ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS
1. NAME OF THE MEDICINAL PRODUCT
Nevirapine Teva 200 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 200 mg of nevirapine (as anhydrous).
Excipient: each tablet contains 168 mg of lactose monohydrate.
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Tablet
White, oval, biconvex tablets. One side is debossed with "N", a scoreline and "200". The opposite side is debossed with a scoreline. 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 Teva 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 Teva 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 Teva 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 Teva 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.

For toxicities that require interruption of Nevirapine Teva therapy, see section 4.4.

Special populations

Renal impairment
For patients with renal dysfunction requiring dialysis an additional 200 mg dose of nevirapine following each dialysis treatment is recommended. Patients with $\text{CLcr} \geq 20 \text{ ml/min}$ 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).

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

Paediatric population
Nevirapine Teva 200 mg tablets, following the dosing schedule described above, are suitable for larger children, particularly adolescents, below the age of 16 who weigh more than 50 kg or whose body surface area is above 1.25 m$^2$ according to the Mosteller formula.

Method of administration
The tablets shall be taken with liquid, and should not be crushed or chewed. Nevirapine Teva may be taken with or without food.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

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 $> 5 \text{ ULN}$ until baseline ASAT/ALAT are stabilised $< 5 \text{ ULN}$.

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

Herbal preparations containing St John’s wort (Hypericum perforatum) must not be used while taking Nevirapine Teva 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 Teva should only be used with at least two other antiretroviral agents (see section 5.1).

Nevirapine Teva 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 ≥ 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 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 Teva 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 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 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 patients with 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 events (5.8 % versus 2.2 %), and treatment-naïve patients of either gender with detectable HIV-1 RNA in plasma with higher CD4 counts at initiation of nevirapine therapy are at higher risk for symptomatic hepatic events with nevirapine. In a retrospective review of predominantly patients with a plasma HIV-1 viral load of 50 copies/ml or higher, women with CD4 counts > 250 cells/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.

5
Abnormal liver function tests have been reported with nevirapine, some in the first few weeks of therapy.

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

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

If ASAT or ALAT ≥ 2.5 ULN before or during treatment, then liver tests should be monitored more frequently during regular clinic visits. Nevirapine must not be administered to patients with 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 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 Teva, 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.

Combination antiretroviral therapy has been associated with the redistribution of body fat (lipodystrophy) in HIV infected patients. The long-term consequences of these events are currently unknown. Knowledge about the mechanism is incomplete. A connection between visceral lipomatosis and PIs and lipatrophy and NRTIs has been hypothesised. A higher risk of lipodystrophy has been associated with individual factors such as older age, and with medicinal product related factors such as longer duration of antiretroviral treatment and associated metabolic disturbances. Clinical examination should include evaluation for physical signs of fat redistribution. Consideration should be given to the measurement of fasting serum lipids and blood glucose. Lipid disorders should be managed as clinically appropriate (see section 4.8).

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 with nevirapine on modifying the cardiovascular risk in HIV infected patients, the clinical impact of these findings is not known. The selection of antiretroviral medicinal products must be guided primarily by their antiviral efficacy.

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.

The available pharmacokinetic data suggest that the concomitant use of rifampicin and nevirapine is not recommended (please also refer to section 4.5).

Lactose: Nevirapine Teva tablets contain 336 mg of lactose per maximum recommended daily dose. Patients with rare hereditary problems of galactose intolerance e.g. galactosaemia, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction
Nevirapine is an inducer of CYP3A and potentially CYP2B6, with maximal induction occurring within 2-4 weeks of initiating multiple-dose therapy.

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

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

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

<table>
<thead>
<tr>
<th>Medicinal products by therapeutic areas</th>
<th>Interaction</th>
<th>Recommendations concerning co-administration</th>
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<tr>
<td><strong>ANTI-INFECTIVES</strong></td>
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<tr>
<td><strong>Antiretrovirals</strong></td>
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<tr>
<td><strong>NRTIs</strong></td>
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<tr>
<td>Didanosine 100-150 mg BID</td>
<td>Didanosine AUC ↔ 1.08 (0.92-1.27) Didanosine C_{min} ND Didanosine C_{max} ↔ 0.98 (0.79-1.21)</td>
<td>Didanosine and Nevirapine Teva can be co-administered without dose adjustments.</td>
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<tr>
<td>Lamivudine 150 mg BID</td>
<td>No changes to lamivudine apparent clearance and volume of distribution, suggesting no induction effect of nevirapine on lamivudine clearance.</td>
<td>Lamivudine and Nevirapine Teva can be co-administered without dose adjustments.</td>
</tr>
<tr>
<td>Stavudine: 30/40 mg BID</td>
<td>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.</td>
<td>Stavudine and Nevirapine Teva can be co-administered without dose adjustments.</td>
</tr>
<tr>
<td>Tenofovir 300 mg QD</td>
<td>Tenofovir plasma levels remain unchanged when co-administered with Nevirapine. Nevirapine plasma levels were not altered by co-administration of tenofovir.</td>
<td>Tenofovir and Nevirapine Teva can be co-administered without dose adjustments.</td>
</tr>
<tr>
<td>Zidovudine 100-200 mg TID</td>
<td>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.</td>
<td>Zidovudine and Nevirapine Teva can be co-administered without dose adjustments.</td>
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<td><strong>NNRTIs</strong></td>
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<tr>
<td>Efavirenz 600 mg QD</td>
<td>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)</td>
<td>It is not recommended to coadminister efavirenz and Nevirapine Teva, because of</td>
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additive toxicity and no benefit in terms of efficacy over either NNRTI alone.

