WHO-PQ RECOMMENDED SUMMARY OF PRODUCT CHARACTERISTICS

This summary of product characteristics focuses on uses of the medicine covered by WHO's Prequalification Team - Medicines. The recommendations for use are based on WHO guidelines and on information from stringent regulatory authorities.[*]
The medicine may be authorised for additional or different uses by national medicines regulatory authorities.

[*]https://extranet.who.int/pqweb/sites/default/files/documents/75%20SRA%20clarification_Feb2017_newtempl.pdf

1. NAME OF THE MEDICINAL PRODUCT

[HA567 trade name]†

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 20 mg of nevirapine.

Excipients with known effects
Each tablet contains about 31.8 mg of lactose monohydrate.
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

White to off-white, oval-shaped, uncoated tablet, debossed with '20' on one side and scored on the other side.

The tablet can be divided into equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

[HA567 trade name] is indicated for prophylaxis against human immunodeficiency virus type 1 (HIV-1) infection in infants of HIV-infected mothers.

Official guidelines (e.g., those of the WHO) on the prevention of mother-to-child transmission (PMCT) of HIV should be consulted.

This product is intended for use in children. Safety information on use in adults is also provided.

4.2 Posology and method of administration

Posology

[HA567 trade name] should be initiated by a health care provider experienced in the management of HIV infection.

Newborn infants

Dosing recommendations for preventing HIV infection in infants born to HIV-positive women are shown below. However, it may not be possible to use [HA567 trade name] for some of the recommended doses and alternative formulations, such as oral solution, may be required.

Infant age	Dose* in mg	Dose*as 20-mg tablet
Birth to 6 weeks		
• Weight at birth less than 2 kg	initially, 2 mg/kg once daily	Use alternative formulation
• Weight at birth 2–2.5 kg	10 mg once daily	½ tablet once daily
• Weight at birth > 2.5 kg	15 mg once daily	Use alternative formulation

† Trade names are not prequalified by WHO. This is the national medicines regulatory agency's responsibility.

6 weeks to 6 months†	20 mg once daily	1 tablet once daily
6 months to 9 months†	30 mg once daily	1½ tablets once daily
over 9 months†	40 mg once daily	2 tablets once daily

* Recommended duration of prophylaxis is 6 weeks but 4 weeks may be considered if formula feeds are used.

† Prophylaxis may be continued for longer than 6 weeks and up to 12 weeks in special circumstances such as mother receiving limited antiretroviral therapy that does not suppress HIV or infant exposed to HIV after birth and breastfeeding

Renal impairment

[HA567 trade name] is intended for use in infants to prevent HIV infection. No dose adjustment is required for infants with creatinine clearance ≥ 20 ml/minute.

Hepatic impairment

[HA567 trade name] is intended for use in infants to prevent HIV infection. It should not be used in infants with severe hepatic impairment. No dose adjustment is necessary in infants with mild to moderate hepatic impairment.

Elderly

[HA567 trade name] is intended for use in infants to prevent HIV infection. Nevirapine has not been specifically investigated in patients over the age of 65 years.

Method of Administration

[HA567 trade name] must be administered orally, with food or between meals.

[HA567 trade name] may be dispersed in water if the child is not able to swallow the tablet. The required number of tablets should be dispersed in drinking water before administration of the dose. Each tablet should be dispersed in a minimum of 10 mL water; the maximum volume of water recommended for dispersion of the full dose is 50 mL.

4.3 Contraindications

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

Nevirapine must not be given if it has previously caused severe rash, rash accompanied by constitutional symptoms, hypersensitivity reactions, or clinical hepatitis.

Nevirapine must not be used in patients with severe hepatic impairment (Child-Pugh C) or pre-treatment aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 5 times upper limit of normal (ULN).

Nevirapine should not be given again to patients who previously developed AST or ALT >5 times ULN during nevirapine therapy and in whom liver function abnormalities recur upon re-administration of nevirapine (see section 4.4).

Rifampicin and herbal preparations containing St John's wort (*Hypericum perforatum*) must not be used while taking nevirapine 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

Effective antiviral therapy can substantially reduce the risk of HIV transmission. However, the risk may not be eliminated entirely. It is therefore essential to take precautions according to national and other authoritative guidelines to prevent transmission through sexual contact or blood contamination

Nevirapine should only be used with at least two other antiretroviral medicines (see section 5.1). It should not be used as the sole active antiretroviral, because monotherapy with any antiretroviral can result in the development of viral resistance.

Combination therapy with nevirapine is not a cure for HIV-1 infection; patients may continue to suffer illnesses associated with HIV-1 infection, including opportunistic infections. Continuous antiretroviral therapy is required to control HIV-1 infection and decrease HIV-related illness.

Patients should be monitored closely during the critical first 18 weeks of nevirapine therapy for **serious skin reactions** and for **severe liver disorders**. Life-threatening skin reactions (e.g. Stevens-Johnson syndrome and toxic epidermal necrolysis) and liver disorders (e.g. hepatitis or hepatic failure) can develop. The risk of hepatic events and skin reactions is greatest in the first 6 weeks of therapy. However, the risk of hepatic events persists beyond this period and monitoring should continue at frequent intervals.

Nevirapine should not be started in a patient at higher risk of hepatic adverse events unless the likely benefit outweighs the risk. The risk of hepatic adverse events is higher if the patient has detectable plasma HIV-1 RNA (i.e., $\geq$ 50 copies/ml), is female and the CD4 count is higher (> 250 cells/mm^3 in women and > 400 cells/mm^3 in men) at the start of therapy.

Patients developing signs or symptoms of hepatitis, severe skin reaction or hypersensitivity reactions must discontinue nevirapine and seek medical evaluation immediately; in some cases, hepatic injury has progressed despite discontinuing nevirapine. Rhabdomyolysis has occurred in patients with skin or liver reactions associated with nevirapine use.

