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

Black subjects (n=80/group) in Trial 1100.1486 showed approximately 30% to 35% higher trough concentrations than Caucasian subjects (250-325 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^2 once daily for two weeks followed by 150 mg/m^2 twice daily thereafter *[see Use in Specific Populations (8.4) and Adverse Reactions (6.2)]*. Dosing of nevirapine at 150 mg/m^2 BID (after a two-week lead-in of 150 mg/m^2 QD) produced geometric mean or mean trough nevirapine concentrations between 4-6 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)		
Antiretrovirals				**AUC**	**C_{max}**	**C_{min}**
Atazanavir/Ritonavir[a, d]	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	Atazanavir 300/100 mg ↓42 (↓52 to ↓29)	Atazanavir 300/100 mg ↓28 (↓40 to ↓14)	Atazanavir 300/100 mg ↓72 (↓80 to ↓60)
				Atazanavir 400/100 mg ↓19 (↓35 to ↑2)	Atazanavir 400/100 mg ↑2 (↓15 to ↑24)	Atazanavir 400/100 mg ↓59 (↓73 to ↓40)
Darunavir/Ritonavir[e]	400/100 mg BID	200 mg BID	8	↑24 (↓3 to ↑57)	↑40 (↑14 to ↑73)	↑2 (↓21 to ↑32)
Didanosine	100-150 mg BID	200 mg QD x 14 days; 200 mg BID x 14 days	18	⇔	⇔	§

Efavirenz[a]	600 mg QD	200 mg QD x 14 days; 400 mg QD x 14 days	17	↓28 (↓34 to ↓14)	↓12 (↓23 to ↑1)	↓32 (↓35 to ↓19)
Fosamprenavir	1400 mg BID	200 mg BID. Subjects 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[a]	800 mg q8H	200 mg QD x 14 days; 200 mg BID x 14 days	19	↓31 (↓39 to ↓22)	↓15 (↓24 to ↓4)	↓44 (↓53 to ↓33)
Lopinavir[a, b]	300/75 mg/m^2 (lopinavir/ ritonavir)[b]	7 mg/kg or 4 mg/kg QD x 2 weeks; BID x 1 week	12, 15[c]	↓22 (↓44 to ↑9)	↓14 (↓36 to ↑16)	↓55 (↓75 to ↓19)
Lopinavir[a]	400/100 mg BID (lopinavir/ ritonavir)	200 mg QD x 14 days; 200 mg BID >1 year	22, 19[c]	↓27 (↓47 to ↓2)	↓19 (↓38 to ↑5)	↓51 (↓72 to ↓26)
Maraviroc[f]	300 mg SD	200 mg BID	8	↑1 (↓35 to ↑55)	↑54 (↓6 to ↑151)	⇔
Nelfinavir[a]	750 mg TID	200 mg QD x 14 days; 200 mg BID x 14 days	23	⇔	⇔	↓32 (↓50 to ↑5)
Nelfinavir-M8 metabolite				↓62 (↓70 to ↓53)	↓59 (↓68 to ↓48)	↓66 (↓74 to ↓55)
Ritonavir	600 mg BID	200 mg QD x 14 days; 200 mg BID x 14 days	18	⇔	⇔	⇔
Stavudine	30-40 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)	§
Other Medications				**AUC**	**C_{max}**	**C_{min}**
Clarithromycin[a]	500 mg BID	200 mg QD x 14 days; 200 mg BID x 14 days	15	↓31 (↓38 to ↓24)	↓23 (↓31 to ↓14)	↓56 (↓70 to ↓36)
Metabolite 14-OH-clarithromycin				↑42 (↑16 to ↑73)	↑47 (↑21 to ↑80)	⇔
Ethinyl estradiol[a] and	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)	⇔	§
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	⇔	⇔	⇔
Fluconazole	200 mg QD	200 mg QD x 14 days; 200 mg BID x 14 days	19	⇔	⇔	⇔
Ketoconazole[a]	400 mg QD	200 mg QD x 14 days; 200 mg	21	↓72	↓44	§

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

§ = C_{min} below detectable level of the assay
↑ = Increase, ↓ = Decrease, ⇔ = No Effect
[a] For information regarding clinical recommendations, see *Drug Interactions (7)*.
[b] Pediatric subjects ranging in age from 6 months to 12 years
[c] Parallel group design; n for VIRAMUNE+lopinavir/ritonavir, n for lopinavir/ritonavir alone.
[d] Parallel group design; n=23 for atazanavir/ritonavir + nevirapine, n=22 for atazanavir/ritonavir without nevirapine. Changes in atazanavir PK are relative to atazanavir/ritonavir 300/100 mg alone.
[e] Based on between-trial comparison.
[f] Based on historical controls.

