

### 6.3 Post-Marketing Experience

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

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

*Gastrointestinal:* vomiting

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

*Hematology:* anemia, eosinophilia, neutropenia

*Investigations:* decreased serum phosphorus

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

*Neurologic:* paraesthesia

*Skin and Appendages:* allergic reactions including anaphylaxis, angioedema, bullous eruptions, ulcerative stomatitis and urticaria have all been reported. In addition, hypersensitivity syndrome and hypersensitivity reactions with rash associated with constitutional findings such as fever, blistering, oral lesions, conjunctivitis, facial edema, muscle or joint aches, general malaise, fatigue, or significant hepatic abnormalities, drug reaction with eosinophilia and systemic symptoms (DRESS) [see *Warnings and Precautions (5.1)*] plus one or more of the following: hepatitis, eosinophilia, granulocytopenia, lymphadenopathy, and/or renal dysfunction have been reported.

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

### 7 DRUG INTERACTIONS

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

The specific pharmacokinetic changes that occur with co-administration of nevirapine and other drugs are listed in *Clinical Pharmacology*, Table 5. Clinical comments about possible dosage modifications based on established drug interactions are listed in Table 4. The data in Tables 4 and 5 are based on the results of drug interaction trials conducted in HIV-1 seropositive subjects unless otherwise indicated. In addition to established drug interactions, there may be potential pharmacokinetic interactions between nevirapine and other drug classes that are metabolized by the cytochrome P450 system. These potential drug interactions are also listed in Table 4. Although specific drug interaction trials in HIV-1 seropositive subjects have not been conducted for some classes of drugs listed in Table 4, additional clinical monitoring may be warranted when co-administering these drugs.

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

**Table 4 Established and Potential Drug Interactions: Use With Caution, Alteration in Dose or Regimen May Be Needed Due to Drug Interaction**  
Established Drug Interactions: See *Clinical Pharmacology (12.3)*, Table 5 for Magnitude of Interaction.

Drug Name	Effect on Concentration of Nevirapine or Concomitant Drug	Clinical Comment
<b>HIV Antiviral Agents: Protease Inhibitors (PIs)</b>		
Atazanavir/Ritonavir*	↓ Atazanavir ↑ Nevirapine	Do not co-administer nevirapine with atazanavir because nevirapine substantially decreases atazanavir exposure and there is a potential risk for nevirapine-associated toxicity due to increased nevirapine exposures.
Fosamprenavir*	↓ Amprenavir ↑ Nevirapine	Co-administration of nevirapine and fosamprenavir without ritonavir is not recommended.
Fosamprenavir/Ritonavir*	↓ Amprenavir ↑ Nevirapine	No dosing adjustments are required when nevirapine is co-administered with 700/100 mg of fosamprenavir/ritonavir twice daily. The combination of nevirapine administered with fosamprenavir/ritonavir once daily has not been studied.
Indinavir*	↓ Indinavir	The appropriate doses of this combination of indinavir and nevirapine with respect to efficacy and safety have not been established.
Lopinavir/Ritonavir*	↓ Lopinavir	Dosing in adult patients:  A dose adjustment of lopinavir/ritonavir to 500/125 mg tablets twice daily or 533/133 mg (6.5 mL) oral solution twice daily is recommended when used in combination with nevirapine. Neither lopinavir/ritonavir tablets nor oral solution should be administered once daily in combination with nevirapine.  Dosing in pediatric patients:

		Please refer to the Kaletra <sup>®</sup> prescribing information for dosing recommendations based on body surface area and body weight. Neither lopinavir/ritonavir tablets nor oral solution should be administered once daily in combination with nevirapine.
Nelfinavir*	↓Nelfinavir M8 Metabolite ↓Nelfinavir C <sub>min</sub>	The appropriate doses of the combination of nevirapine and nelfinavir with respect to safety and efficacy have not been established.
Saquinavir/ritonavir	The interaction between nevirapine and saquinavir/ritonavir has not been evaluated	The appropriate doses of the combination of nevirapine and saquinavir/ritonavir with respect to safety and efficacy have not been established.
<b>HIV Antiviral Agents: Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)</b>		
Efavirenz*	↓ Efavirenz	The appropriate doses of these combinations with respect to safety and efficacy have not been established.
Delavirdine Etravirine Rilpivirine		Plasma concentrations may be altered. Nevirapine should not be coadministered with another NNRTI as this combination has not been shown to be beneficial.
<b>Hepatitis C Antiviral Agents</b>		
Boceprevir	Plasma concentrations of boceprevir may be decreased due to induction of CYP3A4/5 by nevirapine.	Nevirapine and boceprevir should not be coadministered because decreases in boceprevir plasma concentrations may result in a reduction in efficacy.
Telaprevir	Plasma concentrations of telaprevir may be decreased due to induction of CYP3A4 by nevirapine and plasma concentrations of nevirapine may be increased due to inhibition of CYP3A4 by telaprevir.	Nevirapine and telaprevir should not be coadministered because changes in plasma concentrations of nevirapine, telaprevir, or both may result in a reduction in telaprevir efficacy or an increase in nevirapine-associated adverse events.
<b>Other Agents</b>		
Analgesics: Methadone*	↓ Methadone	Methadone levels were decreased; increased dosages may be required to prevent symptoms of opiate withdrawal. Methadone-maintained patients beginning nevirapine therapy should be monitored for evidence of withdrawal and methadone dose should be adjusted accordingly.
Antiarrhythmics: Amiodarone, disopyramide, lidocaine	Plasma concentrations may be decreased.	Appropriate doses for this combination have not been established.
Antibiotics: Clarithromycin*	↓ Clarithromycin ↑ 14-OH clarithromycin	Clarithromycin exposure was significantly decreased by nevirapine; however, 14-OH metabolite concentrations were increased. Because clarithromycin active metabolite has reduced activity against <i>Mycobacterium avium-intracellulare complex</i> , overall activity against this pathogen may be altered. Alternatives to clarithromycin, such as azithromycin, should be considered.
Rifabutin*	↑Rifabutin	Rifabutin and its metabolite concentrations were moderately increased. Due to high intersubject variability, however, some patients may experience large increases in rifabutin exposure and may be at higher risk for rifabutin toxicity. Therefore, caution should be used in concomitant administration.
Rifampin*	↓ Nevirapine	Nevirapine and rifampin should not be administered concomitantly because decreases in nevirapine plasma concentrations may reduce the efficacy of the drug. Physicians needing to treat patients co-infected with tuberculosis and using a nevirapine-containing regimen may use rifabutin instead.

