NEVIREX 200
P1538337

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P1538337

AUROBINDO

SUMMARY OF PRODUCT CHARACTERISTICS

NEVIREX 200

Nevirapine Tablets USP 200 mg

Rx Only

1 NAME OF THE FINISHED PHARMACEUTICAL PRODUCT
Nevirex 200 (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
For use in combination with other antiretroviral agents for the treatment of HIV-1 infection. Resistant virus emerges r apidly and uniformly when Nevirapine is administered as monotherapy. Therefore, Nevirapine should always be adm inistered in combination with at least 2 additional antiretroviral agents.

Avoid usage of Nevirapine in patient with CD4+cell count greater than 250cells/mm3.

4.2 Posology and method of administration
Adults: 1 tab daily for the first 14 days (this lead-in period should be used because it has been found to lessen the frequency of rash), followed by 1 tab twice daily, in combination with at least 2 additional antiretroviral agents. For concomitantly administered therapy, the manufacturer's recommended dosage and monitoring should be followed.

Children ≥8 years: 4 mg/kg once daily for 2 weeks followed by 4 mg/kg twice daily thereafter; 2 months up to 8 years; 4 mg/kg once daily for 2 weeks followed by 7 mg/kg twice daily thereafter. The total daily dose should not exceed 400 mg for any patient.

Patients should be advised of the need to take Nevirapine every day as prescribed. If a dose is missed, the patient should not double the next dose but should take the next dose as soon as possible.

Clinical chemistry test, including liver function tests, should be performed prior to initiating Nevirapine therapy and at appropriate intervals during therapy.

Nevirapine administration should be discontinued if patients experience severe rash or a rash accompanied by constitutional symptoms. Patients experiencing rash during the 14-days lead-in period of 200mg daily should not have their dose increased until the rash has resolved.

Nevirapine administration should be interrupted in patients experiencing moderate or severe liver function test abnormalities (excluding GGT) until liver function tests have returned to baseline. Nevirapine may then be restarted at 200mg daily increasing to 200mg twice daily with caution, after extended observation. Nevirapine should be permanently discontinued if moderate or severe liver function test abnormalities recur. Patients who interrupt Nevirapine dosing for >7 days should restart the recommended dosing regimen, using 200mg once daily (lead-in) followed by one 200-mg tab twice daily.

4.3 Contraindications :
Hypersensitivity to the active substance or to any of the excipients. Nevirapine tablets should not be readministered to patients who have required permanent discontinuation for severe rash, rash accompanied by constitutional symptoms, hypersensitivity reactions, or clinical hepatitis due to nevirapine.

Nevirapine tablets should not be used in patients with severe hepatic impairment or pre-treatment ASAT or ALAT > 5 ULN until baseline ASAT/ALAT are stabilised < 5 ULN. Nevirapine tablets should not be readministered in patients who previously had ASAT or ALAT > 5 ULN during nevirapine tablets therapy and had recurrence of liver function abnormalities upon readministration of nevirapine tablets, (see section 4.4).

Herbal preparations containing St John's wort *(Hypericum perforatum*) must not be used while taking nevirapine tablets due to the risk of decreased plasma concentrations and reduced clinical effects of nevirapine (see section 4.5).

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

4.4 Special warnings and precautions for use
On the basis of pharmacodynamic data nevirapine tablets should only be used with at least two other antiretroviral agents (see section 5.1).

The first 18 weeks of therapy with Nevirapine are a critical period which requires close monitoring of patients to disclose the potential appearance of severe and life-threatening skin reactions (including cases of Stevens-Johnson syndrome and toxic epidermal necrolysis) or serious hepatitis/hepatic failure. The greatest risk of hepatic events and skin reactions occurs in the first 6 weeks of therapy. However, the risk of any hepatic event continues past this period and monitoring should continue at frequent intervals. Female gender and higher CD4 counts at the initiation of therapy place patients at greater risk of hepatic adverse events. Unless the benefit outweighs the risk Nevirapine should not be initiated in adult females with CD4 cell counts greater than 250 cells/mm3 or in adult males with CD4 cell counts greater than 400 cells/mm3 . This is based on the occurrence of serious and life threatening hepatotoxicity in controlled and uncontrolled studies.

