SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Nevirapine Tablets USP 200mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Uncoated tablet contains Nevirapine 200 mg

3. PHARMACEUTICAL FORM

Uncoated tablet.

Off-white to pale yellow colored, capsule shaped, biconvex tablets debossed with ‘H’ on one side and ‘7’ on other side with break line on both sides.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Nevirapine is indicated for use in combination with other antiretroviral agents for the treatment of HIV-1-infection. This indication is based on one principal clinical trial (BI 1090) that demonstrated prolonged suppression of HIV-RNA and two smaller supportive studies.

For a summary of clinical and Pharmacodynamic information, see section 5.1.

4.2 Posology and method of administration

Adults:

The recommended dose for nevirapine 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 other antiretroviral agents. For concomitantly administered antiretroviral therapy, the manufacturer’s recommended dosage and monitoring should be followed.

Pediatric Patients:

The recommended oral dose of nevirapine for pediatric patients 2 months up to 8 years of age is 4 mg/kg once daily for the first 14 days followed by 7 mg/kg twice daily thereafter. For patients 8 years and older the recommended dose is 4 mg/kg once daily for two weeks

followed by 4 mg/kg twice daily thereafter. The total daily dose should not exceed 400 mg for any patient.

Monitoring of Patients:

Intensive clinical and laboratory monitoring, including liver function tests, is essential at baseline and during the first 18 weeks of treatment with nevirapine. The optimal frequency of monitoring during this period has not been established. Some experts recommend clinical and laboratory monitoring more often than once per month, and in particular, would include monitoring of liver function tests at baseline, prior to dose escalation, and at two weeks post dose escalation. After the initial 18 week period, frequent clinical and laboratory monitoring should continue throughout nevirapine treatment. In some cases, hepatic injury has progressed despite discontinuation of treatment.

Dosage Adjustment:

Nevirapine should be discontinued if patients experience severe rash or a rash accompanied by constitutional findings. Patients experiencing rash during the 14-day lead-in period of 200 mg/day (4 mg/kg/day in pediatric patients) should not have their nevirapine dose increased until the rash has resolved.

If a clinical (symptomatic) hepatic event occurs, nevirapine should be permanently discontinued. Do not restart nevirapine after recovery.

Patients who interrupt nevirapine dosing for more than 7 days should restart the recommended dosing, using one 200 mg tablet daily (4 mg/kg/day in pediatric patients) for the first 14 days (lead-in) followed by one 200 mg tablet twice daily (4 or 7 mg/kg twice daily, according to age, for pediatric patients).

An additional 200 mg dose of nevirapine following each dialysis treatment is indicated in patients requiring dialysis. Nevirapine metabolites may accumulate in patients receiving dialysis; however, the clinical significance of this accumulation is not known. Patients with CrCL ≥20 mL/min do not require an adjustment in nevirapine dosing.

4.3 Contraindications

Nevirapine is contraindicated in patients with clinically significant hypersensitivity to any of the components contained in the tablet or the oral suspension.

4.4 Special warnings and special precautions for use

General:

The most serious adverse reactions associated with nevirapine are hepatitis/hepatic failure, Stevens-Johnson syndrome, toxic epidermal necrolysis, and hypersensitivity reactions. Hepatitis/hepatic failure may be associated with signs of hypersensitivity which can include severe rash or rash accompanied by fever, general malaise, fatigue, muscle or joint aches, blisters, oral lesions, conjunctivitis, facial edema, eosinophilia, granulocytopenia, lymphadenopathy, or renal dysfunction.

The first 18 weeks of therapy with nevirapine are a critical period during which intensive clinical and laboratory monitoring of patients is required to detect potentially life-threatening hepatic events and skin reactions. The optimal frequency of monitoring during this time period has not been established. Some experts recommend clinical and laboratory monitoring more often than once per month, and in particular, would include monitoring of liver function tests at baseline, prior to dose escalation and at two weeks post-dose escalation. After the initial 18 week period, frequent clinical and laboratory monitoring should continue throughout nevirapine treatment. In addition, the 14-day lead-in period with nevirapine 200 mg daily dosing has been demonstrated to reduce the frequency of rash**.**

Hepatic Events:

Severe, life-threatening, and in some cases fatal hepatotoxicity, including fulminant and cholestatic hepatitis, hepatic necrosis and hepatic failure, have been reported in patients treated with nevirapine. In controlled clinical trials, symptomatic hepatic events regardless of severity occurred in 4% (range 0% to 11.0%) of patients who received nevirapine and 1.2% of patients in control groups.