<b>Anticonvulsants:</b> Carbamazepine, clonazepam, ethosuximide	Plasma concentrations of nevirapine and the anticonvulsant may be decreased.	Use with caution and monitor virologic response and levels of anticonvulsants.
<b>Antifungals:</b> Fluconazole*	↑Nevirapine	Because of the risk of increased exposure to nevirapine, caution should be used in concomitant administration, and patients should be monitored closely for nevirapine-associated adverse events.
Ketoconazole*	↓ Ketoconazole	Nevirapine and ketoconazole should not be administered concomitantly because decreases in ketoconazole plasma concentrations may reduce the efficacy of the drug.
Itraconazole	↓ Itraconazole	Nevirapine and itraconazole should not be administered concomitantly due to potential decreases in itraconazole plasma concentrations that may reduce efficacy of the drug.
<b>Antithrombotics:</b> Warfarin	Plasma concentrations may be increased.	Potential effect on anticoagulation. Monitoring of anticoagulation levels is recommended.
<b>Calcium channel blockers:</b> Diltiazem, nifedipine, verapamil	Plasma concentrations may be decreased.	Appropriate doses for these combinations have not been established.
<b>Cancer chemotherapy:</b> Cyclophosphamide	Plasma concentrations may be decreased.	Appropriate doses for this combination have not been established.
<b>Ergot alkaloids:</b> Ergotamine	Plasma concentrations may be decreased.	Appropriate doses for this combination have not been established.
<b>Immunosuppressants:</b> Cyclosporine, tacrolimus, sirolimus	Plasma concentrations may be decreased.	Appropriate doses for these combinations have not been established.
<b>Motility agents:</b> Cisapride	Plasma concentrations may be decreased.	Appropriate doses for this combination have not been established.
<b>Opiate agonists:</b> Fentanyl	Plasma concentrations may be decreased.	Appropriate doses for this combination have not been established.
<b>Oral contraceptives:</b> Ethinyl estradiol and Norethindrone*	↓ Ethinyl estradiol ↓ Norethindrone	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. An alternative or additional method of contraception is recommended.

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

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

#### *Pregnancy Category B*

There are no adequate and well-controlled trials of VIRAMUNE in pregnant women. The Antiretroviral Pregnancy Registry, which has been surveying pregnancy outcomes since January 1989, has not found an increased risk of birth defects following first trimester exposures to nevirapine. The prevalence of birth defects after any trimester exposure to nevirapine is comparable to the prevalence observed in the general population.

Severe hepatic events, including fatalities, have been reported in pregnant women receiving chronic VIRAMUNE therapy as part of combination treatment of HIV-1 infection. Regardless of pregnancy status, women with CD4<sup>+</sup> cell counts greater than 250 cells/mm<sup>3</sup> should not initiate VIRAMUNE unless the benefit outweighs the risk. It is unclear if pregnancy augments the risk observed in non-pregnant women [see *Boxed Warning*].

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

### Antiretroviral Pregnancy Registry

To monitor maternal-fetal outcomes of pregnant women exposed to VIRAMUNE, an Antiretroviral Pregnancy Registry has been established. Physicians are encouraged to register patients by calling (800) 258-4263.

### Animal Data

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

### 8.3 Nursing Mothers

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

### 8.4 Pediatric Use

The safety, pharmacokinetic profile, and virologic and immunologic responses of VIRAMUNE have been evaluated in HIV-1 infected pediatric subjects age 3 months to 18 years [see *Adverse Reactions (6.2)* and *Clinical Studies (14.2)*]. The safety and pharmacokinetic profile of VIRAMUNE has been evaluated in HIV-1 infected pediatric subjects age 15 days to less than 3 months [see *Adverse Reactions (6.2)* and *Clinical Studies (14.2)*].

The most frequently reported adverse events related to VIRAMUNE in pediatric subjects were similar to those observed in adults, with the exception of granulocytopenia, which was more commonly observed in children receiving both zidovudine and VIRAMUNE [see *Adverse Reactions (6.2)* and *Clinical Studies (14.2)*].

### 8.5 Geriatric Use

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

### 8.6 Renal Impairment

In subjects with renal impairment (mild, moderate or severe), there were no significant changes in the pharmacokinetics of nevirapine. Nevirapine is extensively metabolized by the liver and nevirapine metabolites are extensively eliminated by the kidney. Nevirapine metabolites may accumulate in patients receiving dialysis; however, the clinical significance of this accumulation is not known. No adjustment in nevirapine dosing is required in patients with CrCL greater than or equal to 20 mL per min. The pharmacokinetics of nevirapine have not been evaluated in patients with CrCL less than 20 mL per min. In patients undergoing chronic hemodialysis, an additional 200 mg dose following each dialysis treatment is indicated [see *Dosage and Administration (2.4)* and *Clinical Pharmacology (12.3)*].

### 8.7 Hepatic Impairment

Because increased nevirapine levels and nevirapine accumulation may be observed in patients with serious liver disease, do not administer VIRAMUNE to patients with moderate or severe (Child-Pugh Class B or C, respectively) hepatic impairment [see *Contraindications (4.1)*, *Warnings and Precautions (5.1)*, and *Clinical Pharmacology (12.3)*].

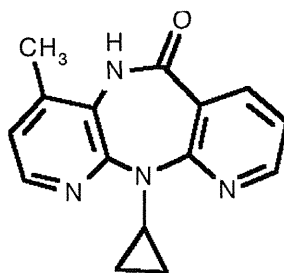
### 10 OVERDOSAGE

There is no known antidote for VIRAMUNE overdose. Cases of VIRAMUNE 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 VIRAMUNE.

### 11 DESCRIPTION

VIRAMUNE is the brand name for nevirapine, a non-nucleoside reverse transcriptase inhibitor (NNRTI) with activity against Human Immunodeficiency Virus Type 1 (HIV-1). Nevirapine is structurally a member of the dipyrindiazepinone 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:



VIRAMUNE Tablets are for oral administration. Each tablet contains 200 mg of nevirapine and the inactive ingredients microcrystalline cellulose, lactose monohydrate, povidone, sodium starch glycolate, colloidal silicon dioxide, and magnesium stearate.

VIRAMUNE Oral Suspension is for oral administration. Each 5 mL of VIRAMUNE suspension contains 50 mg of nevirapine (as nevirapine hemihydrate). The suspension also contains the following excipients: carbomer 934P, methylparaben, propylparaben, sorbitol, sucrose, polysorbate 80, sodium hydroxide and purified water.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

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

### 12.3 Pharmacokinetics

#### Adults

##### Absorption and Bioavailability

Nevirapine is readily absorbed (greater than 90%) after oral administration in healthy volunteers and in adults with HIV-1 infection. Absolute bioavailability in 12 healthy adults following single-dose administration was  $93 \pm 9\%$  (mean  $\pm$  SD) for a 50 mg tablet and  $91 \pm 8\%$  for an oral solution. Peak plasma nevirapine concentrations of  $2 \pm 0.4$  mcg/mL (7.5 micromolar) were attained by 4 hours following a single 200 mg dose. Following multiple doses, nevirapine peak concentrations appear to increase linearly in the dose range of 200 to 400 mg/day. Steady-state trough nevirapine concentrations of  $4.5 \pm 1.9$  mcg/mL ( $17 \pm 7$  micromolar), (n=242) were attained at 400 mg per day. Nevirapine tablets and suspension have been shown to be comparably bioavailable and interchangeable at doses up to 200 mg. When VIRAMUNE (200 mg) was administered to 24 healthy adults (12 female, 12 male), with either a high-fat breakfast (857 kcal, 50 g fat, 53% of calories from fat) or antacid (Maalox<sup>®</sup> 30 mL), the extent of nevirapine absorption (AUC) was comparable to that observed under fasting conditions. In a separate trial in HIV-1 infected subjects (n=6), nevirapine steady-state systemic exposure (AUC<sub>0-24</sub>) was not significantly altered by didanosine, which is formulated with an alkaline buffering agent. VIRAMUNE may be administered with or without food, antacid or didanosine.

