir	The interaction between nevirapine and saquinavir/ritonavir has not been evaluated	The appropriate doses of the combination of nevirapine and saquinavir/ritonavir with respect to safety and efficacy have not been established.
HIV Antiviral Agents: Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)		
Efavirenz*	↓ Efavirenz	The appropriate doses of these combinations with respect to safety and efficacy have not been established.
Delavirdine Etravirine Rilpivirine		Plasma concentrations may be altered. Nevirapine should not be coadministered with another NNRTI as this combination has not been shown to be beneficial.
Hepatitis C Antiviral Agents		
Boceprevir	Plasma concentrations of boceprevir may be decreased due to induction of CYP3A4/5 by nevirapine.	Nevirapine and boceprevir should not be coadministered because decreases in boceprevir plasma concentrations may result in a reduction in efficacy.
	Plasma concentrations of telaprevir may be decreased due to induction of CYP3A4 by nevirapine and plasma concentrations of nevirapine may be increased due to inhibition of CYP3A4 by telaprevir.	Nevirapine and telaprevir should not be coadministered because changes in plasma concentrations of nevirapine, telaprevir, or both may result in a reduction in telaprevir efficacy or an increase in nevirapine-associated adverse events.
	↓ Methadone	Methadone levels were decreased; increased

Methadone*		dosages may be required to prevent symptoms of opiate withdrawal. Methadone-maintained patients beginning nevirapine therapy should be monitored for evidence of withdrawal and methadone dose should be adjusted accordingly.
Antiarrhythmics: Amiodarone, disopyramide, lidocaine	Plasma concentrations may be decreased.	Appropriate doses for this combination have not been established.
Antibiotics: Clarithromycin*	↓ Clarithromycin ↑ 14-OH clarithromycin	Clarithromycin exposure was significantly decreased by nevirapine; however, 14-OH metabolite concentrations were increased. Because clarithromycin active metabolite has reduced activity against *Mycobacterium avium-intracellulare complex*, overall activity against this pathogen may be altered. Alternatives to clarithromycin, such as azithromycin, should be considered.
Rifabutin*	↑Rifabutin	Rifabutin and its metabolite concentrations were moderately increased. Due to high intersubject variability, however, 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.
Rifampin*	↓ Nevirapine	Nevirapine and rifampin should not be administered concomitantly because decreases in nevirapine plasma concentrations may reduce the efficacy of the drug. Physicians needing to treat patients co-infected with tuberculosis and using a nevirapine-containing regimen may use rifabutin instead.
Anticonvulsants: Carbamazepine, clonazepam, ethosuximide	Plasma concentrations of nevirapine and the anticonvulsant may be decreased.	Use with caution and monitor virologic response and levels of anticonvulsants.
Antifungals: Fluconazole*	↑Nevirapine	Because of the risk of increased exposure to nevirapine, caution should be used in concomitant administration, and patients should be monitored closely for nevirapine-associated adverse events.
Ketoconazole*	↓ Ketoconazole	Nevirapine and ketoconazole should not be administered concomitantly because decreases in ketoconazole plasma concentrations may reduce the efficacy of the drug.
Itraconazole	↓ Itraconazole	Nevirapine and itraconazole should not be administered concomitantly due to potential decreases in itraconazole plasma concentrations that may reduce efficacy of the drug.
Antithrombotics: Warfarin	Plasma concentrations may be increased.	Potential effect on anticoagulation. Monitoring of anticoagulation levels is recommended.
Calcium channel blockers: Diltiazem, nifedipine, verapamil	Plasma concentrations may be decreased.	Appropriate doses for these combinations have not been established.
Cancer chemotherapy: Cyclophosphamide	Plasma concentrations may be decreased.	Appropriate doses for this combination have not been established.
Ergot alkaloids: Ergotamine	Plasma concentrations may be decreased.	Appropriate doses for this combination have not been established.
Immunosuppressants: Cyclosporine, tacrolimus, sirolimus	Plasma concentrations may be decreased.	Appropriate doses for these combinations have not been established.
Motility agents: Cisapride	Plasma concentrations may be decreased.	Appropriate doses for this combination have been established.
Opiate agonists:		

Fentanyl	Plasma concentrations may be decreased.	Appropriate doses for this combination have not been established.
Oral contraceptives:		
Ethinyl estradiol and Norethindrone*	↓ Ethinyl estradiol ↓ Norethindrone	Despite lower ethinyl estradiol and norethindrone exposures when coadministered with nevirapine, literature reports suggest that nevirapine has no effect on pregnancy rates among HIV-infected women on combined oral contraceptives. When coadministered with VIRAMUNE, no dose adjustment of ethinyl estradiol or norethindrone is needed when used in combination for contraception. When these oral contraceptives are used for hormonal regulation during VIRAMUNE therapy, the therapeutic effect of the hormonal therapy should be monitored.

* The interaction between VIRAMUNE and the drug was evaluated in a clinical study. All other drug interactions shown are predicted.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to nevirapine during pregnancy. Healthcare providers are encouraged to register patients by calling the Antiretroviral Pregnancy Registry (APR) at 1-800-258-4263.

Risk Summary

Available data from the APR show no difference in the risk of overall major birth defects for nevirapine compared with the background rate for major birth defects of 2.7% in the U.S. reference population of the Metropolitan Atlanta Congenital Defects Program (MACDP) *[see Data]*. The rate of miscarriage is not reported in the APR. The estimated background rate of miscarriage in clinically recognized pregnancies in the U.S. general population is 15-20%. The background risk of birth defects and miscarriage for the indicated population is unknown. Methodological limitations of the APR include the use of MACDP as the external comparator group. The MACDP population is not disease-specific, evaluates women and infants from a limited geographic area, and does not include outcomes for births that occurred at <20 weeks gestation.

In literature reports, immediate-release nevirapine exposure (C_{min}) can be up to 29% lower during pregnancy. However, as this reduction was not found to be clinically meaningful, dose adjustment is not necessary *[see Data]*.

There is a risk for severe hepatic events in pregnant women exposed to VIRAMUNE *[see Clinical Considerations]*. In animal reproduction studies, no evidence of adverse developmental outcomes were observed following oral administration of nevirapine during organogenesis in the rat and rabbit, at systemic exposures (AUC) to nevirapine approximately equal (rats) and 50% higher (rabbits) than the exposure in humans at the recommended 400 mg daily dose *[see Data]*.

Clinical Considerations

Maternal adverse reactions

Severe hepatic events, including fatalities, have been reported in pregnant women receiving chronic VIRAMUNE therapy as part of combination treatment of HIV-1 infection. Regardless of pregnancy status, women with $CD4^+$ cell counts greater than 250 cells/mm^3 should not initiate VIRAMUNE unless the benefit outweighs the risk. It is unclear if pregnancy augments the risk observed in non-pregnant women *[see Warnings and Precautions (5.1)]*.

Data

Human Data

Based on prospective reports to the APR of over 2600 exposures to nevirapine during pregnancy resulting in live births (including over 1100 exposed in the first trimester), there was no difference between nevirapine and overall birth defects compared with the background birth defect rate of 2.7% in the U.S. reference population of the MACDP. The prevalence of birth defects in live births was 2.8% (95% CI: 1.9 %, 4.0%) following first trimester exposure to nevirapine- containing regimens and 3.2% (95% CI: 2.4%, 4.3%) for second/third trimester exposure to nevirapine-containing regimens.

There are several literature reports of chronic administration of immediate-release nevirapine during pregnancy, in which nevirapine pharmacokinetics were compared between pregnancy and postpartum. In these studies, the mean difference in nevirapine C_{min} during pregnancy as compared to postpartum ranged from no difference to approximately 29% lower.

Animal Data

Nevirapine was administered orally to pregnant rats (at 0, 12.5, 25 and 50 mg per kg per day) and rabbits (at 0, 30, 100, and 300 mg per kg per day) through organogenesis (on gestation days 7 through 16, and 6 through 18, respectively). No adverse developmental effects were observed at doses producing systemic exposures (AUC) approximately equivalent to (rats) or approximately 50% higher (rabbits) than human exposure at the recommended daily dose. In rats, decreased fetal body weights were observed at a maternally toxic dose at an exposure approximately 50% higher than the recommended daily dose.

8.2 Lactation

Summary

...ers for Disease Control and Prevention recommend that HIV-1 infected mothers in the United States not breastfeed their infants to avoid risking postnatal ...of HIV-1 infection. Published data report that nevirapine is present in human milk *[see Data]*. There are limited data on the effects of nevirapine on the ... There is no information on the effects of nevirapine on milk production. Because of the potential for (1) HIV-1 transmission (in HIV-negative infants), ...esistance (in HIV-positive infants), and (3) serious adverse reactions in nursing infants, mothers should not breastfeed if they are receiving

...iate-release nevirapine was excreted in breast-milk at median concentrations ranging from 4080 to 6795 ng/mL, and the median ...a concentration ratio range was 59 to 88%. Reported infant nevirapine median plasma concentrations were low, ranging from

...hts microcrystalline cellulose, lactose ... of nevirapine (as nevirapine hemihydrate). The ...se, polysorbate 80, sodium hydroxide and purified ...ts with HIV-1 infection. A ... for an oral solution ...% ...

734 to 1140 ng/mL. The estimated nevirapine dose of 704 to 682 µg/kg/day for infants fed exclusively with breast-milk was lower than the daily recommended nevirapine dose for infants. Published literature indicates that rash and hyperbilirubinemia have been seen in infants exposed to nevirapine through breastmilk.

