

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Nevirapine 200mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 200 mg of anhydrous nevirapine.

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Tablet.

Off-white to pale yellow coloured, capsule shaped, biconvex tablets, debossed with 'H' on one side and '7' on the other side with breakline on both sides. The tablets are approximately 14.7mm in length and 5.7mm in width. The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Nevirapine 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 4.4.).

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

4.2 Posology and method of administration

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

Posology

Patients 16 years and older

The recommended dose of Nevirapine 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 Nevirapine dose increased until the rash has resolved. The isolated rash should be closely monitored (please refer to 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 Nevirapine therapy (see section 4.4).

Special populations

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 \geq 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

Nevirapine 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 m² 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 m².

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. Nevirapine 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

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

Nevirapine 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 events 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/mm³ in adult females and >400/mm³ in adult males) at the initiation of nevirapine therapy are associated with a greater risk of hepatic adverse events if the patient has detectable plasma HIV-1 RNA - i.e. a concentration \geq 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/mm³ or in adult males with CD4 cell counts greater than 400 cells/mm³, 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 dosage 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 Nevirapine 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 or any other nevirapine-containing product 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, 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 events 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 events. Women have a three fold higher risk than men for symptomatic, often rash-associated, hepatic reactions (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 reactions 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/mm³ had a 12 fold higher risk of symptomatic hepatic adverse events compared to women with CD4 counts < 250 cells/mm³ (11.0% versus 0.9%). An increased risk was observed in men with detectable HIV-1 RNA in plasma and CD4 counts > 400 cells/mm³ (6.3% versus 1.2% for men with CD4 counts < 400 cells/mm³). 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. 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 dosage regimen of 200 mg/day for 14 days followed by 400 mg/day. In these cases, more frequent liver monitoring is required. If liver function abnormalities recur, 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. Nevirapine must not be readministered to patients who have required permanent discontinuation for clinical hepatitis due to nevirapine.

Liver Disease

The safety and efficacy of nevirapine has not been established in patients with significant underlying liver disorders. Nevirapine 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 events. In the case of concomitant antiviral therapy for hepatitis B or C, please refer also to the relevant product information for these medicinal products.

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

Other warnings

Post-Exposure-Prophylaxis: Serious hepatotoxicity, including liver failure requiring transplantation, has been reported in HIV-uninfected individuals receiving multiple doses of nevirapine in the setting of post-exposure-prophylaxis (PEP), an unapproved use. The use of nevirapine 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.

Combination therapy with nevirapine has not been shown to eliminate the risk of transmission of HIV-1 to others through sexual contact or contaminated blood.

Hormonal methods of birth control other than Depo-medroxyprogesterone acetate (DMPA) should not be used as the sole method of contraception in women taking Nevirapine, 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, nevirapine 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, Nevirapine 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 jiroveci* 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 Nevirapine is not recommended: efavirenz, ketoconazole, delavirdine, etravirine, rilprvirine, elvitegravir (in combination with cobicistat_, atazanavir (in combination with ritonavir), boceprevir, fosameprenavir (if not co-administered with low dose ritonavir) (please also refer to 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.

4.5 Interaction with other medicinal products and other forms of interactions

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		
<i>NRTIs</i>		
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 Nevirapine can be co-administered without dose adjustments.
Emtricitabine	Emtricitabine is not an inhibitor of human CYP 450 enzymes	Nevirapine and emtricitabine may be coadministered without dose adjustments.
Abacavir	IN human liver microsomes, abacavir did not inhibit cytochrome P450 isoforms.	Nevirapine 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 Nevirapine 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} ↔	Stavudine and Nevirapine can be co-administered without dose adjustments.

	0.94 (0.86-1.03) Nevirapine: compared to historical controls, levels appeared to be unchanged.	
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 Nevirapine 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 its pharmacokinetics.	Zidovudine and Nevirapine 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 Nevirapine (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 Nevirapine 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 Nevirapine with NNRTIs is not recommended (see section 4.4).

