ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Viramune 200 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 200 mg of nevirapine (as anhydrous).

Excipients with known effect
Each tablet contains 318 mg of lactose (as monohydrate).
Each tablet contains less than 1 mmol sodium (23 mg), that is to say essentially 'sodium-free'.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet.

White, oval, biconvex tablets. One side is embossed with the code "54 193", with a single bisect separating the "54" and "193". The opposite side is marked with the company symbol. The score line is not intended for breaking the tablet.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Viramune is indicated in combination with other anti-retroviral medicinal products for the treatment of HIV-1 infected adults, adolescents, and children of any age (see section 4.2).

Most of the experience with Viramune is in combination with nucleoside reverse transcriptase inhibitors (NRTIs). The choice of a subsequent therapy after Viramune should be based on clinical experience and resistance testing (see section 5.1).

4.2 Posology and method of administration

Viramune should be administered by physicians who are experienced in the treatment of HIV infection.

Posology

Patients 16 years and older
The recommended dose of 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.

If a dose is recognized as missed within 8 hours of when it was due, the patient should take the missed dose as soon as possible. If a dose is missed and it is more than 8 hours later, the patient should only take the next dose at the usual time.

Dose management considerations
Patients experiencing rash during the 14-day lead-in period of 200 mg/day should not have their Viramune dose increased until the rash has resolved. The isolated rash should be closely monitored (see section 4.4). The 200 mg once daily dosing regimen should not be continued beyond 28 days at

which point in time an alternative treatment should be sought due to the possible risk of underexposure and resistance.

Patients who interrupt nevirapine dosing for more than 7 days should restart the recommended dosing regimen using the two week lead-in period.

There are toxicities that require interruption of Viramune therapy (see section 4.4).

Elderly
Nevirapine has not been specifically investigated in patients over the age of 65.

Renal impairment
For patients with renal dysfunction requiring dialysis an additional 200 mg dose of nevirapine following each dialysis treatment is recommended. Patients with CLcr ≥ 20 ml/min do not require a dose adjustment, see section 5.2.

Hepatic impairment
Nevirapine should not be used in patients with severe hepatic impairment (Child-Pugh C, see section 4.3). No dose adjustment is necessary in patients with mild to moderate hepatic impairment (see sections 4.4 and 5.2).

Paediatric population
Viramune 200 mg tablets, following the dosing schedule described above, are suitable for larger children, particularly adolescents, below the age of 16 who weigh more than 50 kg or whose body surface area is above 1.25 m^2 according to the Mosteller formula. An oral suspension dosage form, which can be dosed according to body weight or body surface area, is available for children in this age group weighing less than 50 kg or whose body surface area is below 1.25 m^2 (please refer to the Summary of Product Characteristics of Viramune oral suspension).

Children less than three years old.

For patients less than 3 years and for all other age groups, an immediate-release oral suspension dosage form is available (please refer to the respective Summary of Product Characteristics).

Method of administration

The tablets shall be taken with liquid, and should not be crushed or chewed. Viramune may be taken with or without food.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Readministration to patients who have required permanent discontinuation for severe rash, rash accompanied by constitutional symptoms, hypersensitivity reactions, or clinical hepatitis due to nevirapine.

Patients with severe hepatic impairment (Child-Pugh C) or pre-treatment ASAT or ALAT > 5 ULN until baseline ASAT/ALAT are stabilised < 5 ULN.

Readministration to patients who previously had ASAT or ALAT > 5 ULN during nevirapine therapy and had recurrence of liver function abnormalities upon readministration of nevirapine (see section 4.4).

Coadministration with herbal preparations containing St. John's wort *(Hypericum perforatum*) due to the risk of decreased plasma concentrations and reduced clinical effects of nevirapine (see section 4.5).

4.4 Special warnings and precautions for use

Viramune should only be used with at least two other antiretroviral agents (see section 5.1).

Viramune should not be used as the sole active antiretroviral, as monotherapy with any antiretroviral has shown to result in viral resistance.

The first 18 weeks of therapy with nevirapine 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 (SJS) and toxic epidermal necrolysis (TEN)) and serious hepatitis/hepatic failure. The greatest risk of hepatic and skin reactions occurs in the first 6 weeks of therapy. However, the risk of any hepatic event continues past this period and monitoring should continue at frequent intervals. Female gender and higher CD4 counts (>250/mm^3 in adult females and >400/mm^3 in adult males) at the initiation of nevirapine therapy are associated with a greater risk of hepatic adverse reactions if the patient has detectable plasma HIV-1 RNA - i.e. a concentration ≥ 50 copies/ml - at the initiation of nevirapine. As serious and life threatening hepatotoxicity has been observed in controlled and uncontrolled studies predominantly in patients with a plasma HIV-1 viral load of 50 copies/ml or higher, nevirapine should not be initiated in adult females with CD4 cell counts greater than 250 cells/mm^3 or in adult males with CD4 cell counts greater than 400 cells/mm^3, who have a detectable plasma HIV-1 RNA unless the benefit outweighs the risk.
In some cases, hepatic injury has progressed despite discontinuation of treatment. Patients developing signs or symptoms of hepatitis, severe skin reaction or hypersensitivity reactions must discontinue nevirapine and seek medical evaluation immediately. Nevirapine must not be restarted following severe hepatic, skin or hypersensitivity reactions (see section 4.3).

The dose must be strictly adhered to, especially the 14-days lead-in period (see section 4.2).

Cutaneous reactions

Severe and life-threatening skin reactions, including fatal cases, have occurred in patients treated with nevirapine 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. Nevirapine 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. Nevirapine 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 section 4.4.

Viramune administration above the recommended dose might increase the frequency and seriousness of skin reactions, such as Stevens-Johnson syndrome and toxic epidermal necrolysis.

Rhabdomyolysis has been observed in patients experiencing skin and/or liver reactions associated with Viramune use.

Concomitant prednisone use (40 mg/day for the first 14 days of Viramune administration) has been shown not to decrease the incidence of nevirapine-associated rash, and may be associated with an increase in incidence and severity of rash during the first 6 weeks of nevirapine therapy.

Some risk factors for developing serious cutaneous reactions have been identified; they include failure to follow the initial dosing of 200 mg daily 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 nevirapine or non-nevirapine containing therapy.

Patients should be instructed that a major toxicity of nevirapine 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 nevirapine 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. The 200 mg once daily dosing regimen should not be continued beyond 28 days at which point in time an alternative treatment should be sought due to the possible risk of underexposure and resistance.

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 the medicinal product and immediately seek medical evaluation. In these patients nevirapine must not be restarted.

If patients present with a suspected nevirapine-associated rash, liver function tests should be performed. Patients with moderate to severe elevations (ASAT or ALAT > 5 ULN) should be permanently discontinued from nevirapine.

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, nevirapine must be permanently stopped and not be re-introduced (see section 4.3).

Hepatic reactions

Severe and life-threatening hepatotoxicity, including fatal fulminant hepatitis, has occurred in patients treated with nevirapine. The first 18 weeks of treatment is a critical period which requires close monitoring. The risk of hepatic reactions is greatest in the first 6 weeks of therapy. However the risk continues past this period and monitoring should continue at frequent intervals throughout treatment.

Rhabdomyolysis has been observed in patients experiencing skin and/or liver reactions associated with nevirapine use.

Increased ASAT or ALAT levels $\geq$ 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 nevirapine containing regimens.

Female gender and higher CD4 counts at the initiation of nevirapine therapy in treatment-naïve patients is associated with increased risk of hepatic adverse reactions. Women have a three fold higher risk than men for symptomatic, often rash-associated, hepatic events (5.8 % versus 2.2 %), and treatment-naïve patients of either gender with detectable HIV-1 RNA in plasma with higher CD4 counts at initiation of nevirapine therapy are at higher risk for symptomatic hepatic events with nevirapine. In a retrospective review of predominantly patients with a plasma HIV-1 viral load of 50 copies/ml or higher, women with CD4 counts >250 cells/mm^3 had a 12 fold higher risk of symptomatic hepatic adverse reactions compared to women with CD4 counts <250 cells/mm^3 (11.0 % versus 0.9 %). An increased risk was observed in men with detectable HIV-1 RNA in plasma and CD4 counts > 400 cells/mm^3 (6.3 % versus 1.2 % for men with CD4 counts <400 cells/mm^3). This increased risk for toxicity based on CD4 count thresholds has not been detected in patients with undetectable (i.e. < 50 copies/ml) plasma viral load.

Patients should be informed that hepatic reactions are a major toxicity of nevirapine requiring close monitoring during the first 18 weeks. They should be informed that occurrence of symptoms

suggestive of hepatitis should lead them to discontinue nevirapine and immediately seek medical evaluation, which should include liver function tests.

Liver monitoring

Clinical chemistry tests, which include liver function tests, should be performed prior to initiating nevirapine therapy and at appropriate intervals during therapy.

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

Asymptomatic elevations of liver enzymes are frequently described and are not necessarily a contraindication to use nevirapine. 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 $\geq$ 2.5 ULN before or during treatment, then liver tests should be monitored more frequently during regular clinic visits. Nevirapine must not be administered to patients with pre-treatment ASAT or ALAT > 5 ULN until baseline ASAT/ALAT are stabilised < 5 ULN (see section 4.3).

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, nevirapine 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 nevirapine, on a case by case basis, at the starting dose 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, nevirapine 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)), nevirapine must be permanently stopped. Viramune must 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 (Child-Pugh C, see section 4.3). Pharmacokinetic results suggest caution should be exercised when nevirapine is administered to patients with moderate hepatic dysfunction (Child-Pugh B). 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 reactions. 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

Post-Exposure-Prophylaxis: 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 and therefore, is strongly discouraged.

Combination therapy with nevirapine 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.

Hormonal methods of birth control other than Depo-medroxyprogesterone acetate (DMPA) should not be used as the sole method of contraception in women taking Viramune, since nevirapine might lower the plasma concentrations of these medicinal products. For this reason, and to reduce the risk of HIV transmission, barrier contraception (e.g., condoms) is recommended. Additionally, when postmenopausal hormone therapy is used during administration of nevirapine, its therapeutic effect should be monitored.

Weight and metabolic parameters:
An increase in weight and in levels of blood lipids and glucose may occur during antiretroviral therapy. Such changes may in part be linked to disease control and life style. For lipids, there is in some cases evidence for a treatment effect, while for weight gain there is no strong evidence relating this to any particular treatment. For monitoring of blood lipids and glucose reference is made to established HIV treatment guidelines. Lipid disorders should be managed as clinically appropriate.

In clinical studies, Viramune has been associated with an increase in HDL- cholesterol and an overall improvement in the total to HDL-cholesterol ratio. However, in the absence of specific studies, the clinical impact of these findings is not known. In addition, Viramune has not been shown to cause glucose disturbances.

Osteonecrosis: Although the etiology is considered to be multifactorial (including corticosteroid use, alcohol consumption, severe immunosuppression, higher body mass index), cases of osteonecrosis have been reported particularly in patients with advanced HIV-disease and/or long-term exposure to combination antiretroviral therapy (CART). Patients should be advised to seek medical advice if they experience joint aches and pain, joint stiffness or difficulty in movement.

Immune Reactivation Syndrome: In HIV-infected patients with severe immune deficiency at the time of institution of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic pathogens may arise and cause serious clinical conditions, or aggravation of symptoms. Typically, such reactions have been observed within the first few weeks or months of initiation of CART. Relevant examples are cytomegalovirus retinitis, generalised and/or focal mycobacterial infections, and Pneumocystis jirovecii pneumonia. Any inflammatory symptoms should be evaluated and treatment instituted when necessary. Autoimmune disorders (such as Graves' disease and autoimmune hepatitis) have also been reported to occur in the setting of immune reactivation; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment.

The available pharmacokinetic data suggest that the concomitant use of rifampicin and nevirapine is not recommended. Furthermore, combining the following compounds with Viramune is not recommended: efavirenz, ketoconazole, etravirine, rilpivirine, elvitegravir (in combination with cobicistat), atazanavir (in combination with ritonavir), fosamprenavir (if not co-administered with low dose ritonavir) (see section 4.5).

Granulocytopenia is commonly associated with zidovudine. Therefore, patients who receive nevirapine and zidovudine concomitantly and especially paediatric patients and patients who receive higher zidovudine doses or patients with poor bone marrow reserve, in particular those with advanced HIV disease, have an increased risk of granulocytopenia. In such patients haematological parameters should be carefully monitored.

Lactose: Viramune tablets contain 636 mg lactose per maximum recommended daily dose.
Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Nevirapine is an inducer of CYP3A and potentially CYP2B6, with maximal induction occurring within 2-4 weeks of initiating multiple-dose therapy.

Compounds using this metabolic pathway may have decreased plasma concentrations when co-administered with nevirapine. Careful monitoring of the therapeutic effectiveness of P450 metabolised medicinal products is recommended when taken in combination with nevirapine.

The absorption of nevirapine is not affected by food, antacids or medicinal products which are formulated with an alkaline buffering agent.

The interaction data is presented as geometric mean value with 90% confidence interval (90% CI) whenever these data were available. ND = Not Determined, ↑ = Increased, ↓ = Decreased, ↔ = No Effect

Medicinal products by therapeutic areas	**Interaction**	**Recommendations concerning co-administration**
ANTI-INFECTIVES		
ANTIRETROVIRALS		
NRTIs		
Didanosine 100-150 mg BID	Didanosine AUC ↔ 1.08 (0.92-1.27) Didanosine C_{min} ND Didanosine C_{max} ↔ 0.98 (0.79-1.21)	Didanosine and Viramune can be co-administered without dose adjustments.
Emtricitabine	Emtricitabine is not an inhibitor of human CYP 450 enzymes.	Viramune and emtricitabine may be coadministered without dose adjustments.
Abacavir	In human liver microsomes, abacavir did not inhibit cytochrome P450 isoforms.	Viramune and abacavir may be coadministered without dose adjustments.
Lamivudine 150 mg BID	No changes to lamivudine apparent clearance and volume of distribution, suggesting no induction effect of nevirapine on lamivudine clearance.	Lamivudine and Viramune can be co-administered without dose adjustments.
Stavudine: 30/40 mg BID	Stavudine AUC ↔ 0.96 (0.89-1.03) Stavudine C_{min} ND Stavudine C_{max} ↔ 0.94 (0.86-1.03) Nevirapine: compared to historical controls, levels appeared to be unchanged.	Stavudine and Viramune can be co-administered without dose adjustments.

Tenofovir 300 mg QD	Tenofovir plasma levels remain unchanged when co-administered with nevirapine. Nevirapine plasma levels were not altered by co-administration of tenofovir.	Tenofovir and Viramune can be co-administered without dose adjustments.
Zidovudine 100-200 mg TID	Zidovudine AUC ↓ 0.72 (0.60-0.96) Zidovudine C_{min} ND Zidovudine C_{max} ↓ 0.70 (0.49-1.04) Nevirapine: Zidovudine had no effect on its pharmacokinetics.	Zidovudine and Viramune can be co-administered without dose adjustments Granulocytopenia is commonly associated with zidovudine. Therefore, patients who receive nevirapine and zidovudine concomitantly and especially paediatric patients and patients who receive higher zidovudine doses or patients with poor bone marrow reserve, in particular those with advanced HIV disease, have an increased risk of granulocytopenia. In such patients haematological parameters should be carefully monitored.
NNRTIs		
Efavirenz 600 mg QD	Efavirenz AUC ↓ 0.72 (0.66-0.86) Efavirenz C_{min} ↓ 0.68 (0.65-0.81) Efavirenz C_{max} ↓ 0.88 (0.77-1.01)	It is not recommended to co-administer efavirenz and Viramune (see section 4.4), because of additive toxicity and no benefit in terms of efficacy over either NNRTI alone (for results of 2NN study, see section 5.1).
Etravirine	Concomitant use of etravirine with nevirapine may cause a significant decrease in the plasma concentrations of etravirine and loss of therapeutic effect of etravirine.	The concomitant administration of Viramune with NNRTIs is not recommended (see section 4.4).
Rilpivirine	Interaction has not been studied.	The concomitant administration of Viramune with NNRTIs is not recommended (see section 4.4).
PIs		
Atazanavir/ritonavir 300/100 mg QD 400/100 mg QD	<u>Atazanavir/r 300/100mg</u>: Atazanavir/r AUC ↓ 0.58 (0.48-0.71) Atazanavir/r C_{min} ↓ 0.28 (0.20-0.40) Atazanavir/r C_{max} ↓ 0.72 (0.60-0.86) <u>Atazanavir/r 400/100mg:</u> Atazanavir/r AUC ↓ 0.81 (0.65-1.02) Atazanavir/r C_{min} ↓ 0.41 (0.27-0.60)	It is not recommended to co-administer atazanavir/ritonavir and Viramune (see section 4.4).

	Atazanavir/r C_{max} ↔ 1.02 (0.85–1.24) (compared to 300/100mg without nevirapine) Nevirapine AUC ↑ 1.25 (1.17-1.34) Nevirapine C_{min} ↑ 1.32 (1.22–1.43) Nevirapine C_{max} ↑ 1.17 (1.09-1.25)	
Darunavir/ritonavir 400/100 mg BID	Darunavir AUC ↑ 1.24 (0.97-1.57) Darunavir C_{min} ↔ 1.02 (0.79-1.32) Darunavir C_{max} ↑ 1.40 (1.14-1.73) Nevirapine AUC ↑ 1.27 (1.12-1.44) Nevirapine C_{min} ↑ 1.47 (1.20-1.82) Nevirapine C_{max} ↑ 1.18 (1.02-1.37)	Darunavir and Viramune can be co-administered without dose adjustments.
Fosamprenavir 1,400 mg BID	Amprenavir AUC ↓ 0.67 (0.55-0.80) Amprenavir C_{min} ↓ 0.65 (0.49-0.85) Amprenavir C_{max} ↓ 0.75 (0.63-0.89) Nevirapine AUC ↑ 1.29 (1.19-1.40) Nevirapine C_{min} ↑ 1.34 (1.21-1.49) Nevirapine C_{max} ↑ 1.25 (1.14-1.37)	It is not recommended to co-administer fosamprenavir and Viramune if fosamprenavir is not co-administered with ritonavir (see section 4.4).
Fosamprenavir/ritonavir 700/100 mg BID	Amprenavir AUC ↔ 0.89 (0.77-1.03) Amprenavir C_{min} ↓ 0.81 (0.69-0.96) Amprenavir C_{max} ↔ 0.97 (0.85-1.10) Nevirapine AUC ↑ 1.14 (1.05-1.24) Nevirapine C_{min} ↑ 1.22 (1.10-1.35) Nevirapine C_{max} ↑ 1.13 (1.03-1.24)	Fosamprenavir/ritonavir and Viramune can be co-administered without dose adjustments
Lopinavir/ritonavir (capsules) 400/100 mg BID	<u>Adult patients</u>: Lopinavir AUC ↓ 0.73 (0.53-0.98) Lopinavir C_{min} ↓ 0.54 (0.28-0.74) Lopinavir C_{max} ↓ 0.81 (0.62-0.95)	An increase in the dose of lopinavir/ritonavir to 533/133 mg (4 capsules) or 500/125 mg (5 tablets with 100/25 mg each) twice daily with food is recommended in combination with Viramune. Dose adjustment of Viramune is not required when co-administered with lopinavir.
Lopinavir/ritonavir (oral solution) 300/75 mg/m^2 BID	<u>Paediatric patients</u>: Lopinavir AUC ↓ 0.78 (0.56-1.09) Lopinavir C_{min} ↓ 0.45 (0.25-0.82) Lopinavir C_{max} ↓ 0.86 (0.64-1.16)	For children, increase of the dose of lopinavir/ritonavir to 300/75 mg/m^2 twice daily with food should be considered when used in combination with Viramune, particularly for patients in whom reduced susceptibility to lopinavir/ritonavir is suspected.

Ritonavir 600 mg BID	Ritonavir AUC↔ 0.92 (0.79-1.07) Ritonavir C_{min} ↔ 0.93 (0.76-1.14) Ritonavir C_{max} ↔ 0.93 (0.78-1.07) Nevirapine: Co-administration of ritonavir does not lead to any clinically relevant change in nevirapine plasma levels.	Ritonavir and Viramune can be co-administered without dose adjustments.
Saquinavir/ritonavir	The limited data available with saquinavir soft gel capsule boosted with ritonavir do not suggest any clinically relevant interaction between saquinavir boosted with ritonavir and nevirapine	Saquinavir/ritonavir and Viramune can be co-administered without dose adjustments.
Tipranavir/ritonavir 500/200 mg BID	No specific drug-drug interaction study has been performed. The limited data available from a phase IIa study in HIV-infected patients have shown a clinically non significant 20% decrease of TPV C_{min}.	Tipranavir and Viramune can be co-administered without dose adjustments.
ENTRY INHIBITORS		
Enfuvirtide	Due to the metabolic pathway no clinically significant pharmacokinetic interactions are expected between enfuvirtide and nevirapine.	Enfuvirtide and Viramune can be co-administered without dose adjustments.
Maraviroc 300 mg QD	Maraviroc AUC ↔ 1.01 (0.6 -1.55) Maraviroc C_{min} ND Maraviroc C_{max} ↔ 1.54 (0.94-2.52) compared to historical controls Nevirapine concentrations not measured, no effect is expected.	Maraviroc and Viramune can be co-administered without dose adjustments.
INTEGRASE INHIBITORS		
Elvitegravir/ cobicistat	Interaction has not been studied. Cobicistat, a cytochrome P450 3A inhibitor significantly inhibits hepatic enzymes, as well as other metabolic pathways. Therefore coadministration would likely result in altered plasma levels of cobicistat and Viramune.	Coadministration of Viramune with elvitegravir in combination with cobicistat is not recommended (see section 4.4).
Raltegravir 400 mg BID	No clinical data available. Due to the metabolic pathway of raltegravir no interaction is expected.	Raltegravir and Viramune can be co-administered without dose adjustments.
ANTIBIOTICS		
Clarithromycin	Clarithromycin AUC ↓ 0.69 (0.62-	Clarithromycin exposure was

500 mg BID	0.76) Clarithromycin C_{min} ↓ 0.44 (0.30-0.64) Clarithromycin C_{max} ↓ 0.77 (0.69-0.86) Metabolite 14-OH clarithromycin AUC ↑ 1.42 (1.16-1.73) Metabolite 14-OH clarithromycin C_{min} ↔ 0 (0.68-1.49) Metabolite 14-OH clarithromycin C_{max} ↑ 1.47 (1.21-1.80) Nevirapine AUC ↑ 1.26 Nevirapine C_{min} ↑ 1.28 Nevirapine C_{max} ↑ 1.24 compared to historical controls.	significantly decreased, 14-OH metabolite exposure increased. Because the clarithromycin active metabolite has reduced activity against *Mycobacterium avium-intracellulare complex* overall activity against the pathogen may be altered. Alternatives to clarithromycin, such as azithromycin should be considered. Close monitoring for hepatic abnormalities is recommended
Rifabutin 150 or 300 mg QD	Rifabutin AUC ↑ 1.17 (0.98-1.40) Rifabutin C_{min} ↔ 1.07 (0.84-1.37) Rifabutin C_{max} ↑ 1.28 (1.09-1.51) Metabolite 25-O-desacetylrifabutin AUC ↑ 1.24 (0.84-1.84) Metabolite 25-O-desacetylrifabutin C_{min} ↑ 1.22 (0.86-1.74) Metabolite 25-O-desacetylrifabutin C_{max} ↑ 1.29 (0.98-1.68) A clinically not relevant increase in the apparent clearance of nevirapine (by 9%) compared to historical data was reported.	No significant effect on rifabutin and Viramune mean PK parameters is seen. Rifabutin and Viramune can be co-administered without dose adjustments. However, due to the high interpatient variability 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.
Rifampicin 600 mg QD	Rifampicin AUC ↔ 1.11 (0.96-1.28) Rifampicin C_{min} ND Rifampicin C_{max} ↔ 1.06 (0.91-1.22) Nevirapine AUC ↓ 0.42 Nevirapine C_{min} ↓ 0.32 Nevirapine C_{max} ↓ 0.50 compared to historical controls.	It is not recommended to co-administer rifampicin and Viramune (see section 4.4). Physicians needing to treat patients co-infected with tuberculosis and using a Viramune containing regimen may consider co-administration of rifabutin instead.
ANTIFUNGALS		
Fluconazole 200 mg QD	Fluconazole AUC ↔ 0.94 (0.88-1.01) Fluconazole C_{min} ↔ 0.93 (0.86-1.01) Fluconazole C_{max} ↔ 0.92 (0.85-0.99) Nevirapine: exposure: ↑100% compared with historical data where nevirapine was administered alone.	Because of the risk of increased exposure to Viramune, caution should be exercised if the medicinal products are given concomitantly and patients should be monitored closely.
Itraconazole	Itraconazole AUC ↓ 0.39	A dose increase for itraconazole

200 mg QD	Itraconazole C_{min} ↓ 0.13 Itraconazole C_{max} ↓ 0.62 Nevirapine: there was no significant difference in nevirapine pharmacokinetic parameters.	should be considered when these two agents are administered concomitantly.
Ketoconazole 400 mg QD	Ketoconazole AUC ↓ 0.28 (0.20-0.40) Ketoconazole C_{min} ND Ketoconazole C_{max} ↓ 0.56 (0.42-0.73) Nevirapine: plasma levels: ↑ 1.15-1.28 compared to historical controls.	It is not recommended to co-administer ketoconazole and Viramune (see section 4.4).
ANTIVIRALS FOR CHRONIC HEPATITIS B AND C		
Adefovir	Results of *in vitro* studies showed a weak antagonism of nevirapine by adefovir (see section 5.1), this has not been confirmed in clinical trials and reduced efficacy is not expected. Adefovir did not influence any of the common CYP isoforms known to be involved in human drug metabolism and is excreted renally. No clinically relevant drug-drug interaction is expected.	Adefovir and Viramune may be coadministered without dose adjustments.
Entecavir	Entecavir is not a substrate, inducer or an inhibitor of cytochrome P450 (CYP450) enzymes. Due to the metabolic pathway of entecavir, no clinically relevant drug-drug interaction is expected.	Entecavir and Viramune may be coadministered without dose adjustments.
Interferons (pegylated interferons alfa 2a and alfa 2b)	Interferons have no known effect on CYP 3A4 or 2B6. No clinically relevant drug-drug interaction is expected.	Interferons and Viramune may be coadministered without dose adjustments.
Ribavirin	Results of *in vitro* studies showed a weak antagonism of nevirapine by ribavirin (see section 5.1), this has not been confirmed in clinical trials and reduced efficacy is not expected. Ribavirin does not inhibit cytochrome P450 enzymes, and there is no evidence from toxicity studies that ribavirin induces liver enzymes. No clinically relevant drug-drug interaction is expected.	Ribavirin and Viramune may be coadministered without dose adjustments.
Telbivudine	Telbivudine is not a substrate, inducer or inhibitor of the	Telbivudine and Viramune may be coadministered without dose

	cytochrome P450 (CYP450) enzyme system. Due to the metabolic pathway of telbivudine, no clinically relevant drug-drug interaction is expected.	adjustments.
ANTACIDS		
Cimetidine	Cimetidine: no significant effect on cimetidine PK parameters is seen. Nevirapine C_{min} ↑ 1.07	Cimetidine and Viramune can be co-administered without dose adjustments.
ANTITHROMBOTICS		
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.	Close monitoring of anticoagulation levels is warranted.
CONTRACEPTIVES		
Depo-medroxyprogesterone acetate (DMPA) 150 mg every 3 months	DMPA AUC ↔ DMPA C_{min} ↔ DMPA C_{max} ↔ Nevirapine AUC ↑ 1.20 Nevirapine C_{max} ↑ 1.20	Viramune co-administration did not alter the ovulation suppression effects of DMPA. DMPA and Viramune can be co-administered without dose adjustments.
Ethinyl estradiol (EE) 0.035 mg	EE AUC ↓ 0.80 (0.67 - 0.97) EE C_{min} ND EE C_{max} ↔ 0.94 (0.79 - 1.12)	Oral hormonal contraceptives should not be used as the sole method of contraception in women taking Viramune (see section 4.4). Appropriate doses for hormonal contraceptives (oral or other forms of application) other than DMPA in combination with Viramune have not been established with respect to safety and efficacy.
Norethindrone (NET) 1.0 mg QD	NET AUC ↓ 0.81 (0.70 - 0.93) NET C_{min} ND NET C_{max} ↓ 0.84 (0.73 - 0.97)	
ANALGESICS/OPIOIDS		
Methadone Individual Patient Dosing	Methadone AUC ↓ 0.40 (0.31 - 0.51) Methadone C_{min} ND Methadone C_{max} ↓ 0.58 (0.50 - 0.67)	Methadone-maintained patients beginning Viramune therapy should be monitored for evidence of withdrawal and methadone dose should be adjusted accordingly.
HERBAL PRODUCTS		
St. John's Wort	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 medicinal product metabolism enzymes and/or transport proteins by St. John's Wort.	Herbal preparations containing St. John's Wort and Viramune must not be co-administered (see section 4.3). If a 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:

Nevirapine metabolites: 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.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential / Contraception in males and females
Women of childbearing potential should not use oral contraceptives as the sole method for birth control, since nevirapine might lower the plasma concentrations of these medicinal products (see sections 4.4 & 4.5).