##### Distribution

Nevirapine is highly lipophilic and is essentially nonionized at physiologic pH. Following intravenous administration to healthy adults, the apparent volume of distribution (V<sub>ds</sub>) of nevirapine was  $1.21 \pm 0.09$  L/kg, suggesting that nevirapine is widely distributed in humans. Nevirapine readily crosses the placenta and is also found in breast milk [see Use in Specific Populations (8.3)]. Nevirapine is about 60% bound to plasma proteins in the plasma concentration range of 1-10 mcg per 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* trials in humans and *in vitro* studies with human liver microsomes have shown that nevirapine is extensively biotransformed via cytochrome P450 (oxidative) metabolism to several hydroxylated metabolites. *In vitro* studies with human liver microsomes suggest that oxidative metabolism of nevirapine is mediated primarily by cytochrome P450 (CYP) isozymes from the CYP3A and CYP2B6 families, although other isozymes may have a secondary role. In a mass balance/excretion trial in eight healthy male volunteers dosed to steady state with nevirapine 200 mg given twice daily followed by a single 50 mg dose of <sup>14</sup>C-nevirapine, approximately 91.4  $\pm$  10.5% of the radiolabeled dose was recovered, with urine ( $81.3 \pm 11.1\%$ ) representing the primary route of excretion compared to feces ( $10.1 \pm 1.5\%$ ). Greater than 80% of the radioactivity in urine was made up of glucuronide conjugates of hydroxylated metabolites. Thus cytochrome P450 metabolism, glucuronide conjugation, and urinary excretion of glucuronidated metabolites represent the primary route of nevirapine biotransformation and elimination in humans. Only a small fraction (less than 5%) of the radioactivity in urine (representing less than 3% of the total dose) was made up of parent compound; therefore, renal excretion plays a minor role in elimination of the parent compound.

Nevirapine is an inducer of hepatic cytochrome P450 (CYP) metabolic enzymes 3A and 2B6. Nevirapine induces CYP3A and CYP2B6 by approximately 20-25%, 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 200-400 mg per day. Autoinduction also results in a corresponding decrease in the terminal phase half-life of nevirapine in plasma, from approximately 45 hours (single dose) to approximately 25-30 hours following multiple dosing with 200-400 mg per day.

##### Specific Populations

###### Renal Impairment

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

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

###### Hepatic Impairment

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

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

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

##### Gender

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

### Race

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

Black subjects (n=80/group) in Trial 1100.1486 showed approximately 30% to 35% higher trough concentrations than Caucasian subjects (250-325 subjects/group) in both immediate-release VIRAMUNE and VIRAMUNE XR treatment groups over 96 weeks of treatment at 400 mg per day.

### Geriatric Subjects

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

### Pediatric Subjects

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

BI Trial 1100.1368 studied the safety, efficacy, and pharmacokinetics of a weight-based and a body surface area (BSA)-based dosing regimen of nevirapine. In the weight-based regimen, pediatric subjects up to 8 years of age received a dose of 4 mg/kg once daily for two weeks followed by 7 mg per kg twice daily thereafter. Subjects 8 years and older were dosed 4 mg/kg once daily for two weeks followed by 4 mg/kg twice daily thereafter. In the BSA regimen, all pediatric subjects received 150 mg/m<sup>2</sup> once daily for two weeks followed by 150 mg/m<sup>2</sup> twice daily thereafter [see Use in Specific Populations (8.4) and Adverse Reactions (6.2)]. Dosing of nevirapine at 150 mg/m<sup>2</sup> BID (after a two-week lead-in of 150 mg/m<sup>2</sup> QD) produced geometric mean or mean trough nevirapine concentrations between 4-6 mcg per mL (as targeted from adult data). In addition, the observed trough nevirapine concentrations were comparable between the two dosing regimens studied (BSA- and weight-based methods).

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

### Drug Interactions [see Drug Interactions (7)]

Nevirapine induces hepatic cytochrome P450 metabolic isoenzymes 3A and 2B6. Co-administration of VIRAMUNE 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  $K_i$  for the inhibition of CYP3A was 270 micromolar, a concentration that is unlikely to be achieved in patients as the therapeutic range is less than 25 micromolar. Therefore, nevirapine may have minimal inhibitory effect on other substrates of CYP3A.

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

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

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

Co-administered Drug	Dose of Co-administered Drug	Dose Regimen of VIRAMUNE	n	% Change of Co-administered Drug Pharmacokinetic Parameters (90% CI)		
				AUC	$C_{\max}$	$C_{\min}$
<b>Antiretrovirals</b>						
Atazanavir/Ritonavir <sup>a, d</sup>	300/100 mg QD day 4–13, then 400/100 mg QD, day 14–23	200 mg BID day 1-23. Subjects were treated with nevirapine prior to trial entry.	23	<u>Atazanavir</u> <u>300/100 mg</u>	<u>Atazanavir</u> <u>300/100 mg</u>	<u>Atazanavir</u> <u>300/100 mg</u>
				↓42 (↓52 to ↓29)	↓28 (↓40 to ↓14)	↓72 (↓80 to ↓60)
				<u>Atazanavir</u> <u>400/100 mg</u>	<u>Atazanavir</u> <u>400/100 mg</u>	<u>Atazanavir</u> <u>400/100 mg</u>
				↓19 (↓35 to ↑2)	↑2 (↓15 to ↑24)	↓59 (↓73 to ↓40)
Darunavir/Ritonavir <sup>c</sup>	400/100 mg BID	200 mg BID	8	↑24 (↓3 to ↑57)	↑40 (↑14 to ↑73)	↑2 (↓21 to ↑32)
Didanosine	100-150 mg BID	200 mg QD x 14 days; 200 mg BID x 14 days	18	↔	↔	§

Efavirenz <sup>a</sup>	600 mg QD	200 mg QD x 14 days; 400 mg QD x 14 days	17	↓28 (↓34 to ↓14)	↓12 (↓23 to ↑1)	↓32 (↓35 to ↓19)
Fosamprenavir	1400 mg BID	200 mg BID. Subjects were treated with nevirapine prior to trial entry.	17	↓33 (↓45 to ↓20)	↓25 (↓37 to ↓10)	↓35 (↓50 to ↓15)
Fosamprenavir/Ritonavir	700/100 mg BID	200 mg BID. Subjects were treated with nevirapine prior to trial entry	17	↓11 (↓23 to ↑3)	⇔	↓19 (↓32 to ↓4)
Indinavir <sup>a</sup>	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 <sup>a,b</sup>	300/75 mg/m <sup>2</sup> (lopinavir/ ritonavir) <sup>b</sup>	7 mg/kg or 4 mg/kg QD x 2 weeks; BID x 1 week	12, 15 <sup>c</sup>	↓22 (↓44 to ↑9)	↓14 (↓36 to ↑16)	↓55 (↓75 to ↓19)
Lopinavir <sup>a</sup>	400/100 mg BID (lopinavir/ ritonavir)	200 mg QD x 14 days; 200 mg BID >1 year	22, 19 <sup>c</sup>	↓27 (↓47 to ↓2)	↓19 (↓38 to ↑5)	↓51 (↓72 to ↓26)
Maraviroc <sup>f</sup>	300 mg SD	200 mg BID	8	↑1 (↓35 to ↑55)	↑54 (↓6 to ↑151)	⇔
Nelfinavir <sup>a</sup>	750 mg TID	200 mg QD x 14 days; 200 mg BID x 14 days	23	⇔	⇔	↓32 (↓50 to ↑5)
Nelfinavir-M8 metabolite				↓62 (↓70 to ↓53)	↓59 (↓68 to ↓48)	↓66 (↓74 to ↓55)
Ritonavir	600 mg BID	200 mg QD x 14 days; 200 mg BID x 14 days	18	⇔	⇔	⇔
Stavudine	30-40 mg BID	200 mg QD x 14 days; 200 mg BID x 14 days	22	⇔	⇔	§
Zalcitabine	0.125-0.25 mg TID	200 mg QD x 14 days; 200 mg BID x 14 days	6	⇔	⇔	§
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)	§
<b>Other Medications</b>				<b>AUC</b>	<b>C<sub>max</sub></b>	<b>C<sub>min</sub></b>
Clarithromycin <sup>a</sup>	500 mg BID	200 mg QD x 14 days; 200 mg BID x 14 days	15	↓31 (↓38 to ↓24)	↓23 (↓31 to ↓14)	↓56 (↓70 to ↓36)
Metabolite 14-OH-clarithromycin				↑42 (↑16 to ↑73)	↑47 (↑21 to ↑80)	⇔
Ethinyl estradiol <sup>a</sup> and Norethindrone <sup>a</sup>	0.035 mg (as Ortho- Novum® 1/35)  1 mg (as Ortho- Novum® 1/35)	200 mg QD x 14 days; 200 mg BID x 14 days	10	↓20 (↓33 to ↓3)	⇔	§
				↓19 (↓30 to ↓7)	↓16 (↓27 to ↓3)	§
Depomedroxy- progesterone acetate	150 mg every 3 months	200 mg QD x 14 days; 200 mg BID x 14 days	32	⇔	⇔	⇔
Fluconazole	200 mg QD	200 mg QD x 14 days; 200 mg BID x 14 days	19	⇔	⇔	⇔
Ketoconazole <sup>a</sup>	400 mg QD	200 mg QD x 14 days; 200 mg	21	↓72	↓44	§

