NEVIRAPINE - nevirapine tablet
Micro Labs Limited

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use NEVIRAPINE TABLETS safely and effectively. See full prescribing information for NEVIRAPINE TABLETS.

NEVIRAPINE tablets, for oral use
Initial U.S. Approval: 1996

WARNING: LIFE-THREATENING (INCLUDING FATAL) HEPATOTOXICITY and SKIN REACTIONS

See full prescribing information for complete boxed warning.

- **Fatal and non-fatal hepatotoxicity have been reported in patients taking nevirapine. Discontinue immediately if clinical hepatitis or transaminase elevations combined with rash or other systemic symptoms occur. Do not restart nevirapine after recovery. (5.1)**
- **Fatal and non-fatal skin reactions, including Stevens-Johnson syndrome, toxic epidermal necrolysis, and hypersensitivity reactions, have been reported. Discontinue immediately if severe skin reactions, hypersensitivity reactions, or any rash with systemic symptoms occur. Check transaminase levels immediately for all patients who develop a rash in the first 18 weeks of treatment. Do not restart nevirapine after recovery. (5.2)**
- **Monitoring during the first 18 weeks of therapy is essential. Extra vigilance is warranted during the first 6 weeks of therapy, which is the period of greatest risk of these events. (5.1, 5.2)**

INDICATIONS AND USAGE

- Nevirapine tablet is an NNRTI indicated in combination with other antiretroviral agents for the treatment of human immunodeficiency virus (HIV-1) infection in adults and pediatric patients 15 days and older. (1)

Limitations of Use:

Based on serious and life-threatening hepatotoxicity observed in controlled and uncontrolled trials, nevirapine tablet is not recommended to be initiated, unless the benefit outweighs the risk, in:

- adult females with CD4 $^{+}$cell counts greater than 250 cells/mm ^{3}
- adult males with CD4 $^{+}$cell counts greater than 400 cells/mm ^{3}(1, 5.1)

DOSAGE AND ADMINISTRATION

- The 14-day lead-in period must be strictly followed; it has been demonstrated to reduce the frequency of rash. (2.4, 5.2)
- If any patient experiences rash during the 14-day lead-in period, do not increase dose until the rash has resolved. Do not continue the lead-in dosing regimen beyond 28 days. (2.4)
- If dosing is interrupted for greater than 7 days, restart 14-day lead-in dosing. (2.4)

	Adults (≥16 yrs)	**Pediatric Patients*** (≥15 days)
First 14 days	200 mg once daily	150 mg/m ^{2}once daily
After 14 days	200 mg twice daily	150 mg/m ^{2}twice daily

*Total daily dose should not exceed 400 mg for any patient.

DOSAGE FORMS AND STRENGTHS

- 200 mg tablets (3)

CONTRAINDICATIONS

- Patients with moderate or severe (Child-Pugh Class B or C, respectively) hepatic impairment. (4, 5.1, 8.7)
- Use as part of occupational and non-occupational post-exposure prophylaxis (PEP) regimens, an unapproved use. (4, 5.1)

WARNINGS AND PRECAUTIONS

- Monitor patients for immune reconstitution syndrome and fat redistribution. (5.5, 5.6)

ADVERSE REACTIONS

- The most common adverse reaction is rash. In adults, the incidence of rash is 15% versus 6% with placebo, with Grade 3/4 rash occurring in 2% of subjects. (6.1)
- In pediatric subjects the incidence of rash (all causality) was 21%. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Micro Labs USA, Inc. at 1-855-839-8195 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

Co-administration of nevirapine can alter the concentrations of other drugs and other drugs may alter the concentration of nevirapine. The potential for drug interactions must be considered prior to and during therapy. (5.4, 7, 12.3)

USE IN SPECIFIC POPULATIONS

- Lactation: Women infected with HIV-1 should be instructed not to breastfeed due to the potential for HIV-1 transmission. (8.2)
- No dose adjustment is required for patients with renal impairment with a creatinine clearance greater than or equal to 20 mL per min. Patients on dialysis receive an additional dose of 200 mg following each dialysis treatment. (2.4, 8.6)
- Monitor patients with hepatic fibrosis or cirrhosis carefully for evidence of drug-induced toxicity. Do not administer nevirapine to patients with Child-Pugh B or C. (5.1, 8.7)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 6/2022

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: LIFE-THREATENING (INCLUDING FATAL) HEPATOTOXICITY and SKIN REACTIONS

HEPATOTOXICITY:

Severe, life-threatening, and in some cases fatal hepatotoxicity, particularly in the first 18 weeks, has been reported in patients treated with nevirapine. In some cases, patients presented with non-specific prodromal signs or symptoms of hepatitis and progressed to hepatic failure. These events are often associated with rash. Female gender and higher CD4 $^{+}$cell counts at initiation of therapy place patients at increased risk; women with CD4+ cell counts greater than 250 cells/mm ^{3}, including pregnant women receiving nevirapine in combination with other antiretrovirals for the treatment of HIV-1 infection, are at the greatest risk. However, hepatotoxicity associated with nevirapine use can occur in both genders, all CD4 $^{+}$cell counts and at any time during treatment. Hepatic failure has also been reported in patients without HIV taking nevirapine for post-exposure prophylaxis (PEP). Use of nevirapine for occupational and non-occupational PEP is contraindicated *[see Contraindications (4)]* . Patients with signs or symptoms of hepatitis, or with increased transaminases combined with rash or other systemic symptoms, must discontinue nevirapine and seek medical evaluation immediately *[see Warnings and Precautions (5.1)]* .

SKIN REACTIONS:

Severe, life-threatening skin reactions, including fatal cases, have occurred in patients treated with nevirapine. These have included cases of Stevens-Johnson syndrome, toxic epidermal necrolysis, and hypersensitivity reactions characterized by rash, constitutional findings, and organ dysfunction. Patients developing signs or symptoms of severe skin reactions or hypersensitivity reactions must discontinue nevirapine and seek medical evaluation immediately. Transaminase levels should be checked immediately for all patients who develop a rash in the first 18 weeks of treatment. The 14-day lead-in period with nevirapine 200 mg daily dosing has been observed to decrease the incidence of rash and must be followed *[see Warnings and Precautions (5.2)]* .

MONITORING FOR HEPATOTOXICITY AND SKIN REACTIONS:

Patients must be monitored intensively during the first 18 weeks of therapy with nevirapine to detect potentially life-threatening hepatotoxicity or skin reactions. Extra vigilance is warranted during the first 6 weeks of therapy, which is the period of greatest risk of these events. Do not restart nevirapine following clinical hepatitis, or transaminase elevations combined with rash or other systemic symptoms, or following severe skin rash or hypersensitivity reactions. In

some cases, hepatic injury has progressed despite discontinuation of treatment.

1 INDICATIONS AND USAGE

Nevirapine tablet is indicated in combination with other antiretroviral agents for the treatment of human immunodeficiency virus (HIV-1) infection in adults and pediatric patients 15 days and older *[see Clinical Studies (14.1, 14.2)]* .

Limitations of Use:

Based on serious and life-threatening hepatotoxicity observed in controlled and uncontrolled trials, nevirapine tablet is not recommended to be initiated, unless the benefit outweighs the risk, in:

- adult females with CD4 $^{+}$cell counts greater than 250 cells/mm ^{3}or
- adult males with CD4 $^{+}$cell counts greater than 400 cells/mm ^{3}*[see Warnings and Precautions (5.1)]* .

2 DOSAGE AND ADMINISTRATION

2.1 Adult Patients

The recommended dose for nevirapine is one 200 mg tablet daily for the first 14 days, followed by one 200 mg tablet twice daily, in combination with other antiretroviral agents. The 14-day lead-in period with nevirapine 200 mg daily dosing must be strictly followed as the lead-in period has been observed to decrease the incidence of rash *[see Dosage and Administration (2.4)and Warnings and Precautions (5.2)]* . If rash persists beyond the 14-day lead-in period, do not dose escalate to 200 mg twice daily. The 200 mg once-daily dosing regimen should not be continued beyond 28 days, at which point, an alternative regimen should be sought. For concomitantly administered antiretroviral therapy, the manufacturer’s recommended dosage and monitoring should be followed.

2.2 Pediatric Patients

The recommended oral dose for pediatric patients 15 days and older is 150 mg/m ^{2}once daily for 14 days followed by 150 mg/m ^{2}twice daily thereafter. The total daily dose should not exceed 400 mg for any patient.

$$\text{Mosteller Formula:}\quad \text{BSA } (m^2) = \sqrt{\frac{\text{Height (cm) x Wt (kg)}}{3600}}$$

2.3 Monitoring of Patients

Intensive clinical and laboratory monitoring, including liver enzyme 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 enzyme 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 *[see Warnings and Precautions (5)]* . In some cases, hepatic injury has progressed despite discontinuation of treatment.

2.4 Dosage Adjustment

Patients with Rash

Discontinue nevirapine if a patient experiences severe rash or any rash accompanied by constitutional findings *[see Warnings and Precautions (5.2)]* . Do not increase nevirapine dose if a patient experiences mild to moderate rash without constitutional symptoms during the 14-day lead-in period of 200 mg/day (150 mg/m ^{2}/day in pediatric patients) until the rash has resolved *[see Warnings and Precautions (5.2)]* . The total duration of the once daily lead-in dosing period should not exceed 28 days at which point an alternative regimen should be sought.

Patients with Hepatic Events

If a clinical (symptomatic) hepatic event occurs, permanently discontinue nevirapine. Do not restart nevirapine after recovery *[see Warnings and Precautions (5.1)]* .

Patients with Dose Interruption

For patients who interrupt nevirapine dosing for more than 7 days, restart the recommended dosing, using one 200 mg tablet daily (150 mg/m ^{2}/day in pediatric patients) for the first 14 days (lead-in) followed by one 200 mg tablet twice daily (150 mg/m ^{2}twice daily for pediatric patients).

Patients with Renal Impairment

Patients with CrCl greater than or equal to 20 mL per min do not require an adjustment in nevirapine dosing. The pharmacokinetics of nevirapine have not been evaluated in patients with CrCl less than 20 mL per min. 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 *[see Clinical Pharmacology (12.3)]* .

3 DOSAGE FORMS AND STRENGTHS

Tablets: Nevirapine tablets USP, 200 mg are White to off-white, oval, biconvex tablet,

marked on one side as “I” and “11” separated with a breakline and plain on other side.

