1.3 Product Information

1.3.1 Summary of Product Characteristics (SmPC)

Summary of Product Characteristics (SmPC) for **Nevirapine Tablets USP 200 mg** is enclosed overleaf.

SUMMARY OF PRODUCT CHARACTERISTICS
Nevirapine Tablets USP 200 mg

Rx Only

1. NAME OFTHE FINISHED PHARMACEUTICAL PRODUCT

Nevirapine Tablets USP 200 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains Nevirapine USP 200 mg

Excipients: Lactose monohydrate, microcrystalline cellulose, sodium starch glycolate, povidone, colloidal silicon dioxide and magnesium stearate.

3. PHARMACEUTICAL FORM

White to off-white, oval shaped, biconvex tablets, one side debossed with "C" and "35" with a single bisect separating the "C" and "35". The other side has a single bisect.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Nevirapine Tablets are indicated in combination with other antiretroviral medicines for the treatment of human immunodeficiency type 1 (HIV-1) infected adults, adolescents, and children of any age (see section 4.4).

Nevirapine chemoprophylaxis is indicated for use in HIV-positive pregnant women (over 14 weeks of gestation) for prevention of maternal-fetal HIV transmission. 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.

4.2 Posology and method of administration

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

Nevirapine Tablets may be taken with food or between meals.

<u>Adults, children and adolescents weighing over 25 kg</u>

The recommended dose of Nevirapine Tablets is one 200-mg tablet daily for the first 14 days (this lead-in period has been found to lessen the frequency of rash), followed by one 200-mg tablet twice daily, in combination with at least two additional antiretroviral agents.

Dose management considerations

Patients experiencing rash during the 14-day lead-in period of 200 mg once daily 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 200 mg once-daily dosing regimen should not be continued beyond 28 days when an alternative treatment should be sought due to the possible risk of underexposure and resistance.

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

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

Children

Nevirapine Tablets, following the dosing schedule described above, are suitable for children and adolescents who weigh more than 25 kg.

Nevirapine oral suspension can be used for infants and children weighing less than 25 kg; the oral suspension is also used for primary prophylaxis of HIV infection in newborn infants.

Renal impairment

No dose adjustment is required for patients with creatinine clearance ≥ 20 ml/minute, see section 5.2. For patients with renal dysfunction requiring dialysis an additional 200-mg dose of Nevirapine Tablets 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 Tablets have not been specifically investigated in patients over the age of 65 years

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

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 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 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 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 200-mg once-daily dosing regimen should not be continued beyond 28 days when an alternative treatment should be instituted.

Hepatic reactions

Healthcare providers and patients 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 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 starting dose of 200 mg once daily for 14 days followed by 200 mg twice daily. 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 gamma-glutamine 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.

Women have a three-fold higher risk than men for symptomatic, often rash-associated, hepatic events and 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 Tablets, 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 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. 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. Patients 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.

Lactose: Nevirapine Tablets contain 928 mg of lactose per maximum recommended daily dose. Patients with rare hereditary problems of galactose intolerance e.g. galactosaemia, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