<table>
<thead>
<tr>
<th>PIs</th>
<th>Atazanavir/ritonavir 300/100 mg QD 400/100 mg QD</th>
<th>Atazanavir/r 300/100mg: Atazanavir/r AUC ↓ 0.58 (0.48-0.71) Atazanavir/r C_{\text{min}} ↓ 0.28 (0.20-0.40) Atazanavir/r C_{\text{max}} ↓ 0.72 (0.60-0.86) Atazanavir/r 400/100mg: Atazanavir/r AUC ↓ 0.81 (0.65-1.02) Atazanavir/r C_{\text{min}} ↓ 0.41 (0.27-0.60) Atazanavir/r C_{\text{max}} ↔ 1.02 (0.85–1.24) (compared to 300/100mg without nevirapine) Nevirapine AUC ↑ 1.25 (1.17-1.34) Nevirapine C_{\text{min}} ↑ 1.32 (1.22–1.43) Nevirapine C_{\text{max}} ↑ 1.17 (1.09-1.25)</th>
<th>It is not recommended to coadminister atazanavir/ritonavir and Nevirapine Teva.</th>
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<tr>
<td></td>
<td>Darunavir/ritonavir 400/100 mg BID</td>
<td>Darunavir AUC ↑ 1.24 (0.97-1.57) Darunavir C_{\text{min}} ↔ 1.02 (0.79-1.32) Darunavir C_{\text{max}} ↑ 1.40 (1.14-1.73) Nevirapine AUC ↑ 1.27 (1.12-1.44) Nevirapine C_{\text{min}} ↑ 1.47 (1.20-1.82) Nevirapine C_{\text{max}} ↑ 1.18 (1.02-1.37)</td>
<td>Darunavir and Nevirapine Teva can be co-administered without dose adjustments.</td>
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<td>Fosamprenavir 1,400 mg BID,</td>
<td>Amprenavir AUC ↓ 0.67 (0.55-0.80) Amprenavir C_{\text{min}} ↓ 0.65 (0.49-0.85) Amprenavir C_{\text{max}} ↓ 0.75 (0.63-0.89) Nevirapine AUC ↑ 1.29 (1.19-1.40) Nevirapine C_{\text{min}} ↑ 1.34 (1.21-1.49) Nevirapine C_{\text{max}} ↑ 1.25 (1.14-1.37)</td>
<td>It is not recommended to coadminister fosamprenavir and Nevirapine Teva if fosamprenavir is not co-administered with ritonavir.</td>
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<tr>
<td></td>
<td>Fosamprenavir/ritonavir 700/100 mg BID</td>
<td>Amprenavir AUC ↔ 0.89 (0.77-1.03) Amprenavir C_{\text{min}} ↓ 0.81 (0.69-0.96) Amprenavir C_{\text{max}} ↔ 0.97 (0.85-1.10) Nevirapine AUC ↑ 1.14 (1.05-1.24) Nevirapine C_{\text{min}} ↑ 1.22 (1.10-1.35) Nevirapine C_{\text{max}} ↑ 1.13 (1.03-1.24)</td>
<td>Fosamprenavir/ritonavir and Nevirapine Teva can be co-administered without dose adjustments</td>
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<td></td>
<td>Lopinavir/ritonavir (capsules) 400/100 mg BID</td>
<td>Lopinavir AUC ↓ 0.73 (0.53-0.98) Lopinavir C_{\text{min}} ↓ 0.54 (0.28-0.74) Lopinavir C_{\text{max}} ↓ 0.81 (0.62-0.95)</td>
<td>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 Teva. Dose adjustment of Nevirapine Teva is not required.</td>
</tr>
<tr>
<td>Drug Combination</td>
<td>Pediatric patients:</td>
<td>When co-administered with lopinavir.</td>
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<tr>
<td>Lopinavir/ritonavir (oral solution) 300/75 mg/m² BID</td>
<td>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)</td>
<td>For children, increase of the dose of lopinavir/ritonavir to 300/75 mg/m² twice daily with food should be considered when used in combination with Nevirapine Teva, particularly for patients in whom reduced susceptibility to lopinavir/ritonavir is suspected.</td>
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<tr>
<td>Nelfinavir 750 mg TID</td>
<td>Nelfinavir AUC ↔ 1.06 (0.78-1.14) C_{min} ↔ 0.68 (0.50-1.5) C_{max} ↔ 1.06 (0.92-1.22) Nelfinavir metabolite M8: AUC ↓ 0.38 (0.30–0.47) C_{min} ↓ 0.34 (0.26–0.45) C_{max} ↓ 0.41 (0.32–0.52)</td>
<td>Nelfinavir and Nevirapine Teva can be co-administered without dose adjustments.</td>
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<tr>
<td>Ritonavir 600 mg BID</td>
<td>Ritonavir AUC ↔ 0.92 (0.79-1.07) Ritonavir C_{min} ↔ 0.93 (0.76-1.14) Ritonavir C_{max} ↔ 0.93 (0.78-1.07) Nevirapine: Co-administration of ritonavir does not lead to any clinically relevant change in nevirapine plasma levels.</td>
<td>Ritonavir and Nevirapine Teva can be co-administered without dose adjustments.</td>
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<tr>
<td>Saquinavir/ritonavir</td>
<td>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</td>
<td>Saquinavir/ritonavir and Nevirapine Teva can be co-administered without dose adjustments.</td>
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<tr>
<td>Tipranavir/ritonavir 500/200 mg BID</td>
<td>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}.</td>
<td>Tipranavir and Nevirapine Teva can be co-administered without dose adjustments.</td>
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**ENTRY INHIBITORS**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Due to the metabolic pathway no clinically significant pharmacokinetic interactions are expected between enfuvirtide and</th>
<th>Enfuvirtide and Nevirapine Teva can be co-administered without dose adjustments.</th>
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<tbody>
<tr>
<td>Enfuvirtide</td>
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<tr>
<td>INTEGRASE INHIBITORS</td>
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<tr>
<td>Maraviroc 300 mg QD</td>
<td>Maraviroc AUC ↔ 1.01 (0.6 -1.55) Maraviroc C&lt;sub&gt;min&lt;/sub&gt; ND Maraviroc C&lt;sub&gt;max&lt;/sub&gt; ↔ 1.54 (0.94-2.52) compared to historical controls Nevirapine concentrations not measured, no effect is expected.</td>
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<td></td>
<td>Maraviroc and Nevirapine Teva can be co-administered without dose adjustments.</td>
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<thead>
<tr>
<th>ANTIBIOTICS</th>
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<tr>
<td>Clarithromycin 500 mg BID</td>
<td>Clarithromycin AUC ↓ 0.69 (0.62-0.76) Clarithromycin C&lt;sub&gt;min&lt;/sub&gt; ↓ 0.44 (0.30-0.64) Clarithromycin C&lt;sub&gt;max&lt;/sub&gt; ↓ 0.77 (0.69-0.86) Metabolite 14-OH clarithromycin AUC ↑ 1.42 (1.16-1.73) Metabolite 14-OH clarithromycin C&lt;sub&gt;min&lt;/sub&gt; ↔ 0 (0.68-1.49) Metabolite 14-OH clarithromycin C&lt;sub&gt;max&lt;/sub&gt; ↑ 1.47 (1.21-1.80) Nevirapine AUC ↑ 1.26 Nevirapine C&lt;sub&gt;min&lt;/sub&gt; ↑ 1.28 Nevirapine C&lt;sub&gt;max&lt;/sub&gt; ↑ 1.24 compared to historical controls.</td>
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<td>Clarithromycin exposure was significantly decreased, 14-OH metabolite exposure increased. Because the clarithromycin active metabolite has reduced activity against &lt;i&gt;Mycobacterium aviumintracellulare complex&lt;/i&gt; overall activity against the pathogen may be altered. Alternatives to clarithromycin, such as azithromycin should be considered. Close monitoring for hepatic abnormalities is recommended.</td>
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</tbody>
</table>

