SUMMARY OF PRODUCT CHARACTERISTICS

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Nevirapine Oral Suspension USP 50 mg/5 mL

Rx Only

1 NAME OF THE FINISHED PHARMACEUTICAL PRODUCT

Nevirapine Oral Suspension USP 50 mg/5 mL

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5ml of oral suspension contains Nevirapine 50 mg as Nevirapine hemihydrate

Excipients: Carbopol, methyl parahydroxybenzoate, propyl parahydroxybenzoate, sorbitol, sucrose, propylene glycol, polysorbate 80, sodium hydroxide and water.

3 PHARMACEUTICAL FORM

Nevirapine Oral Suspension is a white to off-white, homogenous suspension. It comes in bottles of 100 mL and 240 mL.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Nevirapine Oral Suspension is indicated in combination with other antiretroviral medicines for the treatment of human immunodeficiency type 1 (HIV-1) infected children with a body weight of less than 25 kg (see section 4.4).

Nevirapine is indicated for use in HIV-positive pregnant women (over 14 weeks of gestation) for prevention of maternal-fetal HIV transmission and for primary prophylaxis of HIV infection in newborn infants. The most recent official guidelines on prevention of mother-to-child transmission (PMTCT) of HIV (e.g. those issued by WHO) should be consulted to choose the appropriate regimen.

This product is primarily intended for use in children. Nonetheless, safety information is provided with respect to adult health issues such as liver disease, pregnancy and lactation, to allow full access to all relevant information.

4.2 Posology and method of administration

Nevirapine Oral Suspension should be prescribed by health professionals who are experienced in the treatment of HIV infection.

It is important that the entire measured dose of Nevirapine Oral Suspension oral suspension is administered (which may require rinsing the measuring device with a small quantity of water and administering this to the patient).

Nevirapine can be given with food or between meals.

Treatment of HIV infection (in combination with other antiretroviral medicines)

Dosage in children

For children aged over 6 weeks and weighing up to 25 kg, WHO-recommended doses are tabulated below on the basis of 160–200 mg/m^2 (maximum 200 mg) once daily for two weeks followed by 160–200 mg/m^2 (maximum 200 mg) twice daily thereafter.

Weight range	**'Lead-in' dose for 2**		**Maintenance dose**	
	Dose in mg	**Dose in ml of Nevirapine Oral Suspension**	**Dose in mg**	**Dose in ml of Nevirapine Oral Suspension**
3–5.9 kg	50 mg once daily	5 ml once daily	50 mg twice daily	5 ml twice daily
6–9.9 kg	80 mg once daily	8 ml once daily	80 mg twice daily	8 ml twice daily
10–13.9 kg	100 mg once daily	10 ml once daily	100 mg twice daily	10 ml twice daily
14–19.9 kg	130 mg once daily	13 ml once daily	130 mg twice daily	13 ml twice daily
20–24.9 kg	150 mg once daily	15 ml once daily	150 mg twice daily	15 ml twice daily

Children weighing under 10 kg should have their weight checked regularly to assess if dose adjustment is necessary.

Dosage in patients weighing 25 kg or more

For these patients nevirapine is also available as 200-mg tablets. The recommended dose for nevirapine is 200 mg once daily for the first 14 days followed by 200 mg nevirapine twice daily. When a patient weighing 25 kg or more is unable to swallow

tablets this dose may be administered as oral suspension, i.e. 20 ml Nevirapine Oral Suspension oral suspension.

Dose management considerations

Patients experiencing rash during the 14-day lead-in period of once-daily dosing should not have their nevirapine dose increased until the rash has resolved. The isolated rash should be closely monitored (please refer to section 4.4). The initial once-daily dosing regimen should not be continued beyond 28 days and alternative treatment should be sought due to the possible risk of underexposure and resistance.

Patients who interrupt nevirapine dosing for more than 7 days should restart the recommended dosing regimen using the 14-day lead-in period.

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

Renal impairment

Patients with creatinine clearance > 20 ml/minute do not require a dose adjustment (see section 5.2). For adult patients with renal dysfunction requiring dialysis an additional 200-mg dose of Nevirapine Oral Suspension following each dialysis treatment is recommended.