		BID x 14 days		(↓80 to ↓60)	(↓58 to ↓27)	
Methadone <sup>a</sup>	Individual Subject Dosing	200 mg QD x 14 days; 200 mg BID ≥7 days	9	In a controlled pharmacokinetic trial with 9 subjects receiving chronic methadone to whom steady-state nevirapine therapy was added, the clearance of methadone was increased by 3-fold, resulting in symptoms of withdrawal, requiring dose adjustments in 10 mg segments, in 7 of the 9 subjects. Methadone did not have any effect on nevirapine clearance.		
Rifabutin <sup>a</sup>	150 or 300 mg QD	200 mg QD x 14 days; 200 mg BID x 14 days	19	↑17 (↓2 to ↑40)	↑28 (↑9 to ↑51)	↔
Metabolite 25-O-desacetyl-rifabutin				↑24 (↓16 to ↑84)	↑29 (↓2 to ↑68)	↑22 (↓14 to ↑74)
Rifampin <sup>a</sup>	600 mg QD	200 mg QD x 14 days; 200 mg BID x 14 days	14	↑11 (↓4 to ↑28)	↔	§

§ = C<sub>min</sub> below detectable level of the assay

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

<sup>a</sup> For information regarding clinical recommendations, see *Drug Interactions (7)*.

<sup>b</sup> Pediatric subjects ranging in age from 6 months to 12 years

<sup>c</sup> Parallel group design; n for VIRAMUNE+lopinavir/ritonavir, n for lopinavir/ritonavir alone.

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

<sup>e</sup> Based on between-trial comparison.

<sup>f</sup> Based on historical controls.

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

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

## 12.4 Microbiology

### Mechanism of Action

Nevirapine is a non-nucleoside reverse transcriptase inhibitor (NNRTI) of HIV-1. Nevirapine binds directly to reverse transcriptase (RT) and blocks the RNA-dependent and DNA-dependent DNA polymerase activities by causing a disruption of the enzyme's catalytic site. The activity of nevirapine does not compete with template or nucleoside triphosphates. HIV-2 RT and eukaryotic DNA polymerases (such as human DNA polymerases  $\alpha$ ,  $\beta$ ,  $\gamma$ , or  $\delta$ ) are not inhibited by nevirapine.

### Antiviral Activity

The antiviral activity of nevirapine has been measured in a variety of cell lines including peripheral blood mononuclear cells, monocyte-derived macrophages, and lymphoblastoid cell lines. In an assay using human embryonic kidney 293 cells, the median EC<sub>50</sub> value (50% inhibitory concentration) of nevirapine was 90 nM against a panel of 2923 isolates of HIV-1 that were primarily (93%) clade B clinical isolates from the United States. The 99<sup>th</sup> percentile EC<sub>50</sub> value was 470 nM in this trial. The median EC<sub>50</sub> value was 63 nM (range 14-302 nM, n=29) against clinical isolates of HIV-1 clades A, B, C, D, F, G, and H, and circulating recombinant forms CRF01\_AE, CRF02\_AG and CRF12\_BF. Nevirapine had no antiviral activity in cell culture against group O HIV-1 isolates (n=3) or HIV-2 isolates (n=3) replicating in cord blood mononuclear cells. Nevirapine in combination with efavirenz exhibited strong antagonistic anti-HIV-1 activity in cell culture and was additive to antagonistic with the protease inhibitor ritonavir or the fusion inhibitor enfuvirtide. 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.

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

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

For trial 1100.1486, genotypic analysis was performed for baseline and on-therapy isolates from 23 and 34 subjects who experienced virologic failure in the VIRAMUNE XR and immediate-release VIRAMUNE treatment group, respectively. Nevirapine resistance-associated substitutions developed in the on-therapy isolates of 78% (18/23) of the subjects who had virologic failures in the VIRAMUNE XR treatment group and 88% (30/34) of the subjects in the immediate-release



VIRAMUNE treatment group, respectively. The Y181C nevirapine resistance-associated substitution was found alone or in combination with other nevirapine resistance-associated substitutions (K101E, K103N, V106A, V108I, V179D/E/I, Y188 C/F/H/L/N, G190A, P225H, F227L, M230L) in isolates from 14 subjects failing VIRAMUNE XR treatment and 25 subjects failing immediate-release VIRAMUNE treatment. On-therapy isolates from 1 subject in VIRAMUNE XR treatment group developed a novel amino acid substitution Y181I and isolates from another subject in the immediate-release VIRAMUNE treatment group developed a novel amino acid substitution Y188N. Phenotypic analysis showed that Y188N and Y181I substitutions conferred 103- and 22-fold reductions in susceptibility to nevirapine, respectively.

#### Cross-resistance

Rapid emergence of HIV-1 strains which are cross-resistant to NNRTIs has been observed in cell culture. Nevirapine-resistant HIV-1 isolates were cross-resistant to the NNRTIs delavirdine, efavirenz and etravirine. The Y188N conferred 22- and 7-fold reductions in susceptibility to delavirdine and efavirenz, respectively, but showed no decrease in susceptibility to etravirine. Similarly, the Y181I substitution reduced susceptibility to delavirdine and etravirine 3- and 8-fold, respectively, but did not reduce susceptibility to efavirenz. However, nevirapine-resistant isolates were susceptible to the NRTIs ddI and ZDV. Similarly, ZDV-resistant isolates were susceptible to nevirapine in cell culture.