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

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

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

The interaction data 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 tablets**
Antimicrobials *Antiretrovirals*		
Nucleoside reverse transcriptase inhibitors		
Abacavir	No interaction	Abacavir and Nevirapine tablets can be co-administered without dose adjustments
Didanosine	No interaction	Didanosine and Nevirapine tablets can be co-administered without dose adjustments
Lamivudine 50 mg twice daily	No interaction	Lamivudine and Nevirapine tablets can be co-administered without dose adjustments.
Stavudine: 30/40 mg twice daily	No significant interaction	Stavudine and Nevirapine tablets can be co-administered without dose adjustments.
Tenofovir 300 mg once daily	No interaction	Tenofovir and Nevirapine tablets can be co-administered without dose adjustments.
Zidovudine 100–200 mg three times daily	No significant interaction	Zidovudine and Nevirapine tablets can be co-administered without dose adjustments
Non-nucleoside reverse transcriptase inhibitors (NNRTI)		
Efavirenz 600 mg once daily		Co-administration of efavirenz and Nevirapine tablets 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/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)	Co-administration of atazanavir/ritonavir and Nevirapine tablets is not recommended.
Darunavir/ritonavir 400/100 mg twice daily	No significant interaction	Darunavir and Nevirapine tablets can be co-administered without dose adjustments.
Indinavir		Co-administration of indinavir and Nevirapine tablets 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 ↓ 0.65 (0.49–0.85) Amprenavir Cmax ↓ 0.75 (0.63–0.89) Nevirapine AUC ↑ 1.29 (1.19–1.40) Nevirapine C min ↑ 1.34 (1.21–1.49) Nevirapine Cmax ↑ 1.25 (1.14–1.37)	Co-administration of fosamprenavir and Nevirapine tablets 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 Cmin ↓ 0.81 (0.69–0.96) Amprenavir Cmax ↔ 0.97 (0.85–1.10) Nevirapine AUC ↑ 1.14 (1.05–1.24) Nevirapine C min ↑ 1.22 (1.10–1.35) Nevirapine Cmax ↑ 1.13 (1.03–1.24)	Fosamprenavir/ritonavir and Nevirapine tablets 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 tablets. Dose adjustment of Nevirapine tablets 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 tablets, 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 tablets 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 tablets 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 tablets can be co-administered without dose adjustments.
Maraviroc 300 mg once daily	Maraviroc AUC ↔ 1.01 (0.6–1.55) Maraviroc Cmin ND Maraviroc Cmax ↔ 1.54 (0.94–2.52) compared to historical controls Nevirapine concentrations not measured, no effect is expected.	Maraviroc and Nevirapine tablets 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 tablets can be co-administered without dose adjustments.
Antibiotics		
Clarithromycin 500 mg twice daily	Clarithromycin AUC ↓ 0.69 (0.62–0.76) Clarithromycin C_{min} ↓ 0.44 (0.30–0.64) Clarithromycin C_{max} ↓ 0.77 (0.69–0.86) Metabolite 14-OH clarithromycin AUC ↑ 1.42 (1.16–1.73) Metabolite 14-OH clarithromycin C_{min} ↔ 0 (0.68–1.49) Metabolite 14-OH clarithromycin C_{max} ↑ 1.47 (1.21–1.80) Nevirapine AUC ↑ 1.26 Nevirapine C_{min} ↑ 1.28 Nevirapine C_{max} ↑ 1.24 compared to historical controls.	Clarithromycin exposure was significantly decreased, 14-OH metabolite exposure increased. Because the clarithromycin active metabolite has reduced activity against *Mycobacterium avium-intracellulare complex* overall activity against the pathogen may be altered. Alternatives to clarithromycin, such as azithromycin should be considered. Close monitoring for hepatic abnormalities is recommended
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) Metabolite25-O-desacetylrifabutin AUC ↑ 1.24 (0.84–1.84) Metabolite25-O-desacetylrifabutin C_{min} ↑ 1.22 (0.86–1.74) Metabolite25-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 tablets mean pharmacokinetic parameters is seen. Rifabutin and Nevirapine tablets 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 C_{min} ND Rifampicin C_{max} ↔ 1.06 (0.91–1.22) Nevirapine AUC ↓ 0.42 Nevirapine Cmin ↓ 0.32 Nevirapine Cmax ↓ 0.50 compared to historical controls.	Co-administration of rifampicin and Nevirapine tablets 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 tablets, 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: 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 C_{min} ND Ketoconazole C_{max} ↓ 0.56 (0.42–0.73) Nevirapine: plasma levels: ↑ 1.15–1.28 compared to historical controls.	Co-administration of ketoconazole and Nevirapine tablets 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 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 tablets 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 tablets did not alter the ovulation suppression effects of depot medroxyprogesterone acetate. Depot medroxyprogesterone acetate and Nevirapine tablets 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–	Oral hormonal contraceptives should not be used as the sole method of contraception in women taking Nevirapine tablets (see section 4.4). Appropriate doses for hormonal contraceptives (oral or other forms of application) other than depot medroxyprogesterone acetate in combination with Nevirapine tablets 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 tablets 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	St. John's Wort and Nevirapine tablets must not be co-administered (see section
	preparation St. John's Wort (Hypericum perforatum). This is due to induction of	4.3). The inducing effect may persist for at least 2 weeks after cessation of

4.6 Fertility pregnancy and lactation

Women of childbearing potential

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).

