CD4 cells counts of 200-600/mm3 were treated with either VIRAMUNE + zidovudine (n = 46), zidovudine + didanosine (n = 51) or VIRAMUNE + zidovudine + didanosine (n = 51) and followed for 52 weeks or longer on therapy. Virologic evaluations were performed at baseline, six months and 12 months. The phenotypic resistance test performed required a minimum of 1000 copies/ml HIV RNA in order to be able to amplify the virus. Of the three study groups, 16, 19 and 28 patients respectively had evaluable baseline isolates and subsequently remained in the study for at least 24 weeks. At baseline, there were five cases of phenotypic resistance to nevirapine; the IC50 values were 5 to 6.5-fold increased in three and > 100 fold in two. At 24 weeks, all available isolates recoverable from patients receiving nevirapine were resistant to this agent, while 18/21 (86%) patients carried such isolates at 30-60 weeks. In 16 subjects viral suppression was below the limits of detection (<20 copies/ml = 14, <400 copies/ml = 2). Assuming that suppression below <20 copies/ml implies nevirapine susceptibility of the virus, 45% (17/38) of patients had virus measured or imputed to be susceptible to nevirapine. All 11 subjects receiving VIRAMUNE + zidovudine who were tested for phenotypic resistance were resistant to nevirapine by six months. Over the entire period of observation, one case of didanosine resistance was seen. Zidovudine resistance emerged as more frequent after 30-60 weeks, especially in patients receiving double combination therapy. Based on the increase in IC50, zidovudine resistance appeared lower in the VIRAMUNE + zidovudine + didanosine group than the other treatment groups. With respect to nevirapine resistance, all isolates that were sequenced carried at least one mutation associated with resistance, the most common single changes being K103N and Y181C. Combinations of mutations were found in nine of the 12 patients observed. These data from INCAS illustrate that the use of highly

**Composition**

1 tablet contains: 200 mg 11-cyclopropyl-5,11-dihydro-4-methyl-6H-dipyrido[3,2-b:2′,3′-e][1,4]diazepin-6-one (= nevirapine anhydrate)  
Excipients: avicel, lactose, polyvidone 25, primgoel, aerosil 200, magnesium stearate  
1 ml oral suspension contains: 10 mg 11-cyclopropyl-5, 11-dihydro-4-methyl-6H-dipyrido[3,2-b:2′,3′-e][1,4]diazepin-6-one (nevirapine; as 10.35 mg nevirapine hemihydrate)  
Excipients: carbomer, methyl parahydroxybenzoate, propyl parahydroxybenzoate, sorbitol, sucrose, polysorbate 80, sodium hydroxide and purified water

**Properties**

Nevirapine is a NNRTI of HIV 1. Nevirapine binds directly to reverse transcriptase 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 reverse transcriptase and eukaryotic DNA polymerases (such as human DNA polymerases *, *, *, or *) are not inhibited by nevirapine.

**Resistance**

HIV isolates with reduced susceptibility (100 to 250-fold) to nevirapine emerge in vitro. Phenotypic and genotypic changes occur in HIV isolates from patients treated with VIRAMUNE or VIRAMUNE+ zidovudine over one to 12 weeks. By week 8 of VIRAMUNE monotherapy, 100% of the patients tested had HIV isolates with a >100-fold decrease in susceptibility to nevirapine, regardless of dose. VIRAMUNE + zidovudine combination therapy did not alter the emergence rate of nevirapine-resistant virus. Genotypic and phenotypic resistance was examined for patients receiving VIRAMUNE in triple and double therapy drug combination therapy, and in the non- VIRAMUNE comparative group from the INCAS study. Antiretroviral naive subjects with
active drug therapies is associated with a delay in the development of antiretroviral drug resistance. The genotypic correlates of phenotypic VIRAMUNE resistance were identified in 12 plasma isolates from 11 triple therapy patients. Treatment-emergent, VIRAMUNE resistance-associated mutations were:

<table>
<thead>
<tr>
<th>Mutation</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>K101E</td>
<td>2</td>
</tr>
<tr>
<td>K103N</td>
<td>8</td>
</tr>
<tr>
<td>V106A</td>
<td>2</td>
</tr>
<tr>
<td>Y181C</td>
<td>5</td>
</tr>
<tr>
<td>G190A</td>
<td>5</td>
</tr>
</tbody>
</table>

The clinical relevance of phenotypic and genotypic changes associated with VIRAMUNE therapy has not been established. In addition to the data presented above, there exists a risk of rapid emergence of resistance to NNRTIs in case of virological failure.

Resistance in PMTCT:
Nevirapine resistance mutations were detected within 6-8 weeks after single dose administration in 21 of 111 (19%) women tested in HIVNET 012. K103N was the most frequently observed nevirapine mutation detected (57%) in these women, followed by a mixture of K103N and Y181C (19%). Nevirapine resistance mutations were not detectable in any of the women (n=11) who had detectable mutations at 6-8 weeks, and who were re-tested 12-24 months after delivery. Eleven of 24 (46%) infected infants tested in HIVNET 012 exhibited nevirapine resistance, with Y181C being the most common mutation detected. Nevirapine resistance mutations were not detectable in any of the infants (n=7) who had detectable mutations at 6-8 weeks of age, and who were re-tested by 12 months of age. The clinical significance of these findings and their impact on subsequent NNRTI treatment is not known.

Cross-resistance
Rapid emergence of HIV strains which are cross-resistant to NNRTIs has been observed in vitro. Data on cross-resistance between the NNRTI nevirapine and NRTIs are very limited. In four patients, zidovudine-resistant isolates tested in vitro retained susceptibility to nevirapine and in six patients nevirapine-resistant isolates were susceptible to zidovudine and didanosine. Cross-resistance between nevirapine and HIV PIs is unlikely because the enzyme targets involved are different. Cross-resistance among the currently registered NNRTIs is broad. Some genotypic resistance data indicate that in most patients failing NNRTI viral strains express cross-resistance to the other NNRTIs. The currently available data do not support sequential use of NNRTIs.

Pharmacodynamic Effects
VIRAMUNE has been evaluated in both treatment-naive and treatment-experienced patients.

