Viramune® (nevirapine) Tablets, for oral use
Viramune® (nevirapine) Oral Suspension, for oral use
Initial U.S. Approval: 1996

WARNINGS AND PRECAUTIONS

Hepatotoxicity: Fatal and non-fatal hepatotoxicity has been reported. Monitor liver function tests before and during therapy. Permanently discontinue nevirapine if clinical hepatitis or transaminase elevations combined with rash or other systemic symptoms occur. Do not restart nevirapine after recovery. (5.1)

Rash: Fatal and non-fatal skin reactions, including Stevens-Johnson syndrome, toxic epidermal necrolysis, and hypersensitivity reactions, have been reported. Permanently discontinue nevirapine if severe skin reactions or hypersensitivity reactions occur. Check transaminase immediately for all patients who develop a rash in the first 18 weeks of treatment. (5.2)

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

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: 11/2012

Dosage and Administration

If any patient experiences rash during the 14-day lead-in period, do not discontinue immediately if experiencing:

- Signs or symptoms of hepatitis (5.1)
- Increased transaminases combined with rash or other systemic symptoms (5.1)
- Severe skin or hypersensitivity reactions (5.2)
- Any rash with systemic symptoms (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).

Recent Major Changes

Indications and Usage 11/2012
Warnings and Precautions Immune Reconstitution Syndrome (5.5) 11/2012

VIRAMUNE is an NNRTI indicated for combination antiretroviral treatment of HIV-1 infection in adults and in pediatric patients 15 days and older. (1)

Important Considerations:

- Initiation of treatment is not recommended in the following populations unless the benefits outweigh the risks. (1, 5.1)
  - adult females with CD4+ cell counts greater than 250 cells/mm³
  - adult males with CD4+ cell counts greater than 400 cells/mm³
- The 14-day lead-in period must be strictly followed; it has been demonstrated to reduce the frequency of rash. (2.4, 5.2)

DOSAGE AND ADMINISTRATION

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 (≥16 yrs)</th>
<th>Pediatric Patients* (≥15 days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>First 14 days</td>
<td>200 mg once daily</td>
</tr>
<tr>
<td>After 14 days</td>
<td>200 mg twice daily</td>
</tr>
</tbody>
</table>

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

VIRAMUNE is indicated for combination antiretroviral treatment of HIV-1 infection in adults and in pediatric patients 15 days and older [see Clinical Studies (14.1), 14.2].

Additional important information regarding the use of VIRAMUNE for the treatment of HIV-1 infection:

- Based on serious and life-threatening hepatotoxicity observed in controlled and uncontrolled trials, VIRAMUNE should not be initiated in adult females with CD4+ cell counts greater than 250 cells/mm³ or in adult males with CD4+ cell counts greater than 400 cells/mm³ unless the benefit outweighs the risk [see Boxed Warning and Warnings and Precautions (5.1)].
The 14-day lead-in period with VIRAMUNE 200 mg daily dosing must be strictly followed; it has been demonstrated to reduce the frequency 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.

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 lead-in period has been observed to decrease the incidence of rash. 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/m² once daily for 14 days followed by 150 mg/m² twice daily thereafter. The total daily dose should not exceed 400 mg for any patient.

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

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/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 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 Boxed Warning, Warnings and Precautions (5.2), and Patient Counseling Information (17.1)]. 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) and Patient Counseling Information (17.1)]. 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

4.1 Hepatic Impairment
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)].

Reference ID: 3215206
4.2 Post-Exposure Prophylaxis

VIRAMUNE is contraindicated for use as part of occupational and non-occupational post-exposure prophylaxis (PEP) regimens [see Warnings and Precautions (5.1)].

5 Warnings and Precautions

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 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.

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 and 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)].

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 patients, 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. Patients with signs or symptoms of hepatitis must be advised to discontinue VIRAMUNE and immediately seek medical evaluation, which should include liver enzyme tests.

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, 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 Boxed Warning, Dosage and Administration (2.3), and Patient Counseling Information (17.1)].

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.

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 treatment, 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 1% 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 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 (4.2)]. 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 (4.1), 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 [see Boxed Warning and Patient Counseling Information (17.1)]. Do not restart VIRAMUNE following severe skin rash, skin rash combined with increased transaminases or other symptoms, or hypersensitivity reaction.

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 (12.4)].

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 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 in Adult Patients
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.

