VIRAMUNE® (nevirapine) oral suspension, for oral use

VIRAMUNE® (nevirapine) tablets, for oral use

Boehringer Ingelheim Pharmaceuticals Inc.

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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 transaminitis 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 in patients who develop a rash in the first 18 weeks of treatment. 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)

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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:
  - 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)

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DOSE 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)

<table>
<thead>
<tr>
<th>Adults</th>
<th>Pediatric Patients*</th>
</tr>
</thead>
<tbody>
<tr>
<td>200 mg once daily</td>
<td>20 mL once daily</td>
</tr>
<tr>
<td>200 mg twice daily</td>
<td>20 mL twice daily</td>
</tr>
</tbody>
</table>

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

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WARNINGS AND PRECAUTIONS

- Monitor patients for immune reconstitution syndrome and fat redistribution. (5.1, 5.6)
- The most common adverse reaction in 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 patients the incidence of rash (all causality) was 21%. (6.2)

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ADVERSE REACTIONS

- See full prescribing information for complete boxed warning.

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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)
- Use as part of occupational and non-occupational post-exposure prophylaxis (PEP) regimens, an unapproved use. (5.4)

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USE IN SPECIFIC POPULATIONS

- Lactation: Women infected with HIV-1 should be instructed not to breastfeed due to the potential for HIV-1 transmission. (8.8)
- 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. (8.4)
- See 17 for PATIENT COUNSELING INFORMATION and Medication Guide. Revised: 3/2017

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FULL PRESCRIBING INFORMATION: CONTENTS®

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

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2.4 Dosage Adjustment

Dosage adjustment can be necessary based on the patient's response and the occurrence of side effects. For adult patients, the recommended dose is one 200 mg tablet daily for the first 14 days, followed by one 200 mg tablet twice daily thereafter. The total daily dose should not exceed 400 mg for any given patient. For pediatric patients aged 15 days and older, the recommended oral dose is 150 mg/m² twice daily. The volume of VIRAMUNE Oral Suspension required for pediatric dosing can be calculated based on the body surface area (BSA) using the following formula:

\[ \text{Volume (mL)} = \frac{\text{Height (cm)}}{3000} \times \frac{\text{Weight (kg)}}{50} \times \text{BSA range (m²)} \]

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/m²

<table>
<thead>
<tr>
<th>BSA range (m²)</th>
<th>Volume (mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.06 – 0.12</td>
<td>1.25</td>
</tr>
<tr>
<td>0.12 – 0.25</td>
<td>2.5</td>
</tr>
<tr>
<td>0.25 – 0.42</td>
<td>5</td>
</tr>
<tr>
<td>0.42 – 0.58</td>
<td>7.5</td>
</tr>
<tr>
<td>0.58 – 0.75</td>
<td>10</td>
</tr>
<tr>
<td>0.75 – 0.92</td>
<td>12.5</td>
</tr>
<tr>
<td>0.92 – 1.08</td>
<td>15</td>
</tr>
<tr>
<td>1.08 – 1.25</td>
<td>17.5</td>
</tr>
<tr>
<td>1.25+</td>
<td>20</td>
</tr>
</tbody>
</table>

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

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 frequently than once per month, and in particular, would include monitoring of liver enzyme tests at baseline, prior to dose escalation, and at least twice weekly post-dose escalation. After the initial 18-week period, frequent clinical and laboratory monitoring should continue throughout VIRAMUNE treatment [see Warnings and Precautions (5.2)]. In some cases, hepatic injury has progressed despite discontinuation of treatment.
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/m²/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/m²/day in pediatric patients) for the first 14 days (lead-in) followed by one 200 mg tablet twice daily (150 mg/m² 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) regimen [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. Rhododermia 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, blister, oral lesions, conjunctivitis, facial edema, eosinophilia, granulocytopenia, lymphopenopathy, 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 or hypertransaminase 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, and jaundice, bilirubinemia, 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)].