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

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

Cutaneous reactions
Severe and life-threatening skin reactions, including fatal cases, have occurred in patients treated with nevirapine tablets mainly during the first 6 weeks of therapy. These have included cases of Stevens-Johnson syndrome, toxic epidermal necrolysis and hypersensitivity reactions characterised by rash, constitutional findings and visceral involvement. Patients should be intensively monitored during the first 18 weeks of treatment. Patients should be closely monitored if an isolated rash occurs. Nevirapine tablets must be permanently discontinued in any patient experiencing severe rash or a rash accompanied by constitutional symptoms (such as fever, blistering, oral lesions, conjunctivitis, facial oedema, muscle or joint aches, or general malaise), including Stevens-Johnson syndrome, or toxic epidermal necrolysis. Nevirapine tablets must be permanently discontinued in any patient experiencing hypersensitivity reaction (characterised by rash with constitutional symptoms, plus visceral involvement, such as hepatitis, eosinophilia, granulocytopenia, and renal dysfunction) see section 4.4.

Nevirapine tablets administration above the recommended dose might increase the frequency and seriousness of skin reactions, such as Stevens-Johnson syndrome and toxic epidermal necrolysis. Concomitant prednisone use (40 mg/day for the first 14 days of nevirapine tablets administration) has been shown not to decrease the incidence of nevirapine tablets-associated rash, and may be associated with an increase in incidence and severity of rash during the first 6 weeks of nevirapine tablets therapy. Some risk factors for developing serious cutaneous reactions have been identified, they include failure to follow the initial dosing of 200 mg daily during the lead-in period and a long delay between the initial symptoms and medical consultation. Women appear to be at higher risk than men of developing rash, whether receiving nevirapine tablets or non-nevirapine tablets containing therapy.

Patients should be instructed that a major toxicity of nevirapine tablets is rash. They should be advised to promptly notify their physician of any rash and avoid delay between the initial symptoms and medical consultation**.** The majority of rashes associated with nevirapine tablets occur within the first 6 weeks of initiation of therapy. Therefore, patients should be monitored carefully for the appearance of rash during this period. Patients should be instructed that dose escalation is not to occur if any rash occurs during the two-week lead-in dosing period, until the rash resolves. Any patient experiencing severe rash or a rash accompanied by constitutional symptoms such as fever, blistering, oral lesions, conjunctivitis, facial oedema, muscle or joint aches, or general malaise should discontinue medication and consult a physician. In these patients nevirapine tablets must not be restarted. If patients present with a suspected nevirapine tablets-associated rash, liver function tests should be performed. Patients with moderate to severe elevations (ASAT or ALAT > 5 ULN) should be permanently discontinued from nevirapine tablets. 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 tablets should be permanently stopped and not be re-introduced.

Hepatic reactions
Severe and life-threatening hepatoxicity, including fatal fulminant hepatitis, has occurred in patients treated with Nevirapine. The first 18 weeks of treatment is a critical period which requires close monitoring. The risk of hepatic events is greatest in the first 6 weeks of therapy. However the risk continues past this period and monitoring should continue at frequent intervals throughout treatment.

Increased ASAT or ALAT levels 2.5 ULN and/or co-infection with hepatitis B and/or C at the start of antiretroviral therapy is associated with greater risk of hepatic adverse reactions during antiretroviral therapy in general, including Nevirapine containing regimens.

Female gender and patients with higher CD4 counts are at increased risk of hepatic adverse events.

