SUMMARY OF PRODUCT CHARACTERISTICS
1. NAME OF THE MEDICINAL PRODUCT

Nevirapine 200mg Tablet.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains nevirapine 200 mg.
For excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Nevirapine 200mg Tablet is a white to off white oval shaped tablets engraved “N2” with a single bisect separating “N” and “2” on one side and plain on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Nevirapine 200mg Tablet is indicated for treatment of HIV-1 infection in combination with other antiretroviral agents.

4.2 Posology and method of administration

**Adults:** The recommended starting dose of Nevirapine 200mg Tablet is one tablet per day for the first 14 days of treatment. This lead-in period reduces the incidence of rash. This should be followed by two tablets of Nevirapine 200mg Tablet per day.

**Paediatric patients:** the recommended dose of Nevirapine 200mg Tablet for paediatric patients is:
- From 2 months to 8 years of age: 4 mg/kg once daily for the first 14 days followed by 7 mg/kg twice daily thereafter;
- For children 8 years of age and older: 4 mg/kg once daily for the first 14 days followed by 4 mg/kg twice daily thereafter.

The daily dose should not exceed 2 tablets (400 mg of nevirapine) for any patient.

4.3 Contraindications

- Hypersensitivity to nevirapine or to any of the inactive excipients;
- Nevirapine 200mg Tablet should not be re-administered to patients who required permanent discontinuation for severe rash, rash accompanied by constitutional symptoms, hypersensitivity reactions or clinical hepatitis due to nevirapine;
- Severe hepatic impairment or pre-treatment ASAT or ALAT> 5 ULN until baseline ASAT/ALAT are stabilized < 5 ULN;
- Concurrent administration of herbal preparations containing St John's Wort (*Hypericum perforatum*).

4.4 Special warnings and special precautions for use

**Cutaneous reactions:** Severe and life-threatening skin reactions, including fatal cases, have occurred in patients treated with nevirapine mainly during the first 6 weeks of therapy. These have included cases of Stevens-Johnson syndrome, toxic epidermal necrolysis and hypersensitivity reactions characterized 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 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 edema, muscle or joint aches, or general malaise), including Stevens-Johnson syndrome, or toxic epidermal necrolysis. Nevirapine 200mg Tablet must be permanently discontinued in any patient experiencing hypersensitivity reaction (characterized by rash with constitutional symptoms, plus visceral involvement, such as hepatitis, eosinophilia, granulocytopenia, and renal dysfunction). Nevirapine administration above the recommended dose might increase the frequency and seriousness of skin reactions, such as Stevens-Johnson syndrome and toxic epidermal necrolysis.

**Hepatic reactions:** Severe and life-threatening hepatotoxicity, 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. Women and patients with higher CD4+ cell counts are at increased risk of hepatic adverse events. However, the risk continues past this period and monitoring should continue at frequent intervals throughout treatment.

**Liver Disease:** 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.

### 4.5 Interaction with other medicinal products and other forms of interaction

**Ketoconazole:** Ketoconazole should not be co-administered with nevirapine as this results in reduction of plasma ketoconazole concentration.

**Fluconazole:** Co-administration of fluconazole and nevirapine resulted in approximately 100% increase in nevirapine exposure compared with historical data where nevirapine was administered alone. There was no clinically relevant effect of nevirapine on fluconazole. However, caution should be exercised when co-administering fluconazole with nevirapine.

**Oral Contraceptives:** Oral contraceptives should not be used as the sole method of contraception in HIV infected patients. Other means of contraception (such as barrier methods) are recommended in patients being treated with nevirapine.

**Other medicinal products metabolized by CYP3A:** Nevirapine is an inducer of CYP3A and potentially CYP2B6, with maximal induction occurring within 2-4 weeks of initiating multiple-dose therapy. Based on the known metabolism of methadone, nevirapine may decrease plasma concentrations of methadone by increasing its hepatic metabolism. Narcotic withdrawal syndrome has been reported in patients treated with nevirapine and methadone concomitantly. Methadone-maintained patients beginning nevirapine therapy should be monitored for evidence of withdrawal and methadone dose should be adjusted accordingly.

The concomitant use of rifampicin and nevirapine is not recommended. Physicians needing to treat patients co-infected with tuberculosis and using a nevirapine containing regimen may consider use of rifabutin instead. Rifabutin and nevirapine can be administered concurrently without dose adjustments. Alternatively, physicians may consider switching to a triple NRTI combination for a variable period, depending on the tuberculosis treatment regimen.
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 foetal 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. Therefore, nevirapine should only be used during pregnancy if the expected benefit justifies the possible risk to the fetus. Caution should be exercised when prescribing Nevirapine 200mg Tablet to pregnant women.

