WARNING: LIFE THREATENING (INCLUDING FATAL) HEPATOTOXICITY and SKIN REACTIONS See full prescribing information for complete boxed warning

Fatal and non-fatal hepatotoxicity (5.1)

 Fatal and non-fatal skin reactions (5.2) Discontinue immediately if experiencing:

Signs or symptoms of hepatitis (5.1)

Increased transaminases combined with rash or other systemic symptoms (5.1)

Severe skin or hypersensitivity reactions (5.2)

Any rash with systemic symptoms (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

---INDICATIONS AND USAGE-• Nevirapine tablets for oral suspension are an NNRTI indicated for combination antiretroviral treatment of HIV-1 infection (1)

Important Considerations: • Initiation of treatment is not recommended in the following populations unless the benefits outweigh the risks (1, 5.1)

o adult females with CD4+ cell counts >250 cells/mm3

o adult males with CD4+ cell counts >400 cells/mm³
• The 14-day lead in period must be strictly followed; it may reduce the frequency of rash (2.3, 5.2)

----DOSAGE AND ADMINISTRATION--

Any patient experiencing rash during the 14-day lead-in period should not increase dose until the rash has resolved. The lead-in dosing regimen should not be continued

beyond 28 days (2.3)

• If dosing interrupted for >7 days, restart 14-day lead-in dosing (2.3)

· Pediatric Dosing

Dosing recommendations by weight bands are provided. (2.1) Total daily dose should not exceed 400 mg for any patient.

FULL PRESCRIBING INFORMATION: CONTENTS* WARNING: LIFE THREATENING (INCLUDING FATAL) HEPATOTOXICITY and SKIN REACTIONS

INDICATIONS AND USAGE DOSAGE AND ADMINISTRATION Pediatric Patient

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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 hepatitis failure. These events are often associated with rash. Female gender and higher CD4 counts at initiation of therapy place patients at increased risk; women with CD4 counts >250 cells/mm³, including pregnant women receiving nevirapine in combination with other antiretrovirals for the treatment of HIV infection, are at the greatest risk. However, hepatotoxicity associated with nevirapine use can occur in both genders, all CD4 counts and at any time during treatment. 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 utiliscontinue 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)].

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.

Nevirapine tablets for oral suspension are indicated for use in combination with other antiretroviral agents for the treatment of HIV-1 infection. This indication is based on one principal clinical trial (BI 1090) that demonstrated prolonged suppression of HIV-RNA and two smaller supportive studies, one of which (BI 1046) is described below. Additional important information regarding the use of nevirapine tablets for oral suspension for the treatment

Based on serious and life-threatening hepatotoxicity observed in controlled and uncontrolled studies, nevirapine

Based on serious and life-threatening hepatotoxicity observed in controlled and uncontrolled studies, nevirapine tablets for oral suspension 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 (5.1)].
 The 14-day lead-in period with nevirapine once daily dosing has been demonstrated to reduce the frequency of rash [see Dosage and Administration (2.3) and Warnings and Precautions (5.2)].
 If rash persists beyond the 14 day lead-in period, do not dose escalate to the twice daily dose. The once daily dosing regimen should not be continued beyond 28 days at which point an alternative regimen should be sought.

DOSAGE AND ADMINISTRATION

2.1 Pediatric Patients Dose Recommendations according to Weight Bands are provided below											
Nevirapine Tablet Number of Tablets by Weight Bands Tablets for Oral Strength:											
Suspension	50 mg	5-8 kgs	9-12 kgs	13-18 kgs	19-24 kgs	25-30 kgs	31-38 kgs	>38 kgs			
Lead-in Period (first 14 days)		1 tablet Once Daily	1.5 tablets Once Daily	2 tablets Once Daily	2.5 tablets Once Daily	3 tablets Once Daily	3.5 tablets Once Daily	4 tablets Once Daily			
After the first 14 days		1 tablet Twice Daily	1.5 tablets Twice Daily	2 tablets Twice Daily	2.5 tablets Twice Daily	3 tablets Twice Daily	3.5 tablets Twice Daily	4 tablets Twice Daily			

Calculation of pediatric dose for patients 15 days and older is based on body surface area (BSA), which is 150 mg/m² once daily for 14 days followed by 150 mg/m² twice daily thereafter. However, no calculation is necessary for this formulation because the recommended dose has already been calculated and displayed based on weight band (see table above). The total daily dose should not exceed 400 mg for any patient.

Use the following procedure for taking these tablets. 1. Place the tablet(s) in a container and add one teaspoonful (5 mL) of water per tablet.

2. Swirl the container until tablet(s) breaks up into pieces small enough for the child to swallow.

 Drink the mixture immediately. 4. Rinse the container with additional small amount of water and drink the contents to assure that the entire

DO NOT CHEW NEVIRAPINE TABLET FOR ORAL SUSPENSION OR SWALLOW THE INTACT TABLET. DO NOT MIX NEVIRAPINE TABLET FOR ORAL SUSPENSION WITH ANY LIQUID OTHER THAN WATER

2.2 Monitoring of Patients 2.2 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 tablets for oral suspension. 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 tablets for oral suspension treatment [see Warnings and Precautions (5)]. In some cases, hepatic injury has progressed despite discontinuation of treatment.

2.3 Dosage Adjustment Patients with Rash Patients with Hash
Nevirapine tablets for oral suspension should be discontinued if a patient experiences severe rash or any rash accompanied by constitutional findings (see Boxed Warning, Warnings and Precautions (5.2), and Patient Counseling Information (17.1)]. 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 tablets for oral suspension dose increased until the rash has resolved (see Warnings and Precautions (5.2) and Patient Counseling Information (17.1)]. 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 tablets for oral suspension should be permanently

discontinued. Do not restart nevirapine tablets for oral suspension after recovery [see Warnings and Precaution Patients with Dose Interruption

Patients who interrupt nevirapine tablets for oral suspension dosing for more than 7 days should restart the recommended dosing, using once daily dosing for the first 14 days (lead-in) followed by twice daily dosing

DOSAGE FORMS AND STRENGTHS Nevirapine Tablets for Oral Suspension, 50 mg are white to off-white, round, flat face beveled edge, uncoated tablets debossed with '1' on one side and a break line separating '4' and '7' on other side.

CONTRAINDICATIONS Nevirapine tablets for oral suspension are 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 Popular (8.7)].

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.

In 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 once daily dosing (half of the daily maintenance dose) has been demonstrated to reduce the frequency of rash. 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 patients who received nevirapine and 1.2% of patients in control groups.

The risk of symptomatic hepatic events regardless of severity was greatest in the first 6 weeks of therapy. The risk continued to be greater in the nevirapine groups compared to controls through 18 weeks of treatment. However, hepatic events may occur at any time during treatment. In some cases, patients presented with non-specific, prodromal signs or symptoms of fatigue, malaise, anorexia, nausea, jaundice, liver tenderness or hepatomegaly, with or without initially abnormal serum transaminase levels. Rash was observed in approximately belief of the activation of the parties developed and the parties develop 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 fallure 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. Patients with signs or symptoms of hepatitis must be advised to discontinue nevirapine and immediately seek medical evaluation, which should include liver enzyme

Transaminases should be checked immediately if a patient experiences signs or symptoms suggestive of Iransaminases 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 hepatoxicity should be considered in this setting, even if transaminases are initially normal or alternative diagnoses are possible [see Boxed Warning, Dosage and Administration (2.2), and Patient Counseling Information (17.1)]. If clinical hepatitis or transaminase elevations combined with rash or other systemic symptoms occur, nevirapine should be permanently discontinued. Do not restart nevirapine after recovery. In some cases, hepatic injury progresses despite discontinuation of treatment.

progresses despite discontinuation of treatment. The patients at greatest risk of hepatic events, including potentially fatal events, are women with high CD4 counts. In general, during the first 6 weeks of treatment, women have a three fold higher risk than men for symptomatic, often rash-associated, hepatic events (5.8% versus 2.2%), and patients with higher CD4 counts at initiation of nevirapine therapy are at higher risk for symptomatic hepatic events with nevirapine. In a retrospective review, women with CD4 counts >250 cells/mm³ had a 12 fold higher risk of symptomatic hepatic adverse events compared to women with CD4 counts <250 cells/mm³ (11% versus 0.9%). An increased risk was observed in men with CD4 counts (6.3% versus 1.2% for men with CD4 counts <400 cells/mm³). However, all patients, regardless of gender, CD4 count, or antiretroviral treatment history, should be monitored for hepatotoxicity since symptomatic hepatic adverse events have been reported at all CD4 counts. CO-infection with hepatitis B or C and/or increased transaminase elevations at the start of therapo with nevironine are associated with a greater 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.

prophylaxis, an unapproved use.

propriyaxis, an unapproved use in the content of th 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 1.5% of nevirapine recipients compared to 0.1% of placebo subjects. **th.** The later.