## 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

#### Carcinogenesis

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

#### Mutagenesis

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

#### Impairment of Fertility

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

### 13.2 Animal Toxicology and/or Pharmacology

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

## 14 CLINICAL STUDIES

### 14.1 Adult Patients

Trial BI 1090 was a placebo-controlled, double-blind, randomized trial in 2249 HIV-1 infected subjects with less than 200 CD4<sup>+</sup> cells/mm<sup>3</sup> at screening. Initiated in 1995, BI 1090 compared treatment with VIRAMUNE + lamivudine + background therapy versus lamivudine + background therapy in NNRTI-naïve subjects. Treatment doses were VIRAMUNE, 200 mg daily for two weeks followed by 200 mg twice daily or placebo, and lamivudine, 150 mg twice daily. Other antiretroviral agents were given at approved doses. Initial background therapy (in addition to lamivudine) was one NRTI in 1309 subjects (58%), two or more NRTIs in 771 (34%), and PIs and NRTIs in 169 (8%). The subjects (median age 36.5 years, 70% Caucasian, 79% male) had advanced HIV-1 infection, with a median baseline CD4<sup>+</sup> cell count of 96 cells/mm<sup>3</sup> and a baseline HIV-1 RNA of 4.58 log<sub>10</sub> copies per mL (38,291 copies per mL). Prior to entering the trial, 45% had previously experienced an AIDS-defining clinical event. Eighty-nine percent had antiretroviral treatment prior to entering the trial. BI 1090 was originally designed as a clinical endpoint trial. Prior to unblinding the trial, the primary endpoint was changed to proportion of subjects with HIV-1 RNA less than 50 copies per mL and not previously failed at 48 weeks. Treatment response and outcomes are shown in Table 6.

Table 6 BI 1090 Outcomes Through 48 Weeks

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

<sup>1</sup> including change to open-label nevirapine

<sup>2</sup> includes withdrawal of consent, lost to follow-up, non-compliance with protocol, other administrative reasons

The change from baseline in CD4<sup>+</sup> cell count through one year of therapy was significantly greater for the VIRAMUNE group compared to the placebo group for the overall trial population (64 cells/mm<sup>3</sup> versus 22 cells/mm<sup>3</sup>, respectively), as well as for subjects who entered the trial as treatment-naïve or having received only ZDV (85 cells/mm<sup>3</sup> versus 25 cells/mm<sup>3</sup>, respectively).

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

Trial BI 1046 (INCAS) was a double-blind, placebo-controlled, randomized, three-arm trial with 151 HIV-1 infected subjects with CD4<sup>+</sup> cell counts of 200-600 cells/mm<sup>3</sup> at baseline. BI 1046 compared treatment with VIRAMUNE+zidovudine+didanosine to VIRAMUNE+zidovudine and zidovudine+didanosine. Treatment doses were VIRAMUNE at 200 mg daily for two weeks followed by 200 mg twice daily or placebo, zidovudine at 200 mg three times daily, and didanosine at 125 or 200 mg twice daily (depending on body weight). The subjects had mean baseline HIV-1 RNA of 4.41 log<sub>10</sub> copies/mL (25,704 copies per mL) and mean baseline CD4<sup>+</sup>

cell count of 376 cells/mm<sup>3</sup>. The primary endpoint was the proportion of subjects with HIV-1 RNA less than 400 copies per mL and not previously failed at 48 weeks. The virologic responder rates at 48 weeks were 45% for subjects treated with VIRAMUNE+zidovudine+didanosine, 19% for subjects treated with zidovudine+didanosine, and 0% for subjects treated with VIRAMUNE+zidovudine.

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

#### 14.2 Pediatric Patients

The pediatric safety and efficacy of VIRAMUNE was examined in BI Trial 1100.1368, an open-label, randomized clinical trial performed in South Africa in which 123 HIV-1 infected treatment-naïve subjects between 3 months and 16 years of age received VIRAMUNE oral suspension for 48 weeks. Subjects were divided into 4 age groups (3 months to less than 2 years, 2 to less than 7 years, 7 to less than 12 years, and 12 to less than or equal to 16 years) and randomized to receive one of two VIRAMUNE doses, determined by 2 different dosing methods [body surface area (150 mg/m<sup>2</sup>) and weight-based dosing (4 or 7 mg per 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 VIRAMUNE did not exceed 400 mg in either regimen. There were 66 subjects in the body surface area (BSA) dosing group and 57 subjects in the weight-based (BW) dosing group.

Baseline demographics included: 49% male; 81% Black and 19% Caucasian; 4% had previous exposure to ARVs. Subjects had a median baseline HIV-1 RNA of 5.45 log<sub>10</sub> copies per mL and a median baseline CD4<sup>+</sup> cell count of 527 cells/mm<sup>3</sup> (range 37-2279). One hundred and five (85%) completed the 48-week period while 18 (15%) discontinued prematurely. Of the subjects who discontinued prematurely, 9 (7%) discontinued due to adverse reactions and 3 (2%) discontinued due to virologic failure. Overall the proportion of subjects who achieved and maintained an HIV-1 RNA less than 400 copies per mL at 48 weeks was 47% (58/123).

#### 16 HOW SUPPLIED/STORAGE AND HANDLING

VIRAMUNE tablets, 200 mg, are white, oval, biconvex tablets, 9.3 mm x 19.1 mm. One side is embossed with “54 193”, with a single bisect separating the “54” and “193”. The opposite side has a single bisect.

VIRAMUNE tablets are supplied in bottles of 60 (NDC 0597-0046-60).

VIRAMUNE tablets are supplied in unit dose packages of 14 (NDC 0597-0046-46).

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

VIRAMUNE oral suspension is a white to off-white preserved suspension containing 50 mg nevirapine (as nevirapine hemihydrate) in each 5 mL. VIRAMUNE suspension is supplied in plastic bottles with child-resistant closures containing 240 mL of suspension (NDC 0597-0047-24).

#### Storage

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

#### 17 PATIENT COUNSELING INFORMATION

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

##### • Hepatotoxicity and Skin Reactions

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

Intensive clinical and laboratory monitoring, including liver enzymes, is essential during the first 18 weeks of therapy with VIRAMUNE 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 VIRAMUNE 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. Advise patients with signs and symptoms of hepatitis to discontinue VIRAMUNE and seek medical evaluation immediately. If VIRAMUNE is discontinued due to hepatotoxicity, do not restart it. Patients, particularly women, with increased CD4<sup>+</sup> cell count at initiation of VIRAMUNE therapy (greater than 250 cells/mm<sup>3</sup> in women and greater than 400 cells/mm<sup>3</sup> in men) are at substantially higher risk for development of symptomatic hepatic events, often associated with rash. Advise patients that co-infection with hepatitis B or C and/or increased transaminases at the start of therapy with VIRAMUNE are associated with a greater risk of later symptomatic events (6 weeks or more after starting VIRAMUNE) and asymptomatic increases in AST or ALT [see *Boxed Warning and Warnings and Precautions* (5.1)].

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

##### • Administration

Inform patients to take VIRAMUNE 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. Advise patients to report to their doctor the use of any other medications.

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

Patients should be told that sustained decreases in plasma HIV RNA have been associated with a reduced risk of progression to AIDS and death.

Advise patients to avoid doing things that can spread HIV-1 infection to others.

- Do not share needles or other injection equipment.
- Do not share personal items that can have blood or body fluids on them, like toothbrushes and razor blades.

- **Do not have any kind of sex without protection.** Always practice safe sex by using a latex or polyurethane condom to lower the chance of sexual contact with semen, vaginal secretions, or blood.
- **Do not breastfeed.** We do not know if VIRAMUNE can be passed to your baby in your breast milk and whether it could harm your baby. Also, mothers with HIV-1 should not breastfeed because HIV-1 can be passed to the baby in the breast milk.

Inform patients that they should not take VIRAMUNE tablets or oral suspension and VIRAMUNE XR extended release tablets at the same time.