8.3 Females and Males of Reproductive Potential

Infertility

Limited human data are insufficient to determine the risk of infertility in humans. Based on results from animal fertility studies conducted in rats, VIRAMUNE may reduce fertility in females of reproductive potential. It is not known if these effects on fertility are reversible *[see Nonclinical Toxicology (13.1)]*.

8.4 Pediatric Use

The safety, pharmacokinetic profile, and virologic and immunologic responses of VIRAMUNE have been evaluated in HIV-1 infected pediatric subjects age 3 months to 18 years *[see Adverse Reactions (6.2) and Clinical Studies (14.2)]*. The safety and pharmacokinetic profile of VIRAMUNE has been evaluated in HIV-1 infected pediatric subjects age 15 days to less than 3 months *[see Adverse Reactions (6.2) and Clinical Studies (14.2)]*.

The most frequently reported adverse events related to VIRAMUNE in pediatric subjects were similar to those observed in adults, with the exception of granulocytopenia, which was more commonly observed in children receiving both zidovudine and VIRAMUNE *[see Adverse Reactions (6.2) and Clinical Studies (14.2)]*.

8.5 Geriatric Use

Clinical trials of VIRAMUNE 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.

8.6 Renal Impairment

In subjects with renal impairment (mild, moderate or severe), there were no significant changes in the pharmacokinetics of nevirapine. Nevirapine is extensively metabolized by the liver and nevirapine metabolites are extensively eliminated by the kidney. Nevirapine metabolites may accumulate in patients receiving dialysis; however, the clinical significance of this accumulation is not known. No adjustment in nevirapine dosing is required in patients with CrCL greater than or equal to 20 mL per min. The pharmacokinetics of nevirapine have not been evaluated in patients with CrCl less than 20 mL per min. In patients undergoing chronic hemodialysis, an additional 200 mg dose following each dialysis treatment is indicated *[see Dosage and Administration (2.4) and Clinical Pharmacology (12.3)]*.

8.7 Hepatic Impairment

Because increased nevirapine levels and nevirapine accumulation may be observed in patients with serious liver disease, do not administer VIRAMUNE to patients with moderate or severe (Child-Pugh Class B or C, respectively) hepatic impairment *[see Contraindications (4.1), Warnings and Precautions (5.1), and Clinical Pharmacology (12.3)]*.

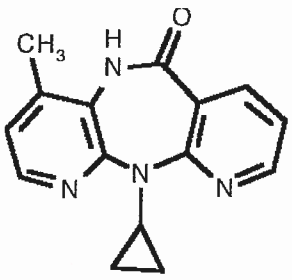
10 OVERDOSAGE

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.

11 DESCRIPTION

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

The chemical name of nevirapine is 11-cyclopropyl-5,11-dihydro-4-methyl-6H-dipyrido [3,2-b:2',3'-e][1,4] diazepin-6-one. Nevirapine is a white to off-white crystalline powder with the molecular weight of 266.30 and the molecular formula $C_{15}H_{14}N_4O$. Nevirapine has the following structural formula:



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 purified water.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Nevirapine is an antiretroviral drug *[see Microbiology (12.4)]*.

12.3 Pharmacokinetics

Adults

Absorption and Bioavailability

Nevirapine is readily absorbed (greater than 90%) after oral administration in healthy volunteers and in adults with HIV-1 infection. A[illegible] healthy adults following single-dose administration was 93 ± 9% (mean ± SD) for a 50 mg tablet and 91 ± 8% for an oral solution [illegible]

[illegible]late-release nevirapine [illegible]a concentration rati[illegible]

8.2 Lactation

Risk Summary

[illegible]nters for Disease Control and Prevention rec[illegible]n of HIV-1 infection. Published data repo[illegible]. There is no information on the effect[illegible]l resistance (in HIV-positive infants[illegible]

[illegible]nevirapine was administered orally to pregna[illegible]organogenesis (on gestation days 7 through 16, [illegible]exposures (AUC) approximately equivalent to ([illegible]body weights were observed at a maternally toxi[illegible]

concentrations of 2 ± 0.4 mcg/mL (7.5 micromolar) 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 mcg/mL (17 ± 7 micromolar), (n=242) were attained at 400 mg per 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 trial in HIV-1 infected subjects (n=6), nevirapine steady-state systemic exposure (AUC_τ) was not significantly altered by didanosine, which is formulated with an alkaline buffering agent. VIRAMUNE may be administered with or without food, antacid or didanosine.

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 also found in breast milk *[see Use in Specific Populations (8.2)]*. Nevirapine is about 60% bound to plasma proteins in the plasma concentration range of 1-10 mcg per 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 trials 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 (CYP) isozymes from the CYP3A and CYP2B6 families, although other isozymes may have a secondary role. In a mass balance/excretion trial 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 (less than 5%) of the radioactivity in urine (representing less than 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 is an inducer of hepatic cytochrome P450 (CYP) metabolic enzymes 3A and 2B6. Nevirapine induces CYP3A and CYP2B6 by approximately 20-25%, as indicated by erythromycin breath test results and urine metabolites. Autoinduction of CYP3A 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 per 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 per day.

Specific Populations

Renal Impairment

HIV-1 seronegative adults with mild (CrCL 50-79 mL per min; n=7), moderate (CrCL 30-49 mL per min; n=6), or severe (CrCL less than 30 mL per min; n=4) renal impairment received a single 200 mg dose of nevirapine in a pharmacokinetic trial. These subjects did not require dialysis. The trial included six additional subjects with renal failure requiring dialysis.

In subjects with renal impairment (mild, moderate or severe), there were no significant changes in the pharmacokinetics of nevirapine. However, subjects requiring dialysis exhibited a 44% reduction in nevirapine AUC over a one-week exposure period. There was also evidence of accumulation of nevirapine hydroxy-metabolites in plasma in subjects requiring dialysis. An additional 200 mg dose following each dialysis treatment is indicated *[see Dosage and Administration (2.4) and Use in Specific Populations (8.6)]*.

Hepatic Impairment

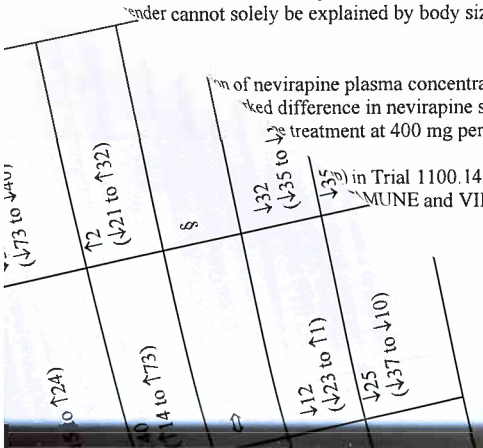
In a steady-state trial comparing 46 subjects with mild (n=17; expansion of some portal areas; Ishak Score 1-2), moderate (n=20; expansion of most portal areas with occasional portal-to-portal and portal-to-central bridging; Ishak Score 3-4), or severe (n=9; marked bridging with occasional cirrhosis without decompensation indicating Child-Pugh A; Ishak Score 5-6) fibrosis as a measure of hepatic impairment, the multiple dose pharmacokinetic disposition of nevirapine and its five oxidative metabolites were not altered. However, approximately 15% of these subjects with hepatic fibrosis had nevirapine trough concentrations above 9,000 mcg per mL (2-fold the usual mean trough). Therefore, patients with hepatic impairment should be monitored carefully for evidence of drug-induced toxicity *[see Warnings and Precautions (5.1)]*. The subjects studied were receiving antiretroviral therapy containing VIRAMUNE 200 mg twice daily for at least 6 weeks prior to pharmacokinetic sampling, with a median duration of therapy of 3.4 years.

In a pharmacokinetic trial where HIV-1 negative cirrhotic subjects with mild (Child-Pugh A; n=6) or moderate (Child-Pugh B; n=4) hepatic impairment received a single 200 mg dose of nevirapine, a significant increase in the AUC of nevirapine was observed in one subject with Child-Pugh B and ascites suggesting that patients with worsening hepatic function and ascites may be at risk of accumulating nevirapine in the systemic circulation. Because nevirapine induces its own metabolism with multiple dosing, this single-dose trial may not reflect the impact of hepatic impairment on multiple-dose pharmacokinetics.

Do not administer nevirapine to patients with moderate or severe (Child-Pugh Class B or C, respectively) hepatic impairment *[see Contraindications (4), Warnings and Precautions (5.1), and Use in Specific Populations (8.7)]*.

Gender

In the multinational 2NN trial, a population pharmacokinetic substudy of 1077 subjects was performed that included 391 females. Female subjects showed a 13.8% lower clearance of nevirapine than did men. Since neither body weight nor Body Mass Index (BMI) had an influence on the clearance of nevirapine, the effect of gender cannot solely be explained by body size.



...m of nevirapine plasma concentrations (pooled data from several clinical trials) from HIV-1-infected subjects (27 Black, 24 Hispanic, 189 Caucasian) ...ked difference in nevirapine steady-state trough concentrations (median C_{minss} = 4.7 mcg/mL Black, 3.8 mcg/mL Hispanic, 4.3 mcg/mL Caucasian) with ... treatment at 400 mg per day. However, the pharmacokinetics of nevirapine have not been evaluated specifically for the effects of ethnicity.

