Nevimune Baby

xxxxxxxx

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Nevimune Baby

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each dispersible tablet contains 50 mg of nevirapine (as anhydrous).
Excipients with known effect: each tablet contains 41 mg of lactose monohydrate and 4.25mg of aspartame (see section 4.4)

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Dispersible tablet

White to off-white coloured, circular shaped, biconvex uncoated dispersible tablet with central break line on one side and 'L' debossed on other side.

The tablets can be divided into equal halves.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Nevimune Baby is indicated in combination with other antiretroviral medicines for the treatment of human immunodeficiency type 1 (HIV-1) infection in children weighing 3-24.9kg.

Official guidelines (e.g. those of the WHO) on the treatment of HIV-1 infection should be consulted.

This product is intended for use in children. Nevertheless, information is included on risks relevant to adults (for example, use in liver disease, pregnancy and breastfeeding); this provides access to the full information.

4.2 Posology and method of administration

Oral Use

Nevimune Baby should be initiated by a healthcare provider experienced in the management of HIV infection.

If a dose is missed and it is 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 of when it was due, the patient should only take the next dose at the usual time.

Newborn infants and children weighing less than 25 kg

For children weighing up to 25 kg, WHO-recommended doses are tabulated below; the dose is given once daily for two weeks followed by twice-daily maintenance dose.

Weight	'Lead-in' dose for 2 weeks[1]		Maintenance dose	
3–5.9 kg	1 tablet once daily	50 mg once daily	1 tablet twice daily	50 mg twice daily
6–9.9 kg	1½ tablets once daily	75 mg once daily	1½ tablets twice daily	75 mg twice daily
10–13.9 kg	2 tablets once daily	100 mg once daily	2 tablets twice daily	100 mg twice daily
14–19.9 kg	2½ tablets once daily	125 mg once daily	2½ tablets twice daily	125 mg twice daily
20–24.9 kg	3 tablets once daily	150 mg once daily	3 tablets twice daily	150 mg twice daily

[1] The lead-in dose for 2 weeks is recommended to avoid toxicity from high initial dose of nevirapine. However, secondary analysis from the CHAPAS-1 trial suggested that younger children have a lower risk of toxicity and consideration should be given to starting with a full dose

Children weighing 25 kg or more, adolescents and adults:

For patients weighing 25 kg or more, other formulations containing higher amounts of nevirapine are more suitable.

Dose management

If a rash develops during the 14-day lead-in period with once-daily dosing then the dose of nevirapine should **not** be increased until the rash has resolved. The uncomplicated rash should be closely monitored (see section 4.4). If the rash persists longer than 28 days and the full nevirapine dose cannot be given then an alternative regimen should be considered because of the risk of developing nevirapine resistance.

If nevirapine is interrupted for longer than 7 days, it should be restarted with once-daily dosing and the dose increased after 14 days to the full, twice-daily regimen.

For adverse effects that require interruption of nevirapine therapy, see section 4.4.

Renal impairment

No dose adjustment is required for patients with creatinine clearance ≥ 20 ml/minute (see section 5.2). For patients on renal dialysis, an additional dose of Nevimune Baby is recommended after each dialysis.

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 years.

Method of administration

Nevimune Baby may be taken with or without food.

Nevimune Baby may be dispersed in water if the child is not able to swallow the tablet. Using dry hands, the recommended dose should be placed in a drinking container such as a tumbler or a beaker.

Drinking water should then be added to the container. The minimum volume of water for dispersing the dose is shown below;

Dose of Nevimune Baby recommended for the child	Minimum volume of drinking water to be used
1 or 1½ tablets	10 ml (about 2 teaspoonfuls)
2 or 2½ tablets	15 ml (about 3 teaspoonfuls)
3 tablets	20 ml (about 4 teaspoonfuls)

The mixture should be swirled or stirred to disperse the tablets completely. The child should drink all the content of the container. The container should then be rinsed with more water and the child should drink this also to ensure that the whole dose is taken.

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 if pre-treatment aspartate aminotransferase (AST) or alanine aminotransferase (ALT) concentration is more than 5 times upper limit of normal until baseline AST and ALT are stabilised to less than 5 times upper limit of normal.