Pregnancy
Currently available data on pregnant women indicate no malformative or foeto/ neonatal toxicity. To date no other relevant epidemiological data are available. No observable teratogenicity was detected in reproductive studies performed in pregnant rats and rabbits (see section 5.3). There are no adequate and well-controlled studies in pregnant women. Caution should be exercised when prescribing nevirapine to pregnant women (see section 4.4). As hepatotoxicity is more frequent in women with CD4 cell counts above 250 cells/mm^3 with detectable HIV-1 RNA in plasma (50 or more copies/ml), these conditions should be taken in consideration on therapeutic decision (see section 4.4). There is not enough evidence to substantiate that the absence of an increased risk for toxicity seen in pre-treated women initiating nevirapine with an undetectable viral load (less than 50 copies/ml of HIV-1 in plasma) and CD4 cell counts above 250 cells/mm^3 also applies to pregnant women. All the randomised studies addressing this issue specifically excluded pregnant women, and pregnant women were under-represented in cohort studies as well as in meta-analyses.

Breast-feeding
It is recommended that women living with HIV do not breast-feed their infants in order to avoid transmission of HIV.

Fertility
In reproductive toxicology studies, evidence of impaired fertility was seen in rats.

4.7 Effects on ability to drive and use machines

There are no specific studies about the ability to drive vehicles and use machinery.
However, patients should be advised that they may experience adverse reactions such as fatigue during treatment with Viramune. Therefore, caution should be recommended when driving a car or operating machinery. If patients experience fatigue they should avoid potentially hazardous tasks such as driving or operating machinery.

4.8 Undesirable effects

Summary of the safety profile
The most frequently reported adverse reactions related to Viramune therapy, across all clinical studies, were rash, allergic reactions, hepatitis, abnormal liver function tests, nausea, vomiting, diarrhoea, abdominal pain, fatigue, fever, headache and myalgia.

The postmarketing experience has shown that the most serious adverse reactions are Stevens-Johnson syndrome/ toxic epidermal necrolysis, serious hepatitis/hepatic failure, and drug reaction with eosinophilia and systemic symptoms, 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 section 4.4).

Tabulated summary of adverse reactions

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

Frequency is defined using the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000).

Blood and lymphatic system disorders

Common	granulocytopenia
Uncommon	anaemia

Immune system disorders

Common	hypersensitivity (incl. anaphylactic reaction, angioedema, urticaria)
Uncommon	anaphylactic reaction
Rare	drug reaction with eosinophilia and systemic symptoms

Nervous system disorders

Common	headache

Gastrointestinal disorders

Common	nausea, vomiting, abdominal pain, diarrhoea

Hepatobiliary disorders

Common	hepatitis (including severe and life-threatening hepatotoxicity) (1.9%)
Uncommon	jaundice
Rare	hepatitis fulminant (which may be fatal)

Skin and subcutaneous tissue disorders

Very common	rash (12.5 %)
Uncommon	Stevens-Johnson syndrome/ toxic epidermal necrolysis (which may be fatal) (0.2 %), angioedema, urticaria

Musculoskeletal and connective tissue disorders

Uncommon	arthralgia, myalgia

General disorders and administration site conditions

Common	pyrexia, fatigue

Investigations

Common	liver function test abnormal (alanine aminotransferase increased; transaminases increased; aspartate aminotransferase increased; gamma-glutamyltransferase increased; hepatic enzyme increased; hypertransaminasaemia)
Uncommon	blood phosphorus decreased ; blood pressure increased

Description of selected adverse reactions

In study 1100.1090, from which the majority of related adverse events (n=28) were received, patients on placebo had a higher incidence of events of granulocytopenia (3.3 %) than patients on nevirapine

(2.5 %).

Anaphylactic reaction was identified through post-marketing surveillance but not observed in randomised, controlled clinical studies. The frequency category was estimated from a statistical calculation based on the total number of patients exposed to nevirapine in randomised controlled clinical studies (n=2,718).

Decreased blood phosphorus and increased blood pressure were observed in clinical studies with co-administration of tenofovir/emtricitabine.

Metabolic parameters
Weight and levels of blood lipids and glucose may increase during antiretroviral therapy (see section 4.4)

The following adverse reactions have also been reported when nevirapine has been used in combination with other anti-retroviral agents: pancreatitis, peripheral neuropathy and thrombocytopaenia. These adverse reactions are commonly associated with other antiretroviral agents and may be expected to occur when nevirapine is used in combination with other agents; however it is unlikely that these adverse reactions are due to nevirapine treatment. Hepatic-renal failure syndromes have been reported rarely.

In HIV-infected patients with severe immune deficiency at the time of initiation of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic infections may arise. Autoimmune disorders (such as Graves' disease and autoimmune hepatitis) have also been reported; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment (see section 4.4).

Cases of osteonecrosis have been reported, particularly in patients with generally acknowledged risk factors, advanced HIV disease or long-term exposure to combination antiretroviral therapy (CART). The frequency of this is unknown (see section 4.4).

Skin and subcutaneous tissues

The most common clinical toxicity of nevirapine is rash, with Viramune attributable rash occurring in 12.5% of patients in combination regimens in controlled studies.

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

Severe and life-threatening skin reactions have occurred in patients treated with nevirapine, including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). Fatal cases of SJS, TEN and drug reaction with eosinophilia and systemic symptoms 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 (see section 4.4).

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 nevirapine. 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 section 4.4).

Paediatric population
Based on clinical study experience of 361 paediatric patients the majority of which received combination treatment with ZDV or/and ddI, the most frequently reported adverse events related to nevirapine were similar to those observed in adults. Granulocytopenia was more frequently observed in children. In an open-label clinical study (ACTG 180) granulocytopenia assessed as medicinal product-related occurred in 5/37 (13.5 %) of patients. In ACTG 245, a double-blind placebo controlled study, the frequency of serious medicinal product-related granulocytopenia was 5/305 (1.6%). Isolated cases of Stevens-Johnson syndrome or Stevens-Johnson/ toxic epidermal necrolysis transition syndrome have been reported in this population.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

There is no known antidote for nevirapine overdose. Cases of Viramune overdose at doses ranging from 800 to 6,000 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, increase in transaminases and weight decrease. All of these effects subsided following discontinuation of nevirapine.

Paediatric population

One case of massive accidental overdose in a newborn was reported. The ingested dose was 40 times the recommended dose of 2 mg/kg/day. Mild isolated neutropenia and hyperlactataemia was observed, which spontaneously disappeared within one week without any clinical complications. One year later, the child's development remained normal.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antivirals for systemic use, non-nucleoside reverse transcriptase inhibitors, ATC code J05AG01.

Mechanism of action

Nevirapine is a NNRTI of HIV-1. Nevirapine is a non-competitive inhibitor of the HIV-1 reverse transcriptase, but it does not have a biologically significant inhibitory effect on the HIV-2 reverse transcriptase or on eukaryotic DNA polymerases α, β, γ, or δ.

Antiviral activity *in vitro*

Nevirapine had a median EC_{50} value (50 % inhibitory concentration) of 63 nM against a panel of group M HIV-1 isolates from clades A, B, C, D, F, G, and H, and circulating recombinant forms (CRF), CRF01_AE, CRF02_AG and CRF12_BF replicating in human embryonic kidney 293 cells. In a panel of 2,923 predominantly subtype B HIV-1 clinical isolates, the mean EC_{50} value was 90nM. Similar EC_{50} values are obtained when the antiviral activity of nevirapine is measured in peripheral blood mononuclear cells, monocyte derived macrophages or lymphoblastoid cell line. Nevirapine had

no antiviral activity in cell culture against group O HIV-1 isolates or HIV-2 isolates.

Nevirapine in combination with efavirenz exhibited a strong antagonistic anti-HIV-1 activity *in vitro* (see section 4.5) 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, 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 medicinal product adefovir and by the anti-HCV medicinal product ribavirin *in vitro*.

Resistance

HIV-1 isolates with reduced susceptibility (100-250-fold) to nevirapine emerge in cell culture. Genotypic analysis showed mutations in the HIV-1 RT gene Y181C and/or V106A 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.

Genotypic analysis of isolates from antiretroviral naïve patients experiencing virologic failure (n=71) receiving nevirapine once daily (n=25) or twice daily (n=46) in combination with lamivudine and stavudine for 48 weeks showed that isolates from 8/25 and 23/46 patients, 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.

Cross-resistance

Rapid emergence of HIV-strains which are cross-resistant to NNRTIs has been observed in vitro. Cross resistance to efavirenz is expected after virologic failure with nevirapine. Depending on resistance testing results, an etravirine-containing regimen may be used subsequently. Cross-resistance between nevirapine and either HIV protease inhibitors, HIV integrase inhibitors or HIV entry inhibitors is unlikely because the enzyme targets involved are different. Similarly the potential for cross-resistance between nevirapine and NRTIs is low because the molecules have different binding sites on the reverse transcriptase.

Clinical results

Viramune has been evaluated in both treatment-naïve and treatment-experienced patients.

Studies in treatment-naïve patients

2NN study

The double non-nucleoside study 2 NN was a randomised, open-label, multicentre prospective study comparing the NNRTIs nevirapine, efavirenz and both medicinal products given together.

1,216 antiretroviral-therapy naïve patients with plasma HIV-1 RNA > 5,000 copies/ml at baseline were assigned to Viramune 400 mg once daily, Viramune 200 mg twice daily, efavirenz 600 mg once daily, or Viramune (400 mg) and efavirenz (800 mg) once daily, plus stavudine and lamivudine for 48 weeks.
The primary endpoint, treatment failure, was defined as less than 1 $\log_{10}$ decline in plasma HIV-1 RNA in the first 12 weeks, or two consecutive measurements of more than 50 copies/ ml from week 24 onwards, or disease progression.

Median age was 34 years and about 64% were male patients, median CD4 cell count was 170 and 190 cells per mm^3 in the Viramune twice daily and efavirenz groups, respectively. There were no significant differences in demographic and baseline characteristics between the treatment groups.

The predetermined primary efficacy comparison was between the Viramune twice daily and the efavirenz treatment groups.

The nevirapine twice daily regimen and the efavirenz regimen were not significantly different (p=0.091) in terms of efficacy as measured by treatment failure, or any component of treatment failure including virological failure.
The simultaneous use of nevirapine (400 mg) plus efavirenz (800 mg) was associated with the highest frequency of clinical adverse events and with the highest rate of treatment failure (53.1 %). As the regimen of nevirapine plus efavirenz did not have additional efficacy and caused more adverse events than each medicinal product separately, this regimen is not recommended.
Twenty per cent of patients assigned to nevirapine twice daily and 18% of patients assigned to efavirenz had at least one grade 3 or 4 clinical adverse event. Clinical hepatitis reported as clinical adverse event occurred in 10 (2.6 %) and 2 (0.5 %) patients in the nevirapine twice daily and efavirenz groups respectively. The proportion of patients with at least one grade 3 or 4 liver-associated laboratory toxicity was 8.3 % for nevirapine twice daily and 4.5 % for efavirenz. Of the patients with grade 3 or 4 liver-associated laboratory toxicity, the proportions coinfected with hepatitis B or hepatitis C virus were 6.7 % and 20.0 % in the nevirapine twice daily group, 5.6 % and 11.1 % in the efavirenz group.

2NN Three-year follow-up-study

This is a retrospective multicentre study comparing the 3-year antiviral efficacy of Viramune and efavirenz in combination with stavudine and lamivudine in 2NN patients from week 49 to week 144. Patients who participated in the 2NN study and were still under active follow-up at week 48 when the study closed and were still being treated at the study clinic, were asked to participate in this study. Primary study endpoints (percentage of patients with treatment failures) and secondary study endpoints as well as backbone therapy were similar to the original 2NN study.

A durable response to Viramune for at least three years was documented in this study, and equivalence within a 10 % range was demonstrated between Viramune 200 mg twice daily and efavirenz with respect to treatment failure. Both, the primary (p = 0.92) and secondary endpoints showed no statistically significant differences between efavirenz and Viramune 200 mg twice daily.

<u>Studies in treatment-experienced patients</u>

NEFA study

The NEFA study is a controlled prospective randomised study which evaluated treatment options for patients who switch from protease inhibitor (PI) based regimen with undetectable load to either Viramune, efavirenz or abacavir.
The study randomly assigned 460 adults who were taking two nucleoside reverse-transcriptase inhibitors and at least one PI and whose plasma HIV-1 RNA levels had been less than 200 c/ml for at least the previous six months to switch from the PI to Viramune (155 patients), efavirenz (156), or abacavir (149).
The primary study endpoint was death, progression to the acquired immunodeficiency syndrome, or an increase in HIV-1 RNA levels to 200 copies or more per millilitre.

At 12 months, the Kaplan–Meier estimates of the likelihood of reaching the endpoint were 10 % in the Viramune group, 6 % in the efavirenz group, and 13 percent in the abacavir group (P=0.10 according to an intention-to-treat analysis).

The overall incidence of adverse events was significantly lower (61 patients, or 41 %) in the abacavir group than in the nevirapine group (83 patients, or 54 %) or the efavirenz group (89 patients, or 57 %). Significantly fewer patients in the abacavir group (9 patients, or 6 %) than in the nevirapine group (26 patients, or 17 %) or the efavirenz group (27 patients, or 17 %) discontinued the medicinal product because of adverse events.

Perinatal Transmission

Numerous studies have been performed examining the use of Viramune in regards to perinatal transmission, most notably HIVNET 012. This study demonstrated a significant reduction in transmission using single dose nevirapine (13.1 % (n = 310) in the Viramune group, versus 25.1 % (n = 308) in the ultra-short zidovudine group (p = 0.00063)). Monotherapy with Viramune has been associated with the development of NNRTI resistance. Single dose nevirapine in mothers or infants may lead to reduced efficacy if an HIV treatment regimen using nevirapine is later instituted within 6 months or less in these patients. Combination of other antiretrovirals with single-dose nevirapine attenuates the emergence of nevirapine resistance. Where other antiretroviral medicines are accessible, the single dose Viramune regimen should be combined with additional effective antiretroviral medicines (as recommended in internationally recognized guidelines).

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.

Paediatric population
Results of a 48-week analysis of the South African study BI 1100.1368 confirmed that the 4/7 mg/kg and 150 mg/m^2 nevirapine dose groups were well tolerated and effective in treating antiretroviral naive paediatric patients. A marked improvement in the CD4+ cell percent was observed through Week 48 for both dose groups. Also, both dosing regimens were effective in reducing the viral load. In this 48-week study no unexpected safety findings were observed in either dosing group.

5.2 Pharmacokinetic properties

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

Absorption: 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 C_{max} of 5.74 μg/ml (5.00-7.44) and C_{min} 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.

Distribution: 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.

Biotransformation and elimination: *In vivo* studies in humans and *in vitro* studies with human liver microsomes have shown that nevirapine is extensively biotransformed via cytochrome P450 (oxidative) metabolism to several hydroxylated metabolites. *In vitro* studies with human liver microsomes suggest that oxidative metabolism of nevirapine is mediated primarily by cytochrome P450 isozymes from the CYP3A family, although other isozymes may have a secondary role. In a mass balance/excretion study in eight healthy male volunteers dosed to steady state with nevirapine 200 mg given twice daily followed by a single 50 mg dose of 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 is characterised 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 impairment: The single-dose pharmacokinetics of nevirapine has been compared in 23 patients 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 patients 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, patients 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 nevirapine 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 nevirapine dosing.

*Hepatic impairment:*A steady state study comparing 46 patients with
mild (n=17: Ishak Score 1-2),
moderate (n=20; Ishak Score 3-4),
or severe (n=9; Ishak Score 5-6, Child-Pugh A in 8 pts., for 1 Child-Pugh score not applicable)
liver fibrosis as a measure of hepatic impairment was conducted.

The patients 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 this study, the multiple dose pharmacokinetic disposition of nevirapine and the five oxidative metabolites were not altered.

However, approximately 15 % of these patients with hepatic fibrosis had nevirapine trough concentrations above 9,000 ng/ml (2 fold the usual mean trough). Patients with hepatic impairment should be monitored carefully for evidence of medicinal product induced toxicity.

In a 200 mg nevirapine single dose pharmacokinetic study of HIV-negative patients with mild and moderate hepatic impairment (Child-Pugh A, n=6; Child-Pugh B, n=4), a significant increase in the AUC of nevirapine was observed in one Child-Pugh B patient with ascites suggesting that patients with worsening hepatic function and ascites may be at risk of accumulating nevirapine in the systemic circulation. Because nevirapine induces its own metabolism with multiple dosing, this single dose study may not reflect the impact of hepatic impairment on multiple dose pharmacokinetics (see section 4.4).

Gender and elderly
In the multinational 2NN study, a population pharmacokinetic substudy of 1,077 patients was performed that included 391 females. Female patients showed a 13.8 % lower clearance of nevirapine than did male patients. This difference is not considered clinically relevant. Since neither body weight nor Body Mass Index (BMI) had influence on the clearance of nevirapine, the effect of gender cannot be explained by body size. Nevirapine pharmacokinetics in HIV-1 infected adults does not appear to

change with age (range 19-68 years) or race (Black, Hispanic, or Caucasian). Nevirapine has not been specifically investigated in patients over the age of 65.

Paediatric population
Data concerning the pharmacokinetics of nevirapine have been derived from two major sources: a 48 week paediatric study in South Africa (BI 1100.1368) involving 123 HIV-1 positive, antiretroviral naïve patients aged 3 months to 16 years; and a consolidated analysis of five Paediatric AIDS Clinical Trials Group (PACTG) protocols comprising 495 patients aged 14 days to 19 years.

Pharmacokinetic data on 33 patients (age range 0.77 – 13.7 years) in the intensive sampling group demonstrated that clearance of nevirapine increased with increasing age in a manner consistent with increasing body surface area. Dosing of nevirapine at 150 mg/m^2 BID (after a two-week lead in at 150 mg/m^2 QD) produced geometric mean or mean trough nevirapine concentrations between 4-6 µg/ml (as targeted from adult data). In addition, the observed trough nevirapine concentrations were comparable between the two methods.

The consolidated analysis of Paediatric AIDS Clinical Trials Group (PACTG) protocols 245, 356, 366, 377, and 403 allowed for the evaluation of paediatric patients less than 3 months of age (n=17) enrolled in these PACTG studies. The plasma nevirapine concentrations observed were within the range observed in adults and the remainder of the paediatric population, but were more variable between patients, particularly in the second month of age.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans other than those observed in clinical studies based on conventional studies of safety, pharmacology, repeated dose toxicity, and genotoxicity. In carcinogenicity studies, nevirapine induces hepatic tumours in rats and mice. These findings are most likely related to nevirapine being a strong inducer of liver enzymes, and not due to a genotoxic mode of action.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose
Lactose (as monohydrate)
Povidone K25
Sodium starch glycolate
Colloidal silicon dioxide
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Treatment initiation pack
Polyvinyl chloride (PVC)/aluminium foil push-through blister units (blister card of 7 tablets).
Cartons containing 2 blister cards (14 tablets).

Maintenance packs
Polyvinyl chloride (PVC)/aluminium foil push-through blister units (blister card of 10 tablets).
Cartons containing 6 or 12 blister cards (60 or 120 tablets).

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Boehringer Ingelheim International GmbH
Binger Strasse 173
55216 Ingelheim am Rhein, Germany

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/97/055/001 (60 tablets)
EU/1/97/055/003 (120 tablets)
EU/1/97/055/004 (14 tablets)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 5 February 1998
Date of latest renewal: 20 December 2012

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

1. NAME OF THE MEDICINAL PRODUCT

Viramune 50 mg/5 ml oral suspension

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of oral suspension contains 10 mg of nevirapine (as hemihydrate).

Each bottle contains 2.4 g of nevirapine (as hemihydrate) in 240 ml of Viramune oral suspension.

Excipients with known effect
Each ml of oral suspension contains 150 mg sucrose, 162 mg sorbitol, 1.8 mg of methyl parahydroxybenzoate and 0.24 mg of propyl parahydroxybenzoate.
This medicine contains less than 1 mmol sodium (23 mg) per dosage unit, that is to say essentially 'sodium-free'.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Oral suspension

White to off-white homogenous suspension.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Viramune is indicated in combination with other anti-retroviral medicinal products for the treatment of HIV-1 infected adults, adolescents, and children of any age (see section 4.2).

Most of the experience with Viramune is in combination with nucleoside reverse transcriptase inhibitors (NRTIs). The choice of a subsequent therapy after Viramune should be based on clinical experience and resistance testing (see section 5.1).

4.2 Posology and method of administration

Viramune should be administered by physicians who are experienced in the treatment of HIV infection.

Posology

Patients 16 years and older
The recommended dose for Viramune is 20 ml (200 mg) oral suspension once 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 20 ml (200 mg) oral suspension twice daily, in combination with at least two additional antiretroviral agents.

Viramune is also available as a 200 mg tablet for patients 16 years and older, or for older children, particularly adolescents, weighing 50 kg or more or whose BSA is above 1.25 m^2.

If a dose is recognized as missed within 8 hours of when it was due, the patient should take the missed dose as soon as possible. If a dose is missed and it is more than 8 hours later, the patient should only

take the next dose at the usual time.

Dose management considerations
Patients experiencing rash during the 14-day lead-in period of 200 mg/day (4 mg/kg/day or 150 mg/m^2/day for paediatric patients) should not have their Viramune dose increased until the rash has resolved. The isolated rash should be closely monitored (see section 4.4). The 200 mg once daily dosing regimen should not be continued beyond 28 days at which point in time an alternative treatment should be sought due to the possible risk of underexposure and resistance.

Patients who interrupt nevirapine dosing for more than 7 days should restart the recommended dosing regimen using the two week lead-in period.

There are toxicities that require interruption of Viramune therapy (see section 4.4).

Elderly
Nevirapine has not been specifically investigated in patients over the age of 65.

Renal impairment
For patients with renal dysfunction requiring dialysis an additional 200 mg dose of nevirapine following each dialysis treatment is recommended. Patients with CLcr ≥ 20 ml/min do not require a dose adjustment, see section 5.2.

Hepatic impairment
Nevirapine should not be used in patients with severe hepatic impairment (Child-Pugh C, see section 4.3). No dose adjustment is necessary in patients with mild to moderate hepatic impairment (see sections 4.4 and 5.2).

Paediatric population
The total daily dose should not exceed 400 mg for any patient. Viramune may be dosed in paediatric patients either by body surface area (BSA) or by body weight as follows:
By BSA using the Mosteller formula the recommended oral dose for paediatric patients of all ages is 150 mg/m^2 once daily for two weeks followed by 150 mg/m^2 twice daily thereafter.

Calculation of the volume of Viramune oral suspension (50 mg/5 ml) required for paediatric dosing on a body surface basis of 150 mg/m^2:

BSA range (m^2)	**Volume (ml)**
0.08 – 0.25	2.5
0.25 – 0.42	5
0.42 – 0.58	7.5
0.58 – 0.75	10
0.75 – 0.92	12.5
0.92 – 1.08	15
1.08 – 1.25	17.5
1.25+	20

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

By weight the recommended oral dose for paediatric patients 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.

Calculation of the volume of Viramune oral suspension (50 mg/5 ml) required for paediatric dosing after the two weeks lead-in period.

Weight Range (kg) for patients < 8 yrs of age on a body weight basis receiving 7 mg/kg.	Weight Range (kg) for patients ≥ 8 years of age on a body weight basis receiving 4 mg/kg.	Volume (ml)
1.79 – 5.36	3.13 – 9.38	2.5
5.36 – 8.93	9.38 – 15.63	5
8.93 – 12.50	15.63 – 21.88	7.5
12.50 – 16.07	21.88 – 28.12	10
16.07 – 19.64	28.12 – 34.37	12.5
19.64 – 23.21	34.37 – 40.62	15
23.21 – 26.79	40.62– 46.88	17.5
26.79+	46.88+	20

All patients less than 16 years of age receiving Viramune oral suspension should have their weight or BSA checked frequently to assess if dose adjustments are necessary.

Method of administration
It is important that the entire measured dose of Viramune oral suspension is administered. This is assisted by the use of a dispensing syringe. If an alternative measuring device is used (e.g. a dispensing cup or teaspoon for larger doses) it should be thoroughly rinsed with water and the rinse should also be administered to the patient. Viramune may be taken with or without food.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Readministration to patients who have required permanent discontinuation for severe rash, rash accompanied by constitutional symptoms, hypersensitivity reactions, or clinical hepatitis due to nevirapine.

Patients with severe hepatic impairment (Child-Pugh C) or pre-treatment ASAT or ALAT > 5 ULN until baseline ASAT/ALAT are stabilised < 5 ULN.

Readministration to patients who previously had ASAT or ALAT > 5 ULN during nevirapine therapy and had recurrence of liver function abnormalities upon readministration of nevirapine (see section 4.4).

Coadministration with herbal preparations containing St. John's wort *(Hypericum perforatum)* due to the risk of decreased plasma concentrations and reduced clinical effects of nevirapine (see section 4.5).

4.4 Special warnings and precautions for use

Viramune should only be used with at least two other antiretroviral agents (see section 5.1).