Rilpivirine	Interaction has not been studied.	The concomitant administration of Nevirapine with NNRTIs is not recommended (see section 4.4).
PIs		
Atazanavir/ritonavir 300/100 mg QD 400/100 mg QD	<u>Atazanavir/r</u> 300/100mg: 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</u> 400/100mg: 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 Nevirapine (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 Nevirapine 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} ↑	It is not recommended to co-administer fosamprenavir and Nevirapine if fosamprenavir is not co-administered with ritonavir (see section 4.4).

	1.25 (1.14-1.37)	
Fosamprenavir/ritonavir 700/100 mg BID	<p>Amprenavir AUC ↔ 0.89 (0.77-1.03)</p> <p>Amprenavir C_{min} ↓ 0.81 (0.69-0.96)</p> <p>Amprenavir C_{max} ↔ 0.97 (0.85-1.10)</p> <p>Nevirapine AUC ↑ 1.14 (1.05-1.24)</p> <p>Nevirapine C_{min} ↑ 1.22 (1.10-1.35)</p> <p>Nevirapine C_{max} ↑ 1.13 (1.03-1.24)</p>	Fosamprenavir/ritonavir and Nevirapine can be co-administered without dose adjustments
Lopinavir/ritonavir (capsules) 400/100 mg BID	<p><u>Adult patients:</u></p> <p>Lopinavir AUC ↓ 0.73 (0.53-0.98)</p> <p>Lopinavir C_{min} ↓ 0.54 (0.28-0.74)</p> <p>Lopinavir C_{max} ↓ 0.81 (0.62-0.95)</p>	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 Nevirapine. Dose adjustment of Nevirapine is not required when co-administered with lopinavir.
Lopinavir/ritonavir (oral solution) 300/75 mg/m ² BID	<p><u>Paediatric patients:</u></p> <p>Lopinavir AUC ↓ 0.78 (0.56-1.09)</p> <p>Lopinavir C_{min} ↓ 0.45 (0.25-0.82)</p> <p>Lopinavir C_{max} ↓ 0.86 (0.64-1.16)</p>	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 Nevirapine, particularly for patients in whom reduced susceptibility to lopinavir/ritonavir is suspected.
Ritonavir 600 mg BID	<p>Ritonavir AUC ↔ 0.92 (0.79-1.07)</p> <p>Ritonavir C_{min} ↔ 0.93 (0.76-1.14)</p> <p>Ritonavir C_{max} ↔ 0.93 (0.78-1.07)</p> <p>Nevirapine: Co-administration of ritonavir does not lead to any clinically relevant change in nevirapine plasma levels.</p>	Ritonavir and Nevirapine 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	Saquinavir/ritonavir and Nevirapine can be co-administered without dose adjustments.

	nevirapine	
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 Nevirapine 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 Nevirapine 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 Nevirapine 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 Nevirapine.	Coadministration of Nevirapine 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 Nevirapine can be co-administered without dose adjustments.