If clinical hepatitis or transaminase elevations combined with rash or other systemic symptoms occur, permanently discontinue VIRAMUNE. Do not restart VIRAMUNE after recovery. In some cases, hepatic injury progresses despite discontinuation of treatment. In the patients at greatest risk of hepatic events, including potentially fatal events, are women with high CD4+ cell counts. In general, during the first 6 weeks of therapy, women have a 3-fold higher risk than men for symptomatic, often rash-associated, hepatic events (6% versus 2%), and patients with higher CD4+ cell counts at initiation of VIRAMUNE therapy are at higher risk for symptomatic hepatic events with VIRAMUNE. In a retrospective review, women with CD4+ cell counts greater than 250 cells/mm³ had a 12-fold higher risk of symptomatic hepatic adverse events compared to women with CD4+ cell counts less than 250 cells/mm³ (11% versus 1%). An increased risk was observed in men with CD4+ cell counts greater than 400 cells/mm³ (6% versus 3% for men with CD4+ cell counts less than 400 cells/mm³). However, all patients, regardless of gender, CD4+ cell count, or antiretroviral treatment history, should be monitored for hepatotoxicity since symptomatic hepatic adverse events have been reported at all CD4+ cell counts. 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 liver 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 in 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, lymphopenopathy, 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-week 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/m² 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/m²/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 (12.6)).

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

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. Hepatic/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, lymphopenopathy, or renal dysfunction (see Bosed 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/mm³) in women and greater than 400 cells/mm³ in men) place patients at increased risk of these events (see Bosed 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 Bosed 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 or symmetric, and resolve with or without pruritus, located on the trunk, face and extremities. In controlled clinical trials (Trials 1037, 1038, 1046, and 1050), Grade 1 and 2 rashes were reported in 15% 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 Bosed 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.
drug interactions are also listed in Table 4. Although specific drug interaction trials in HIV-1 nevirapine and other drug classes that are metabolized by the cytochrome P450 system. These potential

In addition to established drug interactions, there may be potential pharmacokinetic interactions between

results of drug interaction trials conducted in HIV-1 seropositive subjects unless otherwise indicated. The data in Tables 4 and 5 are based on the

Nevirapine is principally metabolized by the liver via the cytochrome P450 isoenzymes, 3A and 2B6.

In post-marketing surveillance anemia has been more commonly observed in children although

In addition to the adverse events identified during clinical trials, the following adverse reactions have

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 in (n=305) in which pediatric subjects received combination treatment with VIRAMUNE. In this trial, adverse events were reported in 31% of subjects, 40 (13%) of whom discontinued treatment due to adverse events. The most frequently reported adverse events related to VIRAMUNE in pediatric subjects were similar to those observed in adults, with the exception of nausea, which was more commonly observed in children receiving both azidothymidine 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-naive 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 treatment 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: arthritis, rhabdomyolysis associated with skin and/or liver reactions Neurologic: parasthesia Skin and Appendages: allergic reactions including 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 (5.13) plus one or more of the following: hepatopathy, 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 comments 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 interaction trials conducted in HIV-1 seropositive subjects unless otherwise indicated. In addition to established drug interactions, there may be potential pharmacokinetic interactions between nevirapine and other drug classes that are metabolized by the cytochrome P450 system. These potential drug interaction are also listed in Table 4. Although specific drug interaction trials in HIV-1

<table>
<thead>
<tr>
<th>Controlled Trials</th>
<th>Trial 1090(^1)</th>
<th>Trials 1037, 1038, 1046(^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VIRAMUNE</td>
<td>Placebo</td>
<td>VIRAMUNE</td>
</tr>
<tr>
<td>(n=1121)</td>
<td>(n=1128)</td>
<td>(n=253)</td>
</tr>
<tr>
<td>Any adverse event</td>
<td>11%</td>
<td>13%</td>
</tr>
<tr>
<td>Rash</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Muscle or joint aches</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Fatigue</td>
<td>&lt;1</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>&lt;1</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Myalgia</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

\(^1\) Background therapy included FTC for all subjects and combinations of NNRTIs and PIs. Subjects had CD4\(^+\) cell counts less than 200 cells/mm\(^3\).