| Rifabutin 150 or 300 mg QD | Rifabutin AUC ↑ 1.17 (0.98-1.40) Rifabutin C<sub>min</sub> ↔ 1.07 (0.84-1.37) Rifabutin C<sub>max</sub> ↑ 1.28 (1.09-1.51) Metabolite 25-O-desacetylrifabutin AUC ↑ 1.24 (0.84-1.84) Metabolite 25-O-desacetylrifabutin C<sub>min</sub> ↑ 1.22 (0.86-1.74) Metabolite 25-O-desacetylrifabutin C<sub>max</sub> ↑ 1.29 (0.98-1.68) A clinically not relevant increase in the apparent clearance of nevirapine (by 9%) compared to historical data was reported. |
|                      | No significant effect on rifabutin and Nevirapine mean PK parameters is seen. Rifabutin and Nevirapine Teva can be co-administered without dose adjustments. However, due to the high interpatient variability some patients may experience large increases in rifabutin exposure and may be at higher risk for rifabutin toxicity. Therefore, caution should be used in concomitant administration. |

| Rifampicin 600 mg QD | Rifampicin AUC ↔ 1.11 (0.96-1.28) Rifampicin C<sub>min</sub> ND Rifampicin C<sub>max</sub> ↔ 1.06 (0.91-1.22) |
|                      | It is not recommended to co-administer rifampicin and Nevirapine Teva (see section 4.4). Physicians needing to treat patients |
| Table | Nevirapine AUC ↓ 0.42  
Nevirapine C<sub>min</sub> ↓ 0.32  
Nevirapine C<sub>max</sub> ↓ 0.50 compared to historical controls. | co-infected with tuberculosis and using a Nevirapine Teva containing regimen may consider coadministration of rifabutin instead. |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ANTIFUNGALS</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Fluconazole 200 mg QD | Fluconazole AUC ↔ 0.94 (0.88-1.01)  
Fluconazole C<sub>min</sub> ↔ 0.93 (0.86-1.01)  
Fluconazole C<sub>max</sub> ↔ 0.92 (0.85-0.99) | Because of the risk of increased exposure to Nevirapine Teva, 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<sub>min</sub> ↓ 0.13  
Itraconazole C<sub>max</sub> ↓ 0.62 | 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<sub>min</sub> ND  
Ketoconazole C<sub>max</sub> ↓ 0.56 (0.42-0.73) | It is not recommended to co-administer ketoconazole and Nevirapine Teva. |
| **ANTACIDS** | | |
| Cimetidine | Cimetidine: no significant effect on cimetidine PK parameters is seen.  
Nevirapine C<sub>min</sub> ↑ 1.07 | Cimetidine and Nevirapine Teva 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<sub>min</sub> ↔  
DMPA C<sub>max</sub> ↔  
Nevirapine AUC ↑ 1.20  
Nevirapine C<sub>max</sub> ↑ 1.20 | Nevirapine co-administration did not alter the ovulation suppression effects of DMPA. DMPA and Nevirapine Teva can be co-administered without dose adjustments. |
<table>
<thead>
<tr>
<th>Drug</th>
<th>AUC Effect</th>
<th>Cmin Effect</th>
<th>Cmax Effect</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethinyl estradiol (EE) 0.035 mg</td>
<td>EE AUC ↓ 0.80 (0.67 - 0.97)</td>
<td>EE Cmin ND</td>
<td>EE Cmax ↔ 0.94 (0.79 - 1.12)</td>
<td>Oral hormonal contraceptives should not be used as the sole method of contraception in women taking Nevirapine Teva (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.</td>
</tr>
<tr>
<td>Norethindrone (NET) 1.0 mg QD</td>
<td>NET AUC ↓ 0.81 (0.70 - 0.93)</td>
<td>NET Cmin ND</td>
<td>NET Cmax ↓ 0.84 (0.73 - 0.97)</td>
<td></td>
</tr>
</tbody>
</table>