Women have a three fold higher risk than men for symptomatic, often rash-associated, hepatic events (5.8% versus 2.2%), and patients with higher CD4 counts at initiation of Nevirapine therapy are at higher risk for symptomatic hepatic events with Nevirapine. In a retrospective review, women with CD4 counts >250 cells/mm^3 had a 12 fold higher risk of symptomatic hepatic adverse events compared to women with CD4 counts <250 cells/mm3 (11.0% versus 0.9%). An increased risk was observed in men with CD4 counts > 400 cells/mm^3 (6.3% versus 1,2 % for men with CD4 counts <400 cells/mm^3).

Patients should be informed that hepatic reactions are a major toxicity of Nevirapine requiring close monitoring during the first 18 weeks. They should be informed that occurrence of symptoms suggestive of hepatitis should lead them to discontinue Nevirapine and immediately seek medical evaluation, which should include liver function tests.

Liver monitoring
Abnormal liver function tests have been reported with nevirapine tablets, some in the first few weeks of therapy. Asymptomatic elevations of liver enzymes are frequently described and are not necessarily a contraindication to use nevirapine tablets. Asymptomatic GGT elevations are not a contraindication to continue therapy. Monitoring of hepatic tests should be done every two weeks during the first 2 months of treatment, at the 3rd month and then regularly thereafter. Liver test monitoring should be performed if the patient experiences signs or symptoms suggestive of hepatitis and/or hypersensitivity.

If ASAT or ALAT ≥ 2.5 ULN before or during treatment, then liver tests should be monitored more frequently during regular clinic visits. Nevirapine tablets should not be administered to patients with pre-treatment ASAT or ALAT > 5 ULN until baseline ASAT/ALAT are stabilised < 5 ULN. Physicians and patients should be vigilant for prodromal signs or findings of hepatitis, such as anorexia, nausea, jaundice, bilirubinuria, acholic stools, hepatomegaly or liver tenderness. Patients should be instructed to seek medical attention promptly if these occur.

If ASAT or ALAT increase to > 5 ULN during treatment, nevirapine tablets should be immediately stopped. If ASAT and ALAT return to baseline values and if the patient had no clinical signs or symptoms of hepatitis, rash, constitutional symptoms or other findings suggestive of organ dysfunction, it may be possible to reintroduce nevirapine tablets, on a case by case basis, at the starting dosage regimen of 200 mg/day for 14 days followed by 400 mg/day. In these cases, more frequent liver monitoring is required. If liver function abnormalities recur, nevirapine tablets should be permanently discontinued.

If clinical hepatitis occurs, characterised by anorexia, nausea, vomiting, icterus AND laboratory findings (such as moderate or severe liver function test abnormalities (excluding GGT), nevirapine tablets must be permanently stopped. Nevirapine tablets should not be readministered to patients who have required permanent discontinuation for clinical hepatitis due to nevirapine.

Liver Disease
The safety and efficacy of nevirapine tablets has not been established in patients with significant underlying liver disorders. Nevirapine tablets are contraindicated in patients with severe hepatic impairment (see section 4.3). Patients with chronic hepatitis B or C and treated with combination antiretroviral therapy are at an increased risk for severe and potentially fatal hepatic adverse events. In the case of concomitant antiviral therapy for hepatitis B or C, please refer also to the relevant product information for these medicinal products.

Patients with pre-existing liver dysfunction including chronic active hepatitis have an increased frequency of liver function abnormalities during combination antiretroviral therapy and should be monitored according to standard practice. If there is evidence of worsening liver disease in such patients, interruption or discontinuation of treatment must be considered.

Post-exposure-prophylaxis :
Serious hepatotoxicity, including liver failure requiring transplantation, has been reported in HIV-uninfected individuals receiving multiple doses of Nevirapine in the setting of post-exposure-prophylaxis (PEP), an unapproved use. The use of Nevirapine has not been evaluated within a specific study on PEP, especially in term of treatment duration and therefore, is strongly discouraged.