...) in Trial 1100.1486 showed approximately 30% to 35% higher trough concentrations than Caucasian subjects (250-325 subjects/group) in ...MUNE and VIRAMUNE XR treatment groups over 96 weeks of treatment at 400 mg per day.

Geriatric Subjects
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 subjects beyond the age of 55 years *[see Use in Specific Populations (8.5)]*.

Pediatric Subjects
Pharmacokinetic data for nevirapine have been derived from two sources: a 48-week pediatric trial in South Africa (BI Trial 1100.1368) involving 123 HIV-1 positive, antiretroviral-naïve subjects aged 3 months to 16 years; and a consolidated analysis of five Pediatric AIDS Clinical Trials Group (PACTG) protocols comprising 495 subjects aged 14 days to 19 years.

BI Trial 1100.1368 studied the safety, efficacy, and pharmacokinetics of a weight-based and a body surface area (BSA)-based dosing regimen of nevirapine. In the weight-based regimen, pediatric subjects up to 8 years of age received a dose of 4 mg/kg once daily for two weeks followed by 7 mg per kg twice daily thereafter. Subjects 8 years and older were dosed 4 mg/kg once daily for two weeks followed by 4 mg/kg twice daily thereafter. In the BSA regimen, all pediatric subjects received 150 mg/m^2 once daily for two weeks followed by 150 mg/m^2 twice daily thereafter *[see Use in Specific Populations (8.4) and Adverse Reactions (6.2)]*. Dosing of nevirapine at 150 mg/m^2 BID (after a two-week lead-in of 150 mg/m^2 QD) produced geometric mean or mean trough nevirapine concentrations between 4-6 mcg per mL (as targeted from adult data). In addition, the observed trough nevirapine concentrations were comparable between the two dosing regimens studied (BSA- and weight-based methods).

The consolidated analysis of Pediatric AIDS Clinical Trials Group (PACTG) protocols 245, 356, 366, 377, and 403 allowed for the evaluation of pediatric subjects less than 3 months of age (n=17). The plasma nevirapine concentrations observed were within the range observed in adults and the remainder of the pediatric population, but were more variable between subjects, particularly in the second month of age. For dose recommendations for pediatric patients *[see Dosage and Administration (2.2)]*.

Drug Interactions [see Drug Interactions (7)]
Nevirapine induces hepatic cytochrome P450 metabolic isoenzymes 3A and 2B6. Co-administration of VIRAMUNE and drugs primarily metabolized by CYP3A or CYP2B6 may result in decreased plasma concentrations of these drugs and attenuate their therapeutic effects.

While primarily an inducer of cytochrome P450 3A and 2B6 enzymes, nevirapine may also inhibit this system. Among human hepatic cytochrome P450s, nevirapine was capable *in vitro* of inhibiting the 10-hydroxylation of (R)-warfarin (CYP3A). The estimated K_i for the inhibition of CYP3A was 270 micromolar, a concentration that is unlikely to be achieved in patients as the therapeutic range is less than 25 micromolar. Therefore, nevirapine may have minimal inhibitory effect on other substrates of CYP3A.

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 5 (see below) contains the results of drug interaction trials performed with VIRAMUNE and other drugs likely to be co-administered. The effects of VIRAMUNE on the AUC, C_{max}, and C_{min} of co-administered drugs are summarized.

Table 5 Drug Interactions: Changes in Pharmacokinetic Parameters for Co-administered Drug in the Presence of VIRAMUNE (All interaction trials were conducted in HIV-1 positive subjects)

Co-administered Drug	Dose of Co-administered Drug	Dose Regimen of VIRAMUNE	n	% Change of Co-administered Drug Pharmacokinetic Parameters (90% CI)		
Antiretrovirals				**AUC**	**C_{max}**	**C_{min}**
Atazanavir/Ritonavir[a, d]	300/100 mg QD day 4–13, then 400/100 mg QD, day 14–23	200 mg BID day 1-23. Subjects were treated with nevirapine prior to trial entry.	23	Atazanavir 300/100 mg ↓42 (↓52 to ↓29)	Atazanavir 300/100 mg ↓28 (↓40 to ↓14)	Atazanavir 300/100 mg ↓72 (↓80 to ↓60)
				Atazanavir 400/100 mg ↓19 (↓35 to ↑2)	Atazanavir 400/100 mg ↑2 (↓15 to ↑24)	Atazanavir 400/100 mg ↓59 (↓73 to ↓40)
Darunavir/Ritonavir[e]	400/100 mg BID	200 mg BID	8	↑24 (↓3 to ↑57)	↑40 (↑14 to ↑73)	↑2 (↓21 to ↑32)
Didanosine	100-150 mg BID	200 mg QD x 14 days; 200 mg BID x 14 days	18	⇔	⇔	§
Efavirenz[a]	600 mg QD	200 mg QD x 14 days; 400 mg QD x 14 days	17	↓28 (↓34 to ↓14)	↓12 (↓23 to ↑1)	↓32 (↓35 to ↓19)
Fosamprenavir	1400 mg BID	200 mg BID. Subjects were treated with nevirapine prior to trial entry.	17	↓33 (↓45 to ↓20)	↓25 (↓37 to ↓10)	↓35 (↓ to ↓)

...ion of nevirapine plasma concentrations (p... ...arked difference in nevirapine treatment at 400 mg per day. How... ...ine steady-sta... ...AMUNE and VIRAMUNE ... ...in Trial 1100.1486 showed ...

Gender
In the multinational 2NN trial, a population pharm... lower clearance of nevirapine than did men. Since... gender cannot solely be explained by body size.

...ations (5.1), and Use in Specific Popula... ...ver nevirapine to patients with ... ...ild may n...

Fosamprenavir/Ritonavir	700/100 mg BID	200 mg BID. Subjects were treated with nevirapine prior to trial entry	17	↓11 (↓23 to ↑3)	⇔	↓19 (↓32 to ↓4)
Indinavir[a]	800 mg q8H	200 mg QD x 14 days; 200 mg BID x 14 days	19	↓31 (↓39 to ↓22)	↓15 (↓24 to ↓4)	↓44 (↓53 to ↓33)
Lopinavir[a, b]	300/75 mg/m^2 (lopinavir/ ritonavir)[b]	7 mg/kg or 4 mg/kg QD x 2 weeks; BID x 1 week	12, 15[c]	↓22 (↓44 to ↑9)	↓14 (↓36 to ↑16)	↓55 (↓75 to ↓19)
Lopinavir[a]	400/100 mg BID (lopinavir/ ritonavir)	200 mg QD x 14 days; 200 mg BID >1 year	22, 19[c]	↓27 (↓47 to ↓2)	↓19 (↓38 to ↑5)	↓51 (↓72 to ↓26)
Maraviroc[f]	300 mg SD	200 mg BID	8	↑1 (↓35 to ↑55)	↑54 (↓6 to ↑151)	⇔
Nelfinavir[a]	750 mg TID	200 mg QD x 14 days; 200 mg BID x 14 days	23	⇔	⇔	↓32 (↓50 to ↑5)
Nelfinavir-M8 metabolite				↓62 (↓70 to ↓53)	↓59 (↓68 to ↓48)	↓66 (↓74 to ↓55)
Ritonavir	600 mg BID	200 mg QD x 14 days; 200 mg BID x 14 days	18	⇔	⇔	⇔
Stavudine	30-40 mg BID	200 mg QD x 14 days; 200 mg BID x 14 days	22	⇔	⇔	§
Zalcitabine	0.125-0.25 mg TID	200 mg QD x 14 days; 200 mg BID x 14 days	6	⇔	⇔	§
Zidovudine	100-200 mg TID	200 mg QD x 14 days; 200 mg BID x 14 days	11	↓28 (↓40 to ↓4)	↓30 (↓51 to ↑14)	§
Other Medications				**AUC**	**C_{max}**	**C_{min}**
Clarithromycin[a]	500 mg BID	200 mg QD x 14 days; 200 mg BID x 14 days	15	↓31 (↓38 to ↓24)	↓23 (↓31 to ↓14)	↓56 (↓70 to ↓36)
Metabolite 14-OH-clarithromycin				↑42 (↑16 to ↑73)	↑47 (↑21 to ↑80)	⇔
Ethinyl estradiol[a] and Norethindrone[a]	0.035 mg (as Ortho-Novum® 1/35) 1 mg (as Ortho-Novum® 1/35)	200 mg QD x 14 days; 200 mg BID x 14 days	10	↓20 (↓33 to ↓3)	⇔	§
				↓19 (↓30 to ↓7)	↓16 (↓27 to ↓3)	§
Depomedroxy-progesterone acetate	150 mg every 3 months	200 mg QD x 14 days; 200 mg BID x 14 days	32	⇔	⇔	⇔
Fluconazole	200 mg QD	200 mg QD x 14 days; 200 mg BID x 14 days	19	⇔	⇔	⇔
[illegible]conazole[a]	400 mg QD	200 mg QD x 14 days; 200 mg BID x 14 days	21	↓72 (↓80 to ↓60)	↓44 (↓58 to ↓27)	§
	Individual Subject Dosing	200 mg QD x 14 days; 200 mg BID ≥7 days	9	In a controlled pharmacokinetic trial with 9 subjects receiving chronic methadone to whom steady-state nevirapine therapy was added, the clearance of methadone was increased by 3-fold, resulting in symptoms of withdrawal, requiring dose adjustments in 10 mg segments, in 7 of the 9 subjects. Methadone did not have any effect on nevirapine clearance.		