**DRUG ABUSE**

| Methadone Individual Patient Dosing | Methadone AUC ↓ 0.40 (0.31 - 0.51) | Methadone Cmin ND | Methadone Cmax ↓ 0.58 (0.50 - 0.67) | Methadone-maintained patients beginning Nevirapine Teva 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 Teva 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 Teva 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 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 pretreated 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 Teva. 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

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

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

**b. 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 (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000).

**Blood and lymphatic system disorders**
- Common: granulocytopenia*
- Uncommon: anaemia

**Immune system disorders**
- Common: hypersensitivity (incl. anaphylactic reaction, angioedema, urticaria)
- Uncommon: anaphylactic reaction**
Rare drug rash with eosinophilia and systemic symptoms

**Nervous system disorders**
Common headache

**Gastrointestinal disorders**
Common nausea, vomiting, abdominal pain, diarrhoea

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

**Skin and subcutaneous tissue disorders**
Very common rash (12.5 %)
Uncommon Stevens Johnson syndrome/toxic epidermal necrolysis (which may be fatal) (0.2 %), angiodema, urticaria

**Musculoskeletal and connective tissue disorders**
Uncommon arthralgia, myalgia

**General disorders and administration site conditions**
Common pyrexia, fatigue

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

* 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%).

** This adverse 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).

*** This adverse reaction was observed in clinical studies with co-administration of tenofovir/emtricitabine.

c. Description of selected adverse reactions
Combination antiretroviral therapy has been associated with redistribution of body fat (lipodystrophy) in HIV infected patients including the loss of peripheral and facial subcutaneous fat, increased intraabdominal and visceral fat, breast hypertrophy and dorsocervical fat accumulation (buffalo hump).

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

d. **Paediatric population**

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

**4.9 Overdose**

There is no known antidote for nevirapine overdose. Cases of nevirapine overdose at doses ranging from 800 to 6000 mg per day for up to 15 days have been reported. Patients have experienced oedema, erythema nodosum, fatigue, fever, headache, insomnia, nausea, pulmonary infiltrates, rash, vertigo,
vomiting, 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 \textit{in vitro} 

Nevirapine had a median EC\textsubscript{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\textsubscript{50} value was 90nM. Similar EC\textsubscript{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 \textit{in vitro} (see section 4.5) and was additive to synergistic activity 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 medicinal product ribavirin \textit{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.

1,216 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).

<table>
<thead>
<tr>
<th></th>
<th>Nevirapine 200 mg twice daily (n = 387)</th>
<th>Efavirenz 600 mg once daily (n = 400)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment failure on or before week 48, % (95% IC)</td>
<td>43.7% (38.7-48.8)</td>
<td>37.8% (33.0-42.7)</td>
</tr>
</tbody>
</table>
Components of failure (%)

<table>
<thead>
<tr>
<th>Component</th>
<th>Efavirenz Group</th>
<th>Nevirapine Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Virological Progression</td>
<td>18.9%</td>
<td>15.3%</td>
</tr>
<tr>
<td>Change of treatment</td>
<td>22.0%</td>
<td>20.0%</td>
</tr>
<tr>
<td>Permanent change of NNRTI (n)</td>
<td>61</td>
<td>51</td>
</tr>
<tr>
<td>Temporary discontinuation of NNRTI (n)</td>
<td>13</td>
<td>8</td>
</tr>
<tr>
<td>Additional antiretroviral medicinal products (n)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Non-allowable change of NNRTI (n)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Never started ART* (n)</td>
<td>9</td>
<td>19</td>
</tr>
</tbody>
</table>

Plasma HIV-1 RNA concentration <50 c/ml at 48 weeks, % (95% IC)

<table>
<thead>
<tr>
<th>Component</th>
<th>Efavirenz Group</th>
<th>Nevirapine Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma HIV-1 RNA concentration ≤ 50 c/ml at 48 weeks</td>
<td>65.4% (60.4-70.1)</td>
<td>70.0% (65.2-74.5)</td>
</tr>
</tbody>
</table>

* 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 coinfected with hepatitis B or hepatitis C virus were 6.7% and 20.0% in the nevirapine twice daily group, 5.6% and 11.1% in the efavirenz group.
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).

