VIRAMUNE 200 MG TABLETS

Nevirapine

PRESCRIBING INFORMATION

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 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 (nevirapine) is a non nucleoside reverse transcriptase inhibitor of HIV-1. It is indicated for use in combination with other antiretroviral agents for the treatment of HIV-1 infection (see section 4.4). This indication is based on analyses of changes in surrogate endpoints. At present, there are no results from controlled clinical trials evaluating the effect of Viramune in combination with other antiretroviral agents on the clinical progression of HIV-1 infection, such as the incidence of opportunistic infections or survival.
Resistant virus emerges rapidly and uniformly when Viramune is administered as monotherapy. Therefore, Viramune should always be administered in combination with at least one additional antiretroviral agent.

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 one additional antiretroviral agent.

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).

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 one 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 hepatoxicity, 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 > 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 > 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.

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While effective viral suppression with antiretroviral therapy has been proven to substantially reduce the risk of sexual transmission, a residual risk cannot be excluded. Precautions to prevent transmission should be taken in accordance with national guidelines.

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, delavirdine, etravirine, rilpivirine, elvitegravir (in combination with cobicistat), atazanavir (in combination with ritonavir), boceprevir; fosamprenavir (if not co-administered with low dose ritonavir) (please 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 of 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).
Delavirdine	Interaction has not been studied.	The concomitant administration of Viramune with NNRTIs is not recommended (see section 4.4).
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)	Darunavir and Viramune can be co-administered without dose adjustments.

	Nevirapine C_{min} ↑ 1.47 (1.20-1.82) Nevirapine C_{max} ↑ 1.18 (1.02-1.37)	
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) 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 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	Adefovir and Viramune may be coadministered without dose adjustments.

	involved in human drug metabolism and is excreted renally. No clinically relevant drug-drug interaction is expected.	
Boceprevir	Boceprevir is partly metabolized by CYP3A4/5. Co-administration of boceprevir with medicines that induce or inhibit CYP3A4/5 could increase or decrease exposure. Plasma trough concentrations of boceprevir were decreased when administered with an NNRTI with a similar metabolic pathway as nevirapine. The clinical outcome of this observed reduction of boceprevir trough concentrations has not been directly assessed.	It is not recommended to coadminister boceprevir and Viramune (see section 4.4).
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.
Telaprevir	Telaprevir is metabolised in the liver by CYP3A and is a P-glycoprotein substrate. Other enzymes may be involved in the metabolism. Co-administration of telaprevir and medicinal products that induce CYP3A and/or P-gp may decrease telaprevir plasma concentrations. No drug-drug interaction study of telaprevir with nevirapine has been conducted, however, interaction studies of telaprevir with an NNRTI with a similar metabolic pathway as nevirapine demonstrated reduced levels of both. Results of DDI studies of telaprevir with efavirenz indicate that caution should be exercised when co-administering telaprevir with P450 inducers.	Caution should be exercised when co-administering telaprevir with nevirapine. If co-administered with Viramune, an adjustment in the telaprevir dose should be considered.
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
Nevirapine readily crosses the placenta and is found in breast milk.

It is recommended that HIV-infected mothers do not breast-feed their infants to avoid risking postnatal transmission of HIV and that mothers should discontinue breast-feeding if they are receiving nevirapine.

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 hepatoxicity, 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

You can report side effects to the Ministry of Health by following the link 'Reporting Side Effects of Drug Treatment' on the Ministry of Health home page (www.health.gov.il) which links to an online form for reporting side effects. You can also use this link:
https://sideeffects.health.gov.il

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 delavirdine and 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 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 pharamcokinetics (see section 4.4).

Gender and elderly
In the multinational 2NN study, 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 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

Lactose monohydrate
Microcrystalline cellulose
Povidone
Sodium starch glycolate
Colloidal silicon dioxide
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Packs of 60 tablets.

6.6 Special precautions for disposal

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

7. MANUFACTURER

Boehringer Ingelheim Pharma GmbH & Co.Kg
Binger strasse 173,55216, ingelheim am rhein, Germany

8. MARKETING AUTHORISATION HOLDER

Boehringer Ingelheim Israel Ltd.
Medinat Hayehudim St.
89 B.O.X 4124 4676672 Herzliya Pituach

9. MARKETING AUTHORISATION NUMBER

119-78-30052-00

Revised in April 2020