SUMMARY OF PRODUCT CHARACTERISTICS

Nevirapine Tablets USP 200 mg

Rx Only

1. NAME OF THE 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 as part of combination therapy for the antiviral treatment of HIV-1 infected patients with advanced or progressive immunodeficiency.

Most of the experience with nevirapine tablets is in combination with nucleoside reverse transcriptase inhibitors (NRTIs). There is at present insufficient data on the efficacy of subsequent use of triple combination including protease inhibitors (PIs) after nevirapine tablets therapy. Refer to section 5.1.

4.2 Posology and method of administration

The therapy should be initiated by physician experienced in the management of HIV infection.

Patients 16 years and older: The recommended dose of nevirapine tablets is one 200 mg tablet 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 one 200 mg tablet twice daily, in combination with at least two additional antiretroviral agents to which the patient has not been previously exposed. Resistant virus emerges rapidly and uniformly when nevirapine tablets are administered as monotherapy; therefore nevirapine tablets should always be administered in combination therapy. For concomitantly administered antiretroviral therapy, the recommended dosage and monitoring should be followed.

Paediatric (adolescent) patients: Following the dosing schedule described above, is suitable for larger children, particularly adolescents, below the age of 16 who weigh 50 kg or more. An oral suspension dosage form, which can be dosed according to body weight, is available for children in this age group weighing less than 50 kg.

Dose Management Considerations

Clinical chemistry tests, which include liver function tests, should be performed prior to initiating nevirapine tablets therapy and at appropriate intervals during therapy. For toxicities that require interruption of nevirapine tablets therapy, see section 4.4.

Patients experiencing rash during the 14-day lead-in period of 200 mg/day should not have their nevirapine tablets dose increased until the rash has resolved. The isolated rash should be closely monitored (please refer to section 4.4).

Patients who interrupt nevirapine tablets dosing for more than 7 days should restart the recommended lead-in dosing, using one 200 mg tablet daily for the first 14 days followed by one 200 mg tablet twice daily. Nevirapine tablets should be administered by physicians who are experienced in the treatment of HIV infection.

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

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 other side effects of a hypersensitivity reaction, YOU MUST CONTACT your doctor IMMEDIATELY as such reactions can be potentially life - threatening.
If you ever have any rash symptoms please inform your doctor immediately, who will advise you whether you should stop taking nevirapine tablets.
If you develop a severe rash whilst taking nevirapine tablets, NEVER TAKE nevirapine tablets again without referring to your doctor.

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 tablets 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. Women and patients with higher CD4+ cell counts are at increased risk of hepatic adverse events. 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 tablets. 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.

Serious hepatotoxicity, including liver failure requiring transplantation, has been reported in HIV-uninfected individuals receiving multiple doses of nevirapine tablets in the setting of post-exposure-prophylaxis (PEP), an unapproved use. The use of nevirapine tablets has not been evaluated within a specific study on PEP, especially in term of treatment duration. 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 tablets containing regimens. Women appear to have a three fold higher risk than men for rash associated hepatic events (4.6 % vs. 1.5 %). Patients with higher CD4+ cell counts may also be at higher risk for rash-associated hepatic events with nevirapine tablets. In a retrospective review, women with CD4+ cell counts >250 cells/mm^3 had a 9 fold higher risk of rash-associated hepatic adverse events compared to women with CD4+ cell counts <250 cells/mm^3 (8.4 % vs. 0.9 %). An increased risk was observed in men with CD4+ cell counts > 400 cells/mm^3 compared to men with CD4+ cell counts < 400 cells/mm^3 (4.5% vs. 0.7%).

Patients should be informed that hepatic reactions are a major toxicity of nevirapine tablets requiring close monitoring during the first 18 weeks. They should be informed that occurrence of symptoms suggestive of hepatitis should lead them to contact promptly their physician.

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 contraindircdation 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 orALAT 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.

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.

The following events have also been reported when nevirapine tablets have been used in combination with other anti-retroviral agents: pancreatitis, peripheral neuropathy and thrombocytopaenia. These events are commonly associated with other antiretroviral agents and may be expected to occur when nevirapine tablets are used in combination with other agents; however it is unlikely that these events are due to nevirapine tablets treatment. Hepatic-renal failure syndromes have been rarely reported.

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 (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).