<table>
<thead>
<tr>
<th></th>
<th>Nevirapine 200 mg twice daily (n=224)</th>
<th>Efavirenz 600 mg once daily (n=223)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment failure (%)</td>
<td>35.7</td>
<td>35.0</td>
</tr>
<tr>
<td>Virologic failure (&gt;400 c/ml) (%)</td>
<td>5.8</td>
<td>4.9</td>
</tr>
<tr>
<td>pVL &lt;400 c/ml at week 144 (%)</td>
<td>87.2</td>
<td>87.4</td>
</tr>
<tr>
<td>CD4 increase (cells/mm³)</td>
<td>+135</td>
<td>+130</td>
</tr>
<tr>
<td>Disease progression / death (%)</td>
<td>5.8</td>
<td>6.3</td>
</tr>
</tbody>
</table>

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

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

<table>
<thead>
<tr>
<th>Number of patients who had one or more adverse events*</th>
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<tbody>
<tr>
<td>Adverse Event</td>
</tr>
<tr>
<td>Any adverse event</td>
</tr>
<tr>
<td>Grade 3 or 4 adverse event</td>
</tr>
<tr>
<td>Adverse event leading to discontinuation</td>
</tr>
<tr>
<td>Any adverse event</td>
</tr>
<tr>
<td>Grade 3 or 4 adverse event</td>
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<tr>
<td>Adverse event leading to discontinuation</td>
</tr>
<tr>
<td>Any adverse event</td>
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<tr>
<td>Grade 3 or 4 adverse event</td>
</tr>
<tr>
<td>Adverse event leading to discontinuation</td>
</tr>
</tbody>
</table>

Number of patients (percent)

<table>
<thead>
<tr>
<th>Clinical</th>
<th>Nevirapine (N=155)</th>
<th>Efavirenz (N=156)</th>
<th>Abacavir (N=149)</th>
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</thead>
<tbody>
<tr>
<td>- Neuropsychiatric</td>
<td>11</td>
<td>6</td>
<td>7</td>
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<tr>
<td>- Cutaneous</td>
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<td>13</td>
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<tr>
<td>- Gastrointestinal</td>
<td>6</td>
<td>2</td>
<td>0</td>
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<tr>
<td>- Systemic**</td>
<td>7</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>- Other</td>
<td>25</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>Laboratory</td>
<td>12</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>- Increased aminotransferase levels</td>
<td>4</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>- Hyperglycemia</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>83 (54)**</td>
<td>38 (17)***</td>
<td>61 (41)*****</td>
</tr>
<tr>
<td></td>
<td>26 (17)***</td>
<td>39 (27)***</td>
<td>16 (6)****</td>
</tr>
</tbody>
</table>

* 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 studies. 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 medicinal products. 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 medicinal products 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 study 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\text{max} of 5.74 μg/ml (5.00-7.44) and C\text{min} of 3.73 μg/ml (3.20-5.08) with an AUC of 109.0 h*μg/ml (96.0-143.5) in patients taking 200 mg of nevirapine bid. Other published data support these conclusions. Long-term efficacy appears to be most likely in patients whose nevirapine trough levels exceed 3.5 μg/ml.

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

**Biotransformation and elimination:** In vivo studies in humans and in vitro studies with human liver microsomes have shown that nevirapine is extensively biotransformed via cytochrome P450 (oxidative) metabolism to several hydroxylated metabolites. In vitro studies with human liver microsomes suggest that oxidative metabolism of nevirapine is mediated primarily by cytochrome P450 isoforms from the CYP3A family, although other isoforms 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.

**Special populations:**

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

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

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

**Paediatric population**

Data concerning the pharmacokinetics of nevirapine have been derived from two major sources: a 48 week paediatric study in South Africa (BI 1100.1368) involving 123 HIV-1 positive, antiretroviral naive 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.

### 6. PHARMACEUTICAL PARTICULARS

#### 6.1 List of excipients

- Microcrystalline cellulose
- Lactose monohydrate
- Povidone K25
- Sodium starch glycolate (Type A)
- Colloidal silicon dioxide
- Magnesium stearate
6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

White opaque PVC/PE/PVdC – Aluminium blisters or OPA/Alu/PVC – Aluminium blisters. Cartons containing 60 or 120 tablets. Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

Teva Pharma B.V.
Computerweg 10, 3542 DR Utrecht
The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

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

A. MANUFACTURING AUTHORISATION HOLDERS RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OF THE MARKETING AUTHORISATION
A. MANUFACTURING AUTHORISATION HOLDERS RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers responsible for batch release

TEVA Pharmaceutical Works Private Limited Company
Pallagi út 13,
4042 Debrecen,
Hungary

TEVA Pharmaceutical Works Private Limited Company
H-2100 Gödöllő,
Táncsics Mihály út 82
Hungary

TEVA UK Ltd
Brampton Road, Hampden Park
Eastbourne
East Sussex, BN22 9AG
United Kingdom

Pharmachemie B.V.
Swensweg 5,
2031 GA Haarlem
The Netherlands

TEVA Santé SA,
Rue Bellocier, 89107,
Sens,
France

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

B. CONDITIONS OF THE MARKETING AUTHORISATION

- CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORISATION HOLDER

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

- OTHER CONDITIONS

Pharmacovigilance system

The MAH must ensure that the system of pharmacovigilance, presented in Module 1.8.1. of the Marketing Authorisation, is in place and functioning before and whilst the product is on the market.

