

**Nevirapine Tablets
Nevirapine Oral Suspension**

NEVIMUNE

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 >250 cells/mm³, 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 NONOCCUPATIONAL PEP IS CONTRAINDICATED (SEE CONTRAINDICATIONS). 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).

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).

MONITORING

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 SEVERE HEPATIC, SKIN OR HYPERSENSITIVITY REACTIONS. IN SOME CASES, HEPATIC INJURY HAS PROGRESSED DESPITE DISCONTINUATION OF TREATMENT.

COMPOSITION

NEVIMUNE Tablets

Each tablet contains

Nevirapine..... 200 mg

NEVIMUNE Oral Suspension

Each 5 ml contains

Nevirapine..... 50 mg

PHARMACOLOGY

Pharmacodynamics

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 , β , γ or δ) are not inhibited by nevirapine.

Pharmacokinetics

Absorption and Bioavailability

Nevirapine is readily absorbed (>90%) after oral administration in healthy volunteers and in adults with HIV-1 infection. Absolute bioavailability in 12 healthy adults following single-dose administration was $93 \pm 9\%$ (mean \pm SD) for a 50 mg tablet and $91 \pm 8\%$ for an oral solution. Peak plasma nevirapine concentrations of $2 \pm 0.4 \mu\text{g/mL}$ ($7.5 \mu\text{M}$) 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 $4.5 \pm 1.9 \mu\text{g/mL}$ ($17 \pm 7 \mu\text{M}$), (n=242) were attained at 400 mg/day. Nevirapine tablets and suspension have been shown to be comparably bioavailable and interchangeable at doses up to 200 mg. When nevirapine (200 mg) was administered to 24 healthy adults (12 female, 12 male), with either a high-fat breakfast (857 kcal, 50 g fat, 53% of calories from fat) or antacid, the extent of nevirapine absorption (AUC) was comparable to that observed under fasting conditions. In a separate study in HIV-1 infected patients (n=6), nevirapine steady-state systemic exposure ($\text{AUC}_0\text{-}\infty$) 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 non-ionized at physiologic pH. Following intravenous administration to healthy adults, the apparent volume of distribution (V_{dss}) of nevirapine was 1.21 ± 0.09 L/kg, suggesting that nevirapine is widely distributed in humans. Nevirapine readily crosses the placenta and is also found in breast milk. Nevirapine is about 60% bound to plasma proteins in the plasma concentration range of 1-10 µg/mL. Nevirapine concentrations in human cerebrospinal fluid (n=6) were 45% ($\pm 5\%$) of the concentrations in plasma; this ratio is approximately equal to the fraction not bound to plasma protein.

Metabolism/Elimination

In vivo studies in humans and *in vitro* studies with human liver microsomes have shown that nevirapine is extensively biotransformed via cytochrome P450 (oxidative) metabolism to several hydroxylated metabolites. *In vitro* studies with human liver microsomes suggest that oxidative metabolism of nevirapine is mediated primarily by cytochrome P450 (CYP) isozymes from the CYP3A and CYP2B6 families, although other isozymes may have a secondary role. In a mass balance/excretion study in eight healthy male volunteers dosed to steady state with nevirapine 200 mg given twice daily followed by a single 50 mg dose of ¹⁴C-nevirapine, approximately $91.4 \pm 10.5\%$ of the radiolabeled dose was recovered, with urine ($81.3 \pm 11.1\%$) representing the primary route of excretion compared to feces ($10.1 \pm 1.5\%$). Greater than 80% of the radioactivity in urine was made up of glucuronide conjugates of hydroxylated metabolites. Thus cytochrome P450 metabolism, glucuronide conjugation, and urinary excretion of glucuronidated metabolites represent the primary route of nevirapine biotransformation and elimination in humans. Only a small fraction (<5%) of the radioactivity in urine (representing <3% of the total dose) was made up of parent compound; therefore, renal excretion plays a minor role in elimination of the parent compound.