• The most common adverse reaction is rash. In adults the incidence of rash is 14.8% vs. 5.9% with placebo, with Grade 3/4 rash occurring in 1.5% of patients (6.1) In pediatric patients the incidence of rash (all causality) was 21% (6.2)

8.5 Geriatric Use

OVERDOSAGE

DESCRIPTION

8.7

Renal Impairmen

CLINICAL PHARMACOLOGY

12.1 Mechanism of Action 12.3 Pharmacokinetics

Microbiology

Hepatic Impairment

. Tablets for Oral Suspension: 50 mg (3)

· Stevens-Johnson syndrome: (5) Toxic epidermal necrolysis: (5)

-DOSAGE FORMS AND STRENGTHS

-CONTRAINDICATIONS

---WARNINGS AND PRECAUTIONS

. Hepatitis and hepatic failure: (5)

• Patients with moderate or severe (Child Pugh Class B or C, respectively) hepatic impairment (4, 5.1, 8.7)

. Hypersensitivity reactions: (5) -- ADVERSE REACTIONS-

To report SUSPECTED ADVERSE REACTIONS, contact Aurobindo Pharma USA, Inc. at 1-866-850-2876 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 (7, 12.3) -USE IN SPECIFIC POPULATIONS-Patients with hepatic fibrosis or cirrhosis should be monitored carefully for evidence of drug induced toxicity. Patients with Child Pugh B or C should not receive nevirapine (5.1, 8.7)

No dose adjustment is required for patients with renal impairment. Patients on dialysis should receive an additional dose of 200 mg following each dialysis treat (8.6)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved Medication Guide.

Issued: February 2010

NONCLINICAL TOXICOLOGY 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility Animal Toxicology and/or Pharmacology **CLINICAL STUDIES** Clinical Studies in Adults Clinical Studies in Pediatric Patients HOW SUPPLIED/STORAGE AND HANDLING PATIENT COUNSELING INFORMATION Hepatotoxicity and Skin Reactions

17.3 Drug Interactions

Contraceptives 17.5 Methadone

17.6 Fat Redistributio

*Sections or sub-sections omitted from the full prescribing information are not listed

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 [see Boxed Warning and Patient Counseling Information (17.1)]. 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 (5.1)]. Therapy with nevirapine must be initiated with a 14-day lead-in period of once daily dosing (150 mg/m²/day in pediatric patients), which has been shown to reduce the frequency of rash. Nevirapine should be discontinued in 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 (150 mg/m²/day in pediatric patients) should not 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 (2.3)]. Patients should be monitored closely if isolated rash of any severity occurs.

severity occurs. Delay in stopping nevirapine treatment after the onset of rash may result in a more serious reactic

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

Nevirapine must not be used as a single agent to treat HIV 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 swith spoter half-lives than nevirapine, the long half-life of nevirapine should be taken into account; far intertrovirals with shorter half-lives than nevirapine are stopped concurrently, low para concentrations of nevirapine alone may persist for a week or longer and virus resistance may subsequently develop [see Clinical Pharmacology (12.4)].

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 suboptimal levels of nevirapine and lead to loss of virologic response and possible resistance to nevirapine or to the class of NNRTIs. 5.5 Immune Reconstitution Syndrome

5.4 Drug Interactions

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

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. ADVERSE REACTIONS 6.1 Clinical Trials in 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 (5.1, 5.2)]. Hepatic Reaction

In controlled clinical trials, symptomatic hepatic events regardless of severity occurred in 4% (range 0% to 11%) of patients who received nevirapine and 1.2% of patients in control groups. Female gender and higher CD4 counts (>250 cells/mm³ in women and >400 cells/mm³ in men) place patients at increased risk of these events [see Boxed Varning and Warnings and Precautions (5.1)]. Asymptomatic transaminase elevations (AST or ALT > 5X ULN) were observed in 5.8% (range 0% to 9.2%) of patients who received nevirapine and 5.5% of patients in control groups. Co-infection with hepatitis B or C and/or increased 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 (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 13.3% of patients receiving nevirapine compared to 5.8% receiving placebo during the first 6 weeks of therapy. Grade 3 and 4 rashes were reported in 1.5% of nevirapine recipients compared to 0.1% of subjects receiving placebo. Women tend to be at higher risk for development of nevirapine associated rash [see Boxed Warning and Warnings and Precautions (5.2)].

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 trials of a drug cannot be orates observed in practice.

Trial 1090¹

Treatment related, adverse experiences of moderate or severe intensity observed in >2% of patients receiving nevirapine in placebo-controlled trials are shown in Table 1 Table 2 Percentage of Patients with Moderate or Severe Drug Related Events in Adult Placebo Controlled Trials

Trials 1037, 1038, 1046²

	Nevirapine	Placebo	Nevirapine	Placebo
	(n=1121)	(n=1128)	(n=253)	(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	0.5
Abdominal pain	0.1	0.4	2	0
Myalgia	0.2	0	1.2	2

Background therapy included 3TC for all patients and combinations of NRTIs and PIs. Patients had CD4+ cell counts <200 cells/mm³. Background therapy included ZDV and ZDV+ddl; nevirapine monotherapy was administered in some patients. Patients had CD4+ cell count \geq 200 cells/mm³.

Laboratory Abnormalities Liver enzyme test abnormalities (AST, ALT) were observed more frequently in patients 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 Patients with Laboratory Abnormalities

	Trial 1090 ¹		Trials 1037, 1038, 1046 ²		
	Nevirapine	Placebo	Nevirapine	Placebo	
Laboratory Abnormality	(n=1121)	(n=1128)	(n=253)	(n=203)	
Blood Chemistry					
SGPT (ALT) >250 U/L	5.3	4.4	14	4	
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 g/dL	3.2	4.1	0	0	
Platelets <50,000/mm ³	1.3	1	0.4	1.5	
Neutrophils <750/mm ³	13.3	13.5	3.6	1	
Background therapy included 3 counts <200 cells/mm³.	TC for all patients an	d combinations of	NRTIs and PIs. Pati	ents had CD4+ cel	

Background therapy included ZDV and ZDV+ddl; nevirapine monotherapy was administered in some patients. Patients had CD4+ cell count ≥200 cells/mm³. 6.2 Clinical Trials in Pediatric Patients

Adverse events were assessed in BI Trial 1100.1032 (ACTG 245), a double-blind, placebo-controlled trial of

Adverse events were assessed in Bi Trial 110.1032 (ACTG 245), a double-billio, placebor-controller trial of nevirapine (n = 305) in which pediatric patients received combination treatment with nevirapine. In this trial two patients were reported to experience Stevens-Johnson syndrome or Stevens-Johnson/foxic 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 1100.882). 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. 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 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 [see Use in Specific Populations (8.4) and Clinical Pharmacology (12.3)]. Rash (all causality) was reported in 21% of the patients, 4 (3%) of whom discontinued drug due to rash. All 4 patients experienced the rash early in the course of therapy (< 4 weeks) and resolved upon nevirapine discontinuation. Other clinically important adverse events (all causality) include neutropenia (8.9%), anemia (7.3%) and hepatotoxicity (2.4%) [see Use in Specific Populations (8.4) and Clinical Studies (14.2)].

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. 6.3 Post-Marketing Surveillance

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

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

Neurologic: paresthesia Skin and Appendages: allergic reactions including anaphylaxis, angioedema, bullous eruptions, ulcerative stomatitis

bitor" (NNRTI). It virapine with other d and increase the oine may not have AIDS (Acquired nevirapine?'

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 (5.11) 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.

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.

may have lower than expected plasma levels when co-administered with nevirapine.