[illegible] 100% of the [illegible]
[illegible]d had one or more of the
[illegible] of dose.
[illegible]e once daily (n=25) or twice daily (n=46) in
respectively, contained one or more of the
A98G, F227L, and M230L.
[illegible]no experienced virologic failure in the on-therapy isol
[illegible]d substitutions developed in the immediate-release
[illegible] of the subjects in the immediate nevirapir
[illegible]one or in combination with other nevirapir
[illegible] F227L, M230L) in isolates from 14 s
[illegible] from 1 subject in VIRAMUNE XR
[illegible]AMUNE treatment group develor
[illegible]-fold reductions in susceptibil

Rifabutin[a]	150 or 300 mg QD	200 mg QD x 14 days; 200 mg BID x 14 days	19	↑17 (↓2 to ↑40)	↑28 (↑9 to ↑51)	⇔
Metabolite 25-O-desacetyl-rifabutin				↑24 (↓16 to ↑84)	↑29 (↓2 to ↑68)	↑22 (↓14 to ↑74)
Rifampin[a]	600 mg QD	200 mg QD x 14 days; 200 mg BID x 14 days	14	↑11 (↓4 to ↑28)	⇔	§

§ = C_{min} below detectable level of the assay
↑ = Increase, ↓ = Decrease, ⇔ = No Effect
[a] For information regarding clinical recommendations, see *Drug Interactions (7)*.
[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] Parallel group design; n=23 for atazanavir/ritonavir + nevirapine, n=22 for atazanavir/ritonavir without nevirapine. Changes in atazanavir PK are relative to atazanavir/ritonavir 300/100 mg alone.
[e] Based on between-trial comparison.
[f] Based on historical controls.

Because of the design of the drug interaction trials (addition of 28 days of VIRAMUNE therapy to existing HIV-1 therapy), the effect of the concomitant drug on plasma nevirapine steady-state concentrations was estimated by comparison to historical controls.

Administration of rifampin had a clinically significant effect on nevirapine pharmacokinetics, decreasing AUC and C_{max} by greater than 50%. Administration of fluconazole resulted in an approximate 100% increase in nevirapine exposure, based on a comparison to historic data *[see Drug Interactions (7)]*. The effect of other drugs listed in Table 5 on nevirapine pharmacokinetics was not significant. No significant interaction was observed when tipranavir was co-administered with low-dose ritonavir and nevirapine.

12.4 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, β, γ, or δ) are not inhibited by nevirapine.

Antiviral Activity

The 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 an assay using human embryonic kidney 293 cells, the median EC_{50} value (50% inhibitory concentration) of nevirapine was 90 nM against a panel of 2923 wild-type isolates of HIV-1 that were primarily (93%) clade B clinical isolates from the United States. The 99th percentile EC_{50} value was 470 nM in this trial. The median EC_{50} value was 63 nM (range 14-302 nM, n=29) against clinical isolates of HIV-1 clades A, B, C, D, F, G, and H, and circulating recombinant forms CRF01_AE, CRF02_AG and CRF12_BF. Nevirapine had no antiviral activity in cell culture against group O HIV-1 isolates (n=3) or HIV-2 isolates (n=3) replicating in cord blood mononuclear cells. Nevirapine in combination with efavirenz exhibited strong antagonistic anti-HIV-1 activity in cell culture and was additive to antagonistic with the protease inhibitor ritonavir or the fusion inhibitor enfuvirtide. The anti-HIV-1 activity of nevirapine was not antagonistic in combination with the NRTIs abacavir, didanosine, emtricitabine, lamivudine, stavudine, tenofovir and zidovudine, and the protease inhibitors amprenavir, atazanavir, indinavir, lopinavir, nelfinavir, saquinavir and tipranavir. The anti-HIV-1 activity of nevirapine was antagonized by the anti-HBV drug adefovir and by the anti-HCV drug ribavirin in cell culture.

Resistance

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

Phenotypic and genotypic changes in HIV-1 isolates from treatment-naïve subjects receiving either nevirapine (n=24) or nevirapine and zidovudine (n=14) were monitored in Phase 1 and 2 trials ranging from 1 to 12 weeks or longer. After 1 week of nevirapine monotherapy, isolates from 3/3 subjects had decreased susceptibility to nevirapine in cell culture. One or more of the RT mutations resulting in amino acid substitutions K103N, V106A, V108I, Y181C, Y188C, and G190A were detected in HIV-1 isolates from some subjects as early as 2 weeks after therapy initiation. By week eight of nevirapine monotherapy, 100% of the subjects tested (n=24) had HIV-1 isolates with a greater than 100-fold decrease in susceptibility to nevirapine in cell culture compared to baseline, and had one or more of the nevirapine-associated RT resistance substitutions. Nineteen of these subjects (80%) had isolates with Y181C substitutions regardless of dose.

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

For trial 1100.1486, genotypic analysis was performed for baseline and on-therapy isolates from 23 and 34 subjects who experienced virologic failure in the VIRAMUNE XR and immediate-release VIRAMUNE treatment group, respectively. Nevirapine resistance-associated substitutions developed in the on-therapy isolates of 78% (18/23) of the subjects who had virologic failures in the VIRAMUNE XR treatment group and 88% (30/34) of the subjects in the immediate-release VIRAMUNE treatment group, respectively. The Y181C nevirapine resistance-associated substitution was found alone or in combination with other nevirapine resistance-associated substitutions (K101E, K103N, V106A, V108I, V179D/E/I, Y188 C/F/H/L/N, G190A, P225H, F227L, M230L) in isolates from 14 subjects failing VIRAMUNE XR treatment and 25 subjects failing immediate-release VIRAMUNE treatment. On-therapy isolates from 1 subject in VIRAMUNE XR treatment group developed a novel amino acid substitution Y181I and isolates from another subject in the immediate-release VIRAMUNE treatment group developed amino acid substitution Y188N. Phenotypic analysis showed that Y188N and Y181I substitutions conferred 103- and 22-fold reductions in susceptibility, respectively.

Individual Subject Dosing	Fluconazole[a]	Medroxyprogesterone acetate
400 mg QD		
200 mg QD		150 mg every 3 months
200 mg BID		

Cross-resistance
Rapid emergence of HIV-1 strains which are cross-resistant to NNRTIs has been observed in cell culture. Nevirapine-resistant HIV-1 isolates were cross-resistant to the NNRTIs delavirdine, efavirenz and etravirine. The Y188N conferred 22- and 7-fold reductions in susceptibility to delavirdine and efavirenz, respectively, but showed no decrease in susceptibility to etravirine. Similarly, the Y181I substitution reduced susceptibility to delavirdine and etravirine 3- and 8-fold, respectively, but did not reduce susceptibility to efavirenz. However, nevirapine-resistant isolates were susceptible to the NRTIs ddI and ZDV. Similarly, ZDV-resistant isolates were susceptible to nevirapine in cell culture.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis
Long-term carcinogenicity studies in mice and rats were carried out with nevirapine. Mice were dosed with 0, 50, 375 or 750 mg/kg/day for two years. Hepatocellular adenomas and carcinomas were increased at all doses in males and at the two high doses in females. In studies in which rats were administered nevirapine at doses of 0, 3.5, 17.5 or 35 mg/kg/day for two years, 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 was lower than that measured in humans at the 200 mg twice daily dose. The mechanism of the carcinogenic potential is unknown.

Mutagenesis
However, in genetic toxicology assays, nevirapine showed no evidence of mutagenic or clastogenic activity in a battery of *in vitro* and *in vivo* studies. These included microbial assays for gene mutation (Ames: Salmonella strains and *E. coli*), mammalian cell gene mutation assay (CHO/HGPRT), cytogenetic assays using a Chinese hamster ovary cell line and a mouse bone marrow micronucleus assay following oral administration. Given the lack of genotoxic activity of nevirapine, the relevance to humans of hepatocellular neoplasms in nevirapine-treated mice and rats is not known.

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

13.2 Animal Toxicology and/or Pharmacology
Animal studies have shown that nevirapine is widely distributed to nearly all tissues and readily crosses the blood-brain barrier.

14 CLINICAL STUDIES

14.1 Adult Patients
Trial BI 1090 was a placebo-controlled, double-blind, randomized trial in 2249 HIV-1 infected subjects with less than 200 $CD4^+$ cells/mm^3 at screening. Initiated in 1995, BI 1090 compared treatment with VIRAMUNE + lamivudine + background therapy versus lamivudine + background therapy in NNRTI-naïve subjects. Treatment doses were VIRAMUNE, 200 mg daily for two weeks followed by 200 mg twice daily or placebo, and lamivudine, 150 mg twice daily. Other antiretroviral agents were given at approved doses. Initial background therapy (in addition to lamivudine) was one NRTI in 1309 subjects (58%), two or more NRTIs in 771 (34%), and PIs and NRTIs in 169 (8%). The subjects (median age 36.5 years, 70% Caucasian, 79% male) had advanced HIV-1 infection, with a median baseline $CD4^+$ cell count of 96 cells/mm^3 and a baseline HIV-1 RNA of 4.58 $\log_{10}$ copies per mL (38,291 copies per mL). Prior to entering the trial, 45% had previously experienced an AIDS-defining clinical event. Eighty-nine percent had antiretroviral treatment prior to entering the trial. BI 1090 was originally designed as a clinical endpoint trial. Prior to unblinding the trial, the primary endpoint was changed to proportion of subjects with HIV-1 RNA less than 50 copies per mL and not previously failed at 48 weeks. Treatment response and outcomes are shown in Table 6.