\(^2\) Background therapy included FTC and drug interactions were observed 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 |
|---------------------------|-----------------------------|
| Laboratory Abnormality    | VIRAMUNE Placebo            | VIRAMUNE Placebo |
| (n=1121)                  | (n=1128)                    | (n=253)         |
| Blood Chemistry           |                             |                 |
| SGPT (AST) >250 U/L       | 5                           | 4               |
| SGOT (AST) >250 U/L       | 4                           | 3               |
| Bilirubin >2.5 mg/dL      | 2                           | 2               |
| Hematology                |                             |                 |
| Hemoglobin <8.0 g/dL      | 3                           | 4               |
| Platelets <50,000/mm\(^3\) | 1                       | 1               |
| Neutrophils <750/mm\(^3\) | 13                         | 14              |

\(^3\) Background therapy included FTC for all subjects and combinations of NNRTIs and PIs. Subjects had CD4\(^+\) cell counts less than 200 cells/mm\(^3\).

\(^4\) 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 TESTS

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).
seropositive subjects have not been conducted for some classes of drugs listed in Table 4, additional clinical monitoring may be warranted when co-administering these drugs.

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 Clinical Comment** | **Drug Name** |
| **HIV Antiviral Agents: Protease Inhibitors (PIs)** | | **HIV Antiviral Agents: Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)** |
| Atazanavir/Ritonavir* | ↓ Atazanavir ↑ Nevirapine | Efavirenz* | ↓ Efavirenz | The appropriate doses of these combinations with respect to safety and efficacy have not been established. |
| Fosamprenavir* | ↓ Amprenavir ↑ Nevirapine | Delavirdine | | Plasma concentrations may be altered. Nevirapine should not be coadministered with another NNRTI as this combination has not been shown to be beneficial. |
| Fosamprenavir/Ritonavir* | ↓ Amprenavir ↑ Nevirapine | Etravirine | | |
| Indinavir* | ↓ Indinavir | Rilpivirine | | |
| Lopinavir/Ritonavir* | ↓ Lopinavir | | | |
| Nelfinavir* | ↓ Nelfinavir M8 ↓ Nelfinavir C | | | |
| Saquinavir/ritonavir | | | | |
| **Hepatitis C Antiviral Agents** | | **Other Agents** |
| | | Analgesics: |
| | | Methadone* | ↓ Methadone | Methadone levels were decreased; increased dosages may be required to prevent symptoms of opioid withdrawal. Methadone-maintained patients beginning nevirapine |
therapy should be monitored for evidence of withdrawal and methadone dose should be adjusted accordingly.

<table>
<thead>
<tr>
<th>Class</th>
<th>Drug</th>
<th>Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antiarrhythmics</td>
<td>Amiodarone, disopyramide, lidocaine</td>
<td>Plasma concentrations may be decreased. Appropriate doses for this combination have not been established.</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>Clarithromycin*</td>
<td>Clarithromycin exposure was significantly decreased by nevirapine; however, 14-OH clarithromycin 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.</td>
</tr>
<tr>
<td></td>
<td>Rifabutin*</td>
<td>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.</td>
</tr>
<tr>
<td></td>
<td>Rifampin*</td>
<td>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.</td>
</tr>
<tr>
<td>Anticonvulsants</td>
<td>Carbamazepine, clonazepam, ethosuximide</td>
<td>Plasma concentrations of nevirapine and the anticonvulsant may be decreased. Use with caution and monitor virologic response and levels of anticonvulsants.</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>Fluconazole*</td>
<td>Nevirapine and ketoconazole should not be administered concomitantly because decreases in ketoconazole plasma concentrations may reduce the efficacy of the drug.</td>
</tr>
<tr>
<td></td>
<td>Ketoconazole*</td>
<td>Nevirapine and ketoconazole should not be administered concomitantly because decreases in ketoconazole plasma concentrations may reduce the efficacy of the drug.</td>
</tr>
<tr>
<td></td>
<td>Itraconazole</td>
<td>Nevirapine and itraconazole should not be administered concomitantly due to potential decreases in itraconazole plasma concentrations that may reduce efficacy of the drug.</td>
</tr>
<tr>
<td>Antithrombotics</td>
<td>Warfarin</td>
<td>Plasma concentrations may be increased. Potential effect on anticoagulation. Monitoring of anticoagulation levels is recommended.</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>Diltiazem, nifedipine, verapamil</td>
<td>Plasma concentrations may be decreased. Appropriate doses for these combinations have not been established.</td>
</tr>
<tr>
<td>Cancer chemotherapy</td>
<td>Cyclophosphamide</td>
<td>Plasma concentrations may be decreased. Appropriate doses for this combination have not been established.</td>
</tr>
<tr>
<td>Ergot alkaloids</td>
<td>Ergotamine</td>
<td>Plasma concentrations may be decreased. Appropriate doses for this combination have not been established.</td>
</tr>
<tr>
<td>Immunosuppressants</td>
<td>Cyclosporine, tacrolimus, sirolimus</td>
<td>Plasma concentrations may be decreased. Appropriate doses for these combinations have not been established.</td>
</tr>
<tr>
<td>Motility agents</td>
<td>Cisapride</td>
<td>Plasma concentrations may be decreased. Appropriate doses for this combination have not been established.</td>
</tr>
<tr>
<td>Opiate agonists</td>
<td>Fentanyl</td>
<td>Plasma concentrations may be decreased. Appropriate doses for this combination have not been established.</td>
</tr>
<tr>
<td>Oral contraceptives</td>
<td>Oral contraceptives</td>
<td>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...</td>
</tr>
</tbody>
</table>
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, evolves over time, and is not national or disease-specific, and does not include outcomes for births that occurred before 20 weeks gestation.