Other warnings
Combination therapy with nevirapine tablets is not a curative treatment of patients infected with HIV-1; patients may continue to experience illnesses associated with advanced HIV-1 infection, including opportunistic infections. The long-term effects of nevirapine are unknown at this time. Combination therapy with nevirapine tablets has not been shown to reduce the risk of transmission of HIV-1 to others through sexual contact or contaminated blood.

Combination antiretroviral therapy has been associated with the redistribution of body fat (lipodystrophy) in HIV infected patients. The long-term consequences of these events are currently unknown. Knowledge about the mechanism is incomplete. A connection between visceral lipomatosis and PIs and lipoatrophy and NRTIs has been hypothesised. 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).

Nevirapine may interact with some medicinal products; therefore, patients should be advised to report to their doctor the use of any other medications. Oral contraceptives and other hormonal methods of birth control 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

DETACH BEFORE DISPENSING

NEVIREX 200

NEVIRAPINE TABLETS USP 200 mg

What is in this leaflet

1. What Nevirapine Tablets USP 200 mg is used for
Nevirapine tablets belong to a group of medicines called antiretrovirals, used in the treatment of Human Immunodeficiency Virus (HIV-1) infection.
Nevirapine tablets are indicated for the treatment of HIV-1 infected adults, adolescents, and children. You must take Nevirapine tablets together with other antiretroviral medicines. Your doctor will recommend the best medicines for you

2. How Nevirapine Tablets USP 200 mg works
The active substance of your medicine is called nevirapine. Nevirapine reduces the amount of viruses in the blood thus improving your medical condition.
Nevirapine belongs to a class of anti-HIV medicines called non-nucleoside reverse transcriptase inhibitors (NNRTIs). Reverse transcriptase is an enzyme that HIV needs in order to multiply. Nevirapine stops reverse transcriptase from working. By stopping reverse transcriptase from working, Nevirapine tablets helps control HIV-1 infection.

3. Before you use Nevirapine Tablets USP 200 mg
- *When you must not use it*
  Do not take Nevirapine tablets if:
- if you are allergic to nevirapine or any of the other ingredients of this medicine
- *Before you start use it*
During the first 18 weeks of treatment with Nevirapine Tablets it is very important that you and your doctor watch out for signs of liver or skin reactions. These can become severe and even life threatening. You are at greatest risk of such a reaction during the first 6 weeks of treatment

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

Talk to your doctor or pharmacist before taking Nevirapine Tablets USP, especially:
- If you have taken Nevirapine tablets USP 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 feelings of illness, abdominal pain
*hypersensitivity (allergic) 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 a medicine containing the herbal substance St. John's Wort (*Hypericum perforatum*). This herbal substance may stop Nevirapine tablets USP from working properly.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.
You should stop breast-feeding if you are taking Nevirapine tablets. It is in general recommended that you do not breast-feed if you have HIV infection because it is possible that your baby can become infected with HIV through your breast milk.

Driving and using machines
You may experience fatigue when taking Nevirapine tablets. Use caution when engaging in activities such as driving, using any tools or machines. If you experience fatigue you should avoid potentially hazardous tasks such as driving or using any tools or machines.
Driving and using machines
You may experience fatigue when taking Nevirapine tablets. Use caution when engaging in activities such as driving, using any tools or machines. If you experience fatigue you should avoid potentially hazardous tasks such as driving or using any tools or machines.
Nevirapine tablets contains lactose
Nevirapine tablets contain lactose (milk sugar).
If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking Nevirapine tablets.
- *Taking other medicines*
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. Inform your doctor about all other medicines you are taking before you start taking Nevirapine tablets. Your doctor might need to monitor whether your other medicines are still working and adjust doses.
It is particularly important that you tell your doctor if you are taking or have recently taken:
-St. John's Wort (Hypericum perforatum, medicine to treat depression)
-rifampicin (medicine to treat tuberculosis)
-ketoconazole (medicine to treat fungal infections)
-hormonal contraceptives (e.g. the "pil")
-atazanavir (another medicine to treat HIV-infection)
-fosamprenavir (another medicine to treat HIV-infection)
-efavirenz (another medicine to treat HIV-infection)
Your doctor will carefully monitor the effect of Nevirapine tablets and any of these medicines if you are taking them together.
If you are undergoing kidney dialysis, your doctor may consider a dose adjustment of Nevirapine tablets. This is because Nevirapine tablets can be partly washed out of your blood by dialysis.