The risk of symptomatic hepatic events regardless of severity was greatest in the first 6 weeks of therapy. The risk continued to be greater in the nevirapine groups compared to controls through 18 weeks of treatment. However, hepatic events may occur at any time during

treatment. In some cases, patients presented with non-specific, prodromal signs or symptoms of fatigue, malaise, anorexia, nausea, jaundice, liver tenderness or hepatomegaly, with or without initially abnormal serum transaminase levels. Rash was observed in approximately half of the patients with symptomatic hepatic adverse events. Fever and flu-like symptoms accompanied some of these hepatic events. Some events, particularly those with rash and other symptoms, have progressed to hepatic failure with transaminase elevation, with or without hyperbilirubinemia, hepatic encephalopathy, prolonged partial thromboplastin time, or eosinophilia. Patients with signs or symptoms of hepatitis must be advised to discontinue nevirapine and immediately seek medical evaluation, which should include liver function tests.

Liver function tests should be performed immediately if a patient experiences signs or symptoms suggestive of hepatitis and/or hypersensitivity reaction. Liver function tests should also be obtained immediately for all patients who develop a rash in the first 18 weeks of treatment. Physicians and patients should be vigilant for the appearance of signs or symptoms of hepatitis, such as fatigue, malaise, anorexia, nausea, jaundice, bilirubinuria, acholic stools, liver tenderness or hepatomegaly. The diagnosis of hepatotoxicity should be considered in this setting, even if liver function tests are initially normal or alternative diagnoses are possible

If clinical hepatitis or transaminase elevations combined with rash or other systemic symptoms occur, nevirapine should be permanently discontinued. Do not restart nevirapine after recovery. In some cases, hepatic injury progresses despite discontinuation of treatment.

The patients at greatest risk of hepatic events, including potentially fatal events, are women with high CD4 counts. In general, during the first 6 weeks of treatment, 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/mm^3 (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). However, all patients, regardless of gender, CD4 count, or antiretroviral treatment history, should be monitored for hepatotoxicity since symptomatic

hepatic adverse events have been reported at all CD4 counts. Co-infection with hepatitis B or C and/or increased liver function tests at the start of therapy with nevirapine are associated with a greater risk of later symptomatic events (6 weeks or more after starting nevirapine) and asymptomatic increases in AST or ALT.

In addition, serious hepatotoxicity (including liver failure requiring transplantation in one instance) has been reported in HIV-uninfected individuals receiving multiple doses of nevirapine in the setting of post-exposure prophylaxis, an unapproved use.

Because increased nevirapine levels and nevirapine accumulation may be observed in patients with serious liver disease, nevirapine should not be administered to patients with severe hepatic impairment.

Skin Reactions:

Severe and life-threatening skin reactions, including fatal cases, have been reported, occurring most frequently 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 organ dysfunction including hepatic failure. In controlled clinical trials, Grade 3 and 4 rashes were reported during the first 6 weeks in 1.5% of nevirapine recipients compared to 0.1% of placebo subjects.

Patients developing signs or symptoms of severe skin reactions or hypersensitivity reactions (including, but not limited to, severe rash or rash accompanied by fever, general malaise, fatigue, muscle or joint aches, blisters, oral lesions, conjunctivitis, facial edema, and/or hepatitis, eosinophilia, granulocytopenia, lymphadenopathy, and renal dysfunction) must permanently discontinue nevirapine and seek medical evaluation immediately. Do not restart nevirapine following severe skin rash, skin rash combined with increased transaminases or other symptoms, or hypersensitivity reaction.