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/mm³ in women and greater than 400 cells/mm³ 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

<table>
<thead>
<tr>
<th>Trial 1090†</th>
<th>VIRAMUNE (n=1121)</th>
<th>Placebo (n=1128)</th>
<th>Trials 1037, 1038, 1046‡</th>
<th>VIRAMUNE (n=253)</th>
<th>Placebo (n=203)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median exposure (weeks)</td>
<td>58</td>
<td>52</td>
<td>28</td>
<td>28</td>
<td></td>
</tr>
<tr>
<td>Any adverse event</td>
<td>15%</td>
<td>11%</td>
<td>32%</td>
<td>13%</td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>5</td>
<td>2</td>
<td>7</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>1</td>
<td>1</td>
<td>9</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Granulocytopenia</td>
<td>2</td>
<td>3</td>
<td>&lt;1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>1</td>
<td>&lt;1</td>
<td>4</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>&lt;1</td>
<td>&lt;1</td>
<td>5</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>&lt;1</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>&lt;1</td>
<td>&lt;1</td>
<td>2</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Myalgia</td>
<td>&lt;1</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>

† Background therapy included 3TC for all subjects and combinations of NRTIs and PIs. Subjects had CD4⁺ cell counts less than 200 cells/mm³.
‡ Background therapy included ZDV and ZDV+ddl; VIRAMUNE monotherapy was administered in some subjects. Subjects had CD4⁺ cell count greater than or equal to 200 cells/mm³.

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

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>Trial 1090†</th>
<th>VIRAMUNE (n=1121)</th>
<th>Placebo (n=1128)</th>
<th>Trials 1037, 1038, 1046‡</th>
<th>VIRAMUNE (n=253)</th>
<th>Placebo (n=203)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood Chemistry</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SGPT (ALT) &gt;250 U/L</td>
<td>5</td>
<td>4</td>
<td>14</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SGOT (AST) &gt;250 U/L</td>
<td>4</td>
<td>3</td>
<td>8</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bilirubin &gt;2.5 mg/dL</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hematology</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemoglobin &lt;8.0 g/dL</td>
<td>3</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platelets &lt;50,000/mm³</td>
<td>1</td>
<td>1</td>
<td>&lt;1</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutrophils &lt;750/mm³</td>
<td>13</td>
<td>14</td>
<td>4</td>
<td>1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

† Background therapy included 3TC for all subjects and combinations of NRTIs and PIs. Subjects had CD4⁺ cell counts less than 200 cells/mm³.
‡ Background therapy included ZDV and ZDV+ddl; VIRAMUNE monotherapy was administered in some subjects. Subjects had CD4⁺ cell count greater than or equal to 200 cells/mm³.

6.2 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.

6.3 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)]

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 [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 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 drugs that are metabolized by the cytochrome P450 system. These potential drug interactions are also listed in Table 4. Although specific drug interaction trials in HIV-1 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

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Effect on Concentration of Nevirapine or Concomitant Drug</th>
<th>Clinical Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HIV Antiviral Agents: Protease Inhibitors (PIs)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atazanavir/Ritonavir*</td>
<td>↓ Atazanavir ↑ Nevirapine</td>
<td>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.</td>
</tr>
<tr>
<td>Fosamprenavir*</td>
<td>↓Amprenavir ↑Nevirapine</td>
<td>Co-administration of nevirapine and fosamprenavir without ritonavir is not recommended.</td>
</tr>
<tr>
<td>Fosamprenavir/Ritonavir*</td>
<td>↓Amprenavir ↑Nevirapine</td>
<td>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.</td>
</tr>
<tr>
<td>Indinavir*</td>
<td>↓ Indinavir</td>
<td>The appropriate doses of this combination of indinavir and nevirapine with respect to efficacy and safety have not been established.</td>
</tr>
<tr>
<td>Lopinavir/Ritonavir*</td>
<td>↓Lopinavir</td>
<td>Dosing in adult patients:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>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.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dosing in pediatric patients:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Please refer to the Kaletra® prescribing information for dosing recommendations based</td>
</tr>
</tbody>
</table>
on body surface area and body weight. Neither lopinavir/ritonavir tablets nor oral solution should be administered once daily in combination with nevirapine.

| 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 | | |

| Other Agents |
|---|---|
| Analgesics: Methadone* | ↓ Methadone | Methadone levels were decreased; increased 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 | 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 |
Itraconazole

\[ \downarrow \text{Itraconazole} \]

administered concomitantly because decreases in ketoconazole plasma concentrations may reduce the efficacy of the drug.

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 not 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*

\[ \downarrow \text{Ethinyl estradiol} \]
\[ \downarrow \text{Norethindrone} \]

Oral contraceptives and other hormonal methods of birth control should not be used as the sole method of contraception in women taking nevirapine, since nevirapine may lower the plasma levels of these medications. An alternative or additional method of contraception is recommended.