ANTIBIOTICS

Clarithromycin 500 mg BID	<p>Clarithromycin AUC ↓ 0.69 (0.62-0.76)</p> <p>Clarithromycin C_{min} ↓ 0.44 (0.30-0.64)</p> <p>Clarithromycin C_{max} ↓ 0.77 (0.69-0.86)</p> <p>Metabolite 14-OH clarithromycin AUC ↑ 1.42 (1.16-1.73)</p> <p>Metabolite 14-OH clarithromycin C_{min} ↔ 0 (0.68-1.49)</p> <p>Metabolite 14-OH clarithromycin C_{max} ↑ 1.47 (1.21-1.80)</p> <p>Nevirapine AUC ↑ 1.26</p> <p>Nevirapine C_{min} ↑</p>	Clarithromycin exposure was significantly decreased, 14-OH metabolite exposure increased. Because the clarithromycin active metabolite has reduced activity against <i>Mycobacterium avium-intracellulare complex</i> overall activity against the pathogen may be altered. Alternatives to clarithromycin, such as azithromycin should be considered. Close monitoring for hepatic abnormalities is recommended
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	1.28 Nevirapine C_{max} ↑ 1.24 compared to historical controls.	
Rifabutin 150 or 300 mg QD	<p>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)</p> <p>Metabolite 25-O-desacetylri- fabutin AUC ↑ 1.24 (0.84-1.84) Metabolite 25-O-desacetylri- fabutin C_{min} ↑ 1.22 (0.86-1.74) Metabolite 25-O-desacetylri- fabutin C_{max} ↑ 1.29 (0.98-1.68)</p> <p>A clinically not relevant increase in the apparent clearance of nevirapine (by 9%) compared to historical data was reported.</p>	<p>No significant effect on rifabutin and nevirapine mean PK parameters is seen. Rifabutin and Nevirapine can be co-administered without dose adjustments. However, due to the high intersubject 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.</p>
Rifampicin 600 mg QD	<p>Rifampicin AUC ↔ 1.11 (0.96-1.28) Rifampicin C_{min} ND Rifampicin C_{max} ↔ 1.06 (0.91-1.22)</p> <p>Nevirapine AUC ↓ 0.42 Nevirapine C_{min} ↓ 0.32 Nevirapine C_{max} ↓ 0.50 compared to historical controls.</p>	<p>It is not recommended to co-administer rifampicin and Nevirapine (see section 4.4). Physicians needing to treat patients co-infected with tuberculosis and using a nevirapine containing regimen may consider co-administration of rifabutin instead.</p>

ANTIFUNGALS

Fluconazole 200 mg QD	<p>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)</p> <p>Nevirapine: exposure: ↑100% compared with historical data where nevirapine was administered alone.</p>	Because of the risk of increased exposure to nevirapine, caution should be exercised if the medicinal products are given concomitantly and patients should be monitored closely.
Itraconazole 200 mg QD	<p>Itraconazole AUC ↓ 0.39 Itraconazole C_{min} ↓ 0.13 Itraconazole C_{max} ↓ 0.62</p> <p>Nevirapine: there was no significant difference in Nevirapine pharmacokinetic parameters.</p>	A dose increase for itraconazole should be considered when these two agents are administered concomitantly.
Ketoconazole 400 mg QD	<p>Ketoconazole AUC ↓ 0.28 (0.20-0.40) Ketoconazole C_{min} ND Ketoconazole C_{max} ↓ 0.56 (0.42-0.73)</p> <p>Nevirapine: plasma levels: ↑ 1.15-1.28 compared to historical controls.</p>	It is not recommended to co-administer ketoconazole and Nevirapine (see section 4.4).

ANTIVIRALS FOR CHRONIC HEPATITIS B AND C

Adefovir	Results of <i>in vitro</i> 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 Nevirapine may be co-administered without dose adjustments.
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 administration with an NNRTI with a similar metabolic pathway as nevirapine. The clinical outcome of this observed reduction of boceprevir through concentrations has not been directly assessed.	It is not recommended to co-administer boceprevir and Nevirapine (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 Nevirapine may be co-administered 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 Nevirapine may be co-administered without dose adjustments.
Ribavirin	Results of <i>in vitro</i> 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 Nevirapine may be co-administered 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	Caution should be exercised when co-administering telaprevir with nevirapine. If co-administered with Nevirapine, an adjustment in the telaprevir dose should be considered.

	<p>medicinal products that induce CYP3A and/or P-gp may decrease delaprevir 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.</p>	
Telbivudine	<p>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.</p>	<p>Telbivudine and Nevirapine may be co-administered without dose adjustments.</p>
ANTACIDS		

Cimetidine	<p>Cimetidine: no significant effect on cimetidine PK parameters is seen.</p> <p>Nevirapine C_{min} ↑ 1.07</p>	Cimetidine and Nevirapine can be co-administered without dose adjustments.
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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.
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CONTRACEPTIVES