Nevirapine is an inducer of hepatic cytochrome P450 (CYP) metabolic enzymes 3A and 2B6. Nevirapine induces CYP3A and CYP2B6 by approximately 20-25%, as indicated by erythromycin breath test results and urine metabolites. Autoinduction of CYP3A and CYP2B6 mediated metabolism leads to an approximately 1.5- to 2fold increase in the apparent oral clearance of nevirapine as treatment continues from a single dose to two-to-four weeks of dosing with 200-400 mg/day. Autoinduction also results in a corresponding decrease in the terminal phase half-life of nevirapine in plasma, from

approximately 45 hours (single dose) to approximately 25-30 hours following multiple dosing with 200-400 mg/day.

Special Populations

Renal Impairment

HIV seronegative adults with mild (CrCL 50 - 79 mL/min; n=7), moderate (CrCL 30 -49 mL/min; n=6), or severe (CrCL <30 mL/min; n=4) renal impairment received a single 200 mg dose of nevirapine in a pharmacokinetic study. These subjects did not require 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**).

Hepatic Impairment

In a steady-state study comparing 46 patients with mild (n=17; expansion of some portal areas; Ishak Score 1-2), moderate (n=20; expansion of most portal areas with occasional portal-to-portal and portal-to-central bridging; Ishak Score 3-4), or severe (n=9; marked bridging with occasional cirrhosis without decompensation indicating Child-Pugh A; Ishak Score 5-6) 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 patients with hepatic fibrosis had nevirapine trough concentrations above 9,000 µg/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**). The patients 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 study where HIV-1 negative cirrhotic patients 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 patient 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 study 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 and WARNINGS AND PRECAUTIONS**).

Gender

In the multinational 2NN study, a population pharmacokinetic substudy of 1077 patients was performed that included 391 females. Female patients showed a 13.8% lower clearance of nevirapine than did men. Since neither body weight nor the 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 patients (27 Black, 24 Hispanic, 189 Caucasian) revealed no marked difference in nevirapine steady-state trough concentrations (median C_{minss} = 4.7 $\mu\text{g/mL}$ Black, 3.8 $\mu\text{g/mL}$ Hispanic, 4.3 $\mu\text{g/mL}$ Caucasian) with long-term nevirapine treatment at 400 mg/day. However, the pharmacokinetics of nevirapine has not been evaluated specifically for the effects of ethnicity.

Geriatric Patients

Nevirapine pharmacokinetics in HIV-1-infected adults do not appear to change with age (range 18–68 years); however, nevirapine has not been extensively evaluated in patients beyond the age of 55 years.

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 patients aged 3 months to 16 years; and a consolidated analysis of five Pediatric AIDS Clinical Trials Group (PACTG) protocols comprising 495 patients 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 patients up to 8 years of age received a dose of 4 mg/kg once daily for 2 weeks followed by 7 mg/kg twice daily thereafter. Patients 8 years and older were dosed 4 mg/kg once daily for 2 weeks followed by 4 mg/kg twice daily thereafter. In the BSA regimen, all pediatric patients received 150 mg/m² once daily for two weeks followed by 150 mg/m² twice daily thereafter. Dosing of nevirapine at 150 mg/m² B.I.D (after a two-week lead in of 150 mg/m² qd) produced geometric mean or mean trough nevirapine concentrations between 4 - 6 $\mu\text{g/mL}$ (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 patients 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 patients, particularly in the second month of age. For dose recommendations for pediatric patients (see **DOSAGE AND ADMINISTRATION**).

INDICATIONS

NEVIMUNE is indicated for use in combination with other antiretroviral agents for the treatment of HIV-1 infection.

Additional important information regarding the use of nevirapine for the treatment of HIV-1 infection is given below

- Based on serious and life-threatening hepatotoxicity observed in controlled and uncontrolled studies, **NEVIMUNE** should not be initiated in adult females with CD4⁺ cell counts greater than 250 cells/mm³ or in adult males with CD4⁺ cell counts greater than 400 cells/mm³ unless the benefit outweighs the risk (**see BOXED WARNING AND WARNINGS AND PRECAUTIONS**)
- The 14-day lead-in period with nevirapine 200 mg daily dosing has been demonstrated to reduce the frequency of rash (see **WARNINGS AND PRECAUTIONS AND DOSAGE AND ADMINISTRATION**).
- 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 after which point an alternative regimen should be sought.