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

NRTIs: No dosage adjustments are required when nevirapine tablets are taken in combination with zidovudine, didanosine, or zalcitabine. When the zidovudine data were pooled from two studies (n = 33) in which HIV-1 infected patients received nevirapine tablets 400 mg/day either alone or in combination with 200-300 mg/day didanosine or 0.375 to 0.75 mg/day zalcitabine on a background of zidovudine therapy, nevirapine produced a non-significant decline of 13 % in zidovudine area under the curve (AUC) and a non-significant increase of 5.8 % in zidovudine C_{max}. In a subset of patients (n = 6) who were administered nevirapine tablets 400 mg/day and didanosine on a background of zidovudine therapy, nevirapine produced a significant decline of 32 % in zidovudine AUC and a non-significant decline of 27 % in zidovudine C_{max} . Paired data suggest that zidovudine had no effect on the pharmacokinetics of nevirapine. In one crossover study, nevirapine had no effect on the steady-state pharmacokinetics of either didanosine (n = 18) or zalcitabine (n = 6).

Results from a 36 day study in HIV infected patients (n = 25) administered nevirapine tablets, nelfinavir (750 mg t.i.d.) and stavudine (30-40 mg b.i.d.) showed no statistically significant changes in the AUC or C_{max} of stavudine. Furthermore, a population pharmacokinetic study of 90 patients assigned to receive lamivudine with nevirapine tablets or placebo revealed no changes to lamivudine apparent clearance and volume of distribution, suggesting no induction effect of nevirapine on lamivudine clearance.

Non-nucleoside reverse transcriptase inhibitors (NNRTIs): Results from a clinical trial (n=14) showed that steady-state pharmacokinetic parameters of nevirapine were not affected by co-administration of efavirenz. However, drug levels of efavirenz were significantly reduced in the presence of nevirapine. The AUC of efavirenz decreased by 22% and the C_{min} by 36%. When co-administered with nevirapine a dose increase of efavirenz to 800mg once daily may be warranted.

PIs: Nevirapine is a mild to moderate inducer of the hepatic enzyme CYP3A; therefore, it is possible that co-administration with PIs (also metabolised by CYP3A) may result in an alteration in the plasma concentration of either agent.

Results from a clinical trial (n = 31) with HIV infected patients administered nevirapine tablets and saquinavir (hard gelatin capsules; 600 mg t.i.d.) indicated that their co-administration leads to a mean reduction of 24 % ($p = 0.041$) in saquinavir AUC and no significant change in nevirapine plasma levels. The reduction in saquinavir levels due to this interaction may further reduce the marginal plasma levels of saquinavir which are achieved with the hard gelatin capsule formulation.

Another study (n=20) evaluated once daily dosing of saquinavir soft gel capsule (sgc) with a 100 mg dose of ritonavir. All patients concomitantly received nevirapine tablets. The study showed that the combination of saquinavir sgc and 100 mg of ritonavir had no measurable effect on the pharmacokinetic parameters of nevirapine, compared to historical controls. The effect of nevirapine on the pharmacokinetics of saquinavir sgc in the presence of 100 mg of ritonavir, was modest and clinically insignificant.

Results from a clinical trial (n = 25) with HIV infected patients administered nevirapine tablets and indinavir (800 mg q8h) indicated that their co-administration leads to a 28 % mean decrease ($p < 0.01$) in indinavir AUC and no significant change in nevirapine plasma levels. No definitive clinical conclusions have been reached regarding the potential impact of co-administration of nevirapine and indinavir. A dose increase of indinavir to 1000 mg q8h should be considered when indinavir is given with nevirapine 200 mg b.i.d.; however, there are no data currently available to establish that the short term or long term antiviral activity of indinavir 1000 mg q8h with nevirapine 200 mg b.i.d. will differ from that of indinavir 800 mg q8h with nevirapine 200 mg b.i.d.

Results from a clinical trial (n = 25) with HIV infected patients administered nevirapine tablets and ritonavir (600 mg b.i.d. [using a gradual dose escalation regimen]) indicated that their coadministration leads to no significant change in ritonavir or nevirapine plasma levels.