The specific pharmacokinetic changes that occur with co-administered with 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 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 their drug classes that are metabolized by the cytochrome P450 system. These potential drug interactions are also listed in Table 4. Although specific drug interaction studies 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

Drug Name	Effect on Concentration of Nevirapine or Concomitant Drug	Clinical Comment			
Clarithromycin	↓ Clarithromycin ↑14-OH clarithromycin	Clarithromycin exposure was significant decreased by nevirapine; however, 14-0 metabolite concentrations were increase Because clarithromycin active metabolite ha reduced activity against Mycobacterium aviur intracellulare complex, overall activity against the pathogen may be altered. Alternatives clarithromycin, such as azithromycin, should I considered.			
Efavirenz	↓ Efavirenz	Appropriate doses for this combination are no established.			
Ethinyl estradiol and Norethindrone	↓ Ethinyl estradiol ↓ Norethindrone	Oral contraceptives and other hormonal metho of birth control should not be used as the so method of contraception in women takin nevirapine, since nevirapine may lower the plasn levels of these medications. An alternative additional method of contraception recommended.			
Fluconazole	↑ Nevirapine	Because of the risk of increased exposure nevirapine, caution should be used in concomital administration, and patients should be monitor closely for nevirapine-associated adverse event			
Indinavir	↓ Indinavir	Appropriate doses for this combination are n established, but an increase in the dosage indinavir may be required.			
Ketoconazole	↓ Ketoconazole	Nevirapine and ketoconazole should not administered concomitantly because decreas in ketoconazole plasma concentrations may redu the efficacy of the drug.			
	↓ Lopinavir	KALETRA 400/100 mg tablets can be used twic daily in combination with nevirapine with no do adjustment in antiretroviral-naïve patients. A dose increase of KALETRA tablets to 60 150 mg (3 tablets) twice daily may be consider when used in combination with nevirapine treatment experienced patients where decrease susceptibility to lopinavir is clinically suspect (by treatment history or laboratory evidence). A dose increase of lopinavir/ritonavir oral soluti to 533/133 mg twice daily with food recommended in combination with nevirapine. In children 6 months to 12 years of acconsideration should be given to increasing t dose of lopinavir/ritonavir to 13/3.25 mg/kg f those? To £15 kg; 11/2.75 mg/kg for those 15 45 kg; and up to a maximum dose of 533/133 for those × 45 kg twice daily when used combination with nevirapine, particularly for patier in whom reduced susceptibility to lopinavir/ritona is suspected. Methadone levels may be decreased; increasi			
		dosages may be required to prevent symptor of opiate withdrawal. Methadone maintain patients beginning nevirapine therapy should monitored for evidence of withdrawal methado dose should be adjusted accordingly.			
Nelfinavir	↓ Nelfinavir M8 Metabolite ↓ Nelfinavir C _{min}	The appropriate dose for nelfinavir in combinati- with nevirapine, with respect to safety and efficac has not been established.			
Rifabutin	↑ Rifabutin	Rifabutin and its metabolite concentrations we moderately increased. Due to high intersubje variability, however, some patients may experien large increases in rifabutin exposure and may at higher risk for rifabutin toxicity. Therefor caution should be used in concomita administration.			
Rifampin	↓ Nevirapine	Nevirapine and rifampin should not administered concomitantly because decreasin nevirapine plasma concentrations may redu the efficacy of the drug. Physicians needing treat patients co-infected with tuberculosis a using a nevirapine containing regimen may u rifabutin instead.			
Saquinavir	↓ Saquinavir	Appropriate doses for this combination are n established, but an increase in the dosage saquinavir may be required.			

		administered concomitantly because decreases in nevirapine plasma concentrations may reduce the efficacy of the drug. Physicians needing to treat patients co-infected with tuberculosis and using a nevirapine containing regimen may use rifabutin instead.
Saquinavir	↓ Saquinavir	Appropriate doses for this combination are not established, but an increase in the dosage of saquinavir may be required.
Potential Drug Interaction	is:	
Drug Class	Examples of Drugs	
Antiarrhythmics	Amiodarone, disopyramide, lidocaine	Plasma Concentrations May Be Decreased
Anticonvulsants	Carbamazepine, clonazepam, ethosuximide	Plasma Concentrations May Be Decreased
Antifungals	Itraconazole	Plasma Concentrations May Be Decreased
Calcium channel blockers Diltiazem, nifedipine, verapamil		Plasma Concentrations May Be Decreased
Cancer chemotherapy	Cyclophosphamide	Plasma Concentrations May Be Decreased
Ergot alkaloids	Ergotamine	Plasma Concentrations May Be Decreased
Immunosuppressants	Cyclosporin, tacrolimus, sirolimus	Plasma Concentrations May Be Decreased
Motility agents	Cisapride	Plasma Concentrations May Be Decreased
Opiate agonists	Fentanyl	Plasma Concentrations May Be Decreased
Antithrombotics	Warfarin	Plasma Concentrations May Be Increased. Potentia effect on anticoagulation. Monitoring of anticoagulation levels is recommended.

Teratogenic Effects, Pregnancy Category B. No observable teratogenicity was detected in reproductive studies performed in pregnant rats and rabbits. The

8.4 Pediatric Use

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 There are no adequate and well-controlled studies of nevirapine in pregnant women. The prevalence of birth defects after any trimester exposure to nevirapine is comparable to the prevalence observed in the general

Severe hepatic events, including fatalities, have been reported in pregnant women receiving chronic nevirapine therapy as part of combination treatment of HIV infection. Regardless of pregnancy status women with CD4 counts >250 cells/mm³ should not initiate nevirapine unless the benefit outweighs the risk. It is unclear if pregnancy augments the risk observed in non-pregnant women [see Boxed Warning]

Nevirapine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. 8.3 Nursing Mothers The Centers for Disease Control and Prevention recommend that HIV-infected mothers not breastfeed their infants to avoid risking postnatal transmission of HIV. Nevirapine is excreted in breast milk. Because of both the potential for HIV transmission and the potential for serious adverse reactions in nursing infants, mothers should be instructed not to breastfeed if they are receiving nevirapine.

The safety, pharmacokinetic profile, and virologic and immunologic responses of nevirapine have been evaluated in HIV-infected pediatric patients age 3 months to 18 years [see Adverse Reactions (6.2) and Clinical Studies (14.2)]. The safety and pharmacokinetic profile of nevirapine has been evaluated in HIV-infected pediatric patients age 15 days to < 3 months [see Adverse Reactions (6.2) and Clinical Studies (14.2)]. 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 Adverse Reactions (6.2) and Clinical Studies (14.2)]. 8.5 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. 8.6 Renal Impairment

In adult 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 adult patients with CrCL >20 mL/min. In adult patients undergoing chronic hemodialysis, an additional 200 mg dose following each dialysis treatment is indicated [see Dosage and Administration (2.3) and Clinical Pharmacology (12.3)]. No dosage recommendations are available for pediatric patients with renal impairment.

ents. The active ingredients. important medicines live longer with HI^v ections). Therefore, including if: most other redie tive ir tions i

the product ATTENTION PHARMACISTS: Detach "Medication Guide" and dispense wif mg Tablets for Oral Suspension **MEDICATION GUIDE**

your child or you get a liking with your doctor. and at regular checkups. ou should consult with rcumstances described Read this Medication Guide before your child or you start taking nevirapine and each time yo refill because there may be new information. This information does not take the place of talki You and your doctor should discuss nevirapine when your child or you start taking medicine and Your child or you should stay under a doctor's care while using nevirapine. Your child or you your doctor before making any changes to your medications, except in any of the special circubelow regarding rash or liver problems. Nevirapine 50

SO SO What is the most important information I should know about nevirapine?
Patients taking nevirapine may develop severe liver disease or skin reactions that carrisk of these reactions is greatest during the first 18 weeks of treatment, but these reactions a

ping liver damage. If you are a woman virapine unless you **cause deat** o can occur l <u>=</u>_5 e <u>S</u> ᄝᅙ higher CD4 counts when they begin nevirapine treatment have a greater chance of develo Women with CD4 counts higher than 250 cells/mm³ are at the greatest risk of these events. with CD4>250 cells/mm³ or a man with CD4>400 cells/mm³ you should not begin taking nevand your doctor have decided that the benefit of doing so outweighs the risk. Liver problems are can experience liver problems while taking nevirapine. However, women an

. Therefore, if and call your death. rapine В B or C have In rare cases liver problems have led to liver failure and can lead to a liver transplant or your child or you develop any of the following symptoms of liver problems stop taking nevi Patients starting nevirapine with abnormal liver tests and patients with hepatitis B or C roof developing further increases in liver tests after starting nevirapine and throughout therapy. doctor right away: by a rash.

 pain, ache, or sensitivity to touch on right side below the ribs pale stools (bowel movements) general ill feeling or "flu-like" symptoms • dark urine (tea colored)

shild's | uring tı

s liver function y treatment with Your doctor should check your child or you and do blood tests often to check your or your or during the first 18 weeks of therapy. Checks for liver problems should continue regularly d 9 **Skin Reactions** Skin rash is the most common side effect of nevirapine. Most rashes occur in the first

⋛ of treati a rash w B Therefore, if you deve small number of patients, rash can be serious and result in death. Therefore, if the following symptoms stop using nevirapine and call your doctor right away:

blisters

tment. In s

swelling of face mouth sores tiredness any of the symptoms of liver problems discussed above conjunctivitis (red or inflamed eyes, like "pink eye") general ill feeling or "flu-like" symptoms

If your doctor tells your child or you to stop treatment with nevirapine because your child or you the serious liver or skin reactions described above, never take neviranine anain ē. These are not all the side effects of nevirapine. See the section **"What are the possible side eff**i for more information. Tell your doctor if your child or you have any side effects from nevirapin serious liver or skin reactions described above, never take nevirapine again

ō

hibi What is nevirapine?

nevi oad rapii Nevirapine is a medicine used to treat Human Immunodeficiency Virus (HIV), the virus that cal Immune Deficiency Syndrome).