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, and should be taken in 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

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 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

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

General disorders and administration site conditions

Common: fever, fatigue

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).

4.9 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.

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 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 (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.

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).

Perinatal Transmission

The HIVNET 012 study in Kampala (Uganda) evaluated the efficacy of nevirapine to prevent vertical transmission of HIV-1 infection. 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 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 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 readily absorbed (> 90%) after oral administration.

Following single dose administration of Nevirapine tablet 1 tablet (200 mg nevirapine) in healthy adult volunteers, the mean (± SD) nevirapine C_{max} value was 2.9 µg/ml (± 0.7 µg/ml), and the corresponding value for the area under the concentration–time curve (AUC) was 107 µg.h/ml (± 23 µg.h/ml). The median (± SD) nevirapine t_{max} value was 3.75 (± 2.54) 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 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 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 evidence of drug-induced toxicity.

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans other than those observed in clinical studies based on conventional studies of safety, pharmacology, repeated-dose toxicity, and genotoxicity. In reproductive toxicology studies, evidence of impaired fertility was seen in rats. In carcinogenicity studies, nevirapine induces hepatic tumours in rats and mice. These findings are most likely related to nevirapine being a strong inducer of liver enzymes, and not due to a genotoxic mode of action.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate, microcrystalline cellulose, sodium starch glycolate, povidone, colloidal silicon dioxide and magnesium stearate.

6.2 Incompatibilities

None

6.3 Shelf-life

Please refer outer package for expiry date.

6.4 Special precautions for storage

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

6.5 Nature andc ontentsofcontainer

Container containing 60 tablets each.

6.6 Instructions for use and handling

No special requirements.

7 MARKETING AUTHORIZATION HOLDER:

AUROBINDO

M/s. Aurobindo Pharma Ltd.

Plot No.: 2, Maitrivihar,

Ameerpet, Hyderabad-500 038

India

8 DATE OF REVISION OFTHE TEXT: March 2018

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Tanzania Reg. No.: TAN 05, 727 J05A AUR

Zambia Reg. No.: 127/027

POM

Patient Information Leaflet

NEVIRAPINE TABLETS USP 200 mg

Read all of this leaflet carefully before you start taking this medicine.

- Keep this leaflet since you may need to read it again
- If you have further questions, please ask your doctor
- This medicine has been prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.

In this leaflet:

Nevirapine Tablets USP 200 mg

Nevirapine tablets each contain 200 mg of active pharmaceutical ingredient nevirapine, used in the treatment of HIV infection.

The other ingredients are lactose monohydrate, microcrystalline cellulose, sodium starch glycolate, povidone, colloidal silicon dioxide , magnesium stearate .

Nevirapine tablets are white to off-white, oval shaped, biconvex tablets, one side debossed with "C" and "35" with a single bisect separating the "C" and "35". The other side has a single bisect.

The Marketing Authorisation Holder for Nevirapine tablets is:

M/s Aurobindo Pharma Ltd

Plot No.: 2, Maitrivihar

Ameerpet, Hyderabad-500 038

India

Nevirapine tablets are manufactured by:

M/s Aurobindo Pharma Limited,

Unit III, Survey No. 313 & 314,

Bachupally, Bachupally Mandal,

Medchal-Malkajgiri District, Telangana State,

India, ZIP Code – 500 090

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

Nevirapine Tablets belongs to a group of medicines called antiretrovirals, which are used for the treatment of human immunodeficiency virus (HIV-1) infection in children, adolescents and adults weighing over 25 kg. Nevirapine Tablets is also used to prevent passing HIV-1 infection from mother to baby at birth and during breast-feeding.

The active ingredient of Nevirapine Tablets is called nevirapine. Nevirapine helps to control HIV-1 infection by reducing 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.
Because of the way it works, nevirapine is called *non-nucleoside reverse transcriptase inhibitor* (often abbreviated NNRTI).

