SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Nevirapine Milpharm 400 mg Prolonged release tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each prolonged release tablet contains 400 mg nevirapine.

Excipient with known effect: Each tablet contains 383.70 mg of lactose monohydrate.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Prolonged release tablet (tablet)

Light yellow to yellow, oval, biconvex tablets debossed with “N” on one side and “400” on the other side. The size is: 19 x 9.3 mm.

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

Most of the experience with 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

Adults

The recommended dose of nevirapine for patients initiating nevirapine therapy is one 200 mg immediate-release tablet daily for the first 14 days (this lead-in period should be used because it has been found to lessen the frequency of rash), followed by one 400 mg prolonged-release tablet once daily, in combination with at least two additional antiretroviral agents.

Patients currently on a nevirapine immediate-release twice daily regimen: Patients already on a regimen of nevirapine immediate-release twice daily in combination with other antiretroviral agents can be switched to nevirapine 400 mg prolonged-release tablets once daily in combination with other antiretroviral agents without a lead-in period of nevirapine immediate-release.

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

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

Paediatric population

Children three years and older and adolescents

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

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

Children less than three years old

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

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

Dose management considerations

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

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

Patients who interrupt nevirapine dosing for more than 7 days should restart the recommended dosing regimen using the two week lead-in period of nevirapine immediate-release. There are toxicities that require interruption of nevirapine therapy (see section 4.4).

Elderly

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

Renal impairment

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

Hepatic impairment

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

Method of administration

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

4.3 Contraindications

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

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

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

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

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

4.4 Special warnings and precautions for use

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 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.

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 immediate-release administration) has been shown not to decrease the incidence of nevirapine-associated rash, and may be associated with an increase in incidence and severity of rash during the first 6 weeks of nevirapine therapy.

Some risk factors for developing serious cutaneous reactions have been identified; they include failure to follow the initial dosing of 200 mg daily during the lead-in period and a long delay between the initial symptoms and medical consultation. Women appear to be at higher risk than men of developing rash, whether receiving nevirapine or non-nevirapine containing therapy.

Patients should be instructed that a major toxicity of nevirapine is rash. They should be advised to promptly notify their physician of any rash and avoid delay between the initial symptoms and medical consultation. The majority of rashes associated with nevirapine occur within the first 6 weeks of initiation of therapy. Therefore, patients should be monitored carefully for the appearance of rash during this period.

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

Any patient experiencing severe rash or a rash accompanied by constitutional symptoms such as fever, blistering, oral lesions, conjunctivitis, facial oedema, muscle or joint aches, or general malaise should discontinue the medicinal product and immediately seek medical evaluation. In these patients nevirapine must not be restarted.

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

If a hypersensitivity reaction occurs, characterised by rash with constitutional symptoms such as fever, arthralgia, myalgia and lymphadenopathy, plus visceral involvement, such as hepatitis, eosinophilia, granulocytopenia, and renal dysfunction, nevirapine must be permanently stopped and not be reintroduced (see section 4.3).

Hepatic reactions

Severe and life-threatening hepatotoxicity, including fatal fulminant hepatitis, has occurred in patients treated with nevirapine. The first 18 weeks of

treatment is a critical period which requires close monitoring. The risk of hepatic reactions is greatest in the first 6 weeks of therapy. However the risk continues past this period and monitoring should continue at frequent intervals throughout treatment.

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

Increased ASAT or ALAT levels ≥ 2.5 ULN and/or co-infection with hepatitis B and/or C at the start of antiretroviral therapy is associated with greater risk of hepatic adverse reactions during antiretroviral therapy in general, including nevirapine containing regimens.

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

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

<u>Liver monitoring</u>
Clinical chemistry tests, which include liver function tests, should be performed prior to initiating nevirapine therapy and at appropriate intervals during therapy.

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

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

Monitoring of hepatic tests should be done every two weeks during the first 2 months of treatment, at the 3rd month and then regularly thereafter. Liver test

monitoring should be performed if the patient experiences signs or symptoms suggestive of hepatitis and/or hypersensitivity.

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

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 pretreatment ASAT or ALAT > 5 ULN until baseline ASAT/ALAT are stabilised < 5 ULN (see section 4.3).

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

If ASAT or ALAT increase to > 5 ULN during treatment, nevirapine should be immediately stopped. If ASAT and ALAT return to baseline values and if the patient had no clinical signs or symptoms of hepatitis, rash, constitutional symptoms or other findings suggestive of organ dysfunction, it may be possible to reintroduce nevirapine, on a case by case basis, at the starting dose regimen of one immediate-release 200 mg nevirapine tablet daily for 14 days followed by one nevirapine 400 mg prolonged-release tablet daily. In these cases, more frequent liver monitoring is required. If liver function abnormalities recur, nevirapine should be permanently discontinued.