4. How to take Nevirapine Tablet USP 200mg
- *How much to take*
You should not use Nevirapine tablets on its own. You must take it with at least two other antiretroviral medicines. Your doctor will recommend the best medicines for you.
Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.
Dose:
The dose for adult is one 200 mg tablet per 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.
The dose for adolescent and children is based on the patient's body weight. Your doctor will decide the correct dose for you or your child.
- *When to take it*
As Nevirapine tablets must always be taken together with other HIV antiretroviral medicines, you should follow the instructions for your other medicines carefully.
Only take Nevirapine tablets by mouth. Do not chew your tablets. You may take Nevirapine tablets with or without food.
- *How long to take it*
You should continue to take Nevirapine tablets for as long as instructed by your doctor.
- *If you forget to take it*
Try not to miss a dose. If you are not sure what to do, please consult your doctor or pharmacist. Do not take a double dose to replace the missed dose.
- *If you take too much (overdose)*
Do not take more Nevirapine tablets than prescribed by your doctor and described in this leaflet. There is at present little information on the effects of Nevirapine tablets overdose.
Consult your doctor if you have taken more Nevirapine tablets than you should.

5. While you are using it
- *Things you must do*

A/s: 210 x 420 mm ■ Black

AUROBINDO		**Product Name**	**Component**	**Item Code**	**Date & Time**
		NEVIREX 200	Leaflet	P1538337	29.11.2024 & 12.15 pm
		Contry	**Version No.**	**Reason of Issue**	**Reviewed / Approved By**
		Malaysia-U3	00	Submission	
Team Leader	Lova Raju	**Dimension (mm)**	**Colours**		
Initiator	Subrahmanyam	210 x 420 mm	No. of Colours: 01		
Artist	**Advnt - Anji**	**Pharma Code:** 38337			
Additional Information: Supersede- P1511577			38337		

(e.g., condoms) is recommended. Additionally, when oral contraceptives are used for hormonal regulation during administration of nevirapine tablets the therapeutic effect should be monitored.
Pharmacokinetic results suggest caution should be exercised when nevirapine tablets are administered to patients with moderate hepatic dysfunction and should not be administered in patients with severe hepatic dysfunction. Overall, the results suggest that patients with mild to moderate hepatic dysfunction, defined as Child-Pugh Classification Score ≤7, do not require an adjustment in nevirapine tablets dosing. In patients with renal dysfunction, who are undergoing dialysis, pharmacokinetic results suggest that supplementing nevirapine tablets therapy with an additional 200 mg dose of nevirapine tablets following each dialysis treatment would help offset the effects of dialysis on nevirapine clearance. Otherwise patients with CLcr≥20 ml/min do not require an adjustment in nevirapine tablets dosing (see section 5.2).

Immune reactivation syndrome
In HIV-infected patients with severe immune deficiency at the time of institution of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic pathogens may arise and cause serious clinical conditions, or aggravation of symptoms. Typically, such reactions have been observed within the first few weeks or months of initiation of CART. Relevant examples are cytomegalovirus retinitis, generalised and/or focal mycobacterial infections, and Pneumocystis carinii pneumonia. Any inflammatory symptoms should be evaluated and treatment instituted when necessary.