Results from a 36 day study in HIV infected patients (n = 25) administered nevirapine tablets, nelfinavir (750 mg t.i.d.) and stavudine (30-40 mg b.i.d.) showed no statistically significant changes in nelfinavir pharmacokinetic parameters after the addition of nevirapine (AUC + 4%, C_{max} + 14 % and C_{min} - 2 %). Compared to historical controls nevirapine levels appeared to be unchanged.

There were no increased safety concerns noted with the coadministration of nevirapine tablets with any of these PIs when used in combination.

There was no apparent change in the pharmacokinetics of lopinavir when used concomitantly with nevirapine tablets in healthy volunteers. In single PI experienced patients, nevirapine, used in combination with lopinavir / ritonavir 400/100 mg (3 capsules) twice daily and NRTIs, provided very good virological response rates. Results from a pharmacokinetic study in paediatric patients revealed a decrease in lopinavir concentrations during nevirapine co-administration. The clinical significance of this interaction is unknown. However a dose increase of lopinavir / ritonavir to 533/133 mg (4 capsules or 6.5 ml) may be considered when used in combination with nevirapine in patients where reduced susceptibility to lopinavir / ritonavir is clinically suspected (by treatment history or laboratory evidence).

Ketoconazole: In one study, administration of nevirapine 200 mg b.i.d. with ketoconazole 400 mg q.d. resulted in a significant reduction (63 % median reduction in ketoconazole AUC and a 40 % median reduction in ketoconazole C_{max}). In the same study, ketoconazole administration resulted in a 15-28 % increase in the plasma levels of nevirapine compared to historical controls. Ketoconazole and nevirapine tablets should not be given concomitantly. The effects of nevirapine on itraconazole are not known.

Fluconazole: Co-administration of fluconazole and nevirapine tablets resulted in approximately 100% increase in nevirapine exposure compared with historical data where nevirapine tablets was administered alone. Because of the risk of increased exposure to nevirapine, caution should be exercised if the medicinal products are given concomitantly and patients should be monitored closely. There was no clinically relevant effect of nevirapine on fluconazole.

Oral Contraceptives: As 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 tablets. Furthermore a pharmacokinetic interaction has been identified. Nevirapine 200 mg b.i.d. was co-administered with a single dose of an oral contraceptive containing ethinyl estradiol (EE) 0.035mg and norethindrone (NET) 1.0 mg. Compared to plasma concentrations observed prior to nevirapine administration, the median AUC for 17a-EE was significantly decreased by 29% after 28 days of nevirapine dosing. There was a significant reduction in EE mean resident time and half-life. There was a significant reduction (18%) in median AUC for NET, without changes in mean resident time or half-life. The magnitude of the effect suggests that the dose of the oral contraceptive should be adjusted to allow

adequate treatment for indications other than contraception (e.g., endometriosis), if used with nevirapine.

Other medicinal products metabolised 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 tablets and methadone concomitantly. Methadone-maintained patients beginning nevirapine tablets therapy should be monitored for evidence of withdrawal and methadone dose should be adjusted accordingly.

Other compounds that are substrates of *CYP3A and CYP2B6* may have decreased plasma concentrations when co-administered with nevirapine tablets. Therefore, careful monitoring of the therapeutic effectiveness of P450 metabolised medicinal products is recommended when taken in combination with nevirapine tablets.

CYP isoenzyme inhibitors: The results of a nevirapine-clarithromycin interaction study (n = 18) resulted in a significant reduction in clarithromycin AUC (30 %) and Cmax (- 21 %) but a significant increase in the AUC (58 %) and C_{max} (62 %) of the active metabolite 14-OH clarithromycin. There was a significant increase in the nevirapine C_{min} (28 %) and a non-significant increase in nevirapine AUC (26 %) and C_{max} (24 %). These results would suggest that no dose adjustment is necessary for eitherclarithromycin and nevirapine tablets when the two medicinal products are co-administered. Close monitoring of hepatic abnormalities and activity against *Myobacterium avium-intracellular complex* (MAC) is nevertheless recommended. Monitoring of steady-state nevirapine trough plasma concentrations in patients who received long-term nevirapine tablets treatment revealed that nevirapine trough concentrations were elevated in patients who received cimetidine (+ 7 %, n = 13).

CYP isoenzyme inducers*:* An open-label study (n = 14) to determine the effects of nevirapine on the steady state pharmacokinetics of rifampicin resulted in no significant change in rifampicin C_{max} and AUC. In contrast, rifampicin produced a significant lowering of nevirapine AUC (- 58 %), C_{max} (- 50 %) and C_{min} (- 68 %) compared to historical data.