Nevirapine is a type of anti-HIV medicine called a "non-nucleoside reverse transcriptase in works by lowering the amount of HIV in the blood ("viral load"). Your child or you must take n anti-HIV medicines. When taken with other anti-HIV medicines, nevirapine can reduce viral knumber of CD4 cells ("T cells"). CD4 cells are a type of immune helper cell in the blood. Nevirthese effects in every patient.

Nevirapine does not cure HIV or AIDS, and it is not known if it will help you or your child I People taking nevirapine may still get infections common in people with HIV (opportunistic infis very important that you or your child stay under the care of a doctor.

Who should not take nevirapine?

Do not take nevirapine if you or your child are allergic to nevirapine or any of its ing ingredient is nevirapine. Your doctor or pharmacist can tell you or your child about the inac Do not restart nevirapine after you or your child recover from serious liver or skin reac when you or your child took nevirapine.

Do not take nevirapine if you or your child have severe liver problems. Do not take nevirapine if you or your child take certain medicines. (See "Can I or my child twith nevirapine?" for a list of medicines.) Do not take nevirapine if you or your child are not infected with HIV.

Before starting nevirapine, tell the doctor about all of your and your child's medical conditions,

You or your child have problems with liver or have had hepatitis What should I or my child tell the doctor before taking nevirapine?

Take the exact amount of nevirapine as the doctor prescribes. See the first section "What is information I should know about nevirapine?" You are pregnant, planning to become pregnant, or are breast feeding You or your child have skin conditions, such as a rash You or your child are undergoing dialysis How should I or my child take nevirapine?

Black

nausea (feeling sick to your stomach)

lack of appetite

yellowing of skin or whites of eyes

muscle or joint aches

patient

(12.3)].

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 is a non-nucleoside reverse transcriptase inhibitor (NNRTI) with activity against Human Immunodeficiency Virus Type 1 (HIV-1). Nevirapine 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 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 for oral suspension are for oral administration. The tablets also contain the following excipients: acesulfame potassium, art pineapple flavor, colloidal silicon dioxide, lactose monohydrate, magnesium stearate, microcrystalline cellulose, peppermint flavor, povidone, and sodium starch glycolate. The art pineapple flavor and peppermint flavor contains sulfur dioxide.

12 CLINICAL PHARMACOLOGY

Nevirapine is an antiviral drug [see Clinical Pharmacology (12.4)].

12.3 Pharmacokinetics

Adults

Absorption and Bioavailability
Nevirapine is readily absorbed (>90%) after oral administration in healthy volunteers and in adults with HIV-1
infection. Absolute bioavailability in healthy adults following single-dose administration was 93 ± 9% (mean ±
SD) for a 50 mg tablet. Peak plasma nevirapine concentrations of 2 ± 0.4 mcg/mL (7.5 µM) were attained by 4
hours following a single 200 mg dose. Following multiple doses, nevirapine peak concentrations appear to
increase linearly in the dose range of 200 to 400 mg/day. Steady state trough nevirapine concentrations of 4.5
± 1.9 mcg/mL (17 ± 7 µM), (n = 242) were attained at 400 mg/day. The absorption of nevirapine is not affected
by food, antacids or didanosine. Hence, nevirapine may be administered with or without food, antacids or
didanosine.

Nevirapine tablets for oral suspension, 50 mg (Aurobindo Pharma Ltd.) were bioequivalent to Viramune oral suspension, 50 mg/mL (Boehringer Ingelheim Pharmaceuticals, Inc.) under both fasted and fed conditions when evaluated in healthy adult male subjects. Nevirapine tablets for oral suspension, 50 mg may be taken with or without food. 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 $1.21 \pm 0.09 \, \text{L/kg}$, 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 (8.3)]. Nevirapine is about 60% bound to plasma proteins in the plasma concentration range of 1 to 10 mcg/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 are have a secondary related to the place of the cytochrome P450 (CYP) isozymes from the CYP3A and CYP2B6 families, although other isozymes primarily by cytochrome P450 (CYP) isozymes from the CYP3A and CYP2Bb families, athough other isozymes may have a secondary role. In a mass balance/excretion study in eight healthy male volunteers dosed to steady state with nevirapine 200 mg given twice daily followed by a single 50 mg dose of ¹⁴C-nevirapine, approximately 91.4 ± 10.5% of the radiolabeled dose was recovered, with urine (81.3 ± 11.1%) representing the primary route of excretion compared to feces (10.1 ± 1.5%). Greater than 80% of the radioactivity in urine was made up of glucuronide conjugates of hydroxylated metabolites. Thus cytochrome P450 metabolism, glucuronide conjugation, and urinary excretion of glucuronidated metabolites represent the primary route of nevirapine biotransformation and elimination in humans. Only a small fraction (<5%) of the radioactivity in urine (representing <3% of the total dose) was made up of parent compound; therefore, renal excretion plays a minor role in elimination of the pagent 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/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/day.

HIV serongative adults with mild (CrCL 50 to 79 mL/min; n=7), moderate (CrCL 30 to 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. The study 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 for adults *[see Dosage and Administration (2.3) and Use in Specific Populations (8.6)].* The pharmacokinetics of nevirapine have not been evaluated in pediatric patients with renal impairment. Hepatic Impairment

In a steady state study comparing 46 patients with mild (n=17; expansion of some portal areas; Ishak Score 1 In a steady state study comparing 4b patients with mild (n=17; expansion of some portal areas; shark 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 patients with hepatic fibrosis had nevirapine trough concentrations above 9,000 mcg/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 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. a median duration of therapy of 3.4 years. In a pharmacokinetic study where HIV-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 revirapine 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 (4), Warnings and Precautions (5.1), and Use in Specific Populations (8.7)].

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 Body Mass Index (BMI) had an influence on the clearance of nevirapine, the effect of gender cannot solely be explained by body size.

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 mcg/mL Black, 3.8 mcg/mL Hispanic, 4.3 mcg/mL Caucasian) with long-term nevirapine treatment at 400 mg/day. However, the pharmacokinetics of nevirapine have not been evaluated specifically for the effects of ethnicity.

Geriatric Patients

Antiretrovirals

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 inpatients 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 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.

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 two weeks followed by 7 mg/kg twice daily thereafter. Patients 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 patients received 150 mg/m² once daily for two weeks followed by 150 mg/m² twice daily thereafter (see Use in Specific Populations (8.4) and Adverse Reactions (6.2)]. Dosing of nevirapine at 150 mg/m² BID (after a two-week lead in of 150 mg/m² QD) produced geometric mean or mean trough nevirapine concentrations between 4 to 6 mcg/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 (2.1)*. 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 K_1 for the inhibition of CYP3A was 270 μ M, a concentration that is unlikely to be achieved in patients as the therapeutic range is <25 μ M. Therefore, nevirapine may have minimal inhibitory effect on other substrates of CYP3A.

Nevirapine does not appear to affect the plasma concentration 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 studies 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. To measure the full potential pharmacokinetic interaction effect following induction, patients on the concomitant drug at steady state were administered 28 days of nevirapine (200 mg QD for 14 days followed by 200 mg BID for 14 days) followed by a steady state reassessment of the concomitant drug.

= C_{min} below detectable level of the assay = Increase, J = Decrease, ⇔ = No Effect For information regarding clinical recommendations see *Drug Interactions (7)*. Pediatric subjects ranging in age from 6 months to 12 years Parallel group design; n for nevirapine+lopinavir/ritonavir, n for lopinavir/ritonavir alone

Because of the design of the drug interaction trials (addition of 28 days of nevirapine therapy to existing HIV 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 4 on nevirapine pharmacokinetics was not significant. No significant interaction was observed when tipranavir was co-administered with low dose ritonavir and nevirapine.

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

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 recent studies using human cord blood lymphocytes and human embryonic kidney 293 cells, EC₅₀ values (50% inhibitory concentration) ranged from 14 os 302 nM against laboratory and clinical Isolates of HIV-1. Nevirapine exhibited antiviral activity in cell culture against group M HIV-1 isolates from clades A, B, C, D, F, G, and H, and circulating recombinant forms (CRF) CRF01_AE, CRF02_AG and CRF12_BF (median EC₅₀ value of 63 nM). Nevirapine had no antiviral activity in cell culture against group 0 HIV-1 isolates or HIV-2 isolates. Nevirapine in combination with environment exhibited strong antagonistic anti-HIV-1 activity in cell culture and was additive to antagonistic with the protease inhibitor ritonavir or the fusion inhibitor enfouviridic. Nevirapine exhibited additive to synergistic anti-HIV-1 activity in combination with the protease inhibitors amprenavir, atazanavir, indinavir, lopinavir, nelfinavir, saquinavir and tipranavir, and the NRTIs abacavir, didanosine, emtricitabine, lamivudine, stavudine, tenofovir and zidovudine. 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.

selection included nevirapine in combination with several other NNRTIs.