In literature reports, immediate-release nevirapine exposure (C_rmax) 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 count greater than 250 cells/mm3 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 regimen and 3.2% (95% CI: 2.4%, 4.0%) for second/third trimester exposure to nevirapine-containing regimen.

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_rmax 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 400 mg 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

Risk Summary

The Centers for Disease Control and Prevention recommend that HIV-1-infected mothers in the United States not breastfeed their infants to avoid risking postnatal transmission 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 breastfeeding infant. 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), (2) developing viral resistance (in HIV-positive infants), and (3) serious adverse reactions in nursing infants, mothers should not breastfeed if they are receiving VIRAMUNE.

Data

Based on five publications, immediate-release nevirapine was excreted in breast-milk at median plasma concentration ratio range of 59 to 88%. Reported infant nevirapine median plasma concentrations ranging from 4080 to 6795 ng/mL, and the median maternal breast-milk to maternal plasma concentration ratio was 59 to 88%. Reported infant nevirapine median plasma concentrations were low, ranging from 734 to 1140 ng/mL. The estimated nevirapine dose of 764 to 861 µg/kg/day for infants fed exclusively with breast-milk was lower than the daily recommended dose. Published literature indicates that rash and hyperbilirubinemia have been observed 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 (14.1)].

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 17 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
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. Absolute bioavailability in 12 healthy adults following single-dose administration was 93 ± 5% (mean ± SD) for a 50 mg tablet and 91 ± 8% for an oral solution. Peak plasma nevirapine concentration of 2 ± 0.6 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) were attained by 400 mg/day. Nevirapine tablets and suspension have been shown to be comparable 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) 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 ± 0.29 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=4) were 45% (45%) of the concentration 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) metabolisims to several hydroxylated metabolites. In vitro studies with human liver microsomes suggest that oxidative metabolism of nevirapine is mediated primarily by cytochrome P450 (CYP) isoforms from the CYP3A and CYP2B6 families, although other isoforms 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 14C-nevirapine, approximately 91.4 ± 10.5% of the radio labeled dose was recovered, with urine (81.3 ± 11.1%) representing the primary route of excretion compared to feces (10.1 ± 1.5%). Greater than 85% 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. Akemidination 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. Akemidination 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

HIV-1 Infected Adults

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.)