Nevirapine should not be given again to patients who previously had AST or ALT more than 5 times upper limit of normal during nevirapine therapy and had recurrence of liver function abnormalities upon re-administration of nevirapine (see section 4.4).

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. ≥ 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/or 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 be discontinued 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 hepatotoxicity, 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 4.4). Concomitant use of nevirapine with elvitegravir/cobicistat or with boceprevir is also not recommended (see section 4.4).

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 (see also section 4.5). 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 *post-menopausal* 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 jiroveci* (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.

Important information about some of the other ingredients of Nevimune Baby

Nevimune Baby contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance (e.g. galactosaemia, the Lapp lactase deficiency or glucose-galactose malabsorption) should not take this medicine.

Nevimune Baby contains aspartame, which may be a source of phenylalanine. May be harmful for people with phenylketonuria.

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
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)		
Efavirenz 600 mg once daily	Efavirenz AUC ↓0.72 (0.66–0.86) Efavirenz C_{max} ↓0.68 (0.65–0.81) Efavirenz C_{min} ↓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.
Delavirdine	Interaction has not been studied	Concomitant administration of nevirapine with NNRTIs is not recommended (see section 5.1)
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	Atazanavir/ritonavir 300/100 mg: 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) Atazanavir/ritonavir 400/100 mg: Atazanavir/r AUC ↓0.81 (0.65–1.02) Atazanavir /ritonavir C_{min} ↓0.41 (0.27– 0.60) Atazanavir/ ritonavir 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 nevirapine 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) NevirapineC_{max} ↑ 1.18 (1.02–1.37)	Darunavir and nevirapine can be given together without dose adjustments.
Fosamprenavir 1.4 g twice daily	Amprenavir AUC ↓ 0.67 (0.55–0.80) Amprenavir C_{max} ↓ 0.65 (0.49–0.85) Amprenavir C_{min} ↓ 0.75 (0.63–0.89) Nevirapine AUC ↑ 1.29 (1.19–1.40) Nevirapine C_{max} ↑ 1.34 (1.21–1.49) Nevirapine C_{min} ↑ 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_{max} ↓ 0.81 (0.69–0.96) Amprenavir C_{min} ↔ 0.97 (0.85–1.10) Nevirapine AUC ↑ 1.14 (1.05–1.24) Nevirapine C_{max} ↑ 1.22 (1.10–1.35) Nevirapine C_{min} ↑ 1.13 (1.03–1.24)	Fosamprenavir/ritonavir and nevirapine can be given together without dose adjustments
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	Children: 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_{max} ↓ 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.
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 significant pharmacokinetic 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 nevirapine with elvitegravir in combination with cobicistat is not recommended (see section 4.4)
Raltegravir 400 mg twice daily	No clinical data available. Due to the metabolic pathway of raltegravir no interaction is expected.	Raltegravir and nevirapine 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 nevirapine may be given together without dose adjustment
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 nevirapine together is not recommended (see section 4.4)
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 nevirapine may be given together without dose adjustment
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

PATIENT INFORMATION LEAFLET

PATIENT INFORMATION LEAFLET: INFORMATION FOR THE USER

Nevimune Baby

Nevirapine 50mg Dispersible Tablets

Read all of this leaflet carefully before you start giving this medicine to your child

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your healthcare provider.
- This medicine has been prescribed for your child. Do not pass it on to others. It may harm them, even if their signs of illness are the same as those of your child.
- If your child gets any side effects, talk to your healthcare provider. This includes any possible side effects not listed in this leaflet. See section 4.

In this leaflet:

1. WHAT NEVIMUNE BABY IS AND WHAT IT IS USED FOR

Nevimune Baby belongs to a group of antiviral medicines also known as antiretrovirals, called non- nucleoside reverse transcriptase inhibitors (NNRTIs). which are used for the treatment of Human Immunodeficiency Virus (HIV-1) infection in children weighing 3- 24.9kg.