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 Oral Suspension has not been specifically investigated in patients over the age of 65years.

Dosage in the prevention of maternal-fetal transmission

Pregnant women should be given a single dose of 200 mg (20 ml of oral suspension) at the onset of labour (check most recent official guidelines on prevention of mother-to-child transmission (MTCT) of HIV for full regimens).

Newborn infants should be given nevirapine preferably within 6 hours after birth, continuing until 6 weeks old at doses shown below; in the case of breast-fed infants of mothers who are not continuing to receive triple therapy after birth, the infant should continue to receive nevirapine until 1 week after breast-feeding has stopped.

Age	**Dose in mg**	**Dose in ml of Nevirapine Oral Suspension oral suspension 50 mg/5 ml**
Birth to 6 weeks weighing under 2.5 kg	10 mg daily	1 ml daily
Birth to 6 weeks weighing over 2.5 kg	15 mg daily	1.5 ml daily
6 weeks–6 months	20 mg daily	2 ml daily
6–9 months	30 mg daily	3 ml daily
9 months to 1 week after end of breastfeeding	40 mg daily	4 ml daily

4.3 Contraindications:

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

Nevirapine must not be re-administered to patients who have required permanent discontinuation for severe rash, rash accompanied by constitutional symptoms, hypersensitivity reactions, or clinical hepatitis due to nevirapine.

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).

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

For antiretroviral therapy nevirapine should only be used with at least two other antiretroviral agents (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. Nevirapine persists in the blood for significant period after interrupting or discontinuing treatment; the resulting subtherapeutic concentration can induce viral resistance against nevirapine (see section 5.1).

Combination therapy with nevirapine is not a curative treatment for HIV-1; patients may continue to experience illnesses associated with advanced HIV-1 infection including opportunistic infections.

Patients should be advised that current antiretroviral therapy has not been proven to eliminate the risk of transmission of HIV-1 to others through sexual contact or contaminated blood. Appropriate precautions should continue to be taken.

The first 18 weeks of therapy with nevirapine are a critical period during which patients should be closely monitored for severe and life-threatening skin reactions (including Stevens-Johnson syndrome and toxic epidermal necrolysis) and for serious and life-threatening hepatitis or hepatic failure. The risk of hepatic events and skin reactions is greatest in the first 6 weeks of therapy.

Intensive clinical and laboratory monitoring, including liver function tests, should be performed when initiating therapy and during the first 6 weeks of treatment. However, the risk of hepatic events persists beyond this period and monitoring should continue at frequent intervals. Female gender and higher CD4 counts at the initiation of therapy increase the risk of hepatic adverse events. Unless the benefit outweighs the risk nevirapine should not be initiated in women with CD4 cell count greater than 250 cells/mm^3 or in men with CD4 cell count greater than 400 cells/mm^3.

Patients developing signs or symptoms of hepatitis, severe skin reaction or hypersensitivity reactions must discontinue nevirapine and seek medical evaluation immediately. Nevirapine must not be restarted following severe hepatic, skin or hypersensitivity reactions (see section 4.3). In some cases, hepatic injury has progressed despite discontinuation of treatment.

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. Any patient who has 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 **immediately** seek medical evaluation. In these patients nevirapine must not be restarted.

If patients present with a suspected nevirapine-associated rash, liver function tests should be performed. Patients with moderate to severe elevations (AST or ALT > 5 times ULN) should permanently discontinue nevirapine.

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

The risk of developing serious cutaneous reactions is increased by failure to follow the initial dosing of 200 mg once daily (160–200 mg/m^2 for patients weighing under 25 kg) during the lead-in period or by delaying medical consultation after initial cutaneous symptoms. Exceeding the recommended dose of nevirapine might increase the frequency and seriousness of skin reactions, such as Stevens-Johnson syndrome and toxic epidermal necrolysis. Women may be at higher risk of developing rash, whether receiving nevirapine or non-nevirapine containing therapy.

Patients and their caregivers 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. The majority of rashes associated with nevirapine occur within the first 6 weeks of initiation of therapy. Patients and their caregivers 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 instead.