- **Drug Interactions**

VIRAMUNE 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)*].

- **Contraceptives**

Hormonal methods of birth control, other than depomedroxy-progesterone acetate (DMPA), should not be used as the sole method of contraception in women taking VIRAMUNE, since VIRAMUNE may lower the plasma levels of these medications. Additionally, when oral contraceptives are used for hormonal regulation during VIRAMUNE therapy, the therapeutic effect of the hormonal therapy should be monitored [see *Drug Interactions (7)*].

- **Methadone**

VIRAMUNE may decrease plasma concentrations of methadone by increasing its hepatic metabolism. Narcotic withdrawal syndrome has been reported in patients treated with VIRAMUNE and methadone concomitantly. Monitor methadone-maintained patients beginning nevirapine therapy for evidence of withdrawal and adjust methadone dose accordingly [see *Drug Interactions (7)*].

- **Fat Redistribution**

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

Distributed by:  
Boehringer Ingelheim Pharmaceuticals, Inc.  
Ridgefield, CT 06877 USA

Copyright 2014 Boehringer Ingelheim Pharmaceuticals, Inc.  
ALL RIGHTS RESERVED

OT1801XA292014  
10003354/12

OT1803O  
090340228/08

IT5407J  
10007241/06

## MEDICATION GUIDE

**VIRAMUNE® (VIH-rah-mune)**  
(nevirapine)  
tablets

**VIRAMUNE® (VIH-rah-mune)**  
(nevirapine)  
oral suspension

**VIRAMUNE XR® (VIH-rah-mune)**  
(nevirapine)  
extended-release tablets

**Read this Medication Guide before you start taking VIRAMUNE and each time you get a refill.** There may be new information. This information does not take the place of talking to your doctor about your medical condition or treatment.

### **What is the most important information I should know about VIRAMUNE?**

**VIRAMUNE can cause serious side effects. These include severe liver and skin problems that can cause death. These problems can happen at any time during treatment, but your risk is higher during the first 18 weeks of treatment.**

- 1. Severe liver problems:** Anyone who takes VIRAMUNE may get severe liver problems. In some cases these liver problems can lead to liver failure and the need for a liver transplant, or death.

People who have a higher CD4<sup>+</sup> cell count when they begin VIRAMUNE treatment have a higher risk of liver problems, especially:

- Women with CD4<sup>+</sup> counts higher than 250 cells/mm<sup>3</sup>. This group has the highest risk.
- Men with CD4<sup>+</sup> counts higher than 400 cells/mm<sup>3</sup>.

If you are a woman with CD4<sup>+</sup> counts higher than 250 cells/mm<sup>3</sup> or a man with CD4<sup>+</sup> counts higher than 400 cells/mm<sup>3</sup>, you and your doctor will decide whether starting VIRAMUNE is right for you.

In general, women have a higher risk of liver problems compared to men.

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

You may get a rash if you have liver problems.

**Stop taking VIRAMUNE and call your doctor right away if you have any of the following symptoms of liver problems:**

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

Your doctor should see you and do blood tests often to check your liver function during the first 18 weeks of treatment with VIRAMUNE. You should continue to have your liver checked regularly during your treatment with VIRAMUNE. It is important for you to keep all of your doctor appointments.

**2. Severe rash and skin reactions:** Skin rash is the most common side effect of VIRAMUNE. Most rashes happen in the first 6 weeks of taking VIRAMUNE. **Rashes and skin reactions may be severe, life-threatening, and in some people, may lead to death. Stop using VIRAMUNE and call your doctor right away if you get a rash with any of the following symptoms:**

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

**If your doctor tells you to stop treatment with VIRAMUNE because you have had any of the serious liver or skin problems described above, you should never take VIRAMUNE again.**

See the section **“What are the possible side effects of VIRAMUNE?”** for more information.

**What is VIRAMUNE?**

- VIRAMUNE tablets and VIRAMUNE oral solution are prescription HIV medicines used with other HIV medicines to treat HIV (Human Immunodeficiency Virus). HIV is the virus that causes AIDS (Acquired Immune Deficiency Syndrome).
- VIRAMUNE XR extended-release tablets are a prescription medicine used with other HIV medicines to treat HIV (Human Immunodeficiency Virus) in adults and in children who are 6 years of age to less than 18 years of age.
- VIRAMUNE and VIRAMUNE XR are a type of HIV medicine called a non-nucleoside reverse transcriptase inhibitor (NNRTI).

VIRAMUNE XR extended-release tablets are not for use in children less than 6 years of age.

When used with other HIV medicines, VIRAMUNE may:

1. Reduce the amount of HIV in your blood (called “viral load”).

2. Help increase the number of CD4 (T) cells in your blood which help fight off other infections.

Reducing the amount of HIV and increasing the CD4 (T) cell count may improve your immune system. This may reduce your risk of death or infections that can happen when your immune system is weak (opportunistic infections).

### **VIRAMUNE does not cure HIV infection or AIDS.**

VIRAMUNE does not cure HIV or AIDS and you may continue to experience illnesses associated with HIV-1 infection, including opportunistic infections. You should remain under the care of a doctor when using VIRAMUNE.

You must stay on continuous HIV therapy to control HIV infection and decrease HIV-related illnesses.

Avoid doing things that can spread HIV-1 infection to others:

- **Do not share needles or other injection equipment.**
- **Do not share personal items that can have blood or body fluids on them, like toothbrushes and razor blades.**
- **Do not have any kind of sex without protection.** Always practice safe sex by using a latex or polyurethane condom to lower the chance of sexual contact with semen, vaginal secretions, or blood.

Ask your doctor if you have any questions on how to prevent passing HIV to other people.

### **Who should not take VIRAMUNE?**

Tell your doctor if you have or have had liver problems. Your doctor may tell you not to take VIRAMUNE if you have certain liver problems.

VIRAMUNE is only for people diagnosed with HIV. If you have not been diagnosed as HIV positive, then do not take VIRAMUNE.

### **What should I tell my doctor before taking VIRAMUNE?**

#### **Before you take VIRAMUNE, tell your doctor if you:**

- have or have had hepatitis (inflammation of your liver) or problems with your liver. See **“What is the most important information I should know about VIRAMUNE?”** and **“Who should not take VIRAMUNE?”**
- receive dialysis
- have skin problems, such as a rash
- or your child has trouble swallowing pills
- have any other medical conditions
- are pregnant or plan to become pregnant. It is not known if VIRAMUNE will harm your unborn baby.  
**Pregnancy Registry:** There is a pregnancy registry for women who take antiviral medicines during pregnancy. The purpose of the registry is to collect information about the health of you and your baby. Talk to your doctor about how you can take part in this registry.
- are breast-feeding or plan to breast-feed. VIRAMUNE can pass into your breast milk and may harm your baby. You should not breastfeed if you have HIV

because of the risk of passing HIV to your baby. Do not breast-feed during treatment with VIRAMUNE. Talk to your doctor about the best way to feed your baby.

**Tell your doctor and pharmacist about all the medicines you take**, including prescription and over-the-counter medicines, vitamins and herbal supplements. VIRAMUNE may affect the way other medicines work, and other medicines may affect how VIRAMUNE works.