DOSAGE AND ADMINISTRATION

Adults

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 lead-in period has been observed to decrease the incidence of rash. For concomitantly administered antiretroviral therapy, the manufacturer's recommended dosage and monitoring should be followed.

Pediatric patients

The recommended oral dose for pediatric patients 15 days and older is 150 mg/m² once daily for 14 days followed by 150 mg/m² twice daily thereafter. The total daily dose should not exceed 400 mg for any patient.

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

Table 1: Calculation of the Volume of NEVIMUNE Oral Suspension (50 mg/5 mL) required for Pediatric Dosing Based on Body Surface and a Dose of 150 mg/m²

BSA range (m ²)	Volume (mL)
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0.06 – 0.12	1.25
0.12 – 0.25	2.5
0.25 – 0.42	5
0.42 – 0.58	7.5
0.58 – 0.75	10
0.75 – 0.92	12.5
0.92 – 1.08	15
1.08 – 1.25	17.5
1.25+	20

NEVIMUNE Oral suspension should be shaken gently prior to administration. It is important to administer the entire measured dose of suspension by using an oral dosing syringe or dosing cup. An oral dosing syringe is recommended, particularly for volumes of 5 ml or less. If a dosing cup is used, it should be thoroughly rinsed with water and the rinse should also be administered to the patient.

Monitoring of patients

Intensive clinical and laboratory monitoring, including liver function tests, is essential at baseline and during the first 18 weeks of treatment with nevirapine. The optimal frequency of monitoring during this period has not been established. Some experts recommend clinical and laboratory monitoring more often than once per month, and in particular, would include monitoring of liver 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**). In some cases, hepatic injury has progressed despite discontinuation of treatment.

Dosage Adjustment

Patients with Rash

Nevirapine should be discontinued if patients experiences severe rash or any rash accompanied by constitutional findings (see **WARNINGS AND PRECAUTIONS**). A patient experiencing mild to moderate rash without constitutional symptoms during the 14-day lead-in period of 200 mg/day (150 mg /m²/ day in pediatric patients) should not have their nevirapine dose increased until the rash has resolved (see **WARNINGS AND PRECAUTIONS**). 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, nevirapine should be permanently discontinued. Do not restart nevirapine after recovery (see **WARNINGS AND PRECAUTIONS**).

Patients with Dose Interruption

Patients who interrupt nevirapine dosing for more than 7 days should restart the recommended dosing, using one 200 mg tablet daily (150 mg /m² / day in pediatric patients) for the first 14 days (lead-in) followed by one 200 mg tablet twice daily (150 mg / m² twice daily for pediatric patients).

Patients on Dialysis

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

CONTRAINDICATIONS

NEVIMUNE is contraindicated in patients with moderate or severe (Child Pugh Class B or C, respectively) hepatic impairment (see **WARNINGS AND PRECAUTIONS**).

Post-Exposure Prophylaxis

NEVIMUNE is contraindicated for use as part of occupational and non-occupational post-exposure prophylaxis (PEP) regimens. (see **WARNINGS AND PRECAUTIONS**).

WARNINGS AND PRECAUTIONS

Drug Interactions

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

Clinical comments about possible dosage modifications based on established drug interactions are listed in Table 2. This data is based on the results of drug interaction studies conducted in HIV-1 seropositive subjects unless otherwise indicated.