4 CONTRAINDICATIONS

Nevirapine is contraindicated:

- in patients with moderate or severe (Child-Pugh Class B or C, respectively) hepatic impairment *[see Warnings and Precautions (5.1)and Use in Specific Populations (8.7)].*
- for use as part of occupational and non-occupational post-exposure prophylaxis (PEP) regimens *[see Warnings and Precautions (5.1)]* .

5 WARNINGS AND PRECAUTIONS

5.1 Hepatotoxicity and Hepatic Impairment

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%) of subjects who received nevirapine and 1% of subjects 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, subjects 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 subjects 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. Rhabdomyolysis has been observed in some patients experiencing skin and/or liver reactions associated with nevirapine use. 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. Patients with signs or symptoms of hepatitis must be advised to discontinue nevirapine and immediately seek medical evaluation, which should include liver enzyme tests.

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. 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, include monitoring of liver enzyme 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.

Transaminases should be checked immediately if a patient experiences signs or symptoms suggestive of hepatitis and/or hypersensitivity reaction. Transaminases should also be checked 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 transaminases are initially normal or alternative diagnoses are possible *[see Dosage and Administration (2.3)]* **.**

If clinical hepatitis or transaminase elevations combined with rash or other systemic symptoms occur, permanently discontinue nevirapine. 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 $^{+}$cell counts. In general, during the first 6 weeks of treatment, women have a 3-fold higher risk than men for symptomatic, often rash-associated, hepatic events (6% versus 2%), and patients with higher CD4 $^{+}$cell counts at initiation of nevirapine therapy are at higher risk for symptomatic hepatic events with nevirapine. In a retrospective review, women with CD4 $^{+}$cell counts greater than 250 cells/mm ^{3}had a 12-fold higher risk of symptomatic hepatic adverse events compared to women with CD4 $^{+}$cell counts less than 250 cells/mm ^{3}(11% versus 1%). An increased risk was observed in men with CD4 $^{+}$cell counts greater than 400 cells/mm ^{3}(6% versus 1% for men with CD4 $^{+}$cell counts less than 400 cells/mm ^{3}). However, all patients, regardless of gender, CD4 $^{+}$cell count, or antiretroviral treatment history, should be monitored for hepatotoxicity since symptomatic hepatic adverse events have been reported at all CD4 $^{+}$cell counts. Co-infection with hepatitis B or C and/or increased transaminase elevations 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-1 uninfected individuals receiving multiple doses of nevirapine in the setting of post-exposure prophylaxis (PEP), an unapproved use. Use of nevirapine for occupational and non-occupational PEP is contraindicated *[see Contraindications (4)]* .

Increased nevirapine trough concentrations have been observed in some patients with hepatic fibrosis or cirrhosis. Therefore, carefully monitor patients with either hepatic fibrosis or cirrhosis for evidence of drug-induced toxicity. Do not administer nevirapine to patients with moderate or severe (Child-Pugh Class B or C, respectively) hepatic impairment *[see Contraindications (4), Use in Specific Populations (8.7), and Clinical Pharmacology (12.3)]* .

5.2 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. Rhabdomyolysis has been observed in some patients experiencing skin and/or liver reactions associated with nevirapine use. In controlled clinical trials, Grade 3 and 4 rashes were reported during the first 6 weeks in 2% of nevirapine recipients compared to less than 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.

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 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, include monitoring of liver enzyme 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 *[see Dosage and Administration (2.1)]* .

If patients present with a suspected nevirapine-associated rash, measure transaminases immediately. Permanently discontinue nevirapine in patients with rash-associated transaminase elevations *[see Warnings and Precautions (5.1)]* .

Therapy with nevirapine must be initiated with a 14-day lead-in period of 200 mg per day (150 mg/m ^{2}per day in pediatric patients), which has been shown to reduce the frequency of rash. Discontinue nevirapine if a patient experiences severe rash or any rash accompanied by constitutional findings. Do not increase nevirapine dose to a patient experiencing a mild to moderate rash without constitutional symptoms during the 14-day lead-in period of 200 mg per day (150 mg/m ^{2}/day in pediatric patients) until the rash has resolved .The total duration of the once-daily lead-in dosing period must not exceed 28 days at which point an alternative regimen should be sought *[see Dosage and Administration (2.4)]* . Patients must 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 per 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.

5.3 Resistance

Nevirapine must not be used as a single agent to treat HIV-1 or added on as a sole agent to a failing regimen. 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 *[see Microbiology (12.4)]* .

5.4 Drug Interactions

See Table 4 for listings of established and potential drug interactions *[see Drug Interactions (7)]* .

Concomitant use of St. John's wort (*Hypericum perforatum*) or St. John's wort-containing products and nevirapine is not recommended. Co-administration of St. John’s wort with non-nucleoside reverse transcriptase inhibitors (NNRTIs), including nevirapine, 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. Co-administration of nevirapine and efavirenz is not recommended as this combination has been associated with an increase in adverse reactions and no improvement in efficacy.

5.5 Immune Reconstitution Syndrome

Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including nevirapine. During the initial phase of combination antiretroviral treatment, patients whose immune system responds may develop an inflammatory response to indolent or residual opportunistic infections (such as *Mycobacterium avium*infection, cytomegalovirus, *Pneumocystis jiroveci*pneumonia, or tuberculosis), which may necessitate further evaluation and treatment.

Autoimmune disorders (such as Graves’ disease, polymyositis, and Guillain-Barré syndrome) have also been reported to occur in the setting of immune reconstitution, however, the time to onset is more variable, and can occur many months after initiation of treatment.

5.6 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.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Clinical Trial Experience in Adult Patients

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 *[see Boxed Warning and Warnings and Precautions (5.1, 5.2)]* .

Hepatic Reaction

In controlled clinical trials, symptomatic hepatic events regardless of severity occurred in 4% (range 0% to 11%) of subjects who received nevirapine and 1% of subjects in control groups. Female gender and higher CD4 $^{+}$cell counts (greater than 250 cells/mm ^{3}in women and greater than 400 cells/mm ^{3}in men) place patients at increased risk of these events *[see Boxed Warning and Warnings and Precautions (5.1)]* .

Asymptomatic transaminase elevations (AST or ALT greater than 5X ULN) were observed in 6% (range 0% to 9%) of subjects who received nevirapine and 6% of subjects in control groups. Co-infection with hepatitis B or C and/or increased transaminase elevations 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.

Liver enzyme abnormalities (AST, ALT, GGT) were observed more frequently in subjects receiving nevirapine than in controls (see Table 3).

Skin Reaction

The most common clinical toxicity of nevirapine is rash, which can be severe or life-threatening *[see Boxed Warning and Warnings and Precautions (5.2)]* . 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 (Trials 1037, 1038, 1046, and 1090), Grade 1 and 2 rashes were reported in 13% of subjects receiving nevirapine compared to 6% receiving placebo during the first 6 weeks of therapy. Grade 3 and 4 rashes were reported in 2% of nevirapine recipients compared to less than 1% of subjects receiving placebo. Women tend to be at higher risk for development of

nevirapine-associated rash *[see Boxed Warning and Warnings and Precautions (5.2)]* .

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

Table 2 Percentage of Subjects 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
Any adverse event	15%	11%	32%	13%
Rash	5	2	7	2
Nausea	1	1	9	4
Granulocytopenia	2	3	<1	0
Headache	1	<1	4	1
Fatigue	<1	<1	5	4
Diarrhea	<1	1	2	1
Abdominal pain	<1	<1	2	0
Myalgia	<1	0	1	2

[1]Background therapy included 3TC for all subjects and combinations of NRTIs and PIs. Subjects had CD4 $^{+}$cell counts less than 200 cells/mm ^{3}.

[2]Background therapy included ZDV and ZDV+ddI; nevirapine monotherapy was administered in some subjects. Subjects had CD4 $^{+}$cell count greater than or equal to 200 cells/mm ^{3}.

Laboratory Abnormalities

Liver enzyme test abnormalities (AST, ALT) were observed more frequently in subjects receiving nevirapine than in controls (Table 3). Asymptomatic elevations in GGT occur frequently but are not a contraindication to continue nevirapine therapy in the absence of elevations in other liver enzyme tests. Other laboratory abnormalities (bilirubin, anemia, neutropenia, thrombocytopenia) were observed with similar frequencies in clinical trials comparing nevirapine and control regimens (see Table 3).

Table 3 Percentage of Adult Subjects 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	4	14	4
SGOT (AST) >250 U/L	4	3	8	2
Bilirubin >2.5 mg/dL	2	2	2	2
Hematology				
Hemoglobin <8.0 g/dL	3	4	0	0
Platelets <50,000/mm ^{3}	1	1	<1	2
Neutrophils <750/mm ^{3}	13	14	4	1

[1]Background therapy included 3TC for all subjects and combinations of NRTIs and PIs. Subjects had CD4 $^+$cell counts less than 200 cells/mm ^{3}.

[2]Background therapy included ZDV and ZDV+ddI; nevirapine monotherapy was administered in some subjects. Subjects had CD4 $^+$cell count greater than or equal to 200 cells/mm ^{3}.

Clinical Trial Experience in Pediatric Patients

Adverse events were assessed in BI Trial 1100.1032 (ACTG 245), a double-blind, placebo-controlled trial of nevirapine (n=305) in which pediatric subjects received

combination treatment with nevirapine. In this trial two subjects were reported to experience Stevens-Johnson syndrome or Stevens-Johnson/toxic epidermal necrolysis transition syndrome. Safety was also assessed in trial BI 1100.882 (ACTG 180), an open-label trial of nevirapine (n=37) in which subjects 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 subjects in trial BI 1100.892). The most frequently reported adverse events related to nevirapine in pediatric subjects were similar to those observed in adults, with the exception of granulocytopenia, which was more commonly observed in children receiving both zidovudine and nevirapine. Cases of allergic reaction, including one case of anaphylaxis, were also reported.

The safety of nevirapine was also examined in BI Trial 1100.1368, an open-label, randomized clinical trial performed in South Africa in which 123 HIV-1 infected treatment-naïve subjects between 3 months and 16 years of age received combination treatment with lamivudine and zidovudine for 48 weeks *[see Use in Specific Populations (8.4) and Clinical Pharmacology (12.3)]* . Rash (all causality) was reported in 21% of the subjects, 4 (3%) of whom discontinued drug due to rash. All 4 subjects experienced the rash early in the course of therapy (less than 4 weeks) and resolved upon nevirapine discontinuation. Other clinically important adverse events (all causality) include neutropenia (9%), anemia (7%), and hepatotoxicity (2%) *[see Use in Specific Populations (8.4) and Clinical Studies (14.2)]* .