Because of the design of the drug interaction trials (addition of 28 days of 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_{max} by greater than 50%. Administration of fluconazole resulted in an approximate 100% increase in nevirapine exposure, based on a comparison to historic data *[see Drug Interactions (7)]*. The effect of other drugs listed in Table 5 on nevirapine pharmacokinetics was not significant. No significant interaction was observed when tipranavir was co-administered with low-dose ritonavir and nevirapine.

12.4 Microbiology

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

Antiviral Activity
The antiviral activity of nevirapine has been measured in a variety of cell lines including peripheral blood mononuclear cells, monocyte-derived macrophages, and lymphoblastoid cell lines. In an assay using human embryonic kidney 293 cells, the median EC_{50} value (50% inhibitory concentration) of nevirapine was 90 nM against a panel of 2923 isolates of HIV-1 that were primarily (93%) clade B clinical isolates from the United States. The 99th percentile EC_{50} value was 470 nM in this trial. The median EC_{50} 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 $CD4^+$ cells/mm^3 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 $CD4^+$ cell count of 96 cells/mm^3 and a baseline HIV-1 RNA of 4.58 $\log_{10}$ 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[1] while <50 copies/mL	5	1
Discontinued trial therapy due to AE	7	6
Discontinued trial <48 weeks[2]	9	10

[1] including change to open-label nevirapine
[2] includes withdrawal of consent, lost to follow-up, non-compliance with protocol, other administrative reasons

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

At two years into the trial, 16% of subjects on 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 $CD4^+$ cell counts of 200-600 cells/mm^3 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 $\log_{10}$ copies/mL (25,704 copies per mL) and mean baseline $CD4^+$

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

CD4$^+$ cell counts in the VIRAMUNE+ZDV+ddI group increased above baseline by a mean of 139 cells/mm^3 at one year, significantly greater than the increase of 87 cells/mm^3 in the ZDV+ddI subjects. The VIRAMUNE+ZDV group mean decreased by 6 cells/mm^3 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^2) 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 $\log_{10}$ copies per mL and a median baseline CD4$^+$ cell count of 527 cells/mm^3 (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$^+$ cell count at initiation of VIRAMUNE therapy (greater than 250 cells/mm^3 in women and greater than 400 cells/mm^3 in men) are at substantially higher risk for development of symptomatic hepatic events, often associated with rash. Advise patients that co-infection with hepatitis B or C and/or increased transaminases at the start of therapy with 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)]*.

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Ridgefield, CT 06877 USA

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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 $CD4^+$ cell count when they begin VIRAMUNE treatment have a higher risk of liver problems, especially:

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

If you are a woman with $CD4^+$ counts higher than 250 cells/mm^3 or a man with $CD4^+$ counts higher than 400 cells/mm^3, you and your doctor will decide 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®, Atripla®) , etravirine (Intelence®), rilpivirine (Edurant® Complera®), or delavirdine (Rescriptor®)
- boceprevir (Victrelis®)
- telaprevir (Incivek®)
- atazanavir (Reyataz®)
- lopinavir and ritonavir (Kaletra®) once daily
- fosamprenavir calcium (Lexiva®) without ritonavir (Norvir®)
- itraconazole (Sporanox®)
- ketoconazole (Nizoral®)
- rifampin (Rifadin®, Rifamate®, Rifater®)
- 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®)
- fluconazole (Diflucan®)
- indinavir sulfate (Crixivan®)
- methadone
- nelfinavir mesylate (Viracept®)
- rifabutin (Mycobutin®)
- warfarin (Coumadin®, Jantoven®)
- saquinavir mesylate (Invirase®)
- amiodarone, disopyramide (Norpace®), lidocaine
- carbamazepine, clonazepam (Klonopin®), ethosuximide (Zarontin®)
- diltiazem, nifedipine, verapamil
- cyclophosphamide
- ergotamine
- cyclosporine, tacrolimus, sirolimus (Rapamune®)
- cisapride (Propulsid®)
- 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.
    - o VIRAMUNE tablets
    - o VIRAMUNE oral suspension
    - o 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 or 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

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PRESCRIBING INFORMATION

ZIAGEN®
(abacavir sulfate)
Tablets

ZIAGEN®
(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.