<table>
<thead>
<tr>
<th>Co-administered Drug</th>
<th>Dose of Co-administered Drug</th>
<th>Dose Regimen of VIRAMUNE</th>
<th>% Change of Co-administered Drug Pharmacokinetic Parameters (90% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antiretrovirals</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atazanavir/Ritonavir</td>
<td>300/100 mg QD for 4–13 days, then 400/100 mg QD for day 14–23</td>
<td>VIRAMUNE 200 mg QD for 1-day lead-in, followed by 4 mg BID for 13 days</td>
<td>AUC ↓42 (52 to 129.3), Cmax ↓28 (-40 to -141), Cmin ↓72 (80 to -60)</td>
</tr>
</tbody>
</table>

Note: All values are geometric means except those noted as arithmetic. The coefficient of variation (CV) for the change in the geometric mean for AUC, Cmax, and Cmin are: 5.1%, 5.1%, and 5.3%, respectively.
### Drugs Known to Increase Nevirapine Clearance

- **Doravirine**
  - 400/100 mg BID
  - AUC<sub>max</sub> x 14 days: 200 mg BID
  - 0.19 (35 to 12) 0.32 (15 to 124) 0.59 (73 to 149)
- **Dinorbidine**
  - 100-150 mg BID
  - 200 mg QD x 14 days; 200 mg BID x 14 days
  - 0.18
- **Efavirenz**
  - 600 mg QD
  - 200 mg QD x 14 days; 400 mg QD x 14 days
  - 0.28 (34 to 1.14) 0.12 (22 to 11) 0.42 (35 to 119)
- **Fosamprenavir**
  - 1400 mg BID
  - 200 mg BID. Subjects were treated with nevirapine prior to trial entry.
  - 0.33 (45 to 20) 0.25 (37 to 10) 0.35 (50 to 1.15)
- **Darunavir/Ritonavir**
  - 700/100 mg BID
  - 200 mg BID. Subjects were treated with nevirapine prior to trial entry.
  - 0.11 (23 to 23) 0
- **Indinavir**
  - 800 mg q4H
  - 200 mg QD x 14 days; 200 mg BID x 14 days
  - 0.31 (39 to 22) 0.15 (24 to 4) 0.44 (33 to 33)
- **Lopinavir<sup>a,b</sup>**
  - 300/75 mg/m<sup>2</sup> (Lopinavir/Ritonavir)<sup>a</sup>
  - 7 mg/kg or 4 mg/kg QD in 2 weeks; BID x 1 week
  - 0.22 (4 to 19) 0.14 (36 to 156) 0.55 (175 to 1.19)
- **Lopinavir<sup>a</sup>**
  - 400/100 mg BID (Lopinavir/Ritonavir)<sup>a</sup>
  - 200 mg QD x 14 days; 200 mg BID x 1 year
  - 0.27 (47 to 23) 0.19 (30 to 15) 0.51 (72 to 1.26)
- **Maraviroc**
  - 300 mg SD
  - 200 mg BID
  - 0.15 (55 to 151) 0
- **Nelfinavir**
  - 750 mg TID
  - 200 mg QD x 14 days; 200 mg BID x 14 days
  - 0.33 (80 to 15)
- **Nelfinavir-MB metabolite**
  - 620 mg BID
  - 0.68 (30 to 155) 0.86 (74 to 155)
- **Ritonavir**
  - 600 mg BID
  - 200 mg QD x 14 days; 200 mg BID x 14 days
  - 0.38 (41 to 14)
- **Stavudine**
  - 30-40 mg BID
  - 200 mg QD x 14 days; 200 mg BID x 14 days
  - 0.38 (27 to 15)
- **Zalcitabine**
  - 0.125-0.25 mg TID
  - 200 mg QD x 14 days; 200 mg BID x 14 days
  - 0.39 (80 to 14)
- **Zidovudine**
  - 100-200 mg TID
  - 200 mg QD x 14 days; 200 mg BID x 14 days
  - 0.30 (150 to 14)