In addition to established drug interactions, there may be potential pharmacokinetic interactions between nevirapine and other drug classes that are metabolized by the cytochrome P450 system. These potential drug interactions are listed in Table 2. Although specific drug interaction studies in HIV-1 seropositive subjects have not been conducted for the classes of drugs listed in Table 2, 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 2: Established and Potential Drug Interactions: Use With Caution Alteration in Dose or Regimen May Be Needed due to Drug Interaction Studies

Drug Name	Effect on Concentration of Nevirapine or Concomitant Drug	Clinical Comment
Atazanavir/Ritonavir	↓Atazanavir ↑Nevirapine	Do not co-administer nevirapine with atazanavir because nevirapine substantially decreases atazanavir exposure.
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 <i>Mycobacterium avium-intracellulare</i> complex, overall activity against this pathogen may be altered. Alternatives to clarithromycin, such as azithromycin, should be considered.
Efavirenz	↓Efavirenz	There has been no determination of appropriate doses for the safe and effective use of this combination. (see WARNINGS AND PRECAUTIONS).
Ethinyl estradiol and Norethindrone	↓Ethinyl estradiol	Oral contraceptives and other hormonal methods of birth control

	↓ Norethindrone	should not be used as the sole method of contraception in women taking nevirapine, since nevirapine may lower the plasma levels of these medications. An alternative or additional method of contraception is recommended.
Fluconazole	↑ Nevirapine	Because of the risk of increased exposure to nevirapine, caution should be used in concomitant administration, and patients should be monitored closely for nevirapine-associated adverse events.
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.
Indinavir	↓ Indinavir	Appropriate doses for this combination are not established, but an increase in the dosage of indinavir may be required.
Ketoconazole	↓ Ketoconazole	Nevirapine and ketoconazole should not be administered concomitantly because decreases in ketoconazole plasma concentrations may reduce the efficacy of

		the drug.
Lopinavir/Ritonavir	↓ Lopinavir	<p>A dose increase of lopinavir/ritonavir tablets to 500/125 mg twice daily is recommended when used in combination with nevirapine.</p> <p>A dose increase of lopinavir/ritonavir oral solution to 533/133 mg twice daily with food is recommended in combination with nevirapine.</p> <p>In children, 6 months to 12 years of age receiving lopinavir/ritonavir solution, consideration should be given to increasing the dose of lopinavir/ritonavir to 13/3.25 mg/kg for those weighing 7 to <15 kg; 11/2.75 mg/kg for those weighing 15 to 45 kg; and up to a maximum dose of 533/133 mg for those >45 kg, twice daily.</p> <p>Refer to the lopinavir/ritonavir package insert for complete pediatric dosing instructions when lopinavir/ritonavir tablets are used in combination with nevirapine</p>
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.
Nelfinavir	<p>↓ Nelfinavir M8 Metabolite</p> <p>↓ Nelfinavir C_{min}</p>	The appropriate dose for nelfinavir in combination with nevirapine, with respect to safety and efficacy, has not been established.
Rifabutin	↑Rifabutin	Rifabutin and its metabolite concentrations were moderately increased. Due to high intersubject variability, however, some patients may experience large increases in rifabutin exposure and may be at higher risk for rifabutin toxicity. Therefore, caution should be used in concomitant administration.
Rifampin	↓ Nevirapine	Nevirapine and rifampin should not be administered concomitantly because decreases in nevirapine plasma concentrations may reduce the efficacy of the drug. Physicians needing to treat patients co-infected with tuberculosis and using a nevirapine- containing regimen may use

		rifabutin instead.
Saquinavir /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.

Table 3: Potential Drug Interactions:

Examples of drugs in which plasma concentrations may be decreased by co-administration with nevirapine	
Drug Class	Examples of Drugs
Antiarrhythmics	Amiodarone, disopyramide, lidocaine
Anticonvulsants	Carbamazepine, clonazepam, ethosuximide
Antifungals	Itraconazole Plasma concentrations of some azole antifungals may be decreased. Nevirapine and itraconazole should not be administered concomitantly due to a potential decrease in itraconazole plasma concentrations.
Calcium channel blockers	Diltiazem, nifedipine, verapamil
Cancer chemotherapy	Cyclophosphamide
Ergot alkaloids	Ergotamine
Immunosuppressants	Cyclosporine, tacrolimus, sirolimus
Motility agents	Cisapride
Opiate agonists	Fentanyl
Examples of drugs in which plasma concentrations may be increased by co-administration with nevirapine	
Antithrombotics	Warfarin Potential effect on anticoagulation. Monitoring of anticoagulation levels is recommended.