If patients present with a suspected nevirapine-associated rash, liver function tests should be performed. Patients with rash-associated AST or ALT elevations should be permanently discontinued from nevirapine.

Therapy with nevirapine must be initiated with a 14-day lead-in period of 200 mg/day (4 mg/kg/day in pediatric patients), which has been shown to reduce the frequency of rash. If

rash is observed during this lead-in period, dose escalation should not occur until the rash has resolved. Patients should be monitored closely if isolated rash of any severity occurs. Delay in stopping nevirapine treatment after the onset of rash may result in a more serious reaction.

Women appear to be at higher risk than men of developing rash with nevirapine.

In a clinical trial, concomitant prednisone use (40 mg/day for the first 14 days of nevirapine administration) was associated with an increase in incidence and severity of rash during the first 6 weeks of nevirapine therapy. Therefore, use of prednisone to prevent nevirapine-associated rash is not recommended.

Resistance

Nevirapine must not be used as a single agent to treat HIV or added on as a sole agent to a failing regimen. As with all other non-nucleoside reverse transcriptase inhibitors, resistant virus emerges rapidly when nevirapine is administered as monotherapy. The choice of new antiretroviral agents to be used in combination with nevirapine should take into consideration the potential for cross-resistance. When discontinuing an antiretroviral regimen containing nevirapine, the long half-life of nevirapine should be taken into account; if antiretrovirals with shorter half-lives than nevirapine are stopped concurrently, low plasma concentrations of nevirapine alone may persist for a week or longer and virus resistance may subsequently develop.

St. John’s wort:

Concomitant use of St. John's wort (hypericum perforatum) or St. John's wort containing products and nevirapine is not recommended. Co-administration of non-nucleoside reverse transcriptase inhibitors (NNRTIs), including nevirapine, with St. John's wort is expected to substantially decrease NNRTI concentrations and may result in sub-optimal levels of nevirapine and lead to loss of virologic response and possible resistance to nevirapine or to the class of NNRTIs.

4.5 Interaction with other medicinal products and other forms of interaction

Drug Interactions

Nevirapine is principally metabolized by the liver via the cytochrome P450 isoenzymes, 3A4 and 2B6. Nevirapine is known to be an inducer of these enzymes. As a result, drugs that are metabolized by these enzyme systems may have lower than expected plasma levels when coadministered with nevirapine.

The specific pharmacokinetic changes that occur with co-administration of nevirapine and other drugs are listed in clinical pharmacology. Clinical comments about possible dosage modifications based on these pharmacokinetic changes are listed in below Table. The data in below Table is based on the results of drug interaction studies conducted in HIV-1 seropositive subjects unless otherwise indicated.

In addition to established drug interactions, there may be potential pharmacokinetic interactions between nevirapine and other drug classes that are metabolized by the cytochrome P450 system. These potential drug interactions are listed in below Table. Although specific drug interaction studies in HIV-1 seropositive subjects have not been conducted for the classes of drugs listed in below Table, additional clinical monitoring may be warranted when co-administering these drugs.

The in vitro interaction between nevirapine and the antithrombotic agent warfarin is complex. As a result, when giving these drugs concomitantly, plasma warfarin levels may change with the potential for increases in coagulation time. When warfarin is co-administered with nevirapine, anticoagulation levels should be monitored frequently.

Table: Established Drug Interactions: Alteration in Dose or Regimen May Be Recommended Based on Drug Interaction Studies

Drug Name	**Effect on Concentration Of Nevirapine or Concomitant Drug**	**Clinical Comment**

Drug Name	Effect on Concentration Of Nevirapine or Concomitant Drug	Clinical Comment
Clarithromycin	↓ Clarithromycin ↑ 14-OH clarithromycin	Clarithromycin exposure was significantly decreased by nevirapine; however, 14-OH metabolite concentrations were increased. Because clarithromycin active metabolite has reduced activity against Mycobacterium avium-intracellulare complex, overall activity against this pathogen may be altered. Alternatives to clarithromycin, such as azithromycin, should be considered
Efavirenz	↓ Efavirenz	Appropriate doses for this combination are not established.
Ethinyl estradiol and Norethindrone	↓ Ethinyl estradiol ↓ Norethindrone	Oral contraceptives and other and hormonal methods of birth control should not be used as the sole method of contraception in women taking nevirapine, since nevirapine may lower the plasma levels of these medications. An alternative or additional method of contraception is recommended.
Fluconazole	↑Nevirapine	Because of the risk of increased exposure to nevirapine, caution should be used in concomitant administration, and patients should be monitored closely for nevirapine-associated adverse events.