### Other Medications

<table>
<thead>
<tr>
<th>Drug</th>
<th>AUC&lt;sub&gt;max&lt;/sub&gt;</th>
<th>AUC&lt;sub&gt;min&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clarithromycin&lt;sup&gt;a&lt;/sup&gt;</td>
<td>500 mg BID</td>
<td>0.33 (38 to 124) 0.23 (11 to 141) 0.56 (70 to 136)</td>
</tr>
<tr>
<td>34-25-HH clarithromycin</td>
<td>340 mg BID</td>
<td>0.42 (16 to 173) 0.47 (21 to 180)</td>
</tr>
<tr>
<td>Ethinyl estradiol and</td>
<td>0.035 mg (as Ortho-Novum 1/35)</td>
<td>0.20 (133 to 13) 0</td>
</tr>
<tr>
<td>Norethindrone&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1 mg (as Ortho-Novum 1/35)</td>
<td>0.19 (30 to 7) 0.16 (27 to 13) 0</td>
</tr>
<tr>
<td>Depomedroxyprogesterone acetate</td>
<td>150 mg monthly</td>
<td>0.32 (30 to 14) 0</td>
</tr>
<tr>
<td>Fluconazole&lt;sup&gt;a&lt;/sup&gt;</td>
<td>200 mg QD</td>
<td>0.32 (160 to 160) 0.44 (38 to 27) 0</td>
</tr>
<tr>
<td>Ketoconazole&lt;sup&gt;a&lt;/sup&gt;</td>
<td>400 mg QD</td>
<td>0.32 (160 to 160) 0.44 (38 to 27) 0</td>
</tr>
<tr>
<td>Methadone&lt;sup&gt;a&lt;/sup&gt; Individual Subject DOSING</td>
<td>200 mg QD x 14 days; 200 mg BID x 7 days</td>
<td>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 6 of the 9 subjects. Methadone did not have any effect on nevirapine clearance.</td>
</tr>
<tr>
<td>Rifabutin&lt;sup&gt;a&lt;/sup&gt;</td>
<td>150 or 300 mg QD</td>
<td>0.79 (2 to 40) 0.28 (9 to 51) 0</td>
</tr>
<tr>
<td>Mebeverine&lt;sup&gt;a&lt;/sup&gt; 25-200 mg per day</td>
<td>24 (16 to 84) 29 (2 to 68) 22 (14 to 74)</td>
<td></td>
</tr>
<tr>
<td>Rifampin&lt;sup&gt;a&lt;/sup&gt;</td>
<td>800 mg QD</td>
<td>0.31 (4 to 28) 0</td>
</tr>
</tbody>
</table>

<sup>a</sup> = AUC<sub>max</sub> below detectable level of the assay
<sup>b</sup> = Increase, <sup>c</sup> = Decrease, <sup>d</sup> = No Effect

*For information regarding clinical recommendations, see Drug Interactions (7).
13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Long-term carcinogenicity studics 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 6, 35, 175 or 350 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 toxicity assays, nevirapine showed no evidence of mutagenic or clastogenic activity in a battery of tests including 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 treated mice 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- naive 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 PI and NRTIs in 109 (5%). The subjects (median age 36.5 years, 79% 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 ARVs-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>
<thead>
<tr>
<th>Outcome</th>
<th>VIRAMUNE (N=1121)</th>
<th>Placebo (N=4129)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Responders at 48 weeks: HIV-1 RNA &lt;50 copies/mL</td>
<td>18%</td>
<td>2%</td>
</tr>
<tr>
<td>Treatment Failure</td>
<td>82%</td>
<td>98%</td>
</tr>
<tr>
<td>Never suppressed viral load</td>
<td>45%</td>
<td>66%</td>
</tr>
<tr>
<td>Virologic failure after response</td>
<td>7%</td>
<td>4%</td>
</tr>
<tr>
<td>CDC category C event or death</td>
<td>10%</td>
<td>11%</td>
</tr>
<tr>
<td>Added antiretroviral therapy (^2) while &lt;50 copies/mL</td>
<td>5%</td>
<td>1%</td>
</tr>
<tr>
<td>Discontinued trial therapy due to AE</td>
<td>7%</td>
<td>6%</td>
</tr>
<tr>
<td>Discontinued trial &lt;48 weeks (^3)</td>
<td>9%</td>
<td>10%</td>
</tr>
</tbody>
</table>