Results from a trial (ACTG 241) evaluated triple therapy with VIRAMUNE, zidovudine and didanosine compared to zidovudine + didanosine, in 398 HIV-1 infected patients (mean baseline 153 CD4+ cells/mm3; plasma HIV-1 RNA 4.59 log10 copies/ml), who had received at least 6 months of NRTI therapy prior to enrolment (median 115 weeks). These heavily experienced patients demonstrated a significant improvement of the triple therapy group over the double therapy group for one year in both viral RNA and CD4+ cell counts. A durable response for at least one year was documented in a trial (INCAS) for the triple therapy arm with VIRAMUNE, zidovudine and didanosine compared to zidovudine + didanosine or VIRAMUNE + zidovudine in 151 HIV-1 infected, treatment naive patients with CD4+ cell counts of 200-600 cells/mm3 (mean 376 cells/mm3) and a mean baseline plasma HIV-1 RNA concentration of 4.41 log10 copies/ml (25,704 copies/ml). Treatment doses were VIRAMUNE, 20 mg daily for two weeks, followed by 200 mg twice daily, or placebo; zidovudine, 200 mg three times daily; didanosine, 125 or 200 mg twice daily (depending on the weight). VIRAMUNE has also been studied in combination with other antiretroviral agents, e.g., zalcitabine, stavudine, lamivudine, indinavir, ritonavir, nelfinavir, saquinavir and lopinavir. No new and overt safety problems have been reported for these combinations. Studies are ongoing to evaluate the efficacy and safety of combination therapies with VIRAMUNE in patients failing PI therapy.
**Perinatal Transmission**

Two studies evaluated the efficacy of VIRAMUNE to prevent vertical transmission of HIV-1 infection. Mothers received only study antiretroviral therapy during these trials. In the HIVNET 012 study in Kampala (Uganda) mother-infant pairs were randomised to receive oral VIRAMUNE (mother: 200 mg at the onset of labour; infant: 2 mg/kg within 72 hours of birth), or an ultra-short oral zidovudine regimen (mother: 600 mg at the onset of labour and 300 mg every 3 hours until delivery; infant 4 mg/kg twice daily for 7 days). The cumulative HIV-1 infection rate at 14-16 weeks was 13.1% (n = 310) in the VIRAMUNE group, versus 25.1% (n = 308 in the ultra-short zidovudine group (p = 0.00063). In the SAINT study conducted in South Africa, mother-infant pairs were randomised to receive oral VIRAMUNE (mother: 200 mg during labor and 200 mg 24 to 48 hours postdelivery; infant: 6 mg 24 to 48 hours postdelivery); or a short oral zidovudine plus lamivudine regimen (mother: zidovudine 600 mg, then 300 mg every 3 hours during labour, followed by 300 mg b.i.d. for 7 days postdelivery plus lamivudine 150 mg b.i.d. during labour and for 7 days postdelivery; infant: zidovudine 12 mg b.i.d. plus lamivudine 6 mg b.i.d. for 7 days [if infant weight <2 kg, zidovudine 4 mg/kg b.i.d. plus lamivudine 2 mg/kg b.i.d. for 7 days]). There was no significant difference in HIV-1 transmission rates through 6 to 8 weeks between the VIRAMUNE group (5.7%, n = 652) and the zidovudine plus lamivudine group (3.6%, n = 649). There was greater risk of HIV-1 transmission to babies whose mothers received their VIRAMUNE or their zidovudine plus lamivudine doses less than 2 hours before delivery. In the SAINT study 68% of nevirapine-exposed mothers had resistant strains at approximately 4 weeks after delivery.

The clinical relevance of these data in European populations has not been established. Furthermore in the case VIRAMUNE is used as single dose to prevent vertical transmission of HIV-1 infection, the risk of hepatotoxicity in mother and child cannot be excluded.

A blinded randomized clinical trial in women already taking antiretroviral therapy throughout pregnancy (PACTG 316) demonstrated no further reduction of vertical HIV-1 transmission when the mother and the child received a single VIRAMUNE dose during labour and after birth respectively. HIV-1 transmission rates were similarly low in both treatment groups (1.3% in the VIRAMUNE group, 1.4% in the placebo group). The vertical transmission decreased neither in women with HIV-1 RNA below the limit of quantification nor in women with HIV-1 RNA above the limit of quantification prior to partus. Of the 95 women who received intrapartum VIRAMUNE, 15% developed nevirapine resistance mutations at 6 weeks post partus.

**Pharmacokinetic properties**

**Adults**

Nevirapine is readily absorbed (>90%) after oral administration in healthy volunteers and in adults with HIV 1 infection. Absolute bioavailability in 12 healthy adults following single-dose administration was 93 * 9% (mean SD) for a 50 mg tablet and 91 * 8% for an oral solution. Peak plasma nevirapine concentrations of 2 * 0.4 µg/ml (7.5 µM) were attained by 4 hours following a single 200 mg dose. Following multiple doses, nevirapine peak concentrations appear to increase linearly in the dose range of 200 to 400 mg/day. Data reported in the literature from 20 HIV infected patients suggest a steady state Cmax of 5.74 µg/ml (5.00-7.44) and Cmin of 3.73 µg/ml (3.20-5.08) with an AUC of 109.0 h*µg/ml (96.0-143.5) in patients taking 200 mg of nevirapine bid. Other published data support these conclusions. Long-term efficacy appears to be most likely in patients whose nevirapine trough levels exceed 3.5 µg/ml.

VIRAMUNE tablets and oral suspension have been shown to be comparably bioavailable and interchangeable at doses up to 200 mg.

The absorption of nevirapine is not affected by food, antacids or medicinal products which are formulated with an alkaline buffering agent (e.g., didanosine).
Nevirapine is lipophilic and is essentially nonionized at physiologic pH. Following intravenous administration to healthy adults, the volume of distribution (Vdss) of nevirapine was 1.21 ± 0.09 l/kg, suggesting that nevirapine is widely distributed in humans. Nevirapine readily crosses the placenta and is found in breast milk. Nevirapine is about 60% bound to plasma proteins in the plasma concentration range of 1-10 µg/ml. Nevirapine concentrations in human cerebrospinal fluid (n = 6) were 45% (*5%) of the concentrations in plasma; this ratio is approximately equal to the fraction not bound to plasma protein.