If clinical hepatitis occurs, characterised by anorexia, nausea, vomiting, icterus AND laboratory findings (such as moderate or severe liver function test abnormalities (excluding GGT)), nevirapine must be permanently stopped. 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 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 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.

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 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 nevirapine is not recommended: efavirenz, ketoconazole, etravirine, rilpivirine, elvitegravir (in combination with cobicistat), atazanavir (in combination with ritonavir), fosamprenavir (if not co-administered with low dose ritonavir) (see section 4.5).

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

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

Lactose: This medicine contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Sodium: This medicine contains less than 1 mmol sodium (23 mg) per each prolonged release tablets, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

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

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

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

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

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

Medicinal products by therapeutic areas	**Interaction**	**Recommendations concerning co-administration**
ANTI-INFECTIVES		
ANTIRETROVIRALS		
NRTIs		
Didanosine 100-150 mg BID	Didanosine AUC ↔ 1.08 (0.92-1.27) Didanosine C_{min} ND Didanosine C_{max} ↔ 0.98 (0.79-1.21)	Didanosine and nevirapine can be co-administered without dose adjustments.
Emtricitabine	Emtricitabine is not an inhibitor of human CYP 450 enzymes.	Nevirapine and emtricitabine may be co-administered without dose adjustments.
Abacavir	In human liver microsomes, abacavir did not inhibit cytochrome P450 isoforms.	Nevirapine and abacavir may be co-administered 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} ↔ 0.94 (0.86-1.03) Nevirapine: compared to historical controls, levels appeared to be unchanged.	Stavudine and nevirapine can be co-administered without dose adjustments.
Tenofovir 300 mg QD	Tenofovir plasma levels remain unchanged when co-administered with nevirapine. Nevirapine plasma levels	Tenofovir and nevirapine can be co-administered without dose adjustments.

	were not altered by co-administration of tenofovir.	
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 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 nevirapine immediate-release formulations).
Etravirine	Concomitant use of etravirine with nevirapine may cause a significant decrease in the plasma concentrations of etravirine and loss of therapeutic effect of etravirine.	The concomitant administration of 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 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 400/100 mg:</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 300/100 mg 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 1400 mg BID	Amprenavir AUC ↓ 0.67 (0.55-0.80) Amprenavir C_{min} ↓ 0.65 (0.49-0.85) Amprenavir C_{max} ↓ 0.75 (0.63-0.89) Nevirapine AUC ↑ 1.29 (1.19-1.40)	It is not recommended to co-administer fosamprenavir and nevirapine if fosamprenavir is not co-administered with ritonavir (see section 4.4).

	Nevirapine C_{min} ↑ 1.34 (1.21-1.49) Nevirapine C_{max} ↑ 1.25 (1.14-1.37)	
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 nevirapine 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 nevirapine. Dose adjustment of nevirapine 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 nevirapine, 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-	Ritonavir and nevirapine can be co-administered without dose adjustments.

	administration of ritonavir does not lead to any clinically relevant change in nevirapine plasma levels.	
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 nevirapine 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 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 co-administration would	Coadministration of nevirapine with elvitegravir in combination with cobicistat is not recommended (see section 4.4).

	likely result in altered plasma levels of cobicistat and nevirapine.	
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	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	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 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.

	clearance of nevirapine (by 9%) compared to historical data was reported.	
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 coadminister rifampicin and nevirapine (see section 4.4). Physicians needing to treat patients co-infected with tuberculosis and using a nevirapine containing regimen may consider coadministration 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 nevirapine, 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 nevirapine (see section 4.4).
ANTIVIRALS FOR CHRONIC HEPATITIS B AND C		
Adefovir	Results of *in vitro* studies	Adefovir and nevirapine

	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.	may be co-administered without dose adjustments.
Entecavir	Entecavir is not a substrate, inducer or an inhibitor of cytochrome P450 (CYP450) enzymes. Due to the metabolic pathway of entecavir, no clinically relevant drug-drug interaction is expected.	Entecavir and 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 *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 nevirapine may be co-administered without dose adjustments.
Telbivudine	Telbivudine is not a substrate, inducer or inhibitor of the	Telbivudine and nevirapine may be co-administered without dose adjustments.