To prevent the virus becoming resistant to nevirapine, you must take Nevirapine Tablets together with other antiretroviral medicines. Your doctor or health care provider will recommend the best medicines for you. Nevirapine can sometimes be used alone to prevent passing HIV infection from mother to baby but your doctor or health care provider will give advice on exactly how it should be used.

This medicine is not a cure for HIV infection. While taking Nevirapine Tablets you may still develop infections or other illnesses associated with HIV infection.

You can also pass on HIV to others, so you must take precautions to avoid infecting other people.

2. BEFORE YOU TAKE Nevirapine Tablets

Do not take Nevirapine Tablets :

- if you are allergic (hypersensitive) to nevirapine or any of the other ingredients of Nevirapine 200 mg Tablets (see section 6, 'What Nevirapine Tablets contains').
- if you have taken nevirapine before and had to stop the treatment because you 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 you have severe liver disease
- if you have had to stop Nevirapine Tablets treatment in the past because of changes in your liver function
- If you are taking St John's wort (*Hypericum perforatum*, a herbal remedy against depression).

This herbal substance may stop Nevirapine Tablets from working properly.

Take special care with Nevirapine Tablets

During the first 18 weeks of treatment with Nevirapine Tablets it is very important that you and your doctor or health care provider watch out for signs of liver or skin reactions. The reactions can become severe and even life threatening. You are at greatest risk of such a reaction during the first 6 weeks of treatment.

If you develop severe liver, skin or allergic (hypersensitivity) reactions whilst taking Nevirapine Tablets, never **take** Nevirapine Tablets again without checking with your doctor or health care provider. You must take the dosage of Nevirapine Tablets as prescribed. This is especially important in the first 14 days of treatment (see more information in 'How to take Nevirapine Tablets ').

Nevirapine is not a cure for HIV infection. Therefore, you may continue to develop infections and other illnesses associated with HIV infection. You should, therefore, remain in regular contact with your doctor or health care provider. Nevirapine does not prevent the risk of passing on HIV to others through blood or sexual contact and you must take precautions to prevent passing on HIV to other people. Please ask your doctor or health care provider for more information.

Skin reactions

If you have severe rash or you develop allergic reactions (hypersensitivity) accompanied by other side effects such as:

- fever
- blistering
- mouth sores
- inflammation of the eye
- swelling of the face
- general swelling
- shortness of breath
- muscle or joint pain
- general feelings of illness
- abdominal pain

you **should stop taking** Nevirapine Tablets and you **must contact** your doctor or health care provider **immediately** as such reactions can be potentially life threatening.

If you get mild rash without any other reaction please tell your doctor or health care provider **immediately**, who will advise you whether you should stop taking Nevirapine Tablets . Liver disease If you have symptoms suggesting damage of the liver, such as

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

you should stop taking Nevirapine Tablets and must contact your doctor or health care provider **immediately**.

The following patients are at increased risk of developing liver problems:

- women
- those infected with hepatitis B or C
- those with abnormal liver function tests
- those with higher CD4 cell count at the start of nevirapine therapy (women more than 250 cells per cubic millimetre, men more than 400 cells per cubic

millimetre)

Immune reactivation syndrome

In some patients with advanced HIV infection (AIDS) who have had other infections that can occur in AIDS patients (AIDS defining illness), signs and symptoms of previous infections 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 to fight infections that may have been present with no obvious symptoms. If you notice any symptoms of infection, please tell your doctor or health care provider immediately.

Bone problems

Some patients taking combination antiretroviral therapy may develop a bone disease called osteonecrosis (death of bone tissue caused by loss of blood supply to the bone). So far, this disease has been reported mainly in adults. The risk of developing this disease may be higher with long-term combination antiretroviral therapy, corticosteroid use, excessive alcohol use, very weak immune system and being overweight. If you have signs of joint stiffness, aches and pains (especially of the hip, knee and shoulder) and difficulty in movement please tell your doctor or health care provider.

Use in children

Nevirapine Tablets tablets can be taken by children weighing 25 kg or more. Nevirapine oral suspension 50 mg/5 ml is available for use by children under 25 kg.