Depo-medroxyprogesterone acetate (DMPA) 150 mg every 3 months	<p>DMPA AUC ↔ DMPA C_{min} ↔ DMPA C_{max} ↔</p> <p>Nevirapine AUC ↑ 1.20 Nevirapine C_{max} ↑ 1.20</p>	Nevirapine co-administration did not alter the ovulation suppression effects of DMPA. DMPA and Nevirapine can be co-administered without dose adjustments.
Ethinyl estradiol (EE) 0.035 mg	<p>EE AUC ↓ 0.80 (0.67 - 0.97) EE C_{min} ND EE C_{max} ↔ 0.94 (0.79 - 1.12)</p>	Oral hormonal contraceptives should not be used as the sole method of contraception in women taking Nevirapine (see section 4.4). Appropriate doses for hormonal contraceptives (oral or other forms of application) other than DMPA in combination with Nevirapine 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/OPIODS		
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 Nevirapine 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 (<i>Hypericum perforatum</i>). This is due to induction of drug metabolism enzymes and/or transport proteins by St. John's Wort.	Herbal preparations containing St. John's Wort and Nevirapine 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 Nevirapine 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 lactationWomen 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 medications (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/mm³ 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/mm³ 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.

Breastfeeding

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 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 Nevirapine therapy, across all clinical trials, 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 rash 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 nevirapine have been reported. The frequencies estimated are based on pooled clinical study data for adverse reactions considered related to Nevirapine treatment.

Frequency is defined using the following convention: very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ 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 rash with eosinophilia and systemic symptoms

Nervous system disorders

Common headache

Gastrointestinal disorders

Common nausea, vomiting, abdominal pain, diarrhea

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 coadministration 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 events 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 (see section 4.4). 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 Nevirapine 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 rash 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 rash 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 trial 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 trial (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 of suspected adverse reactions after authorization 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 HPRA Pharmacovigilance, Earlsfort Terrace, IRL-Dublin 2; Tel +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; e-mail: medsafety@hpra.ie.

4.9 Overdose

There is no known antidote for nevirapine overdose. Cases of Nevirapine 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 2mg/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 EC₅₀ 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 EC₅₀ value was 90nM. Similar EC₅₀ 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, nelfinavir, saquinavir and tipranavir, and the NRTIs abacavir, didanosine, emtricitabine, lamivudine, stavudine, tenofovir and zidovudine. The anti-HIV-1 activity of nevirapine was antagonized by the anti-HBV medicinal product adefovir and by the anti-HCV drug 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.

Phenotypic and genotypic changes in HIV-1 isolates from treatment-naïve patients receiving either nevirapine (n=24) or nevirapine and ZDV (n=14) were monitored in Phase I/II studies over 1 to ≥12 weeks. After 1 week of nevirapine monotherapy, isolates from 3/3 patients had decreased susceptibility to nevirapine in cell culture. One or more of the RT mutations resulting in amino acid substitutions K103N, V106A, V108I, Y181C, Y188C and G190A were detected in HIV-1 isolates from some patients as early as 2 weeks after therapy initiation. By week eight of nevirapine monotherapy, 100% of the patients tested (n=24) had HIV-1 isolates with a >100-fold decrease in susceptibility to nevirapine in cell culture compared to baseline, and had one or more of the nevirapine-associated RT resistance mutations. Nineteen of these patients (80%) had isolates with Y181C substitutions regardless of dose.

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

Nevirapine 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.

1216 antiretroviral-therapy naïve patients with plasma HIV-1 RNA > 5,000 copies/ml at baseline were assigned to nevirapine 400 mg once daily, nevirapine 200 mg twice daily, efavirenz 600 mg once daily, or nevirapine (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 log₁₀ 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 (new Centers for Disease Control and Prevention grade C event or death), or change of allocated treatment.

Median age was 34 years and about 64% were male patients, median CD4 cell count was 170 and 190 cells per mm³ in the nevirapine 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 nevirapine twice daily and the efavirenz treatment groups. Details of the primary efficacy comparison are given in table 1.

Table 1: Number of patients with treatment failure, components of treatment failure, and number of patients with plasma HIV-RNA concentration < 50 c/ml, at week 48 (Intention-To-Treat (ITT) Analysis).