Table 6 BI 1090 Outcomes Through 48 Weeks

Outcome	VIRAMUNE (N=1121) %	Placebo (N=1128) %
Responders at 48 weeks: HIV-1 RNA <50 copies/mL	18	2
Treatment Failure	82	98
Never suppressed viral load	45	66
Virologic failure after response	7	4
CDC category C event or death	10	11
Added antiretroviral therapy[1] while <50 copies/mL	5	1
Discontinued trial therapy due to AE	7	6
Discontinued trial <48 weeks[2]	9	10

[1] including change to open-label nevirapine
[2] includes withdrawal of consent, lost to follow-up, non-compliance with protocol, other administrative reasons

The change from baseline in $CD4^+$ cell count through one year of therapy was significantly greater for the VIRAMUNE group compared to the placebo group for the overall trial population (64 cells/mm^3 versus 22 cells/mm^3, respectively), as well as for subjects who entered the trial as treatment-naïve or having received only ZDV (85 cells/mm^3 versus 25 cells/mm^3, respectively).

At two years into the trial, 16% of subjects on VIRAMUNE had experienced class C CDC events as compared to 21% of subjects on the control arm.

rial BI 1046 (INCAS) was a double-blind, placebo-controlled, randomized, three-arm trial with 151 HIV-1 infected subjects with $CD4^+$ cell counts of 200-600 mm^3 at baseline. BI 1046 compared treatment with VIRAMUNE+zidovudine+didanosine to VIRAMUNE+zidovudine and zidovudine+didanosine. Treatment e VIRAMUNE at 200 mg daily for two weeks followed by 200 mg twice daily or placebo, zidovudine at 200 mg three times daily, and didanosine at 125 or daily (depending on body weight). The subjects had mean baseline HIV-1 RNA of 4.41 $\log_{10}$ copies/mL (25,704 copies per mL) and mean baseline $CD4^+$ cells/mm^3. The primary endpoint was the proportion of subjects with HIV-1 RNA less than 400 copies per mL and not previously failed at 48 weeks. der rates at 48 weeks were 45% for subjects treated with VIRAMUNE+zidovudine+didanosine, 19% for subjects treated with and 0% for subjects treated with VIRAMUNE+zidovudine.

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

RAMUNE XR conc... ...cription, non-prescription medication or herbal ...tion from previous infection may occur soon after ...apy and that the cause and long-term healt... ...RAMUNE during pregnancy [se...

14.2 Pediatric Patients

The pediatric safety and efficacy of VIRAMUNE was examined in BI Trial 1100.1368, an open-label, randomized clinical trial performed in South Africa in which 123 HIV-1 infected treatment-naïve subjects between 3 months and 16 years of age received VIRAMUNE oral suspension for 48 weeks. Subjects were divided into 4 age groups (3 months to less than 2 years, 2 to less than 7 years, 7 to less than 12 years, and 12 to less than or equal to 16 years) and randomized to receive one of two VIRAMUNE doses, determined by 2 different dosing methods [body surface area (150 mg/m^2) and weight-based dosing (4 or 7 mg per kg)] in combination with zidovudine and lamivudine *[see Adverse Reactions (6.2), Use in Specific Populations (8.4), and Clinical Pharmacology (12.3)]*. The total daily dose of VIRAMUNE did not exceed 400 mg in either regimen. There were 66 subjects in the body surface area (BSA) dosing group and 57 subjects in the weight-based (BW) dosing group.

Baseline demographics included: 49% male; 81% Black and 19% Caucasian; 4% had previous exposure to ARVs. Subjects had a median baseline HIV-1 RNA of 5.45 $\log_{10}$ copies per mL and a median baseline CD4$^+$ cell count of 527 cells/mm^3 (range 37-2279). One hundred and five (85%) completed the 48-week period while 18 (15%) discontinued prematurely. Of the subjects who discontinued prematurely, 9 (7%) discontinued due to adverse reactions and 3 (2%) discontinued due to virologic failure. Overall the proportion of subjects who achieved and maintained an HIV-1 RNA less than 400 copies per mL at 48 weeks was 47% (58/123).

16 HOW SUPPLIED/STORAGE AND HANDLING

VIRAMUNE 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 60 (NDC 0597-0046-60).

Dispense in tight container as defined in the USP/NF.

VIRAMUNE 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 0597-0047-24).

Storage

Store at 25°C (77°F); excursions permitted to 15°C–30°C (59°F–86°F) [see USP Controlled Room Temperature]. Store in a safe place out of the reach of children.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Hepatotoxicity and Skin Reactions

Inform patients of the possibility of severe liver disease or skin reactions associated with VIRAMUNE that may result in death. Instruct patients developing signs or symptoms of liver disease or severe skin reactions to discontinue VIRAMUNE and seek medical attention immediately, including performance of laboratory monitoring. Symptoms of liver disease include fatigue, malaise, anorexia, nausea, jaundice, acholic stools, liver tenderness or hepatomegaly. Symptoms of severe skin or hypersensitivity reactions include rash accompanied by fever, general malaise, fatigue, muscle or joint aches, blisters, oral lesions, conjunctivitis, facial edema, and/or hepatitis.

Intensive clinical and laboratory monitoring, including liver enzymes, is essential during the first 18 weeks of therapy with VIRAMUNE to detect potentially life-threatening hepatotoxicity and skin reactions. However, liver disease can occur after this period; therefore, monitoring should continue at frequent intervals throughout VIRAMUNE treatment. Extra vigilance is warranted during the first 6 weeks of therapy, which is the period of greatest risk of hepatic events. Advise patients with signs and symptoms of hepatitis to discontinue VIRAMUNE and seek medical evaluation immediately. If VIRAMUNE is discontinued due to hepatotoxicity, do not restart it. Patients, particularly women, with increased CD4$^+$ cell count at initiation of VIRAMUNE therapy (greater than 250 cells/mm^3 in women and greater than 400 cells/mm^3 in men) are at substantially higher risk for development of symptomatic hepatic events, often associated with rash. Advise patients that co-infection with hepatitis B or C and/or increased transaminases at the start of therapy with VIRAMUNE are associated with a greater risk of later symptomatic events (6 weeks or more after starting VIRAMUNE) and asymptomatic increases in AST or ALT *[see Warnings and Precautions (5.1)]*.

The majority of rashes associated with VIRAMUNE occur within the first 6 weeks of initiation of therapy. Instruct patients that if any rash occurs during the two-week lead-in period, do not escalate the VIRAMUNE dose until the rash resolves. The total duration of the once-daily lead-in dosing period should not exceed 28 days, at which point an alternative regimen may need to be started. Any patient experiencing a rash should have their liver enzymes (AST, ALT) evaluated immediately. Patients with severe rash or hypersensitivity reactions should discontinue VIRAMUNE immediately and consult a physician. VIRAMUNE should not be restarted following severe skin rash or hypersensitivity reaction. Women tend to be at higher risk for development of VIRAMUNE-associated rash *[see Warnings and Precautions (5.2)]*.

Administration and Missed Dosage

Inform patients to take VIRAMUNE every day as prescribed. Advise patients not to 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.

To avoid overdose, inform patients that they should never take immediate-release VIRAMUNE and extended-release VIRAMUNE XR concomitantly.

Drug Interactions

VIRAMUNE may interact with some drugs; therefore, advise patients to report to their doctor the use of any other prescription, non-prescription medication or herbal products, particularly St. John's wort *[see Warnings and Precautions (5.4) and Drug Interactions (7)]*.

Immune Reconstitution Syndrome

Advise patients to inform their healthcare provider immediately of any signs or symptoms of infection, as inflammation from previous infection may occur soon after combination antiretroviral therapy, including when VIRAMUNE is started *[see Warnings and Precautions (5.5)]*.

Fat Redistribution

Inform patients that redistribution or accumulation of body fat may occur in patients receiving antiretroviral therapy and that the cause and long-term health e… these conditions are not known at this time *[see Warnings and Precautions (5.6)]*.

Pregnancy Registry

Advise patients that there is a pregnancy registry that monitors pregnancy outcomes in women exposed to VIRAMUNE during pregnancy *[see … Populations (8.1)]*.

…Trial BI 1046 (INCAS) was a double-blind, placebo-controlled trial in which 1216 subjects … were VIRAMUNE. BI 1046 compared treatment-naïve subjects … ice daily (depending on body weight) for two weeks, followed by … 6 cells/mm^3. The primary endpoint was the proportion of subjects … nder rates at 48 weeks were 45% for subjects treated with … and 0% for subjects treated with … MUNE+ZDV+ddI group in … The VIRAMUNE+ZDV+ddI … At two years into the trial, 16% of subjects on … versus 25 cells/mm^3, respectively … versus … Overall trial … ge from baseline in CD4$^+$ cell … (85 cells/mm^3 versus 25 cells/mm^3 … consent, lost to fo… virapi…

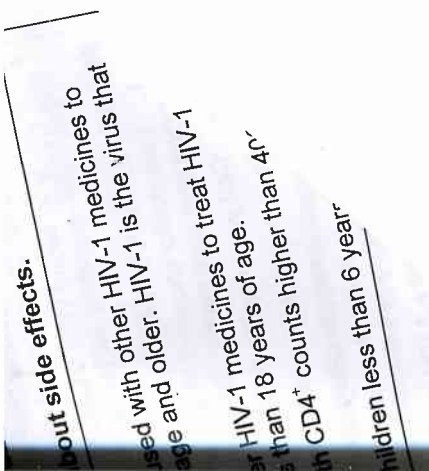
Lactation
Instruct women with HIV-1 infection not to breastfeed because HIV-1 can be passed to the baby in the breast milk *[see Use in Specific Populations (8.2)]*.