Taking other medicines

Tell your doctor, health care provider or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription before you start taking Nevirapine Tablets. Your doctor or health care provider might need to check if your other medicines are still needed and adjust doses. Carefully read the package leaflet of all other HIV medicines you are taking in combination with Nevirapine Tablets.

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

- atazanavir, lopinavir with ritonavir, fosamprenavir, or efavirenz (other antiretroviral medicines)
- rifampicin or rifabutin (medicines to treat tuberculosis)
- clarithromycin (medicine to treat bacterial infections)
- fluconazole, itraconazole or ketoconazole (medicines to treat fungal infections)
- quinine (medicine to treat malaria)
- methadone (medicine for managing opioid addiction)
- warfarin (medicine to reduce blood clotting)
- hormonal contraceptives (e.g. the 'pill')
- carbamazepine, phenobarbital or phenytoin (medicines for managing epilepsy)
- St John's Wort (*Hypericum perforatum*, medicine to treat depression)

Your doctor or health care provider will carefully monitor the effect of Nevirapine Tablets and any of these medicines if you are taking them together.

If you are undergoing kidney dialysis, your doctor may adjust the dose of Nevirapine Tablets. This is because Nevirapine Tablets can be partly removed from your blood by dialysis.

Taking Nevirapine Tablets with food and drink

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

Pregnancy and breast-feeding

Ask your doctor, health care professional or pharmacist for advice before taking any medicine.

In babies born to mothers who have taken antiretroviral medicines comprising nucleoside and nucleotide analogues, the benefit of reduced risk of becoming infected with HIV outweighs the

risk of side effects of these medicines.

If a mother wants to breastfeed her baby, she should ask her doctor or healthcare provider for advice on the risks and benefits. Treatment of mother and/or child with medicines 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

There are no specific studies on the ability to drive vehicles and use machinery. If you feel that your ability to drive or use machines may be affected you should not drive or use machines.

Important information about some of the ingredients of Nevirapine Tablets

Nevirapine Tablets contains lactose (milk sugar). If you have been told by your doctor or health care provider that you have an intolerance to some sugars, contact your doctor or health care provider before taking Nevirapine Tablets.

3. HOW TO TAKE NEVIRAPINE TABLETS

You should not use Nevirapine Tablets on its own. You must take it with at least two other antiretroviral medicines.

Your doctor or health care provider will recommend the best medicines for you.

Always take Nevirapine Tablets exactly as your doctor or health care provider has told you. You should check with your doctor, health care provider or pharmacist if you are not sure.

Only take Nevirapine Tablets by mouth. Do not chew your tablets. You may take Nevirapine Tablets with food or between meals.

Dosage:

The dose is one 200-mg tablet once a day for the first 14 days of treatment ('lead-in' period). After 14 days, the usual dose is one 200-mg tablet twice a day.

It is very important that you take only one Nevirapine Tablets a day for the first 14 days ('lead-in' period). If you have any rash during this period, do not increase the dose but see your doctor or health care provider.

The 14-day ‘lead-in’ period has been shown to lower the risk of skin rash.

As Nevirapine Tablets must always be taken with other HIV antiretroviral medicines, you should follow the instructions for your other medicines carefully. These are supplied in the package leaflets for those medicines.

You should continue to take Nevirapine Tablets for as long as instructed by your doctor or health care provider.

Your doctor or health care provider will watch out for unwanted effects such as signs of liver or skin reactions. In case of problems your doctor or health care provider may decide to interrupt or stop Nevirapine tablets treatment. Your doctor or health care provider might then decide to restart nevirapine at a lower dose.

If you take more Nevirapine Tablets than you should

Do not take more Nevirapine Tablets than prescribed by your doctor or health care provider and described in this leaflet. There is very little information on the effects of Nevirapine Tablets overdose. See your doctor or health care provider if you have taken more Nevirapine Tablets than you should.

If you forget to take Nevirapine Tablets

Try not to miss a dose. If you notice that you have missed a dose within 8 hours, take the next dose as soon as possible. If you notice it more than 8 hours later, take the next dose at the usual time.