4.5Interaction with other medicinal products and other forms of interaction :
Similarly to the HIV-protease inhibitors, nevirapine is metabolized-mainly by cytochrome P450 isoenzymes of the CYP3A family. Consequently it may compete with other drugs metabolized by this system, possibly resulting in mutually increased plasma concentrations. Alternatively enzyme inducers may decrease plasma concentrations of nevirapine; nevirapine itself acts as a mild to moderate enzyme inducer and may thus reduce plasma concentrations of other drugs.

Antibacterials. Plasma concentrations of nevirapine may be decreased by rifabutin and rifampicin, probably as a result of enzyme induction.

Antifungals. Concurrent administration of nevirapine and ketoconazole may result in reduction in the plasma concentration of ketoconazole and increase in that of nevirapine. The manufacturers recommend that his combination should be avoided.

Hormonal contraceptives. The manufacturers suggest that nevirapine may decrease the plasma concentrations of hormonal contraceptives. Although the clinical significance of this potential interaction is unknown they advise the use of alternative contraceptive methods.

Methadone. Nevirapine may induce the metabolism of methadone resulting in plasma-methadone concentrations.

4.6 Pregnancy and lactation
No observable teratogenicity was detected in reproductive studies performed in pregnant rats and rabbits. In rats, a significant decrease in fetal body weight occurred at doses providing systemic exposure approximately 50% higher, based on AUC, than that seen at the recommended human clinical dose.

The maternal and developmental no-observable-effect level dosages in rats and rabbits produced systemic exposures approximately equivalent to or approximately 50% higher, respectively, than those seen at the recommended daily human dose, based on AUC. There are no adequate and well-controlled studies in pregnant women. Nevirapine tablets should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Severe hepatic events, including fatalities, have been reported in pregnant women receiving chronic nevirapine tablets therapy as part of combination treatment of HIV infection. It is unclear if pregnancy augments the already increased risk observed in non-pregnant women.

Nursing Mothers:
The Centers for Disease Control and Prevention recommend that HIV-infected mothers not breast-feed their infants to avoid risking postnatal transmission of HIV. Nevirapine is excreted in breast milk. Because of both the potential for HIV transmission and the potential for serious adverse reactions in nursing infants, mothers should be instructed not to breast-feed if they are receiving nevirapine tablets.

4.7 Effects on ability to drive and use machines:
There are no specific studies on the ability to drive vehicles and use machinery.

4.8 Undesirable effects:
Like all medicines, nevirapine tablets can have side effects. The major side effects of nevirapine tablets are severe and life threatening cutaneous reactions and serious hepatic injuries. These reactions occur mainly in the first 8 weeks of treatment with nevirapine tablets. This is therefore an important period which requires a close surveillance. When rash does occur it is normally mild to moderate. However, in about 7% of patients a rash, which appears as a blistering skin reaction, can be severe or life-threatening and fatalities have been recorded. Most of the cases of both severe rash and mild/moderate rash occur in the first eight weeks of treatment. If you ever do observe any rash symptoms please inform your doctor immediately. If the symptoms are severe you must stop treatment and visit your doctor immediately.

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

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

Abnormal liver functioning has been reported with the use of nevirapine tablets, including some cases of hepatitis, which have resulted in recorded fatalities.

If you experience clinical symptoms suggesting an injury of the liver, such as loss of appetite, nausea, vomiting, jaundice, you should inform your doctor.

Other side effects which can occur are fever, nausea, headache, sleepiness, vomiting, diarrhoea, stomach pain, muscle pain and allergic reactions. Many of these side effects can occur together with the rash side effect (hypersensitivity reaction). Joint pain has been reported as a stand-alone event in rare instances in patients receiving nevirapine containing regimens.