* 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 Category B.**

There are no adequate and well-controlled trials of VIRAMUNE in pregnant women. The Antiretroviral Pregnancy Registry, which has been surveying pregnancy outcomes since January 1989, has not found an increased risk of birth defects following first trimester exposures to nevirapine. The prevalence of birth defects after any trimester exposure to nevirapine is comparable to the prevalence observed in the general population.

Severe hepatic events, including fatalities, have been reported in pregnant women receiving chronic VIRAMUNE therapy as part of combination treatment of HIV-1 infection. Regardless of pregnancy status, women with CD4+ cell counts 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 Boxed Warning].

VIRAMUNE should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

**Antiretroviral Pregnancy Registry**

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

**Animal Data**

No observable teratogenicity was detected in reproductive studies performed in pregnant rats and rabbits. The maternal and developmental no-observable-effect level dosages produced systemic exposures approximately equivalent to or approximately 50% higher in rats and rabbits, respectively, than those seen at the recommended daily human dose (based on AUC). In rats, decreased fetal body weights were observed due to administration of a maternally toxic dose (exposures approximately 50% higher than that seen at the recommended human clinical dose).

8.3 Nursing Mothers

Reference ID: 3215206
The Centers for Disease Control and Prevention recommend that HIV-1 infected mothers not breastfeed their infants to avoid risking postnatal transmission of HIV-1. Nevirapine is excreted in breast milk. Because of both the potential for HIV-1 transmission and the potential for serious adverse reactions in nursing infants, mothers should be instructed not to breastfeed if they are receiving VIRAMUNE.

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 conjugated in the liver and 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 overdose. 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_{4}O. Nevirapine has the following structural formula:

![Nevirapine Structural Formula](image)

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: carboxmer 934P, methylparaben, propylparaben, sorbitol, sucrose, polysorbate 80, sodium hydroxide and purified water.

12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
Nevirapine is an antiviral drug [see Microbiology (12.4)].

12.2 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 ± 9% (mean ± SD) for a 50 mg tablet and 91 ± 8% for an oral solution. Peak plasma nevirapine 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) 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 (8.3)]. 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 14C-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 subjects with renal failure requiring dialysis.

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 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; 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), and Use in Specific Populations (8.7)].

Gender
In the multinational 2NN trial, a population pharmacokinetic sub-study 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.

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

Black subjects (n=80/group) in Trial 1100.1486 showed approximately 30% to 35% higher trough concentrations than Caucasian subjects (250-325 subjects/group) in both immediate-release VIRAMUNE 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)].

Reference ID: 3215206
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 old 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/m² once daily for two weeks followed by 150 mg/m² twice daily thereafter [see Use in Specific Populations (8.4) and Adverse Reactions (6.2)]. Dosing of nevirapine at 150 mg/m² BID (after a two-week lead-in of 150 mg/m² 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 Ki 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, Cmax, and Cmin 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)

<table>
<thead>
<tr>
<th>Co-administered Drug</th>
<th>Dose of Co-administered Drug</th>
<th>Dose Regimen of VIRAMUNE</th>
<th>n</th>
<th>% Change of Co-administered Drug Pharmacokinetic Parameters (90% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>AUC</td>
</tr>
<tr>
<td><strong>Antiretrovirals</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atazanavir/Ritonavir</td>
<td>300/100 mg QD day 4–13, then 400/100 mg QD, day 14–23</td>
<td>200 mg BID day 1–23. Subjects were treated with nevirapine prior to trial entry.</td>
<td>23</td>
<td>Atazanavir 300/100 mg ↓42 (Δ52 to Δ29)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Atazanavir 400/100 mg ↓19 (Δ35 to Δ2)</td>
</tr>
<tr>
<td>Darunavir/Ritonavir</td>
<td>400/100 mg BID</td>
<td>200 mg BID</td>
<td>8</td>
<td>↑24 (Δ3 to Δ57)</td>
</tr>
<tr>
<td>Didanosine</td>
<td>100-150 mg BID</td>
<td>200 mg QD x 14 days; 200 mg BID x 14 days</td>
<td>18</td>
<td>⇔</td>
</tr>
<tr>
<td>Efavirenz</td>
<td>600 mg QD</td>
<td>200 mg QD x 14 days; 400 mg QD x 14 days</td>
<td>17</td>
<td>↓28 (Δ34 to Δ14)</td>
</tr>
<tr>
<td>Fosamprenavir</td>
<td>1400 mg BID</td>
<td>200 mg BID. Subjects were treated with nevirapine prior to trial entry.</td>
<td>17</td>
<td>↓33 (Δ45 to Δ20)</td>
</tr>
<tr>
<td>Fosamprenavir/Ritonavir</td>
<td>700/100 mg BID</td>
<td>200 mg BID. Subjects were treated with nevirapine prior to trial entry.</td>
<td>17</td>
<td>↓11 (Δ23 to Δ3)</td>
</tr>
</tbody>
</table>