Nevirapine must be permanently discontinued in case of severe hepatic injury, skin reactions or hypersensitivity reactions (characterised by rash with constitutional symptoms such as fever, arthralgia, myalgia and lymphadenopathy together with other features such as hepatitis, eosinophilia, granulocytopenia, and renal dysfunction).

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

Cutaneous reactions

Patients should be closely monitored for cutaneous reactions during the first 18 weeks of treatment; special care is required for infants and children because of their inability to notice and report skin reactions. Any patient who develops 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 nevirapine and seek medical evaluation **immediately**. In these patients nevirapine must not be restarted.

In patients with nevirapine-associated rash, liver function should be tested. Nevirapine should be discontinued permanently if liver enzymes are moderately or severely elevated (AST or ALT more than 5 times upper limit of normal).

The risk of developing serious cutaneous reactions is increased by failure to follow the initial dosing recommendations during the lead-in period or by delaying medical consultation for initial cutaneous symptoms. Exceeding the recommended dose of nevirapine might increase the frequency and seriousness of skin reactions. Women may be at higher risk of developing rash, whether receiving nevirapine or non-nevirapine containing therapy.

Patients or their guardians should be instructed that a major toxicity of nevirapine is rash. They should be advised to seek medical evaluation **without delay** if any rash occurs. They should be instructed that the dose should not be increased if any rash occurs during the two-week lead-in dosing period, until the rash resolves. The once-daily dosing regimen should not be continued beyond 28 days when an alternative treatment should be instituted.

Prednisone is **not** suitable treatment for nevirapine-induced rash.

Hepatic reactions

Severe and life-threatening hepatoxicity, including fatal fulminant hepatitis, has occurred in patients treated with nevirapine. Close monitoring is required during the critical first 18 weeks of treatment. The risk of hepatic events is greatest in the first 6 weeks of therapy but it continues past this period and monitoring should continue at frequent intervals throughout treatment.

AST or ALT levels more than 2.5 times upper limit of normal or infection with hepatitis B 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.

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

Healthcare providers and patients (and their guardians) should be vigilant for prodromal features 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 AST or ALT increase to more than 5 times upper limit of normal during treatment, nevirapine should be **stopped immediately**. If AST and ALT return to baseline values and if the patient had no signs or symptoms of hepatitis, rash, constitutional symptoms or other findings suggestive of organ dysfunction, nevirapine may be reintroduced, on a case-by-case basis, at the age-appropriate once-daily starting dose for 14 days followed by the twice-daily maintenance dose. In these cases, more frequent liver monitoring is required. If liver function abnormalities recur, nevirapine should be discontinued permanently.

In case of clinical hepatitis, characterised by anorexia, nausea, vomiting, icterus and laboratory findings, such as moderate or severe liver function test abnormalities (excluding gamma-glutamyltransferase, GGT), nevirapine must be permanently stopped. Nevirapine must not be re-administered to patients who have required permanent discontinuation for clinical hepatitis due to nevirapine.

Liver monitoring

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

Asymptomatic elevation of liver enzymes occurs frequently but is not necessarily a contraindication to using nevirapine.

Liver function should be tested every two weeks during the first 2 months of treatment, at the third month, and regularly thereafter. Liver function should be tested if the patient has signs or symptoms of hepatitis or hypersensitivity.

If AST or ALT concentration is more than 2.5 upper limit of normal before or during treatment, then liver function should be monitored more frequently during regular clinic visits. Nevirapine must not be given to patients with pre-treatment AST or ALT more than 5 times upper limit of normal until baseline AST and ALT are stabilised to less than 5 times upper limit of normal.

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). Pharmacokinetic results suggest that nevirapine should be used with caution in patients with moderate hepatic dysfunction (Child-Pugh B, see section 5.2). Patients with chronic hepatitis B or C and treated with combination antiretroviral therapy are at increased risk for severe and potentially fatal hepatic adverse

events. In the case of concomitant antiviral therapy for hepatitis B or C, refer also to the product information for these medicines.

Patients with liver dysfunction including chronic active hepatitis have 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.

Drug interaction with other antimicrobials

Concomitant use of nevirapine with non-nucleoside reverse transcriptase inhibitors efavirenz, delavirdine, etravirine and rilpivirine is not recommended (see section 4.5). Concomitant use of nevirapine with elvitegravir/cobicistat or with boceprevir is also not recommended (see section 4.5).

Based on pharmacokinetic data, concomitant use of rifampicin and nevirapine is not recommended. Rifampicin reduces nevirapine plasma concentration due to enzyme induction and may therefore increase the risk of treatment failure. Increasing the dose of nevirapine, however, may increase the risk of hypersensitivity reactions, including rash and hepatitis. Rifabutin should be considered instead of rifampicin. If nevirapine needs to be started during rifampicin therapy, the lead-in dose of nevirapine should be omitted. Close monitoring of adherence and of plasma HIV RNA is warranted if rifampicin and nevirapine are used concomitantly. Therapeutic drug monitoring of nevirapine, if available, should be considered.

Hormonal contraception and hormone therapy

Hormonal methods of birth control other than with depot medroxyprogesterone acetate should not be used as the sole method of contraception in women taking nevirapine because nevirapine might lower the plasma concentration of these medications. 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.

Lipodystrophy

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 higher risk of lipodystrophy has been associated with individual factors such as older age, and with drug-related factors such as longer duration of antiretroviral treatment and associated metabolic disturbances. Clinical examination should include evaluation for physical signs of fat redistribution.

Lipid disorders

Nevirapine has been associated with raised HDL-cholesterol and improved total to HDL-cholesterol ratio. However, the clinical impact of these findings is not known; the selection of antiretroviral medicines must be guided primarily by their antiviral efficacy. Measurement of fasting serum lipids and blood glucose should be considered. Lipid disorders should be managed as clinically appropriate.