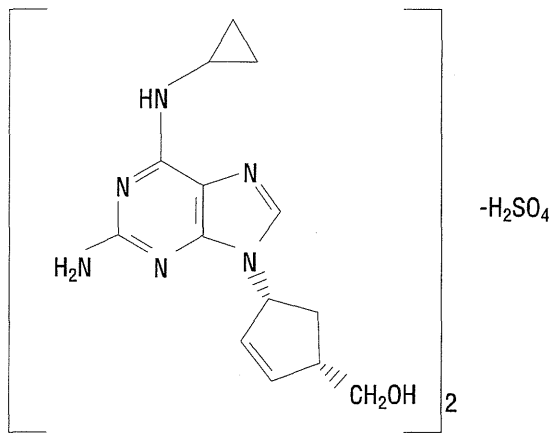
SEVERE OR FATAL HYPERSENSITIVITY REACTIONS CAN OCCUR WITHIN HOURS AFTER REINTRODUCTION OF ZIAGEN IN PATIENTS WHO HAVE NO IDENTIFIED HISTORY OR UNRECOGNIZED SYMPTOMS OF HYPERSENSITIVITY TO ABACAVIR THERAPY (SEE WARNINGS, PRECAUTIONS: INFORMATION FOR PATIENTS, AND ADVERSE REACTIONS).

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 *(1S,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 $(C_{14}H_{18}N_6O)_2 \cdot H_2SO_4$ 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 μM against HIV-1 IIIB, and was 0.26 ± 0.18 μM (1 μM = 0.28 mcg/mL) against 8 clinical isolates. The IC_{50} of abacavir against HIV-1 BaL varied from 0.07 to 1.0 μM. Abacavir had synergistic activity in combination with

amprenavir, nevirapine, and zidovudine, and additive activity in combination with didanosine, lamivudine, stavudine, and zalcitabine in vitro. These drug combinations have not been adequately studied in humans. The relationship between in vitro susceptibility of HIV to abacavir and the inhibition of HIV replication in humans has not been established.

Drug Resistance: HIV-1 isolates with reduced sensitivity to abacavir have been selected in vitro and were also obtained from patients treated with abacavir. Genetic analysis of isolates from abacavir-treated patients showed point mutations in the reverse transcriptase gene that resulted in amino acid substitutions at positions K65R, L74V, Y115F, and M184V. Phenotypic analysis of HIV-1 isolates that harbored abacavir-associated mutations from 17 patients after 12 weeks of abacavir monotherapy exhibited a 3-fold decrease in susceptibility to abacavir in vitro.

Genetic analysis of HIV-1 isolates from 21 previously antiretroviral therapy-naive patients with confirmed virologic failure (plasma HIV-1 RNA ≥400 copies/mL) after 16 to 48 weeks of abacavir/lamivudine/zidovudine therapy showed that 16/21 isolates had abacavir/lamivudine-associated mutation M184V, either alone (11/21), or in combination with Y115F (1/21) or zidovudine-associated (4/21) mutations at the last time point. Phenotypic data available on isolates from 10 patients showed that 7 of the 10 isolates had 25- to 86-fold decreases in susceptibility to lamivudine in vitro. Likewise, isolates from 2 of these 7 patients had 7- to 10-fold decreases in susceptibility to abacavir in vitro. The clinical relevance of genotypic and phenotypic changes associated with abacavir therapy has not been established, but is currently under evaluation.

Cross-Resistance: Recombinant laboratory strains of HIV-1 (HXB2) containing multiple reverse transcriptase mutations conferring abacavir resistance exhibited cross-resistance to lamivudine, didanosine, and zalcitabine in vitro. For clinical information in treatment-experienced patients, see INDICATIONS AND USAGE: Description of Clinical Studies and PRECAUTIONS.

CLINICAL PHARMACOLOGY

Pharmacokinetics in Adults: The pharmacokinetic properties of abacavir have been studied in asymptomatic, HIV-infected adult patients after administration of a single intravenous (IV) dose of 150 mg and after single and multiple oral doses. The pharmacokinetic properties of abacavir were independent of dose over the range of 300 to 1,200 mg/day.

Absorption and Bioavailability: Abacavir was rapidly and extensively absorbed after oral administration. The geometric mean absolute bioavailability of the tablet was 83%. After oral administration of 300 mg twice daily in 20 patients, the steady-state peak serum abacavir concentration (C_{max}) was 3.0 ± 0.89 mcg/mL (mean ± SD) and $AUC_{(0\text{-}12\ hr)}$ was 6.02 ± 1.73 mcg•hr/mL. Bioavailability of abacavir tablets was assessed in the fasting and fed states. There was no significant difference in systemic exposure ($AUC\infty$) in the fed and fasting states; therefore, ZIAGEN Tablets may be administered with or without food. Systemic exposure to abacavir was comparable after administration of ZIAGEN Oral Solution and ZIAGEN Tablets. Therefore, these products may be used interchangeably.