Hepatic reactions

Healthcare providers, patients and their caregivers should be informed that hepatic reactions are major adverse effects of nevirapine and that they should look out for hepatic reactions. They should be vigilant for prodromal signs and features of hepatitis, such as anorexia, nausea, jaundice, bilirubinuria, acholic stools, hepatomegaly or liver tenderness. Patients and their caregivers should be instructed to seek medical attention promptly if these occur.

If AST or ALT increase to > 5 times ULN during treatment, nevirapine should be immediately stopped. If AST and ALT return to baseline values and if the patient had no clinical signs or symptoms of hepatitis, rash, constitutional symptoms or other findings suggestive of organ dysfunction, 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 permanently discontinued.

In case of clinical hepatitis, characterised by anorexia, nausea, vomiting, icterus AND laboratory findings (such as moderate or severe liver function test abnormalities (excluding increase in gamma- glutamyl transferase, 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.

Nevirapine must not be administered to patients with pre-treatment AST or ALT > 5 times ULN until baseline AST and ALT are stabilised < 5 times ULN (see section 4.3).

Liver function should be monitored if the patient has signs or symptoms of liver toxicity (e.g. anorexia, nausea, jaundice, bilirubinuria, acholic stools, hepatomegaly or liver tenderness) or hypersensitivity.

If the patient has moderate hepatic impairment, or has hepatitis B or hepatitis C infection, or if AST or ALT > 2.5 times ULN before or during treatment, then liver function should be monitored more frequently during regular clinic visits.

Asymptomatic elevation of liver enzymes occurs frequently but is not necessarily a contraindication to use of nevirapine. Asymptomatic elevation of gamma-glutamyl transferase (GGT) is not a contraindication to nevirapine therapy.

Data from adults indicate that women have a three-fold higher risk than men for symptomatic, often rash- associated, hepatic events and that patients with higher CD4 counts at initiation of nevirapine therapy are at higher risk of hepatic events with nevirapine.

Contraception

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 Oral Suspension since nevirapine might lower the plasma concentrations of these medications. For this reason, and to reduce the risk of HIV transmission, barrier contraception (e.g. condoms) is recommended.

Lipid disorders

Combination antiretroviral therapy has been associated with the redistribution of body fat (lipodystrophy) in HIV infected patients. The long-term consequences of this effect are currently unknown. Knowledge about the mechanism is incomplete. In adults, 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. Consideration should be given to the measurement of fasting serum lipids and blood glucose. Lipid disorders should be managed as clinically appropriate (see section 4.8).

Osteonecrosis

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

Immune Reactivation Syndrome

In HIV-infected patients with severe immune deficiency at the time of institution of combination antiretroviral therapy, an inflammatory reaction to asymptomatic or residual opportunistic pathogens may arise and cause serious clinical conditions, or aggravation of symptoms. Typically, such reactions occur in the first few weeks or months of initiation of

combined antiretroviral therapy. Relevant examples are cytomegalovirus (CMV) retinitis, mycobacterial infections, and pneumocystis pneumonia. Any inflammatory symptoms should be evaluated and treatment instituted when necessary.

Other warnings

Nevirapine Oral Suspension contains methyl parahydroxybenzoate and propyl parahydroxybenzoate, which may cause allergic reactions (possibly delayed), and exceptionally, bronchospasm.

4.5 Interaction with other medicinal products and other forms of interaction

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

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

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

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

Drugs by therapeutic area	**Interaction**	**Recommendations concerning co- administration of Nevirapine Oral Suspension**
Antimicrobials *Antiretrovirals*		
Nucleoside reverse transcriptase inhibitors		
Abacavir	No interaction	Abacavir and Nevirapine Oral Suspension can be co- administered without dose adjustments
Didanosine	No interaction	Didanosine and Nevirapine Oral Suspension can be co- administered without dose adjustments
Lamivudine 50 mg twice daily	No interaction	Lamivudine and Nevirapine Oral Suspension can be co- administered without dose adjustments.
Stavudine: 30/40 mg twice daily	No significant interaction	Stavudine and Nevirapine Oral Suspension can be co- administered without dose adjustments.
Tenofovir 300 mg once daily	No interaction	Tenofovir and Nevirapine Oral Suspension can be co- administered without dose adjustments.