The available pharmacokinetic data suggest that the concomitant use of rifampicin and nevirapine tablets is not recommended. Therefore, these medicinal products should not be used in combination. Physicians needing to treat patients co-infected with tuberculosis and using

nevirapine tablets containing regimen may consider use of rifabutin instead. Rifabutin and nevirapine tablets can be administered concurrently without dose adjustments (see below). Alternatively physicians may consider switching to a triple NRTI combination for a variable period of time, depending on the tuberculosis treatment regimen (see section 4.3).

In a pharmacokinetic study the concomitant administration of nevirapine tablets with rifabutin resulted in a non-significant 12 % (median) increase in the steady-state AUC, a non-significant 3% decrease in C_{minss} and a significant 20 % increase in the C_{maxss}. Non-significant changes were found on 25-O-desacetyl-rifabutin (rifabutin active metabolite) AUC, C_{minss} or C_{maxss}. A statistically significant increase in the apparent clearance of nevirapine (9 %) compared to historical pharmacokinetic data was reported.

This study suggests that there is no clinically relevant interaction between nevirapine and rifabutin. Therefore, the two drugs can be administered concurrently without dose adjustments provided that a careful monitoring of the adverse reactions is performed.

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. The net effect of the interaction may change during the first weeks of co-administration or upon discontinuation of nevirapine tablets, and close monitoring of anticoagulation levels is therefore warranted.

Hypericum perforatum: Serum levels of nevirapine can be reduced by concomitant use of the herbal preparation St John's Wort (*Hypericum perforatum*). This is due to induction of drug metabolism enzymes and/or transport proteins by St John's Wort. Herbal preparations containing St John's Wort should therefore not be combined with nevirapine tablets. If patient is already taking St John's Wort check nevirapine and if possible viral levels and stop St John's Wort. Nevirapine levels may increase on stopping St John's Wort. The dose of nevirapine tablets may need adjusting. The inducing effect may persist for at least 2 weeks after cessation of treatment with St John's Wort.

Other information: Studies using human liver microsomes indicated that the formation of nevirapine hydroxylated metabolites was not affected by the presence of dapsone, rifabutin, rifampicin, and trimethoprim/sulfamethoxazole. Ketoconazole and erythromycin significantly inhibited the formation of nevirapine hydroxylated metabolites.

4.6 Pregnancy and lactation

No observable teratogenicity was detected in reproductive studies performed in pregnant rats and rabbits. There are no adequate and well-controlled studies in pregnant women. Therefore nevirapine tablets should only be used during pregnancy if the expected benefit justifies the possible risk to the child and caution should be exercised when prescribing nevirapine tablets 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 tablets 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 tablets.

4.7 Effects on abilityto 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 tablets therapy, across all clinical trials, were rash, nausea, fatigue, fever, headache, vomiting, diarrhoea, abdominal pain and myalgia.

The postmarketing experience has shown that the most serious adverse reactions are Stevens-Johnson syndrome and toxic epidermal necrolysis and serious hepatitis/hepatic failure and hypersensitivity reactions, characterised by rash with constitutional symptoms such as fever, arthralgia, myalgia and lymphadenopathy, plus visceral involvement, such as hepatitis, eosinophilia, granulocytopenia, and renal dysfunction. The first 18 weeks of treatment is a critical period which requires close monitoring (see section 4.4).

The following adverse events which may be causally related to the administration of nevirapine tablets have been reported. The frequencies estimated are based on pooled clinical trial data for events considered related to nevirapine tablets treatment.

Frequency classes: very common (>1/10); common (>1/100, <1/10); uncommon (>1/1,000, <1/100); rare (>1/10,000, <1/1,000); very rare (<1/10,000)

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 %), liver function tests abnormal

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

Combination antiretroviral therapy has been associated with redistribution of body fat (lipodystrophy) in HIV infected patients including the loss of peripheral and facial subcutaneous

fat, increased intra-abdominal and visceral fat, breast hypertrophy and dorsocervical fat accumulation (buffalo hump).

Combination antiretroviral therapy has been associated with metabolic abnormalities such as hypertriglyceridaemia, hypercholesterolaemia, insulin resistance, hyperglycaemia and hyperlactataemia (see section 4.4).