If you stop taking Nevirapine Tablets

Taking all doses at the right time:

- ensures that the combination of antiretroviral medicines work as well as possible
- reduces the chances of the HIV infection becoming resistant to the antiretroviral medicines you are taking.

It is important that you continue taking Nevirapine Tablets correctly unless your doctor or health care provider instructs you to stop.

If you stop taking Nevirapine Tablets for more than 7 days your doctor or health care provider

will instruct you to start the 14-day 'lead-in' period (described above) once again, before returning to the twice-daily dose.

If you have any questions about your treatment, ask your doctor, health care provider or pharmacist.

POSSIBLE SIDE EFFECTS

Like all medicines, Nevirapine Tablets can cause side effects, but not everybody gets them.

As mentioned in 'Take special care with Nevirapine Tablets ', above, the most important side effects of nevirapine are severe and life-threatening skin reactions and serious liver damage.

When rash occurs it is generally 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 been recorded. Most of the cases of both severe rash and mild/moderate rash occur in the first six weeks of treatment.

Allergic (hypersensitivity) reactions can occur. Such reactions may appear in the form of anaphylaxis (a severe form of allergic reaction) with symptoms such as:

- rash
- swelling of the face
- difficulty breathing
- anaphylactic shock

Allergic (hypersensitivity) reactions can also occur as rash with other side effects such as:

- fever
- blistering of your skin
- mouth sores
- inflammation of the eye
- swelling of the face
- general swelling
- shortness of breath
- muscle or joint pain
- a reduction in the numbers of your white blood cells (granulocytopenia)
- general feelings of illness

- severe problems with liver or kidneys (liver or kidney failure).

Abnormal liver functioning has been reported with the use of nevirapine. This includes some cases of inflammation of the liver (hepatitis), which can be sudden and intense (fulminant hepatitis), and liver failure, which can be both fatal. Any of the following symptoms can suggest liver damage:

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

Evaluation of the side effects is based on the following frequencies:

- Very common: in at least 1 out of 10 patients treated
- Common: in at least 1 out of 100 and less than 1 out 10 patients treated
- Uncommon: in at least 1 out of 1000 and less than 1 out 100 patients treated
- Rare: in at least 1 out of 10,000 and less than 1 out 1000 patients treated

The side effects described below have been experienced by patients given nevirapine: Very common:

- rash

Common:

- decreased numbers of white blood cells (granulocytopenia)
- allergic reactions (hypersensitivity)
- headache
- feeling sick (nausea)
- vomiting
- abdominal pain
- loose stools
- inflammation of the liver
- muscle pain

- feeling tired (fatigue)
- fever
- abnormal liver function tests

Uncommon:

- decreased numbers of red blood cells (anaemia)
- yellow skin (jaundice)
- severe and life-threatening skin rashes (Stevens-Johnson syndrome/toxic epidermal necrolysis)
- hives (urticaria)
- accumulation of fluid and swelling under the skin (angioedema)
- joint pain

Rare:

- sudden and intense inflammation of the liver (fulminant hepatitis)

Frequency not known:

- drug rash with systemic symptoms (drug rash with eosinophilia and systemic symptoms)
- allergic reaction characterized by rash, swelling of the face, difficulty breathing (bronchial spasm) or anaphylactic shock

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

Combination antiretroviral therapy may also cause raised lactic acid, resistance to insulin, raised sugar in the blood, and increased fats in the blood (hyperlipaemia).

Use in children

Reduction in white blood cells (granulocytopenia) is more common in children. A reduction in red blood cells (anaemia), which may be related to nevirapine therapy, is also more common in children. As with rash, please inform your doctor or health care provider of any side effects.

If any side effect gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor, health care provider or pharmacist.

5. HOW TO STORE NEVIRAPINE TABLETS

Keep out of the reach and sight of children. There are no special storage instructions.

Do not use after the expiry date stated on the label.

Do not use Nevirapine Tablets 200 mg after the expiry date which is stated on the bottle. The expiry date refers to the last day of that month.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. FURTHER INFORMATION

If you notice any side effect (s) with the use of this drug, please report it immediately via internet to the following e-mail address:

pharmacovigilance@aurobindo.com

For any information about this medicinal product please contact the local representative of the Marketing Authorization Holder