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. Coadministration of nevirapine and efavirenz is not recommended as this combination has been associated with an increase in adverse reactions and no improvement in efficacy.

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

The first 18 weeks of therapy with nevirapine are a critical period during which intensive clinical and laboratory monitoring of patients is required to detect potentially life-threatening hepatic events and skin reactions. The optimal frequency of monitoring during this time period has not been established. Some experts recommend clinical and laboratory monitoring more often than once per month, and in particular, would include monitoring of liver 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**).

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 11.0%) of patients who received nevirapine and 1.2% of patients in control groups.

The risk of symptomatic hepatic events regardless of severity was greatest in the first 6 weeks of therapy. The risk continued to be greater in the nevirapine groups compared to controls through the 18 weeks of treatment. However, hepatic events may occur at any time during treatment. In some cases, patients presented with non-specific, prodromal signs or symptoms of fatigue, malaise, anorexia, nausea, jaundice, liver tenderness or hepatomegaly, with or without initially abnormal serum transaminase levels. Rash was observed in approximately half of the patients with symptomatic hepatic adverse events. Fever and flu-like symptoms accompanied some of these hepatic events. Some events, particularly those with rash and other symptoms have progressed to hepatic failure with transaminase elevation, with or without

hyperbilirubinemia, hepatic encephalopathy, prolonged partial thromboplastin time, or eosinophilia. Patients with signs or symptoms of hepatitis must be advised to discontinue nevirapine and immediately seek medical evaluation, which should include liver enzyme tests.

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 **BOXED WARNING, DOSAGE AND ADMINISTRATION)**

If clinical hepatitis or transaminase elevations combined with rash or other systemic symptoms occur, **NEVIMUNE** should be permanently discontinued. Do not restart **NEVIMUNE** 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 (5.8% versus 2.2%), and patients with higher CD4 counts at initiation of nevirapine therapy are at higher risk for symptomatic hepatic events with nevirapine. In a retrospective review, women with CD4⁺ cell counts > 250 cells/mm³ had a 12 fold higher risk of symptomatic hepatic adverse events compared to women with CD4⁺ cell counts < 250 cells/mm³ (11.0% versus 0.9%). An increased risk was observed in men with CD4⁺ cell counts > 400 cells/mm³ (6.3% versus 1.2% for men with CD4⁺ cell counts < 400 cells/mm³). 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 transaminases 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, an unapproved use. Use of nevirapine for occupational and non-occupational PEP is contraindicated. (see **CONTRAINDICATIONS**).

Increased nevirapine trough concentrations have been observed in some patients with hepatic fibrosis or cirrhosis. Therefore, patients with either hepatic fibrosis or cirrhosis

should be monitored carefully for evidence of drug induced toxicity. Nevirapine should not be administered to patients with moderate or severe (Child Pugh Class B or C, respectively) hepatic impairment (see **CONTRAINDICATIONS AND CLINICAL PHARMACOLOGY**).

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 1.5% of nevirapine recipients compared to 0.1% of placebo subjects.

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

If patients present with a suspected nevirapine-associated rash, transaminases should be measured immediately. Patients with rash-associated transaminase elevations should be permanently discontinued from nevirapine. (see **WARNINGS AND PRECAUTIONS**).

Therapy with nevirapine must be initiated with a 14-day lead-in period of 200 mg/day (150 mg / m²/ day in pediatric patients), which has been shown to reduce the frequency of rash. Nevirapine should be discontinued if a patient experiences severe rash or any rash accompanied by constitutional findings. A patient experiencing a mild to moderate rash without constitutional symptoms during the 14-day lead-in period of 200 mg/day (150 mg /m²/ day in pediatric patients) should have their nevirapine dose increased until the rash has resolved. 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 (see **DOSAGE AND ADMINISTRATION**). Patients should be monitored closely if isolated rash of any severity occurs. Delay in stopping nevirapine treatment after the onset of rash may result in a more serious reaction. Women appear to be at higher risk than men of developing rash with nevirapine.