Infertility
Advise females of reproductive potential of the potential for impaired fertility from VIRAMUNE *[see Use in Specific Populations (8.3) and Nonclinical Toxicology (13.1)]*

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OT1801ZD32017



MEDICATION GUIDE

VIRAMUNE® (VIH-rah-mune) (nevirapine) oral suspension	**VIRAMUNE® (VIH-rah-mune) (nevirapine) tablets**	**VIRAMUNE XR® (VIH-rah-mune) (nevirapine) extended-release tablets**

What is the most important information I should know about VIRAMUNE?

VIRAMUNE can cause severe liver and skin problems that may lead to death. These problems can happen at any time during treatment, but your risk is higher during the first 18 weeks of treatment.

VIRAMUNE can cause serious side effects, including:

- **Severe liver problems.** Some people taking VIRAMUNE may develop severe liver problems that can lead to liver failure and the need for a liver transplant, or death. If you have liver problems you may get a rash.
  - Women have a higher risk of developing liver problems during treatment with VIRAMUNE than men.
  - People who have abnormal liver test results before starting VIRAMUNE and people with hepatitis B or C also have a greater risk of getting liver problems.

  People who have higher $CD4^+$ cell counts when they begin VIRAMUNE have a higher risk of liver problems, especially:
  - Women with $CD4^+$ counts higher than 250 cells/mm^3. This group has the highest risk.
  - Men with $CD4^+$ counts higher than 400 cells/mm^3.

  Stop taking VIRAMUNE and call your doctor right away if you have any of the following symptoms of liver problems with or without a skin rash:
  - dark (tea colored) urine
  - light-colored bowel movements (stools)
  - feeling sick to your stomach (nausea)
  - pain or tenderness on your right side below your ribs
  - loss of appetite
  - yellowing of your skin or whites of your eyes
  - fever
  - feel unwell or like you have the flu
  - tiredness
- **Severe skin reactions and rash**. Some skin reactions and rashes may be severe, life-threatening, and in some people, may lead to death. Most severe skin reactions and rashes happen in the first 6 weeks of treatment with VIRAMUNE.
  - Women have a higher risk of developing a rash during treatment with VIRAMUNE than men.

  Stop taking VIRAMUNE and call your doctor right away if you get a rash with any of the following symptoms:
  - blisters
  - red or inflamed eyes, like "pink eye" (conjunctivitis)
  - swelling of your face
  - feel unwell or like you have the flu
  - muscle or joint aches
  - mouth sores
  - fever
  - tiredness
- Your doctor should do blood tests often to check your liver function and check for severe skin reactions during the first 18 weeks of treatment with VIRAMUNE. You should continue to see your doctor and have your liver checked regularly during your treatment with VIRAMUNE. It is important for you to keep all of your doctor appointments.
- **If your doctor tells you to stop treatment with VIRAMUNE because you have had any of the severe liver or skin symptoms listed above, you should never take VIRAMUNE again.**

See "What are the possible side effects of VIRAMUNE?" for more information about side effects.

What is VIRAMUNE?

VIRAMUNE tablets and VIRAMUNE oral solution are prescription HIV-1 medicines used with other HIV-1 medicines to treat HIV-1 (Human Immunodeficiency Virus 1) in adults and in children 15 days of age and older. HIV-1 is the virus that causes AIDS (Acquired Immune Deficiency Syndrome).

VIRAMUNE XR extended-release tablets is a prescription medicine used with other HIV-1 medicines to treat HIV-1 (Human Immunodeficiency Virus 1) in adults and in children 6 years of age to less than 18 years of age.

- If you are a woman with $CD4^+$ counts higher than 250 cells/mm^3 or a man with $CD4^+$ counts higher than 400 you and your doctor will decide if starting VIRAMUNE is right for you.
- VIRAMUNE XR extended-release tablets are not recommended for use in children less than 6 years

Do not take VIRAMUNE:

- if you have liver problems.
- as part of occupational and non-occupational post-exposure prophylaxis (PEP) regimens. VIRAMUNE is only for people diagnosed with HIV-1. If you have not been diagnosed as HIV positive, then do not take VIRAMUNE.

Before taking VIRAMUNE, tell your doctor about all your or your child's medical conditions, including if you or your child:

- have or have had hepatitis (inflammation of your liver) or problems with your liver. See **"What is the most important information I should know about VIRAMUNE?"**
- receive dialysis
- have trouble swallowing pills
- are pregnant or plan to become pregnant. It is not known if VIRAMUNE will harm your unborn baby.
  Pregnancy Registry: There is a pregnancy registry for women who take VIRAMUNE during pregnancy. The purpose of the registry is to collect information about the health of you and your baby. Talk to your doctor about how you can take part in this registry.
- are breastfeeding or plan to breastfeed. VIRAMUNE can pass into your breast milk and may harm your baby. You should not breastfeed if you have HIV-1 because of the risk of passing HIV-1 to your baby. Do not breastfeed during treatment with VIRAMUNE. Talk to your doctor about the best way to feed your baby.

Tell your doctor about all the medicines you take, including prescription and over-the-counter medicines, vitamins and herbal supplements. **Especially tell your doctor if you take St. John's wort.**

- Some medicines interact with VIRAMUNE. Keep a list of your medicines to show your doctor or pharmacist.
- You can ask your doctor or pharmacist for a list of medicines that interact with VIRAMUNE.
- **Do not start taking a new medicine without telling your doctor.** Your doctor can tell you if it is safe to take VIRAMUNE with other medicines.

How should I take VIRAMUNE?

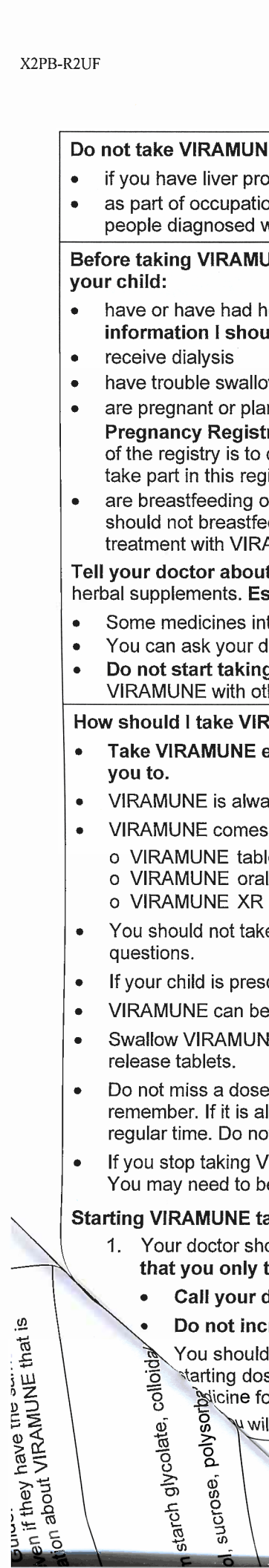
- **Take VIRAMUNE exactly as your doctor tells you to take it. Do not change your dose unless your doctor tells you to.**
- VIRAMUNE is always taken in combination with other antiretroviral medicines.
- VIRAMUNE comes in three different forms. Your doctor will prescribe the form of VIRAMUNE that is right for you.
  - VIRAMUNE tablets
  - VIRAMUNE oral suspension
  - VIRAMUNE XR extended-release tablets
- You should not take more than one form of VIRAMUNE at the same time. Talk to your doctor if you have any questions.
- If your child is prescribed VIRAMUNE, your child's doctor will tell you exactly how VIRAMUNE should be taken.
- VIRAMUNE can be taken with or without food.
- Swallow VIRAMUNE XR extended-release tablets whole. Do not chew, crush, or divide VIRAMUNE XR extended-release tablets.
- Do not miss a dose of VIRAMUNE. If you miss a dose of VIRAMUNE, take the missed dose as soon as you remember. If it is almost time for your next dose, do not take the missed dose. You should take the next dose at your regular time. Do not take 2 doses at the same time.
- If you stop taking VIRAMUNE for more than 7 days, ask your doctor how much to take before you start taking it again. You may need to begin taking the VIRAMUNE starting dose again, which is taken 1 time each day for 14 days.

Starting VIRAMUNE tablets:

1. Your doctor should start you with 1 dose each day to lower your chance of getting a serious rash. **It is important that you only take 1 dose of VIRAMUNE each day for the first 14 days.**
   - **Call your doctor right away if you get a skin rash during the first 14 days of VIRAMUNE treatment.**
   - **Do not increase your dose to 2 times a day if you have a rash.**

   You should never take your starting dose for longer than 28 days. If after 28 days you are still receiving this starting dose because you have a rash, you and your doctor should talk about prescribing another HIV-1 medicine for you instead of VIRAMUNE.