Reference ID: 3215206
<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose/Strength</th>
<th>Start Dosing</th>
<th>End Dosing</th>
<th>Cmax</th>
<th>Cmin</th>
<th>Reference ID</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indinavir</td>
<td>800 mg q8H</td>
<td>200 mg QD x 14 days; 200 mg BID x 14 days</td>
<td>19  ↓15 (↓24 to ↓4)</td>
<td>↓44 (↓53 to ↓33)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lopinavir</td>
<td>300/75 mg/m² (lopinavir/ritonavir)</td>
<td>7 mg/kg or 4 mg/kg QD x 2 weeks; BID x 1 week</td>
<td>12, 15  ↓14 (↓36 to ↑16)</td>
<td>↓55 (↓75 to ↓19)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lopinavir</td>
<td>400/100 mg BID (lopinavir/ritonavir)</td>
<td>200 mg QD x 14 days; 200 mg BID &gt;1 year</td>
<td>22, 19  ↓19 (↓38 to ↑5)</td>
<td>↓51 (↓72 to ↓26)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maraviroc</td>
<td>300 mg SD</td>
<td>200 mg BID</td>
<td>8  ↑1 (↑35 to ↑55)</td>
<td>↑54 (↑6 to ↑151)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nelfinavir</td>
<td>750 mg TID</td>
<td>200 mg QD x 14 days; 200 mg BID x 14 days</td>
<td>23  ⇔</td>
<td>⇔</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nelfinavir-M8 metabolite</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ritonavir</td>
<td>600 mg BID</td>
<td>200 mg QD x 14 days; 200 mg BID x 14 days</td>
<td>18  ⇔</td>
<td>⇔</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stavudine</td>
<td>30-40 mg BID</td>
<td>200 mg QD x 14 days; 200 mg BID x 14 days</td>
<td>22  ⇔</td>
<td>⇔</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zalcitabine</td>
<td>0.125-0.25 mg TID</td>
<td>200 mg QD x 14 days; 200 mg BID x 14 days</td>
<td>6  ⇔</td>
<td>⇔</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zidovudine</td>
<td>100-200 mg TID</td>
<td>200 mg QD x 14 days; 200 mg BID x 14 days</td>
<td>11  ↓28 (↓40 to ↓4)</td>
<td>↓30 (↓51 to ↑14)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other Medications</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clarithromycina Metabolite</td>
<td>500 mg BID</td>
<td>200 mg QD x 14 days; 200 mg BID x 14 days</td>
<td>15  ↓31 (↓38 to ↓24)</td>
<td>↓56 (↓70 to ↓36)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethinyl estradiol and Norethindrone</td>
<td>0.035 mg (as Ortho-Novum® 1/35) and 1 mg (as Ortho-Novum® 1/35)</td>
<td>200 mg QD x 14 days; 200 mg BID x 14 days</td>
<td>10  ↓20 (↓33 to ↓3)</td>
<td>⇔</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depomedroxy-progesterone acetate</td>
<td>150 mg every 3 months</td>
<td>200 mg QD x 14 days; 200 mg BID x 14 days</td>
<td>32  ⇔</td>
<td>⇔</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluconazole</td>
<td>200 mg QD</td>
<td>200 mg QD x 14 days; 200 mg BID x 14 days</td>
<td>19  ⇔</td>
<td>⇔</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ketoconazole</td>
<td>400 mg QD</td>
<td>200 mg QD x 14 days; 200 mg BID x 14 days</td>
<td>21  ↓72 (↓80 to ↓60)</td>
<td>↓44 (↓58 to ↓27)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methadone Individual Subject Dosing</td>
<td>200 mg QD x 14 days; 200 mg BID ≥7 days</td>
<td>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.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rifabutin</td>
<td>150 or 300 mg QD</td>
<td>200 mg QD x 14 days; 200 mg BID x 14 days</td>
<td>19  ↑17 (↑2 to ↑40)</td>
<td>↑28 (↑9 to ↑51)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Reference ID: 3215206
Reference ID: 3215206