	Nevirapine 200 mg twice daily (n = 387)	Efavirenz 600 mg once daily (n = 400)
Treatment failure on or before week 48, % (95% IC)	43.7% (38.7-48.8)	37.8% (33.0-42.7)
Components of failure (%)		
Virological	18.9%	15.3%
Progression	2.8%	2.5%
Change of treatment	22.0%	20.0%
Permanent change of NNRTI (n)	61	51
Temporary discontinuation of NNRTI (n)	13	8
Additional antiretroviral medicinal products (n)	1	1
Non-allowable change of NNRTI (n)	1	1
Never started ART* (n)	9	19
Plasma HIV-1 RNA concentration <50 c/mL at 48 weeks, %(95% IC)	65.4% (60.4-70.1)	70.0% (65.2-74.5)

* ART = antiretroviral therapy

Although, overall, treatment failure was numerically lower in the efavirenz group than in the nevirapine-only groups, the findings of this study show no evidence that efavirenz is superior to nevirapine twice daily in terms of treatment failure. However, equivalence within the 10% limits of these treatment groups was not shown even though the study was adequately powered for such an analysis. The nevirapine twice daily regimen and the efavirenz regimen were not significantly different (p= 0.091) in terms of efficacy as measured by incidence of treatment failure. There was also no significant difference between nevirapine twice daily and efavirenz regarding any components 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 coinfecting 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 nevirapine 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. Table 2 shows the main efficacy results of this study.

Table 2: Number of patients with treatment failure, components of treatment failure, and number of patients with plasma HIV-RNA concentration < 400 copies/ml, between week 49 to 144 (ITT analysis).

	Nevirapine 200 mg twice daily (n=224)	Efavirenz 600 mg once daily (n=223)
Treatment failure (%)	35.7	35.0
Virologic failure (>400 c/ml) (%)	5.8	4.9
pVL <400 c/ml at week 144 (%)	87.2	87.4
CD4 increase (cells/mm ³)	+135	+130
Disease progression / death (%)	5.8	6.3

A durable response to nevirapine for at least three years was documented in this study. Equivalence within a 10% range was demonstrated between nevirapine 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 nevirapine 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 nevirapine, 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 nevirapine (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. The main results regarding the primary endpoint are given in table 3.

Table 3: Outcome of Therapy 12 months after switch from PI based therapy

	Nevirapine (n=155)	Efavirenz (n=156)	Abacavir (n=149)
	Number of patients		
Death	1	2	1
Progression to AIDS	0	0	2
Virologic failure	14	7	16
While taking medicinal product	8	5	16
After switching medicinal product	6	2	0
Lost to follow-up	3	6	8
Switched study medication without virologic failure	20	29	9
Response; still taking study medication at 12 months	117	112	113

At 12 months, the Kaplan–Meier estimates of the likelihood of reaching the endpoint were 10 % in the nevirapine 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 (see table below).

Number of patients who had one or more adverse events *									
Adverse Event	Nevirapine (N=155)			Efavirenz (N=156)			Abacavir (N=149)		
	Any adverse event	Grade 3 or 4 adverse event	Adverse event leading to discontinuation	Any adverse event	Grade 3 or 4 adverse event	Adverse event leading to discontinuation	Any adverse event	Grade 3 or 4 adverse event	Adverse event leading to discontinuation
	Number of patients (percent)								
Clinical									
- Neuropsychiatric	11	6	6	48	22	19	14	1	0
- Cutaneous	20	13	12	11	3	3	7	0	0
- Gastrointestinal	6	2	0	8	4	4	12	2	1
- Systemic**	7	1	1	5	2	0	10	8	8
- Other	25	8	1	11	5	1	12	3	0
Laboratory									
- Increased aminotransferase levels	12	6	4	4	1	0	5	1	0

- Hyperglycemia	2	2	2	2	2	0	1	1	0
Total	83 (54)***	38	26 (17)****	89 (57)***	39	27 (17) ****	61 (41)***	16	9 (6)****