Osteonecrosis

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

Immune reactivation syndrome

In HIV-infected patients with severe immune deficiency when combination antiretroviral therapy is started, an inflammatory reaction to asymptomatic or residual opportunistic pathogens may occur and cause serious clinical conditions, or aggravation of symptoms. Typically, such reactions occur in the first few weeks or months of starting combined antiretroviral therapy. Examples of infection include cytomegalovirus (CMV)

retinitis, mycobacterial infections, and *Pneumocystis jirovecii* (formerly known as *Pneumocystis carinii*) pneumonia. Autoimmune disorders such as Graves disease have also been reported; such reactions may occur many months after starting antiretroviral treatment. Any inflammatory symptoms should be evaluated and treated if necessary.

Excipients

[HA567 trade name] contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

It is important to consider the contribution of excipients from all the medicines that the patient is taking.

4.5 Interaction with other medicinal products and other forms of interaction

Nevirapine induces CYP3A and potentially CYP2B6, with maximal induction within 2–4 weeks of initiating multiple-dose therapy. The plasma concentration of compounds using this metabolic pathway may decrease when given with nevirapine. Careful monitoring of the therapeutic effectiveness of P450-metabolised medicines is recommended when taken in combination with nevirapine.

The absorption of nevirapine is not affected by food, antacids or medicines formulated with an alkaline buffer.

The interaction data are presented as geometric mean value with 90% confidence interval (90% CI) when these data were available. ND = not determined, ↑ = increased, ↓ = decreased, ↔ = no effect

Medicines by therapeutic area	**Interaction**	**Recommendations concerning co-administration of nevirapine**
Antimicrobials		
Antiretrovirals		
Nucleoside reverse transcriptase inhibitors (NRTIs)		
Abacavir	No interaction	Abacavir and nevirapine can be given together without dose adjustments
Didanosine 100–150 mg twice daily	No interaction	Didanosine and nevirapine can be given together without dose adjustments
Emtricitabine	No interaction	Emtricitabine and nevirapine can be given together without dose adjustments
Lamivudine 150 mg twice daily	No interaction	Lamivudine and nevirapine can be given together without dose adjustments.
Stavudine 30/40 mg twice daily	No significant interaction	Stavudine and nevirapine can be given together without dose adjustments.
Tenofovir 300 mg once daily	No interaction	Tenofovir and nevirapine can be given together without dose adjustments.

Medicines by therapeutic area	Interaction	Recommendations concerning co-administration of nevirapine
Zidovudine 100–200 mg three times daily	No significant interaction	Zidovudine and nevirapine can be given together without dose adjustments Concomitant use of zidovudine and nevirapine, especially in children, may increase the risk of granulocytopenia
Non-nucleoside reverse transcriptase inhibitors (NNRTI)		
Delavirdine	Interaction has not been studied	Concomitant administration of nevirapine with NNRTIs is not recommended (see section 5.1)
Efavirenz 600 mg once daily	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)	Giving efavirenz and nevirapine together is not recommended because of additive toxicity and no benefit in efficacy over either NNRTI alone.
Etravirine	Concomitant use of etravirine with nevirapine may significantly decrease the plasma concentration of etravirine and reduce etravirine's therapeutic effect	The concomitant administration of nevirapine with NNRTIs is not recommended (see section 5.1)
Rilpivirine	Interaction has not been studied	The concomitant administration of nevirapine with NNRTIs is not recommended (see section 5.1)
Protease inhibitors		
Atazanavir/ritonavir 300/100 mg once daily 400/100 mg once daily	<u>Atazanavir/ritonavir 300/100 mg:</u> Atazanavir/ritonavir AUC ↓ 0.58 (0.48–0.71) Atazanavir/ritonavir C_{min} ↓ 0.28 (0.20–0.40) Atazanavir/ritonavir C_{max} ↓ 0.72 (0.60–0.86) <u>Atazanavir/ritonavir 400/100 mg:</u> Atazanavir/r AUC ↓ 0.81 (0.65–1.02) Atazanavir/ <u>ritonavir</u> C_{min}↓ 0.41 (0.27–0.60) Atazanavir/ <u>ritonavir</u> C_{max} ↔ 1.02 (0.85–1.24) Compared to 300/100 mg without nevirapine: Nevirapine AUC ↑ 1.25 (1.17–1.34) Nevirapine C_{min} ↑ 1.32 (1.22–1.43) Nevirapine C_{max} ↑ 1.17 (1.09–1.25)	Giving atazanavir/ritonavir and [HA567 trade name] together is not recommended.
Darunavir/ritonavir 400/100 mg twice daily	Darunavir AUC ↑ 1.24 (0.97–1.57) Darunavir C_{min} ↔ 1.02 (0.79–1.32) Darunavir C_{max} ↑ 1.40 (1.14–1.73) Nevirapine AUC ↑ 1.27 (1.12–1.44) Nevirapine C_{min}↑ 1.47 (1.20–1.82) Nevirapine C_{max} ↑ 1.18 (1.02–1.37)	Darunavir and nevirapine can be given together without dose adjustments.