Phenotypic and genotypic changes in HIV-1 isolates from treatment-naïve patients receiving either nevirapine (n=24) or nevirapine and ZDV (n=14) were monitored in Phase 1 and 2 trials over 1 to > 12 weeks. After 1 week of nevirapine monotherapy, isolates from 3/3 patients had decreased susceptibility to nevirapine in cell culture. One or more of the RT mutations resulting in amino acid substitutions K103N, V106A, V1081 and G190A were detected in HIV-1 isolates from some patients as early as 2 weeks after therapy initiation. By week eight of nevirapine monotherapy, 100% of the patients tested (n=24) had HIV-1 isolates with a >100-fold decrease in susceptibility to nevirapine in cell culture compared to baseline, and had one or more of the nevirapine-associated RT resistance mutations. Nineteen of these patients (80%) had isolates with Y181C mutations regardless of dose. Genotypic analysis of isolates from antiretroviral naïve patients experiencing virologic failure (n=71) receiving nevirapine once daily (n=25) or twice daily (n=46) in combination with lamivudine and stayduline (study 2NN) for nevirapine once daily (n=25) or twice daily (n=46) in combination with lamivudine and stavudine (study 2MN) for 48 weeks showed that isolates from 8/25 and 23/46 patients, respectively, contained one or of the following NNRTI resistance-associated substitutions: Y181C, K101E, G190A/S, K103N, V106A/M, V108I, Y188C/L, A98G, F227L and M230L.

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

in cell culture. NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term carcinogenicity studies in mice and rats were carried out with nevirapine. Mice were dosed with 0, 50, a75 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 were lower than that measured in humans at the 200 mg bid dose. The mechanism of the carcinogenic potential is unknown. 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. 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. 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

13.2 Animal Toxicology and/or Pharmacology Animal studies have shown that nevirapine is widely distributed to nearly all tissues and readily crosses the bloodbrain barrier.

14 CLINICAL STUDIES

14.1 Clinical Studies in Adults

Trial BI 1090, was a placebo-controlled, double-blind, randomized trial in 2249 HIV-1 infected patients with 200 CD4+ cells/mm³ at screening. Initiated in 1995, BI 1090 compared treatment with nevirapine + lamivudine + background therapy versus lamivudine + background therapy in NNRTI naïve patients. 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 patients (58%), two or more NRTIs in 771 (34%), and PIs and NRTIs in 169 (8%). The patients (median age 36 5 years, 70% Caucasian, 79% male) had advanced HIV infection, with a median baseline CD4+ cell count of 96 cells/mm³ and a baseline HIV RNA of 4.58 log₁₀ copies/mL (38,291 copies/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 1000 was originally designed as a clinical endpoint study. Prior to unblinding the trial, the primary endpoint was changed to proportion of patients with HIV RNA <50 copies/mL and not previously failed at 48 weeks. Treatment response and outcomes are shown in Table 6. 14.1 Clinical Studies in Adults

Outcome	Nevirapine (N=1121) %	Placebo (N=1128) %
Responders at 48 weeks: HIV RNA <50 copies/mL	18	1.6
Treatment Failure	82	98.4
Never suppressed viral load	44.6	66.4
Virologic failure after response	7.2	4.3
CDC category C event or death	9.6	11.2
Added antiretroviral therapy¹ while <50 copies/mL	5	0.9
Discontinued trial therapy due to AE	7	5.9
Discontinued trial <48 weeks ²	8.5	9.8

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 study population (64 cells/mm³ vs 22 cells/mm³, respectively), as well as for patients who entered the trial as treatment naïve or having received only ZDV (85 cells/mm³ vs 25 cells/mm³ vs 25 cells/mm² vs 25 cells/mm² vs 25 cells/mm² vs 26 cells/mm² vs 26 cells/mm² vs 26 cells/mm² vs 27 cells/m² vs 27 cells/m² vs 27 cells/m² vs 28 cells/m² vs 27 cells/m² vs 28 25 cells/mm³, respectively). At two years into the study, 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 patients with CD4+ cell counts of 200 to 600 cells/mm³ at baseline. BI 1046 compared treatment with nevirapine+ 200 mg daily for two weeks followed by 200 mg twice daily or placebo, zidovudine 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 patients had mean baseline HIV RNA of 4.4 II 0g₁₀ opies/ml (25,704 copies/ml), and mean baseline CD4+ cell count of 376 cells/mm³. The primary endpoint was the proportion of patients with HIV-RNA < 400 copies/ml. and not previously failed at 48 weeks. The virologic responder rates at 48 weeks were 45% for patients treated with nevirapine+zidovudine.

CD4+ cell counts in the nevirapine+ZDV+ddl group increased above baseline by a mean of 139 cells/mm³ at one year, significantly greater than the increase of 87 cells/mm³ in the ZDV+ddl patients. The nevirapine+ZDV group mean decreased by 6 cells/mm³ below baseline. 14.2 Clinical Studies in Pediatric Patients

The pediatric safety and efficacy of nevirapine was examined in 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 nevirapine oral suspension for 48 weeks. Patients were divided into 4 age groups (3 months to <2 years, 2 to <7 years, 7 to <12 years, and 12 to ≤16 years) and randomized to receive one of two nevirapine doses, determined by 2 different dosing methods [body surface area (150 mg/m²) and weight-based dosing (4 or 7 mg/kg)] in combination with zidovudine and lamivudine [see Adverse Reactions (6.2). 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 patients in the body surface area (BSA) dosing group and 57 patients in the weight-based (BW) dosing group.

Baseline demographics included: 49% male; 81% Black and 19% Caucasian; 4% had previous exposure to ARVs. Patients had a median baseline HIV RNA of 5.45 log₁₀ copies/mL and a median baseline CD4 cell count of 527 cells/mm³ (range 37 to 2279). One hundred and five (85%) completed the 48 weeks period while 18 (15%) discontinued prematurely. Of the patients who discontinued prematurely, 9 (7%) discontinued due to adverse reactions and 3 (2%) discontinued due to virologic failure. Overall the proportion of patients who achieved and maintained an HIV RNA <400 copies/mL at 48 weeks was 47% (58/123).

For dose recommendations for pediatric patients see Dosage and Administration (2.1). 16 HOW SUPPLIED/STORAGE AND HANDLING

 $\textbf{Nevirapine Tablets for Oral Suspension, 50 mg} \ \text{are white to off-white, round, flat face beveled edge, uncoated} \\$ tablets debossed with 'l' on one side and a break line separating '4' and '7' on other side. NDC 65862-498-30

Bottles of 180 NDC 65862-498-18

Store in a safe place out of the reach of children. 17 PATIENT COUNSELING INFORMATION See Medication Guide

The Medication Guide provides written information for the patient, and should be dispensed with each new prescription and refill.

17.1 Hepatotoxicity and Skin Reactions

Patients should be informed of the possibility of severe liver disease or skin reactions associated with nevirapine that may result in death. Patients developing signs or symptoms of liver disease or severe skin reactions should be instructed to discontinue nevirapine and seek medical attention immediately, including performance of laboratory monitoring. Symptoms of liver disease include fatigue, malaise, anorexi, anusea, jaundice, acholic stools, liver tenderness or hepatomegaly. Symptoms of severe skin or hypersensitivity reactions include

AUC

Table 5 Drug Interactions: Changes in Pharmacokinetic Parameters for Co-administered Drug in the Presence of Nevirapine (All interaction studies were conducted in HIV-1 positive patients) Co-administered % Change of Co-administered Drug Pharmacokinetic Parameters (90% Cl) Dose of Co-administered Dose Regimen of n

Alluleuviiais				AUG	Umax	Umin
Didanosine	100-150 mg BID	200 mg QD x 14 days; 200 mg BID x 14 days	18	\leftrightarrow	\leftrightarrow	§
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)
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 ^è	↓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)
Nelfinavir ^a	750 mg TID	200 mg QD x 14 days; 200 mg BID x 14 days	23	\Leftrightarrow	\Leftrightarrow	↓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	\leftrightarrow	\leftrightarrow	\Leftrightarrow
Saquinavir ^a	600 mg TID	200 mg QD x 14 days; 200 mg BID x 21 days	23	↓38 (↓47 to ↓11)	↓32 (↓44 to ↓6)	§
Stavudine	30-40 mg BID	200 mg QD x 14 days; 200 mg BID x 14 days	22	\Leftrightarrow	\Leftrightarrow	8
Zalcitabine	0.125-0.25 mg TID	200 mg QD x 14 days; 200 mg BID x 14 days	6	\Leftrightarrow	\Leftrightarrow	§
Zidovudine	100-200 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)	\Leftrightarrow
Ethinyl estradiol ^a and	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)	\Leftrightarrow	§
Norethindrone ^a	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	\leftrightarrow	↔	\Leftrightarrow
Fluconazole	200 mg QD	200 mg QD x 14 days; 200 mg BID x 14 days	19	\Leftrightarrow	↔	\Leftrightarrow
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 Patient Dosing	200 mg QD x 14 days; 200 mg BID ≥ 7 days	9	In a controlled pharmacokinet steady state nevirapine thera 3-fold resulting in symptoms in 7 of the 9 patients. Methado	ic study with 9 patients receiving py was added, the clearance of of withdrawal, requiring dose ad one did not have any effect on no	g chronic methadone to whor methadone was increased b justments in 10 mg segments evirapine 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)	\Leftrightarrow
Metabolite 25-0-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)	\leftrightarrow	§