Nevirapine helps to control HIV-1 infection by preventing the multiplication of HIV in the blood. Specifically, nevirapine interferes with the virus enzyme called *reverse transcriptase*, which is needed for making copies of the virus.

To prevent the virus becoming resistant to nevirapine, your child must take Nevimune Baby together with other antiretroviral medicines. Your healthcare provider will recommend the best medicines for your child.

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

2. BEFORE YOUR CHILD TAKES NEVIMUNE BABY Your child should not be given Nevimune Baby:

- if your child is allergic to nevirapine or to any of the other ingredients of this medicine (listed in section 6)
- if your child has taken a medicine containing nevirapine before and had to stop the treatment because your child suffered from:
  - severe skin rash
  - skin rash with other symptoms for example:
    - fever
    - blistering
    - mouth sores
    - inflammation of the eye
    - swelling of the face
    - general swelling
    - shortness of breath
    - muscle or joint pain
    - general feeling of illness
    - abdominal pain
  - allergic (hypersensitivity) reactions
  - inflammation of the liver (hepatitis)
- if your child has severe liver disease
- if your child has had to stop nevirapine treatment in the past because of changes in liver function
- if your child is taking St John's wort (*Hypericum perforatum*, herbal remedy against depression). This herbal substance may stop Nevimune Baby from working properly.

Warnings and precautions

During the first 18 weeks of treatment with Nevimune Baby, you and your healthcare provider must watch out for signs of liver or skin reactions in your child. The reactions can become severe and even life threatening. Your child is at greatest risk of such reactions in the first 6 weeks of treatment.

Your child should **stop** taking Nevimune Baby and you **must** contact your healthcare provider **at once** if your child has severe rash or develops **allergic reactions** (hypersensitivity) together with other side effects such as:

- fever
- blistering
- mouth sores
- redness and swelling of the eye
- swelling of the face
- swelling in various parts of the body
- shortness of breath
- muscle or joint pain
- general feeling of illness
- abdominal (belly) pain

If your child has a mild rash without any other reaction please tell your healthcare provider **at once**-the healthcare provider will advise you whether your child should stop taking Nevimune Baby.

Your child should **stop** taking Nevimune Baby and you **must** contact your healthcare provider **at once** if your child has symptoms of **liver damage**. The following symptoms can suggest liver damage:

- loss of appetite
- feeling sick (nausea)
- vomiting
- yellow skin and eyes (jaundice)
- dark urine
- discoloured stool
- abdominal (belly) pain

If your child develops severe liver, skin or allergic (hypersensitivity) reactions whilst taking Nevimune Baby, your child should never take Nevimune Baby again without checking with your healthcare provider.

Your child must take the dose of Nevimune Baby as prescribed. This is especially important in the first 2 weeks of treatment (see more information in 'How to administer Nevimune Baby').

The following are at higher risk of liver problems while taking Nevimune Baby:

- women
- people who have hepatitis B or C infection
- people whose liver function tests are abnormal
- people with higher CD4 cell count at the start of nevirapine therapy (women more than 250 CD4- cells per cubic millimetre, men more than 400 CD4-cells per cubic millimetre)

In some patients with advanced HIV infection (AIDS) who have had other infections, signs and symptoms of these previous infection may occur soon after starting antiretroviral treatment ('immune reactivation syndrome'). These symptoms probably result from improvement in the body's immune response, enabling the body once again to fight infections that may be present but caused no obvious symptoms. If you notice any symptoms of infection, tell your healthcare provider immediately.

Also, autoimmune disorders (involving the immune system attacking healthy body tissue) may occur after starting treatment with HIV medicines. Autoimmune disorders may occur many months after the start of treatment. Tell your healthcare provider immediately if you notice any infection or other symptoms such as muscle weakness, weakness starting in the hands and feet and moving towards the trunk of the body, palpitations, tremor or hyperactivity.

Changes of body fat may occur in patients receiving combination antiretroviral therapy. Contact your health care provider if you notice changes in body fat (see section 4, Possible side effects).