In addition, a reduction in white blood cells (granulocytopaenia) can occur, which is more common in children. In very rare instances a reduction in red blood cells or white blood cells (neutropenia) may be related to nevirapine therapy. As with rash symptoms, please inform your doctor of any side effects. If you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

4.9 Overdose
There is no known antidote for nevirapine tablets overdosage. Cases of nevirapine tablets overdose at doses ranging from 800 to 6000 mg per day for up to 15 days have been reported. Patients have experienced oedema, erythema nodosum, fatigue, fever, headache, insomnia, nausea, pulmonary infiltrates, rash, vertigo, vomiting, increase in transaminases and weight decrease. All of these effects subsided following discontinuation of nevirapine tablets.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: antiviral agent, ATC code J05A G01.

Mechanism of Action
Nevirapine is a NNRTI of HIV-1. Nevirapine binds directly to reverse transcriptase and blocks the RNA-dependent and DNA-dependent DNA polymerase activities by causing a disruption of the enzyme's catalytic site. The activity of nevirapine does not compete with template or nucleoside triphosphates. HIV-2 reverse transcriptase and eukaryotic DNA polymerases (such as human DNA polymerases α, β, γ, or δ) are not inhibited by nevirapine.

In Vitro HIV Susceptibility:
The in vitro antiviral activity of nevirapine was measured din peripheral blood mononuclear cells, monocyte derived macrophages, and lymphoblastoid cell lines. IC50 values (50% inhibitory concentration) ranged from 10-100 nM against laboratory and clinical isolates of HIV-1. In cell culture, nevirapine demonstrated additive to synergistic activity against HIV-1 in drug combination regimens with zidovudine (ZDV), didanosine (ddI), stavudine (d4T), lamivudine (3TC), saquinavir, and indinavir. The relationship between in vitro susceptibility of HIV-1 to nevirapine and the inhibition of HIV-1 replication in humans has not been established.

Resistance:
HIV-1 isolates with reduced susceptibility (100-250-fold) to nevirapine emerge in vitro. Genotypic analysis showed mutations in the HIV-1 RT gene Y181C and/or V106A depending upon the virus strain and cell line employed. Time to emergence of nevirapine resistance in vitro was not altered when selection included nevirapine in combition with several other NNRTIs. Nevirapine+ZDV combination therapy did not alter the emergence rate of nevirapine resistance virus or the magnitude of nevirapine resistance in vitro.

Cross-resistance:
Rapid emergence of HIV-1 strains which are cross-resistant to NNRTIs has been observed in vitro. Nevirapine resistant HIV-1 isolates were cross-resistant to the NNRTIs efavirenz and delavirdine. However, nevirapine-resistant isolates were susceptible to the nucleoside analogues ZDV and ddI. Similarly, ZDV-resistant isolates were susceptible to nevirapine in vitro.

5.2 Pharmacokinetic properties
Nevirapine is readily absorbed following oral administration and absorption is not affected by food. Bioavailability is greater than 90%. Peak plasma concentrations occur 4 hours after a single dose. Nevirapine is about 60% bound to plasma proteins. Concentrations in the CSF are about 45% of those in plasma. Nevirapine crosses the placenta and is distributed into breast milk. It is extensively metabolized by hepatic microsomal enzymes, principally by cytochrome P450 isoenzymes of the CYP3A family. Autoinduction of these enzymes results in a 1.5- to 2-fold increase in apparent oral clearance after 2 to 4 weeks administration of usual doses, and a decrease in terminal half-life from 45 hours to 25 to 30 hours over the same period. In children, half-life at steady state varies with age, being 32 hours in children less than 1 year of age, 21 hours in children aged 1 to 4 years, 18 hours in children over 4 to 8 years, and 28 hours in children over 8 years. Apparent clearance, adjusted for body-weight, also varies with age, that in children under 8 years being approximately twice that in adults. Nevirapine is mainly excreted in the urine as glucuronide conjugates of the hydroxylated metabolites.

5.3 Preclinical safety data
Preclinical data revealed 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. In rats these findings are most likely related to nevirapine being a strong inducer of liver enzymes, and not due to a genotoxic mode of action. The mechanism of tumours in mice is not yet clarified and therefore their relevance in humans remains to be determined.