Viramune should not be used as the sole active antiretroviral, as monotherapy with any antiretroviral has shown to result in viral resistance.

The first 18 weeks of therapy with nevirapine 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 (SJS) and toxic epidermal necrolysis (TEN)) and serious hepatitis/hepatic failure. The greatest risk of hepatic and skin reactions occurs in the first 6 weeks of therapy. However, the risk of any hepatic event continues past this period and monitoring should continue at frequent intervals. Female gender and higher CD4 counts (>250/mm^3 in adult females and >400/mm^3 in adult males) at the initiation of nevirapine therapy are associated with a greater risk of hepatic adverse reactions if the patient has detectable plasma HIV-1 RNA - i.e. a concentration ≥ 50 copies/ml - at the initiation of nevirapine. As serious and life threatening hepatotoxicity has been observed in controlled and uncontrolled studies predominantly in patients with a plasma HIV-1 viral load of 50 copies/ml or higher, nevirapine should not be initiated in adult females with CD4 cell counts greater than 250 cells/mm^3 or in adult males with CD4 cell counts greater than 400 cells/mm^3, who have a detectable plasma HIV-1 RNA unless the benefit outweighs the risk.

In some cases, hepatic injury has progressed despite discontinuation of treatment. Patients developing signs or symptoms of hepatitis, severe skin reaction or hypersensitivity reactions must discontinue nevirapine and seek medical evaluation immediately. Nevirapinemust not be restarted following severe hepatic, skin or hypersensitivity reactions (see section 4.3).

The dose must be strictly adhered to, especially the 14-days lead-in period (see section 4.2).

Cutaneous reactions

Severe and life-threatening skin reactions, including fatal cases, have occurred in patients treated with nevirapine 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. Nevirapine 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. Nevirapine 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 section 4.4.

Nevirapine administration above the recommended dose might increase the frequency and seriousness of skin reactions, such as Stevens-Johnson syndrome and toxic epidermal necrolysis.

Rhabdomyolysis has been observed in patients experiencing skin and/or liver reactions associated with nevirapine use.

Concomitant prednisone use (40 mg/day for the first 14 days of Viramune administration) has been shown not to decrease the incidence of nevirapine-associated rash, and may be associated with an increase in incidence and severity of rash during the first 6 weeks of nevirapine 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 or 150 mg/m^2 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 nevirapine or non-nevirapine containing therapy.

Patients should be instructed that a major toxicity of nevirapine 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 nevirapine 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. The 200 mg once daily dosing regimen should not be continued beyond 28 days at which point in time an alternative treatment should be sought due to the possible risk of underexposure and resistance. 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 the medicinal product and immediately seek medical evaluation. In these patients nevirapine must not be restarted.

If patients present with a suspected nevirapine-associated rash, liver function tests should be performed. Patients with moderate to severe elevations (ASAT or ALAT > 5 ULN) should be permanently discontinued from nevirapine.

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, nevirapine must be permanently stopped and not be re-introduced (see section 4.3).

Hepatic reactions

Severe and life-threatening hepatotoxicity, including fatal fulminant hepatitis, has occurred in patients treated with nevirapine. The first 18 weeks of treatment is a critical period which requires close monitoring. The risk of hepatic reactions is greatest in the first 6 weeks of therapy. However the risk continues past this period and monitoring should continue at frequent intervals throughout treatment.

Rhabdomyolysis has been observed in patients experiencing skin and/or liver reactions associated with nevirapine use.

Increased ASAT or ALAT levels $\geq$ 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 nevirapine containing regimens.

Female gender and higher CD4 counts at the initiation of nevirapine therapy in treatment-naïve patients is associated with increased risk of hepatic adverse reactions. Women have a three fold higher risk than men for symptomatic, often rash-associated, hepatic events (5.8 % versus 2.2 %), and treatment-naïve patients of either gender with detectable HIV-1 RNA in plasma with higher CD4 counts at initiation of nevirapine therapy are at higher risk for symptomatic hepatic events with nevirapine. In a retrospective review of predominantly patients with a plasma HIV-1 viral load of 50 copies/ml or higher, women with CD4 counts >250 cells/mm^3 had a 12 fold higher risk of symptomatic hepatic adverse reactions compared to women with CD4 counts <250 cells/mm^3 (11.0% versus 0.9 %). An increased risk was observed in men with detectable HIV-1 RNA in plasma and CD4 counts > 400 cells/mm^3 (6.3 % versus 1.2 % for men with CD4 counts <400 cells/mm^3). This increased risk for toxicity based on CD4 count thresholds has not been detected in patients with undetectable (i.e. < 50 copies/ml) plasma viral load.

Patients should be informed that hepatic reactions are a major toxicity of nevirapine requiring a close monitoring during the first 18 weeks. They should be informed that occurrence of symptoms suggestive of hepatitis should lead them to discontinue nevirapine and immediately seek medical evaluation, which should include liver function tests.

Liver monitoring

Clinical chemistry tests, which include liver function tests, should be performed prior to initiating nevirapine therapy and at appropriate intervals during therapy.

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

Asymptomatic elevations of liver enzymes are frequently described and are not necessarily a contraindication to use nevirapine. 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 $\geq$ 2.5 ULN before or during treatment, then liver tests should be monitored more frequently during regular clinic visits. Nevirapine must not be administered to patients with pre-treatment ASAT or ALAT > 5 ULN until baseline ASAT/ALAT are stabilised < 5 ULN (see section 4.3).

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, nevirapine 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 nevirapine, on a case by case basis, at the starting dose 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, nevirapine 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)), nevirapine must be permanently stopped. Viramune must 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 (Child-Pugh C, see section 4.3). Pharmacokinetic results suggest caution should be exercised when nevirapine is administered to patients with moderate hepatic dysfunction (Child-Pugh B). 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 reactions. 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

Post-Exposure-Prophylaxis: 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 and therefore, is strongly discouraged.

Combination therapy with nevirapine 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.

Hormonal methods of birth control other than Depo-medroxyprogesterone acetate (DMPA) should not be used as the sole method of contraception in women taking Viramune, since nevirapine might lower the plasma concentrations of these medicinal products. For this reason, and to reduce the risk of HIV transmission, barrier contraception (e.g. condoms) is recommended. Additionally, when postmenopausal hormone therapy is used during administration of nevirapine, its therapeutic effect should be monitored.

Weight and metabolic parameters:
An increase in weight and in levels of blood lipids and glucose may occur during antiretroviral therapy. Such changes may in part be linked to disease control and life style. For lipids, there is in some cases evidence for a treatment effect, while for weight gain there is no strong evidence relating this to any particular treatment. For monitoring of blood lipids and glucose reference is made to established HIV treatment guidelines. Lipid disorders should be managed as clinically appropriate.

In clinical studies, Viramune has been associated with an increase in HDL- cholesterol and an overall improvement in the total to HDL-cholesterol ratio. However, in the absence of specific studies, the clinical impact of these findings is not known. In addition, Viramune has not been shown to cause glucose disturbances.

Osteonecrosis: Although the etiology is considered to be multifactorial (including corticosteroid use, alcohol consumption, severe immunosuppression, higher body mass index), cases of osteonecrosis have been reported particularly in patients with advanced HIV-disease and/or long-term exposure to combination antiretroviral therapy (CART). Patients should be advised to seek medical advice if they experience joint aches and pain, joint stiffness or difficulty in movement.

Immune Reactivation Syndrome: In HIV-infected patients with severe immune deficiency at the time of institution of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic pathogens may arise and cause serious clinical conditions, or aggravation of symptoms. Typically, such reactions have been observed within the first few weeks or months of initiation of CART. Relevant examples are cytomegalovirus retinitis, generalised and/or focal mycobacterial infections, and Pneumocystis jirovecii pneumonia. Any inflammatory symptoms should be evaluated and treatment instituted when necessary. Autoimmune disorders (such as Graves' disease and autoimmune hepatitis) have also been reported to occur in the setting of immune reactivation; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment.

The available pharmacokinetic data suggest that the concomitant use of rifampicin and nevirapine is not recommended. Furthermore, combining the following compounds with Viramune is not recommended: efavirenz, ketoconazole, etravirine, rilpivirine, elvitegravir (in combination with cobicistat), atazanavir (in combination with ritonavir), fosamprenavir (if not co-administered with low dose ritonavir) (see section 4.5).

Granulocytopenia is commonly associated with zidovudine. Therefore, patients who receive nevirapine and zidovudine concomitantly and especially paediatric patients and patients who receive

higher zidovudine doses or patients with poor bone marrow reserve, in particular those with advanced HIV disease, have an increased risk of granulocytopenia. In such patients haematological parameters should be carefully monitored.

Hypersensitivity
Sucrose: Viramune oral suspension contains 150 mg of sucrose per ml. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

Sorbitol: Viramune oral suspension contains 162 mg of sorbitol per ml. Patients with hereditary fructose intolerance (HFI) should not take/be given this medicinal product.

Methyl and propyl parahydroxybenzoates: Viramune oral suspension contains methyl parahydroxybenzoate and propyl parahydroxybenzoate, which may cause allergic reaction (possibly delayed).

4.5 Interaction with other medicinal products and other forms of interaction

Nevirapine is an inducer of CYP3A and potentially CYP2B6, with maximal induction occurring within 2-4 weeks of initiating multiple-dose therapy.

Compounds using this metabolic pathway may have decreased plasma concentrations when co-administered with nevirapine. Careful monitoring of the therapeutic effectiveness of P450 metabolised medicinal products is recommended when taken in combination with nevirapine.

The absorption of nevirapine is not affected by food, antacids or medicinal products which are formulated with an alkaline buffering agent.

The interaction data is presented as geometric mean value with 90% confidence interval (90% CI) whenever these data were available. ND = Not Determined, ↑ = Increased, ↓ = Decreased, ↔ = No Effect

Medicinal products by therapeutic areas	**Interaction**	**Recommendations concerning co-administration**
ANTI-INFECTIVES		
ANTIRETROVIRALS		
NRTIs		
Didanosine 100-150 mg BID	Didanosine AUC ↔ 1.08 (0.92-1.27) Didanosine C_{min} ND Didanosine C_{max} ↔ 0.98 (0.79-1.21)	Didanosine and Viramune can be co-administered without dose adjustments.
Emtricitabine	Emtricitabine is not an inhibitor of human CYP 450 enzymes.	Viramune and emtricitabine may be coadministered without dose adjustments.
Abacavir	In human liver microsomes, abacavir did not inhibit cytochrome P450 isoforms.	Viramune and abacavir may be coadministered without dose adjustments.
Lamivudine 150 mg BID	No changes to lamivudine apparent clearance and volume of distribution, suggesting no induction effect of nevirapine on lamivudine clearance.	Lamivudine and Viramune can be co-administered without dose adjustments.
Stavudine:	Stavudine AUC ↔ 0.96 (0.89-1.03)	Stavudine and Viramune can be co-

30/40 mg BID	Stavudine C_{min} ND Stavudine C_{max} ↔ 0.94 (0.86-1.03) Nevirapine: compared to historical controls, levels appeared to be unchanged.	administered without dose adjustments.
Tenofovir 300 mg QD	Tenofovir plasma levels remain unchanged when co-administered with nevirapine. Nevirapine plasma levels were not altered by co-administration of tenofovir.	Tenofovir and Viramune can be co-administered without dose adjustments.
Zidovudine 100-200 mg TID	Zidovudine AUC ↓ 0.72 (0.60-0.96) Zidovudine C_{min} ND Zidovudine C_{max} ↓ 0.70 (0.49-1.04) Nevirapine: Zidovudine had no effect on its pharmacokinetics.	Zidovudine and Viramune can be co-administered without dose adjustments Granulocytopenia is commonly associated with zidovudine. Therefore, patients who receive nevirapine and zidovudine concomitantly and especially paediatric patients and patients who receive higher zidovudine doses or patients with poor bone marrow reserve, in particular those with advanced HIV disease, have an increased risk of granulocytopenia. In such patients haematological parameters should be carefully monitored.
NNRTIs		
Efavirenz 600 mg QD	Efavirenz AUC ↓ 0.72 (0.66-0.86) Efavirenz C_{min} ↓ 0.68 (0.65-0.81) Efavirenz C_{max} ↓ 0.88 (0.77-1.01)	It is not recommended to co-administer efavirenz and Viramune (see section 4.4), because of additive toxicity and no benefit in terms of efficacy over either NNRTI alone (for results of 2NN study, see section 5.1).
Etravirine	Concomitant use of etravirine with nevirapine may cause a significant decrease in the plasma concentrations of etravirine and loss of therapeutic effect of etravirine .	The concomitant administration of Viramune with NNRTIs is not recommended (see section 4.4).
Rilpivirine	Interaction has not been studied.	The concomitant administration of Viramune with NNRTIs is not recommended (see section 4.4).

PIs		
Atazanavir/ritonavir 300/100 mg QD 400/100 mg QD	<u>Atazanavir/r 300/100mg</u>: Atazanavir/r AUC ↓ 0.58 (0.48-0.71) Atazanavir/r C_{min} ↓ 0.28 (0.20-0.40) Atazanavir/r C_{max} ↓ 0.72 (0.60-0.86) <u>Atazanavir/r 400/100mg:</u> Atazanavir/r AUC ↓ 0.81 (0.65-1.02) Atazanavir/r C_{min} ↓ 0.41 (0.27-0.60) Atazanavir/r C_{max} ↔ 1.02 (0.85–1.24) (compared to 300/100mg without nevirapine) Nevirapine AUC ↑ 1.25 (1.17-1.34) Nevirapine C_{min} ↑ 1.32 (1.22–1.43) Nevirapine C_{max} ↑ 1.17 (1.09-1.25)	It is not recommended to co-administer atazanavir/ritonavir and Viramune (see section 4.4).
Darunavir/ritonavir 400/100 mg BID	Darunavir AUC ↑ 1.24 (0.97-1.57) Darunavir C_{min} ↔ 1.02 (0.79-1.32) Darunavir C_{max} ↑ 1.40 (1.14-1.73) Nevirapine AUC ↑ 1.27 (1.12-1.44) Nevirapine C_{min} ↑ 1.47 (1.20-1.82) Nevirapine C_{max} ↑ 1.18 (1.02-1.37)	Darunavir and Viramune can be co-administered without dose adjustments.
Fosamprenavir 1,400 mg BID	Amprenavir AUC ↓ 0.67 (0.55-0.80) Amprenavir C_{min} ↓ 0.65 (0.49-0.85) Amprenavir C_{max} ↓ 0.75 (0.63-0.89) Nevirapine AUC ↑ 1.29 (1.19-1.40) Nevirapine C_{min} ↑ 1.34 (1.21-1.49) Nevirapine C_{max} ↑ 1.25 (1.14-1.37)	It is not recommended to co-administer fosamprenavir and Viramune if fosamprenavir is not co-administered with ritonavir (see section 4.4).
Fosamprenavir/ritonavir 700/100 mg BID	Amprenavir AUC ↔ 0.89 (0.77-1.03) Amprenavir C_{min} ↓ 0.81 (0.69-0.96) Amprenavir C_{max} ↔ 0.97 (0.85-1.10) Nevirapine AUC ↑ 1.14 (1.05-1.24) Nevirapine C_{min} ↑ 1.22 (1.10-1.35) Nevirapine C_{max} ↑ 1.13 (1.03-1.24)	Fosamprenavir/ritonavir and Viramune can be co-administered without dose adjustments
Lopinavir/ritonavir (capsules) 400/100 mg BID	<u>Adult patients</u>: Lopinavir AUC ↓ 0.73 (0.53-0.98) Lopinavir C_{min} ↓ 0.54 (0.28-0.74) Lopinavir C_{max} ↓ 0.81 (0.62-0.95)	An increase in the dose of lopinavir/ritonavir to 533/133 mg (4 capsules) or 500/125 mg (5 tablets with 100/25 mg each) twice daily with food is recommended in combination with Viramune. Dose adjustment of Viramune is not required when co-administered with lopinavir.

Lopinavir/ritonavir (oral solution) 300/75 mg/m^2 BID	<u>Paediatric patients</u>: Lopinavir AUC ↓ 0.78 (0.56-1.09) Lopinavir C_{min} ↓ 0.45 (0.25-0.82) Lopinavir C_{max} ↓ 0.86 (0.64-1.16)	For children, increase of the dose of lopinavir/ritonavir to 300/75 mg/m^2 twice daily with food should be considered when used in combination with Viramune, particularly for patients in whom reduced susceptibility to lopinavir/ritonavir is suspected.
Ritonavir 600 mg BID	Ritonavir AUC↔ 0.92 (0.79-1.07) Ritonavir C_{min} ↔ 0.93 (0.76-1.14) Ritonavir C_{max} ↔ 0.93 (0.78-1.07) Nevirapine: Co-administration of ritonavir does not lead to any clinically relevant change in nevirapine plasma levels.	Ritonavir and Viramune can be co-administered without dose adjustments.
Saquinavir/ritonavir	The limited data available with saquinavir soft gel capsule boosted with ritonavir do not suggest any clinically relevant interaction between saquinavir boosted with ritonavir and nevirapine	Saquinavir/ritonavir and Viramune can be co-administered without dose adjustments.
Tipranavir/ritonavir 500/200 mg BID	No specific drug-drug interaction study has been performed. The limited data available from a phase IIa study in HIV-infected patients have shown a clinically non significant 20% decrease of TPV C_{min}.	Tipranavir and Viramune can be co-administered without dose adjustments.
ENTRY INHIBITORS		
Enfuvirtide	Due to the metabolic pathway no clinically significant pharmacokinetic interactions are expected between enfuvirtide and nevirapine.	Enfuvirtide and Viramune can be co-administered without dose adjustments.
Maraviroc 300 mg QD	Maraviroc AUC ↔ 1.01 (0.6 -1.55) Maraviroc C_{min} ND Maraviroc C_{max} ↔ 1.54 (0.94-2.52) compared to historical controls Nevirapine concentrations not measured, no effect is expected.	Maraviroc and Viramune can be co-administered without dose adjustments.

INTEGRASE INHIBITORS		
Elvitegravir/ cobicistat	Interaction has not been studied. Cobicistat, a cytochrome P450 3A inhibitor significantly inhibits hepatic enzymes, as well as other metabolic pathways. Therefore coadministration would likely result in altered plasma levels of cobicistat and Viramune.	Coadministration of Viramune with elvitegravir in combination with cobicistat is not recommended (see section 4.4).
Raltegravir 400 mg BID	No clinical data available. Due to the metabolic pathway of raltegravir no interaction is expected.	Raltegravir and Viramune can be co-administered without dose adjustments.
ANTIBIOTICS		
Clarithromycin 500 mg BID	Clarithromycin AUC ↓ 0.69 (0.62-0.76) Clarithromycin C_{min} ↓ 0.44 (0.30-0.64) Clarithromycin C_{max} ↓ 0.77 (0.69-0.86) Metabolite 14-OH clarithromycin AUC ↑ 1.42 (1.16-1.73) Metabolite 14-OH clarithromycin C_{min} ↔ 0 (0.68-1.49) Metabolite 14-OH clarithromycin C_{max} ↑ 1.47 (1.21-1.80) Nevirapine AUC ↑ 1.26 Nevirapine C_{min} ↑ 1.28 Nevirapine C_{max} ↑ 1.24 compared to historical controls.	Clarithromycin exposure was significantly decreased, 14-OH metabolite exposure increased. Because the clarithromycin active metabolite has reduced activity against *Mycobacterium avium-intracellulare complex* overall activity against the pathogen may be altered. Alternatives to clarithromycin, such as azithromycin should be considered. Close monitoring for hepatic abnormalities is recommended
Rifabutin 150 or 300 mg QD	Rifabutin AUC ↑ 1.17 (0.98-1.40) Rifabutin C_{min} ↔ 1.07 (0.84-1.37) Rifabutin C_{max} ↑ 1.28 (1.09-1.51) Metabolite 25-O-desacetylrifabutin AUC ↑ 1.24 (0.84-1.84) Metabolite 25-O-desacetylrifabutin C_{min} ↑ 1.22 (0.86-1.74) Metabolite 25-O-desacetylrifabutin C_{max} ↑ 1.29 (0.98-1.68) A clinically not relevant increase in the apparent clearance of nevirapine (by 9%) compared to historical data was reported.	No significant effect on rifabutin and Viramune mean PK parameters is seen. Rifabutin and Viramune can be co-administered without dose adjustments. However, due to the high interpatient variability 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.
Rifampicin 600 mg QD	Rifampicin AUC ↔ 1.11 (0.96-1.28) Rifampicin C_{min} ND Rifampicin C_{max} ↔ 1.06 (0.91-1.22)	It is not recommended to co-administer rifampicin and Viramune (see section 4.4). Physicians needing to treat patients co-infected with

	Nevirapine AUC ↓ 0.42 Nevirapine C_{min} ↓ 0.32 Nevirapine C_{max} ↓ 0.50 compared to historical controls.	tuberculosis and using a Viramune containing regimen may consider co-administration of rifabutin instead.
ANTIFUNGALS		
Fluconazole 200 mg QD	Fluconazole AUC ↔ 0.94 (0.88-1.01) Fluconazole C_{min} ↔ 0.93 (0.86-1.01) Fluconazole C_{max} ↔ 0.92 (0.85-0.99) Nevirapine: exposure: ↑100% compared with historical data where nevirapine was administered alone.	Because of the risk of increased exposure to Viramune, caution should be exercised if the medicinal products are given concomitantly and patients should be monitored closely.
Itraconazole 200 mg QD	Itraconazole AUC ↓ 0.39 Itraconazole C_{min} ↓ 0.13 Itraconazole C_{max} ↓ 0.62 Nevirapine: there was no significant difference in nevirapine pharmacokinetic parameters.	A dose increase for itraconazole should be considered when these two agents are administered concomitantly.
Ketoconazole 400 mg QD	Ketoconazole AUC ↓ 0.28 (0.20-0.40) Ketoconazole C_{min} ND Ketoconazole C_{max} ↓ 0.56 (0.42-0.73) Nevirapine: plasma levels: ↑ 1.15-1.28 compared to historical controls.	It is not recommended to co-administer ketoconazole and Viramune (see section 4.4).
ANTIVIRALS FOR CHRONIC HEPATITIS B AND C		
Adefovir	Results of *in vitro* studies showed a weak antagonism of nevirapine by adefovir (see section 5.1), this has not been confirmed in clinical trials and reduced efficacy is not expected. Adefovir did not influence any of the common CYP isoforms known to be involved in human drug metabolism and is excreted renally. No clinically relevant drug-drug interaction is expected.	Adefovir and Viramune may be coadministered without dose adjustments.
Entecavir	Entecavir is not a substrate, inducer or an inhibitor of cytochrome P450 (CYP450) enzymes. Due to the metabolic pathway of entecavir, no clinically relevant drug-drug interaction is expected.	Entecavir and Viramune may be coadministered without dose adjustments.
Interferons (pegylated interferons alfa 2a and alfa 2b)	Interferons have no known effect on CYP 3A4 or 2B6. No clinically relevant drug-drug interaction is	Interferons and Viramune may be coadministered without dose adjustments.

	expected.	
Ribavirin	Results of *in vitro* studies showed a weak antagonism of nevirapine by ribavirin (see section 5.1), this has not been confirmed in clinical trials and reduced efficacy is not expected. Ribavirin does not inhibit cytochrome P450 enzymes, and there is no evidence from toxicity studies that ribavirin induces liver enzymes. No clinically relevant drug-drug interaction is expected.	Ribavirin and Viramune may be coadministered without dose adjustments.
Telbivudine	Telbivudine is not a substrate, inducer or inhibitor of the cytochrome P450 (CYP450) enzyme system. Due to the metabolic pathway of telbivudine, no clinically relevant drug-drug interaction is expected.	Telbivudine and Viramune may be coadministered without dose adjustments.
ANTACIDS		
Cimetidine	Cimetidine: no significant effect on cimetidine PK parameters is seen. Nevirapine C_{min} ↑ 1.07	Cimetidine and Viramune can be co-administered without dose adjustments.
ANTITHROMBOTICS		
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.	Close monitoring of anticoagulation levels is warranted.
CONTRACEPTIVES		
Depo-medroxyprogesterone acetate (DMPA) 150 mg every 3 months	DMPA AUC ↔ DMPA C_{min} ↔ DMPA C_{max} ↔ Nevirapine AUC ↑ 1.20 Nevirapine C_{max} ↑ 1.20	Viramune co-administration did not alter the ovulation suppression effects of DMPA. DMPA and Viramune can be co-administered without dose adjustments.
Ethinyl estradiol (EE) 0.035 mg	EE AUC ↓ 0.80 (0.67 - 0.97) EE C_{min} ND EE C_{max} ↔ 0.94 (0.79 - 1.12)	Oral hormonal contraceptives should not be used as the sole method of contraception in women taking Viramune (see section 4.4). Appropriate doses for hormonal contraceptives (oral or other forms of application) other than DMPA in combination with Viramune have not been established with respect to safety and efficacy.
Norethindrone (NET) 1.0 mg QD	NET AUC ↓ 0.81 (0.70 - 0.93) NET C_{min} ND NET C_{max} ↓ 0.84 (0.73 - 0.97)	

ANALGESICS/OPIOIDS		
Methadone Individual Patient Dosing	Methadone AUC ↓ 0.40 (0.31 - 0.51) Methadone C_{min} ND Methadone C_{max} ↓ 0.58 (0.50 - 0.67)	Methadone-maintained patients beginning Viramune therapy should be monitored for evidence of withdrawal and methadone dose should be adjusted accordingly.
HERBAL PRODUCTS		
St. John's Wort	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 medicinal product metabolism enzymes and/or transport proteins by St. John's Wort.	Herbal preparations containing St. John's Wort and Viramune must not be co-administered (see section 4.3). If a 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:

Nevirapine metabolites: 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.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential / Contraception in males and females
Women of childbearing potential should not use oral contraceptives as the sole method for birth control, since nevirapine might lower the plasma concentrations of these medicinal products (see sections 4.4 & 4.5).

Pregnancy
Currently available data on pregnant women indicate no malformative or foeto/ neonatal toxicity. To date no other relevant epidemiological data are available. No observable teratogenicity was detected in reproductive studies performed in pregnant rats and rabbits (see section 5.3). There are no adequate and well-controlled studies in pregnant women. Caution should be exercised when prescribing nevirapine to pregnant women (see section 4.4). As hepatotoxicity is more frequent in women with CD4 cell counts above 250 cells/mm^3 with detectable HIV-1 RNA in plasma (50 or more copies/ml), these conditions should be taken in consideration on therapeutic decision (see section 4.4). There is not enough evidence to substantiate that the absence of an increased risk for toxicity seen in pre-treated women initiating nevirapine with an undetectable viral load (less than 50 copies/ml of HIV-1 in plasma) and CD4 cell counts above 250 cells/mm^3 also applies to pregnant women. All the randomised studies addressing this issue specifically excluded pregnant women, and pregnant women were under-represented in cohort studies as well as in meta-analyses.

Breast-feeding
It is recommended that women living with HIV do not breast-feed their infants in order to avoid transmission of HIV.

Fertility
In reproductive toxicology studies, evidence of impaired fertility was seen in rats.