In vivo studies in humans and in vitro studies with human liver microsomes have shown that nevirapine is extensively biotransformed via cytochrome P450 (oxidative) metabolism to several hydroxylated metabolites. In vitro studies with human liver microsomes suggest that oxidative metabolism of nevirapine is mediated primarily by cytochrome P450 isoymes from the CYP3A family, although other isoymes may have a secondary role. In a mass balance/excretion study in eight healthy male volunteers dosed to steady state with nevirapine 200 mg given twice daily followed by a single 50 mg dose of 14C-nevirapine, approximately 91.4 ± 10.5% of the radiolabelled dose was recovered, with urine (81.3 ± 11.1%) representing the primary route of excretion compared to faeces (10.1 ± 1.5%). Greater than 80% of the radioactivity in urine was made up of glucuronide conjugates of hydroxylated metabolites. Thus cytochrome P450 metabolism, glucuronide conjugation, and urinary excretion of glucuronidated metabolites represent the primary route of nevirapine biotransformation and elimination in humans. Only a small fraction (<5%) of the radioactivity in urine (representing <3% of the total dose) was made up of parent compound; therefore, renal excretion plays a minor role in elimination of the parent compound.

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

Renal dysfunction: The single-dose pharmacokinetics of nevirapine have been compared in 23 subjects with either mild (50 ≤ CLcr < 80 ml/min), moderate (30 ≤ CLcr < 50 ml/min) or severe renal dysfunction (CLcr <30 ml/min), renal impairment or end-stage renal disease (ESRD) requiring dialysis, and 8 subjects with normal renal function (CLcr >80 ml/min). Renal impairment (mild, moderate and severe) resulted in no significant change in the pharmacokinetics of nevirapine. However, subjects with ESRD requiring dialysis exhibited a 43.5% reduction in nevirapine AUC over a one-week exposure period. There was also accumulation of nevirapine hydroxy metabolites in plasma. The results suggest that supplementing VIRAMUNE therapy with an additional 200 mg dose of VIRAMUNE following each dialysis treatment would help offset the effects of dialysis on nevirapine clearance. Otherwise patients with CLcr ≥20 ml/min do not require an adjustment in VIRAMUNE dosing.

Hepatic dysfunction: The single-dose pharmacokinetics of nevirapine have been compared in 10 subjects with hepatic dysfunction and 8 subjects with normal hepatic function. Overall, the results suggest that patients with mild to moderate hepatic dysfunction, defined as Child-Pugh Classification Score ≤7, do not require an adjustment in VIRAMUNE dosing. However, the pharmacokinetics of nevirapine in one subject with a Child-Pugh score of 8 and moderate to severe ascites suggests that patients with worsening hepatic function may be at risk of accumulating nevirapine in the systemic circulation. Although a slightly higher weight adjusted volume of distribution of nevirapine was found in female subjects compared to males, no significant gender differences in nevirapine plasma concentrations following single or multiple dose administrations were
py for the antiviral treatment of HIV-1 infected patients with advanced or progressive immunodeficiency. Most of the experience with VIRAMUNE is in combination with nucleoside reverse transcriptase inhibitors (NRTIs). There is at present insufficient data on the efficacy of subsequent use of triple combination including protease inhibitors (PIs) after VIRAMUNE therapy.

For the prevention of mother to child transmission of HIV-1 in pregnant women who are not taking antiretroviral therapy at time of labour, VIRAMUNE is indicated and may be used alone, as a single oral dose to the mother during labour and a single oral dose to the infant after birth (see dosage and administration). When feasible, extended treatment of the mother with combination antiretroviral agents prior to delivery is recommended, to minimize HIV-1 transmission to the infant.

Contraindications

Hypersensitivity to the active substance or to any of the excipients. VIRAMUNE should not be readministered to patients who have required permanent discontinuation for severe rash, rash accompanied by constitutional symptoms, hypersensitivity reactions, or clinical hepatitis due to nevirapine. VIRAMUNE should not be used in patients with severe hepatic impairment or pre-treatment ASAT or ALAT >5 ULN until baseline ASAT/ALAT are stabilised <5 ULN. VIRAMUNE should not be readministered in patients who previously had ASAT or ALAT >5 ULN during VIRAMUNE therapy and had recurrence of liver function abnormalities upon readministeration of VIRAMUNE (see Special warnings and Precautions).

Herbal preparations containing St John’s wort (Hypericum perforatum) must not be used while taking VIRAMUNE due to the risk of decreased plasma concentrations and reduced clinical effects of nevirapine (see Interactions). The available pharmacokinetic data suggest that the concomitant use of rifampicin and VIRAMUNE is not recommended (see Interactions).

Paediatric patients

The pharmacokinetics of nevirapine have been studied in two open-label studies in children with HIV-1 infection. In one study, nine HIV infected children ranging in age from 9 months to 14 years were administered a single dose (7.5 mg, 30 mg, or 120 mg per m2; n = 3 per dose) of VIRAMUNE oral suspension after an overnight fast. Nevirapine AUC and peak concentration increased in proportion with dose. Following absorption nevirapine mean plasma concentrations declined log linearly with time. Nevirapine terminal phase half-life following a single dose was 30.6 * 10.2 hours.

In a second multiple dose study, VIRAMUNE suspension or tablets (240 to 400 mg/m2/day) were administered as monotherapy or in combination with zidovudine or didanosine to 37 HIV-1 infected pediatric patients with the following demographics: male (54%), racial minority groups (73%), median age of 11 months (range: 2 months – 15 years). These patients received 120 mg/ m2/day of nevirapine for approximately 4 weeks followed by 120 mg/ m2/b.i.d. (patients >9 years of age) or 200 mg/ m2/b.i.d. (patients ≤9 years of age). Nevirapine clearance adjusted for body weight reached maximum values by age 1 to 2 years and then decreased with increasing age. Nevirapine apparent clearance adjusted for body weight was approximately two-fold greater in children younger than 8 years compared to adults. Nevirapine half life for the study group as a whole after dosing to steady state was 25.9 * 9.6 hours. With long term drug administration, the mean values for nevirapine terminal half-life changed with age as follows: 2 months to 1 year (32 hours), 1 to 4 years (21 hours), 4 to 8 years (18 hours), greater than 8 years (28 hours).

Indications

VIRAMUNE is indicated as part of combination thera-
Special Warnings and Precautions

On the basis of pharmacodynamic data VIRAMUNE should only be used with at least two other antiretroviral agents (see Properties).

The first 18 weeks of therapy with VIRAMUNE are a critical period which requires close monitoring of patients to disclose the potential appearance of severe and life-threatening skin reactions (including cases of Stevens-Johnson syndrome and toxic epidermal necrolysis) or serious hepatitis/hepatic failure. The greatest risk of hepatic events and skin reactions occurs in the first 6 weeks of therapy. Women and patients with higher CD4+ cell counts are at increased risk of hepatic adverse events. The dosage must be strictly adhered to, especially the 14-days lead-in period (see Dosage & method of administration).