Safety information on use of nevirapine in combination therapy in pediatric subjects 2 weeks to less than 3 months of age was assessed in 36 subjects from the BI 1100.1222 (PACTG 356) trial. No unexpected safety findings were observed although granulocytopenia was reported more frequently in this age group compared to the older pediatric age groups and adults.

6.2 Postmarketing Experience

In addition to the adverse events identified during clinical trials, the following adverse reactions have been identified during post-approval use of nevirapine. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

*Body as a Whole:*fever, somnolence, drug withdrawal *[see Drug Interactions (7)]* , redistribution/accumulation of body fat *[see Warnings and Precautions (5.6)]*

*Gastrointestinal:*vomiting

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

*Hematology:*anemia, eosinophilia, neutropenia

*Investigations:*decreased serum phosphorus

*Musculoskeletal:*arthralgia, rhabdomyolysis associated with skin and/or liver reactions

*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, drug reaction with eosinophilia and systemic symptoms (DRESS) *[see Warnings and Precautions (5.1)]* plus one or more of the following: hepatitis, eosinophilia, granulocytopenia, lymphadenopathy, and/or renal dysfunction have been reported.

In post-marketing surveillance anemia has been more commonly observed in children although development of anemia due to concomitant medication use cannot be ruled out.

7 DRUG INTERACTIONS

Nevirapine is principally metabolized by the liver via the cytochrome P450 isoenzymes, 3A 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 co-administered with nevirapine.

The specific pharmacokinetic changes that occur with co-administration of nevirapine and other drugs are listed in *Clinical Pharmacology*, Table 5. Clinical comments about possible dosage modifications based on established drug interactions are listed in Table 4. The data in Tables 4 and 5 are based on the results of drug interaction trials 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 also listed in Table 4. Although specific drug interaction trials in HIV-1 seropositive subjects have not been conducted for some classes of drugs listed in Table 4, 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 4 Established and Potential Drug Interactions: Use with Caution, Alteration in Dose or Regimen May Be Needed Due to Drug Interaction Established Drug Interactions: See Clinical Pharmacology (12.3), Table 5 for Magnitude of Interaction.

Drug Name	Effect on Concentration of Nevirapine or Concomitant Drug	Clinical Comment
HIV Antiviral Agents: Protease Inhibitors (PIs)		
Atazanavir/Ritonavir*	↓Atazanavir	Do not co-administer

	↑Nevirapine	nevirapine with atazanavir because nevirapine substantially decreases atazanavir exposure and there is a potential risk for nevirapine-associated toxicity due to increased nevirapine exposures.
Fosamprenavir*	↓Amprenavir ↑Nevirapine	Co-administration of nevirapine and fosamprenavir without ritonavir is not recommended.
Fosamprenavir/Ritonavir*	↓Amprenavir ↑Nevirapine	No dosing adjustments are required when nevirapine is co-administered with 700/100 mg of fosamprenavir/ritonavir twice daily. The combination of nevirapine administered with fosamprenavir/ritonavir once daily has not been studied.
Indinavir*	↓Indinavir	The appropriate doses of this combination of indinavir and nevirapine with respect to efficacy and safety have not been established.
Lopinavir/Ritonavir*	↓Lopinavir	Dosing in adult patients: A dose adjustment of lopinavir/ritonavir to 500/125 mg tablets twice daily or 533/133 mg (6.5 mL) oral solution twice daily is recommended when used in combination with nevirapine. Neither lopinavir/ritonavir tablets nor oral solution should be administered once daily in combination with nevirapine. Dosing in pediatric patients: Please refer to the Kaletra ®prescribing information for dosing recommendations based on body surface area and body weight. Neither

		lopinavir/ritonavir tablets nor oral solution should be administered once daily in combination with nevirapine.
Nelfinavir*	↓Nelfinavir M8 Metabolite ↓Nelfinavir C_{min}	The appropriate doses of the combination of nevirapine and nelfinavir with respect to safety and efficacy have not been established.
Saquinavir/Ritonavir	The interaction between nevirapine and saquinavir/ritonavir has not been evaluated	The appropriate doses of the combination of nevirapine and saquinavir/ritonavir with respect to safety and efficacy have not been established.
HIV Antiviral Agents: Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)		
Efavirenz*	↓Efavirenz	The appropriate doses of these combinations with respect to safety and efficacy have not been established.
Etravirine Rilpivirine		Plasma concentrations may be altered. Nevirapine should not be co-administered with another NNRTI as this combination has not been shown to be beneficial.
Other Agents		
Analgesics: Methadone*	↓Methadone	Methadone levels were 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.
Antiarrhythmics: Amiodarone, disopyramide, lidocaine	Plasma concentrations may be decreased.	Appropriate doses for this combination have not been established.
Antibiotics: 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.
Rifabutin*	↑Rifabutin	Rifabutin and its metabolite concentrations were moderately increased. Due to high intersubject 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.
Anticonvulsants: Carbamazepine, clonazepam, ethosuximide	Plasma concentrations of nevirapine and the anticonvulsant may be decreased.	Use with caution and monitor virologic response and levels of anticonvulsants.
Antifungals:		
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.
Ketoconazole*	↓Ketoconazole	Nevirapine and ketoconazole should not be administered concomitantly because decreases in ketoconazole plasma concentrations may reduce the efficacy of the drug.

Itraconazole	↓Itraconazole	Nevirapine and itraconazole should not be administered concomitantly due to potential decreases in itraconazole plasma concentrations that may reduce efficacy of the drug.
Antithrombotics: Warfarin	Plasma concentrations may be increased.	Potential effect on anticoagulation. Monitoring of anticoagulation levels is recommended.
Calcium Channel blockers: Diltiazem, nifedipine, verapamil	Plasma concentrations may be decreased.	Appropriate doses for these combinations have not been established.
Cancer Chemotherapy:		
Cyclophosphamide	Plasma concentrations may be decreased.	Appropriate doses for this combination have not been established.
Ergot Alkaloids: Ergotamine	Plasma concentrations may be decreased.	Appropriate doses for this combination have not been established.
Immunosuppressants: Cyclosporine, tacrolimus, sirolimus	Plasma concentrations may be decreased.	Appropriate doses for these combinations have not been established.
Motility Agents: Cisapride	Plasma concentrations may be decreased.	Appropriate doses for this combination have not been established.
Opiate Agonists: Fentanyl	Plasma concentrations may be decreased.	Appropriate doses for this combination have not been established.
Oral Contraceptives: Ethinyl estradiol and Norethindrone*	↓Ethinyl Estradiol ↓Norethindrone	Despite lower ethinyl estradiol and norethindrone exposures when co-administered with nevirapine, literature reports suggest that nevirapine has no effect on pregnancy rates among HIV-infected women on combined oral contraceptives. When co-administered with nevirapine, no dose adjustment of ethinyl estradiol or norethindrone is needed when used in combination for contraception. When these oral contraceptives are used for hormonal regulation during

		nevirapine therapy, the therapeutic effect of the hormonal therapy should be monitored.

*The interaction between nevirapine and the drug was evaluated in a clinical study. All other drug interactions shown are predicted.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to nevirapine during pregnancy. Healthcare providers are encouraged to register patients by calling the Antiretroviral Pregnancy Registry (APR) at 1-800-258-4263.

Risk Summary

Available data from the APR show no difference in the risk of overall major birth defects for nevirapine compared with the background rate for major birth defects of 2.7% in the U.S. reference population of the Metropolitan Atlanta Congenital Defects Program (MACDP) *[see Data]*. The rate of miscarriage is not reported in the APR. The estimated background rate of miscarriage in clinically recognized pregnancies in the U.S. general population is 15 to 20%. The background risk of birth defects and miscarriage for the indicated population is unknown. Methodological limitations of the APR include the use of MACDP as the external comparator group. The MACDP population is not disease-specific, evaluates women and infants from a limited geographic area, and does not include outcomes for births that occurred at <20 weeks gestation.

In literature reports, immediate-release nevirapine exposure (C_{min}) can be up to 29% lower during pregnancy. However, as this reduction was not found to be clinically meaningful, dose adjustment is not necessary *[see Data]*.

There is a risk for severe hepatic events in pregnant women exposed to nevirapine *[see Clinical Considerations].*In animal reproduction studies, no evidence of adverse developmental outcomes was observed following oral administration of nevirapine during organogenesis in the rat and rabbit, at systemic exposures (AUC) to nevirapine approximately equal (rats) and 50% higher (rabbits) than the exposure in humans at the recommended 400 mg daily dose *[see Data].*

Clinical Considerations

Maternal adverse reactions

Severe hepatic events, including fatalities, have been reported in pregnant women

receiving chronic nevirapine therapy as part of combination treatment of HIV-1 infection. Regardless of pregnancy status, women with CD4 $^{+}$cell counts greater than 250 cells/mm ^{3}should not initiate nevirapine unless the benefit outweighs the risk. It is unclear if pregnancy augments the risk observed in non-pregnant women *[see Warnings and Precautions (5.1)]* .

Data

Human Data

Based on prospective reports to the APR of exposures to nevirapine during pregnancy resulting in live births (including over 1100 exposed in the first trimester and over 1500 exposed in the second/third trimester), the prevalence of birth defects in live births was 3.0% (95% CI: 2.1 %, 4.1%) and 3.3% (95% CI: 2.4%, 4.3%) following first and second/third trimester exposure, respectively, to nevirapine-containing regimens, compared with the background birth defect rate of 2.7% in a U.S. reference population of the MACDP.

There are several literature reports of chronic administration of immediate-release nevirapine during pregnancy, in which nevirapine pharmacokinetics were compared between pregnancy and postpartum. In these studies, the mean difference in nevirapine C_{min}during pregnancy as compared to postpartum ranged from no difference to approximately 29% lower.

Animal Data

Nevirapine was administered orally to pregnant rats (at 0, 12.5, 25, and 50 mg per kg per day) and rabbits (at 0, 30, 100, and 300 mg per kg per day) through organogenesis (on gestation days 7 through 16, and 6 through 18, respectively). No adverse developmental effects were observed at doses producing systemic exposures (AUC) approximately equivalent to (rats) or approximately 50% higher (rabbits) than human exposure at the recommended daily dose. In rats, decreased fetal body weights were observed at a maternally toxic dose at an exposure approximately 50% higher than the recommended daily dose.