Drug Name	Effect on Concentration Of Nevirapine or Concomitant Drug	Clinical Comment
Indinavir	↓ Indinavir	Appropriate doses for this combination are not established, but an increase in the dosage of indinavir may be required.
Ketoconazole	↓ Ketoconazole	Nevirapine and ketoconazole should not be administered concomitantly because decreases in ketoconazole plasma concentrations may reduce the efficacy of the drug.
Lopinavir/Ritonavir	↓Lopinavir	A dose increase of lopinavir/ritonavir to 533/133 mg twice daily with food is recommended in combination with nevirapine.
Methadone	↓ Methadone[a]	Methadone levels may be decreased; increased dosages may be required to prevent symptoms of opiate withdrawal. Methadone maintained patients beginning nevirapine therapy should be monitored for evidence of withdrawal and methadone dose should be adjusted accordingly.
Nelfinavir	↓Nelfinavir M8 Metabolite ↓Nelfinavir C_{min}	The appropriate dose for nelfinavir in combination with nevirapine, with respect to safety and efficacy, has not been established.
Rifabutin	↑Rifabutin	Rifabutin and its metabolite concentrations were moderately increased. Due to high intersubject

Drug Name	Effect on Concentration Of Nevirapine or Concomitant Drug	Clinical Comment
		variability, however, some patients may experience large increases in rifabutin exposure and may be at higher risk for rifabutin toxicity. Therefore, caution should be used in concomitant administration.
Rifampin	↓ Nevirapine	Nevirapine and rifampin should not be administered concomitantly because decreases in nevirapine plasma concentrations may reduce the efficacy of the drug. Physicians needing to treat patients co-infected with tuberculosis and using a nevirapine containing regimen may use rifabutin instead.
Saquinavir	↓Saquinavir	Appropriate doses for this combination are not established, but an increase in the dosage of saquinavir may be required.

[a] Based on reports of narcotic withdrawal syndrome in patients treated with nevirapine and methadone concurrently, and evidence of decreased plasma concentrations of methadone.

Table: Potential Drug Interactions: Use With Caution, Dose Adjustment of Co-administered Drug May Be Needed due to Possible Decrease in Clinical Effect

Examples of Drugs in Which Plasma Concentrations May Be Decreased By Co-administration With Nevirapine	
Drug Class	**Examples of Drugs**
Antiarrhythmics	Amiodarone, disopyramide, lidocaine
Anticonvulsants	Carbamazepine, clonazepam, ethosuximide
Antifungals	Itraconazole
Calcium channel blockers	Diltiazem, nifedipine, verapamil
Cancer chemotherapy	Cyclophosphamide
Ergot alkaloids	Ergotamine
Immunosuppressants	Cyclosporin, tacrolimus, sirolimus
Motility agents	Cisapride
Opiate agonists	Fentanyl
Examples of Drugs in Which Plasma Concentrations May Be Increased By Co-administration With Nevirapine	
Antithrombotics	Warfarin Potential effect on anticoagulation. Monitoring of anticoagulation levels is recommended.

Fat redistribution: Redistribution/accumulation of body fat including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and “cushingoid appearance” have been observed in patients receiving

antiretroviral therapy. The mechanism and long-term consequences of these events are currently unknown. A causal relationship has not been established.

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.

Women of childbearing potential should not use oral contraceptives as the sole method for birth control, since nevirapine might lower the plasma concentrations of these medications.