Skin and subcutaneous tissues

The most common clinical toxicity of nevirapine tablets is rash, with nevirapine tablets attributable rash occurring in 9 % of patients in combination regimens in controlled studies. In these clinical trials 24 % of patients treated with a nevirapine tablets containing regimen experienced rash compared with 15 % of patients treated in control groups. Severe rash occurred in 1.7 % of nevirapine tablets-treated patients compared with 0.2 % of patients treated in the control groups.

Rashes are usually mild to moderate, maculopapular erythematous cutaneous eruptions, with or without pruritus, located on the trunk, face and extremities. Allergic reactions (anaphylaxis, angioedema and urticaria) have been reported. Rashes occur alone or in the context of hypersensitivity reactions, characterised by rash with constitutional symptoms such as fever, arthralgia, myalgia and lympadenopathy, plus visceral involvement, such as hepatitis, eosinophilia, granulocytopenia, and renal dysfunction.

Severe and life-threatening skin reactions have occurred in patients treated with nevirapine tablets, including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). Fatal cases of SJS, TEN and hypersensitivity reactions have been reported. The majority of severe rashes occurred within the first 6 weeks of treatment and some required hospitalisation, with one patient requiring surgical intervention.

Hepato-biliary

The most frequently observed laboratory test abnormalities are elevations in liver function tests (LFTs), including ALAT, ASAT, GGT, total bilirubin and alkaline phosphatase. Asymptomatic elevations of GGT levels are the most frequent. Cases of jaundice have been reported. Cases of hepatitis (severe and life-threatening hepatoxicity, including fatal fulminant hepatitis) have been reported in patients treated with nevirapine tablets. In a large clinical trial, the risk of a serious hepatic event among 1121 patients receiving nevirapine tablets for a median duration of greater than one year was 1.2 % (versus 0.6 % in placebo group). The best predictor of a serious hepatic

event was elevated baseline liver function tests. The first 18 weeks of treatment is a critical period which requires close monitoring (see section 4.4).

Paediatric patients

Based on experience of 361 paediatric patients treated in clinical trials, the most frequently reported adverse events related to nevirapine tablets were similar to those observed in adults, with the exception of granulocytopaenia which was more commonly observed in children. Isolated cases of Stevens-Johnson syndrome or Stevens-Johnson/toxic epidermal necrolysis transition syndrome have been reported in this population.

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 Pharmacodynamicproperties

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.

Resistance

HIV isolates with reduced susceptibility (100 to 250-fold) to nevirapine emerge *in vitro*. Phenotypic and genotypic changes occur in HIV isolates from patients treated with nevirapine tablets or nevirapine tablets + zidovudine over one to 12 weeks. By week 8 of nevirapine tablets monotherapy, 100 % of the patients tested had HIV isolates with a > 100-fold decrease in susceptibility to nevirapine, regardless of dose. Nevirapine tablets + zidovudine combination therapy did not alter the emergence rate of nevirapine-resistant virus. Genotypic and phenotypic

resistance was examined for patients receiving nevirapine tablets in triple and double therapy drug combination therapy, and in the non-nevirapine tablets comparative group from the INCAS study. Antiretroviral naive subjects with CD4 cells counts of 200-600/mm^3 were treated with either nevirapine tablets + zidovudine (n = 46), zidovudine + didanosine (n = 51) or nevirapine tablets + zidovudine + didanosine (n = 51) and followed for 52 weeks or longer on therapy. Virologic evaluations were performed at baseline, six months and 12 months. The phenotypic resistance test performed required a minimum of 1000 copies/ml HIV RNA in order to be able to amplify the virus. Of the three study groups, 16, 19 and 28 patients respectively had evaluable baseline isolates and subsequently remained in the study for at least 24 weeks. At baseline, there were five cases of phenotypic resistance to nevirapine; the IC_{50} values were 5 to 6.5-fold increased in three and >100 fold in two. At 24 weeks, all available isolates recoverable from patients receiving nevirapine were resistant to this agent, while 18/21 (86 %) patients carried such isolates at 30-60 weeks. In 16 subjects viral suppression was below the limits of detection (< 20 copies/mL = 14, < 400 copies/mL = 2). Assuming that suppression below < 20 copies/mL implies nevirapine susceptibility of the virus, 45 % (17/38) of patients had virus measured or imputed to be susceptible to nevirapine. All 11 subjects receiving nevirapine tablets + zidovudine who were tested for phenotypic resistance were resistant to nevirapine by six months. Over the entire period of observation, one case of didanosine resistance was seen. Zidovudine resistance emerged as more frequent after 30 - 60 weeks, especially in patients receiving double combination therapy. Based on the increase in IC_{50}, zidovudine resistance appeared lower in the nevirapine tablets + zidovudine + didanosine group than the other treatment groups.