Some patients taking combination antiretroviral therapy may develop osteonecrosis (a condition caused by death of bone tissue because of reduced blood supply to the bone). The condition is more likely with long-term combination antiretroviral therapy, corticosteroid use, excessive use of alcohol, very weak immune system, and being overweight. Osteonecrosis causes joint stiffness, aches and pains (especially of the hip, knee and shoulder) and difficulty in movement. If you notice any of these symptoms tell your healthcare provider.

If your child is also taking zidovudine, tell your healthcare provider because it may be necessary to check your child's white blood cells.

Nevirapine is not a cure for HIV infection. Therefore, your child may continue to develop infections and other illnesses associated with HIV infection. Therefore, your child should be in regular contact with the health care provider.

Nevirapine does not prevent the risk of passing on HIV to others through blood or sexual contact and precautions are needed to prevent passing on HIV to other people. Ask your healthcare provider for more information.

Taking other medicines

Before your child starts nevirapine treatment, tell your healthcare provider if your child is taking or has taken any medicines, including medicines obtained without a prescription. Your healthcare provider might need to check if your child's other medicines are still needed and if any doses need to be changed. Carefully read the patient information leaflet of all other HIV medicines your child is taking with Nevimune Baby.

If your child is taking or is prescribed a medicine which contains **rifampicin** to treat tuberculosis, you must tell your health care provider before your child takes this medicine with Nevimune Baby.

Tell your healthcare provider if your child is taking or has recently taken:

- St John's wort (*Hypericum perforatum*, medicine to treat depression)
- rifabutin and rifampicin (medicines to treat tuberculosis)
- clarithromycin and other macrolide antibiotics (medicine to treat bacterial infection)
- fluconazole, itraconazole and ketoconazole (medicines to treat fungal infection)
- methadone (medicine for opioid addiction)
- warfarin (medicine to prevent blood clotting)
- atazanavir, delavirdine, efavirenz, elvitegravir/cobicistat, etravirine, fosamprenavir, lopinavir/ritonavir, rilpivirine, and zidovudine (medicines to treat HIV-infection)
- boceprevir and telaprevir (medicines to treat hepatitis C)

Your health care provider will carefully check the effect of Nevimune Baby and any of these medicines if your child is taking them together.

A contraceptive (birth control) pill or other types of hormonal contraception may not be suitable for a woman starting nevirapine treatment. The woman should ask her health care provider for advice on an alternative method of contraception. Barrier methods of contraception (e.g. condoms) are suitable and they prevent passing on of HIV to another person.

A woman using post-menopausal hormone replacement therapy should take advice from her healthcare provider before starting nevirapine treatment.

Taking Nevimune Baby with food and drink

There are no restrictions on taking Nevimune Baby with food and drink.

Pregnancy, breast-feeding and fertility

A woman who is pregnant or thinks she may be pregnant should ask her healthcare provider before taking any medicine.

If a mother wants to breast-feed her baby, she should ask her healthcare provider for advice on the risks and benefits. Treatment with medicines of mother or child or both may be needed.

It is generally recommended that the infant is not breast-fed if the mother has HIV infection because it is possible that the baby can become infected with HIV through breast milk.

Driving and using machines

The effect of nevirapine on a person's ability to drive vehicles and use machinery has not been specifically studied. Nevirapine may make a person feel tired. If the person feels tired or feels that the ability to drive or use machines may be affected then the person should not drive or use machines.

Important information about some of the other ingredients of Nevimune Baby

Nevimune Baby contains lactose . If a healthcare provider has told you that your child has an intolerance to some sugars, contact your healthcare provider before giving this medicine to your child.

Nevimune Baby contains aspartame, a source of phenylalanine, which may be harmful for children with phenylketonuria.

3. HOW TO TAKE NEVIMUNE BABY

Always give this medicine exactly as described in this leaflet or as your healthcare provider has told you. Check with your healthcare provider if you are not sure.

Your child should not take Nevimune Baby on its own. Your child must take it with at least two other antiretroviral medicines. Your healthcare provider will recommend the best medicines for your child.

Give Nevimune Baby by mouth only. Your child may take Nevimune Baby with food or between meals.