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 EC₅₀ value (50% inhibitory concentration) of nevirapine was 90 nM against a panel of 2923 isolates of HIV-1 that were primarily (93%) clade B clinical isolates from the United States. The 99th percentile EC₅₀ value was 470 nM in this trial. The median EC₅₀ 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. Nevirapine exhibited additive to synergistic anti-HIV-1 activity in combination with the protease inhibitors amprenavir, atazanavir, indinavir, lopinavir, nelfinavir, saquinavir and tipranavir, and the NRTIs abacavir, didanosine, emtricitabine, lamivudine, stavudine, tenofovir and zidovudine. The anti-HIV-1 activity of nevirapine was antagonized by the anti-HBV drug adefovir and by the anti-HCV drug ribavirin in 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, Y188C/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 a novel amino acid substitution Y188N. Phenotypic analysis showed that Y188N and Y181I substitutions conferred 103- and 22-fold reductions in susceptibility to nevirapine, respectively.

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 and Y181I substitutions conferred resistance 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 toxicity 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 toxicity 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/mm3 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 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/mm3 and a baseline HIV-1 RNA of 4.58 log10 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

<table>
<thead>
<tr>
<th>Outcome</th>
<th>VIRAMUNE (N=1121)</th>
<th>Placebo (N=1128)</th>
</tr>
</thead>
<tbody>
<tr>
<td>%</td>
<td></td>
<td>%</td>
</tr>
<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 therapy1 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 weeks2</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/mm³ versus 22 cells/mm³, respectively), as well as for subjects who entered the trial as treatment-naïve or having received only ZDV (85 cells/mm³ versus 25 cells/mm³, 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.

Trial 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 cells/mm³ 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 mean baseline HIV-1 RNA of 4.41 log10 copies/mL (25,704 copies per mL) and mean baseline CD4+ cell count of 376 cells/mm³. 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+d/dd group increased above baseline by a mean of 139 cells/mm³ at one year, significantly greater than the increase of 87 cells/mm³ in the ZDV+d/dd subjects. The VIRAMUNE+ZDV group mean decreased by 6 cells/mm³ 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-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/m²) 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 log₁₀ copies per mL and a median baseline CD4⁺ cell count of 527 cells/mm³ (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).

VIRAMUNE tablets are supplied in unit dose packages of 14 (NDC 0597-0046-46).

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
• “See FDA-approved patient labeling (Medication Guide)”

17.1 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 and skin reactions. 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/mm³ in women and greater than 400 cells/mm³ 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 Boxed Warning and 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 Boxed Warning and Warnings and Precautions (5.2)].

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

VIRAMUNE is not a cure for HIV-1 infection; patients may continue to experience illnesses associated with advanced HIV-1 infection, including opportunistic infections. Advise patients to remain under the care of a physician when using VIRAMUNE.

Patients should be told that sustained decreases in plasma HIV RNA have been associated with a reduced risk of progression to AIDS and death. Patients should be advised to avoid doing things that can spread HIV-1 infection to others.

• Do not share needles or other injection equipment.
• Do not share personal items that can have blood or body fluids on them, like toothbrushes and razor blades.
• Do not have any kind of sex without protection. Always practice safe sex by using a latex or polyurethane condom to lower the chance of sexual contact with semen, vaginal secretions, or blood.
• Do not breastfeed. We do not know if VIRAMUNE can be passed to your baby in your breast milk and whether it could harm your baby. Also, mothers with HIV-1 should not breastfeed because HIV-1 can be passed to the baby in the breast milk.

Inform patients that they should not take VIRAMUNE tablets or oral suspension and VIRAMUNE XR extended release tablets at the same time.
17.3 Drug Interactions
VIRAMUNE may interact with some drugs; therefore, patients should be advised 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)].

17.4 Contraceptives
Hormonal methods of birth control, other than depomedroxy-progesterone acetate (DMPA), should not be used as the sole method of contraception in women taking VIRAMUNE, since VIRAMUNE may lower the plasma levels of these medications. Additionally, when oral contraceptives are used for hormonal regulation during VIRAMUNE therapy, the therapeutic effect of the hormonal therapy should be monitored [see Drug Interactions (7)].

17.5 Methadone
VIRAMUNE may decrease plasma concentrations of methadone by increasing its hepatic metabolism. Narcotic withdrawal syndrome has been reported in patients treated with VIRAMUNE and methadone concomitantly. Monitor methadone-maintained patients beginning nevirapine therapy for evidence of withdrawal and adjust methadone dose accordingly [see Drug Interactions (7)].

17.6 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 effects of these conditions are not known at this time [see Warnings and Precautions (5.6)].

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