With respect to nevirapine resistance, all isolates that were sequenced carried at least one mutation associated with resistance, the most common single changes being K103N and Y181C. Combinations of mutations were found in nine of the 12 patients observed. These data from INCAS illustrate that the use of highly active drug therapies is associated with a delay in the development of antiretroviral drug resistance.

The clinical relevance of phenotypic and genotypic changes associated with nevirapine tablets therapy has not been established.

In addition to the data presented above, there exists a risk of rapid emergence of resistance to NNRTIs in case of virological failure.

Cross-resistance

Rapid emergence of HIV strains which are cross-resistant to NNRTIs has been observed *in vitro*. Data on cross-resistance between the NNRTI nevirapine and NRTIs are very limited. In four patients, zidovudine-resistant isolates tested in vitro retained susceptibility to nevirapine and in six patients, nevirapine-resistant isolates were susceptible to zidovudine and didanosine. Cross-resistance between nevirapine and HIV PIs is unlikely because the enzyme targets involved are different.

Cross-resistance among the currently registered NNRTIs is broad. Some genotypic resistance data indicate that in most patients failing NNRTI, viral strains express cross-resistance to the other NNRTIs. The currently available data do not support sequential use of NNRTIs.

Pharmacodynamic Effects

Nevirapine tablets have been evaluated in both treatment naive and treatment experienced patients.

Results from a trial (ACTG 241) evaluated triple therapy with nevirapine tablets, zidovudine and didanosine compared to zidovudine + didanosine, in 398 HIV-1 infected patients (mean baseline 153 CD4+ cells/mm^3; plasma HIV1 RNA 4.59 $\log_{10}$ copies/ml), who had received at least 6 months of NRTI therapy prior to enrolment (median 115 weeks). These heavily experienced patients demonstrated a significant improvement of the triple therapy group over the double therapy group for one year in both viral RNA and CD4+ cell counts.

A durable response for at least one year was documented in a trial (INCAS) for the triple therapy arm with nevirapine tablets, zidovudine and didanosine compared to zidovudine + didanosine or nevirapine tablets + zidovudine in 151 HIV-1 infected, treatment naive patients with CD4+ cell counts of 200-600 cells/mm3 (mean 376 cells/mm^3) and a mean baseline plasma HIV-1 RNA concentration of 4.41 $\log_{10}$ copies/ml (25,704 copies/ml). Treatment doses were nevirapine tablets, 200 mg daily for two weeks, followed by 200 mg twice daily, or placebo; zidovudine, 200 mg three times daily; didanosine, 125 or 200 mg twice daily (depending on the weight).

Nevirapine tablets have also been studied in combination with other antiretroviral agents, e.g., zalcitabine, stavudine, lamivudine, indinavir, ritonavir, nelfinavir, saquinavir and lopinavir. No new and overt safety problems have been reported for these combinations.

Studies are on-going to evaluate the efficacy and safety of combination therapies with nevirapine tablets in patients failing PI therapy

Perinatal Transmission

Two studies evaluated the efficacy of nevirapine tablets to prevent vertical transmission of HIV-1 infection. Mothers received only study antiretroviral therapy during these trials.

In the HIVNET 012 study in Kampala (Uganda) mother-infant pairs were randomised to receive oral nevirapine tablets (mother: 200 mg at the onset of labor; infant: 2 mg/kg within 72 hours of birth), or an ultra-short oral zidovudine regimen (mother: 600 mg at the onset of labor and 300 mg every 3 hours until delivery; infant: 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 tablets group, versus 25.1 % (n = 308 in the ultra-short zidovudine group (p = 0.00063).