Dose

The dose of nevirapine for a child is calculated according to the child's body weight. Nevimune Baby is intended for children weighing less than 25 kg. For children weighing more than 25 kg, other products, with larger amount of nevirapine, are available.

At the start of treatment, give the dose once a day usually for 2 weeks. This is called the 'lead-in' dose. If your child has any rash during this period, do not increase the dose but see your health care provider. The 2-week 'lead-in' period lowers the risk of skin rash.

If all is well, your healthcare provider will then ask you to give the dose twice daily to continue treatment.

The recommended lead-in and maintenance doses are shown below:

Child's weight	'Lead-in' dose (usually for 2 weeks)	Dose for continuing treatment
3–5.9 kg	1 tablet once daily	1 tablet twice daily
6–9.9 kg	1½ tablets once daily	1½ tablets twice daily

xxxxxxxx

Actual size 684 x 304 mm
size after folding 38 x 38 mm

RAMA - D:\JOBS\WHO\Nevimune Baby\ Nevimune Baby Leaflet.indd
Date: 18-04-2019

10–13.9 kg	2 tablets once daily
14–19.9 kg	2½ tablets once daily
20–24.9 kg	3 tablets once daily

Your healthcare provider will check your child for unwanted effects such as rash and for any problems with the liver. The healthcare provider may decide to stop Nevimune Baby treatment if necessary. The healthcare provider might then restart nevirapine treatment at a lower dose.

For patients on kidney dialysis, the health care provider may adjust the dose of Nevimune Baby because dialysis removes nevirapine from blood.
Your child should continue to take Nevimune Baby for as long as instructed by your health care provider.

If you have any questions on the use of this product, ask your healthcare provider. Ask your child to swallow Nevimune Baby tablets with water. If your child cannot swallow the tablet, you can mix the tablets in a small quantity of water as described below.
- Using dry hands, put the recommended dose in a clean tumbler (or beaker).
- Add a small amount of clean drinking water to the tumbler. The amount of water depends on how much is needed to mix the dose properly (see table, below) and how much your child will drink.

Dose of Nevimune Baby recommended for your child	Amount of clean drinking water to use for mixing the dose
1 or 1½ tablets	10 ml (about 2 teaspoonfuls)
2 or 2½ tablets	15ml (about 3 teaspoonfuls)
3 tablets	20ml (about 4 teaspoonfuls)

- Swirl or stir the tumbler to mix the tablets completely in water.
- The child should drink all the mixture.

If your child takes more Nevimune Baby than the child should
Your child must not be take more Nevimune Baby than prescribed by your healthcare provider. There is little information on the effects of nevirapine overdose. Ask your healthcare provider if your child has taken more Nevimune Baby than your child should.

If your child has missed a dose of Nevimune Baby
Try not to miss giving a dose. If your child has missed a dose within 8 hours, give the missed dose as soon as possible. If more than 8 hours have passed since the dose was due, omit the missed dose and give the next dose at the usual time.

If your child stops taking Nevimune Baby
It is important to give HIV medicines, including Nevimune Baby, regularly and at the right time to:
- ensure that the combination of antiretroviral medicines works as well as possible
- reduce the chances of the HIV becoming resistant to the antiretroviral medicines your child is taking

It is important that your child continues taking Nevimune Baby correctly, unless your health care provider stops the medicine.

If your child has not taken Nevimune Baby for more than 7 days, your healthcare provider will ask that your child starts the 2-week 'lead-in' period once again, before returning to the twice-daily dose.
If you have any questions about your treatment, ask your healthcare provider.

4. POSSIBLE SIDE EFFECTS
The most important side effects of nevirapine are severe and life-threatening skin reactions and serious liver damage. These reactions occur mainly in the first 18 weeks of treatment with nevirapine. Your health care provider will monitor your child closely during this important period.
If your child ever has a rash, tell your healthcare provider immediately.

If a rash occurs, it is normally mild to moderate. However, in some patients a rash, which appears as a blistering skin reaction, can be severe (Stevens-Johnson syndrome and toxic epidermal necrolysis) and deaths have occurred. Most cases of severe rash and mild or moderate rash occur in the first 6 weeks of treatment.