You should not take VIRAMUNE if you also take:

- St. John's Wort. St. John's Wort can lower the amount of VIRAMUNE in your body.
- efavirenz (Sustiva<sup>®</sup>, Atripla<sup>®</sup>), etravirine (Intelence<sup>®</sup>), rilpivirine (Edurant<sup>®</sup> Complera<sup>®</sup>), or delavirdine (Rescriptor<sup>®</sup>)
- boceprevir (Victrelis<sup>®</sup>)
- telaprevir (Incivek<sup>®</sup>)
- atazanavir (Reyataz<sup>®</sup>)
- lopinavir and ritonavir (Kaletra<sup>®</sup>) once daily
- fosamprenavir calcium (Lexiva<sup>®</sup>) without ritonavir (Norvir<sup>®</sup>)
- itraconazole (Sporanox<sup>®</sup>)
- ketoconazole (Nizoral<sup>®</sup>)
- rifampin (Rifadin<sup>®</sup>, Rifamate<sup>®</sup>, Rifater<sup>®</sup>)
- birth control pills. Birth control pills taken by mouth (oral contraceptives) and other hormone types of birth control may not work to prevent pregnancy. Talk with your doctor about other types of birth control that you can use to prevent pregnancy during treatment with VIRAMUNE.

Also tell your doctor if you take:

- clarithromycin (Biaxin<sup>®</sup>)
- fluconazole (Diflucan<sup>®</sup>)
- indinavir sulfate (Crixivan<sup>®</sup>)
- methadone
- nelfinavir mesylate (Viracept<sup>®</sup>)
- rifabutin (Mycobutin<sup>®</sup>)
- warfarin (Coumadin<sup>®</sup>, Jantoven<sup>®</sup>)
- saquinavir mesylate (Invirase<sup>®</sup>)
- amiodarone, disopyramide (Norpace<sup>®</sup>), lidocaine
- carbamazepine, clonazepam (Klonopin<sup>®</sup>), ethosuximide (Zarontin<sup>®</sup>)
- diltiazem, nifedipine, verapamil
- cyclophosphamide
- ergotamine
- cyclosporine, tacrolimus, sirolimus (Rapamune<sup>®</sup>)
- cisapride (Propulsid<sup>®</sup>)
- fentanyl

**If you are not sure if you take a medicine above, ask your doctor or pharmacist.**

Know the medicines you take. Keep a list of them to show your doctor or pharmacist when you get a new medicine.

## How should I take VIRAMUNE?

- VIRAMUNE is always taken in combination with other anti-HIV medications.
- VIRAMUNE comes in 3 different forms. Your doctor will prescribe the form of VIRAMUNE that is right for you.
  - VIRAMUNE tablets
  - VIRAMUNE oral suspension
  - VIRAMUNE XR extended-release tablets
- Take VIRAMUNE exactly as your doctor tells you to take it. Do not change your dose unless your doctor tells you to.
- You should never take more than one form of VIRAMUNE at the same time. Talk to your doctor if you have any questions.
- If your child is prescribed VIRAMUNE, your child's doctor will tell you exactly how VIRAMUNE should be taken.
- Swallow VIRAMUNE XR extended-release tablets whole. Do not chew, crush, or divide VIRAMUNE XR extended-release tablets.
- You may take VIRAMUNE with or without food.
- Do not miss a dose of VIRAMUNE. If you miss a dose of VIRAMUNE, take the missed dose as soon as you remember. If it is almost time for your next dose, do not take the missed dose, just take the next dose at your regular time. Do not take two doses at the same time.
- If you stop taking VIRAMUNE for more than 7 days, ask your doctor how much to take before you start taking it again. You may need to begin taking the VIRAMUNE starting dose again, which is taken 1 time each day for 14 days.

### Starting VIRAMUNE tablets:

1. Your doctor should start you with 1 dose each day to lower your chance of getting a serious rash. **It is important that you only take 1 dose of VIRAMUNE each day for the first 14 days.**
  - **Call your doctor right away if you get a skin rash during the first 14 days of VIRAMUNE treatment.**
  - **Do not increase your dose to 2 times a day if you have a rash.**
  - You should never take your starting dose for longer than 28 days. If after 28 days you are still receiving this starting dose because you have a rash, you and your doctor should talk about prescribing another HIV medicine for you instead of VIRAMUNE.
2. Day 15, you will take 1 VIRAMUNE tablet two times a day.

### Starting VIRAMUNE XR extended-release tablets when this is the first time you are taking any form of VIRAMUNE:

1. Your doctor should start you with 1 dose of VIRAMUNE tablets or oral suspension each day to lower your risk of getting a serious rash. **It is important that you only take 1 dose of VIRAMUNE each day for the first 14 days.**
  - **Call your doctor right away if you get a skin rash during the first 14 days of VIRAMUNE treatment.**
  - You should never take your starting dose for longer than 28 days. If after 28 days you are still receiving this starting dose because you have a rash, you and your doctor should talk about prescribing another HIV medicine for you instead of VIRAMUNE.
  - **Do not start VIRAMUNE XR extended-release tablets if you have a rash.**



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

### **Switching from VIRAMUNE tablets or oral suspension to VIRAMUNE XR extended-release tablets:**

Take VIRAMUNE XR extended-release tablets 1 time a day as prescribed by your doctor.

You may sometimes pass a soft mass in your stools (bowel movement) that looks like your VIRAMUNE XR extended-release tablets. This will not affect the way your medicine works.

### **If you take VIRAMUNE oral suspension:**

- If you or your child takes VIRAMUNE suspension (liquid), shake it gently before each use. Use an oral dosing syringe or dosing cup to measure the right dose. The oral dosing syringe and dosing cup are not provided with VIRAMUNE suspension. Ask your pharmacist for a syringe or cup if you do not have one.
- After drinking the medicine, fill the dosing cup with water and drink it to make sure you get all the medicine.
- If the dose is less than 1 teaspoon (5 mL), use the syringe instead of the dosing cup.

### **What are the possible side effects of VIRAMUNE?**

VIRAMUNE may cause serious side effects, including:

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

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

### **The most common side effect of VIRAMUNE is rash.**

Tell your doctor if you have any side effect that bothers you or that does not go away.

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

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

### **How should I store VIRAMUNE?**

- Store VIRAMUNE at room temperature between 59°F to 86°F (15°C to 30°C).  
Throw away VIRAMUNE that is no longer needed or out-of-date.

### **Keep VIRAMUNE and all medicines out of the reach of children.**

### **General information about VIRAMUNE.**

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not take VIRAMUNE for a condition for which it was not prescribed. Do not give VIRAMUNE to other people, even if they have the same condition you have. It may harm them.

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

For more information, go to [www.viramune.com](http://www.viramune.com) or [www.viramunexr.com](http://www.viramunexr.com) or call Boehringer Ingelheim Pharmaceuticals, Inc., at 1-800-542-6257, or (TTY) 1-800-459-9906.

### What are the ingredients in VIRAMUNE?

Active ingredient: nevirapine

Inactive ingredients:

**VIRAMUNE tablets:** microcrystalline cellulose, lactose monohydrate, povidone, sodium starch glycolate, colloidal silicon dioxide, and magnesium stearate

**VIRAMUNE oral suspension:** carbomer 934P, methylparaben, propylparaben, sorbitol, sucrose, polysorbate 80, sodium hydroxide, and purified water

**VIRAMUNE XR tablets:** lactose monohydrate, hypromellose, iron oxide, and magnesium stearate

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

Distributed by:  
Boehringer Ingelheim Pharmaceuticals, Inc.  
Ridgefield, CT 06877 USA

Revised: January 2014

The brands listed are trademarks of their respective owners and are not trademarks of Boehringer Ingelheim Pharmaceuticals, Inc. The makers of these brands are not affiliated with and do not endorse Boehringer Ingelheim Pharmaceuticals, Inc., or its products.