Cutaneous reactions

Severe and life-threatening skin reactions, including fatal cases, have occurred in patients treated with VIRAMUNE mainly during the first 6 weeks of therapy. These have included cases of Stevens-Johnson syndrome, toxic epidermal necrolysis and hypersensitivity reactions characterised by rash, constitutional findings and visceral involvement. Patients should be intensively monitored during the first 18 weeks of treatment. Patients should be closely monitored if an isolated rash occurs. VIRAMUNE must be permanently discontinued in any patient experiencing severe rash or a rash accompanied by constitutional symptoms (such as fever, blistering, oral lesions, conjunctivitis, facial oedema, muscle or joint aches, or general malaise), including Stevens-Johnson syndrome, or toxic epidermal necrolysis. VIRAMUNE must be permanently discontinued in any patient experiencing hypersensitivity reaction, characterised by rash with constitutional symptoms, plus visceral involvement, such as hepatitis, eosinophilia, granulocytopenia, and renal dysfunction (see Special warnings and precautions).

VIRAMUNE administration above the recommended dose might increase the frequency and seriousness of skin reactions, such as Stevens-Johnson syndrome and toxic epidermal necrolysis. Concomitant prednisone use (40 mg/day for the first 14 days of VIRAMUNE administration) has been shown not to decrease the incidence of VIRAMUNE-associated rash, and may be associated with an increase in incidence and severity of rash during the first 6 weeks of VIRAMUNE therapy.

Some risk factors for developing serious cutaneous reactions have been identified, they include failure to follow the initial dosing of 200 mg daily (4 mg/kg for paediatric patients) during the lead-in period and a long delay between the initial symptoms and medical consultation. Women appear to be at higher risk than men of developing rash, whether receiving VIRAMUNE or non- VIRAMUNE containing therapy. Patients should be instructed that a major toxicity of VIRAMUNE is rash. They should be advised to promptly notify their physician of any rash and avoid delay between the initial symptoms and medical consultation. The majority of rashes associated with VIRAMUNE occur within the first 6 weeks of initiation of therapy. Therefore, patients should be monitored carefully for the appearance of rash during this period. Patients should be instructed that dose escalation is not to occur if any rash occurs during the two-week lead-in dosing period, until the rash resolves. Careful monitoring of paediatric patients is especially warranted, particularly in the first 18 weeks of treatment, since these patients may be less likely than adults to notice, or report, skin reactions.

Any patient experiencing severe rash or a rash accompanied by constitutional symptoms such as fever, blistering, oral lesions, conjunctivitis, facial oedema, muscle or joint aches, or general malaise, should discontinue medication and consult a physician. In these patients VIRAMUNE must be permanently discontinued. VIRAMUNE administration above the recommended dose might increase the frequency and seriousness of skin reactions, such as Stevens-Johnson syndrome and toxic epidermal necrolysis. Concomitant prednisone use (40 mg/day for the first 14 days of VIRAMUNE administration) has been shown not to decrease the incidence of VIRAMUNE-associated rash, and may be associated with an increase in incidence and severity of rash during the first 6 weeks of VIRAMUNE therapy.

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Any patient experiencing severe rash or a rash accompanied by constitutional symptoms such as fever, blistering, oral lesions, conjunctivitis, facial oedema, muscle or joint aches, or general malaise, should discontinue medication and consult a physician. In these patients VIRAMUNE must be permanently discontinued.
If a hypersensitivity reaction occurs, characterised by rash with constitutional symptoms such as fever, arthralgia, myalgia and lymphadenopathy, plus visceral involvement, such as hepatitis, eosinophilia, granulocytopenia, and renal dysfunction, VIRAMUNE should be permanently stopped and not be re-introduced.

**Hepatic reactions**

Severe and life-threatening hepatotoxicity, including fatal fulminant hepatitis, has occurred in patients treated with VIRAMUNE. The first 18 weeks of treatment is a critical period which requires close monitoring. The risk of hepatic events is greatest in the first 6 weeks of therapy. Women and patients with higher CD4+ cell counts are at increased risk of hepatic adverse events. However the risk continues past this period and monitoring should continue at frequent intervals throughout treatment.

Serious hepatotoxicity, including liver failure requiring transplantation, has been reported in HIV-uninfected individuals receiving multiple doses of VIRAMUNE in the setting of post-exposure-prophylaxis (PEP), an unapproved use. The use of VIRAMUNE has not been evaluated within a specific study on PEP, especially in term of treatment duration.

Increased ASAT or ALAT levels >2.5 ULN and/or co-infection with hepatitis B and/or C at the start of antiretroviral therapy is associated with greater risk of hepatic adverse reactions during antiretroviral therapy in general, including VIRAMUNE containing regimens. Women appear to have a three fold higher risk than men for rash-associated hepatic events (4.6% vs. 1.5%). Patients with higher CD4+ cell counts may also be at higher risk for rash-associated hepatic events with VIRAMUNE. In a retrospective review, women with CD4+ cell counts >250 cells/mm3 had a 9 fold higher risk of rash-associated hepatic adverse events compared to women with CD4+ cell counts <250 cells/mm3 (8.4% vs. 0.9%). An increased risk was observed in men with CD4+ cell counts >400 cells/mm3 compared to men with CD4+ cell counts <400 cells/mm3 (4.5% vs. 0.7%). Patients should be informed that hepatic reactions are a major toxicity of VIRAMUNE requiring a close monitoring during the first 18 weeks. They should be informed that occurrence of symptoms suggestive of hepatitis should lead them to contact promptly their physician.

**Liver monitoring**

Abnormal liver function tests have been reported with VIRAMUNE, some in the first few weeks of therapy.

Asymptomatic elevations of liver enzymes are frequently described and are not necessarily a contraindication to use VIRAMUNE. Asymptomatic GGT elevations are not a contraindication to continue therapy.

Monitoring of hepatic tests should be done every two weeks during the first 2 months of treatment, at the 3rd month and then regularly thereafter. Liver test monitoring should be performed if the patient experiences signs or symptoms suggestive of hepatitis and/or hypersensitivity.

If ASAT or ALAT >2.5 ULN before or during treatment, then liver tests should be monitored more frequently during regular clinic visits. VIRAMUNE should not be administered to patients with pre-treatment ASAT or ALAT >5 ULN until baseline ASAT/ALAT are stabilised <5 ULN.

Physicians and patients should be vigilant for prodromal signs or findings of hepatitis, such as anorexia, nausea, jaundice, bilirubinuria, acholic stools, hepatomegaly or liver tenderness. Patients should be instructed to seek medical attention promptly if these occur.