4.7 Effects on ability to drive and use machines

There are no specific studies about the ability to drive vehicles and use machinery.
However, patients should be advised that they may experience adverse reactions such as fatigue during treatment with Viramune. Therefore, caution should be recommended when driving a car or operating machinery. If patients experience fatigue they should avoid potentially hazardous tasks such as driving or operating machinery.

4.8 Undesirable effects

Summary of the safety profile
The most frequently reported adverse reactions related to Viramune therapy, across all clinical studies, were rash, allergic reactions, hepatitis, abnormal liver function tests, nausea, vomiting, diarrhoea, abdominal pain, fatigue, fever, headache and myalgia.

The postmarketing experience has shown that the most serious adverse reactions are Stevens-Johnson syndrome/ toxic epidermal necrolysis, serious hepatitis/hepatic failure, and drug reaction with eosinophilia and systemic symptoms, 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 section 4.4).

Tabulated summary of adverse reactions
The following adverse reactions which may be causally related to the administration of Viramune have been reported. The frequencies estimated are based on pooled clinical study data for adverse reactions considered related to Viramune treatment.

Frequency is defined using the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000).

Blood and lymphatic system disorders

Common	granulocytopenia
Uncommon	anaemia

Immune system disorders

Common	hypersensitivity (incl. anaphylactic reaction, angioedema, urticaria)
Uncommon	anaphylactic reaction
Rare	drug reaction with eosinophilia and systemic symptoms

Nervous system disorders

Common	headache

Gastrointestinal disorders

Common	nausea, vomiting, abdominal pain, diarrhoea

Hepatobiliary disorders

Common	hepatitis (including severe and life-threatening hepatotoxicity) (1.9%)
Uncommon	jaundice
Rare	hepatitis fulminant (which may be fatal)

Skin and subcutaneous tissue disorders

Very common	rash (12.5 %)

Uncommon	Stevens-Johnson syndrome/ toxic epidermal necrolysis (which may be fatal) (0.2 %), angioedema, urticaria

Musculoskeletal and connective tissue disorders

Uncommon	arthralgia, myalgia

General disorders and administration site conditions

Common	pyrexia, fatigue

Investigations

Common	liver function test abnormal (alanine aminotransferase increased; transaminases increased; aspartate aminotransferase increased; gamma-glutamyltransferase increased; hepatic enzyme increased; hypertransaminasaemia)
Uncommon	blood phosphorus decreased; blood pressure increased

Description of selected adverse reactions

In study 1100.1090, from which the majority of related adverse events (n=28) were received, patients on placebo had a higher incidence of events of granulocytopenia (3.3 %) than patients on nevirapine (2.5 %).

Anaphylactic reaction was identified through post-marketing surveillance but not observed in randomised, controlled clinical studies. The frequency category was estimated from a statistical calculation based on the total number of patients exposed to nevirapine in randomised controlled clinical studies (n=2,718).

Decreased blood phosphorus and increased blood pressure were observed in clinical studies with co-administration of tenofovir/emtricitabine.

Metabolic parameters

Weight and levels of blood lipids and glucose may increase during antiretroviral therapy (see section 4.4)

The following adverse reactions have also been reported when nevirapine has been used in combination with other anti-retroviral agents: pancreatitis, peripheral neuropathy and thrombocytopaenia. These adverse reactions are commonly associated with other antiretroviral agents and may be expected to occur when nevirapine is used in combination with other agents; however it is unlikely that these adverse reactions are due to nevirapine treatment. Hepatic-renal failure syndromes have been reported rarely.

In HIV-infected patients with severe immune deficiency at the time of initiation of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic infections may arise. Autoimmune disorders (such as Graves' disease and autoimmune hepatitis) have also been reported; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment (see section 4.4).

Cases of osteonecrosis have been reported, particularly in patients with generally acknowledged risk factors, advanced HIV disease or long-term exposure to combination antiretroviral therapy (CART). The frequency of this is unknown (see section 4.4).

Skin and subcutaneous tissues

The most common clinical toxicity of nevirapine is rash, with Viramune attributable rash occurring in 12.5 % of patients in combination regimens in controlled studies.

Rashes are usually mild to moderate, maculopapular erythematous cutaneous eruptions, with or without pruritus, located on the trunk, face and extremities. Hypersensitivity (anaphylactic reaction,

angioedema and urticaria) have been reported. Rashes occur alone or in the context of drug reaction with eosinophilia and systemic symptoms, characterised by rash 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 nevirapine, including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). Fatal cases of SJS, TEN and drug reaction with eosinophilia and systemic symptoms 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 (see section 4.4).

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 nevirapine. 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 section 4.4).

Paediatric population
Based on clinical study experience of 361 paediatric patients the majority of which received combination treatment with ZDV or/and ddI, the most frequently reported adverse events related to nevirapine were similar to those observed in adults. Granulocytopenia was more frequently observed in children. In an open-label clinical study (ACTG 180) granulocytopenia assessed as medicinal product-related occurred in 5/37 (13.5 %) of patients. In ACTG 245, a double-blind placebo controlled study, the frequency of serious medicinal product-related granulocytopenia was 5/305 (1.6 %). Isolated cases of Stevens-Johnson syndrome or Stevens-Johnson/ toxic epidermal necrolysis transition syndrome have been reported in this population.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

There is no known antidote for nevirapine overdose. Cases of Viramune overdose at doses ranging from 800 to 6,000 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, increase in transaminases and weight decrease. All of these effects subsided following discontinuation of nevirapine.

Paediatric population

One case of massive accidental overdose in a newborn was reported. The ingested dose was 40 times the recommended dose of 2 mg/kg/day. Mild isolated neutropenia and hyperlactataemia was observed, which spontaneously disappeared within one week without any clinical complications. One year later, the child's development remained normal.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antivirals for systemic use, non-nucleoside reverse transcriptase inhibitors, ATC code J05AG01.

Mechanism of action

Nevirapine is a NNRTI of HIV-1. Nevirapine is a non-competitive inhibitor of the HIV-1 reverse transcriptase, but it does not have a biologically significant inhibitory effect on the HIV-2 reverse transcriptase or on eukaryotic DNA polymerases α, β, γ, or δ.

Antiviral activity *in vitro*

Nevirapine had a median EC_{50} value (50% inhibitory concentration) of 63 nM against a panel of group M HIV-1 isolates from clades A, B, C, D, F, G, and H, and circulating recombinant forms (CRF), CRF01_AE, CRF02_AG and CRF12_BF replicating in human embryonic kidney 293 cells. In a panel of 2,923 predominantly subtype B HIV-1 clinical isolates, the mean EC_{50} value was 90nM. Similar EC_{50} values are obtained when the antiviral activity of nevirapine is measured in peripheral blood mononuclear cells, monocyte derived macrophages or lymphoblastoid cell line. Nevirapine had no antiviral activity in cell culture against group O HIV-1 isolates or HIV-2 isolates.

Nevirapine in combination with efavirenz exhibited a strong antagonistic anti-HIV-1 activity in vitro (see section 4.5) 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, 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 medicinal product adefovir and by the anti-HCV medicinal product ribavirin *in vitro*.

Resistance

HIV-1 isolates with reduced susceptibility (100-250-fold) to nevirapine emerge in cell culture. Genotypic analysis showed mutations in the HIV-1 RT gene Y181C and/or V106A 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.

Genotypic analysis of isolates from antiretroviral naïve patients experiencing virologic failure (n=71) receiving nevirapine once daily (n=25) or twice daily (n=46) in combination with lamivudine and stavudine for 48 weeks showed that isolates from 8/25 and 23/46 patients, 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.

Cross-resistance

Rapid emergence of HIV-strains which are cross-resistant to NNRTIs has been observed in vitro. Cross resistance to efavirenz is expected after virologic failure with nevirapine. Depending on resistance testing results, an etravirine-containing regimen may be used subsequently. Cross-resistance between nevirapine and either HIV protease inhibitors, HIV integrase inhibitors or HIV entry inhibitors is unlikely because the enzyme targets involved are different. Similarly the potential for cross-resistance between nevirapine and NRTIs is low because the molecules have different binding sites on the reverse transcriptase.

Clinical results

Viramune has been evaluated in both treatment-naïve and treatment-experienced patients.

Studies in treatment-naïve patients

2NN study

The double non-nucleoside study 2 NN was a randomised, open-label, multicentre prospective study comparing the NNRTIs nevirapine, efavirenz and both medicinal products given together.

1,216 antiretroviral-therapy naïve patients with plasma HIV-1 RNA > 5,000 copies/ml at baseline were assigned to Viramune 400 mg once daily, Viramune 200 mg twice daily, efavirenz 600 mg once daily, or Viramune (400 mg) and efavirenz (800 mg) once daily, plus stavudine and lamivudine for 48 weeks.
The primary endpoint, treatment failure, was defined as less than 1 $\log_{10}$ decline in plasma HIV-1 RNA in the first 12 weeks, or two consecutive measurements of more than 50 copies/ ml from week 24 onwards, or disease progression.

Median age was 34 years and about 64 % were male patients, median CD4 cell count was 170 and 190 cells per mm^3 in the Viramune twice daily and efavirenz groups, respectively. There were no significant differences in demographic and baseline characteristics between the treatment groups.

The predetermined primary efficacy comparison was between the Viramune twice daily and the efavirenz treatment groups.

The nevirapine twice daily regimen and the efavirenz regimen were not significantly different (p= 0.091) in terms of efficacy as measured by treatment failure, or any component of treatment failure including virological failure.
The simultaneous use of nevirapine (400 mg) plus efavirenz (800 mg) was associated with the highest frequency of clinical adverse events and with the highest rate of treatment failure (53.1 %). As the regimen of nevirapine plus efavirenz did not have additional efficacy and caused more adverse events than each medicinal product separately, this regimen is not recommended.

Twenty per cent of patients assigned to nevirapine twice daily and 18% of patients assigned to efavirenz had at least one grade 3 or 4 clinical adverse event. Clinical hepatitis reported as clinical adverse event occurred in 10 (2.6 %) and 2 (0.5 %) patients in the nevirapine twice daily and efavirenz groups respectively. The proportion of patients with at least one grade 3 or 4 liver-associated laboratory toxicity was 8.3 % for nevirapine twice daily and 4.5 % for efavirenz. Of the patients with grade 3 or 4 liver-associated laboratory toxicity, the proportions coinfected with hepatitis B or hepatitis C virus were 6.7 % and 20.0 % in the nevirapine twice daily group, 5.6 % and 11.1 % in the efavirenz group.

2NN Three-year follow-up-study

This is a retrospective multicentre study comparing the 3-year antiviral efficacy of Viramune and efavirenz in combination with stavudine and lamivudine in 2NN patients from week 49 to week 144. Patients who participated in the 2NN study and were still under active follow-up at week 48 when the study closed and were still being treated at the study clinic, were asked to participate in this study. Primary study endpoints (percentage of patients with treatment failures) and secondary study endpoints as well as backbone therapy were similar to the original 2NN study.

A durable response to Viramune for at least three years was documented in this study, and equivalence within a 10 % range was demonstrated between Viramune 200 mg twice daily and efavirenz with respect to treatment failure. Both, the primary (p = 0.92) and secondary endpoints showed no statistically significant differences between efavirenz and Viramune 200 mg twice daily.

Studies in treatment-experienced patients

NEFA study

The NEFA study is a controlled prospective randomised study which evaluated treatment options for patients who switch from protease inhibitor (PI) based regimen with undetectable load to either Viramune, efavirenz or abacavir.
The study randomly assigned 460 adults who were taking two nucleoside reverse-transcriptase inhibitors and at least one PI and whose plasma HIV-1 RNA levels had been less than 200 c/ml for at least the previous six months to switch from the PI to Viramune (155 patients), efavirenz (156), or abacavir (149).
The primary study endpoint was death, progression to the acquired immunodeficiency syndrome, or an increase in HIV-1 RNA levels to 200 copies or more per millilitre.
At 12 months, the Kaplan–Meier estimates of the likelihood of reaching the endpoint were 10 % in the Viramune group, 6 % in the efavirenz group, and 13 percent in the abacavir group (P=0.10 according to an intention-to-treat analysis).

The overall incidence of adverse events was significantly lower (61 patients, or 41 %) in the abacavir group than in the nevirapine group (83 patients, or 54 %) or the efavirenz group (89 patients, or 57 %). Significantly fewer patients in the abacavir group (9 patients, or 6 %) than in the nevirapine group (26 patients, or 17 %) or the efavirenz group (27 patients, or 17 %) discontinued the medicinal product because of adverse events.

Perinatal Transmission

Numerous studies have been performed examining the use of Viramune in regards to perinatal transmission, most notably HIVNET 012. This study demonstrated a significant reduction in transmission using single dose nevirapine (13.1 % (n = 310) in the Viramune group, versus 25.1 % (n = 308) in the ultra-short zidovudine group (p = 0.00063)). Monotherapy with Viramune has been associated with the development of NNRTI resistance. Single dose nevirapine in mothers or infants may lead to reduced efficacy if an HIV treatment regimen using nevirapine is later instituted within 6 months or less in these patients. Combination of other antiretrovirals with single-dose nevirapine attenuates the emergence of nevirapine resistance. Where other antiretroviral medicines are accessible, the single dose Viramune regimen should be combined with additional effective antiretroviral medicines (as recommended in internationally recognized guidelines).

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.

Paediatric population
Results of a 48-week analysis of the South African study BI 1100.1368 confirmed that the 4/7 mg/kg and 150 mg/m2 nevirapine dose groups were well tolerated and effective in treating antiretroviral naive paediatric patients. A marked improvement in the CD4+ cell percent was observed through Week 48 for both dose groups. Also, both dosing regimens were effective in reducing the viral load. In this 48-week study no unexpected safety findings were observed in either dosing group.

5.2 Pharmacokinetic properties

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

Absorption: 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 C_{max} of 5.74 μg/ml (5.00-7.44) and C_{min} 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.

Distribution: 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.

Biotransformation and elimination: *In vivo* studies in humans and *in vitro* studies with human liver microsomes have shown that nevirapine is extensively biotransformed via cytochrome P450 (oxidative) metabolism to several hydroxylated metabolites. *In vitro* studies with human liver microsomes suggest that oxidative metabolism of nevirapine is mediated primarily by cytochrome P450 isozymes from the CYP3A family, although other isozymes may have a secondary role. In a mass balance/excretion study in eight healthy male volunteers dosed to steady state with nevirapine 200 mg given twice daily followed by a single 50 mg dose of 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 is 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 impairment: The single-dose pharmacokinetics of nevirapine has been compared in 23 patients 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 patients 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, patients 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 nevirapine 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 nevirapine dosing.

Hepatic impairment: A steady state study comparing 46 patients with
mild (n=17: Ishak Score 1-2),
moderate (n=20; Ishak Score 3-4),
or severe (n=9; Ishak Score 5-6, Child-Pugh A in 8 pts., for 1 Child-Pugh score not applicable)
liver fibrosis as a measure of hepatic impairment was conducted.

The patients 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 this study, the multiple dose pharmacokinetic disposition of nevirapine and the five oxidative metabolites were not altered.

However, approximately 15 % of these patients with hepatic fibrosis had nevirapine trough concentrations above 9,000 ng/ml (2 fold the usual mean trough). Patients with hepatic impairment should be monitored carefully for evidence of medicinal product induced toxicity.

In a 200 mg nevirapine single dose pharmacokinetic study of HIV-negative patients with mild and moderate hepatic impairment (Child-Pugh A, n=6; Child-Pugh B, n=4), a significant increase in the AUC of nevirapine was observed in one Child-Pugh B patient with ascites suggesting that patients with worsening hepatic function and ascites may be at risk of accumulating nevirapine in the systemic circulation. Because nevirapine induces its own metabolism with multiple dosing, this single dose study may not reflect the impact of hepatic impairment on multiple dose pharmacokinetics (see section 4.4).

Gender and elderly
In the multinational 2NN study, a population pharmacokinetic substudy of 1,077 patients was performed that included 391 females. Female patients showed a 13.8 % lower clearance of nevirapine than did male patients. This difference is not considered clinically relevant. Since neither body weight nor Body Mass Index (BMI) had influence on the clearance of nevirapine, the effect of gender cannot be explained by body size. Nevirapine pharmacokinetics in HIV-1 infected adults does not appear to change with age (range 19-68 years) or race (Black, Hispanic, or Caucasian). Nevirapine has not been specifically investigated in patients over the age of 65.

Paediatric population
Data concerning the pharmacokinetics of nevirapine have been derived from two major sources: a 48 week paediatric study in South Africa (BI 1100.1368) involving 123 HIV-1 positive, antiretroviral naïve patients aged 3 months to 16 years; and a consolidated analysis of five Paediatric AIDS Clinical Trials Group (PACTG) protocols comprising 495 patients aged 14 days to 19 years.

Pharmacokinetic data on 33 patients (age range 0.77 – 13.7 years) in the intensive sampling group demonstrated that clearance of nevirapine increased with increasing age in a manner consistent with increasing body surface area. Dosing of nevirapine at 150 mg/m^2 BID (after a two-week lead in at 150 mg/m^2 QD) produced geometric mean or mean trough nevirapine concentrations between 4-6 μg/ml (as targeted from adult data). In addition, the observed trough nevirapine concentrations were comparable between the two methods.

The consolidated analysis of Paediatric AIDS Clinical Trials Group (PACTG) protocols 245, 356, 366, 377, and 403 allowed for the evaluation of paediatric patients less than 3 months of age (n=17) enrolled in these PACTG studies. The plasma nevirapine concentrations observed were within the range observed in adults and the remainder of the paediatric population, but were more variable between patients, particularly in the second month of age.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans other than those observed in clinical studies based on conventional studies of safety, pharmacology, repeated dose toxicity, and genotoxicity. In carcinogenicity studies, nevirapine induces hepatic tumours in rats and mice. These findings are most likely related to nevirapine being a strong inducer of liver enzymes, and not due to a genotoxic mode of action.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Carbomer
Methyl parahydroxybenzoate (E218)
Propyl parahydroxybenzoate (E216)
Sorbitol
Sucrose
Polysorbate 80
Sodium hydroxide (for pH-adjustment)
Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

The medicinal product should be used within 6 months of opening.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

White high density polyethylene (HDPE) bottle with two piece child-resistant closure (outer shell white polyethylene, inner shell polypropylene) with a polyethylene liner. Each bottle contains 240 ml of oral suspension.

6.6 Special precautions for disposal and other handling

Instructions for administration:
Viramune oral suspension should be shaken gently prior to administration. The required dose volumes should be measured employing a dispensing syringe. Viramune oral suspension should be used within 6 months after first opening of the bottle.

Disposal:
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Boehringer Ingelheim International GmbH
Binger Strasse 173
55216 Ingelheim am Rhein,
Germany

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/97/055/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 5 February 1998
Date of latest renewal: 20 December 2012

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

1. NAME OF THE MEDICINAL PRODUCT

Viramune 400 mg prolonged-release tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each prolonged-release tablet contains 400 mg of nevirapine (as anhydrous).

Excipient with known effect
Each prolonged-release tablet contains 400 mg of lactose (as monohydrate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Prolonged-release tablet

Yellow, oval, biconvex prolonged-release tablets. The prolonged-release tablets are about 9.3 x 19.1 mm, debossed with V04 on one side and the company symbol on the other side. The prolonged-release tablet should not be divided.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Viramune is indicated in combination with other anti-retroviral medicinal products for the treatment of HIV-1 infected adults, adolescents, and children three years and above and able to swallow tablets (see section 4.2).

Prolonged-release tablets are not suitable for the 14-day lead-in phase for patients starting nevirapine. Other nevirapine formulations, such as immediate-release tablets or oral suspension should be used (see section 4.2).

Most of the experience with Viramune is in combination with nucleoside reverse transcriptase inhibitors (NRTIs). The choice of a subsequent therapy after Viramune should be based on clinical experience and resistance testing (see section 5.1).

4.2 Posology and method of administration

Viramune should be administered by physicians who are experienced in the treatment of HIV infection.

Posology

Adults
The recommended dose of Viramune for patients initiating nevirapine therapy is one 200 mg immediate-release 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 400 mg prolonged-release tablet once daily, in combination with at least two additional antiretroviral agents.

Patients currently on a Viramune immediate-release twice daily regimen:
Patients already on a regimen of Viramune immediate-release twice daily in combination with other antiretroviral agents can be switched to Viramune 400 mg prolonged-release tablets once daily in

combination with other antiretroviral agents without a lead-in period of Viramune immediate-release.

Viramune should be combined with at least two additional antiretroviral agents. For concomitantly administered therapy, the manufacturers recommended dose should be followed.

If a dose is recognized as missed within 12 hours of when it was due, the patient should take the missed dose as soon as possible. If a dose is missed and it is more than 12 hours later, the patient should only take the next dose at the usual time.

Paediatric population
Children three years and older and adolescents

According to paediatric dose recommendations Viramune 400 mg prolonged-release tablets can be also taken by children, following the adult dosing schedule, if they

- are ≥ 8 years of age and weigh 43.8 kg or more or
- are < 8 years of age and weigh 25 kg or more or
- have a body surface area of 1.17 m^2 or above according to the Mosteller formula.

Children less than three years old

The safety and efficacy of Viramune prolonged-release tablets in children aged less than 3 years has not been established. No data are available.

For patients less than 3 years and for all other age, weight and BSA groups, an immediate-release oral suspension dosage form is available (please refer to the respective Summary of Product Characteristics).

Dose management considerations
The total daily dose at any time during treatment should not exceed 400 mg for any patient. Patients should be advised of the need to take Viramune every day as prescribed.

Patients experiencing rash during the 14-day lead-in period of 200 mg/day should not initiate treatment with Viramune prolonged-release tablets until the rash has resolved. The isolated rash should be closely monitored (see section 4.4). The 200 mg once daily Viramune immediate-release lead-in dosing regimen should not be continued beyond 28 days at which point in time an alternative treatment should be sought due to the possible risk of underexposure and resistance.

Patients who interrupt nevirapine dosing for more than 7 days should restart the recommended dosing regimen using the two week lead-in period of Viramune immediate-release.

There are toxicities that require interruption of Viramune therapy (see section 4.4).

Elderly
Nevirapine has not been specifically investigated in patients over the age of 65.

Renal impairment
In adult patients with renal dysfunction requiring dialysis an additional 200 mg dose of nevirapine immediate-release following each dialysis treatment is recommended. Patients with CLcr ≥ 20 ml/min do not require a dose adjustment, see section 5.2. In paediatric patients with renal dysfunction who are undergoing dialysis it is recommended that following each dialysis treatment patients receive an additional dose of Viramune oral suspension or immediate-release tablets representing 50 % of the recommended daily dose of Viramune oral suspension or immediate-release tablets which would help offset the effects of dialysis on nevirapine clearance. Viramune prolonged-release tablets have not been studied in patients with renal dysfunction and Viramune immediate-release should be used.

Hepatic impairment
Nevirapine should not be used in patients with severe hepatic impairment (Child-Pugh C, see section 4.3). No dose adjustment is necessary in patients with mild to moderate hepatic impairment (see sections 4.4 and 5.2). Viramune prolonged-release tablets have not been studied in patients with hepatic impairment and Viramune immediate-release should be used.

Method of administration
The prolonged-release tablets shall be taken with liquid, and should not be broken or chewed. Viramune can be taken with or without food.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Readministration to patients who have required permanent discontinuation for severe rash, rash accompanied by constitutional symptoms, hypersensitivity reactions, or clinical hepatitis due to nevirapine

Patients with severe hepatic impairment (Child-Pugh C) or pre-treatment ASAT or ALAT > 5 ULN until baseline ASAT/ALAT are stabilised < 5 ULN

Readministration to patients who previously had ASAT or ALAT > 5 ULN during nevirapine therapy and had recurrence of liver function abnormalities upon readministration of nevirapine (see section 4.4)

Coadministration with herbal preparations containing St. John's wort *(Hypericum perforatum*) due to the risk of decreased plasma concentrations and reduced clinical effects of nevirapine (see section 4.5).

4.4 Special warnings and precautions for use

Viramune should only be used with at least two other antiretroviral agents (see section 5.1).

Viramune should not be used as the sole active antiretroviral, as monotherapy with any antiretroviral has shown to result in viral resistance.

The first 18 weeks of therapy with nevirapine 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 (SJS) and toxic epidermal necrolysis (TEN)) and serious hepatitis/hepatic failure. The greatest risk of hepatic and skin reactions occurs in the first 6 weeks of therapy. However, the risk of any hepatic event continues past this period and monitoring should continue at frequent intervals. Female gender and higher CD4 counts (>250/mm^3 in adult females and >400/mm^3 in adult males) at the initiation of nevirapine therapy are associated with a greater risk of hepatic adverse reactions if the patient has detectable plasma HIV-1 RNA - i.e. a concentration ≥ 50 copies/ml - at the initiation of nevirapine. As serious and life threatening hepatotoxicity has been observed in controlled and uncontrolled studies predominantly in patients with a plasma HIV-1 viral load of 50 copies/ml or higher, nevirapine should not be initiated in adult females with CD4 cell counts greater than 250 cells/mm^3 or in adult males with CD4 cell counts greater than 400 cells/mm^3, who have a detectable plasma HIV-1 RNA unless the benefit outweighs the risk.
In some cases, hepatic injury has progressed despite discontinuation of treatment. Patients developing signs or symptoms of hepatitis, severe skin reaction or hypersensitivity reactions must discontinue nevirapine and seek medical evaluation immediately. Nevirapine must not be restarted following severe hepatic, skin or hypersensitivity reactions (see section 4.3).

The dose must be strictly adhered to, especially the 14-days lead-in period (see section 4.2).

Cutaneous reactions

Severe and life-threatening skin reactions, including fatal cases, have occurred in patients treated with nevirapine 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. Nevirapine 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. Nevirapine 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 section 4.4.

Viramune administration above the recommended dose might increase the frequency and seriousness of skin reactions, such as Stevens-Johnson syndrome and toxic epidermal necrolysis.

Rhabdomyolysis has been observed in patients experiencing skin and/or liver reactions associated with Viramune use.

Concomitant prednisone use (40 mg/day for the first 14 days of Viramune immediate-release administration) has been shown not to decrease the incidence of nevirapine-associated rash, and may be associated with an increase in incidence and severity of rash during the first 6 weeks of nevirapine therapy.

Some risk factors for developing serious cutaneous reactions have been identified; they include failure to follow the initial dosing of 200 mg daily 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 nevirapine or non-nevirapine containing therapy.

Patients should be instructed that a major toxicity of nevirapine 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 nevirapine 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 they should not begin Viramune prolonged-release tablets until any rash that has occurred during the 14-day lead-in period of Viramune immediate-release has resolved. The 200 mg once daily dosing regimen of Viramune immediate-release should not be continued beyond 28 days at which point in time an alternative treatment should be sought due to the possible risk of underexposure and resistance.

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 the medicinal product and immediately seek medical evaluation. In these patients nevirapine must not be restarted.

If patients present with a suspected nevirapine-associated rash, liver function tests should be performed. Patients with moderate to severe elevations (ASAT or ALAT > 5 ULN) should be permanently discontinued from nevirapine.