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 breast-feeding if they are receiving Nevirapine tablets.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Side effects

The most serious adverse reactions associated with nevirapine are hepatitis/hepatic failure, Stevens-Johnson syndrome, toxic epidermal necrolysis, and hypersensitivity reactions. Hepatitis/hepatic failure may be isolated or associated with signs of hypersensitivity which may include severe rash or rash accompanied by fever, general malaise, fatigue, muscle or joint aches, blisters, oral lesions, conjunctivitis, facial edema, eosinophilia, granulocytopenia, lymphadenopathy, or renal dysfunction.

Adults:

The most common clinical toxicity of nevirapine is rash, which can be severe or life-threatening. Rash occurs most frequently within the first 6 weeks of therapy. Rashes are usually mild to moderate, maculopapular erythematous cutaneous eruptions, with or without pruritus, located on the trunk, face and extremities. In controlled clinical trials, Grade 1 and 2 rashes were reported in 13.3% of patients receiving nevirapine compared to 5.8% receiving placebo during the first 6 weeks of therapy. Grade 3 and 4 rashes were reported in 1.5% of nevirapine recipients compared to 0.1% of subjects receiving placebo. Women tend to be at higher risk for development of nevirapine associated rash.

In controlled clinical trials, symptomatic hepatic events regardless of severity occurred in 4.0% (range 0% to 11.0%) of patients who received nevirapine and 1.2% of patients in control groups. Female gender and higher CD4 counts (>250 cells/mm^3 in women and >400 cells/mm^3 in men) place patients at increased risk of these events.

Asymptomatic transaminase elevations (AST or ALT > 5X ULN) were observed in 5.8% (range 0% to 9.2%) of patients who received nevirapine and 5.5% of patients in control groups. Co-infection with hepatitis B or C and/or increased liver function tests at the start of therapy with nevirapine are associated with a greater risk of later symptomatic events (6 weeks or more after starting nevirapine) and asymptomatic increases in AST or ALT.

Treatment related, adverse experiences of moderate or severe intensity observed in >2% of patients receiving nevirapine in placebo-controlled trials are shown in below Table.

Table: Percentage of Patients with Moderate or Severe Drug Related Events in Adult Placebo Controlled Trials

Trial 1090[1]	**Trials 1037,1038, 1046**[2]			
Nevirapine (n=1121)	**Placebo (n=1128)**	**Nevirapine (n=253)**		**Placebo (n=203)**
Median exposure (weeks)	58	52	28	28

Trial 1090[1]	Trials 1037,1038, 1046[2]			
Nevirapine (n=1121)	**Placebo (n=1128)**	**Nevirapine (n=253)**		**Placebo (n=203)**
Any adverse event	14.5%	11.1%	31.6%	13.3%
Rash	5.1	1.8	6.7	1.5
Nausea	0.5	1.1	8.7	3.9
Granulocytopenia	1.8	2.8	0.4	0
Headache	0.7	0.4	3.6	0.5
Fatigue	0.2	0.3	4.7	3.9
Diarrhea	0.2	0.8	2.0	0.5
Abdominal pain	0.1	0.4	2.0	0
Myalgia	0.2	0	1.2	2

[1] Background therapy included 3TC for all patients and combinations of NRTIs and PIs. Patients had CD4+ cell counts <200 cells/mm^3.

[2] Background therapy included ZDV and ZDV+ddI; Nevirapine monotherapy was administered in some patients. Patients had CD4+ cell count >200 cells/mm^3.

Laboratory Abnormalities: Liver function test abnormalities (AST, ALT) were observed more frequently in patients receiving nevirapine than in controls (below Table). Asymptomatic elevations in GGT occur frequently but are not a contraindication to continue nevirapine therapy in the absence of elevations in other liver function tests. Other laboratory abnormalities (bilirubin, anemia, neutropenia, thrombocytopenia) were observed with similar frequencies in clinical trials comparing nevirapine and control regimens (see below Table).