If ASAT or ALAT increase to >5 ULN during treatment, VIRAMUNE should be immediately stopped. If ASAT and ALAT return to baseline values and if the patient had no clinical signs or symptoms of hepatitis, rash, constitutional symptoms or other findings suggestive of organ dysfunction, it may be possible to reintroduce VIRAMUNE, on a case by case basis, at the starting dosage regimen of 200 mg/day for 14 days followed by 400 mg/day. In these cases, more frequent liver monitoring is required. If liver function abnormalities recur, VIRAMUNE should be permanently discontinued.
If clinical hepatitis occurs, characterised by anorexia, nausea, vomiting, icterus AND laboratory findings (such as moderate or severe liver function test abnormalities (excluding GGT), VIRAMUNE must be permanently stopped. VIRAMUNE should not be readministered to patients who have required permanent discontinuation for clinical hepatitis due to nevirapine.

Liver Disease
The safety and efficacy of VIRAMUNE has not been established in patients with significant underlying liver disorders. VIRAMUNE is contraindicated in patients with severe hepatic impairment (see Contraindications). Patients with chronic hepatitis B or C and treated with combination antiretroviral therapy are at an increased risk for severe and potentially fatal hepatic adverse events. In the case of concomitant antiviral therapy for hepatitis B or C, please refer also to the relevant product information for these medicinal products.

Patients with pre-existing liver dysfunction including chronic active hepatitis have an increased frequency of liver function abnormalities during combination antiretroviral therapy and should be monitored according to standard practice. If there is evidence of worsening liver disease in such patients, interruption or discontinuation of treatment must be considered.

Other warnings
Combination therapy with VIRAMUNE is not a curative treatment of patients infected with HIV-1; patients may continue to experience illnesses associated with advanced HIV-1 infection, including opportunistic infections.

The long-term effects of nevirapine are unknown at this time. Combination therapy with VIRAMUNE has not been shown to reduce the risk of transmission of HIV-1 to others through sexual contact or contaminated blood. The following events have also been reported when VIRAMUNE has been used in combination with other anti-retroviral agents: pancreatitis, peripheral neuropathy and thrombocytopenia. These events are commonly associated with other anti-retroviral agents and may be expected to occur when VIRAMUNE is used in combination with other agents; however it is unlikely that these events are due to VIRAMUNE treatment. Hepatic-renal failure syndromes have been rarely reported.

Combination antiretroviral therapy has been associated with the redistribution of body fat (lipodystrophy) in HIV infected patients. The long-term consequences of these events are currently unknown. Knowledge about the mechanism is incomplete. A connection between visceral lipomatosis and PIs and lipoatrophy and NRTIs has been hypothesised. A higher risk of lipodystrophy has been associated with individual factors such as older age, and with drug related factors such as longer duration of antiretroviral treatment and associated metabolic disturbances. Clinical examination should include evaluation for physical signs of fat redistribution. Consideration should be given to the measurement of fasting serum lipids and blood glucose. Lipid disorders should be managed as clinically appropriate (see Undesirable Effects).

Nevirapine may interact with some medicinal products; therefore, patients should be advised to report to their doctor the use of any other medications. Oral contraceptives and other hormonal methods of birth control should not be used as the sole method of contraception in women taking VIRAMUNE, since nevirapine might lower the plasma concentrations of these medications. For this reason, and to reduce the risk of HIV transmission, barrier contraception (e.g. condoms) is recommended. Additionally, when oral contraceptives are used for hormonal regulation during administration of VIRAMUNE the therapeutic effect should be monitored.

Pharmacokinetic results suggest caution should be exercised when VIRAMUNE is administered to patients with moderate hepatic dysfunction and should not be administered in patients with severe hepatic dysfunction. Overall, the results suggest that patients with mild to moderate hepatic dysfunction, defined as Child-Pugh Classification Score ≤7, do not require an adjustment in VIRAMUNE dosing. In patients with renal dysfunction, who are undergoing dialysis, pharmacokinetic results suggest that
supplementing VIRAMUNE therapy with an additional 200 mg dose of VIRAMUNE following each dialysis treatment would help offset the effects of dialysis on nevirapine clearance. Otherwise patients with CLcr ≥ 20 ml/min do not require an adjustment in VIRAMUNE dosing (see Pharmacokinetic properties).

Interactions
NRTIs: No dosage adjustments are required when VIRAMUNE is taken in combination with zidovudine, didanosine, or zalcitabine. When the zidovudine data were pooled from two studies (n = 33) in which HIV 1 infected patients received VIRAMUNE 400 mg/day either alone or in combination with 200-300 mg/day didanosine or 0.375 to 0.75 mg/day zalcitabine on a background of zidovudine therapy, nevirapine produced a non-significant decline of 13% in zidovudine area under the curve (AUC) and a non-significant increase of 5.8% in zidovudine Cmax. In a subset of patients (n = 6) who were administered VIRAMUNE 400 mg/day and didanosine on a background of zidovudine therapy, nevirapine produced a significant decline of 32% in zidovudine AUC and a non-significant decline of 27% in zidovudine Cmax. Paired data suggest that zidovudine had no effect on the pharmacokinetics of nevirapine. In one crossover study, nevirapine had no effect on the steady-state pharmacokinetics of either didanosine (n = 18) or zalcitabine (n = 6).

Results from a 36 day study in HIV infected patients (n = 25) administered VIRAMUNE, nelfinavir (750 mg t.i.d.) and stavudine (30-40 mg b.i.d.) showed no statistically significant changes in the AUC or Cmax of stavudine. Furthermore, a population pharmacokinetic study of 90 patients assigned to receive lamivudine with VIRAMUNE or placebo revealed no changes to lamivudine apparent clearance and volume of distribution, suggesting no induction effect of nevirapine on lamivudine clearance.

Non-nucleoside reverse transcriptase inhibitors (NNRTIs): Results from a clinical trial (n=14) showed that steady-state pharmacokinetic parameters of nevirapine were not affected by co-administration of efavirenz. However, drug levels of efavirenz were significantly reduced in the presence of nevirapine. The AUC of efavirenz decreased by 22% and the Cmin by 36%. When co-administered with nevirapine a dose increase of efavirenz to 800 mg once daily may be warranted.

PIs: Nevirapine is a mild to moderate inducer of the hepatic enzyme CYP3A; therefore, it is possible that co-administration with PIs (also metabolised by CYP3A) may result in an alteration in the plasma concentration of either agent.