* A grade 3 event was defined as severe, and a grade 4 event as life-threatening

** Systemic adverse events included hypersensitivity reactions

*** P=0.02 by the chi-square test

**** P=0.01 by the chi-square test

Perinatal Transmission

The HIVNET 012 study conducted in Kampala (Uganda) evaluated the efficacy of nevirapine to prevent vertical transmission of HIV-1 infection. Mothers received only study antiretroviral therapy during these trials. Mother-infant pairs were randomised to receive oral nevirapine (mother: 200 mg at the onset of labour; infant: 2 mg/kg within 72 hours of birth), or an ultra-short oral zidovudine regimen (mother: 600 mg at the onset of labour and 300 mg every 3 hours until delivery; infant: 4 mg/kg twice daily for 7 days). The cumulative HIV-1 infant infection rate at 14-16 weeks was 13.1% (n = 310) in the nevirapine group, versus 25.1% (n = 308 in the ultra-short zidovudine group (p = 0.00063).

From a study in which infants of HIV infected mothers received either placebo or single dose nevirapine, 30 HIV infected infants, 15 who have received placebo and 15 who have received nevirapine, were subsequently treated with nevirapine combined with other anti-retroviral drugs. Virologic failure after 6 months of treatment with nevirapine combined with other anti-retroviral medicinal products occurred in significantly more infants who had previously received a single dose of nevirapine (10 of 15) than in infants who had received placebo previously (1 of 15). This indicates that in infants previously treated with single-dose nevirapine alone for prevention of mother to child transmission of HIV-1, the efficacy of nevirapine as part of a combination therapy which they receive for their own health may be reduced.

In a study in which women who had received single dose nevirapine for prevention of mother-to-child transmission were treated with nevirapine combined with other anti-retroviral drugs for their own health, 29 of 123, or 24% experienced virologic failure, and five (38%) of 13 women with HIV-1 detected baseline resistance to nevirapine experienced virologic failure. This indicates that in women previously treated with single-dose nevirapine alone for prevention of mother to child transmission of HIV-1, the efficacy of nevirapine as part of a combination therapy which the women receive for their own health may be reduced.

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

The clinical relevance of these data in European populations has not been established. Furthermore, in the case nevirapine 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

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 (V_{dss}) 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% ($\pm 5\%$) 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 ^{14}C -nevirapine, approximately $91.4 \pm 10.5\%$ of the radiolabelled dose was recovered, with urine ($81.3 \pm 11.1\%$) representing the primary route of excretion compared to faeces ($10.1 \pm 1.5\%$). Greater than 80% of the radioactivity in urine was made up of glucuronide conjugates of hydroxylated metabolites. Thus cytochrome P450 metabolism, glucuronide conjugation, and urinary excretion of glucuronidated metabolites represent the primary route of nevirapine biotransformation and elimination in humans. Only a small fraction ($< 5\%$) of the radioactivity in urine (representing $< 3\%$ of the total dose) was made up of parent compound; therefore, renal excretion plays a minor role in elimination of the parent compound.

Nevirapine has been shown to be an inducer of hepatic cytochrome P450 metabolic enzymes. The pharmacokinetics of autoinduction are 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.

Special populations:

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

Hepatic dysfunction: 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 nevirapine 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 drug 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).

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 has been derived from two major sources: a 48 week paediatric trial 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/m² BID (after a two-week lead in at 150 mg/m² 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. In reproductive toxicology studies, evidence of impaired fertility was seen in rats.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline Cellulose
Maize starch
Croscarmellose sodium
Povidone (K30)
Silica, colloidal anhydrous
Sodium starch glycolate (Type A)
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

PVC-Aluminium blisters containing 14 or 60 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

Wockhardt UK Limited
Ash Road North
Wrexham
LL13 9UF
United Kingdom

8 MARKETING AUTHORISATION NUMBER

PA1339/047/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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Date of last renewal: 8th May 2019

10 DATE OF REVISION OF THE TEXT

May 2019