8.2 Lactation

Risk Summary

The Centers for Disease Control and Prevention recommend that HIV-1 infected mothers in the United States not breastfeed their infants to avoid risking postnatal transmission of HIV-1 infection. Published data report that nevirapine is present in human milk *[see Data]*. There are limited data on the effects of nevirapine on the breastfed infant. There is no information on the effects of nevirapine on milk production. Because of the potential for (1) HIV-1 transmission (in HIV-negative infants), (2) developing viral resistance (in HIV-positive infants), and (3) serious adverse reactions in nursing infants, mothers should not breastfeed if they are receiving nevirapine.

Data

Based on five publications, immediate-release nevirapine was excreted in breastmilk at median concentrations ranging from 4080 to 6795 ng/mL, and the median maternal breastmilk to maternal plasma concentration ratio range was 59 to 88%. Reported infant nevirapine median plasma concentrations were low, ranging from 734 to 1140 ng/mL. The estimated nevirapine dose of 704 to 682 mcg/kg/day for infants fed exclusively with breastmilk was lower than the daily recommended nevirapine dose for infants. Published literature indicates that rash and hyperbilirubinemia have been seen in infants exposed to nevirapine through breastmilk.

8.3 Females and Males of Reproductive Potential

Infertility

Limited human data are insufficient to determine the risk of infertility in humans. Based on results from animal fertility studies conducted in rats, nevirapine may reduce fertility in females of reproductive potential. It is not known if these effects on fertility are reversible *[see Nonclinical Toxicology (13.1)].*

8.4 Pediatric Use

The safety, pharmacokinetic profile, and virologic and immunologic responses of nevirapine have been evaluated in HIV-1 infected pediatric subjects aged 3 months to 18 years *[see Adverse Reactions (6.1)and Clinical Studies (14.2)]* . The safety and pharmacokinetic profile of nevirapine has been evaluated in HIV-1 infected pediatric subjects aged 15 days to less than 3 months *[see Adverse Reactions (6.1)and Clinical Studies (14.2)]* .

The most frequently reported adverse events related to nevirapine in pediatric subjects were similar to those observed in adults, with the exception of granulocytopenia, which was more commonly observed in children receiving both zidovudine and nevirapine *[see Adverse Reactions (6.1)and Clinical Studies (14.2)]* .

8.5 Geriatric Use

Clinical trials of nevirapine did not include sufficient numbers of subjects aged 65 and older to determine whether elderly subjects respond differently from younger subjects. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy.

8.6 Renal Impairment

In subjects with renal impairment (mild, moderate or severe), there were no significant changes in the pharmacokinetics of nevirapine. Nevirapine is extensively metabolized by the liver and nevirapine metabolites are extensively eliminated by the kidney. Nevirapine metabolites may accumulate in patients receiving dialysis; however, the clinical significance of this accumulation is not known. No adjustment in nevirapine dosing is required in patients with CrCl greater than or equal to 20 mL per min. The

pharmacokinetics of nevirapine have not been evaluated in patients with CrCl less than 20 mL per min. In patients undergoing chronic hemodialysis, an additional 200 mg dose following each dialysis treatment is indicated *[see Dosage and Administration (2.4)and Clinical Pharmacology (12.3)]* .

8.7 Hepatic Impairment

Because increased nevirapine levels and nevirapine accumulation may be observed in patients with serious liver disease, do not administer nevirapine to patients with moderate or severe (Child-Pugh Class B or C, respectively) hepatic impairment *[see Contraindications (4), Warnings and Precautions (5.1),and Clinical Pharmacology (12.3)]* .

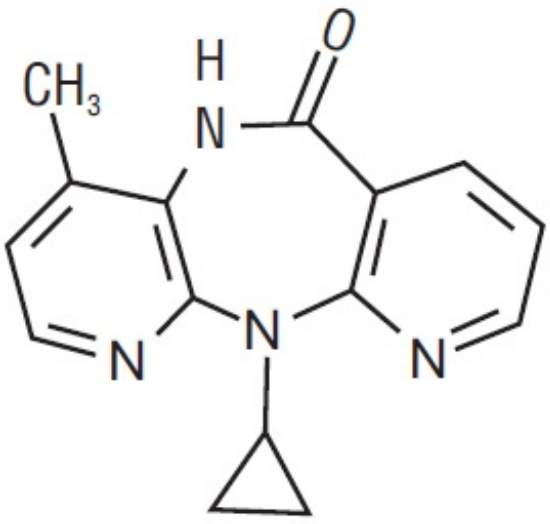
10 OVERDOSAGE

There is no known antidote for nevirapine overdosage. Cases of nevirapine overdose at doses ranging from 800 to 1800 mg per day for up to 15 days have been reported. Patients have experienced events including edema, erythema nodosum, fatigue, fever, headache, insomnia, nausea, pulmonary infiltrates, rash, vertigo, vomiting, and weight decrease. All events subsided following discontinuation of nevirapine.

11 DESCRIPTION

Nevirapine tablets USP, 200 mg is the brand name for nevirapine, a non-nucleoside reverse transcriptase inhibitor (NNRTI) with activity against Human Immunodeficiency Virus Type 1 (HIV-1). Nevirapine USP is structurally a member of the dipyridodiazepinone chemical class of compounds.

The chemical name of nevirapine is 11-cyclopropyl-5, 11-dihydro-4-methyl-6H-dipyrido [3,2-b:2',3'-e][1,4] diazepin-6-one. Nevirapine USP is a white to off-white crystalline powder with the molecular weight of 266.30 and the molecular formula $C_{15}H_{14}N_4O$. Nevirapine has the following structural formula:



Nevirapine tablets USP, 200 mg is for oral administration. Each tablet contains 200 mg of nevirapine anhydrous and the inactive ingredients microcrystalline cellulose, lactose monohydrate, colloidal silicon dioxide, magnesium stearate, povidone, and Sodium starch glycolate.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Nevirapine is an antiretroviral drug *[see Microbiology (12.4)]* .

12.3 Pharmacokinetics

Adults

Absorption and Bioavailability

Nevirapine is readily absorbed (greater than 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 mcg/mL (7.5 micromolar) 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 mcg/mL (17 ± 7 micromolar), (n=242) were attained at 400 mg per 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 trial in HIV-1 infected subjects (n=6), nevirapine steady-state systemic exposure (AUC_{τ}) 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 *[see Use in Specific Populations (8.2)]* . Nevirapine is about 60% bound to plasma proteins in the plasma concentration range of 1 to 10 mcg per 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*trials 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 CYP3A and CYP2B6 families, although other isozymes may have a secondary role. In a mass balance/excretion trial 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 (less than 5%) of the radioactivity in urine (representing less than 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 3A and 2B6. Nevirapine induces CYP3A and CYP2B6 by approximately 20 to 25%, as indicated by erythromycin breath test results and urine metabolites. Autoinduction of CYP3A 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 to 400 mg per 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 to 30 hours following multiple dosing with 200 to 400 mg per day.

Specific Populations

Renal Impairment

HIV-1 seronegative adults with mild (CrCl 50 to 79 mL per min; n=7), moderate (CrCl 30 to 49 mL per min; n=6), or severe (CrCl less than 30 mL per min; n=4) renal impairment received a single 200 mg dose of nevirapine in a pharmacokinetic trial. These subjects did not require dialysis. The trial included six additional subjects with renal failure requiring dialysis.

In subjects with renal impairment (mild, moderate or severe), there were no significant changes in the pharmacokinetics of nevirapine. However, subjects requiring dialysis exhibited a 44% reduction in nevirapine AUC over a one-week exposure period. There was also evidence of accumulation of nevirapine hydroxy-metabolites in plasma in subjects requiring dialysis. An additional 200 mg dose following each dialysis treatment is indicated *[see Dosage and Administration (2.4)and Use in Specific Populations (8.6)]* .

Hepatic Impairment

In a steady-state trial comparing 46 subjects with mild (n=17; expansion of some portal areas; Ishak Score 1 to 2), moderate (n=20; expansion of most portal areas with occasional portal-to-portal and portal-to-central bridging; Ishak Score 3 to 4), or severe (n=9; marked bridging with occasional cirrhosis without decompensation indicating Child-Pugh A; Ishak Score 5 to 6) fibrosis as a measure of hepatic impairment, the multiple dose pharmacokinetic disposition of nevirapine and its five oxidative metabolites were not altered. However, approximately 15% of these subjects with hepatic fibrosis had nevirapine trough concentrations above 9,000 mcg per mL (2-fold the usual mean trough). Therefore, patients with hepatic impairment should be monitored carefully for evidence of drug-induced toxicity *[see Warnings and Precautions (5.1)]* . The subjects studied were receiving antiretroviral therapy containing nevirapine 200 mg twice daily for at least 6 weeks prior to pharmacokinetic sampling, with a median duration of therapy of 3.4 years.

In a pharmacokinetic trial where HIV-1 negative cirrhotic subjects with mild (Child-Pugh A; n=6) or moderate (Child-Pugh B; n=4) hepatic impairment received a single 200 mg dose of nevirapine, a significant increase in the AUC of nevirapine was observed in one subject with Child-Pugh B and ascites suggesting that patients with worsening hepatic function and ascites may be at risk of accumulating nevirapine in the systemic circulation. Because nevirapine induces its own metabolism with multiple dosing, this single-dose trial may not reflect the impact of hepatic impairment on multiple-dose pharmacokinetics.

Do not administer nevirapine to patients with moderate or severe (Child-Pugh Class B or C, respectively) hepatic impairment *[see Contraindications (4), Warnings and Precautions (5.1), and Use in Specific Populations (8.7)]* .

Gender

In the multinational 2NN trial, a population pharmacokinetic substudy of 1077 subjects was performed that included 391 females. Female subjects showed a 13.8% lower clearance of nevirapine than did men. Since neither body weight nor Body Mass Index (BMI) had an influence on the clearance of nevirapine, the effect of gender cannot solely be explained by body size.

Race

An evaluation of nevirapine plasma concentrations (pooled data from several clinical trials) from HIV-1-infected subjects (27 Black, 24 Hispanic, 189 Caucasian) revealed no marked difference in nevirapine steady-state trough concentrations (median C_{minss}= 4.7 mcg/mL Black, 3.8 mcg/mL Hispanic, 4.3 mcg/mL Caucasian) with long-term nevirapine treatment at 400 mg per day. However, the pharmacokinetics of nevirapine have not been evaluated specifically for the effects of ethnicity.