Results from a clinical trial (n = 31) with HIV infected patients administered VIRAMUNE and saquinavir (hard gelatin capsules; 600 mg t.i.d.) indicated that their co-administration leads to a mean reduction of 24% (p = 0.041) in saquinavir AUC and no significant change in nevirapine plasma levels. The reduction in saquinavir levels due to this interaction may further reduce the marginal plasma levels of saquinavir which are achieved with the hard gelatin capsule formulation.

Another study (n=20) evaluated once daily dosing of saquinavir soft gel capsule (sgc) with a 100 mg dose of ritonavir. All patients concomitantly received VIRAMUNE. The study showed that the combination of saquinavir sgc and 100 mg of ritonavir had no measurable effect on the pharmacokinetic parameters of nevirapine, compared to historical controls. The effect of nevirapine on the pharmacokinetics of saquinavir sgc in the presence of 100 mg of ritonavir, was modest and clinically insignificant.

Results from a clinical trial (n = 25) with HIV infected patients administered VIRAMUNE and indinavir (800 mg q8h) indicated that their co-administration leads to a 28% mean decrease (p <0.01) in indinavir AUC and no significant change in nevirapine plasma levels. No definitive clinical conclusions have been reached regarding the potential impact of co-administration of nevirapine and indinavir. A dose increase of indinavir to 1000 mg q8h should be considered when indinavir is given with nevirapine 200 mg b.i.d.; however, there are no data currently available to establish that the short term or long term antiviral activity of indinavir 1000 mg q8h with nevirapine...
200 mg b.i.d. will differ from that of indinavir 800 mg q8h with nevirapine 200 mg b.i.d.

Results from a clinical trial (n = 25) with HIV infected patients administered VIRAMUNE and ritonavir (600 mg b.i.d. [using a gradual dose escalation regimen]) indicated that concomitant use leads to no significant change in ritonavir or nevirapine plasma levels.

Results from a 36 day study in HIV infected patients (n = 25) administered VIRAMUNE, nelfinavir (750 mg t.i.d.) and stavudine (30-40 mg b.i.d.) showed no statistically significant changes in nelfinavir pharmacokinetic parameters after the addition of nevirapine (AUC + 4%, Cmax +14% and Cmin - 2%). Compared to historical controls nevirapine levels appeared to be unchanged.

There were no increased safety concerns noted with the coadministration of VIRAMUNE with any of these PIs when used in combination.

There was no apparent change in the pharmacokinetics of lopinavir when used concomitantly with VIRAMUNE in healthy volunteers. In single PI experienced patients, nevirapine, used in combination with lopinavir / ritonavir 400/100 mg (3 capsules) twice daily and NRTIs, provided very good virological response rates. Results from a pharmacokinetic study in paediatric patients revealed a decrease in lopinavir concentrations during nevirapine co-administration. The clinical significance of this interaction is unknown. However a dose increase of lopinavir / ritonavir to 533/133 mg (4 capsules or 6.5 ml) may be considered when used in combination with nevirapine in patients where reduced susceptibility to lopinavir / ritonavir is clinically suspected (by treatment history or laboratory evidence).

Ketoconazole: In one study, administration of nevirapine 200 mg b.i.d. with ketoconazole 400 mg q.d. resulted in a significant reduction (63% median reduction in ketoconazole AUC and a 40% median reduction in ketoconazole Cmax). In the same study, ketoconazole administration resulted in a 15-28% increase in the plasma levels of nevirapine compared to historical controls. Ketoconazole and VIRAMUNE should not be given concomitantly. The effects of nevirapine on itraconazole are not known.

Fluconazole: Co-administration of fluconazole and VIRAMUNE resulted in approximately 100% increase in nevirapine exposure compared with historical data where VIRAMUNE was administered alone. Because of the risk of increased exposure to nevirapine, caution should be exercised if the medicinal products are given concomitantly and patients should be monitored closely. There was no clinically relevant effect of nevirapine on fluconazole.

Oral Contraceptives: As the oral contraceptives should not be used as the sole method of contraception in HIV infected patients, other means of contraception (such as barrier methods) are recommended in patients being treated with VIRAMUNE. Furthermore a pharmacokinetic interaction has been identified. Nevirapine 200 mg b.i.d. was co-administered with a single dose of an oral contraceptive containing ethinyl estradiol (EE) 0.035 mg and norethindrone (NET) 1.0 mg. Compared to plasma concentrations observed prior to nevirapine administration, the median AUC for 17α-EE was significantly decreased by 29% after 28 days of nevirapine dosing. There was a significant reduction in EE mean resident time and half-life. There was a significant reduction (18%) in median AUC for NET, without changes in mean resident time or half-life. The magnitude of the effect suggests that the dose of the oral contraceptive should be adjusted to allow adequate treatment for indications other than contraception (e.g., endometriosis), if used with nevirapine.

Other medicinal products metabolised by CYP3A: Nevirapine is an inducer of CYP3A and potentially CYP2B6, with maximal induction occurring within 2-4 weeks of initiating multiple-dose therapy. Based on the known metabolism of methadone, nevirapine 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. Methadone-maintained patients beginning...
VIRAMUNE therapy should be monitored for evidence of withdrawal and methadone dose should be adjusted accordingly.

Other compounds that are substrates of CYP3A and CYP2B6 may have decreased plasma concentrations when co-administered with VIRAMUNE. Therefore, careful monitoring of the therapeutic effectiveness of P450 metabolised medicinal products is recommended when taken in combination with VIRAMUNE.

CYP isoenzyme inhibitors: The results of a nevirapine-clarithromycin interaction study (n = 18) resulted in a significant reduction in clarithromycin AUC (30%) and Cmax (-21%) but a significant increase in the AUC (58%) and Cmax (62%) of the active metabolite 14-OH clarithromycin. There was a significant increase in the nevirapine Cmin (28%) and a non-significant increase in nevirapine AUC (26%) and Cmax (24%). These results would suggest that no dose adjustment is necessary for either clarithromycin and VIRAMUNE when the two medicinal products are co-administered. Close monitoring of hepatic abnormalities and activity against Mycobacterium avium-intracellular complex (MAC) is nevertheless recommended.

Monitoring of steady-state nevirapine trough plasma concentrations in patients who received long-term VIRAMUNE treatment revealed that nevirapine trough concentrations were elevated in patients who received cimetidine (+7%, n = 13).