Medicines by therapeutic area	Interaction	Recommendations concerning co-administration of nevirapine
Fosamprenavir 1.4 g twice daily	Amprenavir AUC ↓ 0.67 (0.55–0.80) Amprenavir C_{min}↓ 0.65 (0.49–0.85) Amprenavir C_{max}↓ 0.75 (0.63–0.89) Nevirapine AUC ↑ 1.29 (1.19–1.40) Nevirapine C_{min} ↑ 1.34 (1.21–1.49) Nevirapine C_{max} ↑ 1.25 (1.14–1.37)	Giving fosamprenavir and nevirapine together is not recommended if fosamprenavir is not co-administered with ritonavir.
Fosamprenavir/ritonavir 700/100 mg twice daily	Amprenavir AUC ↔ 0.89 (0.77–1.03) Amprenavir C_{min}↓ 0.81 (0.69–0.96) Amprenavir C_{max} ↔ 0.97 (0.85–1.10) Nevirapine AUC ↑ 1.14 (1.05–1.24) Nevirapine C_{min} ↑ 1.22 (1.10–1.35) Nevirapine C_{max} ↑ 1.13 (1.03–1.24)	Fosamprenavir/ritonavir and nevirapine can be given together without dose adjustments
Indinavir 800 mg three times daily	Indinavir AUC ↓ 28% Nevirapine ↔ (CYP3A4 induction)	A higher dose of indinavir or ritonavir-boosted indinavir should be considered if given with [HA567 trade name]
Lopinavir/ritonavir (capsules) 400/100 mg twice daily	Adults: Lopinavir AUC ↓ 0.73 (0.53–0.98) Lopinavir C_{min}↓ 0.54 (0.28–0.74) Lopinavir C_{max}↓ 0.81 (0.62–0.95)	An increase in the dose of lopinavir/ritonavir to 533/133 mg or 500/125 mg twice daily with food is recommended in combination with nevirapine. Dose adjustment of nevirapine is not required when given together with lopinavir.
Lopinavir/ritonavir (oral solution) 300/75 mg/m^2 twice daily	<u>Children:</u> Lopinavir AUC ↓ 0.78 (0.56–1.09) Lopinavir C_{min}↓ 0.45 (0.25–0.82) Lopinavir C_{max}↓ 0.86 (0.64–1.16)	For children, increasing the dose of lopinavir/ritonavir to 300/75 mg/m^2 twice daily with food should be considered when used in combination with nevirapine, particularly if reduced susceptibility to lopinavir/ritonavir is suspected.
Nelfinavir 750 mg three times daily	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) Nevirapine: compared to historical controls, levels appeared to be unchanged.	Nelfinavir and nevirapine can be given together without dose adjustments.

Medicines by therapeutic area	**Interaction**	**Recommendations concerning co-administration of nevirapine**
Ritonavir 600 mg twice daily	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: Ritonavir does not lead to clinically relevant change in nevirapine plasma levels.	Ritonavir and nevirapine can be given together without dose adjustments.
Saquinavir/ritonavir	Limited data on saquinavir soft gel capsule boosted with ritonavir do not suggest clinically relevant interaction between saquinavir boosted with ritonavir and nevirapine	Saquinavir/ritonavir and nevirapine can be given together without dose adjustments.
Tipranavir/ritonavir 500/200 mg twice daily	No specific drug-drug interaction study has been performed. Limited data from a phase IIa study in HIV-infected patients have shown clinically non-significant 20% decrease of tipranavir C_{min}.	Tipranavir and nevirapine can be given together without dose adjustments.
Entry inhibitors		
Enfuvirtide	Due to the metabolic pathway no clinically significantpharmacokinetic interaction is expected between enfuvirtide and nevirapine.	Enfuvirtide and nevirapine can be given together without dose adjustments.
Maraviroc 300 mg once daily	Maraviroc AUC ↔ 1.01 (0.6–1.55) Maraviroc C_{min} ND Maraviroc C_{max} ↔ 1.54 (0.94–2.52) compared to historical controls Nevirapine concentration not measured, no effect is expected.	Maraviroc and nevirapine can be given together without dose adjustments.
Integrase inhibitors		
Elvitegravir/cobicistat	Interaction has not been studied. Cobicistat, a cytochrome P4503A-inhibitor significantly inhibits hepatic enzymes as well as other metabolic pathways. Therefore, co-administration would likely result in altered plasma levels of cobicistat and nevirapine	Giving [HA567 trade name] with elvitegravir in combination with cobicistat is not recommended
Raltegravir 400 mg twice daily	No clinical data available. Due to the metabolic pathway of raltegravir no interaction is expected.	Raltegravir and [HA567 trade name] can be given together without dose adjustments.
Antivirals for chronic hepatitis B and C		
Adefovir	In vitro studies showed weak antagonism of nevirapine by adefovir (see section 5.1); this has not been confirmed in clinical trials and reduced efficacy is not expected. Adefovir did not influence any of the common cytochrome P450 enzymes involved in drug metabolism and is excreted renally. No clinically relevant interaction is expected.	Adefovir and [HA567 trade name] may be given together without dose adjustment

Medicines by therapeutic area	Interaction	Recommendations concerning co-administration of nevirapine
Boceprevir	Boceprevir is partly metabolised by CYP3A4/5. Giving boceprevir with medicines that induce or inhibit CYP3A4/5 could increase or decrease exposure. Plasma trough concentration of boceprevir was decreased when administered with a non-nucleoside reverse-transcriptase inhibitor with a similar metabolic pathway as nevirapine. The clinical outcome of this reduction of boceprevir trough concentrations has not been directly assessed.	Giving boceprevir and [HA567 trade name] together is not recommended
Daclatasvir	Interaction between nevirapine and daclatasvir has not been studied but daclatasvir concentrations are expected to fall due to induction of CYP3A4 by nevirapine.	Combination of [HA567 trade name] and daclatasvir not recommended
Elbasvir/grazoprevir	Interaction between elbasvir/grazoprevir and nevirapine has not been studied but elbasvir/grazoprevir concentrations are expected to fall because of induction of CYP3A4, CYP2B6 and BCRP by nevirapine; this may lead to reduced therapeutic effect	Combination of [HA567 trade name] and elbasvir/grazoprevir not recommended
Entecavir	Entecavir is not a substrate, inducer or an inhibitor of cytochrome P450 enzymes. Due to the metabolic pathway of entecavir, no clinically relevant drug-drug interaction is expected.	Entecavir and [HA567 trade name] may be given together without dose adjustment
Glecaprevir/pibrentasvir	Co-administration of nevirapine and glecaprevir/pibrentasvir has not been studied but glecaprevir/pibrentasvir concentrations may fall due to induction of CYP3A4 by nevirapine.	Combination of [HA567 trade name] and glecaprevir/pibrentasvir not recommended
Interferons (pegylated interferons alfa 2a and alfa 2b)	Interferons have no known effect on CYP3A4 or CYP2B6. No clinically relevant interaction is expected.	Interferons and nevirapine may be given together without dose adjustment
Ombitasvir/paritaprevir/ritonavir	Co-administration of nevirapine and ombitasvir/paritaprevir/ritonavir has not been studied. Plasma concentrations of ombitasvir/paritaprevir/ritonavir could decrease due to CYP3A4 induction by nevirapine; however, nevirapine exposure could increase due to inhibition by ritonavir	Combination of [HA567 trade name] and ombitasvir/paritaprevir/ritonavir is contraindicated
Ribavirin	In vitro studies showed weak antagonism of nevirapine by ribavirin (see section 5.1); this has not been confirmed in clinical trials and reduced efficacy is not expected. Ribavirin does not inhibit cytochrome P450 enzymes, and there is no evidence from toxicity studies that ribavirin induces liver enzymes. No clinically relevant interaction is expected.	Ribavirin and nevirapine may be given together without dose adjustment
Simeprevir	Interaction between nevirapine and simeprevir has not been studied but simeprevir concentrations are expected to fall due to induction of CYP3A4 by nevirapine.	Combination of [HA567 trade name] and simeprevir not recommended