Do not miss a dose of nevirapine, because this could make the virus harder to treat. If you or your child forget to take nevirapine, take the missed dose right away. If it is almost time for the next dose, do not take the missed dose. Instead, follow the regular dosing schedule by taking the next dose at its regular time. If you or your child stop taking nevirapine for more than 7 days, ask your doctor how much to take before you or your child start taking it again. You or your child may need to start with once-a-day dosing. If you suspect that you or your child have taken too much nevirapine, contact local poison control center or emergency room right away.

ET. DO NOT MIX

TABLE

that the entire

Place the tablet(s) in a container and add one teaspoonful (5 mL) of water per tablet. Swirl the container until tablet(s) breaks up into pieces small enough for the child to swallow. Drink the mixture immediately.

procedure for taking these tablets.

Use the following

first 14 days

Rinse the container with additional small amount of water and drink the contents to assure

dosage is taken. DO NOT CHEW NEVIRAPINE TABLET FOR ORAL SUSPENSION OR SWALLOW THE INTACT NEVIRAPINE TABLET FOR ORAL SUSPENSION WITH ANY LIQUID OTHER THAN WATER. You may take nevirapine with or without food.

4 tablets Once Daily 4 tablets Twice Daily

.5 tablets wice Daily

3 tablets Twice Daily

2.5 tablets Twice Daily

2 tablets Twice Daily

1.5 tablets Twice Daily

1 tablet Twice Daily

3.5 tablets Once Daily

2.5 tablets Once Daily 19-24 kgs

2 tablets Once Daily 13-18 kgs

1.5 tablets Once Daily

1 tablet Once Daily

9-12 kgs

Strength: 50 mg

Suspension

Lead-in Period (first 14 days) After

Nevirapine Tablets

>38 kgs

31-38 kgs

25-30 kgs 3 tablets Once Daily

er)

Number of Tablets by Weight Bands (administered QD \times 14 days, then BID thereaft

0

The dose of nevirapine for children is based on their size. Children's dosing starts with and then twice a day after that.
The usual dosing is as follows.

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 and skin reactions. Patients with signs and symptoms hepatitis should 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 (>250 cells/mm³ in women and +300 cells/mm³ in men) are at substantially higher risk for development of symptomatic hepatic events, often associated with rash. Patients should be advised 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 Boxed Warning and Warnings and Precautions (5.1)].

ALL [see Boxed Warning and Warnings and Precautions (5.1)].

The majority of rashes associated with nevirapine occur within the first 6 weeks of initiation of therapy. Patients should be instructed that if any rash occurs during the two-week lead-in period, the nevirapine dose should not be escalated 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 Boxed Warning and Warnings and Precautions (5.2)].

Patients should be informed to take nevirapine every day as prescribed. Patients should not 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. Patients should be advised to report to their doctor the use of any other medications.

Patients should be informed that nevirapine therapy has not been shown to reduce the risk of transmission of HIV-1 to others through sexual contact or blood contamination. The long-term effects of nevirapine are unknown at this time.

Nevirapine is not a cure for HIV-1 infection; patients may continue to experience illnesses associated with advanced HIV-1 infection, including opportunistic infections. Patients should be advised to remain under the care of a physician when using nevirapine.

Nevirapine may interact with some drugs, therefore, patients should be advised 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)]. Oral contraceptives and other hormonal methods of birth control should not be used as the sole method of

contraception in women taking nevirapine, since nevirapine may lower the plasma levels of these medications. Additionally, when oral contraceptives are used for hormonal regulation during nevirapine therapy, the therapeutic effect of the hormonal therapy should be monitored [see Drug Interactions (7)].

Nevirapine may decrease plasma concentrations of methadone by increasing its hepatic metabolism. Narcotic withdrawal syndrome has been reported in patients treated with nevirapine and methadone concomitantly. Methadone—maintained patients beginning nevirapine therapy should be monitored for evidence of withdrawal and methadone dose should be adjusted accordingly [see Drug Interactions (7)]. 17.6 Fat Redistribution Patients should be informed 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)].

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Manufactured by: **Aurobindo Pharma Limited** Hyderabad-500 072, India

Issued: February 2010

MEDICATION GUIDE Nevirapine 50 mg Tablets for Oral Suspension

Read this Medication Guide before your child or you start taking nevirapine and each time your child or you get a refill because there may be new information. This information does not take the place of talking with your doctor. You and your doctor should discuss nevirapine when your child or you start taking medicine and at regular checkups. Your child or you should stay under a doctor's care while using nevirapine. Your child or you should consult with your doctor before making any changes to your medications, except in any of the special circumstances described below regarding rash or liver problems.

What is the most important information I should know about nevirapine? Patients taking nevirapine may develop severe liver disease or skin reactions that can cause death. The risk of these reactions is greatest during the first 18 weeks of treatment, but these reactions also can occur later.

Any patient can experience liver problems while taking nevirapine. However, women and patients who have higher CD4 counts when they begin nevirapine treatment have a greater chance of developing liver damage. Women with CD4 counts higher than 250 cells/mm³ are at the greatest risk of these events. If you are a woman with CD4>250 cells/mm³ or a man with CD4>400 cells/mm³ you should not begin taking nevirapine unless you and your doctor have decided that the benefit of doing so outweighs the risk. Liver problems are often accompanied by a rash.

Patients starting nevirapine with abnormal liver tests and patients with hepatitis B or C have a greater chance of developing further increases in liver tests after starting nevirapine and throughout therapy.

In rare cases liver problems have led to liver failure and can lead to a liver transplant or death. Therefore, if your child or you develop any of the following symptoms of liver problems stop taking nevirapine and call your doctor right away: dark urine (tea colored)

 general ill feeling or "flu-like" symptoms
 tiredness pale stools (bowel movements)
 pain, ache, or sensitivity to touch
 on right side below the ribs nausea (feeling sick to your stomach) lack of appetite

vellowing of skin or whites of eyes Your doctor should check your child or you and do blood tests often to check your or your child's liver function during the first 18 weeks of therapy. Checks for liver problems should continue regularly during treatment with

Skin rash is the most common side effect of nevirapine. Most rashes occur in the first 6 weeks of treatment. In a small number of patients, rash can be serious and result in death. Therefore, if you develop a rash with any of the following symptoms stop using nevirapine and call your doctor right away:

 general ill feeling or "flu-like" symptoms
 fever blistersmouth sores

swelling of face conjunctivitis (red or inflamed eyes, like "nink eye") tiredness any of the symptoms of liver problems discussed above

If your doctor tells your child or you to stop treatment with nevirapine because your child or you have experienced the serious liver or skin reactions described above, never take nevirapine again. These are not all the side effects of nevirapine. See the section "What are the possible side effects of nevirapine?" for more information. Tell your doctor if your child or you have any side effects from neviraping

What is nevirapine? Nevirapine is a medicine used to treat Human Immunodeficiency Virus (HIV), the virus that causes AIDS (Acquired Immune Deficiency Syndrome). Nevirapine is a type of anti-HIV medicine called a "non-nucleoside reverse transcriptase inhibitor" (NNRTI). It

works by lowering the amount of HIV in the blood ("viral load"). Your child or you must take nevirapine with other anti-HIV medicines. When taken with other anti-HIV medicines, nevirapine can reduce viral load and increase the number of CD4 cells ("T cells"). CD4 cells are a type of immune helper cell in the blood. Nevirapine may not have these effects in every patient. Nevirapine does not cure HIV or AIDS, and it is not known if it will help you or your child live longer with HIV. People taking nevirapine may still get infections common in people with HIV (opportunistic infections). Therefore, it is very important that you or your child stay under the care of a doctor.

Who should not take nevirapine? Do not take nevirapine if you or your child are allergic to nevirapine or any of its ingredients. The active ingredient is nevirapine. Your doctor or pharmacist can tell you or your child about the inactive ingredients. Do not restart nevirapine after you or your child recover from serious liver or skin reactions that happened

when you or your child took nevirapine

Do not take nevirapine if you or your child have severe liver problems.