Distribution: The apparent volume of distribution after IV administration of abacavir was 0.86 ± 0.15 L/kg, suggesting that abacavir distributes into extravascular space. In 3 subjects, the CSF $AUC_{(0\text{-}6\ hr)}$ to plasma abacavir $AUC_{(0\text{-}6\ hr)}$ ratio ranged from 27% to 33%.

Binding of abacavir to human plasma proteins is approximately 50%. Binding of abacavir to plasma proteins was independent of concentration. Total blood and plasma drug-related

radioactivity concentrations are identical, demonstrating that abacavir readily distributes into erythrocytes.

Metabolism: In humans, abacavir is not significantly metabolized by cytochrome P450 enzymes. The primary routes of elimination of abacavir are metabolism by alcohol dehydrogenase (to form the 5′-carboxylic acid) and glucuronyl transferase (to form the 5′-glucuronide). The metabolites do not have antiviral activity. In vitro experiments reveal that abacavir does not inhibit human CYP3A4, CYP2D6, or CYP2C9 activity at clinically relevant concentrations.

Elimination: Elimination of abacavir was quantified in a mass balance study following administration of a 600-mg dose of ^{14}C-abacavir: 99% of the radioactivity was recovered, 1.2% was excreted in the urine as abacavir, 30% as the 5′-carboxylic acid metabolite, 36% as the 5′-glucuronide metabolite, and 15% as unidentified minor metabolites in the urine. Fecal elimination accounted for 16% of the dose.

In single-dose studies, the observed elimination half-life ($t_{1/2}$) was 1.54 ± 0.63 hours. After intravenous administration, total clearance was 0.80 ± 0.24 L/hr/kg (mean ± SD).

Special Populations: ***Adults With Impaired Renal Function:*** The pharmacokinetic properties of ZIAGEN have not been determined in patients with impaired renal function. Renal excretion of unchanged abacavir is a minor route of elimination in humans.

Adults with Impaired Hepatic Function: The pharmacokinetics of abacavir have been studied in patients with mild hepatic impairment (Child-Pugh score 5 to 6). Results showed that there was a mean increase of 89% in the abacavir AUC, and an increase of 58% in the half-life of abacavir after a single dose of 600 mg of abacavir. The AUCs of the metabolites were not modified by mild liver disease; however, the rates of formation and elimination of the metabolites were decreased. A dose of 200 mg (provided by 10 mL of ZIAGEN Oral Solution) administered twice daily is recommended for patients with mild liver disease. The safety, efficacy, and pharmacokinetics of abacavir have not been studied in patients with moderate or severe hepatic impairment, therefore ZIAGEN is contraindicated in these patients.

Pediatric Patients: The pharmacokinetics of abacavir have been studied after either single or repeat doses of ZIAGEN in 68 pediatric patients. Following multiple-dose administration of ZIAGEN 8 mg/kg twice daily, steady-state $AUC_{(0\text{-}12\ hr)}$ and C_{max} were 9.8 ± 4.56 mcg•hr/mL and 3.71 ± 1.36 mcg/mL (mean ± SD), respectively (see PRECAUTIONS: Pediatric Use).

Geriatric Patients: The pharmacokinetics of ZIAGEN have not been studied in patients over 65 years of age.

Gender: The pharmacokinetics of ZIAGEN with respect to gender have not been determined.

Race: The pharmacokinetics of ZIAGEN with respect to race have not been determined.

Drug Interactions: In human liver microsomes, abacavir did not inhibit cytochrome P450 isoforms (2C9, 2D6, 3A4). Based on these data, it is unlikely that clinically significant drug interactions will occur between abacavir and drugs metabolized through these pathways.

Due to their common metabolic pathways via glucuronyl transferase with zidovudine, 15 HIV-infected patients were enrolled in a crossover study evaluating single doses of abacavir (600 mg), lamivudine (150 mg), and zidovudine (300 mg) alone or in combination. Analysis showed no clinically relevant changes in the pharmacokinetics of abacavir with the addition of lamivudine or zidovudine or the combination of lamivudine and zidovudine. Lamivudine

exposure (AUC decreased 15%) and zidovudine exposure (AUC increased 10%) did not show clinically relevant changes with concurrent abacavir.