   You will take 1 VIRAMUNE tablet 2 times a day.



Starting VIRAMUNE XR extended-release tablets when this is the first time you are taking any form of VIRAMUNE:

1. Your doctor should start you with 1 dose of VIRAMUNE tablets or oral suspension each day to lower your risk of getting a serious rash. **It is important that you only take 1 dose of VIRAMUNE each day for the first 14 days.**
   - **Call your doctor right away if you get a skin rash during the first 14 days of VIRAMUNE treatment.**
   - You should never take your starting dose for longer than 28 days. If after 28 days you are still receiving this starting dose because you have a rash, you and your doctor should talk about prescribing another HIV-1 medicine for you instead of VIRAMUNE.
   - **Do not start VIRAMUNE XR extended-release tablets if you have a rash.**
2. Day 15, take VIRAMUNE XR extended-release tablets 1 time a day as prescribed by your doctor.

Switching from VIRAMUNE tablets or oral suspension to VIRAMUNE XR extended-release tablets:

- Take VIRAMUNE XR extended-release tablets 1 time a day as prescribed by your doctor.
- You may sometimes pass a soft mass in your stools (bowel movement) that looks like your VIRAMUNE XR extended-release tablets. This will not affect the way your medicine works.

If you take VIRAMUNE oral suspension:

- If you or your child takes VIRAMUNE oral suspension (liquid), shake it gently before each use. Use an oral dosing syringe or dosing cup to measure the right dose. The oral dosing syringe and dosing cup are not provided with VIRAMUNE oral suspension. Ask your pharmacist for a syringe or cup if you do not have one.
- After drinking the medicine, fill the dosing cup with water and drink it to make sure you get all the medicine.
- If the dose is less than 1 teaspoon (5 mL), use the syringe instead of the dosing cup.

What are the possible side effects of VIRAMUNE?

VIRAMUNE may cause serious side effects, including:

See "**What is the most important information I should know about VIRAMUNE?**"

- **Changes in your immune system (Immune Reconstitution Syndrome)** can happen when you start taking HIV-1 medicines. Your immune system may get stronger and begin to fight infections that have been hidden in your body for a long time. Tell your doctor right away if you start having new symptoms after starting your HIV-1 medicine.
- **Changes in body fat** can happen in people who take HIV-1 medicines. These changes may include increased amount of fat in the upper back and neck ("buffalo hump"), breast, and around the middle of your body (trunk). Loss of fat from your legs, arms, and face may also happen. The exact cause and long-term health effects of these conditions are not known.

The most common side effect of VIRAMUNE is rash.

VIRAMUNE may cause decreased fertility in females. Talk to your doctor if you have concerns about fertility.

These are not all the possible side effects of VIRAMUNE. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store VIRAMUNE?

- Store VIRAMUNE at room temperature between 68°F to 77°F (20°C to 25°C).
- Throw away VIRAMUNE that is no longer needed.

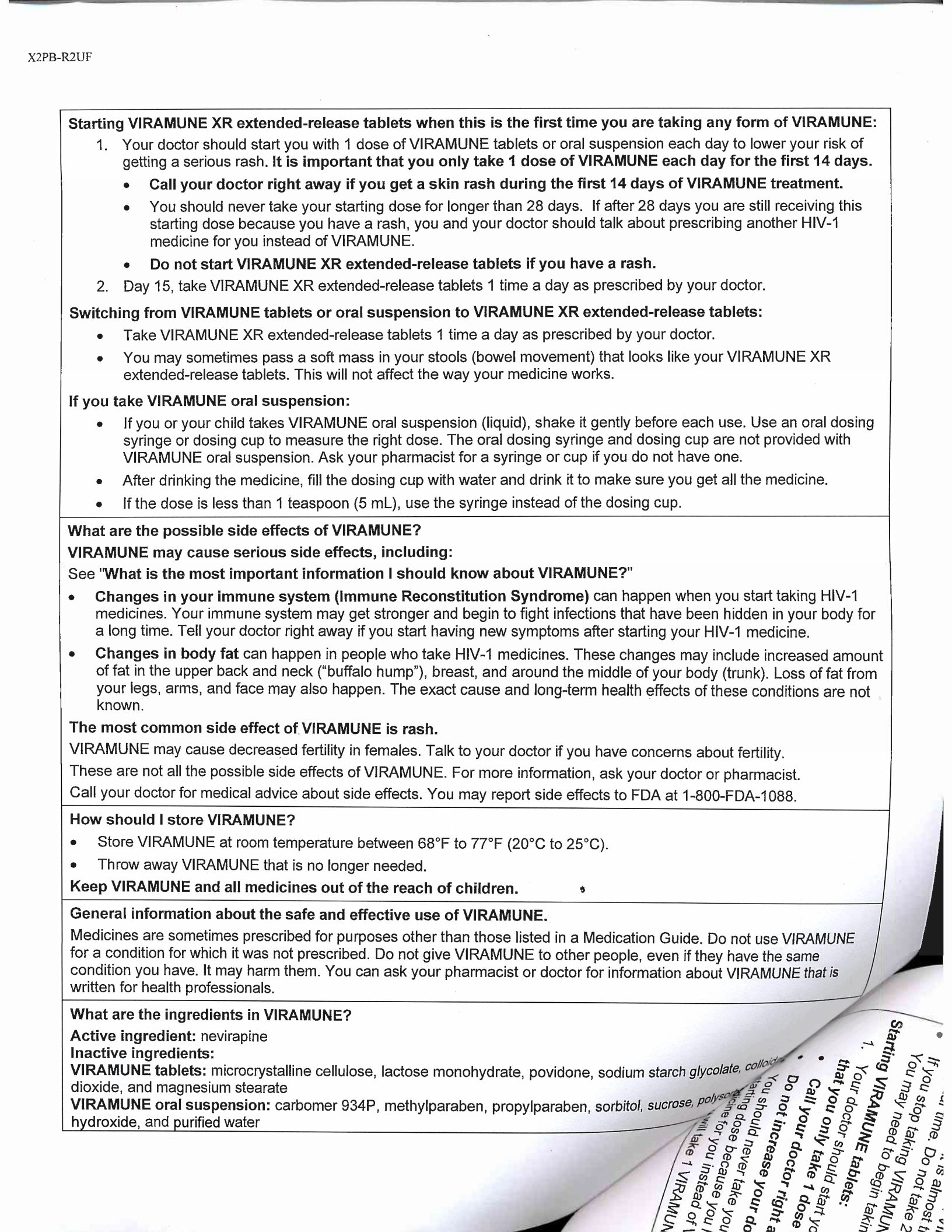
Keep VIRAMUNE and all medicines out of the reach of children.

General information about the safe and effective use of VIRAMUNE.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use VIRAMUNE for a condition for which it was not prescribed. Do not give VIRAMUNE to other people, even if they have the same condition you have. It may harm them. You can ask your pharmacist or doctor for information about VIRAMUNE that is written for health professionals.

What are the ingredients in VIRAMUNE?

Active ingredient: nevirapine
Inactive ingredients:
VIRAMUNE tablets: microcrystalline cellulose, lactose monohydrate, povidone, sodium starch glycolate, colloid
dioxide, and magnesium stearate
VIRAMUNE oral suspension: carbomer 934P, methylparaben, propylparaben, sorbitol, sucrose, polyso
hydroxide, and purified water



VIRAMUNE XR tablets: lactose monohydrate, hypromellose, iron oxide, and magnesium stearate

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Boehringer Ingelheim Pharmaceuticals, Inc. Ridgefield, CT 06877, USA

For current prescribing information for VIRAMUNE or VIRAMUNE XR, scan the codes below or for additional information you may also call Boehringer Ingelheim Pharmaceuticals, Inc., at 1-800-542-6257, (TTY) 1-800-459-9906.

VIRAMUNE tablets and oral suspension

VIRAMUNE XR extended-release tablets

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OT1801ZD32017

This Medication Guide has been approved by the U.S. Food and Drug Administration

Revised: March 2017

Boehringer Ingelheim
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tion by himself as Senior

X2PB-R2UF

Boehringer Ingelheim

BOEHRINGER INGELHEIM PHARMACEUTICALS, INC. certifies that the following information is "true" as it applies to the Qualitative and Quantitative Composition of the following drug product:

VIRAMUNE® (nevirapine) Oral Suspension 50 mg/ 5 mL

Qualitative and Quantitative Composition

Component	Reference to Standards	Concentration (mg/ mL)	Label Claim per 5 mL
Nevirapine Hemihydrate	Company Standard	10.35*	50 mg nevirapine
Carbomer 934P	NF	2.10	
Polysorbate 80	NF	0.50	
Sorbitol Solution	USP	231.30	
Sucrose	NF	150.00	
Methylparaben	NF	1.80	
Propylparaben	NF	0.24	
Sodium hydroxide**	NF	0.35	
Purified water	USP	qs to 1 mL	

* Equivalent to 10 mg anhydrous nevirapine
** 20% solution prepared

We also certify that the Shelf-Life for this product is 36 months, as approved in **VIRAMUNE®** (nevirapine) **Oral Suspension 50 mg/ 5 ml, NDA 20-933.**

Signed: _____ Date: April 9, 2018
Dr. Andrew Gee, Sr. Associate Director, CMC Regulatory Affairs

State of Connecticut)
) ss: Ridgefield
County of Fairfield)

On this 9th day of April 2018, before me, Kristin E. Snow, the undersigned officer, personally appeared Dr. Andrew Gee, who acknowledged himself to be a Senior Associate Director of CMC Regulatory Affairs of Boehringer Ingelheim Pharmaceuticals, Inc., a corporation, and that he as such Senior Associate Director, being authorized so to do executed the foregoing instrument for the purposes therein contained, by signing the name of the corporation by himself as Senior Associate Director.