	cytochrome P450 (CYP450) enzyme system. Due to the metabolic pathway of telbivudine, no clinically relevant drug-drug interaction is expected.	
ANTACIDS		
Cimetidine	Cimetidine: no significant effect on cimetidine PK parameters is seen. Nevirapine C_{min} ↑ 1.07	Cimetidine and nevirapine 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	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	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 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/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 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 (*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 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 lactation

Women of childbearing potential/Contraception in males and females

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

Pregnancy

Currently available data on pregnant women indicate no malformative or foeto/ neonatal toxicity. To date no other relevant epidemiological data are available. No observable teratogenicity was detected in reproductive studies performed in pregnant rats and rabbits (see section 5.3). There are no adequate and well-controlled studies in pregnant women. Caution should be exercised when prescribing nevirapine to pregnant women (see section 4.4). As hepatotoxicity is more frequent in women with CD4+ cell counts above 250 cells/mm^3 with detectable HIV-1 RNA in plasma (50 or more copies/mL), these conditions should be taken in consideration on therapeutic decision (see section 4.4). There is not enough evidence to substantiate that the absence of

an increased risk for toxicity seen in pre-treated women initiating nevirapine with an undetectable viral load (less than 50 copies/mL of HIV-1 in plasma) and CD4+ cell counts above 250 cells/mm^3 also applies to pregnant women. All the randomised studies addressing this issue specifically excluded pregnant women, and pregnant women were under-represented in cohort studies as well as in meta-analyses.

Breast-feeding

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

Fertility

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile

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

The nevirapine post-marketing 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 nevirapine prolonged-release tablets have been reported. The frequencies given below are based on crude incidence rates of adverse reactions observed in the nevirapine immediate-release (lead-in phase, table 1) and nevirapine prolonged-release (randomised-phase/maintenance phase, table 2) groups of clinical study 1100.1486 with 1,068 patients exposed to nevirapine on a backbone of tenofovir/emtricitabine.

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

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

Blood and lymphatic system disorders	
Uncommon	granulocytopenia
Rare	anaemia
Immune system disorders	
Uncommon	hypersensitivity (incl. anaphylactic reaction, angioedema, urticaria), drug reaction with eosinophilia and systemic symptoms, anaphylactic reaction
Nervous system disorders	
Common	headache
Gastrointestinal disorders	
Common	abdominal pain, nausea, diarrhoea
Uncommon	vomiting
Hepatobiliary disorders	
Uncommon	jaundice, hepatitis fulminant (which may be fatal)
Rare	hepatitis (incl. severe and life-threatening hepatotoxicity) (0.09 %)
Skin and subcutaneous tissue disorders	
Common	rash (6.7%)

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

Musculoskeletal and connective tissue disorders

Uncommon	arthralgia, myalgia

General disorders and administration site conditions

Common	fatigue, pyrexia

Investigations

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

Table 2: Maintenance phase of nevirapine prolonged-release

Blood and lymphatic system disorders

Uncommon	anaemia, granulocytopenia

Immune system disorders

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

Nervous system disorders

Common	headache

Gastrointestinal disorders

Common	abdominal pain, nausea, vomiting, diarrhoea

Hepatobiliary disorders

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

Skin and subcutaneous tissue disorders

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

Musculoskeletal and connective tissue disorders

Uncommon	arthralgia, myalgia

General disorders and administration site conditions

Common	fatigue

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

Description of selected adverse reactions

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

Accordingly, as anaemia, granulocytopenia, anaphylactic reaction, jaundice, Stevens-Johnson Syndrome/toxic epidermal necrolysis (which may be fatal), angioedema, decreased blood phosphorus and increased blood pressure during maintenance phase with nevirapine prolonged-release tablets were not seen in study 1100.1486 the frequency category was estimated from a statistical calculation based on the total number of patients exposed to nevirapine prolonged-release in the maintenance phase of the randomised controlled clinical study 1100.1486 (n= 505).

Metabolic parameters

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

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

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

and these events can occur many months after initiation of treatment (see section 4.4).

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

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

Severe and life-threatening skin reactions have occurred in patients treated with nevirapine, including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). Fatal cases of SJS, TEN and drug reaction with eosinophilia and systemic symptoms have been reported. The majority of severe rashes occurred within the first 6 weeks of treatment and some required hospitalisation, with one patient requiring surgical intervention (see section 4.4).