The side effects described below have occurred in patients given nevirapine:

Very common side effects (that occur in at least 1 out of 10 patients treated)
- rash

Common side effects (that occur in up to 1 out 10 patients treated)
- decreased white blood cells (granulocytopenia)—more common in children
- allergic reactions (hypersensitivity)
- headache
- feeling sick (nausea)
- vomiting
- abdominal (belly) pain
- loose stools (diarrhoea)
- inflammation of the liver (hepatitis)
- feeling tired (fatigue)
- fever
- abnormal liver function tests

Uncommon side effects (that occur in up to 1 out 100 patients treated)
- allergic reaction with rash, swelling of the face, difficulty breathing (bronchial spasm) or anaphylactic shock
- decreased red blood cells (anaemia)—more common in children
- yellow skin and eyes (jaundice)
- severe and life-threatening skin rashes (Stevens-Johnson syndrome and toxic epidermal necrolysis)
- hives (urticaria)
- accumulation of fluid under the skin and swelling (angioedema)
- joint pain
- muscle pain
- decreased blood phosphorus
- increased blood pressure

Rare side effects (that occur in up to 1 out 1000 patients treated)
- sudden and intense inflammation of the liver (fulminant hepatitis)
- drug rash with symptoms which affect the whole body (drug rash with eosinophilia and systemic symptoms)

Combination antiretroviral therapy may change body shape by changes in fat distribution. The changes may include legs, arms and face becoming thinner, increased fat in the abdomen (belly) and other internal organs, breast becoming larger, and fatty lumps appearing on the back of the neck ('buffalo hump'). The cause and long-term effects of these changes is not known. Combination antiretroviral therapy may also raise lactic acid, cause resistance to insulin, raise sugar in the blood, and increase fats in the blood.

The following effects have also been reported with nevirapine when it is used with other antiretroviral medicines:
- decreased red blood cells or platelets
- inflammation of the pancreas
- decreased or abnormal skin sensations

These effects are associated with other antiretroviral medicines and it is unlikely that nevirapine causes them.
As with rash, tell your healthcare provider of any side effects.

If any side effects get serious, or if you notice any side effects not listed in this leaflet, tell your healthcare provider.

5. HOW TO STORE NEVIMUNE BABY
Do not store above 30°C.

Keep out of the reach and sight of children.

Do not use Nevimune Baby after the expiry date which is stated on the bottle and on the blister after "EXP". The expiry date refers to the last day of that month.

To protect the environment, medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required.

6. FURTHER INFORMATION What Nevimune Baby contains
- The active substance is nevirapine. Each dispersible tablet contains 50 mg nevirapine.
- The other ingredients are:
  - Aspartame
  - Corn starch
  - Lactose monohydrate
  - Magnesium stearate
  - Microcrystalline cellulose
  - Sodium starch glycolate
  - Strawberry cream flavour (containing natural flavouring substance, maltodextrin, propylene glycol and modified starch)

What Nevimune Baby looks like and contents of the pack
White to off-white coloured, circular shaped, biconvex uncoated dispersible tablet with central break line on one side and 'L' debossed on other side.

The tablet can be divided into equal doses

The tablets are packaged in PVC/PE/PVDC-Al blisters. Each blister card contains 10 tablets. 6 such blisters are packed in one carton

The tablets are also packaged in HDPE bottle with non-CRC HDPE screw cap, containing a 1g silica gel bag as desiccant and rayon sani coil as filler. Each HDPE bottle contains 60 tablets.