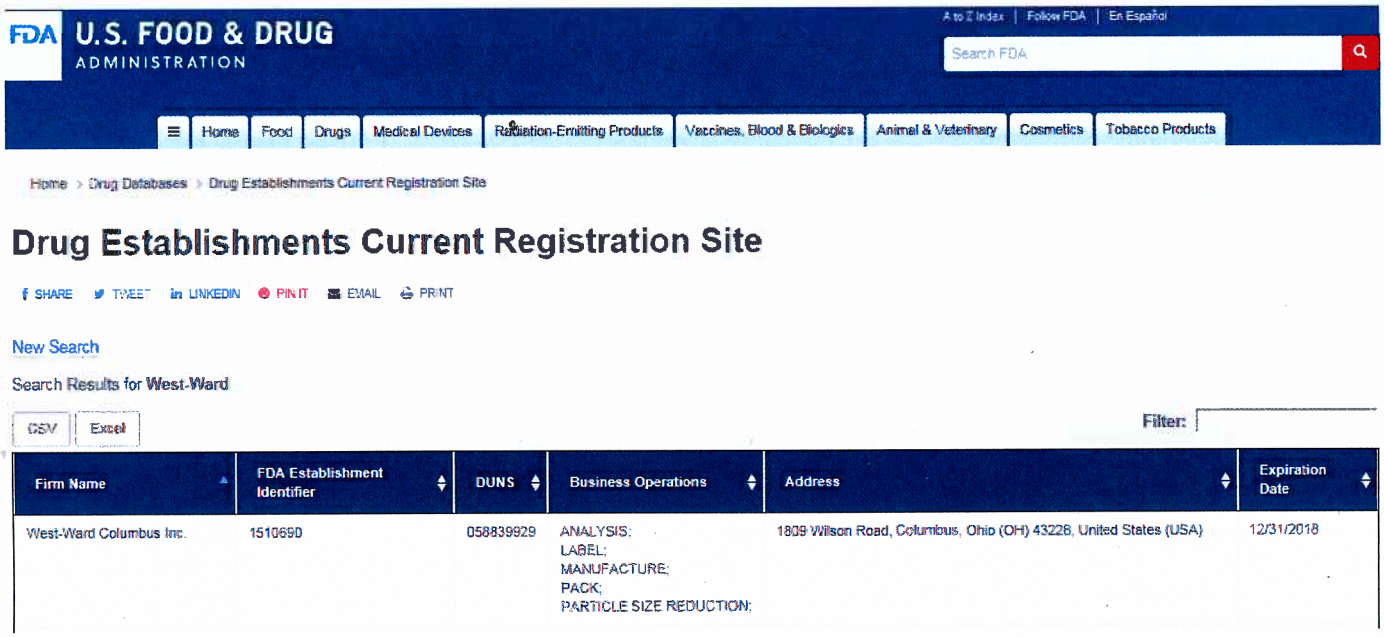
In witness whereof I hereunto set my hand.

_____
Kristin E. Snow
Notary Public
My Commission Expires: March 31, 2022

X2PB-R2UF

Boehringer Ingelheim

FDA Drug Firm Registrations are electronically filed and this is a screen print of the status from the U.S. Food and Drug Administration website: http://www.accessdata.fda.gov/scripts/cder/drls/default.cfm.



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Search Results for West-Ward

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Filter:

Firm Name	FDA Establishment Identifier	DUNS	Business Operations	Address	Expiration Date
West-Ward Columbus Inc.	1510690	058839929	ANALYSIS; LABEL; MANUFACTURE; PACK; PARTICLE SIZE REDUCTION;	1809 Wilson Road, Columbus, Ohio (OH) 43228, United States (USA)	12/31/2018

Traducción oficial de un documento escrito en inglés realizada por Sergio E. Latorre, traductor oficial e intérprete de acuerdo con la Resolución 2839 de 1991 del Ministerio de Justicia

APOSTILLE

(Convención de La Haya de Octubre 5 de 1961)

1. País: Estados Unidos

   Este documento público

2. Ha sido firmado por: Andrei Perlloni
3. Actuando en su capacidad de Jefe de Sucursal, Oficina de Cumplimiento de Exportaciones e Importaciones de Medicamentos
4. Lleva el sello/estampa de: Departamento de Salud y Servicios Humanos de los Estados Unidos

Certifica

5. En Washington D.C.
6. En Julio 5 de 2018
7. Por Funcionario Asistente de Autenticaciones, Departamento de Estado de los Estados Unidos
8. No. 18046402-4
9. Sello/Estampa:
10. Firma:

    (Firmado en el original)

    Chana M Turner

Sergio Eleuterio Latorre Mendoza
Traductor e Interprete Oficial
Resol. No. 2839 Minjusticia 1991

Traducción oficial de un documento escrito en inglés realizada por Sergio E. Latorre, traductor oficial e intérprete de acuerdo con la Resolución 2839 de 1991 del Ministerio de Justicia

Departamento de Alimentos y Medicamentos de los Estados Unidos

Centro para la Evaluación e Investigación de Medicamentos

10903 New Hampshire Ave, Silver Spring, MD 20993, Estados Unidos

CDERExportCertificateProgram@fda.hhs.gov – Teléfono: (301) 796-4950

Certificado de Producto Farmacéutico – Producto Medicinal Aprobado

Certificado No. **X2PB-R2UF** Fecha de Emisión del Certificado: **Mayo 29 de 2018**

Fecha de Expiración del Certificado: **Mayo 28 de 2020**

País importador: **COLOMBIA** País exportador: **ESTADOS UNIDOS**

1.	Nombre comercial, internacional o nacional no exclusivo (si aplica) del medicamento y presentación: **VIRAMUNE®, Suspension**
1.1.	Ingrediente(s) activo(s) y cantidad(es) por dosis (se prefiere la composición cuantitativa completa): **nevirapina 50 MG/5 ML**
1.2.	¿Se encuentra este producto autorizado para ser colocado en el mercado para uso en el país exportador? **Si**
1.3.	¿Se encuentra este producto actualmente en el mercado del país exportador? **Si**
2.A1.	Número de licencia y fecha de emisión: **020933 09/11/1998**
2.A2.	Nombre y dirección del poseedor de la licencia: **Boehringer-Ingelheim Inc., 900 Ridgebury Road, Ridgefield, CT 06877 Estados Unidos**
2.A3.	Estatus del propietario de la licencia del producto: **Ninguno**
2.A3.1.	Nombre y dirección del fabricante: **West-Ward Columbus Inc., 1809 Wilson Road, OH 43228 Estados Unidos**
2.A4.	¿Se ha enmendado un resumen base para la aprobación? **Si**
2.A5.	¿La información adjunta del producto está completa y es consistente con la licencia? **Si**
2.A6.	Nombre y dirección del solicitante del certificado (Si es diferente del propietario de la licencia): **Boehringer-Ingelheim Inc., 900 Ridgebury Road, Ridgefield, CT 06877 Estados Unidos**
2.B4.	Observaciones: **Fabricante API: Zhejian Hunhai Pharmaceutica Co., Ltd., Coastal Industrial zone, Duquiao, Linhai, Zhejiang 317016 CHINA.**
3.	¿La autoridad certificadora organiza inspecciones periódicas de la planta de fabricación donde se produce la presentación? **Si**
3.1.	Periodicidad de las inspecciones (años): **De acuerdo con la sección 510(h)(3) de la Ley Federal de Alimentos, Medicamentos & Cosméticos, las inspecciones tendrán lugar de acuerdo con un cronograma basado en el riesgo**
3.2.	¿Ha sido inspeccionado el fabricante de este tipo de presentación? **Si**
3.3.	¿Las instalaciones y operaciones cumplen con las BPF de acuerdo con lo recomendado por la OMS? (Las BPFs incluyen 21 Código de Regulaciones Federales partes 210, 211 o ICH Q7A): **Si, al momento de la inspección, el sitio cumple con FDA cGDP**
3.4.	¿La información enviada por el solicitante satisface a la autoridad certificadora en todos los aspectos de la fabricación del producto hechos por otra parte? **Si**

Sergio Eleuterio Latorre Mendoza

Traductor e Interprete Oficial
Resol. No. 2839 Minjusticia 1991

(Firmado en el original)

Andrei Perlloni, Director

División de Importaciones, Exportaciones y Retiros del Mercado

Oficina de Seguridad de Medicamentos, Integridad & Respuesta

(Nota del traductor: Adjunto se encuentra un sello del Departamento de Salud y Servicios Humanos de los Estados Unidos)

Lo anterior cumple con el formato recomendado por la Organización Mundial de la Salud (OMS), formato revisado Octubre 1 de 1997. Página Web: www.who.int

Yo, Sergio Latorre, por medio de la presente, Cerífico que la anterior es una traducción verdadera y precisa del documento original escrito en inglés. Bogotá, julio 25 de 2018

Sergio Eleuterio Latorre Mendoza
Traductor e Interprete Oficial
Resol. No. 2839 Minjusticia 1991