In study 1100.1486 (VERxVE) antiretroviral-naïve patients received a lead-in dose of nevirapine 200 mg immediate-release once daily for 14 days (n=1068) and then were randomised to receive either nevirapine 200 mg immediate-release twice daily or nevirapine 400 mg prolonged-release once daily. All patients received tenofovir + emtricitabine as background therapy. Safety data included all the patient visits up to the point in time when the last patient completed 144 weeks in the trial. This also includes safety data for patient visits in the post-week 144 open label extension (which patients in either treatment group who completed the 144 week blinded phase could enter). Severe or life-threatening rash considered related to nevirapine treatment occurred in 1.1 % of patients during the lead-in phase with nevirapine immediate-release. Severe rash occurred in 1.4 % and 0.2 % of the nevirapine immediate-release and nevirapine prolonged-release groups respectively during the randomised phase. No life-threatening (Grade 4) rash events considered related to nevirapine were reported during the randomised phase of this study. Six cases of Stevens-Johnson syndrome were reported in the study; all but one occurred within the first 30 days of nevirapine treatment.

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

Hepato-biliary
The most frequently observed laboratory test abnormalities are elevations in liver function tests (LFTs), including ALAT, ASAT, GGT, total bilirubin and alkaline phosphatase. Asymptomatic elevations of GGT levels are the most frequent. Cases of jaundice have been reported. Cases of hepatitis (severe and life-threatening hepatotoxicity, including fatal fulminant hepatitis) have been reported in patients treated with nevirapine. The best predictor of a serious hepatic event was elevated baseline liver function tests. The first 18 weeks of treatment is a critical period which requires close monitoring (see section 4.4).

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

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

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

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

There is no known antidote for nevirapine overdose. Cases of overdose with nevirapine immediate release at doses ranging from 800 to 6,000 mg per day for up to 15 days have been reported. Patients have experienced oedema, erythema nodosum, fatigue, fever, headache, insomnia, nausea, pulmonary infiltrates, rash, vertigo, vomiting, increase in transaminases and weight decrease. All of these effects subsided following discontinuation of nevirapine.

Paediatric population

One case of massive accidental overdose in a new born 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 90 nM. Similar EC_{50} values are obtained when the antiviral activity of nevirapine is measured in peripheral blood mononuclear cells, monocyte derived macrophages or lymphoblastoid cell line. Nevirapine had no antiviral activity in cell culture against group O HIV-1 isolates or HIV-2 isolates.

Nevirapine in combination with efavirenz exhibited a strong antagonistic anti-HIV-1 activity *in vitro* (see section 4.5) and was additive to antagonistic with

the protease inhibitor ritonavir or the fusion inhibitor enfuvirtide. Nevirapine exhibited additive to synergistic anti-HIV-1 activity in combination with the protease inhibitors amprenavir, atazanavir, indinavir, lopinavir, saquinavir and tipranavir, and the NRTIs abacavir, didanosine, emtricitabine, lamivudine, stavudine, tenofovir and zidovudine. The anti-HIV-1 activity of nevirapine was antagonized by the anti-HBV medicinal product adefovir and by the anti-HCV medicinal product ribavirin *in vitro*.

Resistance

HIV-1 isolates with reduced susceptibility (100-250-fold) to nevirapine emerge in cell culture. Genotypic analysis showed mutations in the HIV-1 RT gene Y181C and/or V106A depending upon the virus strain and cell line employed. Time to emergence of nevirapine resistance in cell culture was not altered when selection included nevirapine in combination with several other NNRTIs.

Genotypic analysis of isolates from antiretroviral naïve patients experiencing virologic failure (n=71) receiving nevirapine once daily (n=25) or twice daily (n=46) in combination with lamivudine and stavudine for 48 weeks showed that isolates from 8/25 and 23/46 patients, respectively, contained one or more of the following NNRTI resistance-associated substitutions: Y181C, K101E, G190A/S, K103N, V106A/M, V108I, Y188C/L, A98G, F227L and M230L.

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

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

Cross-resistance

Rapid emergence of HIV-strains which are cross-resistant to NNRTIs has been observed in vitro. Cross resistance to efavirenz is expected after virologic failure with nevirapine. Depending on resistance testing results, an etravirine-

containing regimen may be used subsequently. Cross-resistance between nevirapine and either HIV protease inhibitors, HIV integrase inhibitors or HIV entry inhibitors is unlikely because the enzyme targets involved are different. Similarly the potential for cross-resistance between nevirapine and NRTIs is low because the molecules have different binding sites on the reverse transcriptase.