Black subjects (n=80/group) in Trial 1100.1486 showed approximately 30% to 35%

higher trough concentrations than Caucasian subjects (250 to 325 subjects/group) in both immediate-release nevirapine and nevirapine extended-release tablets treatment groups over 96 weeks of treatment at 400 mg per day.

Geriatric Patients

Nevirapine pharmacokinetics in HIV-1-infected adults do not appear to change with age (range 18 to 68 years); however, nevirapine has not been extensively evaluated in subjects beyond the age of 55 years *[see Use in Specific Populations (8.5)]* .

Pediatric Patients

Pharmacokinetic data for nevirapine have been derived from two sources: a 48-week pediatric trial in South Africa (BI Trial 1100.1368) involving 123 HIV-1 positive, antiretroviral-naïve subjects aged 3 months to 16 years; and a consolidated analysis of five Pediatric AIDS Clinical Trials Group (PACTG) protocols comprising 495 subjects aged 14 days to 19 years.

BI Trial 1100.1368 studied the safety, efficacy, and pharmacokinetics of a weight-based and a body surface area (BSA)-based dosing regimen of nevirapine. In the weight-based regimen, pediatric subjects up to 8 years of age received a dose of 4 mg/kg once daily for two weeks followed by 7 mg per kg twice daily thereafter. Subjects 8 years and older were dosed 4 mg/kg once daily for two weeks followed by 4 mg/kg twice daily thereafter. In the BSA regimen, all pediatric subjects received 150 mg/m ^{2}once daily for two weeks followed by 150 mg/m ^{2}twice daily thereafter *[see Use in Specific Populations (8.4)and Adverse Reactions (6.1)]* . Dosing of nevirapine at 150 mg/m ^{2}BID (after a two-week lead-in of 150 mg/m ^{2}QD) produced geometric mean or mean trough nevirapine concentrations between 4 to 6 mcg per mL (as targeted from adult data). In addition, the observed trough nevirapine concentrations were comparable between the two dosing regimens studied (BSA- and weight-based methods).

The consolidated analysis of Pediatric AIDS Clinical Trials Group (PACTG) protocols 245, 356, 366, 377, and 403 allowed for the evaluation of pediatric subjects less than 3 months of age (n=17). The plasma nevirapine concentrations observed were within the range observed in adults and the remainder of the pediatric population, but were more variable between subjects, particularly in the second month of age. For dose recommendations for pediatric patients *[see Dosage and Administration (2.2)]* .

Drug Interactions [see Drug Interactions (7)]

Nevirapine induces hepatic cytochrome P450 metabolic isoenzymes 3A and 2B6. Co-administration of nevirapine and drugs primarily metabolized by CYP3A or CYP2B6 may result in decreased plasma concentrations of these drugs and attenuate their therapeutic effects.

While primarily an inducer of cytochrome P450 3A and 2B6 enzymes, nevirapine may

also inhibit this system. Among human hepatic cytochrome P450s, nevirapine was capable *in vitro* of inhibiting the 10-hydroxylation of (R)-warfarin (CYP3A). The estimated Ki for the inhibition of CYP3A was 270 micromolar, a concentration that is unlikely to be achieved in patients as the therapeutic range is less than 25 micromolar. Therefore, nevirapine may have minimal inhibitory effect on other substrates of CYP3A.

Nevirapine does not appear to affect the plasma concentrations of drugs that are substrates of other CYP450 enzyme systems, such as 1A2, 2D6, 2A6, 2E1, 2C9, or 2C19.

Table 5 (see below) contains the results of drug interaction trials performed with nevirapine and other drugs likely to be co-administered. The effects of nevirapine on the AUC, C_{max}, and C_{min} of co-administered drugs are summarized.

Table 5 Drug Interactions: Changes in Pharmacokinetic Parameters for Co-administered Drug in the Presence of Nevirapine (All interaction trials were conducted in HIV-1 positive subjects)

Co-administered Drug	Dose of Co-administered Drug	Dose Regimen of Nevirapine	n	% Change of Co-administered Drug Pharmacokinetic Parameters (90% CI)		
Antiretrovirals				**AUC**	**C_{max}**	**C_{min}**
Atazanavir/Ritonavir [a,d]	300/100 mg QD day 4 to 13, then 400/100 mg QD, day 14 to 23	200 mg BID day 1 to 23. Subjects were treated with nevirapine prior to trial entry.	23	Atazanavir 300/100 mg ↓42 (↓52 to ↓29)	Atazanavir 300/100 mg ↓28 (↓40 to ↓14)	Atazanavir 300/100 mg ↓72 (↓80 to ↓60)
				Atazanavir 400/100 mg ↓19 (↓35 to ↑2)	Atazanavir 400/100 mg ↑2 (↓15 to ↑24)	Atazanavir 400/100 mg ↓59 (↓73 to ↓40)
Darunavir/Ritonavir [e]	400/100 mg BID	200 mg BID	8	↑24 (↓3 to ↑57)	↑40 (↑14 to ↑73)	↑2 (↓21 to ↑32)
Didanosine	100 to 150 mg BID	200 mg QD x 14 days; 200 mg BID x 14 days	18	⇔	⇔	§
Efavirenz [a]	600 mg QD	200 mg QD x 14 days; 400 mg QD x 14 days	17	↓28 (↓34 to ↓14)	↓12 (↓23 to ↑1)	↓32 (↓35 to ↓19)
Fosamprenavir	1400 mg BID	200 mg BID. Subjects		↓33	↓25	↓35

		were treated with nevirapine prior to trial entry.	17	↓33 (↓45 to ↓20)	↓25 (↓37 to ↓10)	↓33 (↓50 to ↓15)
Fosamprenavir/Ritonavir	700/100 mg BID	200 mg BID. Subjects were treated with nevirapine prior to trial entry.	17	↓11 (↓23 to ↑3)	⇔	↓19 (↓32 to ↓4)
Indinavir [a]	800 mg q8H	200 mg QD x 14 days; 200 mg BID x 14 days	19	↓31 (↓39 to ↓22)	↓15 (↓24 to ↓4)	↓44 (↓53 to ↓33)
Lopinavir [a,b]	300/75 mg/m^2(lopinavir/ ritonavir) [b]	7 mg/kg or 4 mg/kg QD x 2 weeks; BID x 1 week	12, 15 [c]	↓22 (↓44 to ↑9)	↓14 (↓36 to ↑16)	↓55 (↓75 to ↓19)
Lopinavir [a]	400/100 mg BID (lopinavir/ ritonavir)	200 mg QD x 14 days; 200 mg BID >1 year	22, 19 [c]	↓27 (↓47 to ↓2)	↓19 (↓38 to ↑5)	↓51 (↓72 to ↓26)
Maraviroc [f]	300 mg SD	200 mg BID	8	↑1 (↓35 to ↑55)	↑54 (↓6 to ↑151)	⇔
Nelfinavir [a]	750 mg TID	200 mg QD x 14 days; 200 mg BID x 14 days	23	⇔	⇔	↓32 (↓50 to ↑5)
Nelfinavir-M8 metabolite				↓62 (↓70 to ↓53)	↓59 (↓68 to ↓48)	↓66 (↓74 to ↓55)
Ritonavir	600 mg BID	200 mg QD x 14 days; 200 mg BID x 14 days	18	⇔	⇔	⇔
Stavudine	30 to 40 mg BID	200 mg QD x 14 days; 200 mg BID x 14 days	22	⇔	⇔	§
Zalcitabine	0.125 to 0.25 mg TID	200 mg QD x 14 days; 200 mg BID x 14 days	6	⇔	⇔	§
Zidovudine	100 to 200 mg TID	200 mg QD x 14 days; 200 mg BID x 14 days	11	↓28 (↓40 to ↓4)	↓30 (↓51 to ↑14)	§

Other Medications				AUC	C_{max}	C_{min}
Clarithromycin [a]	500 mg BID	200 mg QD x 14 days; 200 mg BID x 14 days	15	↓31 (↓38 to ↓24)	↓23 (↓31 to ↓14)	↓56 (↓70 to ↓36)
Metabolite 14-OH-clarithromycin				↑42 (↑16 to ↑73)	↑47 (↑21 to ↑80)	⇔
Ethinyl Estradiol [a] and Norethindrone [a]	0.035 mg (as Ortho-Novum ®1/35)	200 mg QD x 14 days; 200 mg BID x 14 days	10	↓20 (↓33 to ↓3)	⇔	§
	1 mg (as Ortho-Novum ®1/35)			↓19 (↓30 to ↓7)	↓16 (↓27 to ↓3)	§
Depomedroxy-Progesterone Acetate	150 mg every 3 months	200 mg QD x 14 days; 200 mg BID x 14 days	32	⇔	⇔	⇔
Fluconazole	200 mg QD	200 mg QD x 14 days; 200 mg BID x 14 days	19	⇔	⇔	⇔
Ketoconazole [a]	400 mg QD	200 mg QD x 14 days; 200 mg BID x 14 days	21	↓72 (↓80 to ↓60)	↓44 (↓58 to ↓27)	§
Methadone [a]	Individual Subject Dosing	200 mg QD x 14 days; 200 mg BID ≥7 days	9	In a controlled pharmacokinetic trial with 9 subjects receiving chronic methadone to whom steady-state nevirapine therapy was added, the clearance of methadone was increased by 3-fold, resulting in symptoms of withdrawal, requiring dose adjustments in 10 mg segments, in 7 of the 9 subjects. Methadone did not have any effect on nevirapine clearance.		
Rifabutin [a]	150 or 300 mg QD	200 mg QD x 14 days; 200 mg BID x 14 days	19	↑17 (↓2 to ↑40)	↑28 (↑9 to ↑51)	⇔
Metabolite 25-O-desacetyl-rifabutin				↑24 (↓16 to ↑84)	↑29 (↓2 to ↑68)	↑22 (↓14 to ↑74)
Rifampin [a]	600 mg QD	200 mg QD x 14 days; 200 mg BID x 14 days	14	↑11 (↓4 to ↑28)	⇔	§

§ = C_{min} below detectable level of the assay

↑ = Increase, ↓ = Decrease, ⇔ =No Effect

[a]For information regarding clinical recommendations, see *Drug Interactions (7)*.