In the SAINT study conducted in South Africa, mother-infant pairs were randomised to receive oral nevirapine tablets (mother: 200 mg during labor and 200 mg 24 to 48 hours postdelivery; infant: 6 mg 24 to 48 hours postdelivery); or a short oral zidovudine plus lamivudine regimen (mother: zidovudine 600 mg, then 300 mg every 3 hours during labour, followed by 300 mg b.i.d. for 7 days postdelivery plus lamivudine 150 mg b.i.d. during labor and for 7 days postdelivery; infant: zidovudine 12 mg b.i.d. plus lamivudine 6 mg b.i.d. for 7 days [if infant weight <2 kg, zidovudine 4 mg/kg b.i.d. plus lamivudine 2 mg/kg b.i.d. for 7 days]). There was no significant difference in HIV-1 transmission rates through 6 to 8 weeks between the nevirapine tablets group (5.7 %, n = 652) and the zidovudine plus lamivudine group (3.6 %, n = 649). There was greater risk of HIV-1 transmission to babies whose mothers received their nevirapine tablets or their zidovudine plus lamivudine doses less than 2 hours before delivery. In the SAINT study 68% of nevirapine-exposed mothers had resistant strains at approximately 4 weeks after delivery.

In the case nevirapine tablets is used as single dose to prevent vertical transmission of HIV-1 infection, the risk of hepatotoxicity in mother and child cannot be excluded.

A blinded randomized clinical trial in women already taking antiretroviral therapy throughout pregnancy (PACTG 316) demonstrated no further reduction of vertical HIV-1 transmission when the mother and the child received a single nevirapine tablet dose during labour and after birth respectively. HIV-1 transmission rates were similarly low in both treatment groups (1.3% in the nevirapine tablets group, 1.4% in the placebo group). The vertical transmission decreased neither in women with HIV-1 RNA below the limit of quantification nor in women with HIV-1 RNA above the limit of quantification prior to partus. Of the 95 women who received intrapartum nevirapine tablets, 15% developed nevirapine resistance mutations at 6 weeks post partus.

5.2 Pharmacokinetic properties

Adults

Nevirapine is readily absorbed (> 90 %) after oral administration in healthy volunteers and in adults with HIV-1 infection. Absolute bioavailability in 12 healthy adults following single-dose administration was 93 ± 9 % (mean SD) for a 50 mg tablet and 91 ± 8 % for an oral solution. Peak plasma nevirapine concentrations of 2 ± 0.4 pg/ml (7.5 µM) were attained by 4 hours following a single 200 mg dose. Following multiple doses, nevirapine peak concentrations appear to increase linearly in the dose range of 200 to 400 mg/day. Data reported in the literature from 20 HIV infected patients suggest a steady state C_{max} of 5.74 µg/ml (5.00-7.44) and C_{min} of 3.73 µg/ml (3.20-5.08) with an AUC of 109.0 h. µg/ml (96.0-143.5) in patients taking 200 mg of nevirapine b.i.d. Other published data support these conclusions. Long-term efficacy appears to be most likely in patients whose nevirapine trough levels exceed 3.5 µg/ml.

Nevirapine tablets and oral suspension have been shown to be comparably bioavailable and interchangeable at doses up to 200 mg. The absorption of nevirapine is not affected by food, antacids or medicinal products which are formulated with an alkaline buffering agent (e.g., didanosine). Nevirapine is lipophilic and is essentially nonionized at physiologic pH. Following intravenous administration to healthy adults, the volume of distribution (Vdss) of nevirapine was 1.21 ± 0.09 l/kg, suggesting that nevirapine is widely distributed in humans. 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.

In vivo studies in humans and *in vitro* studies with human liver microsomes have shown that nevirapine is extensively biotransformed via cytochrome P450 (oxidative) metabolism to several hydroxylated metabolites. *In vitro* studies with human liver microsomes suggest that oxidative metabolism of nevirapine is mediated primarily by cytochrome P450 isozymes from the CYP3A family, although other isozymes may have a secondary role. In a mass balance/excretion study in eight healthy male volunteers dosed to steady state with nevirapine 200 mg given twice daily followed by a single 50 mg dose of 14C-nevirapine, approximately 91.4 ± 10.5 % of the radiolabelled dose was recovered, with urine (81.3 ± 11.1 %) representing the primary route of excretion compared to faeces (10.1 ± 1.5 %). Greater than 80 % of the radioactivity in urine was made up of glucuronide conjugates of hydroxylated metabolites. Thus cytochrome P450

metabolism, glucuronide conjugation, and urinary excretion of glucuronidated metabolites represent the primary route of nevirapine biotransformation and elimination in humans. Only a small fraction (< 5 %) of the radioactivity in urine (representing < 3 % of the total dose) was made up of parent compound; therefore, renal excretion plays a minor role in elimination of the parent compound.