PSURs

The PSUR submission schedule for Nevirapine Teva tablets should follow the PSURs submission schedule for the reference medicinal product.
ANNEX III

LABELLING AND PACKAGE LEAFLET
A. LABELLING
### PARTICULARS TO APPEAR ON THE OUTER PACKAGING

**Carton**

1. **NAME OF THE MEDICINAL PRODUCT**
   
   Nevirapine Teva 200 mg tablets  
   nevirapine

2. **STATEMENT OF ACTIVE SUBSTANCE(S)**
   
   Each tablet contains 200 mg of nevirapine (as anhydrous)

3. **LIST OF EXCIPIENTS**
   
   Also contains: lactose (see leaflet for further information)

4. **PHARMACEUTICAL FORM AND CONTENTS**
   
   60 tablets  
   120 tablets

5. **METHOD AND ROUTE(S) OF ADMINISTRATION**
   
   Oral use  
   Read the package leaflet before use.

6. **SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN**
   
   Keep out of the reach and sight of children.

7. **OTHER SPECIAL WARNING(S), IF NECESSARY**

8. **EXPIRY DATE**
   
   EXP

9. **SPECIAL STORAGE CONDITIONS**

10. **SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**
11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Teva Pharma B.V.
Computerweg 10, 3542 DR Utrecht
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/598/001
EU/1/09/598/002
EU/1/09/598/003
EU/1/09/598/004

13. BATCH NUMBER

BN

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Nevirapine Teva 200 mg
### Blister

<table>
<thead>
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<th>1. NAME OF THE MEDICINAL PRODUCT</th>
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<table>
<thead>
<tr>
<th>5. OTHER</th>
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</thead>
</table>
B. PACKAGE LEAFLET
Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:
1. What Nevirapine Teva is and what it is used for
2. Before you take Nevirapine Teva
3. How to take Nevirapine Teva
4. Possible side effects
5. How to store Nevirapine Teva
6. Further information

1. WHAT NEVIRAPINE TEVA IS AND WHAT IT IS USED FOR

Nevirapine Teva belongs to a group of medicines called antiretrovirals, used in the treatment of Human Immunodeficiency Virus (HIV-1) infection. HIV is spread by contact with infected blood or sexual contact with an infected individual.

Nevirapine Teva belongs to the class of non-nucleoside reverse transcriptase inhibitors (NNRTIs). Nevirapine Teva fights HIV-1 infection by reducing the amount of the virus in the blood.

Nevirapine Teva is prescribed for use in combination with other HIV antiretrovirals. Your doctor will determine which medicines are best for you.

2. BEFORE YOU TAKE NEVIRAPINE TEVA

Do not take Nevirapine Teva
- if you are allergic (hypersensitive) to nevirapine or any of the other ingredients of Nevirapine Teva.
- if you previously experienced inflammation of the liver (hepatitis), severe skin rash, or liver damage while on nevirapine treatment.
- if you have permanent liver disease or changes in liver function
- if you are taking products containing St John’s Wort (Hypericum perforatum) as this may stop Nevirapine Teva from working properly.

Take special care with Nevirapine Teva

During the first 18 weeks of treatment with Nevirapine Teva you should watch out for signs of liver or skin reactions as these can become severe and even life threatening.
If you experience severe rash or hypersensitivity (allergic reactions) that may appear in the form of rash accompanied by other side effects such as
- fever,
- blistering,
- mouth sores,
- eye inflammation,
- facial swelling,
- general swelling,
- shortness of breath,
- muscle or joint aches,
- general feelings of illness,
- or abdominal pain

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

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

you should discontinue taking Nevirapine Teva and must contact your doctor immediately. If you develop severe hepatic, skin or hypersensitivity reactions whilst taking Nevirapine Teva, NEVER TAKE Nevirapine Teva again without referring to your doctor. You must take the dose of Nevirapine Teva as prescribed by your doctor. This is especially important within the first 14 days of treatment (see more information in How to take Nevirapine Teva).

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

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

Changes of body fat may occur in patients receiving combination antiretroviral therapy. Contact your doctor if you notice changes in body fat.

**Bone problems:** Some patients taking combination antiretroviral therapy may experience death of bone tissue (osteonecrosis). The length of combination antiretroviral therapy, corticosteroïd use, alcohol consumption, severe weakness of the immune system, higher body mass index may be some of the many risk factors for developing this disease. Signs of osteonecrosis are joint stiffness, aches and pains (especially of the hip, knee and shoulder) and difficulty in movement. If you notice any of these symptoms please inform your doctor.

Nevirapine Teva is not a cure for HIV infection and you may continue to develop infections or other illnesses associated with HIV infection. It is therefore important to remain under the care of your
Use in children
Nevirapine Teva tablets can be taken by children 16 years of age or older. Additionally Nevirapine Teva tablets can be taken by adolescents under 16 years of age who weigh 50 kg or more or whose body surface area is above 1.25 m².

Taking other medicines

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. You should inform your doctor of all other medicines you are taking before you start taking Nevirapine Teva because he or she might need to monitor whether the other medicines are still having their desired effects and make necessary dose-adjustments. You should carefully read the package leaflet of the other HIV medicinal products which you will be taking in combination with Nevirapine Teva.

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

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

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

If you are undergoing dialysis, your doctor may consider a dose adjustment of Nevirapine Teva as Nevirapine Teva can be partly washed out of your blood by dialysis.

Taking Nevirapine Teva with food and drink

There are no restrictions on taking Nevirapine Teva with food and drink.

Pregnancy and breast-feeding

Ask your doctor or pharmacist for advice before taking any medicine.

You should discontinue breast-feeding if you are taking Nevirapine Teva. It is in general recommended that you do not breast-feed if you have HIV infection in order to lower the risk of passing the infection on to your baby.