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

Resistance

Nevirapine must not be used as a single agent to treat HIV-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.

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 jirovecii* pneumonia (PCP), or tuberculosis), which may necessitate further evaluation and treatment.

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.

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 ≥ 20 mL/min. In patients undergoing chronic hemodialysis, an additional 200 mg dose following each dialysis treatment is indicated (see **DOSAGE AND ADMINISTRATION**).

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, WARNINGS AND PRECAUTIONS AND PHARMACOLOGY**)

Pregnancy

Pregnancy Category B

No observable teratogenicity was detected in reproductive studies performed in pregnant rats and rabbits. The maternal and developmental no-observable-effect level dosages produced systemic exposures approximately equivalent to or approximately 50% higher in rats and rabbits, respectively, than those seen at the recommended daily human dose (based on AUC). In rats, decreased fetal body weights were observed due to administration of a maternally toxic dose (exposures approximately 50% higher than that seen at the recommended human clinical dose).

There are no adequate and well-controlled studies of nevirapine in pregnant women.

Severe hepatic events, including fatalities, have been reported in pregnant women receiving chronic nevirapine therapy as part of a combination treatment of HIV-1 infection. Regardless of pregnancy status, women with CD4⁺ cell counts >250 cells/mm³ should not initiate **NEVIMUNE** unless the benefit outweighs the risk. It is unclear if pregnancy augments the risk observed in non-pregnant women (see **BOXED WARNING**).

NEVIMUNE should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Lactation

The Centers for Disease Control and Prevention recommend that HIV-1 infected mothers not breast-feed their infants to avoid risking postnatal transmission of HIV-1. Nevirapine is excreted in breast milk. Because of both the potential for HIV-1 transmission and the potential for serious adverse reactions in nursing infants, mothers should be instructed not to breastfeed if they are receiving nevirapine.

Pediatric use

The safety, pharmacokinetic profile, and virologic and immunologic responses of nevirapine have been evaluated in HIV-1 infected pediatric patients age 3 months to 18 years (see **UNDESIRABLE EFFECTS**). The safety and pharmacokinetic profile of nevirapine has been evaluated in HIV-1 infected pediatric patients age 15 days to <3 months (see **UNDESIRABLE EFFECTS**).

The most frequently reported adverse events related to nevirapine in pediatric patients were similar to those observed in adults, with the exception of granulocytopenia, which was more commonly observed in children receiving both zidovudine and nevirapine. (see **UNDESIRABLE EFFECTS**).

Geriatric Use

Clinical studies 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.

UNDESIRABLE EFFECTS

Adults

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**).

Hepatic Reaction

In controlled clinical trials, symptomatic hepatic events regardless of severity occurred in 4.0% (range 0% to 11.0%) of patients who received nevirapine and 1.2% of patients in control groups. Female gender and higher CD4⁺ cell counts (>250 cells/mm³ in women and > 400 cells/mm³ in men) place patients at increased risk of these events (see **BOXED WARNING AND WARNINGS AND PRECAUTIONS**).

Asymptomatic transaminase elevations (AST or ALT > 5 x ULN) were observed in 5.8% (range 0% to 9.2%) of patients who received nevirapine and 5.5% of patients in control groups. Co-infection with hepatitis B or C and/or increased 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 patients receiving nevirapine than in controls.

Skin Reaction

The most common clinically toxicity of nevirapine is rash, which can be severe or life threatening (see **BOXED WARNING AND WARNINGS AND PRECAUTIONS**). 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 13.3% of patients receiving nevirapine compared to 5.8% receiving placebo during the first 6 weeks of therapy. Grade 3 and 4 rashes were reported in 1.5% of nevirapine recipients compared to 0.1% of subjects receiving placebo. Women tend to be at higher risk for the development of nevirapine associated rash. (see **BOXED WARNING AND WARNINGS AND PRECAUTIONS**)

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 practice.

Treatment related, adverse experiences of moderate or severe intensity observed in >2% of patients receiving nevirapine in placebo-controlled trials are shown in Table 4.