Nevirapine has been shown to be an inducer of hepatic cytochrome P450 metabolic enzymes. The pharmacokinetics of autoinduction are characterised by an approximately 1.5 to 2 fold increase in the apparent oral clearance of nevirapine as treatment continues from a single dose to two-to-four weeks of dosing with 200-400 mg/day. Autoinduction also results in a corresponding decrease in the terminal phase half-life of nevirapine in plasma from approximately 45 hours (single dose) to approximately 25-30 hours following multiple dosing with 200-400 mg/day.

Renal dysfunction: The single-dose pharmacokinetics of nevirapine have been compared in 23 subjects with either mild (50 ≥ CLcr < 80 ml/min), moderate (30 ≥ CLcr < 50 ml/min) or severe renal dysfunction (CLcr < 30 ml/min), renal impairment or end-stage renal disease (ESRD) requiring dialysis, and 8 subjects with normal renal function (CLcr > 80 ml/min). Renal impairment (mild, moderate and severe) resulted in no significant change in the pharmacokinetics of nevirapine. However, subjects with ESRD requiring dialysis exhibited a 43.5 % reduction in nevirapine AUC over a one-week exposure period. There was also accumulation of nevirapine hydroxy-metabolites in plasma. The 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.

Hepatic dysfunction: The single-dose pharmacokinetics of nevirapine have been compared in 10 subjects with hepatic dysfunction and 8 subjects with normal hepatic function. 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. However, the pharmacokinetics of nevirapine in one subject with a Child-Pugh score of 8 and moderate to severe ascites suggests that patients with worsening hepatic function may be at risk of accumulating nevirapine in the systemic circulation.

Although a slightly higher weight adjusted volume of distribution of nevirapine was found in female subjects compared to males, no significant gender differences in nevirapine plasma

concentrations following single or multiple dose administrations were seen. Nevirapine pharmacokinetics in HIV-1 infected adults do not appear to change with age (range 19-68 years) or race (Black, Hispanic, or Caucasian). Nevirapine tablets have not been specifically investigated in patients over the age of 65.

Paediatric patients

The pharmacokinetics of nevirapine have been studied in two open-label studies in children with HIV-1 infection. In one study, nine HIV infected children ranging in age from ≤ 9 months to 14 years were administered a single dose (7.5 mg, 30 mg, or 120 mg per m^2; n = 3 per dose) of nevirapine oral suspension after an overnight fast. Nevirapine AUC and peak concentration increased in proportion with dose. Following absorption nevirapine mean plasma concentrations declined log linearly with time. Nevirapine terminal phase half-life following a single dose was 30.6 ± 10.2 hours. In a second multiple dose study, nevirapine oral suspension or tablets (240 to 400 mg/m^2/day) were administered as monotherapy or in combination with zidovudine or zidovudine and didanosine to 37 HIV-1 infected paediatric patients with the following demographics: male (54 %), racial minority groups (73 %), median age of 11 months (range: 2months - 15 years). These patients received 120 mg/ m^2/day of nevirapine for approximately 4 weeks followed by 120 mg/ m^2/b.i.d. (patients > 9 years of age) or 200 mg/ m^2/b.i.d. (patients ≤ 9 years of age). Nevirapine clearance adjusted for body weight reached maximum values by age 1 to 2 years and then decreased with increasing age. Nevirapine apparent clearance adjusted for body weight was approximately two-fold greater in children younger than 8 years compared to adults. Nevirapine half-life for the study group as a whole after dosing to steady state was 25.9 ± 9.6 hours. With long term drug administration, the mean values for nevirapine terminal half-life changed with age as follows: 2 months to 1 year (32 hours), 1 to 4 years (21 hours), 4 to 8 years (18 hours), greater than 8 years (28 hours).

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

Please refer outer package for expiry date.

6.4 Specialprecautionsforstorage

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

6.5 Natureandcontentsofcontainer

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.

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