Driving and using machines

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

**Important information about some of the ingredients of Nevirapine Teva**

Each Nevirapine Teva 200 mg tablet contains 168 mg of lactose monohydrate. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

### 3. HOW TO TAKE NEVIRAPINE TEVA

Always take Nevirapine Teva exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

Nevirapine Teva is in a tablet form. Do not chew or crush the tablet. The usual dose is one 200 mg tablet for the first 14 days of treatment (this 'lead in' period has been shown to lower the incidence of skin rash) followed by one 200 mg tablet twice daily. Nevirapine Teva will always be taken in combination with other HIV antiretrovirals, for which you should follow the instructions within the supplied package leaflet.

It is essential to follow strictly the once a day dosage during the 14-day ‘lead in’ period before rising to the twice daily dosage. If you have any rash within this period see your doctor before increasing the dose.

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

As explained in ‘Take special care with Nevirapine Teva’, above, your doctor will monitor you with liver tests or for undesirable effects such as rash. Depending on the outcome he or she may decide to interrupt or stop your Nevirapine Teva treatment. He or she might then decide to restart you on a lower dose.

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

**If you take more Nevirapine Teva than you should**

Do not exceed the dose prescribed by your doctor and described in this leaflet. There is at present little information on the effects of Nevirapine Teva overdose. Consult your doctor if you have taken an overdose.

**If you forget to take Nevirapine Teva**

Try not to miss a dose. When you notice within 8 hours, take the next dose as soon as possible. If you notice later take the next regular dose at the scheduled time.

**If you stop taking Nevirapine Teva**

Taking all doses at the appropriate times greatly increase the effectiveness of your medicinal product combination regimen and reduces the development of viral resistance. Therefore, unless your doctor instructs you to stop treatment, it is important to keep taking Nevirapine Teva correctly, as described above.
If you stop taking Nevirapine Teva for more than 7 days your doctor will instruct you to start the 14 day 'lead in' period (described above) once again before returning to the twice daily dose.

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

4. POSSIBLE SIDE EFFECTS

Like all medicines, Nevirapine Teva can cause side effects, although not everybody gets them.

As mentioned in ‘Take special care with Nevirapine Teva’, above, the most important side effects of Nevirapine Teva are severe and life threatening skin reactions and serious liver damage. These reactions occur mainly in the first 18 weeks of treatment with Nevirapine Teva. This is therefore an important period which requires close monitoring by your doctor.

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

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

If rash occurs with feeling sick, you must stop treatment and visit your doctor immediately.

Hypersensitivity (allergic) reactions can occur. Such reactions may appear in the form of anaphylaxis (characterised by rash, facial swelling, bronchial spasm or shock), or rash accompanied by other side effects such as fever, blistering, mouth sores, eye inflammation, facial swelling, general swelling, shortness of breath, muscle or joint aches, a reduction in white blood cells (granulocytopaenia), general feelings of illness or severe problems with liver or kidneys.

If you experience rash and any of the other side effects of a hypersensitivity (allergic) reaction, please be sure to tell your doctor immediately as such reactions can be potentially life-threatening.

Abnormal liver functioning has been reported with the use of Nevirapine Teva, including some cases of inflammation of the liver (hepatitis), which can be sudden and intense (fulminant hepatitis) and liver failure, which have resulted in deaths.

If you experience clinical symptoms suggesting an injury of the liver, such as loss of appetite, feeling sick (nausea), vomiting, yellow skin (jaundice), abdominal pain you should inform your doctor.

The side effects described below have been experienced by patients given nevirapine.

The frequency of possible side effects listed below is defined using the following convention:
very common: in at least 1 out of 10 patients treated
common: in at least 1 out of 100 and less than 1 out of 10 patients treated
uncommon: in at least 1 out of 1,000 and less than 1 out of 100 patients treated
rare: in at least 1 out of 10,000 and less than 1 out of 1,000 patients treated

Very common:
- rash

Common:
- reduction in white blood cells (granulocytopaenia)
- allergic reactions (hypersensitivity)
- headache
- feeling sick (nausea)
- vomiting
- abdominal pain
- loose stools (diarrhoea)
- inflammation of the liver (hepatitis)
- fatigue
- fever
- liver function tests abnormal

**Uncommon:**
- allergic reaction characterised by rash, swelling of the face, difficulty breathing (bronchial spasm) or anaphylactic shock
- reduction in red blood cells (anaemia)
- yellow skin (jaundice)
- Stevens Johnson Syndrome/toxic epidermal necrolysis
- hives (urticaria)
- fluid under the skin (angioneurotic oedema)
- joint pain (arthralgia)
- muscle pain (myalgia)
- decreased blood phosphorus
- increased blood pressure

**Rare:**
- sudden and intense inflammation of the liver (hepatitis fulminant)
- drug rash with systemic symptoms (drug rash with eosinophilia and systemic symptoms)

Combination antiretroviral therapy may cause changes in body shape due to changes in fat distribution. These may include loss of fat from legs, arms and face, increased fat in the abdomen (belly) and other internal organs, breast enlargement and fatty lumps on the back of the neck (‘buffalo hump’). The cause and long-term health effects of these conditions are not known at this time. Combination antiretroviral therapy may also cause raised lactic acid and sugar in the blood, hyperlipaemia (increased fats in the blood) and resistance to insulin.

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

These events are commonly associated with other antiretroviral agents and may be expected to occur when Nevirapine Teva is used in combination with other agents; however, it is unlikely that these events are due to a treatment with Nevirapine Teva.