\(^1\) 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-naive or having received only ZDV (85 cells/mm\(^3\) versus 25 cells/mm\(^3\), respectively). At two years into the trial, 36% of subjects on VIRAMUNE had experienced class C CDC events as compared to 21% of subjects on the control arm. Trial BI 1046 (INCAPS) was a double-blind, placebo-controlled, randomized, three-arm trial with 151 HIV-1 infected subjects with CD4 \(^+\) cell counts of 200-600 cells/mm\(^3\) at baseline. BI 1046 compared treatment with VIRAMUNE+zidovudine+didanosine to VIRAMUNE+zidovudine and zidovudine+didanosine. Treatment doses were 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 200 mg twice daily (depending on body weight). The subjects had a mean baseline HIV-1 RNA of 4.41 log\(_{10}\) copies/mL (25,704 copies per mL) and mean baseline CD4 \(^+\) cell count of 376 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. The virologic responder rates at 48 weeks were 45% for subjects treated with VIRAMUNE+zidovudine+didanosine, 19% for subjects treated with zidovudine+didanosine, and 0% for subjects treated with VIRAMUNE+zidovudine. CD4 \(^+\) cell counts in the VIRAMUNE+ZDV+ddI group increased above baseline by a mean of 138 cells/mm\(^3\) at one year, significantly greater than the increase of 87 cells/mm\(^3\) in the ZDV+ddI subjects. The VIRAMUNE+ZDV group mean decreased by 6 cells/mm\(^3\) below baseline.

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-naive subjects between 3 months and 16 years of age received VIRAMUNE oral suspension for 48 weeks. Subjects were divided into four 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 mg per kg per day)] in combination with zidovudine and lamivudine (see Adverse Reactions (6.2), Use in Specific Populations (8.4), and Clinical Pharmacology (12.10)]. 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 37-2278). 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% (56/123).

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.
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.

**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/mm³. This group has the highest risk.
  - Men with CD4+ counts higher than 400 cells/mm³.

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
- high colored bowel movements (stools)
- feeling sick in 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
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"), breasts, 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.

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.

How should I take VIRAMUNE?

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 ingredients: nevirapine

Inactive ingredients:
VIRAMUNE tablets: microcrystalline cellulose, lactose monohydrate, povidone, sodium starch glycolate, colloidal silicon dioxide, and magnesium stearate
VIRAMUNE oral suspension: carmex 934P, methylparaben, propylparaben, sorbitol, sucrose, polysorbate 80, sodium hydroxide, and purified water
VIRAMUNE XR tablets: lactose monohydrate, hypromellose, iron oxide, and magnesium stearate

Distributed by:
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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DT1801ZD322017

This Medication Guide has been approved by the U.S. Food and Drug Administration
Revised: March 2017

Viramune Oral Suspension 50 mg/5mL
240 mL
NDC 0597-0047-24
# Viramune

**Viramune**

**nevirapine suspension**

## Product Information

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<tr>
<th>Product Type</th>
<th>Item Code (Source)</th>
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<tr>
<td>HUMAN PRESCRIPTION DRUG</td>
<td>NDC:0597-0047-07</td>
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## Route of Administration

- **ORAL**

## Active Ingredient/Active Molarity

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<tr>
<th>Ingredient Name</th>
<th>Basis of Strength</th>
<th>Strength</th>
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<tr>
<td>NEVIRAPINE (UNII: 99DK7FVK1H)</td>
<td>NEVIRAPINE (UNII: 99DK7FVK1H)</td>
<td>50 mg in 5 mL</td>
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## Product Characteristics

- **Color**: WHITE
- **Shape**: Score
- **Size**: Size
- **Flavor**: Imprint Code
- **Contains**: Contains

## Packaging

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<td>1157</td>
<td>200 mL in 1 BOTTLE, PLASTIC</td>
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**VIRAMUNE**

**nevrapine suspension**

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- **Shape**: Score
- **Size**: Size
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Boehringer Ingelheim Pharmaceuticals Inc.

Product Information

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Item Code (Source): NDC:0597-0046

Route of Administration: ORAL

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Product Characteristics

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Shape: OVAL
Size: 19mm
Flavor: Imprint Code: 54;193

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Marketing Start Date: 08/01/2001
Marketing End Date: 08/01/2001

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Registrant - Boehringer Ingelheim Pharmaceuticals, Inc. (603175944)

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Revised: 3/2017