Zidovudine 100–200 mg three times daily	No significant interaction	Zidovudine and Nevirapine Oral Suspension can be co- administered without dose adjustments
Non-nucleoside reverse transcriptase inhibitors (NNRTI)		
Efavirenz 600 mg once daily		Co-administration of efavirenz and Nevirapine Oral Suspension is not recommended because of additive toxicity and no benefit in efficacy over either NNRTI alone.
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/ritonavir 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)	Co-administration of atazanavir/ritonavir and Nevirapine Oral Suspension is not recommended.
Darunavir/ritonavir 400/100 mg twice daily	No significant interaction	Darunavir and Nevirapine Oral Suspension can be co- administered without dose adjustments.
Indinavir		Co-administration of indinavir and Nevirapine Oral Suspension is not recommended. Concomitant treatment with ritonavir- boosted indinavir is recommended only if therapeutic drug monitoring is available
Fosamprenavir 1.4 g twice daily	Amprenavir AUC ↑0.67 (0.55–0.80) Amprenavir C_{min}↑.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)	Co-administration of fosamprenavir and Nevirapine Oral Suspension 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 Oral Suspension can be co-administered without dose adjustments

Lopinavir/ritonavir (capsules) 400/100 mg twice daily	Adults: Lopinavir AUC ↑ 0.73 (0.53–0.98) Lopinavir Cmin ↑ □0.54 (0.28–0.74) Lopinavir Cmax ↑ □0.81 (0.62–0.95)	An increase in the dose of lopinavir/ritonavir to 533/133 mg (4 capsules) or 500/125 mg (5 tablets with 100/25 mg each) twice daily with food is recommended in combination with Nevirapine Oral Suspension. Dose adjustment of Nevirapine Oral Suspension is not required when co-administered with lopinavir.
Lopinavir/ritonavir (oral solution) 300/75 mg/m2 twice daily	Children: Lopinavir AUC↑ 0.78 (0.56–1.09) Lopinavir Cmin↑ 0.45 (0.25–0.82) Lopinavir Cmax↑ 0.86 (0.64–1.16)	For children, increase of the dose of lopinavir/ritonavir to 300/75 mg/m2 twice daily with food should be considered when used in combination with Nevirapine Oral Suspension, particularly for patients in whom reduced susceptibility to lopinavir/ritonavir is suspected.
Nelfinavir 750 mg three times daily		Nevirapine could reduce nelfinavir concentration; co-administration should be avoided unless antiviral effect can be monitored closely
Ritonavir 600 mg twice daily	No interaction	Ritonavir and Nevirapine Oral Suspension can be co- administered without dose adjustments.
Saquinavir/ritonavir	The limited data available with saquinavir soft gel capsule boosted with ritonavir do not suggest any clinically relevant interaction between saquinavir boosted with ritonavir and nevirapine	Saquinavir/ritonavir and Nevirapine Oral Suspension can be co-administered without dose adjustments.
Tipranavir/ritonavir 500/200 mg twice daily	Limited data from HIV-infected patients have shown a clinically non-significant 20% decrease of tipranavir Cmin.	Both tipranavir and nevirapine are hepatotoxic and co-administration is not recommended.
Entry inhibitors		
Enfuvirtide	Due to the metabolic pathway no clinically significant pharmacokinetic interactions are expected between enfuvirtide and nevirapine.	Enfuvirtide and Nevirapine Oral Suspension can be co- administered 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 concentrations not measured, no effect is expected.	Maraviroc and Nevirapine Oral Suspension can be co- administered without dose adjustments.
Integrase inhibitors		
Raltegravir 400 mg twice daily	No clinical data available. Due to the metabolic pathway of raltegravir no interaction is expected.	Raltegravir and Nevirapine Oral Suspension can be co- administered without dose adjustments.
Antibiotics		