Supplier
Cipla Limited
Cipla House,
Peninsula Business Park
Ganpatrao Kadam Marg, Lower Parel
Mumbai -400013, India
Phone : 9122 24826000
Fax: 9122 24826120
E-mail: globalrd@cipla.com

Manufacturer
Cipla Limited
Unit II, A-42, MIDC,
Patalganga, Dist: Raigad
410220, Maharashtra,India

Cipla Limited
Unit I, A-33 & A-37/2/2, MIDC
Patalganga, District: Raigad
410220, Maharashtra,India

For any information about this medicinal product, please contact the supplier:

This leaflet was last approved in July 2016

Detailed information on this medicine is available on the World Health Organization (WHO) web site: http://who.int/prequal/

Cipla

xxxxxxxx

Rifabutin	*In vitro* studies showed weak antagonism of nevirapine by rifabutin (see section 5.1); this has not been confirmed in clinical trials and reduced efficacy is not expected. Rifabutin does not inhibit cytochrome P450 enzymes, and there is no evidence from toxicity studies that rifabutin induces liver enzymes. No clinically relevant interaction is expected.	Rifabutin and nevirapine may be given together without dose adjustment
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. Results of interaction studies of telaprevir with efavirenz indicate that caution should be exercised when giving telaprevir with P450 inducers.	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_{max} ↓ 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_{max} ↔ 0 (0.68–1.49) Metabolite 14-OH clarithromycin C_{max} ↑ 1.47 (1.21–1.80) Nevirapine AUC ↑ 1.26 Nevirapine C_{min} ↑ 1.28 Nevirapine C_{max} ↑ 1.24 compared to historical controls.	Clarithromycin exposure was significantly decreased, 14-OH metabolite exposure increased. Because the clarithromycin active metabolite has reduced activity against *Mycobacterium avium- intracellulare complex* overall activity against the pathogen may be altered. Alternatives to clarithromycin, such as azithromycin should be considered. Close monitoring for hepatic abnormalities is recommended
Rifabutin 150 or 300 mg 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 intersubject variability, rifabutin exposure may increase substantially in some patients, raising the risk for rifabutin toxicity. Therefore, caution should be used in concomitant administration.
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 nevirapine together is not recommended (see section 4.4). When treating tuberculosis, substituting *rifabutin* for rifampicin or use of an antiretroviral drug combination that omits rifampicin 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 nevirapine.
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: ↑ 1.15–1.26 compared to historical controls.	Giving ketoconazole and nevirapine together is not recommended.
Antimalarials		
Quinine	Quinine AUC ↓ 0.67 Quinine C_{max} ↓ 0.64	Nevirapine significantly lowers the concentration of quinine and can reduce its antimalarial effect
Atovaquone, chloroquine, mefloquine, proguanil, sulfadoxine, pyrimethamine	No formal interaction study available	On theoretical basis, clinically significant interactions with nevirapine are unlikely
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)
Artemisinin and its derivatives	No formal interaction study available	Nevirapine may reduce the concentration of artemisinin and its derivatives, but clinical consequences are unknown
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_{SS} ↑ 1.07	Cimetidine and nevirapine can be given together without dose adjustments.
Antithrombotics		
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.
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 nevirapine can be given together without dose adjustments.
Ethinylestradiol 35 micrograms Norethisterone 1 mg once daily	Ethinylestradiol AUC ↓ 0.80 (0.67–0.97) Ethinylestradiol C_{min} ND Ethinylestradiol C_{max} ↔ 0.94 (0.79–1.12) Norethisterone AUC ↓ 0.81 (0.70–0.93) Norethisterone C_{min} ND Norethisterone C_{max} ↓ 0.84 (0.73–0.97)	Oral hormonal contraceptives should not be used as the sole method of contraception in women taking nevirapine (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.
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 Pregnancy, Breastfeeding, Fertility
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 and 4.5).

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 (see section 4.4). 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.

It is recommended that HIV-infected mothers do not breastfeed in order to avoid transmission of the virus. Only under specific circumstances may the benefits of breastfeeding be considered to outweigh the risks. The most recent official treatment guidelines (e.g. those issued by WHO) should be consulted before advising patients on this matter.

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****
* In a study from which the majority of related undesirable effects (n = 28) were received, patients on placebo had a higher incidence of granulocytopenia (3.3%) than patients on nevirapine (2.5%)
** This undesirable effect 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 = 2718).
*** This undesirable effect was observed in clinical studies with co-administration of tenofovir/emtricitabine.

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 placebo 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.

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 newborn was reported. The ingested dose was 40 times the recommended dose of 2 mg/kg daily. 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 (see section 4.4).