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, nevirapine must be permanently stopped and not be re-introduced (see section 4.3).

Hepatic reactions

Severe and life-threatening hepatotoxicity, including fatal fulminant hepatitis, has occurred in patients treated with nevirapine. The first 18 weeks of treatment is a critical period which requires close monitoring. The risk of hepatic reactions is greatest in the first 6 weeks of therapy. However the risk continues past this period and monitoring should continue at frequent intervals throughout treatment.

Rhabdomyolysis has been observed in patients experiencing skin and/or liver reactions associated with nevirapine use.

Increased ASAT or ALAT levels $\geq$ 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 nevirapine containing regimens.

Female gender and higher CD4 counts at the initiation of nevirapine therapy in treatment-naïve patients is associated with increased risk of hepatic adverse reactions. In a retrospective analysis of pooled clinical studies with Viramune immediate-release tablets, women had a three fold higher risk than men for symptomatic, often rash-associated, hepatic events (5.8 % versus 2.2 %), and treatment-naïve patients of either gender with detectable HIV-1 RNA in plasma with higher CD4 counts at initiation of nevirapine therapy were at higher risk for symptomatic hepatic events with nevirapine. Predominantly patients with a plasma HIV-1 viral load of 50 copies/ml or higher, women with CD4 counts >250 cells/mm^3 had a 12 fold higher risk of symptomatic hepatic adverse reactions compared to women with CD4 counts <250 cells/mm^3 (11.0 % versus 0.9 %). An increased risk was observed in men with detectable HIV-1 RNA in plasma and CD4 counts > 400 cells/mm^3 (6.3 % versus 1.2 % for men with CD4 counts <400 cells/mm^3). This increased risk for toxicity based on CD4 count thresholds has not been detected in patients with undetectable (i.e. < 50 copies/ml) plasma viral load.

Patients should be informed that hepatic reactions are a major toxicity of nevirapine requiring close monitoring during the first 18 weeks. They should be informed that occurrence of symptoms

suggestive of hepatitis should lead them to discontinue nevirapine and immediately seek medical evaluation, which should include liver function tests.

Liver monitoring

Clinical chemistry tests, which include liver function tests, should be performed prior to initiating nevirapine therapy and at appropriate intervals during therapy.

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

Asymptomatic elevations of liver enzymes are frequently described and are not necessarily a contraindication to use nevirapine. 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.

For patients already on a regimen of Viramune immediate-release twice daily who switch to Viramune prolonged-release once daily there is no need for a change in their monitoring schedule.

If ASAT or ALAT $\geq$ 2.5 ULN before or during treatment, then liver tests should be monitored more frequently during regular clinic visits. Nevirapine must not be administered to patients with pre-treatment ASAT or ALAT > 5 ULN until baseline ASAT/ALAT are stabilised < 5 ULN (see section 4.3).

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, nevirapine 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 nevirapine, on a case by case basis, at the starting dose regimen of one immediate-release 200 mg Viramune tablet daily for 14 days followed by one Viramune 400 mg prolonged-release tablet daily. In these cases, more frequent liver monitoring is required. If liver function abnormalities recur, nevirapine 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)), nevirapine must be permanently stopped. Viramune must 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 (Child-Pugh C, see section 4.3). Pharmacokinetic results suggest caution should be exercised when nevirapine is administered to patients with moderate hepatic dysfunction (Child-Pugh B). 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 reactions. 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

Post-Exposure-Prophylaxis: 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 and therefore, is strongly discouraged.

Combination therapy with nevirapine 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.

Hormonal methods of birth control other than Depo-medroxyprogesterone acetate (DMPA) should not be used as the sole method of contraception in women taking Viramune, since nevirapine might lower the plasma concentrations of these medicinal products. For this reason, and to reduce the risk of HIV transmission, barrier contraception (e.g., condoms) is recommended. Additionally, when postmenopausal hormone therapy is used during administration of nevirapine, its therapeutic effect should be monitored.

Weight and metabolic parameters:
An increase in weight and in levels of blood lipids and glucose may occur during antiretroviral therapy. Such changes may in part be linked to disease control and life style. For lipids, there is in some cases evidence for a treatment effect, while for weight gain there is no strong evidence relating this to any particular treatment. For monitoring of blood lipids and glucose reference is made to established HIV treatment guidelines. Lipid disorders should be managed as clinically appropriate.

In clinical studies, Viramune has been associated with an increase in HDL- cholesterol and an overall improvement in the total to HDL-cholesterol ratio. However, in the absence of specific studies, the clinical impact of these findings is not known. In addition, Viramune has not been shown to cause glucose disturbances.

Osteonecrosis: Although the etiology is considered to be multifactorial (including corticosteroid use, alcohol consumption, severe immunosuppression, higher body mass index), cases of osteonecrosis have been reported particularly in patients with advanced HIV-disease and/or long-term exposure to combination antiretroviral therapy (CART). Patients should be advised to seek medical advice if they experience joint aches and pain, joint stiffness or difficulty in movement.

Immune Reactivation Syndrome: In HIV-infected patients with severe immune deficiency at the time of institution of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic pathogens may arise and cause serious clinical conditions, or aggravation of symptoms. Typically, such reactions have been observed within the first few weeks or months of initiation of CART. Relevant examples are cytomegalovirus retinitis, generalised and/or focal mycobacterial infections, and Pneumocystis jirovecii pneumonia. Any inflammatory symptoms should be evaluated and treatment instituted when necessary. Autoimmune disorders (such as Graves' disease and autoimmune hepatitis) have also been reported to occur in the setting of immune reactivation; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment.

The available pharmacokinetic data suggest that the concomitant use of rifampicin and nevirapine is not recommended. Furthermore, combining the following compounds with Viramune is not recommended: efavirenz, ketoconazole, etravirine, rilpivirine, elvitegravir (in combination with

cobicistat), atazanavir (in combination with ritonavir), fosamprenavir (if not co-administered with low dose ritonavir) (see section 4.5).

Granulocytopenia is commonly associated with zidovudine. Therefore, patients who receive nevirapine and zidovudine concomitantly and especially paediatric patients and patients who receive higher zidovudine doses or patients with poor bone marrow reserve, in particular those with advanced HIV disease, have an increased risk of granulocytopenia. In such patients haematological parameters should be carefully monitored.

Lactose: Viramune prolonged-release tablets contain 400 mg lactose per maximum recommended daily dose.
Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Some patients have reported the occurrence of remnants in faeces which may resemble intact tablets. Based on the data available so far, this has not been shown to affect the therapeutic response.

4.5 Interaction with other medicinal products and other forms of interaction

The following data were generated using the Viramune immediate-release tablets but are expected to apply to all dosage forms.

Nevirapine is an inducer of CYP3A and potentially CYP2B6, with maximal induction occurring within 2-4 weeks of initiating multiple-dose therapy.

Compounds using this metabolic pathway may have decreased plasma concentrations when co-administered with nevirapine. Careful monitoring of the therapeutic effectiveness of P450 metabolised medicinal products is recommended when taken in combination with nevirapine.

The absorption of nevirapine is not affected by food, antacids or medicinal products which are formulated with an alkaline buffering agent.

The interaction data is presented as geometric mean value with 90% confidence interval (90 % CI) whenever these data were available. ND = Not Determined, ↑ = Increased, ↓ = Decreased, ↔ = No Effect

Medicinal products by therapeutic areas	**Interaction**	**Recommendations concerning co-administration**
ANTI-INFECTIVES		
ANTIRETROVIRALS		
NRTIs		
Didanosine 100-150 mg BID	Didanosine AUC ↔ 1.08 (0.92-1.27) Didanosine C_{min} ND Didanosine C_{max} ↔ 0.98 (0.79-1.21)	Didanosine and Viramune can be co-administered without dose adjustments.
Emtricitabine	Emtricitabine is not an inhibitor of human CYP 450 enzymes.	Viramune and emtricitabine may be coadministered without dose adjustments.
Abacavir	In human liver microsomes, abacavir did not inhibit cytochrome P450 isoforms.	Viramune and abacavir may be coadministered without dose adjustments.
Lamivudine 150 mg BID	No changes to lamivudine apparent clearance and volume of distribution,	Lamivudine and Viramune can be co-administered without dose

	suggesting no induction effect of nevirapine on lamivudine clearance.	adjustments.
Stavudine: 30/40 mg BID	Stavudine AUC ↔ 0.96 (0.89-1.03) Stavudine C_{min} ND Stavudine C_{max} ↔ 0.94 (0.86-1.03) Nevirapine: compared to historical controls, levels appeared to be unchanged.	Stavudine and Viramune can be co-administered without dose adjustments.
Tenofovir 300 mg QD	Tenofovir plasma levels remain unchanged when co-administered with nevirapine. Nevirapine plasma levels were not altered by co-administration of tenofovir.	Tenofovir and Viramune can be co-administered without dose adjustments.
Zidovudine 100-200 mg TID	Zidovudine AUC ↓ 0.72 (0.60-0.96) Zidovudine C_{min} ND Zidovudine C_{max} ↓ 0.70 (0.49-1.04) Nevirapine: Zidovudine had no effect on its pharmacokinetics.	Zidovudine and Viramune can be co-administered without dose adjustments Granulocytopenia is commonly associated with zidovudine. Therefore, patients who receive nevirapine and zidovudine concomitantly and especially paediatric patients and patients who receive higher zidovudine doses or patients with poor bone marrow reserve, in particular those with advanced HIV disease, have an increased risk of granulocytopenia. In such patients haematological parameters should be carefully monitored.
NNRTIs		
Efavirenz 600 mg QD	Efavirenz AUC ↓ 0.72 (0.66-0.86) Efavirenz C_{min} ↓ 0.68 (0.65-0.81) Efavirenz C_{max} ↓ 0.88 (0.77-1.01)	It is not recommended to co-administer efavirenz and Viramune (see section 4.4), because of additive toxicity and no benefit in terms of efficacy over either NNRTI alone (for results of 2NN study, see section 5.1 Viramune immediate-release formulations).
Etravirine	Concomitant use of etravirine with nevirapine may cause a significant decrease in the plasma concentrations of etravirine and loss of therapeutic effect of etravirine.	The concomitant administration of Viramune with NNRTIs is not recommended (see section 4.4).
Rilpivirine	Interaction has not been studied.	The concomitant administration of Viramune with NNRTIs is not

		recommended (see section 4.4).
PIs		
Atazanavir/ritonavir 300/100 mg QD 400/100 mg QD	<u>Atazanavir/r 300/100mg</u>: Atazanavir/r AUC ↓ 0.58 (0.48-0.71) Atazanavir/r C_{min} ↓ 0.28 (0.20-0.40) Atazanavir/r C_{max} ↓ 0.72 (0.60-0.86) <u>Atazanavir/r 400/100mg:</u> Atazanavir/r AUC ↓ 0.81 (0.65-1.02) Atazanavir/r C_{min} ↓ 0.41 (0.27-0.60) Atazanavir/r C_{max} ↔ 1.02 (0.85–1.24) (compared to 300/100mg without nevirapine) Nevirapine AUC ↑ 1.25 (1.17-1.34) Nevirapine C_{min} ↑ 1.32 (1.22–1.43) Nevirapine C_{max} ↑ 1.17 (1.09-1.25)	It is not recommended to co-administer atazanavir/ritonavir and Viramune (see section 4.4).
Darunavir/ritonavir 400/100 mg BID	Darunavir AUC ↑ 1.24 (0.97-1.57) Darunavir C_{min} ↔ 1.02 (0.79-1.32) Darunavir C_{max} ↑ 1.40 (1.14-1.73) Nevirapine AUC ↑ 1.27 (1.12-1.44) Nevirapine C_{min} ↑ 1.47 (1.20-1.82) Nevirapine C_{max} ↑ 1.18 (1.02-1.37)	Darunavir and Viramune can be co-administered without dose adjustments.
Fosamprenavir 1400 mg BID	Amprenavir AUC ↓ 0.67 (0.55-0.80) Amprenavir C_{min} ↓ 0.65 (0.49-0.85) Amprenavir C_{max} ↓ 0.75 (0.63-0.89) Nevirapine AUC ↑ 1.29 (1.19-1.40) Nevirapine C_{min} ↑ 1.34 (1.21-1.49) Nevirapine C_{max} ↑ 1.25 (1.14-1.37)	It is not recommended to co-administer fosamprenavir and Viramune if fosamprenavir is not co-administered with ritonavir (see section 4.4).
Fosamprenavir/ritonavir 700/100 mg BID	Amprenavir AUC ↔ 0.89 (0.77-1.03) Amprenavir C_{min} ↓ 0.81 (0.69-0.96) Amprenavir C_{max} ↔ 0.97 (0.85-1.10) Nevirapine AUC ↑ 1.14 (1.05-1.24) Nevirapine C_{min} ↑ 1.22 (1.10-1.35) Nevirapine C_{max} ↑ 1.13 (1.03-1.24)	Fosamprenavir/ritonavir and Viramune can be co-administered without dose adjustments
Lopinavir/ritonavir (capsules) 400/100 mg BID	<u>Adult patients</u>: Lopinavir AUC ↓ 0.73 (0.53-0.98) Lopinavir C_{min} ↓ 0.54 (0.28-0.74) Lopinavir C_{max} ↓ 0.81 (0.62-0.95)	An increase in the dose of lopinavir/ritonavir to 533/133 mg (4 capsules) or 500/125 mg (5 tablets with 100/25 mg each) twice daily with food is recommended in combination with Viramune. Dose adjustment of Viramune is not

		required when co-administered with lopinavir.
Lopinavir/ritonavir (oral solution) 300/75 mg/m^2 BID	Paediatric patients: Lopinavir AUC ↓ 0.78 (0.56-1.09) Lopinavir C_{min} ↓ 0.45 (0.25-0.82) Lopinavir C_{max} ↓ 0.86 (0.64-1.16)	For children, increase of the dose of lopinavir/ritonavir to 300/75 mg/m^2 twice daily with food should be considered when used in combination with Viramune, particularly for patients in whom reduced susceptibility to lopinavir/ritonavir is suspected.
Ritonavir 600 mg BID	Ritonavir AUC↔ 0.92 (0.79-1.07) Ritonavir C_{min} ↔ 0.93 (0.76-1.14) Ritonavir C_{max} ↔ 0.93 (0.78-1.07) Nevirapine: Co-administration of ritonavir does not lead to any clinically relevant change in nevirapine plasma levels.	Ritonavir and Viramune can be co-administered without dose adjustments.
Saquinavir/ritonavir	The limited data available with saquinavir soft gel capsule boosted with ritonavir do not suggest any clinically relevant interaction between saquinavir boosted with ritonavir and nevirapine.	Saquinavir/ritonavir and Viramune can be co-administered without dose adjustments.
Tipranavir/ritonavir 500/200 mg BID	No specific drug-drug interaction study has been performed. The limited data available from a phase IIa study in HIV-infected patients have shown a clinically non significant 20 % decrease of TPV C_{min}.	Tipranavir and Viramune can be co-administered without dose adjustments.
ENTRY INHIBITORS		
Enfuvirtide	Due to the metabolic pathway no clinically significant pharmacokinetic interactions are expected between enfuvirtide and nevirapine.	Enfuvirtide and Viramune can be co-administered without dose adjustments.
Maraviroc 300 mg QD	Maraviroc AUC ↔ 1.01 (0.6 -1.55) Maraviroc C_{min} ND Maraviroc C_{max} ↔ 1.54 (0.94-2.52) compared to historical controls Nevirapine concentrations not measured, no effect is expected.	Maraviroc and Viramune can be co-administered without dose adjustments.

INTEGRASE INHIBITORS		
Elvitegravir/ cobicistat	Interaction has not been studied. Cobicistat, a cytochrome P450 3A inhibitor significantly inhibits hepatic enzymes, as well as other metabolic pathways. Therefore coadministration would likely result in altered plasma levels of cobicistat and Viramune.	Coadministration of Viramune with elvitegravir in combination with cobicistat is not recommended (see section 4.4).
Raltegravir 400 mg BID	No clinical data available. Due to the metabolic pathway of raltegravir no interaction is expected.	Raltegravir and Viramune can be co-administered without dose adjustments.
ANTIBIOTICS		
Clarithromycin 500 mg BID	Clarithromycin AUC ↓ 0.69 (0.62-0.76) Clarithromycin C_{min} ↓ 0.44 (0.30-0.64) Clarithromycin C_{max} ↓ 0.77 (0.69-0.86) Metabolite 14-OH clarithromycin AUC ↑ 1.42 (1.16-1.73) Metabolite 14-OH clarithromycin C_{min} ↔ 0 (0.68-1.49) Metabolite 14-OH clarithromycin C_{max} ↑ 1.47 (1.21-1.80) Nevirapine AUC ↑ 1.26 Nevirapine C_{min} ↑ 1.28 Nevirapine C_{max} ↑ 1.24 compared to historical controls.	Clarithromycin exposure was significantly decreased, 14-OH metabolite exposure increased. Because the clarithromycin active metabolite has reduced activity against *Mycobacterium avium-intracellulare complex* overall activity against the pathogen may be altered. Alternatives to clarithromycin, such as azithromycin should be considered. Close monitoring for hepatic abnormalities is recommended
Rifabutin 150 or 300 mg QD	Rifabutin AUC ↑ 1.17 (0.98-1.40) Rifabutin C_{min} ↔ 1.07 (0.84-1.37) Rifabutin C_{max} ↑ 1.28 (1.09-1.51) Metabolite 25-O-desacetylrifabutin AUC ↑ 1.24 (0.84-1.84) Metabolite 25-O-desacetylrifabutin C_{min} ↑ 1.22 (0.86-1.74) Metabolite 25-O-desacetylrifabutin C_{max} ↑ 1.29 (0.98-1.68) A clinically not relevant increase in the apparent clearance of nevirapine (by 9 %) compared to historical data was reported.	No significant effect on rifabutin and Viramune mean PK parameters is seen. Rifabutin and Viramune can be co-administered without dose adjustments. However, due to the high interpatient variability 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.
Rifampicin 600 mg QD	Rifampicin AUC ↔ 1.11 (0.96-1.28) Rifampicin C_{min} ND Rifampicin C_{max} ↔ 1.06 (0.91-1.22)	It is not recommended to co-administer rifampicin and Viramune (see section 4.4). Physicians needing to treat patients co-infected with

	Nevirapine AUC ↓ 0.42 Nevirapine C_{min} ↓ 0.32 Nevirapine C_{max} ↓ 0.50 compared to historical controls.	tuberculosis and using a Viramune containing regimen may consider co-administration of rifabutin instead.
ANTIFUNGALS		
Fluconazole 200 mg QD	Fluconazole AUC ↔ 0.94 (0.88-1.01) Fluconazole C_{min} ↔ 0.93 (0.86-1.01) Fluconazole C_{max} ↔ 0.92 (0.85-0.99) Nevirapine: exposure: ↑100% compared with historical data where nevirapine was administered alone.	Because of the risk of increased exposure to Viramune, caution should be exercised if the medicinal products are given concomitantly and patients should be monitored closely.
Itraconazole 200 mg QD	Itraconazole AUC ↓ 0.39 Itraconazole C_{min} ↓ 0.13 Itraconazole C_{max} ↓ 0.62 Nevirapine: there was no significant difference in nevirapine pharmacokinetic parameters.	A dose increase for itraconazole should be considered when these two agents are administered concomitantly.
Ketoconazole 400 mg QD	Ketoconazole AUC ↓ 0.28 (0.20-0.40) Ketoconazole C_{min} ND Ketoconazole C_{max} ↓ 0.56 (0.42-0.73) Nevirapine: plasma levels: ↑ 1.15-1.28 compared to historical controls.	It is not recommended to co-administer ketoconazole and Viramune (see section 4.4).
ANTIVIRALS FOR CHRONIC HEPATITIS B AND C		
Adefovir	Results of *in vitro* studies showed a weak antagonism of nevirapine by adefovir (see section 5.1), this has not been confirmed in clinical trials and reduced efficacy is not expected. Adefovir did not influence any of the common CYP isoforms known to be involved in human drug metabolism and is excreted renally. No clinically relevant drug-drug interaction is expected.	Adefovir and Viramune may be coadministered without dose adjustments.
Entecavir	Entecavir is not a substrate, inducer or an inhibitor of cytochrome P450 (CYP450) enzymes. Due to the metabolic pathway of entecavir, no clinically relevant drug-drug interaction is expected.	Entecavir and Viramune may be coadministered without dose adjustments.
Interferons (pegylated interferons alfa 2a and alfa 2b)	Interferons have no known effect on CYP 3A4 or 2B6. No clinically relevant drug-drug interaction is expected.	Interferons and Viramune may be coadministered without dose adjustments.

Ribavirin	Results of *in vitro* studies showed a weak antagonism of nevirapine by ribavirin (see section 5.1), this has not been confirmed in clinical trials and reduced efficacy is not expected. Ribavirin does not inhibit cytochrome P450 enzymes, and there is no evidence from toxicity studies that ribavirin induces liver enzymes. No clinically relevant drug-drug interaction is expected.	Ribavirin and Viramune may be coadministered without dose adjustments.
Telbivudine	Telbivudine is not a substrate, inducer or inhibitor of the cytochrome P450 (CYP450) enzyme system. Due to the metabolic pathway of telbivudine, no clinically relevant drug-drug interaction is expected.	Telbivudine and Viramune may be coadministered without dose adjustments.
ANTACIDS		
Cimetidine	Cimetidine: no significant effect on cimetidine PK parameters is seen. Nevirapine C_{min} ↑ 1.07	Cimetidine and Viramune can be co-administered without dose adjustments.
ANTITHROMBOTICS		
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.	Close monitoring of anticoagulation levels is warranted.
CONTRACEPTIVES		
Depo-medroxyprogesterone acetate (DMPA) 150 mg every 3 months	DMPA AUC ↔ DMPA C_{min} ↔ DMPA C_{max} ↔ Nevirapine AUC ↑ 1.20 Nevirapine C_{max} ↑ 1.20	Viramune co-administration did not alter the ovulation suppression effects of DMPA. DMPA and Viramune can be co-administered without dose adjustments.
Ethinyl estradiol (EE) 0.035 mg	EE AUC ↓ 0.80 (0.67 - 0.97) EE C_{min} ND EE C_{max} ↔ 0.94 (0.79 - 1.12)	Oral hormonal contraceptives should not be used as the sole method of contraception in women taking Viramune (see section 4.4). Appropriate doses for hormonal contraceptives (oral or other forms of application) other than DMPA in combination with Viramune have not been established with respect to safety and efficacy.
Norethindrone (NET) 1.0 mg QD	NET AUC ↓ 0.81 (0.70 - 0.93) NET C_{min} ND NET C_{max} ↓ 0.84 (0.73 - 0.97)	

ANALGESICS/OPIOIDS		
Methadone Individual Patient Dosing	Methadone AUC ↓ 0.40 (0.31 - 0.51) Methadone C_{min} ND Methadone C_{max} ↓ 0.58 (0.50 - 0.67)	Methadone-maintained patients beginning Viramune therapy should be monitored for evidence of withdrawal and methadone dose should be adjusted accordingly.
HERBAL PRODUCTS		
St. John's Wort	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 medicinal product metabolism enzymes and/or transport proteins by St. John's Wort.	Herbal preparations containing St. John's Wort and Viramune must not be co-administered (see section 4.3). If a 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:

Nevirapine metabolites: 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.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential / Contraception in males and females
Women of childbearing potential should not use oral contraceptives as the sole method for birth control, since nevirapine might lower the plasma concentrations of these medicinal products (see sections 4.4 & 4.5).

Pregnancy
Currently available data on pregnant women indicate no malformative or foeto/ neonatal toxicity. To date no other relevant epidemiological data are available. No observable teratogenicity was detected in reproductive studies performed in pregnant rats and rabbits (see section 5.3). There are no adequate and well-controlled studies in pregnant women. Caution should be exercised when prescribing nevirapine to pregnant women (see section 4.4). As hepatotoxicity is more frequent in women with CD4 cell counts above 250 cells/mm^3 with detectable HIV-1 RNA in plasma (50 or more copies/ml), these conditions should be taken in consideration on therapeutic decision (see section 4.4). There is not enough evidence to substantiate that the absence of an increased risk for toxicity seen in pre-treated women initiating nevirapine with an undetectable viral load (less than 50 copies/ml of HIV-1 in plasma) and CD4 cell counts above 250 cells/mm^3 also applies to pregnant women. All the randomised studies addressing this issue specifically excluded pregnant women, and pregnant women were under-represented in cohort studies as well as in meta-analyses.

Breast-feeding
It is recommended that women living with HIV do not breast-feed their infants in order to avoid transmission of HIV.

Fertility
In reproductive toxicology studies, evidence of impaired fertility was seen in rats.

4.7 Effects on ability to drive and use machines

There are no specific studies about the ability to drive vehicles and use machinery. However, patients should be advised that they may experience adverse reactions such as fatigue during treatment with nevirapine. Therefore, caution should be recommended when driving a car or operating machinery. If patients experience fatigue they should avoid potentially hazardous tasks such as driving or operating machinery.

4.8 Undesirable effects

Summary of the safety profile
The most frequently reported adverse reactions related to Viramune prolonged-release therapy in treatment naïve patients (including lead-in phase with immediate-release) in clinical study 1100.1486 (VERxVE) were rash, nausea, liver function test abnormal, headache, fatigue, hepatitis, abdominal pain, diarrhoea and pyrexia. There are no new adverse drug reactions for Viramune prolonged-release tablets that have not been previously identified for Viramune immediate-release tablets and oral suspension.

The nevirapine postmarketing experience has shown that the most serious adverse reactions are Stevens-Johnson syndrome/toxic epidermal necrolysis, serious hepatitis/hepatic failure, and drug reaction with eosinophilia and systemic symptoms, 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 section 4.4).

Tabulated summary of adverse reactions
The following adverse reactions which may be causally related to the administration of Viramune prolonged-release tablets have been reported. The frequencies given below are based on crude incidence rates of adverse reactions observed in the Viramune immediate-release (lead-in phase, table 1) and Viramune prolonged-release (randomised-phase/maintenance phase, table 2) groups of clinical study 1100.1486 with 1,068 patients exposed to Viramune on a backbone of tenofovir/emtricitabine.