Medicines by therapeutic area	**Interaction**	**Recommendations concerning co-administration of nevirapine**
Sofosbuvir/velpatasvir	Co-administration of nevirapine and sofosbuvir/velpatasvir has not been studied but concentrations of velpatasvir and sofosbuvir could decrease due to CYP3A4 induction by nevirapine	Combination of [HA567 trade name]and sofosbuvir/velpatasvir not recommended
Telaprevir	Telaprevir is metabolised in the liver by CYP3A and is a P-glycoprotein (P-gp) substrate. Other enzymes may be involved in its metabolism. Giving telaprevir and substances that induce CYP3A and P-gp (or both) may decrease telaprevir plasma concentration. No interaction study of telaprevir with nevirapine has been conducted; however, interaction studies of telaprevir with an NNRTI with a similar metabolic pathway as nevirapine found reduced levels of both.	Caution should be exercised when giving telaprevir with nevirapine. If given together with nevirapine, an adjustment in the telaprevir dose should be considered
Telbivudine	Telbivudine is not a substrate, inducer or inhibitor of the cytochrome P450 enzyme system. No clinically relevant interaction is expected.	Telbivudine and nevirapine may be given together without dose adjustment
Antibiotics		
Clarithromycin 500 mg twice daily	Clarithromycin AUC ↓ 0.69 (0.62–0.76) Clarithromycin C_{min} ↓ 0.44 (0.30–0.64) Clarithromycin C_{max} ↓ 0.77 (0.69–0.86) Metabolite 14-OH clarithromycin AUC ↑ 1.42 (1.16–1.73) Metabolite 14-OH clarithromycin C_{min} ↔ 0 (0.68–1.49) Metabolite 14-OH clarithromycin C_{max} ↑ 1.47 (1.21–1.80) Nevirapine AUC ↑ 1.26 Nevirapine C_{min} ↑ 1.28 Nevirapine C_{max} ↑ 1.24 compared to historical controls.	Clarithromycin exposure was significantly decreased, 14-OH metabolite exposure increased. Because the clarithromycin active metabolite has reduced activity against *Mycobacterium avium-intracellulare complex* overall activity against the pathogen may be altered. Alternatives to clarithromycin, such as azithromycin should be considered. Close monitoring for hepatic abnormalities is recommended If clarithromycin is used, at least 2-hour gap is recommended between taking [HA567 trade name]and clarithromycin

Medicines by therapeutic area	**Interaction**	**Recommendations concerning co-administration of nevirapine**
Rifabutin 150 or 300 mg once daily	Rifabutin AUC ↑ 1.17 (0.98–1.40) Rifabutin C_{min} ↔ 1.07 (0.84–1.37) Rifabutin C_{max} ↑ 1.28 (1.09–1.51) Metabolite 25-*O*-desacetylrifabutin AUC ↑ 1.24 (0.84–1.84) Metabolite 25-*O*-desacetylrifabutin C_{min} ↑ 1.22 (0.86–1.74) Metabolite 25-*O*-desacetylrifabutin C_{max} ↑ 1.29 (0.98–1.68) A clinically not relevant increase in the apparent clearance of nevirapine (by 9%) compared to historical data was reported.	No significant effect on rifabutin and nevirapine pharmacokinetic parameters is seen. Rifabutin and nevirapine can be given together without dose adjustments. However, due to high inter-subject variability, rifabutin exposure may increase substantially in some patients, raising the risk for rifabutin toxicity. Combination of rifabutin and [HA567 trade name] should be used with caution.
Rifampicin 600 mg once daily	Rifampicin AUC ↔ 1.11 (0.96–1.28) Rifampicin C_{min} ND Rifampicin C_{max} ↔ 1.06 (0.91–1.22) Nevirapine AUC ↓ 0.42 Nevirapine C_{min} ↓ 0.32 Nevirapine C_{max} ↓ 0.50 compared to historical controls.	Giving rifampicin and [HA567 trade name] together is not recommended. When treating tuberculosis, substituting rifabutin for rifampicin or use of an antiretroviral drug combination that omits nevirapine should be considered (see section 4.4).
Antifungals		
Fluconazole 200 mg once daily	Fluconazole AUC ↔ 0.94 (0.88–1.01) Fluconazole C_{min} ↔ 0.93 (0.86–1.01) Fluconazole C_{max} ↔ 0.92 (0.85–0.99) Nevirapine exposure: ↑ 100% compared with historical data where nevirapine was administered alone.	Because of the risk of increased exposure to nevirapine, patients should be monitored closely for nevirapine toxicity.
Itraconazole 200 mg once daily	Itraconazole AUC ↓ 0.39 Itraconazole C_{min} ↓ 0.13 Itraconazole C_{max} ↓ 0.62 Nevirapine: nevirapine pharmacokinetic parameters did not change significantly.	A dose increase for itraconazole should be considered when given with [HA567 trade name].
Ketoconazole 400 mg once daily	Ketoconazole AUC ↓ 0.28 (0.20–0.40) Ketoconazole C_{min} ND Ketoconazole C_{max} ↓ 0.56 (0.42–0.73) Nevirapine: plasma levels: ↑ 1.15–1.28 compared to historical controls.	Giving ketoconazole and [HA567 trade name] together is not recommended.