Clarithromycin 500 mg twice daily	Clarithromycin AUC ↑ 0.69 (0.62–0.76) Clarithromycin Cmin ↑ 0.44 (0.30–0.64) Clarithromycin Cmax ↑ 0.77 (0.69–0.86) Metabolite 14-OH clarithromycin AUC ↑ 1.42 (1.16–1.73) Metabolite 14-OH clarithromycin Cmin ↔ 0 (0.68–1.49) Metabolite 14-OH clarithromycin Cmax ↑ 1.47 (1.21–1.80) Nevirapine AUC ↑ 1.26 Nevirapine Cmin ↑ 1.28 Nevirapine Cmax ↑ 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 Cmin↔ 1.07 (0.84–1.37) Rifabutin Cmax ↑ 1.28 (1.09–1.51) Metabolite 25-O-desacetylrifabutin AUC ↑ 1.24 (0.84–1.84) Metabolite 25-O-desacetylrifabutin Cmin ↑ 1.22 (0.86–1.74) Metabolite 25-O-desacetylrifabutin Cmax ↑ 1.29 (0.98–1.68)	No significant effect on rifabutin and Nevirapine Oral Suspension mean pharmacokinetic parameters is seen. Rifabutin and Nevirapine Oral Suspension can be co-administered without dose adjustments. However, due to high intersubject variability some patients may experience large increases in rifabutin exposure and may be at higher risk for rifabutin toxicity. Therefore, caution should be used in concomitant administration.
Rifampicin 600 mg once daily	Rifampicin AUC ↔ 1.11 (0.96–1.28) Rifampicin Cmin ND Rifampicin Cmax ↔ 1.06 (0.91–1.22) Nevirapine AUC ↑ 0.42 Nevirapine Cmin ↑.32 Nevirapine Cmax ↑ 0.50 compared to historical controls.	Co-administration of rifampicin and Nevirapine Oral Suspension is not recommended (see section 4.4). For treating tuberculosis, co-administration of rifabutin can be considered instead.
Antifungals		
Fluconazole 200 mg once daily	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 Oral Suspension, patients should be monitored closely for nevirapine toxicity.

Itraconazole 200 mg once daily	Itraconazole AUC↑ 0.39 Itraconazole Cmin ↑ 0.13 Itraconazole Cmax ↑ 0.62 Nevirapine: there was no significant difference in nevirapine pharmacokinetic parameters.	A dose increase for itraconazole should be considered when these two agents are administered concomitantly.
Ketoconazole 400 mg once daily	Ketoconazole AUC↑ 0.28 (0.20–0.40) Ketoconazole Cmin ND Ketoconazole Cmax↑ 0.56 (0.42–0.73) Nevirapine: plasma levels: ↑ 1.15–1.28 compared to historical controls.	Co-administration of ketoconazole and Nevirapine Oral Suspension is not recommended.
Antimalarials		
Quinine	Quinine AUC ↑ 0.67 Quinine Cmax ↑ 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 Cmax ↑ 1.24	Preliminary studies suggest no increase in adverse effects of lumefantrine. Nevirapine and artemether + lumefantrine can be co- administered 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; co- 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 Oral Suspension can be co- administered without dose adjustments.
Antithrombotics		

Warfarin	The interaction between nevirapine and the antithrombotic agent warfarin is complex, with the potential for both increases and decreases in coagulation time when used concomitantly.	Close monitoring of anticoagulation levels is warranted.
Contraceptives		
Depot medroxyprogesterone acetate 150 mg every 3 months	Depot medroxyprogesterone acetate AUC ↔ Depot medroxyprogesterone acetate C_{min} ↔ Depot medroxyprogesterone acetate C_{max} ↔ Nevirapine AUC ↑ 1.20 Nevirapine C_{max} ↑ 1.20	Nevirapine Oral Suspension did not alter the ovulation suppression effects of depot medroxyprogesterone acetate. Depot medroxyprogesterone acetate and Nevirapine Oral Suspension can be co-administered 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 Nevirapine Oral Suspension (see section 4.4). Appropriate doses for hormonal contraceptives (oral or other forms of application) other than depot medroxyprogesterone acetate in combination with Nevirapine Oral Suspension have not been established with respect to safety and efficacy.
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 Oral Suspension therapy should be monitored for evidence of withdrawal and methadone dose should be adjusted accordingly.
Herbal products		
St. John's Wort	Serum levels of nevirapine can be reduced by concomitant use of the herbal preparation St. John's Wort (*Hypericum perforatum*). This is due to induction of drug metabolism enzymes and/or transport proteins by St. John's Wort.	St. John's Wort and Nevirapine Oral Suspension must not be co-administered (see section 4.3). The inducing effect may persist for at least 2 weeks after cessation of treatment with St. John's Wort.