[b]Pediatric subjects ranging in age from 6 months to 12 years.

[c]Parallel group design; n for nevirapine +lopinavir/ritonavir, n for lopinavir/ritonavir alone.

[d]Parallel group design; n=23 for atazanavir/ritonavir + nevirapine, n=22 for atazanavir/ritonavir without nevirapine. Changes in atazanavir PK are relative to atazanavir/ritonavir 300/100 mg alone.

[e]Based on between-trial comparison.

[f]Based on historical controls.

Because of the design of the drug interaction trials (addition of 28 days of nevirapine therapy to existing HIV-1 therapy), the effect of the concomitant drug on plasma nevirapine steady-state concentrations was estimated by comparison to historical controls.

Administration of rifampin had a clinically significant effect on nevirapine pharmacokinetics, decreasing AUC and C_{max} by greater than 50%. Administration of fluconazole resulted in an approximate 100% increase in nevirapine exposure, based on a comparison to historic data *[see Drug Interactions (7)]* . The effect of other drugs listed in Table 5 on nevirapine pharmacokinetics was not significant. No significant interaction was observed when tipranavir was co-administered with low-dose ritonavir and nevirapine.

12.4 Microbiology

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 antiviral activity of nevirapine has been measured in a variety of cell lines including peripheral blood mononuclear cells, monocyte-derived macrophages, and lymphoblastoid cell lines. In an assay using human embryonic kidney 293 cells, the median EC_{50} value (50% inhibitory concentration) of nevirapine was 90 nM against a panel of 2923 wild-type isolates of HIV-1 that were primarily (93%) clade B clinical isolates from the United States. The 99 th percentile EC_{50} value was 470 nM in this trial. The median EC_{50} value was 63 nM (range 14 to 302 nM, n=29) against clinical isolates of HIV-1 clades A, B, C, D, F, G, and H, and circulating recombinant forms CRF01_AE, CRF02_AG and CRF12_BF. Nevirapine had no antiviral activity in cell culture against

group O HIV-1 isolates (n=3) or HIV-2 isolates (n=3) replicating in cord blood mononuclear cells. Nevirapine in combination with efavirenz exhibited strong antagonistic anti-HIV-1 activity in cell culture and was additive to antagonistic with the protease inhibitor ritonavir or the fusion inhibitor enfuvirtide. The anti-HIV-1 activity of nevirapine was not antagonistic in combination with the NRTIs abacavir, didanosine, emtricitabine, lamivudine, stavudine, tenofovir and zidovudine, and the protease inhibitors amprenavir, atazanavir, indinavir, lopinavir, nelfinavir, saquinavir and tipranavir. The anti-HIV-1 activity of nevirapine was antagonized by the anti-HBV drug adefovir and by the anti-HCV drug ribavirin in cell culture.

Resistance

HIV-1 isolates with reduced susceptibility (100- to 250-fold) to nevirapine emerge in cell culture. Genotypic analysis showed mutations in the HIV-1 RT gene encoding Y181C and/or V106A substitutions depending upon the virus strain and cell line employed. Time to emergence of nevirapine resistance in cell culture was not altered when selection included nevirapine in combination with several other NNRTIs.

Phenotypic and genotypic changes in HIV-1 isolates from treatment-naïve subjects receiving either nevirapine (n=24) or nevirapine and zidovudine (n=14) were monitored in Phase 1 and 2 trials ranging from 1 to 12 weeks or longer. After 1 week of nevirapine monotherapy, isolates from 3/3 subjects had decreased susceptibility to nevirapine in cell culture. 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 subjects as early as 2 weeks after therapy initiation. By week eight of nevirapine monotherapy, 100% of the subjects tested (n=24) had HIV-1 isolates with a greater than 100-fold decrease in susceptibility to nevirapine in cell culture compared to baseline and had one or more of the nevirapine RT resistance-associated substitutions. Nineteen of these subjects (80%) had isolates with Y181C substitutions regardless of dose.

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

For trial 1100.1486, genotypic analysis was performed for baseline and on-therapy isolates from 23 and 34 subjects who experienced virologic failure in the nevirapine extended-release and immediate-release nevirapine treatment group, respectively. Nevirapine resistance-associated substitutions developed in the on-therapy isolates of 78% (18/23) of the subjects who had virologic failures in the nevirapine extended-release treatment group and 88% (30/34) of the subjects in the immediate-release nevirapine treatment group, respectively. The Y181C nevirapine resistance-associated substitution was found alone or in combination with other nevirapine resistance-associated substitutions (K101E, K103N, V106A, V108I, V179D/E/I, Y188 C/F/H/L/N, G190A, P225H, F227L, M230L) in isolates from 14 subjects failing nevirapine extended-release tablets treatment and 25 subjects failing immediate-release nevirapine treatment. On-therapy

isolates from 1 subject in nevirapine extended-release tablets treatment group developed a novel amino acid substitution Y181I and isolates from another subject in the immediate-release nevirapine treatment group developed a novel amino acid substitution Y188N. Phenotypic analysis showed that Y188N and Y181I substitutions conferred 103- and 22-fold reductions in susceptibility to nevirapine, respectively.

Cross-resistance

Rapid emergence of HIV-1 strains which are cross-resistant to NNRTIs has been observed in cell culture. Nevirapine-resistant HIV-1 isolates were cross-resistant to the NNRTIs efavirenz and etravirine. The Y188N conferred a 7-fold reduction in susceptibility to efavirenz but showed no decrease in susceptibility to etravirine. Similarly, the Y181I substitution reduced susceptibility to etravirine 8-fold, but did not reduce susceptibility to efavirenz. However, nevirapine-resistant isolates were susceptible to the NRTI ZDV. Similarly, ZDV-resistant isolates were susceptible to nevirapine in cell culture.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Long **-**term carcinogenicity studies in mice and rats were carried out with nevirapine. Mice were dosed with 0, 50, 375 or 750 mg/kg/day for two years. Hepatocellular adenomas and carcinomas were increased at all doses in males and at the two high doses in females. In studies in which rats were administered nevirapine at doses of 0, 3.5, 17.5 or 35 mg/kg/day for two years, an increase in hepatocellular adenomas was seen in males at all doses and in females at the high dose. The systemic exposure (based on AUCs) at all doses in the two animal studies was lower than that measured in humans at the 200 mg twice daily dose. The mechanism of the carcinogenic potential is unknown.

Mutagenesis

However, in genetic toxicology assays, nevirapine showed no evidence of mutagenic or clastogenic activity in a battery of *in vitro*and *in vivo*studies. These included microbial assays for gene mutation (Ames: Salmonella strains and *E. coli*), mammalian cell gene mutation assay (CHO/HGPRT), cytogenetic assays using a Chinese hamster ovary cell line and a mouse bone marrow micronucleus assay following oral administration. Given the lack of genotoxic activity of nevirapine, the relevance to humans of hepatocellular neoplasms in nevirapine-treated mice and rats is not known.

Impairment of Fertility

In reproductive toxicology studies, evidence of impaired fertility was seen in female rats at doses providing systemic exposure, based on AUC, approximately equivalent to that provided with the recommended clinical dose of nevirapine.

13.2 Animal Toxicology and/or Pharmacology

Animal studies have shown that nevirapine is widely distributed to nearly all tissues and readily crosses the blood-brain barrier.

14 CLINICAL STUDIES

14.1 Adult Patients

Trial BI 1090 was a placebo-controlled, double-blind, randomized trial in 2249 HIV-1 infected subjects with less than 200 CD4 $^{+}$cells/mm ^{3}at screening. Initiated in 1995, BI 1090 compared treatment with nevirapine + lamivudine + background therapy versus lamivudine + background therapy in NNRTI-naïve subjects. Treatment doses were nevirapine, 200 mg daily for two weeks followed by 200 mg twice daily or placebo, and lamivudine, 150 mg twice daily. Other antiretroviral agents were given at approved doses. Initial background therapy (in addition to lamivudine) was one NRTI in 1309 subjects (58%), two or more NRTIs in 771 (34%), and PIs and NRTIs in 169 (8%). The subjects (median age 36.5 years, 70% Caucasian, 79% male) had advanced HIV-1 infection, with a median baseline CD4 $^{+}$cell count of 96 cells/mm ^{3}and a baseline HIV-1 RNA of 4.58 log10 copies per mL (38,291 copies per mL). Prior to entering the trial, 45% had previously experienced an AIDS-defining clinical event. Eighty-nine percent had antiretroviral treatment prior to entering the trial. BI 1090 was originally designed as a clinical endpoint trial. Prior to unblinding the trial, the primary endpoint was changed to proportion of subjects with HIV-1 RNA less than 50 copies per mL and not previously failed at 48 weeks. Treatment response and outcomes are shown in Table 6.

Table 6 BI 1090 Outcomes Through 48 Weeks

Outcome	Nevirapine(N=1121) %	Placebo (N=1128) %
Responders at 48 weeks: HIV-1 RNA <50 copies/mL	18	2
Treatment Failure	82	98
Never suppressed viral load	45	66
Virologic failure after response	7	4
CDC category C event or death	10	11
Added antiretroviral therapy [1]while <50 copies/mL	5	1
Discontinued trial therapy due to AE	7	6
Discontinued trial <48 weeks [2]	9	10

[1]including change to open-label nevirapine

[2]includes withdrawal of consent, lost to follow-up, non-compliance with protocol, other administrative reasons

The change from baseline in CD4 $^{+}$cell count through one year of therapy was significantly greater for the nevirapine group compared to the placebo group for the overall trial population (64 cells/mm ^{3}versus 22 cells/mm ^{3}, respectively), as well as for subjects who entered the trial as treatment-naïve or having received only ZDV (85

cells/mm ^{3}versus 25 cells/mm ^{3}, respectively).

At two years into the trial, 16% of subjects on nevirapine had experienced class C CDC events as compared to 21% of subjects on the control arm.

Trial BI 1046 (INCAS) was a double-blind, placebo-controlled, randomized, three-arm trial with 151 HIV-1 infected subjects with CD4 $^+$cell counts of 200 to 600 cells/mm ^{3}at baseline. BI 1046 compared treatment with nevirapine +zidovudine+didanosine to nevirapine +zidovudine and zidovudine+didanosine. Treatment doses were nevirapine at 200 mg daily for two weeks followed by 200 mg twice daily or placebo, zidovudine at 200 mg three times daily, and didanosine at 125 or 200 mg twice daily (depending on body weight). The subjects had mean baseline HIV-1 RNA of 4.41 log10 copies/mL (25,704 copies per mL) and mean baseline CD4 $^+$cell count of 376 cells/mm ^{3}. The primary endpoint was the proportion of subjects with HIV-1 RNA less than 400 copies per mL and not previously failed at 48 weeks. The virologic responder rates at 48 weeks were 45% for subjects treated with nevirapine +zidovudine+didanosine, 19% for subjects treated with zidovudine+didanosine, and 0% for subjects treated with nevirapine +zidovudine.