Medicines by therapeutic area	Interaction	Recommendations concerning co-administration of nevirapine
Antimalarials		
Amodiaquine 600 mg once daily (with aretesunate)	Amodiaquine AUC ↓ 29% Desethylamodiaquine AUC ↓ 33%	The patient treated with combination of [HA567 trade name] and amodiaquine/artesunate should be carefully monitored for efficacy and safety. Combined use may increase hepatotoxicity
Atovaquone, chloroquine, mefloquine, proguanil, sulfadoxine, pyrimethamine	No formal interaction study available	On theoretical basis, clinically significant interactions with nevirapine are unlikely
Artemisinin and its derivatives	No formal interaction study available	Nevirapine may reduce the concentration of artemisinin and its derivatives, but clinical consequences are unknown
Halofantrine	No formal interaction study available. Halofantrine is extensively metabolised by CYP3A and an interaction is predicted. Alteration of halofantrine metabolism could affect its plasma concentrations	[HA567 trade name] should be used cautiously with halofantrine, which has a narrow therapeutic index
Lumefantrine	Lumefantrine AUC ↑ 1.56 Lumefantrine C_{max} ↑ 1.24	Preliminary studies suggest no increase in adverse effects of lumefantrine. Nevirapine can be given with artemether + lumefantrine without dose adjustment (see also under Artemisinin and its derivatives)
Quinine	Quinine AUC ↓ 0.67 Quinine C_{max} ↓ 0.64	Nevirapine significantly lowers the concentration of quinine and can reduce its antimalarial effect
Anticonvulsants		
Carbamazepine, phenobarbital, phenytoin	No formal interaction study available	Concentrations of nevirapine and of the anticonvulsant are expected to be reduced, leading to treatment failure; concomitant administration should be avoided unless antiretroviral (and antiepileptic) effect can be monitored closely
Antacids		
Cimetidine	Cimetidine: no significant effect on cimetidine pharmacokinetic parameters is seen. Nevirapine: C_{min} ↑ 1.07	Cimetidine and nevirapine can be given together without dose adjustments.
Anticoagulants		
Warfarin	The interaction between nevirapine and warfarin is complex, with the potential for both increase and decrease in coagulation time when used concomitantly.	Close monitoring of anticoagulation activity is warranted.

Medicines by therapeutic area	Interaction	Recommendations concerning co-administration of nevirapine
Contraceptives		
Depot medroxyprogesterone acetate 150 mg every 3 months	Medroxyprogesterone acetate AUC ↔ Medroxyprogesterone acetate C_{min} ↔ Medroxyprogesterone acetate C_{max} ↔ Nevirapine AUC ↑1.20 Nevirapine C_{max} ↑1.20	Nevirapine did not alter the ovulation suppression effects of depot medroxyprogesterone acetate. Depot medroxyprogesterone acetate and [HA567 trade name] can be given together without dose adjustments.
Ethinylestradiol 35 micrograms	Ethinylestradiol AUC ↓ 0.80 (0.67–0.97) Ethinylestradiol C_{min} ND Ethinylestradiol C_{max} ↔ 0.94 (0.79–1.12)	Oral hormonal contraceptives should not be used as the sole method of contraception in women taking [HA567 trade name] (see section 4.4). Except for medroxyprogesterone acetate, appropriate doses for hormonal contraceptives (oral or other forms of application) in combination with nevirapine have not been established.
Norethisterone 1 mg once daily	Norethisterone AUC ↓ 0.81 (0.70–0.93) Norethisterone C_{min} ND Norethisterone C_{max} ↓ 0.84 (0.73–0.97)	
Drug abuse		
Methadone individual patient dosing	Methadone AUC ↓ 0.40 (0.31–0.51) Methadone C_{min} ND Methadone C_{max} ↓ 0.58 (0.50–0.67)	Methadone-maintained patients beginning nevirapine therapy should be monitored for withdrawal effects 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 drug metabolism enzymes, or transport proteins, or both by St. John's wort.	St. John's wort must not be given with nevirapine (see section 4.3). If a patient is already taking St John's wort, check nevirapine concentration, and if possible viral levels, and stop St John's wort if necessary. Nevirapine levels may increase on stopping St John's wort. The dose of nevirapine may need adjusting. The inducing effect may persist for at least 2 weeks after stopping St John's wort.

Nevirapine metabolites: Studies using human liver microsomes indicated that the formation of nevirapine hydroxylated metabolites was not affected by dapsone, rifabutin, rifampicin, and trimethoprim/sulfamethoxazole. Ketoconazole and erythromycin significantly inhibited the formation of nevirapine hydroxylated metabolites.

4.6 Fertility, pregnancy and breastfeeding

Women of childbearing potential should generally not rely on hormonal contraceptives as the sole method for birth control, since nevirapine might lower the plasma concentration of hormonal contraceptives (see sections 4.4).

Pregnancy

Available data on pregnant women indicate no malformative, fetal or neonatal toxicity. No observable teratogenicity was detected in reproductive studies in rats and rabbits (see section 5.3). Caution should be exercised when prescribing nevirapine to pregnant women. Hepatotoxicity is more frequent in women with CD4 cell counts above 250 cells/mm^3 with detectable HIV-1 RNA in plasma (50 or more copies per ml), and should be taken into consideration when making therapeutic decision (see section 4.4).