Table 4: Percentage of Patients with Moderate or Severe Drug Related Events in Adult Placebo Controlled Trials

	Trial 1090 ¹		Trials 1037, 1038, 1046 ²	
	Nevirapine (n=1121)	Placebo (n=1128)	Nevirapine (n=253)	Placebo (n=203)
Median exposure (weeks)	58	52	28	28
Any adverse event	14.5%	11.1%	31.6%	13.3%
Rash	5.1	1.8	6.7	1.5
Nausea	0.5	1.1	8.7	3.9
Granulocytopenia	1.8	2.8	0.4	0
Headache	0.7	0.4	3.6	0.5
Fatigue	0.2	0.3	4.7	3.9
Diarrhea	0.2	0.8	2.0	0.5
Abdominal pain	0.1	0.4	2.0	0

Myalgia	0.2	0	1.2	2.0
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¹ Background therapy included 3TC for all patients and combinations of NRTIs and PIs. Patients had CD4⁺ cell counts < 200 cells/mm³

² Background therapy included ZDV and ZDV + ddl; Nevirapine monotherapy was administered in some patients. Patients had CD4⁺ cell count ≥ 200 cells/mm³

Laboratory Abnormalities

Liver enzyme test abnormalities (AST, ALT) were observed more frequently in patients receiving nevirapine than in controls (Table 5). 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 5).

Table 5: Percentage of Adult Patients with Laboratory Abnormalities

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

¹ Background therapy included 3TC for all patients and combinations of NRTIs and PIs. Patients had CD4⁺ cell counts < 200 cells/mm³

² Background therapy included ZDV and ZDV+ddl; Nevirapine monotherapy was administered in some patients. Patients had CD4⁺ cell count ≥ 200 cells/mm³

Pediatric Patients

Adverse events were assessed in the BI Trial 1100.1032 (ACTG 245), a double-blind, placebo-controlled trial of nevirapine (n = 305) in which pediatric patients received combination treatment with nevirapine. In this trial 2 patients 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 patients were followed for a mean duration of 33.9 months (range: 6.8 months to 5.3 years, including long-term follow-up in 29 of these patients in trial BI 1100.892). The most frequently reported adverse events related to nevirapine in pediatric patients were similar to those observed in adults, with the exception of granulocytopenia, which was more commonly observed in children receiving both zidovudine and nevirapine. Cases of allergic reaction, including one case of anaphylaxis, were also reported.

The safety of nevirapine was also examined in the BI Trial 1100.1368, an open-label, randomized clinical study performed in South Africa in which 123 HIV-1 infected treatment naïve patients between 3 months and 16 years of age received combination treatment with nevirapine oral suspension, lamivudine and zidovudine for 48 weeks. Rash (all causality) was reported in 21% of the patients, of these 4 (3%) of whom discontinued drug due to rash. All 4 patients experienced the rash early in the course of therapy (< 4 weeks) and it resolved upon nevirapine discontinuation. Other clinically important adverse events (all causality) include neutropenia (8.9%), anemia (7.3%) and hepatotoxicity (2.4%).

Safety information on use of nevirapine in combination therapy in pediatric patients 2 weeks to < 3 months of age was assessed in 36 patients from the BI 1100.1222 (PACTG 356) study. 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.

Observed During Clinical Practice:

In addition to the adverse events identified during clinical trials, the following adverse reactions have been identified during the 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**), redistribution/ accumulation of body fat (see **WARNINGS AND PRECAUTIONS**).

Gastrointestinal: vomiting

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

Hematology: anemia, eosinophilia, neutropenia

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 (see **WARNINGS AND PRECAUTIONS**) plus one or more of the following: hepatitis, eosinophilia, granulocytopenia, lymphadenopathy and/or renal dysfunction have been reported with the use of nevirapine.

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.

OVERDOSAGE

There is no known antidote for nevirapine overdose. 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 adverse 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.

PACKAGING INFORMATION

NEVIMUNE TabletsContainer of 30 tablets
NEVIMUNE Oral SuspensionBottle of 100 ml

Last updated: October 2010