Perinatal Transmission
A study evaluating 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 Nevimune Baby.

A bioequivalence study was conducted with Nevimune Junior of Cipla Ltd., India which is proportionally similar to Nevimune Baby in composition with Viramune® oral suspension (containing nevirapine 50 mg/5 ml as nevirapine hemihydrate) of Boehringer Ingelheim, Inc., USA both administered as Nevirapine 200 mg in healthy adult human subjects under fasting conditions.

Absorption: Nevirapine is readily absorbed (> 90%) after oral administration.

Following single dose administration of Nevimune Junior, 2 tablets (200 mg nevirapine) in healthy adult volunteers, the mean (± SD) nevirapine C_{max} value was 2584 ng/ml (± 477 ng/ml), and the corresponding value for the area under the concentration–time curve (AUC) was 115483 ng.h/ml (± 17745 ng.h/ml). The mean (± SD) nevirapine $t_{1/2}$ value was 3.55 (± 4.80) hours.

Data reported in the literature from 20 HIV-infected patients suggest mean steady state C_{max} of 5.74 µg/ml and C_{min} of 3.73 µg/ml with mean AUC of 109.0 µg.h/ml in patients taking nevirapine 200 mg twice daily.

Long-term efficacy appears to be most likely in patients whose nevirapine trough concentration exceeds 3.5 µg/ml.

Distribution: Nevirapine is lipophilic; the volume of distribution is 1.21 l/kg. Nevirapine is about 60% bound to plasma. Nevirapine readily crosses the placenta and is found in breast milk.

Biotransformation and elimination: Nevirapine is extensively biotransformed via cytochrome P450 (oxidative) metabolism to several hydroxylated metabolites. Oxidative metabolism of nevirapine is mediated primarily by cytochrome P450 isozymes from the CYP3A family; other isozymes may have a secondary role. Urinary excretion is the principal route of elimination with more than 80% of the urinary elimination in the form of glucuronide conjugates of hydroxylated metabolites. Only a small fraction (< 5%) is excreted unchanged in urine (representing < 3% of the total dose.)

Nevirapine is an inducer of hepatic cytochrome P450 metabolic enzymes. After a single dose, the half- life of nevirapine is about 45 hours, which is reduced after multiple dosing for 2–4 weeks to about 25–30 hours because nevirapine induces its own metabolism.

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.

A biowaiver was granted for the additional tablet strength Nevimune Baby (Cipla Ltd., India) in accordance to the WHO guideline. In comparison with the strength of the test product used in the bioequivalence study, the Nevimune Baby was determined to be qualitatively essentially the same, the ratio of active ingredients and excipients between the strengths is considered essentially the same and the dissolution profiles between the formulations for the API were determined to be similar.

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
Aspartame
Corn starch
Lactose monohydrate
Magnesium stearate Microcrystalline cellulose Sodium starch glycolate
Strawberry cream flavour (containing natural flavouring substance, maltodextrin, propylene glycol and modified starch)

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
24 months

6.4 Special precautions for storage
Do not store above 30°C.

6.5 Nature and contents of container
Bottle pack:

HDPE bottle with non-CRC HDPE screw cap, containing a 1 g silica gel bag as desiccant and rayon sani coil as filler (pack size: 60 tablets).

Blister pack:
PVC/PE/PVDC-Al blister card containing 10 tablets. 6 cards per carton.

6.6 Special precautions for disposal
Any unused product or waste material should be disposed of in accordance with local requirements.

7. SUPPLIER
Cipla Limited
Cipla House,
Peninsula Business Park
Ganpatrao Kadam Marg, Lower Parel
Mumbai -400013, India
Phone: 9122 24826000
Fax: 91-22-24826120
E-mail: globalrd@cipla.com

8. WHO REFERENCE NUMBER (PREQUALIFICATION PROGRAMME)
HA 510

9. DATE OF FIRST PREQUALIFICATION/RENEWAL OF PREQUALIFICATION
19 February 2014

10. DATE OF REVISION OF THE TEXT
July 2016

Cipla

xxxxxxxx