CD4+ cell counts in the nevirapine +ZDV+ddI group increased above baseline by a mean of 139 cells/mm ^{3}at one year, significantly greater than the increase of 87 cells/mm ^{3}in the ZDV+ddI subjects. The nevirapine +ZDV group mean decreased by 6 cells/mm ^{3}below baseline.

14.2 Pediatric Patients

The pediatric safety and efficacy of nevirapine was examined in BI Trial 1100.1368, an open-label, randomized clinical trial performed in South Africa in which 123 HIV-1 infected treatment-naïve subjects between 3 months and 16 years of age received for 48 weeks. Subjects were divided into 4 age groups (3 months to less than 2 years, 2 to less than 7 years, 7 to less than 12 years, and 12 to less than or equal to 16 years) and randomized to receive one of two nevirapine doses, determined by 2 different dosing methods [body surface area (150 mg/m ^{2}) and weight-based dosing (4 or 7 mg per kg)] in combination with zidovudine and lamivudine *[see Adverse Reactions (6.1), Use in Specific Populations (8.4), and Clinical Pharmacology (12.3)]* . The total daily dose of nevirapine did not exceed 400 mg in either regimen. There were 66 subjects in the body surface area (BSA) dosing group and 57 subjects in the weight-based (BW) dosing group.

Baseline demographics included: 49% male; 81% Black and 19% Caucasian; 4% had previous exposure to ARVs. Subjects had a median baseline HIV-1 RNA of 5.45 log10 copies per mL and a median baseline CD4 $^+$cell count of 527 cells/mm ^{3}(range 37 to 2279). One hundred and five (85%) completed the 48-week period while 18 (15%) discontinued prematurely. Of the subjects who discontinued prematurely, 9 (7%) discontinued due to adverse reactions and 3 (2%) discontinued due to virologic failure. Overall the proportion of subjects who achieved and maintained an HIV-1 RNA less than 400 copies per mL at 48 weeks was 47% (58/123).

16 HOW SUPPLIED/STORAGE AND HANDLING

Nevirapine Tablets USP, 200 mg are White to off-white, oval, biconvex tablet, marked on one side as “I” and “11” separated with a breakline and plain on other side.

Pack style: Blister Pack of 60 (6 x 10) Unit-dose Tablets

Packing configuration: 10 Tablets packed in a Blister and such 6 Blister are packed in one Carton

(NDC code: 42571-131-29).

Pack style: HDPE Bottle pack of 60s Tablets (NDC code: 42571-131-60).

Dispense in tight container as defined in the USP/NF.

Storage

Store at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F)[see USP Controlled Room Temperature]. Store in a safe place out of the reach of children.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Hepatotoxicity and Skin Reactions

Inform patients of the possibility of severe liver disease or skin reactions associated with nevirapine that may result in death. Instruct patients developing signs or symptoms of liver disease or severe skin reactions to discontinue nevirapine and seek medical attention immediately, including performance of laboratory monitoring. Symptoms of liver disease include fatigue, malaise, anorexia, nausea, jaundice, acholic stools, liver tenderness or hepatomegaly. Symptoms of severe skin or hypersensitivity reactions include rash accompanied by fever, general malaise, fatigue, muscle or joint aches, blisters, oral lesions, conjunctivitis, facial edema, and/or hepatitis.

Intensive clinical and laboratory monitoring, including liver enzymes, is essential during the first 18 weeks of therapy with nevirapine to detect potentially life- threatening hepatotoxicity and skin reactions. However, liver disease can occur after this period; therefore, monitoring should continue at frequent intervals throughout nevirapine treatment. Extra vigilance is warranted during the first 6 weeks of therapy, which is the period of greatest risk of hepatic events. Advise patients with signs and symptoms of hepatitis to discontinue nevirapine and seek medical evaluation immediately. If nevirapine is discontinued due to hepatotoxicity, do not restart it. Patients, particularly women, with increased CD4 $^{+}$cell count at initiation of nevirapine therapy (greater than 250 cells/mm ^{3}in women and greater than 400 cells/mm ^{3}in men) are at substantially higher risk for development of symptomatic hepatic events, often associated with rash. Advise patients that co-infection with hepatitis B or C and/or increased transaminases 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 *[see Warnings and Precautions (5.1)]* .

The majority of rashes associated with nevirapine occur within the first 6 weeks of initiation of therapy. Instruct patients that if any rash occurs during the two-week lead-in period, do not escalate the nevirapine dose until the rash resolves. The total duration of the once-daily lead-in dosing period should not exceed 28 days, at which point an alternative regimen may need to be started. Any patient experiencing a rash should have their liver enzymes (AST, ALT) evaluated immediately. Patients with severe rash or hypersensitivity reactions should discontinue nevirapine immediately and consult a physician. Nevirapine should not be restarted following severe skin rash or hypersensitivity reaction. Women tend to be at higher risk for development of nevirapine-associated rash *[see Warnings and Precautions (5.2)]* .

Administration and Missed Dosage

Inform patients to take nevirapine every day as prescribed. Advise patients not to alter the dose without consulting their doctor. If a dose is missed, patients should take the next dose as soon as possible. However, if a dose is skipped, the patient should not double the next dose.

To avoid overdose, inform patients that they should never take immediate-release nevirapine and nevirapine extended-release concomitantly.

Drug Interactions

Nevirapine may interact with some drugs; therefore, advise patients to report to their doctor the use of any other prescription, non-prescription medication or herbal products, particularly St. John's wort *[see Warnings and Precautions (5.4)and Drug Interactions (7)]* .

Immune Reconstitution Syndrome

Advise patients to inform their healthcare provider immediately of any signs or symptoms of infection, as inflammation from previous infection may occur soon after combination antiretroviral therapy, including when nevirapine is started *[see Warnings and Precautions (5.5)].*

Fat Redistribution

Inform patients that redistribution or accumulation of body fat may occur in patients receiving antiretroviral therapy and that the cause and long-term health effects of these conditions are not known at this time *[see Warnings and Precautions (5.6)]* .

Pregnancy Registry

Advise patients that there is a pregnancy registry that monitors pregnancy outcomes in women exposed to nevirapine during pregnancy *[see Use in Specific Populations (8.1)].*

Lactation

Instruct women with HIV-1 infection not to breastfeed because HIV-1 can be passed to the baby in the breast milk *[see Use in Specific Populations (8.2)]* .

Infertility

Advise females of reproductive potential of the potential for impaired fertility from nevirapine *[see Use in Specific Populations (8.3)and Nonclinical Toxicology (13.1)]*

Manufactured by:
Micro Labs Limited
Goa-403 722, INDIA.

Manufactured for:
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Somerset, NJ 08873

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MEDICATION GUIDE

Nevirapine (ne-VIR-a-peen) tablets, USP

What is the most important information I should know aboutnevirapine?

Nevirapine tabletscan cause severe liver and skin problems that may lead to death. These problems can happen at any time during treatment, but your risk is higher during the first 18 weeks of treatment.

Nevirapine can cause serious side effects, including:

- **Severe liver problems.**Some people taking nevirapine tablets may develop severe liver problems that can lead to liver failure and the need for a liver transplant, or death. If you have liver problems, you may get a rash.
  - Women have a higher risk of developing liver problems during treatment with nevirapine than men.

- People who have abnormal liver test results before starting nevirapine and people with hepatitis B or C also have a greater risk of getting liver problems.

People who have higher CD4 $^{+}$cell counts when they begin nevirapine have a higher risk of liver problems, especially:

- Women with CD4 $^{+}$counts higher than 250 cells/mm ^{3}. This group has the highest risk.
- Men with CD4 $^{+}$counts higher than 400 cells/mm ^{3}.

Stop takingnevirapineand call your doctor right away if you have any of the following symptoms of liver problems with or without a skin rash:

• dark (tea colored) urine	• yellowing of your skin or whites of your eyes
• light-colored bowel movements (stools)	• fever
• feeling sick to your stomach (nausea)	• feel unwell or like you have the flu
• pain or tenderness on your right side below your ribs	• tiredness
• loss of appetite	

- **Severe skin reactions and rash.**Some skin reactions and rashes may be severe, life-threatening, and in some people, may lead to death. Most severe skin reactions and rashes happen in the first 6 weeks of treatment with nevirapine tablets.
- Women have a higher risk of developing a rash during treatment with nevirapine than men.

Stop takingnevirapineand call your doctor right away if you get a rash with any of the following symptoms:

• blisters	• muscle or joint aches
• red or inflamed eyes, like “pink eye” (conjunctivitis)	• mouth sores
• swelling of your face	• fever
• feel unwell or like you have the flu	• tiredness

- Your doctor should do blood tests often to check your liver function and check for severe skin reactions during the first 18 weeks of treatment with nevirapine. You should continue to see your doctor and have your liver checked regularly during your treatment with nevirapine tablets. It is important for you to keep all of your doctor appointments.
- **If your doctor tells you to stop treatment withnevirapinebecause you have had any of the severe liver or skin symptoms listed above, you should never take nevirapine again.**

See "What are the possible side effects ofnevirapine tablets?" for more information about side effects.

What arenevirapine tablets?

Nevirapine tablets are prescription HIV-1 medicines used with other HIV-1 medicines to treat HIV-1 (Human Immunodeficiency Virus 1) in adults and in children 15 days of age or older. HIV-1 is the virus that causes AIDS (Acquired Immune Deficiency Syndrome).

- If you are a woman with CD4 $^{+}$counts higher than 250 cells/mm ^{3}or a man with CD4 $^{+}$counts higher than 400 cells/mm ^{3}, you and your doctor will decide if starting nevirapine tablet is right for you.
- Nevirapine extended-release tablets are not recommended for use in children less than 6 years of age.

Do not takenevirapine:

- if you have liver problems.
- as part of occupational and non-occupational post-exposure prophylaxis (PEP) regimens. Nevirapine tablet is only for people diagnosed with HIV-1. If you have not been diagnosed as HIV positive, then do not take nevirapine tablets.