Frequency is defined using the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000)

Table 1: Lead-in phase with Viramune immediate-release

Blood and lymphatic system disorders

Uncommon	granulocytopenia
Rare	anaemia

Immune system disorders

Uncommon	hypersensitivity (incl. anaphylactic reaction, angioedema, urticaria), drug reaction with eosinophilia and systemic symptoms, anaphylactic reaction

Nervous system disorders

Common	headache

Gastrointestinal disorders

Common	abdominal pain, nausea, diarrhoea
Uncommon	vomiting

Hepatobiliary disorders

Uncommon	jaundice, hepatitis fulminant (which may be fatal)
Rare	hepatitis (incl. severe and life-threatening hepatotoxicity)(0.09 %)

Skin and subcutaneous tissue disorders

Common	rash (6.7 %)
Uncommon	Stevens-Johnson Syndrome/toxic epidermal necrolysis (which may be fatal) (0.2 %), angioedema, urticaria

Musculoskeletal and connective tissue disorders

Uncommon	arthralgia, myalgia

General disorders and administration site conditions

Common	fatigue, pyrexia

Investigations

Uncommon	liver function test-abnormal (alanine aminotransferase increased; transaminases increased; aspartate aminotransferase increased; gamma-glutamyltransferase increased; hepatic enzyme increased; hypertransaminasaemia), blood phosphorus decreased, blood pressure increased

Table 2: Maintenance phase of Viramune prolonged-release

Blood and lymphatic system disorders

Uncommon	anaemia, granulocytopenia

Immune system disorders

Uncommon	hypersensitivity (incl. anaphylactic reaction, angioedema, urticaria), drug reaction with eosinophilia and systemic symptoms, anaphylactic reaction

Nervous system disorders

Common	headache

Gastrointestinal disorders

Common	abdominal pain, nausea, vomiting, diarrhoea

Hepatobiliary disorders

Common	hepatitis (incl. severe and life-threatening hepatotoxicity) (1.6%)
Uncommon	jaundice, hepatitis fulminant (which may be fatal)

Skin and subcutaneous tissue disorders

Common	rash (5.7 %)
Uncommon	Stevens-Johnson Syndrome/toxic epidermal necrolysis (which may be fatal) (0.6 %), angioedema, urticaria

Musculoskeletal and connective tissue disorders

Uncommon	arthralgia, myalgia

General disorders and administration site conditions

Common	fatigue
Uncommon	pyrexia

Investigations

Common	liver function test abnormal (alanine aminotransferase increased; transaminases increased; aspartate aminotransferase increased; gamma-glutamyltransferase increased; hepatic enzyme increased; hypertransaminasaemia), blood phosphorus

decreased, blood pressure increased

Description of selected adverse reactions
The following adverse reactions were identified in other nevirapine studies or by post-marketing surveillance but not observed in the randomised, controlled clinical study 1100.1486.
As granulocytopenia, drug reaction with eosinophilia and systemic symptoms, anaphylactic reaction, jaundice, hepatitis fulminant (which may be fatal), urticaria, decreased blood phosphorus and increased blood pressure during the lead-in phase with Viramune immediate release were not seen in study 1100.1486 the frequency category was estimated from a statistical calculation based on the total number of patients exposed to nevirapine immediate-release in the lead-in phase of the randomised controlled clinical study 1100.1486 (n= 1,068).
Accordingly, as anaemia, granulocytopenia, anaphylactic reaction, jaundice, Stevens-Johnson Syndrome/toxic epidermal necrolysis (which may be fatal), angioedema, decreased blood phosphorus and increased blood pressure during maintenance phase with Viramune prolonged-release tablets were not seen in study 1100.1486 the frequency category was estimated from a statistical calculation based on the total number of patients exposed to nevirapine prolonged-release in the maintenance phase of the randomised controlled clinical study 1100.1486 (n= 505).

Metabolic parameters
Weight and levels of blood lipids and glucose may increase during antiretroviral therapy (see section 4.4)

The following adverse reactions have also been reported when nevirapine has been used in combination with other anti-retroviral agents: pancreatitis, peripheral neuropathy and thrombocytopaenia. These adverse reactions are commonly associated with other antiretroviral agents and may be expected to occur when nevirapine is used in combination with other agents; however it is unlikely that these adverse reactions are due to nevirapine treatment. Hepatic-renal failure syndromes have been reported rarely.

In HIV-infected patients with severe immune deficiency at the time of initiation of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic infections may arise. Autoimmune disorders (such as Graves' disease and autoimmune hepatitis) have also been reported; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment (see section 4.4).

Cases of osteonecrosis have been reported, particularly in patients with generally acknowledged risk factors, advanced HIV disease or long-term exposure to combination antiretroviral therapy (CART). The frequency of this is unknown (see section 4.4).

Skin and subcutaneous tissues

The most common clinical toxicity of nevirapine is rash. Rashes are usually mild to moderate, maculopapular erythematous cutaneous eruptions, with or without pruritus, located on the trunk, face and extremities. Hypersensitivity (incl. anaphylactic reaction, angioedema and urticaria) has been reported. Rashes occur alone or in the context of drug reaction with eosinophilia and systemic symptoms, characterised by rash with constitutional symptoms such as fever, arthralgia, myalgia and lympadenopathy, plus visceral involvement, such as hepatitis, eosinophilia, granulocytopenia, and renal dysfunction.

Severe and life-threatening skin reactions have occurred in patients treated with nevirapine, including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). Fatal cases of SJS, TEN and drug reaction with eosinophilia and systemic symptoms 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 (see section 4.4).

In study 1100.1486 (VERxVE) antiretroviral-naïve patients received a lead-in dose of Viramune

200 mg immediate-release once daily for 14 days (n=1068) and then were randomised to receive either Viramune 200 mg immediate-release twice daily or Viramune 400 mg prolonged-release once daily. All patients received tenofovir + emtricitabine as background therapy. Safety data included all the patient visits up to the point in time when the last patient completed 144 weeks in the trial. This also includes safety data for patient visits in the post-week 144 open label extension (which patients in either treatment group who completed the 144 week blinded phase could enter). Severe or life-threatening rash considered related to nevirapine treatment occurred in 1.1 % of patients during the lead-in phase with Viramune immediate-release. Severe rash occurred in 1.4 % and 0.2 % of the Viramune immediate-release and Viramune prolonged-release groups respectively during the randomised phase. No life-threatening (Grade 4) rash events considered related to Viramune were reported during the randomised phase of this study.Six cases of Stevens-Johnson Syndrome were reported in the study; all but one occurred within the first 30 days of nevirapine treatment.

In study 1100.1526 (TRANxITION) patients on Viramune 200 mg immediate-release twice daily treatment for at least 18 weeks were randomised to either receive Viramune 400 mg prolonged-release once daily (n=295) or remain on their Viramune immediate-release treatment (n=148). In this study, no Grade 3 or 4 rash was observed in either treatment group.

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 nevirapine. 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 section 4.4).

In study 1100.1486 (VERxVE) treatment-naïve patients received a lead-in dose of Viramune 200 mg immediate-release once daily for 14 days and then were randomised to receive either Viramune 200 mg immediate-release twice daily or Viramune 400 mg prolonged-release once daily. All patients received tenofovir + emtricitabine as background therapy. Patients were enrolled with CD4 counts <250 cells/mm^3 for women and <400 cells/mm^3 for men. Data on potential symptoms of hepatic events were prospectively collected in this study. The safety data include all patient visits up to the time of the last patient's completion of study week 144. The incidence of symptomatic hepatic events during the Viramune immediate-release lead-in phase was 0.5 %. After the lead-in period the incidence of symptomatic hepatic events was 2.4 % in the Viramune immediate-release group and 1.6 % in the Viramune prolonged-release group. Overall, there was a comparable incidence of symptomatic hepatic events among men and women enrolled in VERxVE.

In study 1100.1526 (TRANxITION) no Grade 3 or 4 clinical hepatic events were observed in either treatment group.

Paediatric population

Based on clinical study experience with Viramune immediate-release tablets and oral suspension of 361 paediatric patients the majority of which received combination treatment with ZDV or/and ddI, the most frequently reported adverse events related to nevirapine were similar to those observed in adults. Granulocytopenia was more frequently observed in children. In an open-label clinical study (ACTG 180) granulocytopenia assessed as medicinal product-related occurred in 5/37 (13.5 %) of patients. In ACTG 245, a double-blind placebo controlled study, the frequency of serious medicinal product-related granulocytopenia was 5/305 (1.6 %). Isolated cases of Stevens-Johnson syndrome or Stevens-Johnson/toxic epidermal necrolysis transition syndrome have been reported in this population.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare

professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

There is no known antidote for nevirapine overdose. Cases of overdose with Viramune immediate-release at doses ranging from 800 to 6,000 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, increase in transaminases and weight decrease. All of these effects subsided following discontinuation of nevirapine.

Paediatric population

One case of massive accidental overdose in a newborn was reported. The ingested dose was 40 times the recommended dose of 2 mg/kg/day. Mild isolated neutropenia and hyperlactataemia was observed, which spontaneously disappeared within one week without any clinical complications. One year later, the child's development remained normal.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antivirals for systemic use, non-nucleoside reverse transcriptase inhibitors, ATC code J05AG01.

Mechanism of action

Nevirapine is a NNRTI of HIV-1. Nevirapine is a non-competitive inhibitor of the HIV-1 reverse transcriptase, but it does not have a biologically significant inhibitory effect on the HIV-2 reverse transcriptase or on eukaryotic DNA polymerases α, β, γ, or δ.

Antiviral activity *in vitro*

Nevirapine had a median EC_{50} value (50% inhibitory concentration) of 63 nM against a panel of group M HIV-1 isolates from clades A, B, C, D, F, G, and H, and circulating recombinant forms (CRF), CRF01_AE, CRF02_AG and CRF12_BF replicating in human embryonic kidney 293 cells. In a panel of 2,923 predominantly subtype B HIV-1 clinical isolates, the mean EC_{50} value was 90nM. Similar EC_{50} values are obtained when the antiviral activity of nevirapine is measured in peripheral blood mononuclear cells, monocyte derived macrophages or lymphoblastoid cell line. Nevirapine had no antiviral activity in cell culture against group O HIV-1 isolates or HIV-2 isolates.

Nevirapine in combination with efavirenz exhibited a strong antagonistic anti-HIV-1 activity *in vitro* (see section 4.5) 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, 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 medicinal product adefovir and by the anti-HCV medicinal product ribavirin *in vitro*.

Resistance

HIV-1 isolates with reduced susceptibility (100-250-fold) to nevirapine emerge in cell culture. Genotypic analysis showed mutations in the HIV-1 RT gene Y181C and/or V106A 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.

Genotypic analysis of isolates from antiretroviral naïve patients experiencing virologic failure (n=71) receiving nevirapine once daily (n=25) or twice daily (n=46) in combination with lamivudine and stavudine for 48 weeks showed that isolates from 8/25 and 23/46 patients, 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.

Genotypic analysis was performed on isolates from 86 antiretroviral naïve patients who discontinued the VERxVE study (1100.1486) after experiencing virologic failure (rebound, partial response) or due to an adverse event or who had transient increase in viral load during the course of the study. The analysis of these samples of patients receiving Viramune immediate-release twice daily or Viramune prolonged-release once daily in combination with tenofovir and emtricitabine showed that isolates from 50 patients contained resistance mutations expected with a nevirapine-based regimen. Of these 50 patients, 28 developed resistance to efavirenz and 39 developed resistance to etravirine (the most frequently emergent resistance mutation being Y181C). There were no differences based on the formulation taken (immediate-release twice daily or prolonged-release once daily).

The observed mutations at failure were those expected with a nevirapine-based regimen. Two new substitutions on codons previously associated with nevirapine resistance were observed: one patient with Y181I in the Viramune prolonged-release group and one patient with Y188N in the Viramune immediate-release group; resistance to nevirapine was confirmed by phenotype.

Cross-resistance

Rapid emergence of HIV-strains which are cross-resistant to NNRTIs has been observed in vitro. Cross resistance to efavirenz is expected after virologic failure with nevirapine. Depending on resistance testing results, an etravirine-containing regimen may be used subsequently.
Cross-resistance between nevirapine and either HIV protease inhibitors, HIV integrase inhibitors or HIV entry inhibitors is unlikely because the enzyme targets involved are different. Similarly the potential for cross-resistance between nevirapine and NRTIs is low because the molecules have different binding sites on the reverse transcriptase.

Clinical results

Viramune has been evaluated in both treatment-naïve and treatment-experienced patients.

Clinical studies with prolonged-release tablets

The clinical efficacy of Viramune prolonged-release is based on 48-week data from a randomised, double-blind, double-dummy phase 3 study (VERxVE – study 1100.1486) in treatment-naïve patients and on 24-week data from a randomised, open-label study in patients who transitioned from Viramune immediate-release tablets administered twice daily to Viramune prolonged-release tablets administered once daily (TRANxITION – study 1100.1526).

Treatment-naïve patients
VERxVE (study 1100.1486) is a phase 3 study in which treatment-naïve patients received Viramune 200 mg immediate-release once daily for 14 days and then were randomised to receive either Viramune 200 mg immediate-release twice daily or Viramune 400 mg prolonged-release once daily. All patients received tenofovir + emtricitabine as background therapy. Randomisation was stratified by screening HIV-1 RNA level (≤100,000 copies/ml and >100,000 copies/ml). Selected demographic and baseline disease characteristics are displayed in Table 1.

Table 1: Demographic and Baseline Disease Characteristics in study 1100.1486

	Viramune immediate-release n=508*	**Viramune prolonged-release** n=505
Gender		
- Male	85 %	85 %
- Female	15 %	15 %
Race		
- White	74 %	77 %
- Black	22 %	19 %
- Asian	3 %	3 %
- Other**	1 %	2 %
Region		
- North America	30 %	28 %
- Europe	50 %	51 %
- Latin America	10 %	12 %
- Africa	11 %	10 %
Baseline Plasma HIV-1 RNA (log_{10} copies/ml)		
- Mean (SD)	4.7 (0.6)	4.7 (0.7)
- ≤100,000	66 %	67 %
- >100,000	34 %	33 %
Baseline CD4 count (cells/mm^3)		
- Mean (SD)	228 (86)	230 (81)
HIV-1 subtype		
- B	71 %	75 %
- Non-B	29 %	24 %

* Includes 2 patients who were randomised but never received blinded medicinal products.
** Includes American Indians/Alaska natives and Hawaiian/Pacific islanders.

Table 2 describes week 48 outcomes in the VERxVE study (1100.1486). These outcomes include all patients who were randomised after the 14 day lead-in with Viramune immediate-release and received at least one dose of blinded medicinal product.

Table 2: Outcomes at week 48 in study 1100.1486*

	Viramune immediate-release n=506	**Viramune prolonged-release n=505**
Virologic responder (HIV-1 RNA <50 copies/ml)	75.9 %	81.0 %
Virologic failure	5.9 %	3.2 %
- Never suppressed through week 48	2.6 %	1.0 %
- Rebound	3.4 %	2.2 %
Discontinued medicinal product prior to week 48	18.2 %	15.8 %
- Death	0.6 %	0.2 %
- Adverse events	8.3 %	6.3 %
- Other**	9.3 %	9.4 %

* Includes patients who received at least one dose of blinded medicinal product after randomisation.

Patients who discontinued treatment during the lead-in period are excluded.
** Includes lost to follow-up, consent withdrawn, noncompliance, lack of efficacy, pregnancy, and other.

At week 48, mean change from baseline in CD4 cell count was 184 cells/mm^3 and 197 cells/mm^3 for the groups receiving Viramune immediate-release and Viramune prolonged-release respectively.

Table 3 shows outcomes at 48-weeks in study 1100.1486 (after randomization) by baseline viral load.

Table 3: Outcomes at 48 weeks in study 1100.1486 by baseline viral load*

	Number with response/total number (%)		**Difference in % (95 % CI)**
	Viramune immediate-release	**Viramune prolonged-release**	
Baseline HIV−1 viral load stratum (copies/ml)			
- ≤ 100,000	240/303 (79.2 %)	267/311 (85.0 %)	6.6 (0.7, 12.6)
- >100,000	144/203 (70.9 %)	142/194 (73.2 %)	2.3 (−6.6, 11.1)
Total	**384/506 (75.9 %)**	**409/505 (81.0 %)**	**4.9 (−0.1, 10.0)****

* Includes patients who received at least one dose of blinded medicinal product after randomisation. Patients who discontinued treatment during the lead-in period are excluded.
** Based on Cochran's statistic with continuity correction for the variance calculation

The overall percentage of treatment responders observed in study 1100.1486 (including lead-in phase), regardless of the formulation is 793/1,068 = 74.3 %. The denominator 1,068 includes 55 patients who stopped treatment during the lead in phase and two patients randomized but never treated with randomized dose. The numerator 793 is the number of patients who were treatment responders at 48 weeks (384 from immediate-release and 409 from prolonged-release treatment groups).

Lipids, Change from baseline
Changes from baseline in fasting lipids are shown in Table 4.

Table 4: Summary of lipid laboratory values at baseline (screening) and week 48 - study 1100.1486

	Viramune immediate-release			**Viramune prolonged-release**		
	Baseline (mean) n=503	**Week 48 (mean) n=407**	**Percent change* n=406**	**Baseline (mean) n=505**	**Week 48 (mean) n=419**	**Percent change* n=419**
LDL (mg/dL)	98.8	110.0	+9	98.3	109.5	+7
HDL (mg/dL)	38.8	52.2	+32	39.0	50.0	+27
Total cholesterol. (mg/dL)	163.8	186.5	+13	163.2	183.8	+11
Total cholesterol/HDL	4.4	3.8	-14	4.4	3.9	-12
Triglycerides (mg/dL)	131.2	124.5	-9	132.8	127.5	-7

* Percent change is the median of within-patient changes from baseline for patients with both baseline and week 48 values and is not a simple difference of the baseline and week 48 mean values, respectively.

Patients switching from Viramune immediate-release to Viramune prolonged-release
TRANxITION (study 1100.1526) is a Phase 3 study to evaluate safety and antiviral activity in patients switching from Viramune immediate-release to Viramune prolonged-release. In this open-label study, 443 patients already on an antiviral regimen containing Viramune 200 mg immediate-release twice daily with HIV-1 RNA < 50 copies/ml were randomised in a 2:1 ratio to Viramune 400 mg prolonged-release once daily or Viramune 200 mg immediate-release twice daily. Approximately half of the patients had tenofovir + emtricitabine as their background therapy, with the remaining patients

receiving abacavir sulfate + lamivudine or zidovudine + lamivudine. Approximately half of the patients had at least 3 years of prior exposure to Viramune immediate-release prior to entering study 1100.1526.

At 24 weeks after randomisation in the TRANxITION study, 92.6 % and 93.6 % of patients receiving Viramune 200 mg immediate-release twice daily or Viramune 400 mg prolonged-release once daily, respectively, continued to have HIV-1 RNA < 50 copies/ml.

Paediatric population
Results of a 48-week analysis of the South African study BI 1100.1368 confirmed that the 4/7 mg/kg and 150 mg/m^2 nevirapine dose groups were well tolerated and effective in treating antiretroviral naive paediatric patients. A marked improvement in the CD4+ cell percent was observed through Week 48 for both dose groups. Also, both dosing regimens were effective in reducing the viral load. In this 48-week study no unexpected safety findings were observed in either dosing group.

5.2 Pharmacokinetic properties

Absorption:
The pharmacokinetics of nevirapine has been studied in a single dose study (study 1100.1485) of Viramune prolonged-release in 17 healthy volunteers. The relative bioavailability of nevirapine when dosed as one 400 mg Viramune prolonged-release tablet, relative to two 200 mg Viramune immediate-release tablets, was approximately 75 %. The mean peak plasma concentration of nevirapine was 2,060 ng/ml measured at a mean 24.5 hours after administration of 400 mg Viramune prolonged-release tablets.

The pharmacokinetics of Viramune prolonged-release has also been studied in a multiple dose pharmacokinetics study (study 1100.1489) in 24 HIV-1 infected patients who switched from chronic Viramune immediate-release therapy to Viramune prolonged-release. The nevirapine $AUC_{0\text{-}24,ss}$ and $C_{min,ss}$ measured after 19 days of fasted dosing of Viramune 400 mg prolonged-release tablets once daily were approximately 80 % and 90 %, respectively, of the $AUC_{0\text{-}24,ss}$ and $C_{min,ss}$ measured when patients were dosed with Viramune 200 mg immediate-release tablets twice daily. The geometric mean nevirapine $C_{min,ss}$ was 2,770 ng/ml.

When Viramune prolonged-release was dosed with a high fat meal, the nevirapine $AUC_{0\text{-}24,ss}$ and $C_{min,ss}$ were approximately 94 % and 98 %, respectively, of the $AUC_{0\text{-}24,ss}$ and $C_{min,ss}$ measured when patients were dosed with Viramune immediate-release tablets. The difference in nevirapine pharmacokinetics observed when Viramune prolonged-release tablets are dosed under fasted or fed conditions is not considered clinically relevant. Viramune prolonged-release tablets can be taken with or without food.

Some patients have reported the occurrence of remnants in faeces which may resemble intact tablets. Based on the data available so far, this has not been shown to affect the therapeutic response.

Distribution: 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.

Biotransformation and elimination: *In vivo* studies in humans and *in vitro* studies with human liver microsomes have shown that nevirapine is extensively biotransformed via cytochrome P450 (oxidative) metabolism to several hydroxylated metabolites. *In vitro* studies with human liver microsomes suggest that oxidative metabolism of nevirapine is mediated primarily by cytochrome P450 isozymes from the CYP3A family, although other isozymes may have a secondary role. In a mass balance/excretion study in eight healthy male volunteers dosed to steady state with nevirapine 200 mg given twice daily followed by a single 50 mg dose of 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 is characterised 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 impairment: The single-dose pharmacokinetics of nevirapine immediate-release has been compared in 23 patients 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 patients 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, patients 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 nevirapine therapy for adults with an additional 200 mg immediate-release tablet 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 nevirapine dosing. In paediatric patients with renal dysfunction who are undergoing dialysis it is recommended following each dialysis treatment patients receive an additional dose of Viramune oral suspension or immediate-release tablets representing 50% of the recommended daily dose of Viramune oral suspension or immediate-release tablets, which would help offset the effects of dialysis on nevirapine clearance. Viramune prolonged-release tablets have not been studied in patients with renal dysfunction and Viramune immediate-release should be used.

*Hepatic impairment:*A steady state study comparing 46 patients with
mild (n=17: Ishak Score 1-2),
moderate (n=20; Ishak Score 3-4),
or severe (n=9; Ishak Score 5-6, Child-Pugh A in 8 pts., for 1 Child-Pugh score not applicable)
liver fibrosis as a measure of hepatic impairment was conducted.

The patients studied were receiving antiretroviral therapy containing Viramune 200 mg immediate-release tablets twice daily for at least 6 weeks prior to pharmacokinetic sampling, with a median duration of therapy of 3.4 years. In this study, the multiple dose pharmacokinetic disposition of nevirapine and the five oxidative metabolites were not altered.

However, approximately 15 % of these patients with hepatic fibrosis had nevirapine trough concentrations above 9,000 ng/ml (2 fold the usual mean trough). Patients with hepatic impairment should be monitored carefully for evidence of medicinal product induced toxicity.

In a single dose pharmacokinetic study of 200 mg Viramune immediate-release tablets~~of~~ in HIV-negative patients with mild and moderate hepatic impairment (Child-Pugh A, n=6; Child-Pugh B,

n=4), a significant increase in the AUC of nevirapine was observed in one Child-Pugh B patient with ascites suggesting that patients with worsening hepatic function and ascites may be at risk of accumulating nevirapine in the systemic circulation. Because nevirapine induces its own metabolism with multiple dosing, this single dose study may not reflect the impact of hepatic impairment on multiple dose pharmacokinetics (see section 4.4). Viramune prolonged-release tablets have not been evaluated in patients with hepatic impairment and Viramune immediate-release should be used.

Gender
In the multinational 2NN study with Viramune immediate-release, a population pharmacokinetic substudy of 1077 patients was performed that included 391 females. Female patients showed a 13.8 % lower clearance of nevirapine than did male patients. This difference is not considered clinically relevant. Since neither body weight nor Body Mass Index (BMI) had influence on the clearance of nevirapine, the effect of gender cannot be explained by body size.

The effects of gender on the pharmacokinetics of Viramune prolonged-release have been investigated in study 1100.1486. Female patients tend to have higher (approximately 20 – 30 %) trough concentrations in both Viramune prolonged-release and Viramune immediate-release treatment groups.

Elderly
Nevirapine pharmacokinetics in HIV-1 infected adults does not appear to change with age (range 18 - 68 years). Nevirapine has not been specifically investigated in patients over the age of 65. Black patients (n=80/group) in study 1100.1486 showed approximately 30% higher trough concentrations than Caucasian patients (250-325 patients/group) in both the Viramune immediate-release and Viramune prolonged-release treatment groups over 48 weeks of treatment at 400 mg/day.

Paediatric population
Data concerning the pharmacokinetics of nevirapine has been derived from two major sources: a 48 week paediatric study in South Africa (BI 1100.1368) involving 123 HIV-1 positive, antiretroviral naïve patients aged 3 months to 16 years; and a consolidated analysis of five Paediatric AIDS Clinical Trials Group (PACTG) protocols comprising 495 patients aged 14 days to 19 years.

Pharmacokinetic data on 33 patients (age range 0.77 – 13.7 years) in the intensive sampling group demonstrated that clearance of nevirapine increased with increasing age in a manner consistent with increasing body surface area. Dosing of nevirapine at 150 mg/m^2 BID (after a two-week lead in at 150 mg/m^2 QD) produced geometric mean or mean trough nevirapine concentrations between 4-6 µg/ml (as targeted from adult data). In addition, the observed trough nevirapine concentrations were comparable between the two methods.

The consolidated analysis of Paediatric AIDS Clinical Trials Group (PACTG) protocols 245, 356, 366, 377, and 403 allowed for the evaluation of paediatric patients less than 3 months of age (n=17) enrolled in these PACTG studies. The plasma nevirapine concentrations observed were within the range observed in adults and the remainder of the paediatric population, but were more variable between patients, particularly in the second month of age.

The pharmacokinetics of Viramune prolonged-release was assessed in study 1100.1518. Eighty-five patients (3 to < 18 years) received weight or body surface area dose-adjusted Viramune immediate-release for a minimum of 18 weeks and then were switched to Viramune prolonged-release tablets (2 x 100 mg, 3 x 100 mg or 1 x 400 mg once daily) in combination with other antiretrovirals for 10 days. The observed geometric mean ratios of Viramune prolonged-release to Viramune immediate-release were ~90 % for $C_{min,ss}$ and AUC_{ss} with 90% confidence intervals within 80 %-125 %; the ratio for $C_{max,ss}$ was lower and consistent with a once-daily prolonged-release dosage form. Geometric mean steady-state plasma Viramune prolonged-release pre-dose trough concentrations were 3,880 ng/ml, 3,310 ng/ml and 5,350 ng/ml in age groups 3 to <6 years, 6 to <12 years, and 12 to <18 years of age, respectively. Overall, the exposure in children was similar to that observed in adults receiving Viramune prolonged-release in study 1100.1486.