Due to their common metabolic pathways via alcohol dehydrogenase, the pharmacokinetic interaction between abacavir and ethanol was studied in 24 HIV-infected male patients. Each patient received the following treatments on separate occasions: a single 600-mg dose of abacavir, 0.7 g/kg ethanol (equivalent to 5 alcoholic drinks), and abacavir 600 mg plus 0.7 g/kg ethanol. Coadministration of ethanol and abacavir resulted in a 41% increase in abacavir AUC_{∞} and a 26% increase in abacavir $t_{1/2}$. In males, abacavir had no effect on the pharmacokinetic properties of ethanol, so no clinically significant interaction is expected in men. This interaction has not been studied in females.

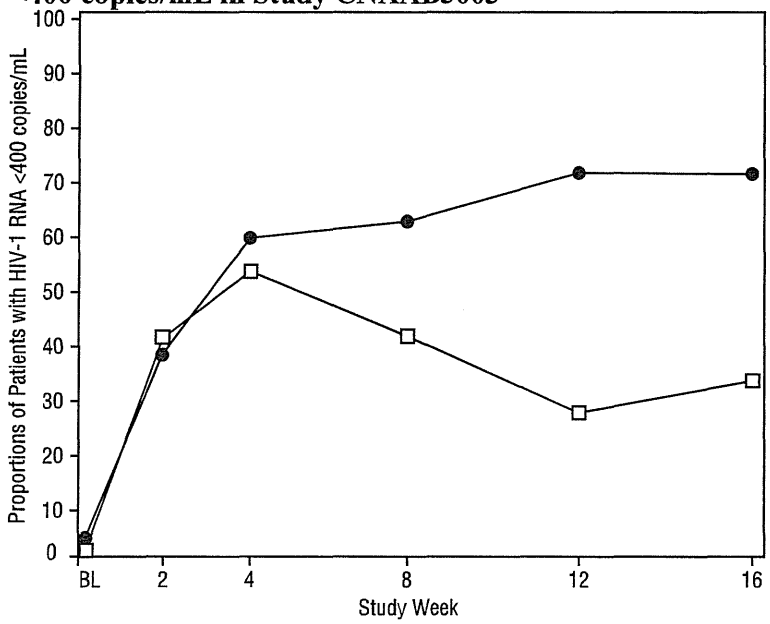
Methadone: In a study of 11 HIV-infected subjects receiving methadone-maintenance therapy (40 mg and 90 mg daily), with 600 mg of ZIAGEN twice daily (twice the currently recommended dose), oral methadone clearance increased 22% (90% CI 6% to 42%). This alteration will not result in a methadone dose modification in the majority of patients; however, an increased methadone dose may be required in a small number of patients.

INDICATIONS AND USAGE

ZIAGEN Tablets and Oral Solution, in combination with other antiretroviral agents, are indicated for the treatment of HIV-1 infection. This indication is based on 2 controlled trials of 16 and 48 weeks' duration that evaluated suppression of HIV RNA and changes in CD4 cell count. At present, there are no results from controlled trials evaluating the effect of ZIAGEN on clinical progression of HIV (see Description of Clinical Studies).

Description of Clinical Studies: ***Therapy-Naive Adults:*** CNAAB3003 is a multicenter, double-blind, placebo-controlled study in which 173 HIV-infected, therapy-naive adults were randomized to receive either ZIAGEN (300 mg twice daily), lamivudine (150 mg twice daily), and zidovudine (300 mg twice daily) or lamivudine (150 mg twice daily) and zidovudine (300 mg twice daily). The duration of double-blind treatment was 16 weeks. Study participants were: male (76%), Caucasian (54%), African-American (28%), and Hispanic (16%). The median age was 34 years, the median pretreatment CD4 cell count was 450 cells/mm^3, and median plasma HIV-1 RNA was 4.5 $\log_{10}$ copies/mL. Proportions of patients with plasma HIV-1 RNA <400 copies/mL (using Roche Amplicor HIV-1 MONITOR® Test) through 16 weeks of treatment are summarized in Figure 1.