Do not take nevirapine if you or your child take certain medicines. (See "Can I or my child take other medicines with nevirapine?" for a list of medicines.)

Do not take nevirapine if you or your child are not infected with HIV. What should I or my child tell the doctor before taking nevirapine?

Fore starting nevirapine, tell the doctor about all of your and your child's medical conditions, including if:
 You or your child have problems with liver or have had hepatitis

You or your child are undergoing dialysis
You or your child have skin conditions, such as a rash

You are pregnant, planning to become pregnant, or are breast feeding How should I or my child take nevirapine?

Take the exact amount of nevirapine as the doctor prescribes. See the first section "What is the most important information I should know about nevirapine?"

The dose of nevirapine for children is based on their size. Children's dosing starts with once a day for 14 days and then twice a day after that.

The usual dosing is as follows. Number of Tablets by Weight Rands

Nevirapine Tablets for Oral	Tablet Strength:	(administered QD x 14 days, then BID thereafter)							
Suspension	50 mg	5-8 kgs	9-12 kgs	13-18 kgs	19-24 kgs	25-30 kgs	31-38 kgs	>38 kgs	
Lead-in Period (first 14 days)		1 tablet Once Daily	1.5 tablets Once Daily	2 tablets Once Daily	2.5 tablets Once Daily	3 tablets Once Daily	3.5 tablets Once Daily	4 tablets Once Daily	
After the first 14 days		1 tablet Twice Daily	1.5 tablets Twice Daily	2 tablets Twice Daily	2.5 tablets Twice Daily	3 tablets Twice Daily	3.5 tablets Twice Daily	4 tablets Twice Daily	

Place the tablet(s) in a container and add one teaspoonful (5 mL) of water per tablet Swirl the container until tablet(s) breaks up into pieces small enough for the child to swallow Drink the mixture immediately

Rinse the container with additional small amount of water and drink the contents to assure that the entire DO NOT CHEW NEVIRAPINE TABLET FOR ORAL SUSPENSION OR SWALLOW THE INTACT TABLET. DO NOT MIX NEVIRAPINE TABLET FOR ORAL SUSPENSION WITH ANY LIQUID OTHER THAN WATER.

You may take nevirapine with or without food. Do not miss a dose of nevirapine, because this could make the virus harder to treat. If you or your child forget to take nevirapine, take the missed dose right away. If it is almost time for the next dose, do not take the missed dose. Instead, follow the regular dosing schedule by taking the next dose at its regular time.

If you or your child stop taking nevirapine for more than 7 days, ask your doctor how much to take before you or your child start taking it again. You or your child may need to start with once-a-day dosing. If you suspect that you or your child have taken too much nevirapine, contact local poison control center or emergency room right away. Can I or my child take other medicines with nevirapine?

Nevirapine may change the effect of other medicines, and other medicines can change the effect of nevirapine. Tell your doctors and pharmacists about **al**l medicines you or your child take, including non-prescription medicines, vitamins and herbal supplements Do **not** take Nizoral® (ketoconazole) or Rifadin®/Rifamate®/Rifater® (rifampin) with nevirapine Tell your doctor if you or your child take Biaxin® (clarithromycin), Diflucan® (fluconazole), methadone, or Mycobutin® (rifabutin). Nevirapine may not be right for you or your child, or you or your child may need careful monitoring.

It is recommended that you or your child not take products containing St. John's wort, which can reduce the amount of nevirapine in the body.

If you take birth control pills, you should not rely on them to prevent pregnancy. They may not work if you take nevirapine. Talk with your doctor about other types of birth control that you can use. What should I or my child avoid while taking nevirapine? Avoid doing things that can spread HIV infection, as nevirapine does not stop you or your child from passing HIV infection to others. Do not share needles, other injection equipment or personal items that can have blood or body fluids on them, like toothbrushes and razor blades. Always practice safer sex by using a latex or polyurethane condom to lower the chance of sexual contact with semen, vaginal secretions, or blood.

The Centers for Disease Control and Prevention advises mothers with HIV not to breast feed so they will not pass HIV to the infant through their milk. Ask your doctor about the best way to feed your infant. What are the possible side effects of nevirapine? Nevirapine can cause serious liver damage and skin reactions that can cause death. Any patient can experience such side effects, but some patients are more at risk than others. See "What is the most important information I should know about nevirapine?" at the beginning of this Medication Guide.

Other common side effects of nevirapine include nausea, fatigue, fever, headache, vomiting, diarrhea, abdominal pain, and myalgia. This list of side effects is not complete. Ask your doctor or pharmacist for more information.

Changes in body fat have also been seen in some patients taking antiretroviral therapy. The changes may include increased amount of fat in the upper back and neck ("buffalo hump"), breast, and around the trunk. Loss of fat from the legs, arms, and face may also happen. The cause and long-term health effects of these conditions are not known at this time. How do I store nevirapine?

Store nevirapine at room temperature, between 59° to 86°F (15° to 30°C). Throw away nevirapine that is no longer needed or out-of-date. Keep neviragine and all medicines out of the reach of children

General information about nevirapine 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 to other people, even if they have the same condition you or your child have. It may harm them. This Medication Guide summarizes the most important information about nevirapine. If you would like more information, talk with your doctor. You can ask your pharmacist or doctor for information about nevirapine that

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

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Nevirapine can cause serious liver damage and skin reactions that can cause death. Any patient side effects, but some patients are more at risk than others. See "What is the most important is know about nevirapine?" at the beginning of this Medication Guide. Other common side effects of nevirapine include nausea, fatigue, fever, headache, vomiting, pain, and myagia. This list of side effects is not complete. Ask your doctor or pharmacist for m Changes in body fat have also been seen in some patients taking antiretroviral therapy. The cincreased amount of fat in the upper back and neck ("buffalo hump"), breast, and around the truthe legs, arms, and face may also happen. The cause and long-term health effects of these cond

child from passing HIV can have blood or body or polyurethane condom

It is reconnicional tital you of your cand not take products containing st. John s wort, will amount of nevirabine in the body.
If you take birth control pills, you should not rely on them to prevent pregnancy. They may n nevirapine. Talk with your doctor about other types of birth control that you can use.
What should I or my child avoid while taking nevirapine?
Avoid doing things that can spread HIV infection, as nevirapine does not stop you or your child infection to others. Do not share needles, other injection equipment or personal items that can fluids on them, like toothbrushes and razor blades. Always practice safer sex by using a latex or poto lower the chance of sexual contact with semen, vaginal secretions, or blood.
The Centers for Disease Control and Prevention advises mothers with HIV not to breast feed so HIV to the infant through their milk. Ask your doctor about the best way to feed your infant.
What are the possible side effects of nevirapine?

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It is recommended that you or your child not take products containing St. John's wort,

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apine. Izole), child n

Can I or my child take other medicines with nevirapine?
Nevirapine may change the effect of other medicines, and other medicines can change the effect of other medicines you or your child take, including non-pre vitamins and herbal supplements.
Do not take Nizoral[®] (ketoconazole) or Rifadin[®]/Rifamate[®]/Rifater[®] (rifampin) with nevirapi
Tell your doctor if you or your child take Biaxin[®] (clarithromycin), Diflucan[®] (fluconazo Mycobutin[®] (rifabutin). Nevirapine may not be right for you or your child, or your child

e effect of nevirapine, rescription medicines,

is written for health professionals

Biaxin is a trademark of Abbott Laboratories. Diflucan is a trademark of Pfizer, Inc. Mycobutin is a trademark of Pharmacia & Upjohn Company, Nizoral is a trademark of Janssen Pharmaceutica. Rifadin, Rifamate and Rifater are trademarks of Aventis Pharmaceuticals Inc. Issued: February 2010

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General information about nevirapine
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How do I store nevirapine?

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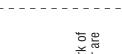
Aurobindo Pharma USA, Inc. 2400 Route 130 North Dayton, NJ 08810

Manufactured for:

Aurobindo Pharma Limited

Hyderabad-500 072, India

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MEDICATION GUIDE

Nevirapine 50 mg Tablets for Oral Suspension

Read this Medication Guide before your child or you start taking nevirapine and each time your child or you get a refill because there may be new information. This information does not take the place of talking with your doctor. You and your doctor should discuss nevirapine when your child or you start taking medicine and at regular checkups. Your child or you should stay under a doctor's care while using nevirapine. Your child or you should consult with your doctor before making any changes to your medications, except in any of the special circumstances described below regarding rash or liver problems.

What is the most important information I should know about nevirapine?

Patients taking nevirapine may develop severe liver disease or skin reactions that can cause death. The risk of these reactions is greatest during the first 18 weeks of treatment, but these reactions also can occur later.