4.6 Fertility, pregnancy and lactation

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; this should be taken in consideration when making the therapeutic decision (see section 4.4).

Women of childbearing potential should not rely on oral contraceptives as the sole method for birth control, since nevirapine might lower the plasma concentrations of oral hormonal contraceptives (see sections 4.4 and 4.5).

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.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

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 and serious hepatitis or hepatic failure and hypersensitivity reactions, characterised by rash with constitutional symptoms such as fever, arthralgia, myalgia, rhabdomyolysis 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 which may be caused by nevirapine have been reported. The estimated frequencies are based on pooled clinical trial data for events considered related to nevirapine treatment.

Frequency is defined using the following convention: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000), not known (cannot be estimated from the available data).

Investigations

Common: liver function tests abnormal
The most frequent laboratory test abnormality is elevation of liver enzymes, including ALT, AST, GGT, total bilirubin and alkaline phosphatase. Asymptomatic elevations of GGT levels are the most frequent. See also section 4.4

Blood and lymphatic system disorders

Common: granulocytopenia (reported more frequently in children)

Uncommon: anaemia

Nervous system disorders *Common:*
headache

Gastrointestinal disorders

Common: vomiting, diarrhoea, abdominal pain, nausea

Skin and subcutaneous tissue disorders (see also section 4.4)

Very common: rash (13.6%)

Uncommon: Stevens-Johnson syndrome/toxic epidermal necrolysis (0.1%), angioneurotic oedema, urticaria

Musculoskeletal and connective tissue disorders

Common: myalgia

Uncommon: arthralgia

Not known: osteonecrosis (see section 4.4)

General disorders and administration site conditions

Common: fever, fatigue

Not known: immune reactivation syndrome (see section 4.4)

Immune system disorders

Common: hypersensitivity

Not known: drug rash with eosinophilia and systemic symptoms, anaphylaxis

Hepatobiliary disorders

Common: hepatitis

(1.4%) *Uncommon:*

jaundice *Rare:* fulminant

hepatitis

Metabolic and nutritional disorders

Combination antiretroviral therapy has been associated with redistribution of body fat and metabolic abnormalities—see section 4.4).

4.8 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: 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 the HIV-2 reverse transcriptase or on eukaryotic DNA polymerases alpha, beta, gamma, and delta.

Clinical efficacy

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

In a multicentre open-label randomised trial (2NN Study) 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 (by the NEFA Study Team) in patients who were taking two nucleoside reverse transcriptase inhibitors and at lease 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.

Perinatal Transmission

The HIVNET 012 study in Uganda evaluated the efficacy of nevirapine to prevent vertical transmission of HIV-1 infection. 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 cumulative HIV-1 infant infection rate at 14–16 weeks was 13.1% (n = 310) in the nevirapine group, versus 25.1% (n = 308 in the ultra-short zidovudine group ($p = 0.00063$).

A study in Malawi, involving 3016 infants being breastfed by mothers with HIV-1 infection, compared three regimens: single-dose nevirapine plus 1 week of zidovudine (control regimen) and extended prophylaxis with either nevirapine or nevirapine plus zidovudine. At 9 months, the infection rate in infants who received the control regimen was 10.6%. In contrast, the HIV-1 infection rate in infants receiving extended regimen of nevirapine was 5.2% ($p < 0.001$) and in infants receiving extended regimen of nevirapine and zidovudine it was 6.4% ($p = 0.002$).