Clinical results

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

Clinical studies with prolonged-release tablets

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

Treatment-naïve patients

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

Table 1: Demographic and Baseline Disease Characteristics in study 1100.1486

	Nevirapine immediate-release n=508*	**Nevirapine prolonged-release** n=505
Gender		
- Male	85 %	85 %
- Female	15 %	15 %
Race		
-White	74 %	77 %
- Black	22 %	19 %
- Asian	3 %	3 %
- Other**	1%	2%
Region		

- North America - Europe - Latin America - Africa	30% 50% 10% 11%	28% 51% 12% 10%
Baseline Plasma HIV-1 RNA (log_{10} copies/mL)		
-Mean (SD) - ≤100,000 ->100,000	4.7 (0.6) 66 % 34 %	4.7 (0.7) 67 % 33 %
Baseline CD4+ count (cells/mm^3)		
- Mean (SD)	228 (86)	230 (81)
HIV-1 subtype		
-B - Non-B	71 % 29 %	75 % 24 %

* Includes 2 patients who were randomised but never received blinded medicinal products.

** Includes American Indians/Alaska natives and Hawaiian/Pacific islanders.

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

Table 2: Outcomes at week 48 in study 1100.1486*

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

* Includes patients who received at least one dose of blinded medicinal product after randomisation. Patients who discontinued treatment during the lead-in period are excluded.

** Includes lost to follow-up, consent withdrawn, noncompliance, lack of efficacy, pregnancy, and other.

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

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

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

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

* Includes patients who received at least one dose of blinded medicinal product after randomisation. Patients who discontinued treatment during the lead-in period are excluded.

** Based on Cochran's statistic with continuity correction for the variance calculation.

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

Lipids, Change from baseline

Changes from baseline in fasting lipids are shown in Table 4.

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

	Nevirapine immediate-release	**Nevirapine prolonged-released**

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

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

Patients switching from nevirapine immediate-release to nevirapine prolonged-release

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

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

Paediatric population

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

5.2 Pharmacokinetic properties

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

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

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

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

Distribution: Nevirapine is lipophilic and is essentially nonionized at physiologic pH. Following intravenous administration to healthy adults, the volume of distribution (Vd_{ss}) of nevirapine was 1.21 ± 0.09 L/kg, suggesting that nevirapine is widely distributed in humans. Nevirapine readily crosses the placenta and is found in breast milk. Nevirapine is about 60 % bound to plasma proteins in the plasma concentration range of 1-10 µg/mL. Nevirapine concentrations in human cerebrospinal fluid (n = 6) were 45 % (± 5 %) of the concentrations in plasma; this ratio is approximately equal to the fraction not bound to plasma protein.

Biotransformation and elimination: *In vivo* studies in humans and *in vitro* studies with human liver microsomes have shown that nevirapine is extensively biotransformed via cytochrome P450 (oxidative) metabolism to several hydroxylated metabolites. *In vitro* studies with human liver microsomes suggest that oxidative metabolism of nevirapine is mediated

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

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

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

In paediatric patients with renal dysfunction who are undergoing dialysis it is recommended following each dialysis treatment patients receive an additional dose of nevirapine oral suspension or immediate-release tablets representing 50% of the recommended daily dose of nevirapine oral suspension or immediate-release tablets, which would help offset the effects of dialysis on nevirapine clearance. Nevirapine prolonged-release tablets have not been studied in patients with renal dysfunction and nevirapine immediate-release should be used.

Hepatic impairment: A steady state study comparing 46 patients with mild (n=17: Ishak Score 1-2),

moderate (n=20; Ishak Score 3-4),
or severe (n=9; Ishak Score 5-6, Child-Pugh A in 8 pts., for 1 Child-Pugh score not applicable)
liver fibrosis as a measure of hepatic impairment was conducted.

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

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

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

Gender
In the multinational 2NN study with nevirapine immediate-release, 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.

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

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

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

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

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

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

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

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans other than those observed in clinical studies based on conventional studies of safety,

pharmacology, repeated dose toxicity, and genotoxicity. In carcinogenicity studies, nevirapine induces hepatic tumours in rats and mice. These findings are most likely related to nevirapine being a strong inducer of liver enzymes, and not due to a genotoxic mode of action.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Hypromellose (4000 mPas, controlled release grade)
Iron oxide yellow (E172)
Silica colloidal anhydrous
Sodium stearyl fumarate

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

Nevirapine Prolonged release tablets are available in Clear PVC-Aluminium foil blister pack.

Blister packs: 30 and 90 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

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United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 16363/0638

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

12/08/2025

10 DATE OF REVISION OF THE TEXT

20/08/2025