Figure 1. Proportions of Patients with HIV-1 RNA <400 copies/mL in Study CNAAB3003[1]



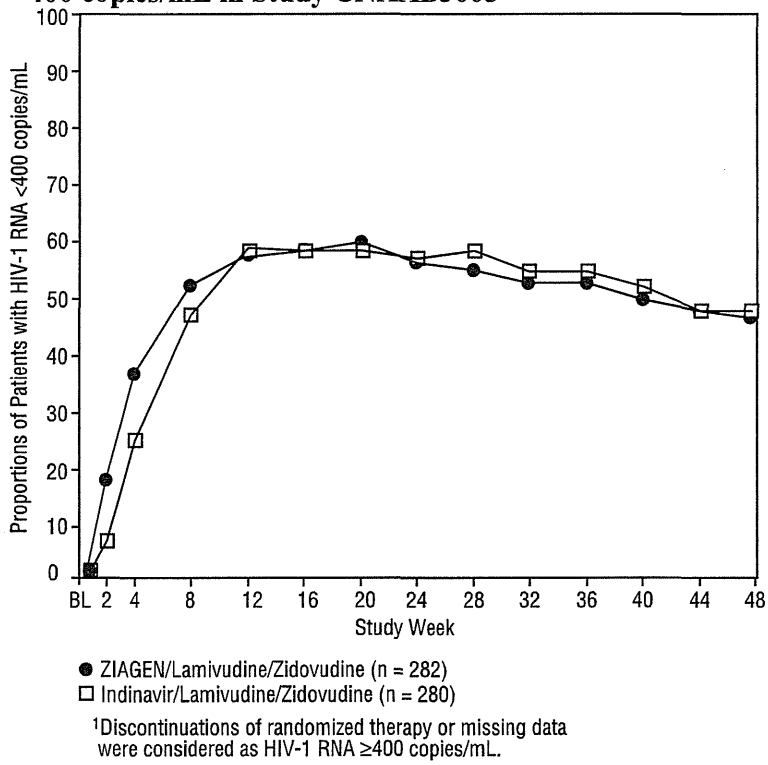
● ZIAGEN/Lamivudine/Zidovudine (n = 87)
□ Lamivudine/Zidovudine (n = 86)

[1]Missing data were considered as HIV-1 RNA ≥400 copies/mL.

After 16 weeks of therapy, the median CD4 increases from baseline were 47 cells/mm^3 in the group receiving ZIAGEN and 112 cells/mm^3 in the placebo group.

CNAAB3005 was a multicenter, double-blind, controlled study in which 562 HIV-infected, therapy-naive adults with a pre-entry plasma HIV-1 RNA >10,000 copies/mL were randomized to receive either ZIAGEN (300 mg twice daily) plus COMBIVIR (lamivudine 150 mg/zidovudine 300 mg twice daily), or indinavir (800 mg 3 times a day) plus COMBIVIR twice daily. Study participants were male (87%), Caucasian (73%), African-American (15%), and Hispanic (9%). At baseline the median age was 36 years, the median pretreatment CD4 cell count was 360 cells/mm^3, and median plasma HIV-1 RNA was 4.8 $\log_{10}$ copies/mL. Proportions of patients with plasma HIV-1 RNA <400 copies/mL (using Roche Amplicor HIV-1 MONITOR Test) through 48 weeks of treatment are summarized in Figure 2.

Figure 2. Proportions of Patients with HIV-1 RNA <400 copies/mL in Study CNAAB3005[1]



[1]Discontinuations of randomized therapy or missing data were considered as HIV-1 RNA ≥400 copies/mL.

Through Week 48, an overall mean increase in CD4 cells of about 150 cells/mm^3 was observed in both treatment arms.

Table 1. Outcomes of Randomized Treatment Through Week 48 (CNAAB3005)

Outcome	ZIAGEN/Lamivudine/ Zidovudine (n = 282)	Indinavir/ Lamivudine/Zidovudine (n = 280)
HIV RNA <400 copies/mL	46%	47%
HIV RNA ≥400 copies/mL*	29%	28%
CDC Class C event	2%	<1%
Discontinued due to adverse reactions	9%	11%
Discontinued due to other reasons†	6%	6%
Randomized but never initiated treatment	7%	5%

*Includes viral rebound and failure to achieve confirmed <400 copies/mL by Week 48.
†Includes consent withdrawn, lost to follow up, protocol violations, those with missing data, and other.

Therapy-Experienced Pediatric Patients: CNAA3006 is a randomized, double-blind study comparing ZIAGEN 8 mg/kg twice daily, lamivudine 4 mg/kg twice daily, and zidovudine 180 mg/m^2 twice daily versus lamivudine 4 mg/kg twice daily and zidovudine 180 mg/m^2 twice daily. Two hundred and five pediatric patients were enrolled: female (56%), Caucasian (17%),