Results from a pharmacokinetic study (ACTG 250) of 10 HIV-1 infected pregnant women who were administered a single oral dose of 100 or 200 mg nevirapine at a median of 5.8 hours before delivery, have shown that nevirapine readily crosses the placenta and is found in breast milk.

It is recommended that HIV-infected mothers do not breast-feed their infants to avoid risking postnatal transmission of HIV and that mothers should discontinue nursing if they are receiving nevirapine.

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

The most frequently reported adverse events related to nevirapine therapy, across all clinical trials, were rash, nausea, fatigue, fever, headache, vomiting, diarrhoea, abdominal pain and myalgia.

The following adverse events that may be causally related to the administration of nevirapine have been reported:

**Blood and lymphatic system disorders:**
- Rare: granulocytopenia, anaemia

**Immune system disorders:**
- Common: allergic reactions
- Rare: hypersensitivity (syndrome), anaphylaxis

**Nervous system disorders**
- Common: headache

**Gastrointestinal disorders**
- Common: nausea
- Uncommon: vomiting, abdominal pain
- Rare: diarrhoea

**Hepato-biliary disorders**
- Common: hepatitis (1.2 %), abnormal liver function tests
- Uncommon: jaundice
- Rare: liver failure / fulminant hepatitis

**Skin and subcutaneous tissue disorders**
- Common: rash (9 %)
- Uncommon: Stevens Johnson syndrome (0.3 %), urticaria
- Rare: toxic epidermal necrolysis, angio-oedema

**Musculoskeletal, connective tissue and bone disorders**
- Uncommon: myalgia
- Rare: arthralgia

**General disorders and administration site conditions**
- Uncommon: fatigue, fever
4.9 Overdose
There is no known antidote for nevirapine overdose. Cases of nevirapine 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 transaminase levels and weight decrease. All of these effects subsided following discontinuation of nevirapine.

5. PHARMACOLOGICAL PROPERTIES

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

*Mechanism of Action:* Nevirapine is a non-nucleoside reverse transcriptase inhibitor 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.

5.2 Pharmacokinetic properties
*Absorption and Bioavailability:* Nevirapine is readily absorbed (>90%) after oral administration in healthy volunteers and in adults with HIV-1 infection. Peak plasma nevirapine concentrations of 2 ± 0.4 µg/mL (7.5 µM) are attained by 4 hours following a single 200 mg dose.

*Distribution:* Nevirapine is highly lipophilic and is essentially nonionized at physiologic pH. Nevirapine readily crosses the placenta and is found in breast milk. Nevirapine is about 60% bound to plasma proteins in the plasma concentration range of 1-10 µg/mL. Nevirapine concentrations in human cerebrospinal fluid (n=6) were 45% (± 5%) of the concentrations in plasma; this ratio is approximately equal to the fraction not bound to plasma protein.

*Metabolism/Elimination:* Human liver microsomes have shown that nevirapine is extensively biotransformed via cytochrome P450 (oxidative) metabolism to several hydroxylated metabolites. Cytochrome P450 metabolism, glucuronide conjugation, and urinary excretion of glucuronidated metabolites represent the primary route of nevirapine bio-transformation and elimination in humans. Renal excretion plays a minor role in elimination of the parent compound.

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
Microcrystalline cellulose, lactose, croscarmellose sodium, povidone, colloidal anhydrous silica, purified talc, magnesium stearate and purified water.

6.2 Incompatibilities
Drug compatibility studies with excipients showed no physical and chemical incompatibilities of the active ingredient.

6.3 Shelf life
36 months from the date of manufacture.

6.4 Special precautions for storage
Store below 30°C. Protect from light. Keep in a well-closed container.

6.5 Nature and contents of container
HDPE container containing 60 tablets each.

6.6 Instructions for use, handling, and disposal
No special requirements.

7. MARKETING AUTHORISATION HOLDER
Strides Pharma Science Limited
'Strides House', Opp. IIM
Bilekahalli, Bannerghatta Road
Bangalore-560076, INDIA

8. MARKETING AUTHORISATION NUMBER(S)
KTK/25/415/98

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHURISATION

10. DATE OF REVISION OF THE TEXT
May 2005
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