Breastfeeding

Nevirapine readily crosses the placenta and is found in breast milk.

Current recommendations on HIV and breastfeeding (e.g., those from the WHO) should be consulted before advising patients on this matter. Preferred options may vary depending on the local circumstances.

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 studies on the effects on the ability to drive and use machines.

However, patients should be advised of undesirable effects, such as fatigue, during treatment with nevirapine. Therefore, caution should be recommended and if patients experience such undesirable effect, they should avoid potentially hazardous tasks such as driving or operating machinery.

4.8 Undesirable effects

The most frequently reported adverse reactions related to nevirapine in clinical trials were rash, allergic reactions, hepatitis, abnormal liver function tests, nausea, vomiting, diarrhoea, abdominal pain, fatigue, fever, headache and myalgia.

Postmarketing experience has shown that the most serious adverse reactions are Stevens-Johnson syndrome and toxic epidermal necrolysis, serious hepatitis or hepatic failure, and hypersensitivity reactions, 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 during which close monitoring is required (see section 4.4).

The following adverse reactions related to nevirapine have been reported. The estimated frequencies are based on pooled clinical trial 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 (1/1000 to 1/100); rare (1/10 000 to 1/1000); very rare (< 1/10 000); not known (cannot be estimated from the available data).

Blood and lymphatic system disorders

Common: granulocytopenia (reported more frequently in children)

Uncommon: anaemia

Immune system disorders

Common: hypersensitivity (including anaphylactic reactions, angioedema and urticaria)

Uncommon: anaphylactic reactions

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: fulminant hepatitis (may be fatal)

Skin and subcutaneous tissue disorders

Very common: rash (12.5%)

Very rare: Severe cutaneous adverse reactions: Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported, angioedema, urticaria

Musculoskeletal and connective tissue disorders

Uncommon: arthralgia, myalgia

General disorders and administration site conditions

Common: fever, fatigue

Investigations

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

Uncommon: blood phosphorus decreased, blood pressure increased

Description of selected adverse reactions

Combination antiretroviral therapy has been associated with redistribution of body fat (lipodystrophy) in HIV patients including the loss of peripheral and facial subcutaneous fat, increased intra-abdominal 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 antiretroviral agents: pancreatitis, peripheral neuropathy and thrombocytopaenia. These adverse reactions are commonly associated with other antiretroviral agents and may be expected 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 starting combination antiretroviral therapy, an inflammatory reaction to asymptomatic or residual opportunistic infections may arise (see section 4.4). Autoimmune disorders (such as Graves' disease) have also been reported; however, the reported time to onset is more variable and these events can occur many months after starting treatment (see section 4.4).

Cases of osteonecrosis have been reported, particularly in patients with risk factors, advanced HIV disease or long-term exposure to combination antiretroviral therapy. 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 and toxic epidermal necrolysis. Fatal cases of Stevens-Johnson syndrome, toxic epidermal necrolysis, 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 disorders

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

Paediatric population

Based on clinical study experience of 361 paediatric patients, the majority of whom received combination treatment with zidovudine or didanosine, or both, the most frequently reported adverse events related to nevirapine were similar to those in adults. Granulocytopenia was more frequent in children. In an open-label clinical study (ACTG 180) granulocytopenia assessed as medicine--related occurred in 5/37 (13.5 %) of patients. In a double-blind, placeb-controlled study, the frequency of serious medicine-related granulocytopenia was 5/305 (1.6 %).

Isolated cases of Stevens-Johnson syndrome or Stevens-Johnson with transition to toxic epidermal necrolysis have been reported in children.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Health care providers are asked to report any suspected adverse reactions to the marketing authorisation holder, or, if available, via the national reporting system.

4.9 Overdose

There is no antidote for nevirapine overdosage. Cases of nevirapine overdose at doses ranging from 800 mg 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.

Children

One case of massive accidental overdose in a new born was reported. The ingested dose was 40 times the recommended dose of 2 mg/kg/day. Mild isolated neutropenia and hyperlactataemia was found, which resolved spontaneously 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 (NNRTI), ATC code J05AG01.

Mechanism of Action

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

Clinical efficacy

Clinical studies on nevirapine have demonstrated significant decrease in plasma HIV RNA and increases in CD4 cell count when used in combination with other nucleoside analogues, or a protease inhibitor, or both.

In a multicentre open-label randomised trial in patients not previously treated with antiretrovirals, 220 patients were assigned to receive nevirapine 400 mg once daily, 387 to nevirapine 200 mg twice daily, 400 to efavirenz once daily and 209 to both efavirenz and nevirapine, all combined with lamivudine and stavudine, for 48 weeks. Treatment failure (the primary endpoint) was reached by 43.7% patients receiving nevirapine once daily, 43.7% receiving nevirapine twice daily, 37.8% receiving efavirenz and 53.1% receiving both drugs. Antiretroviral therapies with nevirapine or efavirenz were considered to have similar efficacy, but the adverse-effects of regimens containing the two were different.

A multicentre open-label randomised trial in patients taking two nucleoside reverse transcriptase inhibitors and at least one protease inhibitor, and in whom viral suppression had been achieved, switched patients from the protease inhibitor to nevirapine (155 patients), efavirenz (156) or abacavir (149). The likelihood of reaching the endpoint (death, progression to AIDS, or an increase in viral RNA level above 200 copies/ml) at 12 months was 10% in the nevirapine group, 6% in the efavirenz group and 13% in the abacavir group. Fewer patients in the abacavir group (6%) than in the nevirapine group (17%) or the efavirenz group (17%) discontinued the study medication because of adverse events.