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
36 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
Container containing 60 tablets each.

6.6 Instructions for use and handling
No special requirements.

7 Manufactured by:

AUROBINDO

Product Registration Holder by:
UNIMED SDN BHD
No. 53, Jalan Tembaga SD 5/2 B,
Bandar Sri Damansara, 52200, Kuala Lumpur, Malaysia.

8. DATE OF REVISION OF TEXT: 29.11.2024
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DETACH BEFORE DISPENSING

It is very important that you take only one Nevirapine tablets tablet a day for the first 14 days ("lead-in" period). If you have any rash during this period, do not increase the dose but consult your doctor.
If you experience symptoms suggesting damage of the liver, such as:
- loss of appetite,
- feeling sick (nausea),
- vomiting,
- yellow skin (jaundice),
- abdominal pain

you should discontinue taking Nevirapine tablets and must contact your doctor immediately.
If you develop severe liver, skin or hypersensitivity reactions whilst taking Nevirapine tablets, NEVER TAKE NEVIRAPINE TABLETS again and visit your doctor immediately.
- *Things you must not do*
Do not change the dose on your own. Continue to take this medicine until your doctor tells you otherwise.
- *Things to be careful of*
In some patients with advanced HIV infection (AIDS) and a history of opportunistic infection (AIDS defining illness), signs and symptoms of inflammation from previous infections may occur soon after anti-HIV treatment is started. If you notice any symptoms of infection, please inform your doctor immediately.
Changes of body fat may occur in patients receiving combination antiretroviral therapy. Contact your doctor if you notice changes in body fat.

6. Side effects
Like all medicines, this medicine can cause side effects, although not everybody gets them.
The most important side effects of Nevirapine tablets are severe and life threatening skin reactions and serious liver damage.
These reactions occur mainly in the first 18 weeks of treatment with Nevirapine tablets. This is therefore an important period which requires close monitoring by your doctor.
The side effects described below have been experienced by patients given Nevirapine tablets:
-rash
-decreased numbers of white blood cells (granulocytopenia)
-allergic reactions (hypersensitivity)
-headache
-feeling sick (nausea)
-vomiting
-abdominal pain
-loose stools (diarrhoea)
-inflammation of the liver (hepatitis)
-feeling tired (fatigue)
-fever
-abnormal liver function tests
This is not a complete list of possible side effects. If you encounter any other side effects, please contact your doctor or pharmacist at the soonest.
You may report any side effects or adverse drug reactions directly to the National Centre for Adverse Drug Reaction Monitoring by calling Tel: 03-78835550, or visiting the website portal.bpfk.gov.my (Consumers → Reporting).

7. Storage and Disposal of *Nevirapine Tablets USP 200 mg*
- *Storage*
Do not store above 30°C.
Store in the original package.

- *Disposal*
Do not use after the expiry date stated on the label.
Return any unused tablets to your pharmacist to be disposed of. Only keep the tablets if your doctor tells you to. Do not throw them away in your normal household drainage or waste. This will help to protect the environment.

8. Product Description
- *What it looks like*
Nevirapine Tablets USP 200 mg are White to off-white, oval shaped, biconvex tablets, one side debossed with "C" and "35" the other side has a single bisect.

Ingredients
Active ingredient(s): Nevirapine USP
Inactive ingredients: Lactose monohydrate, microcrystalline cellulose, sodium starch glycolate, povidone, colloidal silicon dioxide and magnesium stearate.
MAL number(s):
MAL08042461A

9. Manufacturer
Aurobindo Pharma Limited,
Unit III, Survey No. 313 & 314, Bachupally, Bachupally Mandal, Medchal-Malkajgiri District, Telangana State, INDIA

Product Registration Holder by:
UNIMED SDN BHD
No. 53, Jalan Tembaga SD 5/2B,
Bandar Sri Damansara, 52200,
Kuala Lumpur, Malaysia.

10. Date of revision
29.11.2024.