CYP isoenzyme inducers: An open-label study (n = 14) to determine the effects of nevirapine on the steady state pharmacokinetics of rifampicin resulted in no significant change in rifampicin Cmax and AUC. In contrast, rifampicin produced a significant lowering of nevirapine AUC (-55%), Cmax (-50%) and Cmin (-68%) compared to historical data.

The available pharmacokinetic data suggest that the concomitant use of rifampicin and VIRAMUNE is not recommended. Therefore, these medicinal products should not be used in combination. Physicians needing to treat patients co-infected with tuberculosis and using a VIRAMUNE containing regimen may consider use of rifabutin instead. Rifabutin and VIRAMUNE can be administered concurrently without dose adjustments (see below). Alternatively physicians may consider switching to a triple NRTI combination for a variable period of time, depending on the tuberculosis treatment regimen (see Contraindications).

In a pharmacokinetic study the concomitant administration of VIRAMUNE with rifabutin resulted in a non-significant 12% (median) increase in the steady-state AUC, a non-significant 3% decrease in Cminss and a significant 20% increase in the Cmaxss. Non-significant changes were found on 25-O-desacetyl-rifabutin (rifabutin active metabolite) AUC, Cminss or Cmaxss. A statistically significant increase in the apparent clearance of nevirapine (9%) compared to historical pharmacokinetic data was reported. This study suggests that there is no clinically relevant interaction between nevirapine and rifabutin. Therefore, the two drugs can be administered concurrently without dose adjustments provided that a careful monitoring of the adverse reactions is performed.

Warfarin: The interaction between nevirapine and the antithrombotic agent warfarin is complex, with the potential for both increases and decreases in coagulation time when used concomitantly. The net effect of the interaction may change during the first weeks of co-administration or upon discontinuation of VIRAMUNE, and close monitoring of anticoagulation levels is therefore warranted.

Hypericum perforatum: Serum levels of nevirapine can be reduced by concomitant use of the herbal preparation St John's wort (Hypericum perforatum). This is due to induction of drug metabolism enzymes and/or transport proteins by St Johns Wort. Herbal preparations containing St Johns Wort should therefore not be combined with VIRAMUNE. If patient is already taking St John's Wort check nevirapine and if possible viral levels and stop St John's Wort. Nevirapine levels may increase on stopping St John's Wort. The dose of VIRAMUNE may need adjusting. The inducing effect may persist for
at least 2 weeks after cessation of treatment with St John’s Wort.

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

Pregnancy and Lactation
No observable teratogenicity was detected in reproductive studies performed in pregnant rats and rabbits. There are no adequate and well-controlled studies in pregnant women. Therefore VIRAMUNE should only be used during pregnancy if the expected benefit justifies the possible risk to the child and caution should be exercised when prescribing VIRAMUNE to pregnant women. Results from a pharmacokinetic study (ACTG 250) of 10 HIV-1 infected pregnant women who were administered a single oral dose of 100 or 200 mg VIRAMUNE at a median of 5.8 hours before delivery, have shown that nevirapine readily crosses the placenta and is found in breast milk. It is recommended that HIV-infected mothers do not breast-feed their infants to avoid risking postnatal transmission of HIV and that mothers should discontinue nursing if they are receiving VIRAMUNE. VIRAMUNE for the prevention of mother to child transmission of HIV-1 has been demonstrated to be safe and effective when given as part of a regimen that includes a single 200 mg oral dose to mothers during labor followed by a single 2 mg/kg dose to the infant within 72 hours after birth.

Pregnant Women: In HIV-1-infected women in labor, the half-life of VIRAMUNE after a single oral 200 mg dose is prolonged (60-70 hours) and oral clearance is highly variable (2.1±1.5 L/h), consistent with the physiological stresses of labor (studies PACTG 250 [n=17] and HIVNET 006 [n=21]). Nevirapine readily crosses the placenta such that the administration of a 200 mg dose to the mothers resulted in cord concentrations above 100 ng/mL and a cord blood-to-maternal blood ratio of 0.84±0.19 (n=36; range 0.37-1.22).

Neonates: In neonates receiving a 2 mg/kg oral dose of VIRAMUNE suspension within 72 hours after birth, born to HIV-1-infected women administered a single 200 mg dose during labor, the geometric mean half-life of nevirapine was 47 hours (n=36). Plasma levels were maintained above 100 ng/mL for the first week of life (studies PACTG 250 [n=17] and HIVNET 006 [n=19]).

Nursing Mothers: It is recommended that HIV-infected mothers not breast-feed their infants to avoid risking postnatal transmission of HIV. Results from 2 pharmacokinetic studies (ACTG 250 and HIVNET 006) have shown that VIRAMUNE readily crosses the placenta and is found in breast milk. In ACTG 250, breast milk samples collected in 3 of 10 HIV-1-infected pregnant women after administration of a single oral dose of 100 mg or 200 mg VIRAMUNE (at a median of 5.8 hours before delivery), demonstrated a median ratio of the concentration of VIRAMUNE in breast milk to that in maternal serum of 76% (54-104%). Results from study HIVNET 006 (n=20) indicate a median breast milk to maternal plasma concentration of 60.5% (25-122%), after a single oral 200 mg VIRAMUNE dose.

Consistent with the recommendation that HIV-infected mothers not breast-feed their infants to avoid risking postnatal transmission of HIV, mothers should discontinue breast-feeding if they are receiving VIRAMUNE.

Effects on ability to drive and use machines
There are no specific studies on the ability to drive vehicles and use machinery.

Undesirable effects
The most frequently reported adverse events related to VIRAMUNE therapy, across all clinical trials, were rash, nausea, fatigue, fever, headache, vomiting, diarrhoea, abdominal pain and myalgia.

The postmarketing experience has shown that the most serious adverse reactions are Stevens-Johnson syndrome and toxic epidermal necrolysis. 
and serious hepatitis/hepatic failure and hypersensitivity reactions, characterised by rash with constitutional symptoms such as fever, arthralgia, myalgia and lymphadenopathy, plus visceral involvement, such as hepatitis, eosinophilia, granulocytopenia, and renal dysfunction. The first 18 weeks of treatment is a critical period which requires close monitoring (see Special warnings and precautions).

The following adverse events which may be causally related to the administration of VIRAMUNE have been reported. The frequencies estimated are based on pooled clinical trial data for events considered related to VIRAMUNE treatment.