Drug resistance

The most common resistance mutations selected for by nevirapine are Y181C, K103N and G190A. All these mutations cause high-level resistance to nevirapine. Patients failing nevirapine-containing antiretroviral therapy can also develop cross-resistance to efavirenz and delavirdine (http://hivdb.stanford.edu). Similarly, patients failing therapy which includes efavirenz or delavirdine will usually have a virus cross-resistant to nevirapine. If failing therapy is continued, further resistance mutations will accumulate.

High-level resistance to nevirapine can occur after a single dose when used alone, as has been demonstrated by the high prevalence of resistance mutations after using nevirapine for preventing mother-to-child transmission. When effective nevirapine-containing antiretroviral therapy is discontinued, the prolonged persistence of nevirapine in the body may lead to significant nevirapine resistance. This may compromise the effectiveness of NNRTI therapy used in the future.

Perinatal Transmission

A study evaluated the efficacy of nevirapine to prevent transmission of HIV-1 infection from mother to baby. Mothers received only study antiretroviral therapy during these trials. Mother-infant pairs were randomised to receive oral nevirapine (mother: nevirapine 200 mg at the onset of labour; infant: nevirapine 2 mg/kg within 72 hours of birth), or an ultra-short oral zidovudine regimen (mother: zidovudine 600 mg at the onset of labour and 300 mg every 3 hours until delivery; infant zidovudine 4 mg/kg twice daily for 7 days). The 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 ($p = 0.00063$).

A study in 123 women who had received single-dose nevirapine for preventing mother-to-child transmission and who were then treated with nevirapine combined with other antiretroviral drugs indicated that single-

dose nevirapine alone reduces the efficacy of subsequent use of nevirapine as part of combination antiretroviral therapy.

Paediatric population

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

5.2 Pharmacokinetic properties

No pharmacokinetic data are available for [HA567 trade name]. A bioequivalence study was conducted with [HA570 trade name] which contains 200 mg nevirapine and is essentially the same as [HA567 trade name] in qualitative terms and with respect to the ratio of active and other ingredients.

The absorption characteristics of [HA570 trade name] have been determined after administration of one nevirapine 200 mg tablet in healthy volunteers in the fasting state as follows:

Pharmacokinetic variable	**Mean value* (±standard deviation)**
	Nevirapine
Maximum concentration (C_{max})	2.47 ± 0.71 µg/mL
Area under the curve (AUC_{0-72h}), a measure of the extent of absorption	115.12 ± 25.58 µg·h/mL
Time to attain maximum concentration (T_{max})	7.5 ± 8.4 hours

*arithmetic mean

Pharmacokinetics of nevirapine

Absorption	
Oral bioavailability	>90%
Distribution	
Volume of distribution (mean)	1.2 L/kg
Plasma proteinbinding*in vitro*	60%
Metabolism	
	Cytochrome P450 isozymes CYP3A and CYP2B6, and glucuronidation. Autoinduction resulting in decreased plasma half-life after 2-4 weeks of dosing Three major metabolites:2-hydroxy-nevirapine glucoronide, 3-hydroxy-nevirapine glucoronide and 12-hydroxy-nevirapine glucuronide
Active metabolite(s)	None
Elimination	
Elimination half life	45 h after single dose and

	25-30 hours after multiple doses (200-400 mg)
Mean systemic clearance (Cl/F)	1.6 L/h/kg
% of dose excreted in urine	> 80% (<5% excreted unchanged)
% of dose excreted in faeces	10%
Pharmacokinetic linearity	Linear pharmacokinetics
Metabolizing enzymes	CYP3A, CYP2B6, UGT

Special populations

Renal dysfunction: Renal impairment (mild, moderate and severe) does not significantly change the pharmacokinetics of nevirapine. The dose of nevirapine does not need to be adjusted in patients with creatinine clearance ≥ 20 ml/minute. However, in subjects with end-stage renal disease on dialysis, nevirapine AUC was reduced. There is also accumulation of nevirapine hydroxy-metabolites in plasma. An additional 200-mg dose of nevirapine following each dialysis treatment could help offset the effects of dialysis on nevirapine clearance.

Hepatic dysfunction: The disposition of nevirapine and the five oxidative metabolites is not altered in patients with mild to severe liver fibrosis. However, in a few patients with hepatic fibrosis nevirapine trough concentration may be 2-fold higher than the usual mean trough concentration. Patients with hepatic impairment should be monitored carefully for drug-induced toxicity.

5.3 Preclinical safety data

Preclinical 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 reproductive toxicology studies, evidence of impaired fertility was seen in rats. In carcinogenicity studies, nevirapine induces hepatic tumours in rats and mice. These findings are most likely related to nevirapine being a strong inducer of liver enzymes, and not due to a genotoxic mode of action.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

60 months

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

HDPE bottle

Round, opaque, white-coloured HDPE bottle, with a polypropylene child-resistant cap.
Pack sizes: 30, 60 and 90 tablets.

Blisters
PVC/PVDC-Al blisters. Pack size:10 tablets per blister card. 3 or 6 cards in a carton.

6.6 Instructions for use and handling and disposal

No special requirements.
Any unused product or waste material should be disposed of in accordance with local requirements.

7. SUPPLIER

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8. WHO REFERENCE NUMBER (WHO Prequalification Programme)

HA567

9. DATE OF PREQUALIFICATION

19 February 2014

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References

General Reference

The major source for the information in this SmPC is the European SmPC for Viramune available at http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000183/WC500051481.pdf (accessed on 21 May 2019)

For further information, the following sources have also been used.

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4.5 Drug interactions

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Martinez E, Arnaiz JA, Podzamczer D, et al. Substitution of nevirapine, efavirenz, or abacavir for protease inhibitors in patients with human immunodeficiency virus infection. N Engl J Med 2003; 349: 1036–46

Detailed information on this medicine is available on the World Health Organization (WHO) website: https://extranet.who.int/pqweb/medicines