Liver Reactions

Any patient can experience liver problems while taking nevirapine. However, women and patients who have higher CD4 counts when they begin nevirapine treatment have a greater chance of developing liver damage. Women with CD4 counts higher than 250 cells/mm³ are at the greatest risk of these events. If you are a woman with CD4>250 cells/mm³ or a man with CD4>400 cells/mm³ you should not begin taking nevirapine unless you and your doctor have decided that the benefit of doing so outweighs the risk. Liver problems are often accompanied by a rash.

Patients starting nevirapine with abnormal liver tests and patients with hepatitis B or C have a greater chance of developing further increases in liver tests after starting nevirapine and throughout therapy.

In rare cases liver problems have led to liver failure and can lead to a liver transplant or death. Therefore, if your child or you develop any of the following symptoms of liver problems stop taking nevirapine and call your doctor right away:

- general ill feeling or "flu-like" symptoms
 dark urine (tea colored)
- tiredness
- nausea (feeling sick to your stomach)
- lack of appetite
- vellowing of skin or whites of eves
- pale stools (bowel movements)
- pain, ache, or sensitivity to touch on right side below the ribs

blisters

tiredness

 mouth sores swelling of face

Your doctor should check your child or you and do blood tests often to check your or your child's liver function during the first 18 weeks of therapy. Checks for liver problems should continue regularly during treatment with nevirapine.

Skin Reactions

Skin rash is the most common side effect of nevirapine. Most rashes occur in the first 6 weeks of treatment. In a small number of patients, rash can be serious and result in death. Therefore, if you develop a rash with any of the following symptoms stop using nevirapine and call your doctor right away:

- general ill feeling or "flu-like" symptoms
- fever
- muscle or joint aches
- conjunctivitis (red or inflamed eyes, like "pink eye")
- any of the symptoms of liver problems discussed above

If your doctor tells your child or you to stop treatment with nevirapine because your child or you have experienced the serious liver or skin reactions described above, never take nevirapine again.

These are not all the side effects of nevirapine. See the section "What are the possible

side effects of nevirapine?" for more information. Tell your doctor if your child or you have any side effects from nevirapine.

What is nevirapine?

Nevirapine is a medicine used to treat Human Immunodeficiency Virus (HIV), the virus that causes AIDS (Acquired Immune Deficiency Syndrome).

Nevirapine is a type of anti-HIV medicine called a "non-nucleoside reverse transcriptase inhibitor" (NNRTI). It works by lowering the amount of HIV in the blood ("viral load"). Your child or you must take nevirapine with other anti-HIV medicines. When taken with other anti-HIV medicines, nevirapine can reduce viral load and increase the number of CD4 cells ("T cells"). CD4 cells are a type of immune helper cell in the blood. Nevirapine may not have these effects in every patient.

Nevirapine does not cure HIV or AIDS, and it is not known if it will help you or your child live longer with HIV. People taking nevirapine may still get infections common in people with HIV (opportunistic infections). Therefore, it is very important that you or your child stay under the care of a doctor.

Who should not take nevirapine?

- Do not take nevirapine if you or your child are allergic to nevirapine or any of its ingredients. The active ingredient is nevirapine. Your doctor or pharmacist can tell you or your child about the inactive ingredients.
- Do not restart nevirapine after you or your child recover from serious liver or skin reactions that happened when you or your child took nevirapine.
- Do not take nevirapine if you or your child have severe liver problems.
- Do not take nevirapine if you or your child take certain medicines. (See "Can I or my child take other medicines with nevirapine?" for a list of medicines.)
- Do not take nevirapine if you or your child are not infected with HIV.

What should I or my child tell the doctor before taking nevirapine?

Before starting nevirapine, tell the doctor about all of your and your child's medical conditions, including if:

- You or your child have problems with liver or have had hepatitis
- You or your child are undergoing dialysis
- You or your child have skin conditions, such as a rash
- You are pregnant, planning to become pregnant, or are breast feeding

How should I or my child take nevirapine?

- Take the exact amount of nevirapine as the doctor prescribes. See the first section "What is the most important information I should know about nevirapine?"
- The dose of nevirapine for children is based on their size. Children's dosing starts with once a day for 14 days and then twice a day after that. The usual dosing is as follows.

Nevirapine Tablets for Oral	Tablet Strength:	(administrated OD v 41 days than DID thereafter)						
Suspension	50 mg	5-8 kgs	9-12 kgs	13-18 kgs	19-24 kgs	25-30 kgs	31-38 kgs	>38 kgs
Lead-in Period (first 14 days)		1 tablet Once Daily	1.5 tablets Once Daily	2 tablets Once Daily	2.5 tablets Once Daily	3 tablets Once Daily	3.5 tablets Once Daily	4 tablets Once Daily
After the first 14 days		1 tablet Twice Daily	1.5 tablets Twice Daily	2 tablets Twice Daily	2.5 tablets Twice Daily	3 tablets Twice Daily	3.5 tablets Twice Daily	4 tablets Twice Daily

Use the following procedure for taking these tablets.

1. Place the tablet(s) in a container and add one teaspoonful (5 mL) of water per tablet.

- Swirl the container until tablet(s) breaks up into pieces small enough for the child to swallow.
- 3. Drink the mixture immediately.
- 4. Rinse the container with additional small amount of water and drink the contents to assure that the entire dosage is taken.

DO NOT CHEW NEVIRAPINE TABLET FOR ORAL SUSPENSION OR SWALLOW THE INTACT TABLET. DO NOT MIX NEVIRAPINE TABLET FOR ORAL SUSPENSION WITH ANY LIQUID OTHER THAN WATER.

- · You may take nevirapine with or without food.
- Do not miss a dose of nevirapine, because this could make the virus harder to treat. If you or your child forget to take nevirapine, take the missed dose right away. If it is almost time for the next dose, do not take the missed dose. Instead, follow the regular dosing schedule by taking the next dose at its regular time.
- If you or your child stop taking nevirapine for more than 7 days, ask your doctor how much to take before you or your child start taking it again. You or your child may need to start with once-a-day dosing.
- If you suspect that you or your child have taken too much nevirapine, contact local poison control center or emergency room right away.

Can I or my child take other medicines with nevirapine?

- Nevirapine may change the effect of other medicines, and other medicines can change the effect of nevirapine. Tell your doctors and pharmacists about all medicines you or your child take, including non-prescription medicines, vitamins and herbal supplements.
- Do not take Nizoral[®] (ketoconazole) or Rifadin[®]/Rifamate[®]/Rifater[®] (rifampin) with nevirapine.
- Tell your doctor if you or your child take Biaxin® (clarithromycin), Diflucan® (fluconazole), methadone, or Mycobutin® (rifabutin). Nevirapine may not be right for you or your child, or you or your child may need careful monitoring.
- It is recommended that you or your child not take products containing St. John's wort, which can reduce the amount of nevirapine in the body.
- If you take birth control pills, you should not rely on them to prevent pregnancy.
 They may not work if you take nevirapine. Talk with your doctor about other types of birth control that you can use.

What should I or my child avoid while taking nevirapine?

Avoid doing things that can spread HIV infection, as nevirapine does not stop you or your child from passing HIV infection to others. Do not share needles, other injection equipment or personal items that can have blood or body fluids on them, like toothbrushes and razor blades. Always practice safer sex by using a latex or polyurethane condom to lower the chance of sexual contact with semen, vaginal secretions, or blood.

The Centers for Disease Control and Prevention advises mothers with HIV not to breast feed so they will not pass HIV to the infant through their milk. Ask your doctor about the best way to feed your infant.

What are the possible side effects of nevirapine?

Nevirapine can cause serious liver damage and skin reactions that can cause death. Any patient can experience such side effects, but some patients are more at risk than others. See "What is the most important information I should know about nevirapine?" at the beginning of this Medication Guide.

Other common side effects of nevirapine include nausea, fatigue, fever, headache, vomiting, diarrhea, abdominal pain, and myalgia. This list of side effects is not complete. Ask your doctor or pharmacist for more information.

Changes in body fat have also been seen in some patients taking antiretroviral therapy. The changes may include increased amount of fat in the upper back and neck ("buffalo

hump"), breast, and around the trunk. Loss of fat from the legs, arms, and face may also happen. The cause and long-term health effects of these conditions are not known at this time.

How do I store nevirapine?

Store nevirapine at room temperature, between 59° to 86°F (15° to 30°C).

Throw away nevirapine that is no longer needed or out-of-date.

Keep nevirapine and all medicines out of the reach of children.

General information about nevirapine

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 to other people, even if they have the same condition you or your child have. It may harm them.

This Medication Guide summarizes the most important information about nevirapine. If you would like more information, talk with your doctor. You can ask your pharmacist or doctor for information about nevirapine that is written for health professionals.

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

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