In single dose, parallel group bioavailability studies (studies 1100.1517 and 1100.1531), the Viramune 50 and 100 mg prolonged-release tablets exhibited extended release characteristics of prolonged absorption and lower maximal concentrations, similar to the findings when a 400 mg prolonged-release tablet was compared to the Viramune immediate-release 200 mg tablet.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans other than those observed in clinical studies based on conventional studies of safety, pharmacology, repeated dose toxicity, and genotoxicity. In carcinogenicity studies, nevirapine induces hepatic tumours in rats and mice. These findings are most likely related to nevirapine being a strong inducer of liver enzymes, and not due to a genotoxic mode of action.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose (as monohydrate)
Hypromellose
Iron oxide yellow
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

If bottles are taken the medicinal product should be used within 2 months of opening.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Maintenance packs:
Polyvinyl chloride (PVC)/aluminium foil push through blister units. Cartons containing 30 prolonged-release tablets or 90 prolonged-release tablets.
or
High density polyethylene (HDPE) plastic bottle, with a plastic cap and an induction foil seal liner. Bottles contain 30 prolonged-release tablets.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Boehringer Ingelheim International GmbH
Binger Strasse 173
55216 Ingelheim am Rhein, Germany

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/97/055/007 (30 tablets, bottle)
EU/1/97/055/008 (30 tablets, blister)
EU/1/97/055/009 (90 tablets, blister)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 5 February 1998
Date of latest renewal: 20 December 2012

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

ANNEX II

A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers responsible for batch release

Viramune 200 mg Tablets

Boehringer Ingelheim Pharma GmbH & Co. KG
Binger Strasse 173 - 55216 Ingelheim am Rhein
Germany

Boehringer Ingelheim Hellas Single Member S.A.
5th km Paiania – Markopoulo
Koropi Attiki, 19441
Greece

Boehringer Ingelheim France
100-104 avenue de France
75013 Paris
France

Viramune 50 mg/5 ml Oral suspension and Viramune 400 mg prolonged-release tablets

Boehringer Ingelheim Pharma GmbH & Co. KG
Binger Strasse 173 – 55216 Ingelheim am Rhein
Germany

Boehringer Ingelheim France
100-104 avenue de France
75013 Paris
France

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorization holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2. of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency.
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

BLISTER CARTON LABEL

1. NAME OF THE MEDICINAL PRODUCT

Viramune 200 mg tablets
nevirapine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 200 mg of nevirapine (as anhydrous)

3. LIST OF EXCIPIENTS

Excipients: includes lactose (see leaflet for further information)

4. PHARMACEUTICAL FORM AND CONTENTS

60 tablets
120 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Boehringer Ingelheim International GmbH
Binger Strasse 173
55216 Ingelheim am Rhein
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/97/055/001 [60 tablets]
EU/1/97/055/003 [120 tablets]

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Viramune 200 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

BLISTER CARTON LABEL

1. NAME OF THE MEDICINAL PRODUCT

Viramune 200 mg tablets
nevirapine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 200 mg of nevirapine (as anhydrous)

3. LIST OF EXCIPIENTS

Excipients: includes lactose (see leaflet for further information)

4. PHARMACEUTICAL FORM AND CONTENTS

Treatment initiation pack containing 14 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Boehringer Ingelheim International GmbH
Binger Strasse 173
55216 Ingelheim am Rhein
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/97/055/004

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Viramune 200 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

1. NAME OF THE MEDICINAL PRODUCT

Viramune 200 mg tablets
nevirapine

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Boehringer Ingelheim (Logo)

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

BOTTLE CARTON LABEL

1. NAME OF THE MEDICINAL PRODUCT

Viramune 50 mg/5 ml oral suspension
nevirapine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each ml of oral suspension contains 10 mg of nevirapine (as hemihydrate)

3. LIST OF EXCIPIENTS

Excipients: includes sucrose, sorbitol, methyl parahydroxybenzoate, propyl parahydroxybenzoate (see leaflet for further information)

4. PHARMACEUTICAL FORM AND CONTENTS

240 ml oral suspension

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use
Oral use
Shake gently before use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
To be used within 6 months after opening the bottle

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Boehringer Ingelheim International GmbH
Binger Strasse 173
55216 Ingelheim am Rhein
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/97/055/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Viramune 50 mg/5 ml

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

BOTTLE LABEL

1. NAME OF THE MEDICINAL PRODUCT

Viramune 50 mg/5 ml oral suspension
nevirapine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each ml of oral suspension contains 10 mg of nevirapine (as hemihydrate)

3. LIST OF EXCIPIENTS

Excipients: includes sucrose, sorbitol, methyl parahydroxybenzoate, propyl parahydroxybenzoate (see leaflet for further information)

4. PHARMACEUTICAL FORM AND CONTENTS

240 ml oral suspension

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use
Oral use
Shake gently before use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
To be used within 6 months after opening the bottle

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Boehringer Ingelheim International GmbH
Binger Strasse 173
55216 Ingelheim am Rhein
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/97/055/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

BOTTLE CARTON LABEL

1. NAME OF THE MEDICINAL PRODUCT

Viramune 400 mg prolonged-release tablets
nevirapine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each prolonged-release tablet contains 400 mg of nevirapine (as anhydrous)

3. LIST OF EXCIPIENTS

Excipients: includes lactose (see leaflet for further information)

4. PHARMACEUTICAL FORM AND CONTENTS

30 prolonged-release tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use
Oral use
Once daily
Swallow whole, do not chew, divide or crush

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
Use within 2 months after 1st opening

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Boehringer Ingelheim International GmbH
Binger Strasse 173
55216 Ingelheim am Rhein
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/97/055/007

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Viramune 400 mg prolonged-release tablets

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

BOTTLE LABEL

1. NAME OF THE MEDICINAL PRODUCT

Viramune 400 mg prolonged-release tablets
nevirapine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each prolonged-release tablet contains 400 mg of nevirapine (as anhydrous)

3. LIST OF EXCIPIENTS

Contains lactose

4. PHARMACEUTICAL FORM AND CONTENTS

30 prolonged-release tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use
Oral use
Once daily
Swallow whole, do not chew, divide or crush

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
Use within 2 months after 1st opening

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Boehringer Ingelheim International GmbH
Binger Strasse 173
55216 Ingelheim am Rhein
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/97/055/007

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

BLISTER CARTON LABEL

1. NAME OF THE MEDICINAL PRODUCT

Viramune 400 mg prolonged-release tablets
nevirapine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each prolonged-release tablet contains 400 mg of nevirapine (as anhydrous)

3. LIST OF EXCIPIENTS

Excipients: includes lactose (see leaflet for further information)

4. PHARMACEUTICAL FORM AND CONTENTS

30 prolonged-release tablets
90 prolonged-release tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use
Oral use
Once daily
Swallow whole, do not chew, divide or crush

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Boehringer Ingelheim International GmbH
Binger Strasse 173
55216 Ingelheim am Rhein
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/97/055/008 [30 prolonged-release]
EU/1/97/055/009 [90 prolonged-release]

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Viramune 400 mg prolonged-release tablets

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

1. NAME OF THE MEDICINAL PRODUCT

Viramune 400 mg prolonged-release tablets
nevirapine

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Boehringer Ingelheim (Logo)

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Viramune 200 mg
tablets
nevirapine

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Viramune is and what it is used for

Viramune belongs to a group of medicines called antiretrovirals, used in the treatment of Human Immunodeficiency Virus (HIV-1) infection.

The active substance of your medicine is called nevirapine. Nevirapine belongs to a class of anti-HIV medicines called non-nucleoside reverse transcriptase inhibitors (NNRTIs). Reverse transcriptase is an enzyme that HIV needs in order to multiply. Nevirapine stops reverse transcriptase from working. By stopping reverse transcriptase from working, Viramune helps control HIV-1 infection.

Viramune is indicated for the treatment of HIV-1 infected adults, adolescents, and children of any age. You must take Viramune together with other antiretroviral medicines. Your doctor will recommend the best medicines for you.

If Viramune has been prescribed for your child, please note that all information in this leaflet is addressed to your child (in this case please read "your child" instead of "you").

2. What you need to know before you take Viramune

Do not take Viramune
- if you are allergic to nevirapine or any of the other ingredients of this medicine (listed in section 6 *)*.
- if you have taken Viramune before and had to stop the treatment because you suffered from:
    - severe skin rash
    - skin rash with other symptoms for example:
        - fever
        - blistering
        - mouth sores
        - inflammation of the eye
        - swelling of the face

- general swelling
- shortness of breath
- muscle or joint pain
- general feelings of illness
- abdominal pain

- hypersensitivity (allergic) reactions
- inflammation of the liver (hepatitis)

- if you have severe liver disease
- if you have had to stop Viramune treatment in the past because of changes in your liver function
- if you are taking a medicine containing the herbal substance St. John's Wort (*Hypericum perforatum*). This herbal substance may stop Viramune from working properly.

Warnings and precautions
Talk to your doctor or pharmacist before taking Viramune.
During the first 18 weeks of treatment with Viramune it is very important that you and your doctor watch out for signs of liver or skin reactions. These can become severe and even life threatening. You are at greatest risk of such a reaction during the first 6 weeks of treatment.

If you experience severe rash or hypersensitivity (allergic reactions that may appear in the form of rash) accompanied by other side effects such as
- **fever,**
- **blistering,**
- **mouth sores,**
- **inflammation of the eye,**
- **swelling of the face,**
- **general swelling,**
- **shortness of breath,**
- **muscle or joint pain,**
- **general feelings of illness,**
- **or abdominal pain**

YOU SHOULD DISCONTINUE TAKING VIRAMUNE AND YOU MUST CONTACT your doctor IMMEDIATELY as such reactions can be potentially life-threatening or lead to death. If you ever have only mild rash symptoms without any other reaction please inform your doctor immediately, who will advise you whether you should stop taking Viramune.

If you experience symptoms suggesting damage of the liver, such as
- **loss of appetite,**
- **feeling sick (nausea),**
- **vomiting,**
- **yellow skin (jaundice),**
- **abdominal pain**

you should discontinue taking Viramune and must contact your doctor immediately.

If you develop severe liver, skin or hypersensitivity reactions whilst taking Viramune, NEVER TAKE VIRAMUNE again without referring to your doctor.
You must take the dose of Viramune as prescribed by your doctor. This is especially important within the first 14 days of treatment (see more information in "*How to take Viramune*").

The following patients are at increased risk of developing liver problems:
- women
- infected with hepatitis B or C
- abnormal liver function tests
- treatment-naïve patients with higher CD4 cell counts at the start of Viramune therapy (women more than 250 cells/mm³, men more than 400 cells/mm³)
- pre-treated patients with detectable HIV-1 plasma viral load and higher CD4 cell counts at the start of Viramune therapy (women more than 250 cells/mm³, men more than 400 cells/mm³)

In some patients with advanced HIV infection (AIDS) and a history of opportunistic infection (AIDS defining illness), signs and symptoms of inflammation from previous infections may occur soon after anti-HIV treatment is started. It is believed that these symptoms are due to an improvement in the body's immune response, enabling the body to fight infections that may have been present with no obvious symptoms. If you notice any symptoms of infection, please inform your doctor immediately.

In addition to the opportunistic infections, autoimmune disorders (a condition that occurs when the immune system attacks healthy body tissue) may also occur after you start taking medicines for the treatment of your HIV infection. Autoimmune disorders may occur many months after the start of treatment. If you notice any symptoms of infection or other symptoms such as muscle weakness, weakness beginning in the hands and feet and moving up towards the trunk of the body, palpitations, tremor or hyperactivity, please inform your doctor immediately to seek necessary treatment.

Changes of body fat may occur in patients receiving combination antiretroviral therapy. Contact your doctor if you notice changes in body fat (see section 4 "*Possible side effects"*).

Some patients taking combination antiretroviral therapy may develop a bone disease called osteonecrosis (death of bone tissue caused by loss of blood supply to the bone). The length of combination antiretroviral therapy, corticosteroid use, alcohol consumption, severe weakness of the immune system and higher body mass index may be some of the many risk factors for developing this disease. Signs of osteonecrosis are joint stiffness, aches and pains (especially of the hip, knee and shoulder) and difficulty in movement. If you notice any of these symptoms please inform your doctor.

If you are taking nevirapine and zidovudine concomitantly please inform your doctor since he might need to check your white blood cells.
Do not take Viramune after an exposure to HIV unless you have been diagnosed with HIV and instructed to do so by your doctor.

Prednisone should not be used to treat a rash related to Viramune.

If you are taking oral contraceptives (e.g. „pill") or other hormonal methods of birth control during treatment with Viramune, you should use a barrier contraception (e.g. condoms) in addition to prevent pregnancy and further HIV transmission.
If you are receiving post-menopausal hormone therapy, ask your doctor for advice before taking this medicine.

If you are taking or are prescribed rifampicin to treat tuberculosis please inform your doctor before taking this medicine with Viramune.

Children and adolescents
Viramune tablets can be taken by:
- children 16 years of age or older
- children under 16 years of age who:
  - weigh 50 kg or more
  - or have a body surface area above 1.25 square metres.

For smaller children an oral suspension liquid form is available.

Other medicines and Viramune
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. Inform your doctor about all other medicines you are taking before you start taking Viramune. Your doctor might need to monitor whether your other medicines are still working and adjust doses. Carefully read the package leaflet of all other HIV medicinal products you are taking in combination with Viramune.

It is particularly important that you tell your doctor if you are taking or have recently taken:

- St. John's Wort (*Hypericum perforatum*, medicine to treat depression)
- rifampicin (medicine to treat tuberculosis)
- rifabutin (medicine to treat tuberculosis)
- macrolides e.g. clarithromycin (medicine to treat bacterial infections)
- fluconazole (medicine to treat fungal infections)
- ketoconazole (medicine to treat fungal infections)
- itraconazole (medicine to treat fungal infections)
- methadone (medicine used for treatment of opiate addicts)
- warfarin (medicine to reduce blood clotting)
- hormonal contraceptives (e.g. the "pill")
- atazanavir (another medicine to treat HIV-infection)
- lopinavir/ritonavir (another medicine to treat HIV-infection)
- fosamprenavir (another medicine to treat HIV-infection)
- efavirenz (another medicine to treat HIV-infection)
- etravirine (another medicine to treat HIV-infection)
- rilpivirine (another medicine to treat HIV-infection)
- zidovudine (another medicine to treat HIV-infection)
- elvitegravir/cobicistat (another medicine to treat HIV-infection)

Your doctor will carefully monitor the effect of Viramune and any of these medicines if you are taking them together.

If you are undergoing kidney dialysis, your doctor may consider a dose adjustment of Viramune. This is because Viramune can be partly washed out of your blood by dialysis.

Taking Viramune with food and drink
There are no restrictions on taking Viramune with food and drink.

Pregnancy and breast-feeding
If you are pregnant or think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Breast-feeding ***is not recommended*** in women living with HIV because HIV infection can be passed on to the baby in breast milk.
If you are breast-feeding, or thinking about breast-feeding, you ***should discuss it with*** your doctor ***as soon as possibl***e

Driving and using machines
You may experience fatigue when taking Viramune. Use caution when engaging in activities such as driving, using any tools or machines. If you experience fatigue you should avoid potentially hazardous tasks such as driving or using any tools or machines.

Viramune contains lactose and sodium
Viramune tablets contain lactose (milk sugar).
If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.
Viramune tablets contain less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

3. How to take Viramune

You should not use Viramune on its own. You must take it with at least two other antiretroviral medicines. Your doctor will recommend the best medicines for you.

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

Dose:

The dose is one 200 mg tablet per day for the first 14 days of treatment ("lead-in" period). After 14 days, the usual dose is one 200 mg tablet twice a day.

It is very important that you take only one Viramune tablet a day for the first 14 days ("lead-in" period). If you have any rash during this period, do not increase the dose but consult your doctor.

The 14-day "lead-in" period has been shown to lower the risk of skin rash.

As Viramune must always be taken together with other HIV antiretroviral medicines, you should follow the instructions for your other medicines carefully. These are supplied in the package leaflets for those medicines.

Viramune is also available in liquid form as an oral suspension. This is particularly suitable if:
- you have problems swallowing tablets
- or you are a child weighing less than 50 kg
- or you are a child having a body surface area less than 1.25 square metres (your doctor will work out your surface area).

You should continue to take Viramune for as long as instructed by your doctor.

As explained in *'Warnings and precautions'*, above, your doctor will monitor you with liver tests or for undesirable effects such as rash. Depending on the outcome your doctor may decide to interrupt or stop your Viramune treatment. Your doctor might then decide to restart you on a lower dose.

Only take Viramune tablets by mouth. Do not chew your tablets. You may take Viramune with or without food.

If you take more Viramune than you should
Do not take more Viramune than prescribed by your doctor and described in this leaflet. There is at present little information on the effects of Viramune overdose. Consult your doctor if you have taken more Viramune than you should.

If you forget to take Viramune
Try not to miss a dose. If you notice that you have missed a dose within 8 hours of when it was due, take the missed dose as soon as possible. If it has been more than 8 hours since the dose was due only take the next dose at the usual time.

If you stop taking Viramune
Taking all doses at the appropriate times:
- greatly increases the effectiveness of your combination antiretroviral medicines
- reduces the chances of your HIV infection becoming resistant to your antiretroviral medicines.

It is important that you continue taking Viramune correctly, as described above, unless your doctor

instructs you to stop.

If you stop taking Viramune for more than 7 days your doctor will instruct you to start the 14 day 'lead-in' period (described above) once again, before returning to the twice daily dose.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

During HIV therapy there may be an increase in weight and in levels of blood lipids and glucose. This is partly linked to restored health and life style, and in the case of blood lipids sometimes to the HIV medicines themselves. Your doctor will test for these changes.

Like all medicines, this medicine can cause side effects, although not everybody gets them.

As mentioned in *'Warnings and precautions'*, above, the most important side effects of Viramune are severe and life threatening skin reactions and serious liver damage. These reactions occur mainly in the first 18 weeks of treatment with Viramune. This is therefore an important period which requires close monitoring by your doctor.

If you ever observe any rash symptoms, inform your doctor immediately.

When rash occurs it is normally mild to moderate. However, in some patients a rash, which appears as a blistering skin reaction, can be severe or life-threatening (Stevens-Johnson syndrome and toxic epidermal necrolysis) and deaths have been recorded. Most of the cases of both severe rash and mild/moderate rash occur in the first six weeks of treatment.

If rash occurs and you also feel sick, you must stop treatment and visit your doctor immediately.

Hypersensitivity (allergic) reactions can occur. Such reactions may appear in the form of anaphylaxis (a severe form of allergic reaction) with symptoms such as:
- rash
- swelling of the face
- difficulty breathing (bronchial spasm)
- anaphylactic shock

Hypersensitivity reactions can also occur as rash with other side effects such as:
- fever
- blistering of your skin
- mouth sores
- inflammation of the eye
- swelling of the face
- general swelling
- shortness of breath
- muscle or joint pain
- a reduction in the numbers of your white blood cells (granulocytopenia)
- general feelings of illness
- severe problems with liver or kidneys (liver or kidney failure).

Tell your doctor immediately if you experience rash and any of the other side effects of a hypersensitivity (allergic) reaction. Such reactions can be life-threatening.

Abnormal liver functioning has been reported with the use of Viramune. This includes some cases of inflammation of the liver (hepatitis), which can be sudden and intense (fulminant hepatitis), and liver failure, which can be both fatal.

Tell your doctor if you experience any of the following clinical symptoms of liver damage:
- loss of appetite
- feeling sick (nausea)
- vomiting
- yellow skin (jaundice)
- abdominal pain

The side effects described below have been experienced by patients given Viramune:

Very common (may affect more than 1 in 10 people):
- rash

Common (may affect up to 1 in 10 people):
- decreased numbers of white blood cells (granulocytopenia)
- allergic reactions (hypersensitivity)
- headache
- feeling sick (nausea)
- vomiting
- abdominal pain
- loose stools (diarrhoea)
- inflammation of the liver (hepatitis)
- feeling tired (fatigue)
- fever
- abnormal liver function tests

Uncommon (may affect up to 1 in 100 people):
- allergic reaction characterized by rash, swelling of the face, difficulty breathing (bronchial spasm) or anaphylactic shock
- decreased numbers of red blood cells (anaemia)
- yellow skin (jaundice)
- severe and life-threatening skin rashes (Stevens-Johnson syndrome/ toxic epidermal necrolysis)
- hives (urticaria)
- fluid under the skin (angioedema)
- joint pain (arthralgia)
- muscle pain (myalgia)
- decreased blood phosphorus
- increased blood pressure

Rare (may affect up to 1 in 1000 people):
- sudden and intense inflammation of the liver (fulminant hepatitis)
- drug reaction with systemic symptoms (drug reaction with eosinophilia and systemic symptoms)

The following events have also been reported when Viramune has been used in combination with other antiretroviral agents:
- decreased numbers of red blood cells or platelets
- inflammation of the pancreas
- decrease in or abnormal skin sensations

These events are commonly associated with other antiretroviral 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 treatment with Viramune.

Additional side effects in children and adolescents
A reduction in white blood cells (granulocytopenia) can occur, which is more common in children. A reduction in red blood cells (anaemia), which may be related to nevirapine therapy, is also more commonly observed in children. As with rash symptoms, please inform your doctor of any side

effects.

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Viramune

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and on the blister after "EXP". The expiry date refers to the last day of that month.

This medicinal product does not require any special storage conditions.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Viramune contains

- The active substance is nevirapine. Each tablet contains 200 mg nevirapine.
- The other ingredients are:
  microcrystalline cellulose,
  lactose (as monohydrate),
  povidone K25,
  sodium starch glycolate,
  colloidal silicon dioxide and
  magnesium stearate.

What Viramune looks like and contents of the pack

White, oval, biconvex tablets. One side is marked with the code "54 193", with a single bisect separating the "54" and "193". The opposite side is marked with the company symbol. The score line is not intended for breaking the tablet.
Viramune tablets are supplied in blisters, with 14, 60 or 120 tablets per carton. Not all pack sizes may be marketed.

Viramune is also available as an oral suspension.

Marketing Authorisation Holder

Boehringer Ingelheim International GmbH
Binger Strasse 173
55216 Ingelheim am Rhein
Germany

Manufacturer

Boehringer Ingelheim Pharma GmbH & Co. KG
Binger Strasse 173
55216 Ingelheim am Rhein
Germany

or

Boehringer Ingelheim Hellas Single Member S.A.
5th km Paiania – Markopoulo
Koropi Attiki, 19441
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or

Boehringer Ingelheim France
100-104 avenue de France
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For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder.

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United Kingdom (Northern Ireland)
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Tel: +353 1 295 9620

This leaflet was last revised in {MM/YYYY}

Other sources of information
Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu

Package leaflet: Information for the user
Viramune 50 mg/5 ml oral suspension
nevirapine

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

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Viramune is indicated for the treatment of HIV-1 infected adults, adolescents, and children of any age. You must take Viramune together with other antiretroviral medicines. Your doctor will recommend the best medicines for you.

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  - severe skin rash
  - skin rash with other symptoms for example:
    - fever
    - blistering
    - mouth sores
    - inflammation of the eye
    - swelling of the face
    - general swelling
    - shortness of breath

    - muscle or joint pain
    - general feelings of illness
    - abdominal pain
  - hypersensitivity (allergic) reactions
  - inflammation of the liver (hepatitis)
- if you have severe liver disease
- if you have had to stop Viramune treatment in the past because of changes in your liver function
- if you are taking a medicine containing the herbal substance St. John's Wort (*Hypericum perforatum*). This herbal substance may stop Viramune from working properly.

Warnings and precautions
Talk to your doctor or pharmacist before taking Viramune.
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- **blistering,**
- **mouth sores,**
- **inflammation of the eye,**
- **swelling of the face,**
- **general swelling,**
- **shortness of breath,**
- **muscle or joint pain,**
- **general feelings of illness,**
- **or abdominal pain**

YOU SHOULD DISCONTINUE TAKING VIRAMUNE AND YOU MUST CONTACT your doctor IMMEDIATELY as such reactions can be potentially life-threatening or lead to death.
If you ever have only mild rash symptoms without any other reaction please inform your doctor immediately, who will advise you whether you should stop taking Viramune.

If you experience symptoms suggesting damage of the liver, such as
- **loss of appetite,**
- **feeling sick (nausea),**
- **vomiting,**
- **yellow skin (jaundice),**
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you should discontinue taking Viramune and must contact your doctor immediately.

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- women
- infected with hepatitis B or C
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- treatment-naïve patients with higher CD4 cell counts at the start of Viramune therapy (women more than 250 cells/mm³, men more than 400 cells/mm³)
- pre-treated patients with detectable HIV-1 plasma viral load and higher CD4 cell counts at the start of Viramune therapy (women more than 250 cells/mm³, men more than 400 cells/mm³)

In some patients with advanced HIV infection (AIDS) and a history of opportunistic infection (AIDS-defining illness), signs and symptoms of inflammation from previous infections may occur soon after anti-HIV treatment is started. It is believed that these symptoms are due to an improvement in the body's immune response, enabling the body to fight infections that may have been present with no obvious symptoms. If you notice any symptoms of infection, please inform your doctor immediately.

In addition to the opportunistic infections, autoimmune disorders (a condition that occurs when the immune system attacks healthy body tissue) may also occur after you start taking medicines for the treatment of your HIV infection. Autoimmune disorders may occur many months after the start of treatment. If you notice any symptoms of infection or other symptoms such as muscle weakness, weakness beginning in the hands and feet and moving up towards the trunk of the body, palpitations, tremor or hyperactivity, please inform your doctor immediately to seek necessary treatment.

Changes of body fat may occur in patients receiving combination antiretroviral therapy. Contact your doctor if you notice changes in body fat (see section 4 "*Possible side effects*").

Some patients taking combination antiretroviral therapy may develop a bone disease called osteonecrosis (death of bone tissue caused by loss of blood supply to the bone). The length of combination antiretroviral therapy, corticosteroid use, alcohol consumption, severe weakness of the immune system and higher body mass index may be some of the many risk factors for developing this disease. Signs of osteonecrosis are joint stiffness, aches and pains (especially of the hip, knee and shoulder) and difficulty in movement. If you notice any of these symptoms please inform your doctor.

If you are taking nevirapine and zidovudine concomitantly please inform your doctor since he might need to check your white blood cells.Do not take Viramune after an exposure to HIV unless you have been diagnosed with HIV and instructed to do so by your doctor.

Prednisone should not be used to treat a rash related to Viramune.

If you are taking oral contraceptives (e.g. „pill") or other hormonal methods of birth control during treatment with Viramune, you should use a barrier contraception (e.g. condoms) in addition to prevent pregnancy and further HIV transmission.
If you are receiving post-menopausal hormone therapy, ask your doctor for advice before taking this medicine.

If you are taking or are prescribed rifampicin to treat tuberculosis please inform your doctor before taking this medicine with Viramune.

Children and adolescents:
Viramune oral suspension can be taken by children of all age groups. Always follow the exact instructions given by your child's doctor.
Viramune is also available as tablets. Viramune tablets can be taken by:
- children 16 years of age or older
- children under 16 years of age who:
  - weigh 50 kg or more
  - or have a body surface area above 1.25 square metres.

Other medicines and Viramune
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. Inform your doctor about all other medicines you are taking before you start taking Viramune. Your doctor might need to monitor whether your other medicines are still working and adjust doses. Carefully read the package leaflet of all other HIV medicinal products you are taking in combination with Viramune.

It is particularly important that you tell your doctor if you are taking or have recently taken:
- St. John's Wort (*Hypericum perforatum,* medicine to treat depression)

- rifampicin (medicine to treat tuberculosis)
- rifabutin (medicine to treat tuberculosis)
- macrolides e.g. clarithromycin (medicine to treat bacterial infections)
- fluconazole (medicine to treat fungal infections)
- ketoconazole (medicine to treat fungal infections)
- itraconazole (medicine to treat fungal infections)
- methadone (medicine used for treatment of opiate addicts)
- warfarin (medicine to reduce blood clotting)
- hormonal contraceptives (e.g. the "pill")
- atazanavir (another medicine to treat HIV-infection)
- lopinavir/ritonavir (another medicine to treat HIV-infection)
- fosamprenavir (another medicine to treat HIV-infection)
- efavirenz (another medicine to treat HIV-infection)
- etravirine (another medicine to treat HIV-infection)
- rilpivirine (another medicine to treat HIV-infection)
- zidovudine (another medicine to treat HIV-infection)
- elvitegravir/cobicistat (another medicine to treat HIV-infection)

Your doctor will carefully monitor the effect of Viramune and any of these medicines if you are taking them together.