Table: Percentage of Adult Patients with Laboratory Abnormalities

Trial 1090[1]				**Trials 1037, 1038, 1046**[2]
Nevirapine	**Placebo**	**Nevirapine**		**Placebo**
Laboratory Abnormality	**n=1121**	**n=1128**	**n=253**	**n=203**
Blood Chemistry				
SGPT (ALT) >250 U/L	5.3%	4.4%	14.0%	4.0%
SGOT (AST) >250 U/L	3.7	2.5	7.6	1.5
Bilirubin >2.5 mg/dL	1.7	2.2	1.7	1.5
Hematology				
Hemoglobin <8.0 g/dL	3.2	4.1	0	0
Platelets <50,000/mm^3	1.3	1.0	0.4	1.5
Neutrophils <750/mm^3	13.3	13.5	3.6	1.0

[1] Background therapy included 3TC for all patients and combinations of NRTIs and PIs. Patients had CD4+ cell counts <200 cells/mm^3.

[2] Background therapy included ZDV and ZDV+ddI; Nevirapine monotherapy was administered in some patients. Patients had CD4+ cell count >200 cells/mm^3.

Post Marketing Surveillance: In addition to the adverse events identified during clinical trials, the following events have been reported with the use of nevirapine in clinical practice:

Body as a Whole: fever, somnolence, drug withdrawal, redistribution/accumulation of body fat

Gastrointestinal: vomiting

Liver and Biliary: jaundice, fulminant and cholestatic hepatitis, hepatic necrosis, hepatic failure

Hematology: anemia, eosinophilia, neutropenia

Musculoskeletal: arthralgia

Neurologic: paraesthesia

Skin and Appendages: allergic reactions including anaphylaxis, angioedema, bullous eruptions, ulcerative stomatitis and urticaria have all been reported. In addition, hypersensitivity syndrome and hypersensitivity reactions with rash associated with constitutional findings such as fever, blistering, oral lesions, conjunctivitis, facial edema, muscle or joint aches, general malaise, fatigue or significant hepatic abnormalities plus one or more of the following: hepatitis, eosinophilia, granulocytopenia, lymphadenopathy and/or renal dysfunction have been reported with the use of nevirapine.

Pediatric Patients:

Safety was assessed in trial BI 882 in which patients were followed for a mean duration of 33.9 months (range: 6.8 months to 5.3 years, including long-term follow-up in 29 of these patients in trial BI 892). The most frequently reported adverse events related to nevirapine in pediatric patients were similar to those observed in adults, with the exception of granulocytopenia, which was more commonly observed in children receiving both zidovudine and nevirapine. Serious adverse events were assessed in ACTG 245, a double-blind, placebo-controlled trial of nevirapine (n = 305) in which pediatric patients received combination treatment with nevirapine. In this trial two patients were reported to experience Stevens-Johnson syndrome or Stevens-Johnson/toxic epidermal necrolysis transition syndrome. Cases of allergic reaction, including one case of anaphylaxis, were also reported.

4.9 Overdose

There is no known antidote for Nevirapine overdosage. 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 transaminases and weight decrease. All of these effects subsided following discontinuation of Nevirapine

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacodynamics

Mechanism of Action:

Nevirapine is a non-nucleoside reverse transcriptase inhibitor (NNRTI) of HIV-1. Nevirapine binds directly to reverse transcriptase (RT) 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 RT and eukaryotic DNA polymerases (such as human DNA polymerases α, ß, γ, or δ) are not inhibited by nevirapine.

Antiviral Activity:

The in vitro antiviral activity of nevirapine was measured in peripheral blood mononuclear cells, monocyte derived macrophages, and lymphoblastoid cell lines. IC_{50} 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 the nucleoside reverse transcriptase inhibitors (NRTIs) didanosine (ddI), lamivudine (3TC), stavudine (d4T) and zidovudine (ZDV), and the protease inhibitors indinavir and saquinavir.

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 combination with several other NNRTIs.