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

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

**5. HOW TO STORE NEVIRAPINE TEVA**

Keep out of the reach and sight of children.
Do not use Nevirapine Teva after the expiry date which is stated on the carton and on the blister after EXP. The expiry date refers to the last day of that month.

This medicinal product does not require any special storage conditions.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Nevirapine Teva contains

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

What Nevirapine Teva looks like and contents of the pack

Nevirapine Teva tablets are supplied in blisters, with 60 or 120 tablets per carton. Not all pack sizes may be marketed.

Marketing Authorisation Holder

Teva Pharma B.V.
Computerweg 10, 3542 DR Utrecht
The Netherlands

Manufacturer

TEVA Pharmaceutical Works Private Limited Company
Pallagi út 13,
4042 Debrecen,
Hungary

TEVA Pharmaceutical Works Private Limited Company
H-2100 Gödöllő,
Táncsics Mihály út 82
Hungary

TEVA UK Ltd
Brampton Road,
Hampden Park,
Eastbourne,
East Sussex,
BN22 9AG
United Kingdom

Pharmachemie B.V.
Swensweg 5,
2031 GA Haarlem
The Netherlands

TEVA Santé SA,
Rue Bellocier, 89107,
For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

<table>
<thead>
<tr>
<th>Country</th>
<th>Company Name</th>
<th>Phone</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>België/Belgique/Belgien</strong></td>
<td>Teva Pharma Belgium N.V./S.A.</td>
<td>+32 3 820 73 73</td>
</tr>
<tr>
<td><strong>Luxembourg/Luxemburg</strong></td>
<td>Teva Pharma Belgium S.A.</td>
<td>+32 3 820 73 73</td>
</tr>
<tr>
<td><strong>България</strong></td>
<td>Тева Фармасотикълс България ЕООД</td>
<td>+359 2 489 95 82</td>
</tr>
<tr>
<td><strong>Magyarország</strong></td>
<td>Teva Magyarország Zrt</td>
<td>+36 1 288 64 00</td>
</tr>
<tr>
<td><strong>Česká republika</strong></td>
<td>Teva Pharmaceuticals CR, s.r.o.</td>
<td>+420 251 007 111</td>
</tr>
<tr>
<td><strong>Malta</strong></td>
<td>Drugsales ltd</td>
<td>+356 21 419 070/1/2</td>
</tr>
<tr>
<td><strong>Danmark</strong></td>
<td>Teva Denmark A/S</td>
<td>+45 44 98 55 11</td>
</tr>
<tr>
<td><strong>Nederland</strong></td>
<td>Teva Nederland B.V.</td>
<td>+31 (0) 800 0228400</td>
</tr>
<tr>
<td><strong>Deutschland</strong></td>
<td>Teva GmbH</td>
<td>+49 (49) 351 834 0</td>
</tr>
<tr>
<td><strong>Norge</strong></td>
<td>Teva Sweden AB</td>
<td>+46 42 12 11 00</td>
</tr>
<tr>
<td><strong>Eesti</strong></td>
<td>Teva Eesti esindus UAB Sicor Biotech Eesti filiaal</td>
<td>+372 611 0801</td>
</tr>
<tr>
<td><strong>Österreich</strong></td>
<td>ratiopharm Arzneimittel Vertriebs-GmbH</td>
<td>+43 1 97007</td>
</tr>
<tr>
<td><strong>Ελλάδα</strong></td>
<td>Teva Ελλάς A.E.</td>
<td>+30 210 72 79 099</td>
</tr>
<tr>
<td><strong>Polska</strong></td>
<td>Teva Pharmaceuticals Polska Sp. z o.o.</td>
<td>+(48) 22 345 93 00</td>
</tr>
<tr>
<td><strong>España</strong></td>
<td>Teva Pharma, S.L.U.</td>
<td>+(34) 91 387 32 80</td>
</tr>
<tr>
<td><strong>Portugal</strong></td>
<td>Teva Pharma - Produtos Farmacêuticos Lda</td>
<td>(351) 214 235 910</td>
</tr>
<tr>
<td><strong>România</strong></td>
<td>Teva Pharmaceuticals S.R.L</td>
<td>+4021 230 65 24</td>
</tr>
<tr>
<td><strong>Ireland</strong></td>
<td>Teva Pharmaceuticals Ireland</td>
<td>+353 (0)42 9395 892</td>
</tr>
<tr>
<td><strong>Slovenija</strong></td>
<td>Pliva Ljubljana d.o.o.</td>
<td>+386 1 58 90 390</td>
</tr>
<tr>
<td><strong>Ísland</strong></td>
<td>Teva UK Limited</td>
<td>+(44) 1323 501 111</td>
</tr>
<tr>
<td><strong>Slovenská republika</strong></td>
<td>Teva Pharmaceuticals Slovakia s.r.o.</td>
<td>+(421) 2 5726 7911</td>
</tr>
<tr>
<td><strong>Italia</strong></td>
<td>Teva Italia S.r.l.</td>
<td>+(39) 028917981</td>
</tr>
<tr>
<td><strong>Suomi/Finland</strong></td>
<td>Teva Sweden AB</td>
<td>+(46) 42 12 11 00</td>
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<td><strong>Sverige</strong></td>
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</table>
Greek: +30 210 72 79 099
Tel: +(46) 42 12 11 00

Latvia
UAB Sicor Biotech filiāle Latvijā
Tel: +371 67 784 980

United Kingdom
Teva UK Limited
Tel: +(44) 1323 501 111

Lietuva
UAB “Sicor Biotech”
Tel: +370 5 266 02 03

This leaflet was last approved in {MM/YYYY}.

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