Copyright 2014 Boehringer Ingelheim Pharmaceuticals, Inc.

ALL RIGHTS RESERVED

OT1801XA292014  
10003354/12

OT1803O  
090340228/08

IT5407J  
10007241/06

## PRESCRIBING INFORMATION

**ZIAGEN<sup>®</sup>**  
(abacavir sulfate)  
Tablets

**ZIAGEN<sup>®</sup>**  
(abacavir sulfate)  
Oral Solution

### WARNING

FATAL HYPERSENSITIVITY REACTIONS HAVE BEEN ASSOCIATED WITH THERAPY WITH ZIAGEN. PATIENTS DEVELOPING SIGNS OR SYMPTOMS OF HYPERSENSITIVITY (WHICH INCLUDE FEVER; SKIN RASH; FATIGUE; GASTROINTESTINAL SYMPTOMS SUCH AS NAUSEA, VOMITING, DIARRHEA, OR ABDOMINAL PAIN; AND RESPIRATORY SYMPTOMS SUCH AS PHARYNGITIS, DYSPNEA, OR COUGH) SHOULD DISCONTINUE ZIAGEN AS SOON AS A HYPERSENSITIVITY REACTION IS SUSPECTED. TO AVOID A DELAY IN DIAGNOSIS AND MINIMIZE THE RISK OF A LIFE-THREATENING HYPERSENSITIVITY REACTION, ZIAGEN SHOULD BE PERMANENTLY DISCONTINUED IF HYPERSENSITIVITY CANNOT BE RULED OUT, EVEN WHEN OTHER DIAGNOSES ARE POSSIBLE (E.G., ACUTE ONSET RESPIRATORY DISEASES, GASTROENTERITIS, OR REACTIONS TO OTHER MEDICATIONS).

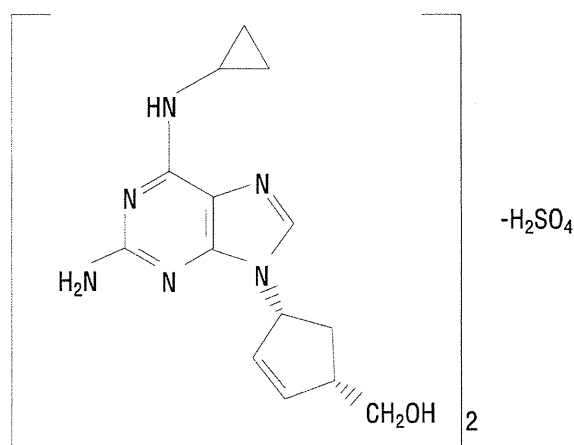
ZIAGEN SHOULD NOT BE RESTARTED FOLLOWING A HYPERSENSITIVITY REACTION BECAUSE MORE SEVERE SYMPTOMS WILL RECUR WITHIN HOURS AND MAY INCLUDE LIFE-THREATENING HYPOTENSION AND DEATH.

SEVERE OR FATAL HYPERSENSITIVITY REACTIONS CAN OCCUR WITHIN HOURS AFTER REINTRODUCTION OF ZIAGEN IN PATIENTS WHO HAVE NO IDENTIFIED HISTORY OR UNRECOGNIZED SYMPTOMS OF HYPERSENSITIVITY TO ABACAVIR THERAPY (SEE WARNINGS, PRECAUTIONS: INFORMATION FOR PATIENTS, AND ADVERSE REACTIONS).

LACTIC ACIDOSIS AND SEVERE HEPATOMEGALY WITH STEATOSIS, INCLUDING FATAL CASES, HAVE BEEN REPORTED WITH THE USE OF NUCLEOSIDE ANALOGUES ALONE OR IN COMBINATION, INCLUDING ZIAGEN AND OTHER ANTIRETROVIRALS (SEE WARNINGS).

### DESCRIPTION

ZIAGEN is the brand name for abacavir sulfate, a synthetic carbocyclic nucleoside analogue with inhibitory activity against HIV. The chemical name of abacavir sulfate is (1*S*,*cis*)-4-[2-amino-6-(cyclopropylamino)-9*H*-purin-9-yl]-2-cyclopentene-1-methanol sulfate (salt) (2:1). Abacavir sulfate is the enantiomer with *1S*, *4R* absolute configuration on the cyclopentene ring. It has a molecular formula of (C<sub>14</sub>H<sub>18</sub>N<sub>6</sub>O)<sub>2</sub>•H<sub>2</sub>SO<sub>4</sub> and a molecular weight of 670.76 daltons. It has the following structural formula:



Abacavir sulfate is a white to off-white solid with a solubility of approximately 77 mg/mL in distilled water at 25°C. It has an octanol/water (pH 7.1 to 7.3) partition coefficient ( $\log P$ ) of approximately 1.20 at 25°C.

**ZIAGEN Tablets** are for oral administration. Each tablet contains abacavir sulfate equivalent to 300 mg of abacavir and the inactive ingredients colloidal silicon dioxide, magnesium stearate, microcrystalline cellulose, and sodium starch glycolate. The tablets are coated with a film that is made of hydroxypropyl methylcellulose, polysorbate 80, synthetic yellow iron oxide, titanium dioxide, and triacetin.

**ZIAGEN Oral Solution** is for oral administration. One milliliter (1 mL) of ZIAGEN Oral Solution contains abacavir sulfate equivalent to 20 mg of abacavir (20 mg/mL) in an aqueous solution and the inactive ingredients artificial strawberry and banana flavors, citric acid (anhydrous), methylparaben and propylparaben (added as preservatives), propylene glycol, saccharin sodium, sodium citrate (dihydrate), and sorbitol solution.

In vivo, abacavir sulfate dissociates to its free base, abacavir. In this insert, all dosages for ZIAGEN are expressed in terms of abacavir.

## MICROBIOLOGY

**Mechanism of Action:** Abacavir is a carbocyclic synthetic nucleoside analogue.

Intracellularly, abacavir is converted by cellular enzymes to the active metabolite carbovir triphosphate. Carbovir triphosphate is an analogue of deoxyguanosine-5'-triphosphate (dGTP). Carbovir triphosphate inhibits the activity of HIV-1 reverse transcriptase (RT) both by competing with the natural substrate dGTP and by its incorporation into viral DNA. The lack of a 3'-OH group in the incorporated nucleoside analogue prevents the formation of the 5' to 3' phosphodiester linkage essential for DNA chain elongation, and therefore, the viral DNA growth is terminated.

**Antiviral Activity In Vitro:** The in vitro anti-HIV-1 activity of abacavir was evaluated against a T-cell tropic laboratory strain HIV-1 IIIB in lymphoblastic cell lines, a monocyte/macrophage tropic laboratory strain HIV-1 BaL in primary monocytes/macrophages, and clinical isolates in peripheral blood mononuclear cells. The concentration of drug necessary to inhibit viral replication by 50 percent ( $IC_{50}$ ) ranged from 3.7 to 5.8  $\mu M$  against HIV-1 IIIB, and was  $0.26 \pm 0.18 \mu M$  ( $1 \mu M = 0.28 \text{ mcg/mL}$ ) against 8 clinical isolates. The  $IC_{50}$  of abacavir against HIV-1 BaL varied from 0.07 to 1.0  $\mu M$ . Abacavir had synergistic activity in combination with