Frequency classes: very common (>1/10); common (>1/100, <1/10); uncommon (>1/1,000, <1/100); rare (>1/10,000, <1/1,000); very rare (<1/10,000)

**Blood and lymphatic system disorders**
- rare: Granulocytopenia, anaemia

**Immune system disorders**
- common: Allergic reactions
- rare: Hypersensitivity (syndrome), anaphylaxis

**Nervous system disorders**
- common: Headache

**Gastrointestinal disorders**
- common: Nausea
- uncommon: Vomiting, abdominal pain
- rare: Diarrhea

**Hepato-biliary disorders**
- common: Hepatitis (1.2%), liver function tests abnormal
- uncommon: Jaundice
- rare: Liver failure / fulminant hepatitis

**Skin and subcutaneous tissue disorders**
- common: Rash (9%)
- uncommon: Stevens Johnson syndrome (0.3%), urticaria
- rare: Toxic epidermal necrolysis, angio-oedema

**Musculoskeletal, connective tissue and bone disorders**
- uncommon: Myalgia
- rare: Arthralgia

**General disorders and administration site conditions**
- uncommon: Fatigue, fever

Combination antiretroviral therapy has been associated with redistribution of body fat (lipodystrophy) in HIV infected patients including the loss of peripheral and facial subcutaneous fat, increased intra-abdominal and visceral fat, breast hypertrophy and dorsal-cervical fat accumulation (buffalo hump).

Combination antiretroviral therapy has been associated with metabolic abnormalities such as hypertriglyceridaemia, hypercholesterolaemia, insulin resistance, hyperglycaemia and hyperlactataemia (see Special warnings and Precautions).

**Skin and subcutaneous tissues**

The most common clinical toxicity of VIRAMUNE is rash, with VIRAMUNE attributable rash occurring in 9% of patients in combination regimens in controlled studies. In these clinical trials 24% of patients treated with a VIRAMUNE containing regimen experienced rash compared with 15% of patients treated in control groups. Severe rash occurred in 1.7% of VIRAMUNE-treated patients compared with 0.2% of patients treated in the control groups.

Rashes are usually mild to moderate, maculopapular erythematous cutaneous eruptions, with or without pruritus, located on the trunk, face and extremities. Allergic reactions (anaphylaxis, angioedema and urticaria) have been reported. Rashes occur alone or in the context of hypersensitivity reactions, characterised by rash associated with constitutional symptoms such as fever, arthralgia, myalgia and lymphadenopathy plus visceral involvement such as hepatitis, eosinophilia, granulocytopenia and renal dysfunction.

Severe and life-threatening skin reactions have occurred in patients treated with VIRAMUNE, including Stevens-Johnson syndrome (SJS) and, toxic epidermal necrolysis (TEN). Fatal cases of SJS, TEN and hypersensitivity reactions have been reported. The majority of severe rashes occurred within the first 6 weeks of treatment and some required hospitalisation, with one patient requiring surgical intervention.

**Hepato-biliary**

The most frequently observed laboratory test abnormalities are elevations in liver function tests (LFTs), including ALAT, ASAT, GGT, total bilirubin and alkaline phosphatase. Asymptomatic elevations of GGT
levels are the most frequent. Cases of jaundice have been reported. Cases of hepatitis (severe and life-threatening hepatotoxicity, including fatal fulminant hepatitis) have been reported in patients treated with VIRAMUNE. In a large clinical trial, the risk of a serious hepatic event among 1121 patients receiving VIRAMUNE for a median duration of greater than one year was 1.2% (versus 0.6% in placebo group). The best predictor of a serious hepatic event was elevated baseline liver function tests. The first 18 weeks of treatment is a critical period which requires close monitoring (see Special Warnings and Precautions).

Paediatric patients
Based on experience of 361 paediatric patients treated in clinical trials, the most frequently reported adverse events related to VIRAMUNE were similar to those observed in adults, with the exception of granulocytopenia which was more commonly observed in children. Isolated cases of Stevens-Johnson syndrome or Stevens-Johnson/toxic epidermal necrolysis transition syndrome have been reported in this population.

Prevention of Vertical Transmission:
The safety of VIRAMUNE when administered as a single 200 mg dose (two doses in one study) to HIV-infected pregnant women at the onset of labour, and a single 2 mg/kg dose (6 mg in one study) of VIRAMUNE suspension administered to the infant within the first 72 hours of life, has been assessed in over 950 mother-infant pairs in randomized, controlled clinical trials. Infant follow-up ranged from 6 weeks to 18 months after receipt of a single dose. Similar low rates of adverse events were observed in the VIRAMUNE and control groups in these studies. No mothers or infants experienced serious rash or hepatic events that were considered to be related to VIRAMUNE.

Dosage and method of administration
Adults: The recommended dose for VIRAMUNE is one 200 mg tablet daily for the first 14 days (this lead-in period should be used because it has been found to lessen the frequency of rash), followed by one 200 mg tablet twice daily, in combination with at least two additional antiretroviral agents to which the patient has not been previously exposed. Resistant virus emerges rapidly and uniformly when VIRAMUNE is administered as monotherapy; therefore VIRAMUNE should always be administered in combination therapy. For concomitantly administered therapy, the manufacturers recommended dosage and monitoring should be followed.

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

General: Patients should be advised of the need to take VIRAMUNE every day as prescribed. If a dose is missed the patient should not double the next dose but should take the next dose as soon as possible.

Clinical chemistry tests, including liver function tests, should be performed prior to initiating VIRAMUNE therapy and at appropriate intervals during therapy (see Special warnings and Precautions).

Patients experiencing rash during the 14 day lead-in period of 200 mg daily should not have their dose increased until the rash has resolved (see Special Warnings and Precautions). The isolated rash should be closely monitored.

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

Prevention of Mother to Child HIV Transmission:
The recommended dosing for administration to pregnant women and their neonates is:

Maternal Dosing: A single 200 mg dose as soon as possible after the onset of labour
Neonatal Dosing: A single dose of 2 mg/kg orally within 72 hours after birth. If the mother received her VIRAMUNE dose less than two hours prior to delivery, the infant should be administered the single 2 mg/kg dose of VIRAMUNE immediately after birth and the second 2 mg/kg dose within 24-72 hours after the first dose.

**Overdose**
Cases of VIRAMUNE overdose at doses ranging from 800 to 6000 mg per day for up to 15 days have been reported. Patients have experienced oedema, erythema nodosum, fatigue, fever, headache, insomnia, nausea, pulmonary infiltrates, rash vertigo, vomiting and weight decrease. All of these effects subsided following discontinuation of VIRAMUNE.

**Availability**
Tablets of 200 mg
Oral suspension 10 mg/ml

**Storage instructions**
Store in a safe place below 30°C.