Before takingnevirapine, tell your doctor about all your or your child's medical conditions, including if you or your child:

- have or have had hepatitis (inflammation of your liver) or problems with your liver. See **"What is the most important information I should know aboutnevirapine?"**
- receive dialysis
- have trouble swallowing pills
- are pregnant or plan to become pregnant. It is not known if nevirapine will harm your unborn baby.

Pregnancy Registry: There is a pregnancy registry for women who take nevirapine during pregnancy. The purpose of the registry is to collect information about the health of you and your baby. Talk to your doctor about how you can take part in this registry.

- are breastfeeding or plan to breastfeed. Nevirapine can pass into your breast milk and may harm your baby. You should not breastfeed if you have HIV-1 because of the risk of passing HIV-1 to your baby. Do not breastfeed during treatment with nevirapine. Talk to your doctor about the best way to feed your baby.

Tell your doctor about all the medicines you take,including prescription and over-the-counter medicines, vitamins and herbal supplements. **Especially tell your doctor if you take St. John's wort.**

- Some medicines interact with nevirapine tablets. Keep a list of your medicines to show your doctor or pharmacist.
- You can ask your doctor or pharmacist for a list of medicines that interact with nevirapine tablets.
- Do not start taking a new medicine without telling your doctor. Your doctor can tell you if it is safe to take nevirapine tablets with other medicines.

How should I takenevirapine?

- **Take nevirapine exactly as your doctor tells you to take it. Do not change your dose unless your doctor tells you to.**
- Nevirapine tablet is always taken in combination with other antiretroviral medicines.
- Nevirapine tablet comes in three different forms. Your doctor will prescribe the form of nevirapine that is right for you.

  - Nevirapine tablets
  - Nevirapine oral suspension

- Nevirapine extended-release tablets

- You should not take more than one form of nevirapine tablets at the same time. Talk to your doctor if you have any questions.
- If your child is prescribed nevirapine, your child's doctor will tell you exactly how nevirapine should be taken.
- Nevirapine can be taken with or without food.
- Swallow nevirapine extended-release tablets whole. Do not chew, crush, or divide nevirapine extended-release tablets.
- Do not miss a dose of nevirapine tablets?". If you miss a dose of nevirapine tablets, take the missed dose as soon as you remember. If it is almost time for your next dose, do not take the missed dose. You should take the next dose at your regular time. Do not take 2 doses at the same time.
- If you stop taking nevirapine tablets for more than 7 days, ask your doctor how much to take before you start taking it again. You may need to begin taking the nevirapine tablets starting dose again, which is taken 1 time each day for 14 days.

Startingnevirapinetablets:

1. Your doctor should start you with 1 dose each day to lower your chance of getting a serious rash **. It is important that you only take 1 dose ofnevirapineeach day for the first 14 days.**

- **Call your doctor right away if you get a skin rash during the first 14 days ofnevirapinetreatment.**
- **Do not increase your dose to 2 times a day if you have a rash.**
- You should never take your starting dose for longer than 28 days. If after 28 days you are still receiving this starting dose because you have a rash, you and your doctor should talk about prescribing another HIV-1 medicine for you instead of nevirapine.

2. Day 15, you will take 1 nevirapine tablet 2 times a day.

Startingnevirapine extended-release tablets when this is the first time you are taking any form of nevirapine:

1. Your doctor should start you with 1 dose of nevirapine tablets each day to lower your risk of getting a serious rash. **It is important that you only take 1 dose ofnevirapine each day for the first 14 days.**

- Call your doctor right away if you get a skin rash during the first 14 days of nevirapine treatment.
- You should never take your starting dose for longer than 28 days. If after 28 days you are still receiving this starting dose because you have a rash, you and your doctor should talk about prescribing another HIV-1 medicine for you instead of nevirapine tablets.
- **Do not startnevirapine extended-release tablets if you have a rash.**

2. Day 15, take nevirapine extended-release tablets 1 time a day as prescribed by your doctor.

Switching from nevirapine tablets to nevirapine extended-release tablets:

- Take nevirapine extended-release tablets 1 time a day as prescribed by your doctor.
- You may sometimes pass a soft mass in your stools (bowel movement) that looks like your nevirapine extended-release tablets. This will not affect the way your medicine works.

What are the possible side effects ofnevirapine?

Nevirapine may cause serious side effects, including:

See "**What is the most important information I should know aboutnevirapine?**"

- **Changes in your immune system (Immune Reconstitution Syndrome)**can happen when you start taking HIV-1 medicines. Your immune system may get stronger and begin to fight infections that have been hidden in your body for a long time. Tell your doctor right away if you start having new symptoms after starting your HIV-1 medicine.
- **Changes in body fat**can happen in people who take HIV-1 medicines. These changes may include increased amount of fat in the upper back and neck (“buffalo hump”), breast, and around the middle of your body (trunk). Loss of fat from your legs, arms, and face may also happen. The exact cause and long-term health effects of these conditions are not known.

The most common side effect ofnevirapineis rash.

Nevirapine may cause decreased fertility in females. Talk to your doctor if you have concerns about fertility.

These are not all the possible side effects of nevirapine. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I storenevirapine?

- Store nevirapine at room temperature between 68°F to 77°F (20°C to 25°C).

Keepnevirapineand all medicines out of the reach of children.

General information about the safe and effective use ofnevirapine.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use nevirapine for a condition for which it was not prescribed. Do not give nevirapine tablets to other people, even if they have the same condition you have. It may harm them. You can ask your pharmacist or doctor for information about nevirapine tablets that is written for health professionals.

For more information, call Micro Labs USA Inc. at 1-855-839-8195.

What are the ingredients innevirapine tablets?

Active ingredient: Nevirapine Anhydrous

Inactive ingredients:

Nevirapine tablets:microcrystalline cellulose, lactose monohydrate, colloidal silicon dioxide, magnesium stearate, povidone, and Sodium starch glycolate.

This Medication Guide has been approved by the U.S. Food and Drug Administration

Manufactured by:
Micro Labs Limited
Goa-403 722, INDIA.

Manufactured for:
Micro Labs USA, Inc.
Somerset, NJ 08873

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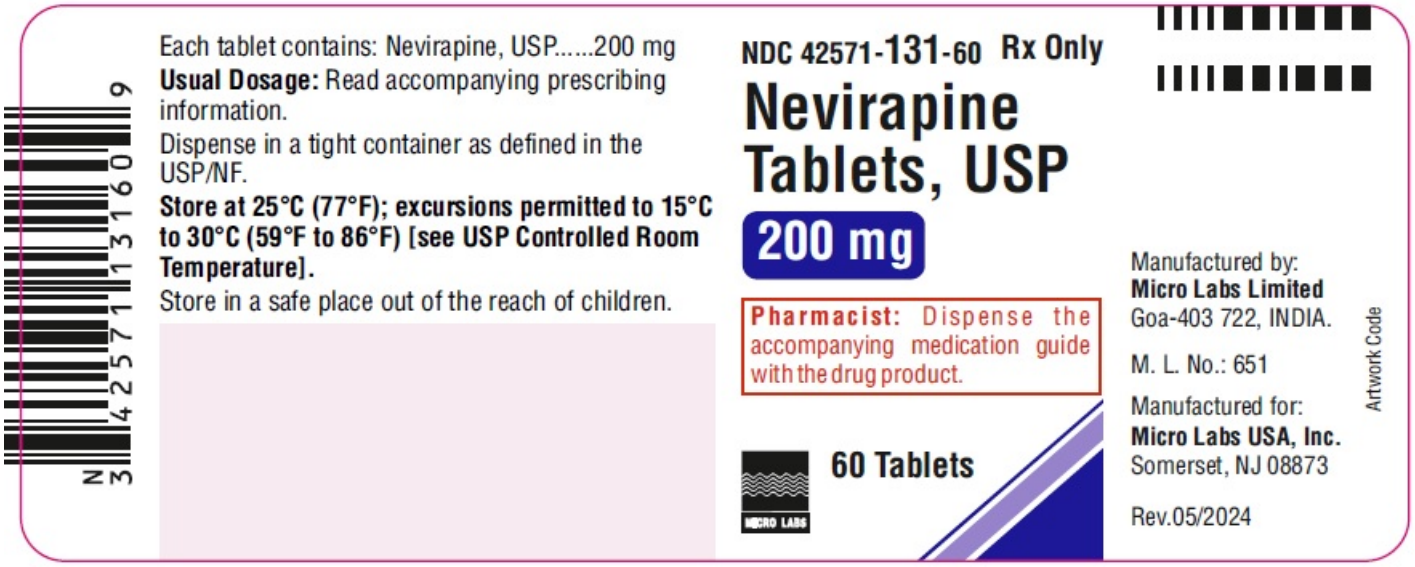
PACKAGE LABEL.PRINCIPAL DISPLAY PANEL

NDC 42571-131-60
Rx Only
Nevirapine
Tablets, USP
200 mg
Pharmacist: Dispense the accompanying
medication guide with the drug product.
60 TABLETS

Micro Labs Limited



NEVIRAPINE

nevirapine tablet

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:42571-131
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
NEVIRAPINE (UNII: 99DK7FVK1H) (NEVIRAPINE - UNII:99DK7FVK1H)	NEVIRAPINE	200 mg

Inactive Ingredients	
Ingredient Name	**Strength**
CELLULOSE, MICROCRYSTALLINE (UNII: OP1R32D61U)	
LACTOSE MONOHYDRATE (UNII: EWQ57Q8I5X)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
POVIDONE K25 (UNII: K0KQV10C35)	
SODIUM STARCH GLYCOLATE TYPE A POTATO (UNII: 5856J3G2A2)	

Product Characteristics			
Color	white (white to off-white)	**Score**	2 pieces
Shape	OVAL (biconvex)	**Size**	19mm
Flavor		**Imprint Code**	I;11
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:42571-131-60	60 in 1 BOTTLE; Type 0: Not a Combination Product	05/22/2012	
2	NDC:42571-131-29	6 in 1 CARTON	05/22/2012	
2		10 in 1 BLISTER PACK; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA203080	05/22/2012	

Labeler - Micro Labs Limited (862174955)

Establishment

Name	Address	ID/FEI	Business Operations
Micro Labs Limited		915793658	analysis(42571-131) , label(42571-131) , manufacture(42571-131) , pack(42571-131)

Revised: 10/2025 Micro Labs Limited