Phenotypic and genotypic changes in HIV-1 isolates from treatment-naïve patients receiving either nevirapine (n=24) or nevirapine and ZDV (n=14) were monitored in Phase I/II trials over 1 to ≥12 weeks. After 1 week of nevirapine monotherapy, isolates from 3/3 patients had decreased susceptibility to nevirapine in vitro. One or more of the RT mutations resulting in amino acid substitutions K103N, V106A, V108I, Y181C, Y188C and G190A were detected in HIV-1 isolates from some patients as early as 2 weeks after therapy initiation. By week eight of nevirapine monotherapy, 100% of the patients tested (n=24) had HIV-1 isolates with a >100-fold decrease in susceptibility to nevirapine *in vitro* compared to baseline, and had one or more of the nevirapine- associated RT resistance mutations. Nineteen of these patients (80%) had isolates with Y181C mutations regardless of dose.

Genotypic analysis of isolates from antiretroviral naïve virologic failure patients (n=71) receiving nevirapine once daily (n=25) or twice daily (n=46) in combination with lamivudine and stavudine (study 2NN) for 48 weeks showed that isolates from 8/25 and 23/46 patients, respectively, contained one or more of the following NNRTI resistance-associated mutations: Y181C, K101E, G190A/S, K103N, V106A/M, V108I, Y188C/L, A98G, F227L and M230L.

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 delavirdine and efavirenz. However, nevirapine-resistant isolates were susceptible to the NRTI's ddI and ZDV. Similarly, ZDV-resistant isolates were susceptible to nevirapine in vitro

5.2 Pharmacokinetic properties

Pharmacokinetics

Pharmacokinetics in Adults:

Absorption and Bioavailability: 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 μg/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. Steady state trough nevirapine concentrations of 4.5 ± 1.9 μg/mL (17 ± 7 μM), (n = 242) were attained at 400 mg/day. Nevirapine tablets and suspension have been shown to be comparably bioavailable and interchangeable at doses up to 200 mg. When nevirapine (200 mg) was administered to 24 healthy adults (12 female, 12 male), with either a high fat breakfast (857 kcal, 50 g fat, 53% of calories from fat) or antacid (Maalox 30 mL), the extent of nevirapine absorption (AUC) was comparable to that observed under fasting conditions. In a separate study in HIV-1 infected patients (n=6), nevirapine steady-state systemic exposure (AUCτ) was not significantly altered by didanosine, which is formulated with an alkaline buffering agent. Nevirapine may be administered with or without food, antacid or didanosine.

Distribution: Nevirapine is highly lipophilic and is essentially nonionized at physiologic pH. Following intravenous administration to healthy adults, the apparent 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 also 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: 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 (CYP) isozymes from the CYP3A4 and CYP2B6 families, 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 ^{14}C-nevirapine, approximately 91.4 ± 10.5% of the radiolabeled dose was recovered, with urine (81.3 ± 11.1%) representing the primary route of excretion compared to feces (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 is an inducer of hepatic cytochrome P450 (CYP) metabolic enzymes 3A4 and 2B6. Nevirapine induces CYP3A4 and CYP2B6 by approximately 20-25%, as indicated by erythromycin breath test results and urine metabolites. Auto induction of CYP3A4 and CYP2B6 mediated metabolism leads to 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.

5.3 Preclinical safety data

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Un coated tablet: Microcrystalline Cellulose (Vivapur 101), Croscarmellose Sodium (Ac-Di-Sol), Corn Starch (Extra white maize starch), Povidone (Kollidon 30), Purified Water, Sodium Starch Glycolate (Primojel), Colloidal Silicon Dioxide (Aerosil), Magnesium Stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

60 months

6.4 Special precautions for storage

Store below 30°C

6.5 Nature and contents of container

Container pack of 60 tablets

6.6 Instructions for use, handling and disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Marketing Authorization Holder:

Name **:** **Hetero Labs Limited**

Business Address **:** 7-2-A2, Hetero Corporate,
Industrial Estates,
Sanath Nagar,
Hyderabad-500 018, Telangana.

Country **:** INDIA

Manufacturer

Name **:** **Hetero Labs Limited (Unit-III)**

Business Address **:** 22-110,
Industrial Development Area (IDA),
Jeedimetla
Hyderabad-500 055
Telangana.

8. MARKETING AUTHORISATION NUMBER(S)

06411/08328/NMR/2020

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Jul 26, 2021

10. DATE OF REVISION OF THE TEXT

04/2016