Drug resistance

The most common resistance mutations selected for by nevirapine are Y181C, K103N and G190A. All of 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). Conversely, 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 is selected for by a single dose when used alone, as has been demonstrated by the high prevalence of resistance mutations following nevirapine use for prevention of mother-to-child transmission. Due to the long half-life of nevirapine, a period of functional monotherapy with nevirapine may follow upon discontinuation of effective nevirapine-containing antiretroviral therapy. This may cause significant nevirapine resistance, and compromise the efficacy of future NNRTI therapy (see section 4.4).

A study involved infants of HIV-infected mothers receiving either placebo or single-dose nevirapine for prevention of mother-to-child HIV transmission, followed by subsequent treatment with nevirapine combined with other antiretroviral drugs. The study indicated reduced efficacy of subsequent nevirapine as part of combined therapy in infants who had previously received single-dose nevirapine alone.

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.

5.2 Pharmacokinetic properties

Absorption: Nevirapine is rapidly absorbed following oral administration. Bioavailability is > 90%.

Following single dose administration of Nevirapine Oral Suspension 10 ml (100 mg nevirapine) in healthy adult volunteers, the mean (± SD) nevirapine C_{max} value was 1.5 µg/ml (± 0.3 µg/ml), and the corresponding value for the area under the concentration–time curve (AUC) was 53 µg.h/ml (± 11 µg.h/ml). The median (± SD) nevirapine t_{max} value was 2.17 (± 0.87) hours.

Literature data from 20 HIV-infected patients reported mean steady-state C_{max} and C_{min} in plasma of 5.7 µg/ml and 3.7 µg/ml, respectively at a dose of 200 mg nevirapine twice daily. The average area under the curve (AUC) was 109 µg.hour/ml.

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 litre/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 of autoinduction (nevirapine inducing its own metabolism).

Special populations:

Renal dysfunction: Renal impairment (mild, moderate and severe) does not significantly change the pharmacokinetics of nevirapine. Patients with creatinine clearance ≥ 20 ml/minute do not require an adjustment in nevirapine dosing. However, in subjects with end-stage renal disease requiring 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 patients with hepatic fibrosis nevirapine trough concentration may be up to 2-fold higher than the usual mean trough

concentration. Patients with hepatic impairment should be monitored carefully for evidence of drug-induced toxicity.

Paediatric patients: Clearance of nevirapine increased with increasing age in a manner consistent with increasing body surface area. From 65 Zambian children who were dosed according to weight bands (as also recommended in section 4.2) with a fixed-dose combination containing stavudine, lamivudine and nevirapine a 12-hour pharmacokinetic curve was obtained in steady-state conditions. Compared to historical data, nevirapine concentrations were higher and more variable than in adults; as nevirapine underdosing is of greater concern than overdosing, the dosing recommendations appear appropriate.

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

Carbopol, methyl parahydroxybenzoate, propyl parahydroxybenzoate, sorbitol, sucrose, polysorbate 80, propylene glycol, sodium hydroxide and water.

6.2 Incompatibilities

None.

6.3 Shelf life

Please refer outer package for expiry date

<u>240 ml</u>

After first opening of the container: 7 months

<u>100 ml</u>

After first opening of the container: 3 months

6.4 Special precautions for storage

Do not store above 30°C. Store in the original package.

6.5 Nature and contents of container

White opaque high density polyethylene bottle, containing 100 mL or 240 mL of oral solution, with child resistant closure. An oral dosing syringe along with adapter is included in the pack.

6.6 Instructions for use and handling

Shake the bottle gently

7 MARKETING AUTHORIZATION HOLDER:

AUROBINDO

M/s Aurobindo Pharma Ltd,

Plot No.: 2, Maitrivihar,

Ameerpet, Hyderabad-500 038

India.

8 DATE OF REVISION OF TEXT: March 2018

NDC 65862-057-24 (240 ml)

NDC 65862-057-11 (100 ml)

Botswana Reg. No. : BOT 0700906 S2

NAFDAC Reg. No. : 04-8377

Tanzania Reg. No. : TAN 06, 347 J05A AUR

Zambia Reg. No. : 127/035

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