If you are undergoing kidney dialysis, your doctor may consider a dose adjustment of Viramune. This is because Viramune can be partly washed out of your blood by dialysis.

Taking Viramune with food and drink
There are no restrictions on taking Viramune with food and drink.

Pregnancy and breast-feeding
If you are pregnant or think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Breast-feeding ***is not recommended*** in women living with HIV because HIV infection can be passed on to the baby in breast milk.
If you are breast-feeding, or thinking about breast-feeding, you ***should discuss it with*** your doctor ***as soon as possible***

Driving and using machines
You may experience fatigue when taking Viramune. Use caution when engaging in activities such as driving, using any tools or machines. If you experience fatigue you should avoid potentially hazardous tasks such as driving or using any tools or machines.

Viramune contains sucrose, sorbitol, methyl parahydroxybenzoate, propyl parahydroxybenzoate and sodium
Viramune oral suspension contains 150 mg sucrose per ml. This should be taken into account in patients with diabetes mellitus. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product. May be harmful to the teeth.
Viramune oral suspension contains 162 mg sorbitol per ml. Sorbitol is a source of fructose. If your doctor has told you that you (or your child) have an intolerance to some sugars or you have been diagnosed with hereditary fructose intolerance (HFI), a rare genetic disorder in which a person cannot break down fructose, talk to your doctor before you (or your child) take or receive this medicine.

Viramune oral suspension contains methyl parahydroxybenzoate and propyl parahydroxybenzoate. These excipients can cause allergic reactions over time.

Viramune oral suspension contains less than 1 mmol sodium (23 mg) per dosage unit, that is to say essentially 'sodium-free'.

3. How to take Viramune

You should not use Viramune on its own. You must take it with at least two other antiretroviral medicines. Your doctor will recommend the best medicines for you.

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

The usual dose is the same for all adults (20 ml).
Your child's doctor will calculate the dose for your child. The calculation will include your child's age and body weight, or body surface area. Make sure that your child's doctor clearly tells you what dose you must give to your child.

For adults

The dose for adults is 20 ml (200 mg) once a day for the first 14 days of treatment (”lead in” period). After 14 days, the usual dose is 20 ml (200 mg) twice a day.

It is very important that you take only 20 ml of Viramune a day for the first 14 days (“lead-in” period). If you have any rash during this period, do not increase the dose but consult your doctor.

Viramune is also available as 200 mg tablets for adults (16 years of age and older).

For children

The dose for children is 4 mg/kg body weight or 150 mg/m^2 body surface area once a day for the first 14 days of treatment (“lead-in period”). Thereafter your child will be switched to a twice daily dosing schedule and your child's doctor will decide the right dose based either on your child's weight or body surface area.

It is very important that your child takes Viramune only once a day for the first 14 days (“lead-in” period). If your child develops any rash during this period, do not increase the dose but consult your child's doctor.

Viramune is also available as 200 mg tablets for older children, particularly adolescents, weighing more than 50 kg or having a body surface of more than 1.25 m^2. Your child's doctor will inform you exactly of the correct dose for your child. Your child's doctor will continually check your child's weight or body surface area to ensure the correct dose.
If you are uncertain please be sure to ask your child's doctor or pharmacist.

Viramune oral suspension should be shaken gently prior to administration. Measure the exact dose using a measuring syringe.

If you are an adult and choose to use another measuring device (e.g. cup or teaspoon) please make sure that you take the whole dose. This is because some Viramune can remain in the cup or spoon. To do so, rinse the used device thoroughly with water and drink it.

The oral dosing syringe, and dosing cup are not provided with Viramune oral suspension. Ask your pharmacist for a syringe or cup if you do not have one.

The 14-day ”lead-in” period has been shown to lower the risk of skin rash.

As Viramune must always be taken together with other HIV antiretroviral medicines, you should

follow the instructions for your other medicines carefully. These are supplied in the package leaflets for those medicines.

You should continue to take Viramune for as long as instructed by your doctor.

As explained in *'Warnings and precautions'*, above, your doctor will monitor you with liver tests or for undesirable effects such as rash. Depending on the outcome your doctor may decide to interrupt or stop Viramune treatment. Your doctor might then decide to restart you on a lower dose.

Viramune oral suspension is in a liquid suspension form and should only be taken by mouth. Shake the bottle gently before you take your medicine.

If you take more Viramune than you should
Do not take more Viramune than prescribed by your doctor and described in this leaflet. There is at present little information on the effects of Viramune overdose. Consult your doctor if you have taken more Viramune than you should.

If you forget to take Viramune
Try not to miss a dose. If you notice that you have missed a dose within 8 hours of when it was due, take the missed dose as soon as possible. If it has been more than 8 hours since the dose was due only take the next dose at the usual time.

If you stop taking Viramune
Taking all doses at the appropriate times:
- greatly increases the effectiveness of your combination antiretroviral medicines
- reduces the chances of your HIV infection becoming resistant to your antiretroviral medicines.

It is important that you continue taking Viramune correctly, as described above, unless your doctor instructs you to stop.

If you stop taking Viramune for more than 7 days your doctor will instruct you to start the 14-day 'lead in' period (described above) once again, before returning to the twice daily dose.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

During HIV therapy there may be an increase in weight and in levels of blood lipids and glucose. This is partly linked to restored health and life style, and in the case of blood lipids sometimes to the HIV medicines themselves. Your doctor will test for these changes.

Like all medicines, this medicine can cause side effects, although not everybody gets them.

As mentioned in *'Warnings and precautions'*, above, the most important side effects of Viramune are severe and life threatening skin reactions and serious liver damage. These reactions occur mainly in the first 18 weeks of treatment with Viramune. This is therefore an important period which requires close monitoring by your doctor.

If you ever observe any rash symptoms, inform your doctor immediately.

When rash occurs it is normally mild to moderate. However, in some patients a rash, which appears as a blistering skin reaction, can be severe or life-threatening (Stevens-Johnson syndrome and toxic epidermal necrolysis) and deaths have been recorded. Most of the cases of both severe rash and mild/moderate rash occur in the first six weeks of treatment.

If rash occurs and you also feel sick, you must stop treatment and visit your doctor immediately. Pay special attention to any rashes that your child develops. Although these may appear normal (for example nappy rash), they might be rashes due to Viramune. If in doubt ask your child's doctor.

Hypersensitivity (allergic) reactions can occur. Such reactions may appear in the form of anaphylaxis (a severe form of allergic reaction) with symptoms such as:
- rash
- swelling of the face
- difficulty breathing (bronchial spasm),
- anaphylactic shock

Hypersensitivity reactions can also occur as rash with other side effects such as:
- fever
- blistering of your skin
- mouth sores
- inflammation of the eye
- swelling of the face
- general swelling
- shortness of breath
- muscle or joint pain
- a reduction in the number of your white blood cells (granulocytopaenia)
- general feelings of illness
- severe problems with liver or kidneys (liver or kidney failure).

Tell your doctor immediately if you experience rash and any of the other side effects of a hypersensitivity (allergic) reaction. Such reactions can be life-threatening.

Abnormal liver functioning has been reported with the use of Viramune. This includes some cases of inflammation of the liver (hepatitis), which can be sudden and intense (fulminant hepatitis), and liver failure, which can be both fatal.

Tell your doctor if you experience any of the following clinical symptoms of liver damage:
- loss of appetite
- feeling sick (nausea)
- vomiting
- yellow skin (jaundice)
- abdominal pain.

The side effects described below have been experienced by patients given Viramune:

<u>Very common (may affect more than 1 in 10 people):</u>
- rash

<u>Common (may affect up to 1 in 10 people):</u>
- decreased number of white blood cells (granulocytopenia)
- allergic reactions (hypersensitivity)
- headache
- feeling sick (nausea)
- vomiting
- abdominal pain
- loose stools (diarrhoea)
- inflammation of the liver (hepatitis)
- feeling tired (fatigue)
- fever
- abnormal liver function tests

Uncommon (may affect up to 1 in 100 people):
- allergic reaction characterized by rash, swelling of the face, difficulty breathing (bronchial spasm) or anaphylactic shock
- decreased numbers of red blood cells (anaemia)
- yellow skin (jaundice)
- severe and life-threatening skin rashes (Stevens-Johnson syndrome/ toxic epidermal necrolysis)
- hives (urticaria)
- fluid under the skin (angioedema)
- joint pain (arthralgia)
- muscle pain (myalgia)
- decreased blood phosphorus
- increased blood pressure

Rare (may affect up to 1 in 1000 people):
- sudden and intense inflammation of the liver (fulminant hepatitis)
- drug reaction with systemic symptoms (drug reaction with eosinophilia and systemic symptoms)

The following events have also been reported when Viramune has been used in combination with other antiretroviral agents:
- decreased numbers of red blood cells or platelets
- inflammation of the pancreas
- decrease in or abnormal skin sensations.

These events are commonly associated with other antiretroviral 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 treatment with Viramune.

Additional side effects in children and adolescents
A reduction in white blood cells (granulocytopenia) can occur, which is more common in children. A reduction in red blood cells (anaemia), which may be related to nevirapine therapy, is also more commonly observed in children. As with rash symptoms, please inform your doctor of any side effects**.**

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Viramune

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and on the bottle after "EXP". The expiry date refers to the last day of that month.
Viramune should be used within 6 months of opening the bottle.

This medicinal product does not require any special storage conditions.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Viramune contains

- The active substance is nevirapine. Each 5 ml contains 50 mg of the active substance nevirapine (as hemihydrate).
- The other ingredients are:
  carbomer,
  methyl parahydroxybenzoate,
  propyl parahydroxybenzoate,
  sorbitol,
  sucrose,
  polysorbate 80,
  sodium hydroxide and
  water.

What Viramune looks like and contents of the pack

Viramune oral suspension is a white to off-white homogenous suspension.
Viramune oral suspension is supplied in plastic bottles of suspension for oral use, with 240 ml suspension per bottle.

Viramune is also supplied as 200 mg tablets for older children and adults.

Marketing Authorisation Holder

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Manufacturer

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Other sources of information
Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu

Package leaflet: Information for the user

Viramune 400 mg prolonged-release tablets
nevirapine

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Viramune is and what it is used for

Viramune belongs to a group of medicines called antiretrovirals, used in the treatment of Human Immunodeficiency Virus (HIV-1) infection.

The active substance of your medicine is called nevirapine. Nevirapine belongs to a class of anti-HIV medicines called non-nucleoside reverse transcriptase inhibitors (NNRTIs). Reverse transcriptase is an enzyme that HIV needs in order to multiply. Nevirapine stops reverse transcriptase from working. By stopping reverse transcriptase from working, Viramune helps control HIV-1 infection.

Viramune is indicated for the treatment of HIV-1 infected adults, adolescents and children three years and above and able to swallow tablets. You must take Viramune together with other antiretroviral medicines. Your doctor will recommend the best medicines for you.

Viramune prolonged-release tablets should only be used after a two-week treatment with another type of Viramune (immediate-release tablets or suspension) unless you are currently on Viramune and are switching to the prolonged-release form.

2. What you need to know before you take Viramune

Do not take Viramune
- if you are allergic to nevirapine or any of the other ingredients of this medicine (listed in section 6 *)*.
- if you have taken Viramune before and had to stop the treatment because you suffered from:
    - severe skin rash
    - skin rash with other symptoms for example:
        - fever
        - blistering
        - mouth sores
        - inflammation of the eye

        - swelling of the face
        - general swelling
        - shortness of breath
        - muscle or joint pain
        - general feelings of illness
        - abdominal pain
    - hypersensitivity (allergic) reactions
    - inflammation of the liver (hepatitis)
- if you have severe liver disease
- if you have had to stop Viramune treatment in the past because of changes in your liver function
- if you are taking a medicine containing the herbal substance St. John's Wort (*Hypericum perforatum*). This herbal substance may stop Viramune from working properly.

Warnings and precautions
Talk to your doctor or pharmacist before taking Viramune.
During the first 18 weeks of treatment with Viramune it is very important that you and your doctor watch out for signs of liver or skin reactions. These can become severe and even life threatening. You are at greatest risk of such a reaction during the first 6 weeks of treatment.

If you experience severe rash or hypersensitivity (allergic reactions that may appear in the form of rash) accompanied by other side effects such as
- **fever,**
- **blistering,**
- **mouth sores,**
- **inflammation of the eye,**
- **swelling of the face,**
- **general swelling,**
- **shortness of breath,**
- **muscle or joint pain,**
- **general feelings of illness,**
- **or abdominal pain**

YOU SHOULD DISCONTINUE TAKING VIRAMUNE AND YOU MUST CONTACT your doctor IMMEDIATELY as such reactions can be potentially life-threatening or lead to death.
If you ever have only mild rash symptoms without any other reaction please inform your doctor immediately, who will advise you whether you should stop taking Viramune.

If you experience symptoms suggesting damage of the liver, such as
- **loss of appetite,**
- **feeling sick (nausea),**
- **vomiting,**
- **yellow skin (jaundice),**
- **abdominal pain**

you should discontinue taking Viramune and must contact your doctor immediately.

If you develop severe liver, skin or hypersensitivity reactions whilst taking Viramune, NEVER TAKE VIRAMUNE again without referring to your doctor.
You must take the dose of Viramune as prescribed by your doctor. This is especially important within the first 14 days of treatment (see more information in "*How to take Viramune*").

The following patients are at increased risk of developing liver problems:
- women
- infected with hepatitis B or C
- abnormal liver function tests
- treatment-naïve patients with higher CD4 cell counts at the start of Viramune therapy (women more than 250 cells/mm^3, men more than 400 cells/mm^3)
- pre-treated patients with detectable HIV-1 plasma viral load and higher CD4 cell counts at the

start of Viramune therapy (women more than 250 cells/mm³, men more than 400 cells/mm³)

In some patients with advanced HIV infection (AIDS) and a history of opportunistic infection (AIDS defining illness), signs and symptoms of inflammation from previous infections may occur soon after anti-HIV treatment is started. It is believed that these symptoms are due to an improvement in the body's immune response, enabling the body to fight infections that may have been present with no obvious symptoms. If you notice any symptoms of infection, please inform your doctor immediately.

In addition to the opportunistic infections, autoimmune disorders (a condition that occurs when the immune system attacks healthy body tissue) may also occur after you start taking medicines for the treatment of your HIV infection. Autoimmune disorders may occur many months after the start of treatment. If you notice any symptoms of infection or other symptoms such as muscle weakness, weakness beginning in the hands and feet and moving up towards the trunk of the body, palpitations, tremor or hyperactivity, please inform your doctor immediately to seek necessary treatment.

Changes of body fat may occur in patients receiving combination antiretroviral therapy. Contact your doctor if you notice changes in body fat (see section 4 "*Possible side effects"*).

Some patients taking combination antiretroviral therapy may develop a bone disease called osteonecrosis (death of bone tissue caused by loss of blood supply to the bone). The length of combination antiretroviral therapy, corticosteroid use, alcohol consumption, severe weakness of the immune system and higher body mass index may be some of the many risk factors for developing this disease. Signs of osteonecrosis are joint stiffness, aches and pains (especially of the hip, knee and shoulder) and difficulty in movement. If you notice any of these symptoms please inform your doctor.

If you are taking nevirapine and zidovudine concomitantly please inform your doctor since he might need to check your white blood cells.

Do not take Viramune after an exposure to HIV unless you have been diagnosed with HIV and instructed to do so by your doctor.

Prednisone should not be used to treat a rash related to Viramune.

If you are taking oral contraceptives (e.g. „pill") or other hormonal methods of birth control during treatment with Viramune, you should use a barrier contraception (e.g. condoms) in addition to prevent pregnancy and further HIV transmission.
If you are receiving post-menopausal hormone therapy, ask your doctor for advice before taking this medicine.

If you are taking or are prescribed rifampicin to treat tuberculosis please inform your doctor before taking this medicine with Viramune.

Viramune prolonged-release tablets or parts of tablets may occasionally be passed and seen in the stool (faeces). These may look like whole tablets, but have not been found to affect the efficacy of nevirapine.

Children and adolescents
Viramune 400 mg prolonged-release tablets can be taken by children if they:

- are ≥ 8 years of age and weigh 43.8 kg or more
- are older than 3 years of age and below 8 years of age and weigh 25 kg or more
- have a body surface area of 1.17 square metres or above.

For smaller children an oral suspension liquid form is available.

Other medicines and Viramune
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other

medicines. Inform your doctor about all other medicines you are taking before you start taking Viramune. Your doctor might need to monitor whether your other medicines are still working and adjust doses. Carefully read the package leaflet of all other HIV medicines you are taking in combination with Viramune.

It is particularly important that you tell your doctor if you are taking or have recently taken:

- St. John's Wort (*Hypericum perforatum*, medicine to treat depression)
- rifampicin (medicine to treat tuberculosis)
- rifabutin (medicine to treat tuberculosis)
- macrolides e.g. clarithromycin (medicine to treat bacterial infections)
- fluconazole (medicine to treat fungal infections)
- ketoconazole (medicine to treat fungal infections)
- itraconazole (medicine to treat fungal infections)
- methadone (medicine used for treatment of opiate addicts)
- warfarin (medicine to reduce blood clotting)
- hormonal contraceptives (e.g. the "pill")
- atazanavir (another medicine to treat HIV-infection)
- lopinavir/ritonavir (another medicine to treat HIV-infection)
- fosamprenavir (another medicine to treat HIV-infection)
- efavirenz (another medicine to treat HIV-infection)
- etravirine (another medicine to treat HIV-infection)
- rilpivirine (another medicine to treat HIV-infection)
- zidovudine (another medicine to treat HIV-infection)
- elvitegravir/cobicistat (another medicine to treat HIV-infection)

Your doctor will carefully monitor the effect of Viramune and any of these medicines if you are taking them together.

Taking Viramune with food and drink
There are no restrictions on taking Viramune with food and drink.

Pregnancy and breast-feeding
If you are pregnant or think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Breast-feeding ***is not recommended*** in women living with HIV because HIV infection can be passed on to the baby in breast milk.
If you are breast-feeding, or thinking about breast-feeding, you ***should discuss it with*** your doctor ***as soon as possible***

Driving and using machines
You may experience fatigue when taking Viramune. Use caution when engaging in activities such as driving, using any tools or machines. If you experience fatigue you should avoid potentially hazardous tasks such as driving or using any tools or machines.

Viramune contains lactose
Viramune prolonged-release tablets contain lactose (milk sugar).
If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

3. How to take Viramune

You should not use Viramune on its own. You must take it with at least two other antiretroviral medicines. Your doctor will recommend the best medicines for you.

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

Dosage:

Adults:
The dose is one 200 mg Viramune tablet per day for the first 14 days of treatment ("lead-in" period). A separate treatment initiation pack with 200 mg Viramune tablets is available for this lead-in period. After 14 days, the usual dose is one 400 mg prolonged-release tablet once a day.

It is very important that you take only one Viramune tablet a day for the first 14 days ("lead-in" period). If you have any rash during this period, do not start taking Viramune prolonged-release tablets but consult your doctor.

The 14-day "lead-in" period has been shown to lower the risk of skin rash.

Patients who are already on immediate-release tablets or oral suspension can switch to prolonged-release tablets without lead-in period.

As Viramune must always be taken together with other HIV antiretroviral medicines, you should follow the instructions for your other medicines carefully. These are supplied in the package leaflets for those medicines.

Viramune is also available as an oral suspension (for all age, weight and BSA groups).

You should continue to take Viramune for as long as instructed by your doctor.

As explained in *'Warnings and precautions'*, above, your doctor will monitor you with liver tests or for undesirable effects such as rash. Depending on the outcome your doctor may decide to interrupt or stop your Viramune treatment. Your doctor might then decide to restart you on a lower dose.

If you have a renal or hepatic dysfunction of any degree please use only Viramune 200 mg tablets or Viramune 50 mg/5 ml oral suspension.

Only take Viramune prolonged-release tablets by mouth. Do not chew your prolonged-release tablets. You may take Viramune with or without food.

If you take more Viramune than you should
Do not take more Viramune than prescribed by your doctor and described in this leaflet. There is at present little information on the effects of Viramune overdose. Consult your doctor if you have taken more Viramune than you should.

If you forget to take Viramune
Try not to miss a dose. If you notice you missed a dose within 12 hours of when it was due, take the missed dose as soon as possible. If it has been more than 12 hours since the dose was due only take the next dose at the usual time.

If you stop taking Viramune
Taking all doses at the appropriate times:
- greatly increases the effectiveness of your combination antiretroviral medicines
- reduces the chances of your HIV infection becoming resistant to your antiretroviral medicines.

It is important that you continue taking Viramune correctly, as described above, unless your doctor instructs you to stop.

If you stop taking Viramune for more than 7 days your doctor will instruct you to start the 14 day 'lead-in' period with Viramune tablets (described above) once again, before returning to the once daily dose with Viramune prolonged-release tablets.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

During HIV therapy there may be an increase in weight and in levels of blood lipids and glucose. This is partly linked to restored health and life style, and in the case of blood lipids sometimes to the HIV medicines themselves. Your doctor will test for these changes.

Like all medicines, this medicine can cause side effects, although not everybody gets them.

As mentioned in *'Warnings and precautions'*, above, the most important side effects of Viramune are severe and life threatening skin reactions and serious liver damage. These reactions occur mainly in the first 18 weeks of treatment with Viramune. This is therefore an important period which requires close monitoring by your doctor.

If you ever observe any rash symptoms, inform your doctor immediately.

When rash occurs it is normally mild to moderate. However, in some patients a rash, which appears as a blistering skin reaction, can be severe or life-threatening (Stevens-Johnson syndrome and toxic epidermal necrolysis) and deaths have been recorded. Most of the cases of both severe rash and mild/moderate rash occur in the first six weeks of treatment.

If rash occurs and you also feel sick, you must stop treatment and visit your doctor immediately.

Hypersensitivity (allergic) reactions can occur. Such reactions may appear in the form of anaphylaxis (a severe form of allergic reaction) with symptoms such as:
- rash
- swelling of the face
- difficulty breathing (bronchial spasm)
- anaphylactic shock

Hypersensitivity reactions can also occur as rash with other side effects such as:
- fever
- blistering of your skin
- mouth sores
- inflammation of the eye
- swelling of the face
- general swelling
- shortness of breath
- muscle or joint pain
- a reduction in the numbers of your white blood cells (granulocytopenia)
- general feelings of illness
- severe problems with liver or kidneys (liver or kidney failure).

Tell your doctor immediately if you experience rash and any of the other side effects of a hypersensitivity (allergic) reaction. Such reactions can be life-threatening.

Abnormal liver functioning has been reported with the use of Viramune. This includes some cases of inflammation of the liver (hepatitis), which can be sudden and intense (fulminant hepatitis), and liver failure, which can be both fatal.

Tell your doctor if you experience any of the following clinical symptoms of liver damage:
- loss of appetite
- feeling sick (nausea)
- vomiting
- yellow skin (jaundice)
- abdominal pain

The side effects described below have been experienced by patients given Viramune 200 mg tablets during the 14 day lead-in phase:

Common (may affect up to 1 in 10 people):
- rash
- fever
- headache
- abdominal pain
- feeling sick (nausea)
- loose stools (diarrhoea)
- feeling tired (fatigue)

Uncommon (may affect up to 1 in 100 people):
- allergic reactions (hypersensitivity)
- allergic reaction characterized by rash, swelling of the face, difficulty breathing (bronchial spasm) or anaphylactic shock
- drug reaction with systemic symptoms (drug reaction with eosinophilia and systemic symptoms)
- sudden and intense inflammation of the liver (fulminant hepatitis)
- severe and life-threatening skin rashes (Stevens Johnson Syndrome/toxic epidermal necrolysis)
- yellow skin (jaundice)
- hives (urticaria)
- fluid under the skin (angioneurotic oedema)
- vomiting
- muscle pain (myalgia)
- joint pain (arthralgia)
- decreased numbers of white blood cells (granulocytopenia)
- abnormal liver function tests
- decreased blood phosphorus
- increased blood pressure

Rare (may affect up to 1 in 1000 people):
- inflammation of the liver (hepatitis)
- decreased numbers of red blood cells (anaemia)

The side effects described below have been experienced by patients given Viramune prolonged-release tablets once daily in the maintenance phase:

Common (may affect up to 1 in 10 people):
- rash
- headache
- abdominal pain

- feeling sick (nausea)
- inflammation of the liver (hepatitis)
- feeling tired (fatigue)
- abnormal liver function tests
- fever
- vomiting
- loose stools (diarrhoea)

Uncommon (may affect up to 1 in 100 people):
- allergic reactions (hypersensitivity)
- allergic reaction characterized by rash, swelling of the face, difficulty breathing (bronchial spasm) or anaphylactic shock
- drug reaction with systemic symptoms (drug reaction with eosinophilia and systemic symptoms)
- sudden and intense inflammation of the liver (fulminant hepatitis)
- severe and life-threatening skin rashes (Stevens Johnson Syndrome/toxic epidermal necrolysis)
- decreased numbers of red blood cells (anaemia)
- decreased numbers of white blood cells (granulocytopenia)
- yellow skin (jaundice)
- hives (urticaria)
- fluid under the skin (angioneurotic oedema)
- muscle pain (myalgia)
- joint pain (arthralgia)
- decreased blood phosphorus
- increased blood pressure

The following events have also been reported when Viramune has been used in combination with other antiretroviral agents:
- decreased numbers of red blood cells or platelets
- inflammation of the pancreas
- decrease in or abnormal skin sensations

These events are commonly associated with other antiretroviral 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 treatment with Viramune.

Additional side effects in children and adolescents
A reduction in white blood cells (granulocytopenia) can occur, which is more common in children. A reduction in red blood cells (anaemia), which may be related to nevirapine therapy, is also more commonly observed in children. As with rash symptoms, please inform your doctor of any side effects.

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Viramune

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and on the blister or bottle after "EXP". The expiry date refers to the last day of that month.
Viramune should be used within 2 months of opening the bottle.

This medicine does not require any special storage conditions.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Viramune contains

- The active substance is nevirapine. Each prolonged-release tablet contains 400 mg nevirapine.
- The other ingredients are lactose (as monohydrate), hypromellose, iron oxide yellow and magnesium stearate.

What Viramune looks like and contents of the pack

Yellow, oval, biconvex prolonged-release tablets. The prolonged-release tablets are about 9.3 x 19.1 mm, debossed with V04 on one side and the company symbol on the other side. Viramune 400 mg prolonged-release tablets are supplied in blisters, with 30 or 90 prolonged-release tablets per carton. Alternatively, 30 Viramune 400 mg prolonged-release tablets are supplied in bottles. Not all pack size may be marketed.

Viramune is also available as an oral suspension or as tablets.

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Other sources of information
Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu