

1 ATTENTION PHARMACISTS: Detach “[Medication Guide](#)” and dispense with the
2 product.
3

Viramune®
(nevirapine) **Tablets**



Viramune®
(nevirapine) **Oral Suspension**

4
5 Rx only

6 **WARNING**

7 **Severe, life-threatening, and in some cases fatal hepatotoxicity, particularly in the first 18**
8 **weeks, has been reported in patients treated with VIRAMUNE®. In some cases, patients**
9 **presented with non-specific prodromal signs or symptoms of hepatitis and progressed to**
10 **hepatic failure. These events are often associated with rash. Female gender and higher**
11 **CD4 counts at initiation of therapy place patients at increased risk; women with CD4**
12 **counts >250 cells/mm³, including pregnant women receiving VIRAMUNE in combination**
13 **with other antiretrovirals for the treatment of HIV infection, are at the greatest risk.**
14 **However, hepatotoxicity associated with VIRAMUNE use can occur in both genders, all**
15 **CD4 counts and at any time during treatment. Patients with signs or symptoms of**
16 **hepatitis, or with increased transaminases combined with rash or other systemic**
17 **symptoms, must discontinue VIRAMUNE and seek medical evaluation immediately (see**
18 **WARNINGS).**

19
20 **Severe, life-threatening skin reactions, including fatal cases, have occurred in patients**
21 **treated with VIRAMUNE. These have included cases of Stevens-Johnson syndrome, toxic**
22 **epidermal necrolysis, and hypersensitivity reactions characterized by rash, constitutional**
23 **findings, and organ dysfunction. Patients developing signs or symptoms of severe skin**
24 **reactions or hypersensitivity reactions must discontinue VIRAMUNE and seek medical**
25 **evaluation immediately (see WARNINGS).**

26
27 **It is essential that patients be monitored intensively during the first 18 weeks of therapy**
28 **with VIRAMUNE to detect potentially life-threatening hepatotoxicity or skin reactions.**
29 **Extra vigilance is warranted during the first 6 weeks of therapy, which is the period of**
30 **greatest risk of these events. Do not restart VIRAMUNE following severe hepatic, skin or**
31 **hypersensitivity reactions. In some cases, hepatic injury has progressed despite**
32 **discontinuation of treatment. In addition, the 14-day lead-in period with VIRAMUNE 200**
33 **mg daily dosing must be strictly followed (see WARNINGS).**
34

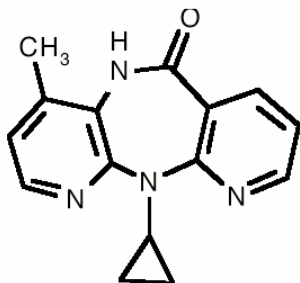
35 **DESCRIPTION**

36 VIRAMUNE is the brand name for nevirapine (NVP), a non-nucleoside reverse transcriptase
37 inhibitor with activity against Human Immunodeficiency Virus Type 1 (HIV-1). Nevirapine is
38 structurally a member of the dipyrindiazepinone chemical class of compounds.
39

40 VIRAMUNE Tablets are for oral administration. Each tablet contains 200 mg of nevirapine and
41 the inactive ingredients microcrystalline cellulose, lactose monohydrate, povidone, sodium starch
42 glycolate, colloidal silicon dioxide and magnesium stearate.
43

44 VIRAMUNE Oral Suspension is for oral administration. Each 5 mL of VIRAMUNE suspension
45 contains 50 mg of nevirapine (as nevirapine hemihydrate). The suspension also contains the
46 following excipients: carbomer 934P, methylparaben, propylparaben, sorbitol, sucrose,
47 polysorbate 80, sodium hydroxide and purified water.
48

49 The chemical name of nevirapine is 11-cyclopropyl-5,11-dihydro-4-methyl-6H-dipyrido [3,2-b:2',
50 3'-e][1,4] diazepin-6-one. Nevirapine is a white to off-white crystalline powder with the molecular
51 weight of 266.30 and the molecular formula $C_{15}H_{14}N_4O$. Nevirapine has the following structural
52 formula:



53

54 **MICROBIOLOGY**

55 ***Mechanism of Action***

56 Nevirapine is a non-nucleoside reverse transcriptase inhibitor (NNRTI) of HIV-1. Nevirapine binds
57 directly to reverse transcriptase (RT) and blocks the RNA-dependent and DNA-dependent DNA
58 polymerase activities by causing a disruption of the enzyme's catalytic site. The activity of
59 nevirapine does not compete with template or nucleoside triphosphates. HIV-2 RT and eukaryotic
60 DNA polymerases (such as human DNA polymerases α , β , γ , or δ) are not inhibited by
61 nevirapine.
62

63 ***Antiviral Activity***

64 The antiviral activity of nevirapine has been measured in a variety of cell lines including
65 peripheral blood mononuclear cells, monocyte derived macrophages, and lymphoblastoid cell
66 lines. In recent studies using human cord blood lymphocytes and human embryonic kidney 293
67 cells, EC₅₀ values (50% inhibitory concentration) ranged from 14-302 nM against laboratory and
68 clinical isolates of HIV-1. Nevirapine exhibited antiviral activity in cell culture against group M
69 HIV-1 isolates from clades A, B, C, D, F, G, and H, and circulating recombinant forms (CRF)
70 CRF01_AE, CRF02_AG and CRF12_BF (median EC₅₀ value of 63 nM). Nevirapine had no
71 antiviral activity in cell culture against group O HIV-1 isolates or HIV-2 isolates. Nevirapine in
72 combination with efavirenz exhibited strong antagonistic anti-HIV-1 activity in cell culture and
73 was additive to antagonistic with the protease inhibitor ritonavir or the fusion inhibitor
74 enfuvirtide. Nevirapine exhibited additive to synergistic anti-HIV-1 activity in combination with
75 the protease inhibitors amprenavir, atazanavir, indinavir, lopinavir, nelfinavir, saquinavir and
76 tipranavir, and the NRTIs abacavir, didanosine, emtricitabine, lamivudine, stavudine, tenofovir
77 and zidovudine. The anti-HIV-1 activity of nevirapine was antagonized by the anti-HBV drug
78 adefovir and by the anti-HCV drug ribavirin in cell culture.
79

80 ***Resistance***

81 HIV-1 isolates with reduced susceptibility (100-250-fold) to nevirapine emerge in cell culture.
82 Genotypic analysis showed mutations in the HIV-1 RT gene Y181C and/or V106A depending
83 upon the virus strain and cell line employed. Time to emergence of nevirapine resistance in cell
84 culture was not altered when selection included nevirapine in combination with several other
85 NNRTIs.
86

87 Phenotypic and genotypic changes in HIV-1 isolates from treatment-naïve patients receiving
88 either nevirapine (n=24) or nevirapine and ZDV (n=14) were monitored in Phase I/II trials over 1
89 to ≥12 weeks. After 1 week of nevirapine monotherapy, isolates from 3/3 patients had decreased
90 susceptibility to nevirapine in cell culture. One or more of the RT mutations resulting in amino
91 acid substitutions K103N, V106A, V108I, Y181C, Y188C and G190A were detected in HIV-1
92 isolates from some patients as early as 2 weeks after therapy initiation. By week eight of
93 nevirapine monotherapy, 100% of the patients tested (n=24) had HIV-1 isolates with a >100-fold
94 decrease in susceptibility to nevirapine in cell culture compared to baseline, and had one or more
95 of the nevirapine-associated RT resistance mutations. Nineteen of these patients (80%) had
96 isolates with Y181C mutations regardless of dose.

97
98 Genotypic analysis of isolates from antiretroviral naïve patients experiencing virologic failure
99 (n=71) receiving nevirapine once daily (n=25) or twice daily (n=46) in combination with lamivudine
100 and stavudine (study 2NN) for 48 weeks showed that isolates from 8/25 and 23/46 patients,
101 respectively, contained one or more of the following NNRTI resistance-associated mutations:
102 Y181C, K101E, G190A/S, K103N, V106A/M, V108I, Y188C/L, A98G, F227L and M230L.

103 **Cross-resistance**

104 Rapid emergence of HIV-1 strains which are cross-resistant to NNRTIs has been observed in cell
105 culture. Nevirapine-resistant HIV-1 isolates were cross-resistant to the NNRTIs delavirdine and
106 efavirenz. However, nevirapine-resistant isolates were susceptible to the NRTI's ddI and ZDV.
107 Similarly, ZDV-resistant isolates were susceptible to nevirapine in cell culture.

108 **ANIMAL PHARMACOLOGY**

109
110 Animal studies have shown that nevirapine is widely distributed to nearly all tissues and readily
111 crosses the blood-brain barrier.

112 **CLINICAL PHARMACOLOGY**

113 **Pharmacokinetics in Adults**

114
115 **Absorption and Bioavailability:** Nevirapine is readily absorbed (>90%) after oral administration
116 in healthy volunteers and in adults with HIV-1 infection. Absolute bioavailability in 12 healthy
117 adults following single-dose administration was $93 \pm 9\%$ (mean \pm SD) for a 50 mg tablet and $91 \pm$
118 8% for an oral solution. Peak plasma nevirapine concentrations of $2 \pm 0.4 \mu\text{g/mL}$ ($7.5 \mu\text{M}$) were
119 attained by 4 hours following a single 200 mg dose. Following multiple doses, nevirapine peak
120 concentrations appear to increase linearly in the dose range of 200 to 400 mg/day. Steady state
121 trough nevirapine concentrations of $4.5 \pm 1.9 \mu\text{g/mL}$ ($17 \pm 7 \mu\text{M}$), (n = 242) were attained at 400
122 mg/day. Nevirapine tablets and suspension have been shown to be comparably bioavailable and
123 interchangeable at doses up to 200 mg. When VIRAMUNE (200 mg) was administered to 24
124 healthy adults (12 female, 12 male), with either a high fat breakfast (857 kcal, 50 g fat, 53% of
125 calories from fat) or antacid (Maalox[®] 30 mL), the extent of nevirapine absorption (AUC) was
126 comparable to that observed under fasting conditions. In a separate study in HIV-1 infected
127 patients (n=6), nevirapine steady-state systemic exposure (AUC_{τ}) was not significantly altered by
128 didanosine, which is formulated with an alkaline buffering agent. VIRAMUNE may be
129 administered with or without food, antacid or didanosine.

130
131 **Distribution:** Nevirapine is highly lipophilic and is essentially nonionized at physiologic pH.
132 Following intravenous administration to healthy adults, the apparent volume of distribution (Vd_{ss})
133 of nevirapine was $1.21 \pm 0.09 \text{ L/kg}$, suggesting that nevirapine is widely distributed in humans.
134 Nevirapine readily crosses the placenta and is also found in breast milk (see **PRECAUTIONS,**
135 **Nursing Mothers**). Nevirapine is about 60% bound to plasma proteins in the plasma
136 concentration range of 1-10 $\mu\text{g/mL}$. Nevirapine concentrations in human cerebrospinal fluid (n=6)
137 were 45% ($\pm 5\%$) of the concentrations in plasma; this ratio is approximately equal to the fraction
138 not bound to plasma protein.

141 **Metabolism/Elimination:** *In vivo* studies in humans and *in vitro* studies with human liver
142 microsomes have shown that nevirapine is extensively biotransformed via cytochrome P450
143 (oxidative) metabolism to several hydroxylated metabolites. *In vitro* studies with human liver
144 microsomes suggest that oxidative metabolism of nevirapine is mediated primarily by cytochrome
145 P450 (CYP) isozymes from the CYP3A4 and CYP2B6 families, although other isozymes may
146 have a secondary role. In a mass balance/excretion study in eight healthy male volunteers dosed
147 to steady state with nevirapine 200 mg given twice daily followed by a single 50 mg dose of ¹⁴C-
148 nevirapine, approximately 91.4 ± 10.5% of the radiolabeled dose was recovered, with urine (81.3
149 ± 11.1%) representing the primary route of excretion compared to feces (10.1 ± 1.5%). Greater
150 than 80% of the radioactivity in urine was made up of glucuronide conjugates of hydroxylated
151 metabolites. Thus cytochrome P450 metabolism, glucuronide conjugation, and urinary excretion
152 of glucuronidated metabolites represent the primary route of nevirapine biotransformation and
153 elimination in humans. Only a small fraction (<5%) of the radioactivity in urine (representing <3%
154 of the total dose) was made up of parent compound; therefore, renal excretion plays a minor role
155 in elimination of the parent compound.

156
157 Nevirapine is an inducer of hepatic cytochrome P450 (CYP) metabolic enzymes 3A4 and 2B6.
158 Nevirapine induces CYP3A4 and CYP2B6 by approximately 20-25%, as indicated by
159 erythromycin breath test results and urine metabolites. Autoinduction of CYP3A4 and CYP2B6
160 mediated metabolism leads to an approximately 1.5 to 2 fold increase in the apparent oral
161 clearance of nevirapine as treatment continues from a single dose to two-to-four weeks of dosing
162 with 200-400 mg/day. Autoinduction also results in a corresponding decrease in the terminal
163 phase half-life of nevirapine in plasma, from approximately 45 hours (single dose) to
164 approximately 25-30 hours following multiple dosing with 200-400 mg/day.

165 166 **Pharmacokinetics in Special Populations**

167 **Renal Impairment:** HIV seronegative adults with mild (CrCL 50-79 mL/min; n=7), moderate
168 (CrCL 30-49 mL/min; n=6), or severe (CrCL <30 mL/min; n=4) renal impairment received a single
169 200 mg dose of nevirapine in a pharmacokinetic study. These subjects did not require dialysis.
170 The study included six additional subjects with renal failure requiring dialysis.

171
172 In subjects with renal impairment (mild, moderate or severe), there were no significant changes in
173 the pharmacokinetics of nevirapine. However, subjects requiring dialysis exhibited a 44%
174 reduction in nevirapine AUC over a one-week exposure period. There was also evidence of
175 accumulation of nevirapine hydroxy-metabolites in plasma in subjects requiring dialysis. An
176 additional 200 mg dose following each dialysis treatment is indicated (see **DOSAGE AND**
177 **ADMINISTRATION** and **PRECAUTIONS**).

178
179 **Hepatic Impairment:** HIV seronegative adults with mild (Child-Pugh Class A; n=6) or moderate
180 (Child-Pugh Class B; n=4) hepatic impairment received a single 200 mg dose of nevirapine in a
181 pharmacokinetic study.

182
183 In the majority of patients with mild or moderate hepatic impairment, no significant changes were
184 seen in the pharmacokinetics of nevirapine. However, a significant increase in the AUC of
185 nevirapine observed in one patient with Child-Pugh Class B and ascites suggests that patients
186 with worsening hepatic function and ascites may be at risk of accumulating nevirapine in the
187 systemic circulation. Because nevirapine induces its own metabolism with multiple dosing, a
188 single dose study may not reflect the impact of hepatic impairment on multiple dose
189 pharmacokinetics (see **PRECAUTIONS**). Nevirapine should not be administered to patients with
190 severe hepatic impairment (see **WARNINGS**).

191
192 **Gender:** In the multinational 2NN study, a population pharmacokinetic substudy of 1077 patients
193 was performed that included 391 females. Female patients showed a 13.8% lower clearance of
194 nevirapine than did men. Since neither body weight nor Body Mass Index (BMI) had an influence
195 on the clearance of nevirapine, the effect of gender cannot solely be explained by body size.

197 **Race:** An evaluation of nevirapine plasma concentrations (pooled data from several clinical trials)
198 from HIV-1- infected patients (27 Black, 24 Hispanic, 189 Caucasian) revealed no marked
199 difference in nevirapine steady-state trough concentrations (median C_{minss} = 4.7 $\mu\text{g/mL}$ Black, 3.8
200 $\mu\text{g/mL}$ Hispanic, 4.3 $\mu\text{g/mL}$ Caucasian) with long-term nevirapine treatment at 400 mg/day.
201 However, the pharmacokinetics of nevirapine have not been evaluated specifically for the effects
202 of ethnicity.

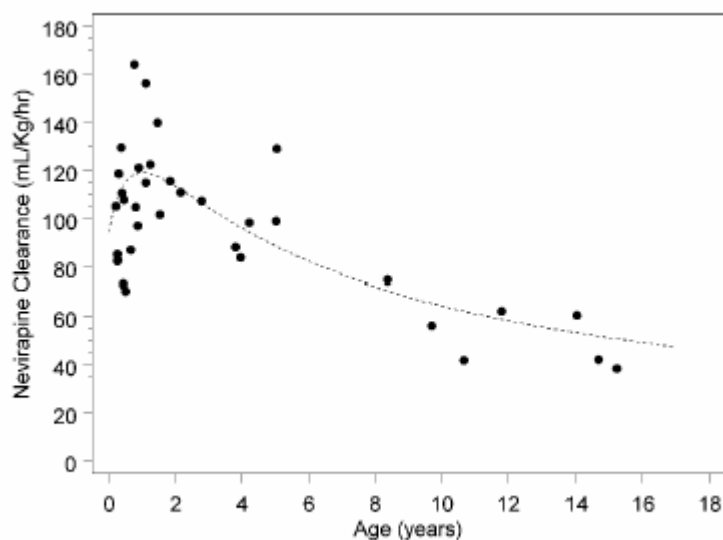
203
204 **Geriatric Patients:** Nevirapine pharmacokinetics in HIV-1-infected adults do not appear to
205 change with age (range 18–68 years); however, nevirapine has not been extensively evaluated in
206 patients beyond the age of 55 years.

207
208 **Pediatric Patients:** The pharmacokinetics of nevirapine have been studied in two open-label
209 studies in children with HIV-1 infection. In one study (BI 853; ACTG 165), nine HIV-1-infected
210 children ranging in age from 9 months to 14 years were administered a single dose (7.5 mg, 30
211 mg, or 120 mg per m^2 ; n=3 per dose) of nevirapine suspension after an overnight fast. The mean
212 nevirapine apparent clearance adjusted for body weight was greater in children compared to
213 adults.

214
215 In a multiple dose study (BI 882; ACTG 180), nevirapine suspension or tablets (240 or 400
216 $\text{mg}/\text{m}^2/\text{day}$) were administered as monotherapy or in combination with ZDV or ZDV+ddl to 37
217 HIV-1-infected pediatric patients with the following demographics: male (54%), racial minority
218 groups (73%), median age of 11 months (range: 2 months-15 years). The majority of these
219 patients received 120 $\text{mg}/\text{m}^2/\text{day}$ of nevirapine for approximately 4 weeks followed by 120
220 $\text{mg}/\text{m}^2/\text{BID}$ (patients > 9 years of age) or 200 $\text{mg}/\text{m}^2/\text{BID}$ (patients \leq 9 years of age). Nevirapine
221 apparent clearance adjusted for body weight reached maximum values by age 1 to 2 years and
222 then decreased with increasing age. Nevirapine apparent clearance adjusted for body weight was
223 at least two-fold greater in children younger than 8 years compared to adults. The relationship
224 between nevirapine clearance with long term drug administration and age is shown in Figure 1.
225 The pediatric dosing regimens were selected in order to achieve steady-state plasma
226 concentrations in pediatric patients that approximate those in adults (see **DOSAGE AND**
227 **ADMINISTRATION, Pediatric Patients**).

228

Figure 1: Nevirapine Apparent Clearance ($\text{mL}/\text{kg}/\text{hr}$) in Pediatric Patients



229
230

231 **Drug Interactions:** (see **PRECAUTIONS, Drug Interactions**) Nevirapine induces hepatic
232 cytochrome P450 metabolic isoenzymes 3A4 and 2B6. Co-administration of VIRAMUNE and
233 drugs primarily metabolized by CYP3A4 or CYP2B6 may result in decreased plasma
234 concentrations of these drugs and attenuate their therapeutic effects.

235
236 While primarily an inducer of cytochrome P450 3A4 and 2B6 enzymes, nevirapine may also
237 inhibit this system. Among human hepatic cytochrome P450s, nevirapine was capable *in vitro* of
238 inhibiting the 10-hydroxylation of (R)-warfarin (CYP3A4). The estimated K_i for the inhibition of
239 CYP3A4 was 270 μM , a concentration that is unlikely to be achieved in patients as the
240 therapeutic range is $<25 \mu\text{M}$. Therefore, nevirapine may have minimal inhibitory effect on other
241 substrates of CYP3A4.

242
243 Nevirapine does not appear to affect the plasma concentrations of drugs that are substrates of
244 other CYP450 enzyme systems, such as 1A2, 2D6, 2A6, 2E1, 2C9 or 2C19.

245
246 Table 1 (see below) contains the results of drug interaction studies performed with VIRAMUNE
247 and other drugs likely to be co-administered. The effects of VIRAMUNE on the AUC, C_{max} , and
248 C_{min} of co-administered drugs are summarized. To measure the full potential pharmacokinetic
249 interaction effect following induction, patients on the concomitant drug at steady state were
250 administered 28 days of VIRAMUNE (200 mg QD for 14 days followed by 200 mg BID for 14
251 days) followed by a steady state reassessment of the concomitant drug.

252
253
254
255
256

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

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}
Antiretrovirals						
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)
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)
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	↔	↔	↔
Saquinavir ^a	600 mg TID	200 mg QD x 14 days; 200 mg BID x 21 days	23	↓38 (↓47 to ↓11)	↓32 (↓44 to ↓6)	§
Stavudine	30-40 mg BID	200 mg QD x 14 days; 200 mg BID x 14 days	22	↔	↔	§
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						
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)

257

Metabolite 14-OH- clarithromycin				↑42 (↑16 to ↑73)	↑47 (↑21 to ↑80)	↔
Ethinyl estradiol ^a and Norethindrone ^a	0.035 mg (as Ortho- Novum® 1/35) 1 mg (as Ortho- Novum® 1/35)	200 mg QD x 14 days; 200 mg BID x 14 days	10	↓20 (↓33 to ↓3)	↔	§
Fluconazole	200 mg QD	200 mg QD x 14 days; 200 mg BID x 14 days	19	↔	↔	↔
Ketoconazole ^a	400 mg QD	200 mg QD x 14 days; 200 mg BID x 14 days	21	↓72 (↓80 to ↓60)	↓44 (↓58 to ↓27)	§
Methadone ^a	Individual Patient Dosing	200 mg QD x 14 days; 200 mg BID ≥ 7 days	9	In a controlled pharmacokinetic study with 9 patients 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 patients. 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)	↔	§

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

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

260 ^aFor information regarding clinical recommendations see **PRECAUTIONS, Drug Interactions, Table 3.**

261 ^bPediatric subjects ranging in age from 6 months to 12 years

262 ^cParallel group design; n for VIRAMUNE +lopinavir/ritonavir, n for lopinavir/ritonavir alone

263

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

267

268 Administration of rifampin had a clinically significant effect on nevirapine pharmacokinetics,
269 decreasing AUC and C_{max} by greater than 50%. Administration of fluconazole resulted in an
270 approximate 100% increase in nevirapine exposure, based on a comparison to historic data (see
271 **PRECAUTIONS, Drug Interactions, Table 3**). The effect of other drugs listed in Table 1 on
272 nevirapine pharmacokinetics was not significant.

273

INDICATIONS AND USAGE

274 VIRAMUNE (nevirapine) is indicated for use in combination with other antiretroviral agents for the
 275 treatment of HIV-1-infection. This indication is based on one principal clinical trial (BI 1090) that
 276 demonstrated prolonged suppression of HIV-RNA and two smaller supportive studies, one of
 277 which (BI 1046) is described below.

278
 279 Additional important information regarding the use of VIRAMUNE for the treatment of HIV-1
 280 infection:

- 281 • Based on serious and life-threatening hepatotoxicity observed in controlled and uncontrolled
 282 studies, VIRAMUNE should not be initiated in adult females with CD4+ cell counts greater
 283 than 250 cells/mm³ or in adult males with CD4+ cell counts greater than 400 cells/mm³ unless
 284 the benefit outweighs the risk (see **WARNINGS**).
- 285 • The 14-day lead-in period with VIRAMUNE 200 mg daily dosing has been demonstrated to
 286 reduce the frequency of rash (see **WARNINGS** and **DOSAGE AND ADMINISTRATION**).

287
 288 **Description of Clinical Studies**

289 **Trial BI 1090**, was a placebo-controlled, double-blind, randomized trial in 2249 HIV-1-infected
 290 patients with <200 CD4+ cells/mm³ at screening. Initiated in 1995, BI 1090 compared treatment
 291 with VIRAMUNE + lamivudine + background therapy versus lamivudine + background therapy in
 292 NNRTI naïve patients. Treatment doses were VIRAMUNE, 200 mg daily for two weeks followed
 293 by 200 mg twice daily or placebo, and lamivudine 150 mg twice daily. Other antiretroviral agents
 294 were given at approved doses. Initial background therapy (in addition to lamivudine) was one
 295 NRTI in 1309 patients (58%), two or more NRTIs in 771 (34%), and PIs and NRTIs in 169 (8%).
 296 The patients (median age 36.5 years, 70% Caucasian, 79% male) had advanced HIV infection,
 297 with a median baseline CD4+ cell count of 96 cells/mm³ and a baseline HIV RNA of 4.58 log₁₀
 298 copies/mL (38,291 copies/mL). Prior to entering the trial, 45% had previously experienced an
 299 AIDS-defining clinical event. Eighty-nine percent had antiretroviral treatment prior to entering the
 300 trial. BI 1090 was originally designed as a clinical endpoint study. Prior to unblinding the trial, the
 301 primary endpoint was changed to proportion of patients with HIV RNA <50 copies/mL and not
 302 previously failed at 48 weeks. Treatment response and outcomes are shown in Table 2.

303
 304 **Table 2 BI 1090 Outcomes through 48 weeks**

Outcome	VIRAMUNE (N=1121) %	Placebo (N=1128) %
Responders at 48 weeks: HIV RNA <50 copies/mL	18.0	1.6
Treatment Failure	82.0	98.4
Never suppressed viral load	44.6	66.4
Virologic failure after response	7.2	4.3
CDC category C event or death	9.6	11.2
Added antiretroviral therapy ¹ while <50 copies/mL	5.0	0.9
Discontinued trial therapy due to AE	7.0	5.9
Discontinued trial <48 weeks ²	8.5	9.8

306 ¹ including change to open-label NVP

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

308
 309 The change from baseline in CD4+ cell count through one year of therapy was significantly
 310 greater for the VIRAMUNE group compared to the placebo group for the overall study population
 311 (64 cells/mm³ vs 22 cells/mm³, respectively), as well as for patients who entered the trial as
 312 treatment naïve or having received only ZDV (85 cells/mm³ vs 25 cells/mm³, respectively).

313
 314 At two years into the study, 16% of subjects on VIRAMUNE had experienced class C CDC events
 315 as compared to 21% of subjects on the control arm.

316
 317 **Trial BI 1046** (INCAS) was a double-blind, placebo-controlled, randomized, three arm trial with
 318 151 HIV-1 infected patients with CD4+ cell counts of 200-600 cells/mm³ at baseline. BI 1046

319 compared treatment with VIRAMUNE+zidovudine+didanosine to VIRAMUNE+zidovudine and
320 zidovudine+didanosine. Treatment doses were VIRAMUNE at 200 mg daily for two weeks
321 followed by 200 mg twice daily or placebo, zidovudine at 200 mg three times daily, and
322 didanosine at 125 or 200 mg twice daily (depending on body weight). The patients had mean
323 baseline HIV RNA of 4.41 log₁₀ copies/mL (25,704 copies/mL) and mean baseline CD4+ cell
324 count of 376 cells/mm³. The primary endpoint was the proportion of patients with HIV-RNA < 400
325 copies/mL and not previously failed at 48 weeks. The virologic responder rates at 48 weeks were
326 45% for patients treated with VIRAMUNE+zidovudine+didanosine, 19% for patients treated with
327 zidovudine+didanosine, and 0% for patients treated with VIRAMUNE+zidovudine.

328
329 CD4+ cell counts in the VIRAMUNE+ZDV+ddl group increased above baseline by a mean of 139
330 cells/mm³ at one year, significantly greater than the increase of 87 cells/mm³ in the ZDV+ddl
331 patients. The VIRAMUNE+ZDV group mean decreased by 6 cells/mm³ below baseline.
332

333 **CONTRAINDICATIONS**

334 VIRAMUNE (nevirapine) is contraindicated in patients with clinically significant hypersensitivity to
335 any of the components contained in the tablet or the oral suspension.
336

337 **WARNINGS**

338 **General**

339 The most serious adverse reactions associated with VIRAMUNE (nevirapine) are
340 hepatitis/hepatic failure, Stevens-Johnson syndrome, toxic epidermal necrolysis, and
341 hypersensitivity reactions. Hepatitis/hepatic failure may be associated with signs of
342 hypersensitivity which can include severe rash or rash accompanied by fever, general malaise,
343 fatigue, muscle or joint aches, blisters, oral lesions, conjunctivitis, facial edema, eosinophilia,
344 granulocytopenia, lymphadenopathy, or renal dysfunction.
345

346 **The first 18 weeks of therapy with VIRAMUNE are a critical period during which intensive**
347 **clinical and laboratory monitoring of patients is required to detect potentially life-**
348 **threatening hepatic events and skin reactions.** The optimal frequency of monitoring during this
349 time period has not been established. Some experts recommend clinical and laboratory
350 monitoring more often than once per month, and in particular, would include monitoring of liver
351 function tests at baseline, prior to dose escalation and at two weeks post-dose escalation. After
352 the initial 18 week period, frequent clinical and laboratory monitoring should continue throughout
353 VIRAMUNE treatment. In addition, the 14-day lead-in period with VIRAMUNE 200 mg daily
354 dosing has been demonstrated to reduce the frequency of rash.
355

356 **Hepatic Events**

357 Severe, life-threatening, and in some cases fatal hepatotoxicity, including fulminant and
358 cholestatic hepatitis, hepatic necrosis and hepatic failure, have been reported in patients treated
359 with VIRAMUNE. In controlled clinical trials, symptomatic hepatic events regardless of severity
360 occurred in 4% (range 0% to 11.0%) of patients who received VIRAMUNE and 1.2% of patients in
361 control groups.
362

363 The risk of symptomatic hepatic events regardless of severity was greatest in the first 6 weeks of
364 therapy. The risk continued to be greater in the VIRAMUNE groups compared to controls through
365 18 weeks of treatment. However, hepatic events may occur at any time during treatment. In
366 some cases, patients presented with non-specific, prodromal signs or symptoms of fatigue,
367 malaise, anorexia, nausea, jaundice, liver tenderness or hepatomegaly, with or without initially
368 abnormal serum transaminase levels. Rash was observed in approximately half of the patients
369 with symptomatic hepatic adverse events. Fever and flu-like symptoms accompanied some of
370 these hepatic events. Some events, particularly those with rash and other symptoms, have
371 progressed to hepatic failure with transaminase elevation, with or without hyperbilirubinemia,
372 hepatic encephalopathy, prolonged partial thromboplastin time, or eosinophilia. Patients with

373 signs or symptoms of hepatitis must be advised to discontinue VIRAMUNE and immediately seek
374 medical evaluation, which should include liver function tests.

375
376 **Liver function tests should be performed immediately if a patient experiences signs or**
377 **symptoms suggestive of hepatitis and/or hypersensitivity reaction. Liver function tests**
378 **should also be obtained immediately for all patients who develop a rash in the first 18**
379 **weeks of treatment. Physicians and patients should be vigilant for the appearance of signs**
380 **or symptoms of hepatitis, such as fatigue, malaise, anorexia, nausea, jaundice,**
381 **bilirubinuria, acholic stools, liver tenderness or hepatomegaly. The diagnosis of**
382 **hepatotoxicity should be considered in this setting, even if liver function tests are initially**
383 **normal or alternative diagnoses are possible (see PRECAUTIONS, *Information for Patients***
384 **and DOSAGE AND ADMINISTRATION).**

385
386 If clinical hepatitis or transaminase elevations combined with rash or other systemic symptoms
387 occur, VIRAMUNE should be permanently discontinued. Do not restart VIRAMUNE after
388 recovery. In some cases, hepatic injury progresses despite discontinuation of treatment.

389
390 The patients at greatest risk of hepatic events, including potentially fatal events, are women with
391 high CD4 counts. In general, during the first 6 weeks of treatment, women have a three fold
392 higher risk than men for symptomatic, often rash-associated, hepatic events (5.8% versus 2.2%),
393 and patients with higher CD4 counts at initiation of VIRAMUNE therapy are at higher risk for
394 symptomatic hepatic events with VIRAMUNE. In a retrospective review, women with CD4 counts
395 >250 cells/mm³ had a 12 fold higher risk of symptomatic hepatic adverse events compared to
396 women with CD4 counts <250 cells/mm³ (11.0% versus 0.9%). An increased risk was observed in
397 men with CD4 counts >400 cells/mm³ (6.3% versus 1.2% for men with CD4 counts <400
398 cells/mm³). However, all patients, regardless of gender, CD4 count, or antiretroviral treatment
399 history, should be monitored for hepatotoxicity since symptomatic hepatic adverse events have
400 been reported at all CD4 counts. Co-infection with hepatitis B or C and/or increased liver function
401 tests at the start of therapy with VIRAMUNE® are associated with a greater risk of later
402 symptomatic events (6 weeks or more after starting VIRAMUNE) and asymptomatic increases in
403 AST or ALT.

404
405 In addition, serious hepatotoxicity (including liver failure requiring transplantation in one instance)
406 has been reported in HIV-uninfected individuals receiving multiple doses of VIRAMUNE in the
407 setting of post-exposure prophylaxis, an unapproved use.

408
409 Because increased nevirapine levels and nevirapine accumulation may be observed in patients
410 with serious liver disease, VIRAMUNE should not be administered to patients with severe
411 hepatic impairment (see **CLINICAL PHARMACOLOGY, *Pharmacokinetics in Special***
412 ***Populations: Hepatic Impairment; PRECAUTIONS, General***).

413 414 ***Skin Reactions***

415 Severe and life-threatening skin reactions, including fatal cases, have been reported, occurring
416 most frequently during the first 6 weeks of therapy. These have included cases of Stevens-
417 Johnson syndrome, toxic epidermal necrolysis, and hypersensitivity reactions characterized by
418 rash, constitutional findings, and organ dysfunction including hepatic failure. In controlled clinical
419 trials, Grade 3 and 4 rashes were reported during the first 6 weeks in 1.5% of VIRAMUNE
420 recipients compared to 0.1% of placebo subjects.

421
422 Patients developing signs or symptoms of severe skin reactions or hypersensitivity reactions
423 (including, but not limited to, severe rash or rash accompanied by fever, general malaise, fatigue,
424 muscle or joint aches, blisters, oral lesions, conjunctivitis, facial edema, and/or hepatitis,
425 eosinophilia, granulocytopenia, lymphadenopathy, and renal dysfunction) must permanently
426 discontinue VIRAMUNE and seek medical evaluation immediately (see **PRECAUTIONS,**
427 ***Information for Patients***). Do not restart VIRAMUNE following severe skin rash, skin rash
428 combined with increased transaminases or other symptoms, or hypersensitivity reaction.

429
430 If patients present with a suspected VIRAMUNE-associated rash, liver function tests should be
431 performed. Patients with rash-associated AST or ALT elevations should be permanently
432 discontinued from VIRAMUNE.

433
434 Therapy with VIRAMUNE must be initiated with a 14-day lead-in period of 200 mg/day (4
435 mg/kg/day in pediatric patients), which has been shown to reduce the frequency of rash. If rash
436 is observed during this lead-in period, dose escalation should not occur until the rash has
437 resolved (see **DOSAGE AND ADMINISTRATION**). Patients should be monitored closely if
438 isolated rash of any severity occurs. Delay in stopping VIRAMUNE treatment after the onset of
439 rash may result in a more serious reaction.

440
441 Women appear to be at higher risk than men of developing rash with VIRAMUNE.
442

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

447

448 **Resistance**

449 VIRAMUNE must not be used as a single agent to treat HIV or added on as a sole agent to a
450 failing regimen. As with all other non-nucleoside reverse transcriptase inhibitors, resistant virus
451 emerges rapidly when nevirapine is administered as monotherapy. The choice of new
452 antiretroviral agents to be used in combination with nevirapine should take into consideration the
453 potential for cross resistance. When discontinuing an antiretroviral regimen containing
454 VIRAMUNE, the long half-life of nevirapine should be taken into account; if antiretrovirals with
455 shorter half-lives than VIRAMUNE are stopped concurrently, low plasma concentrations of
456 nevirapine alone may persist for a week or longer and virus resistance may subsequently
457 develop.

458

459 **St. John's wort**

460 Concomitant use of St. John's wort (*Hypericum perforatum*) or St. John's wort containing products
461 and VIRAMUNE is not recommended. Co-administration of non-nucleoside reverse transcriptase
462 inhibitors (NNRTIs), including VIRAMUNE, with St. John's wort is expected to substantially
463 decrease NNRTI concentrations and may result in sub-optimal levels of VIRAMUNE and lead to
464 loss of virologic response and possible resistance to VIRAMUNE or to the class of NNRTIs.

465

466 **PRECAUTIONS**

467 **General**

468 The most serious adverse reactions associated with VIRAMUNE (nevirapine) are
469 hepatitis/hepatic failure, Stevens-Johnson syndrome, toxic epidermal necrolysis, and
470 hypersensitivity reactions. Hepatitis/hepatic failure may be isolated or associated with signs of
471 hypersensitivity which may include severe rash or rash accompanied by fever, general malaise,
472 fatigue, muscle or joint aches, blisters, oral lesions, conjunctivitis, facial edema, eosinophilia,
473 granulocytopenia, lymphadenopathy, or renal dysfunction (see **WARNINGS**).

474

475 Nevirapine is extensively metabolized by the liver and nevirapine metabolites are extensively
476 eliminated by the kidney. No adjustment in nevirapine dosing is required in patients with CrCL
477 ≥ 20 mL/min. In patients undergoing chronic hemodialysis, an additional 200 mg dose following
478 each dialysis treatment is indicated. Nevirapine metabolites may accumulate in patients receiving
479 dialysis; however, the clinical significance of this accumulation is not known (see **CLINICAL**
480 **PHARMACOLOGY, Pharmacokinetics in Special Populations: Renal Impairment; DOSAGE**
481 **AND ADMINISTRATION, Dosage Adjustment**).

482

483 It is not clear whether a dosing adjustment is needed for patients with mild to moderate hepatic
484 impairment, because multiple dose pharmacokinetic data are not available for this population.
485 However, patients with moderate hepatic impairment and ascites may be at risk of accumulating
486 nevirapine in the systemic circulation. Caution should be exercised when nevirapine is
487 administered to patients with moderate hepatic impairment. Nevirapine should not be
488 administered to patients with severe hepatic impairment (see **WARNINGS; CLINICAL**
489 **PHARMACOLOGY, *Pharmacokinetics in Special Populations: Hepatic Impairment***).

490
491 The duration of clinical benefit from antiretroviral therapy may be limited. Patients receiving
492 VIRAMUNE or any other antiretroviral therapy may continue to develop opportunistic infections
493 and other complications of HIV infection, and therefore should remain under close clinical
494 observation by physicians experienced in the treatment of patients with associated HIV diseases.

495
496 When administering VIRAMUNE as part of an antiretroviral regimen, the complete product
497 information for each therapeutic component should be consulted before initiation of treatment.

498 499 ***Drug Interactions***

500 Nevirapine is principally metabolized by the liver via the cytochrome P450 isoenzymes, 3A4 and
501 2B6. Nevirapine is known to be an inducer of these enzymes. As a result, drugs that are
502 metabolized by these enzyme systems may have lower than expected plasma levels when co-
503 administered with nevirapine.

504
505 The specific pharmacokinetic changes that occur with co-administration of nevirapine and other
506 drugs are listed in **CLINICAL PHARMACOLOGY**, Table 1. Clinical comments about possible
507 dosage modifications based on these pharmacokinetic changes are listed in Table 3. The data in
508 Tables 1 and 3 are based on the results of drug interaction studies conducted in HIV-1
509 seropositive subjects unless otherwise indicated.

510
511 In addition to established drug interactions, there may be potential pharmacokinetic interactions
512 between nevirapine and other drug classes that are metabolized by the cytochrome P450 system.
513 These potential drug interactions are listed in Table 4. Although specific drug interaction studies
514 in HIV-1 seropositive subjects have not been conducted for the classes of drugs listed in Table 4,
515 additional clinical monitoring may be warranted when co-administering these drugs.

516
517 The *in vitro* interaction between nevirapine and the antithrombotic agent warfarin is complex. As
518 a result, when giving these drugs concomitantly, plasma warfarin levels may change with the
519 potential for increases in coagulation time. When warfarin is co-administered with nevirapine,
520 anticoagulation levels should be monitored frequently.

Table 3 *Established Drug Interactions: Alteration in Dose or Regimen May Be Recommended Based on Drug Interaction Studies (see CLINICAL PHARMACOLOGY, Table 1 for Magnitude of Interaction)*

Drug Name	Effect on Concentration of Nevirapine or Concomitant Drug	Clinical Comment
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.
Efavirenz	↓ Efavirenz	Appropriate doses for this combination are not established.
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.
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.
Indinavir	↓ Indinavir	Appropriate doses for this combination are not established, but an increase in the dosage of indinavir may be required.
Ketoconazole	↓ Ketoconazole	Nevirapine and ketoconazole should not be administered concomitantly because decreases in ketoconazole plasma concentrations may reduce the efficacy of the drug.
Lopinavir/Ritonavir	↓ Lopinavir	KALETRA 400/100 mg tablets can be used twice-daily in combination with nevirapine with no dose adjustment in antiretroviral-naïve patients. A dose increase of KALETRA tablets to 600/150 mg (3 tablets) twice daily may be considered when used in combination with nevirapine in treatment experienced patients where decreased susceptibility to lopinavir is clinically suspected (by treatment history or laboratory evidence). A dose increase of lopinavir/ritonavir oral solution to 533/133 mg twice daily with

		<p>food is recommended in combination with nevirapine.</p> <p>In children 6 months to 12 years of age, consideration should be given to increasing the dose of lopinavir/ritonavir to 13/3.25 mg/kg for those 7 to < 15 kg; 11/2.75 mg/kg for those 15 to 45 kg; and up to a maximum dose of 533/133 mg for those > 45 kg twice daily when used in combination with nevirapine, particularly for patients in whom reduced susceptibility to lopinavir/ritonavir is suspected.</p>
Methadone	↓ Methadone	<p>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.</p>
Nelfinavir	↓Nelfinavir M8 Metabolite ↓Nelfinavir C _{min}	<p>The appropriate dose for nelfinavir in combination with nevirapine, with respect to safety and efficacy, has not been established.</p>
Rifabutin	↑Rifabutin	<p>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.</p>
Rifampin	↓ Nevirapine	<p>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.</p>
Saquinavir	↓Saquinavir	<p>Appropriate doses for this combination are not established, but an increase in the dosage of saquinavir may be required.</p>

522
523

Table 4 Potential Drug Interactions: Use With Caution, Dose Adjustment of Co-administered Drug May Be Needed due to Possible Decrease in Clinical Effect

Examples of Drugs in Which Plasma Concentrations May Be Decreased By Co-administration With Nevirapine	
Drug Class	Examples of Drugs
Antiarrhythmics	Amiodarone, disopyramide, lidocaine
Anticonvulsants	Carbamazepine, clonazepam, ethosuximide
Antifungals	Itraconazole
Calcium channel blockers	Diltiazem, nifedipine, verapamil

Cancer chemotherapy	Cyclophosphamide
Ergot alkaloids	Ergotamine
Immunosuppressants	Cyclosporin, tacrolimus, sirolimus
Motility agents	Cisapride
Opiate agonists	Fentanyl
Examples of Drugs in Which Plasma Concentrations May Be Increased By Co-administration With Nevirapine	
Antithrombotics	Warfarin Potential effect on anticoagulation. Monitoring of anticoagulation levels is recommended.

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Fat Redistribution

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Immune Reconstitution Syndrome

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Information for Patients

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Patients should be informed of the possibility of severe liver disease or skin reactions associated with VIRAMUNE that may result in death. Patients developing signs or symptoms of liver disease or severe skin reactions should be instructed 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.

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Intensive clinical and laboratory monitoring, including liver function tests, 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. Patients with signs and symptoms of hepatitis should 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 (>250 cells/mm³ in women and >400 cells/mm³ in men) are at substantially higher risk for development of symptomatic hepatic events, often associated with rash. Patients should be advised that co-infection with hepatitis B or C and/or increased liver function tests 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 **WARNINGS, Hepatic Events**).

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569

The majority of rashes associated with VIRAMUNE occur within the first 6 weeks of initiation of therapy. Patients should be instructed that if any rash occurs during the two-week lead-in period, the VIRAMUNE dose should not be escalated until the rash resolves. Any patient experiencing a rash should have their liver function evaluated immediately. Patients with severe rash or hypersensitivity reactions should discontinue VIRAMUNE immediately and consult a physician.

570 VIRAMUNE should not be restarted following severe skin rash or hypersensitivity reaction.
571 Women tend to be at higher risk for development of VIRAMUNE associated rash.

572
573 Oral contraceptives and other hormonal methods of birth control should not be used as the sole
574 method of contraception in women taking VIRAMUNE, since VIRAMUNE may lower the plasma
575 levels of these medications. Additionally, when oral contraceptives are used for hormonal
576 regulation during VIRAMUNE therapy, the therapeutic effect of the hormonal therapy should be
577 monitored (see **PRECAUTIONS, Drug Interactions**).

578
579 VIRAMUNE may decrease plasma concentrations of methadone by increasing its hepatic
580 metabolism. Narcotic withdrawal syndrome has been reported in patients treated with
581 VIRAMUNE and methadone concomitantly. Methadone-maintained patients beginning nevirapine
582 therapy should be monitored for evidence of withdrawal and methadone dose should be adjusted
583 accordingly.

584
585 VIRAMUNE may interact with some drugs, therefore, patients should be advised to report to their
586 doctor the use of any other prescription, non-prescription medication or herbal products,
587 particularly St. John's wort.

588
589 Patients should be informed that VIRAMUNE therapy has not been shown to reduce the risk of
590 transmission of HIV-1 to others through sexual contact or blood contamination. The long-term
591 effects of VIRAMUNE are unknown at this time.

592
593 VIRAMUNE is not a cure for HIV-1 infection; patients may continue to experience illnesses
594 associated with advanced HIV-1 infection, including opportunistic infections. Patients should be
595 advised to remain under the care of a physician when using VIRAMUNE.

596
597 Patients should be informed to take VIRAMUNE every day as prescribed. Patients should not
598 alter the dose without consulting their doctor. If a dose is missed, patients should take the next
599 dose as soon as possible. However, if a dose is skipped, the patient should not double the next
600 dose. Patients should be advised to report to their doctor the use of any other medications.

601
602 Patients should be informed that redistribution or accumulation of body fat may occur in patients
603 receiving antiretroviral therapy and that the cause and long term health effects of these conditions
604 are not known at this time.

605
606 **The Medication Guide provides written information for the patient, and should be**
607 **dispensed with each new prescription and refill.**

608
609 ***Carcinogenesis, Mutagenesis, Impairment of Fertility***

610 Long-term carcinogenicity studies in mice and rats were carried out with nevirapine. Mice were
611 dosed with 0, 50, 375 or 750 mg/kg/day for two years. Hepatocellular adenomas and carcinomas
612 were increased at all doses in males and at the two high doses in females. In studies in which
613 rats were administered nevirapine at doses of 0, 3.5, 17.5 or 35 mg/kg/day for two years, an
614 increase in hepatocellular adenomas was seen in males at all doses and in females at the high
615 dose. The systemic exposure (based on AUCs) at all doses in the two animal studies were lower
616 than that measured in humans at the 200 mg BID dose. The mechanism of the carcinogenic
617 potential is unknown. However, in genetic toxicology assays, nevirapine showed no evidence of
618 mutagenic or clastogenic activity in a battery of *in vitro* and *in vivo* studies. These included
619 microbial assays for gene mutation (Ames: Salmonella strains and *E. coli*), mammalian cell gene
620 mutation assay (CHO/HGPRT), cytogenetic assays using a Chinese hamster ovary cell line and a
621 mouse bone marrow micronucleus assay following oral administration. Given the lack of
622 genotoxic activity of nevirapine, the relevance to humans of hepatocellular neoplasms in
623 nevirapine treated mice and rats is not known. In reproductive toxicology studies, evidence of
624 impaired fertility was seen in female rats at doses providing systemic exposure, based on AUC,
625 approximately equivalent to that provided with the recommended clinical dose of VIRAMUNE.

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Pregnancy: Pregnancy Category B

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

There are no adequate and well-controlled studies of 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 infection. Regardless of pregnancy status women with CD4 counts >250 cells/mm³ 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.

Nursing Mothers

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

Pediatric Use

The pharmacokinetics of nevirapine have been studied in two open-label studies in children with HIV-1 infection (see **CLINICAL PHARMACOLOGY, Pharmacokinetics in Special Populations**). For dose recommendations for pediatric patients see **DOSAGE AND ADMINISTRATION**. The most frequently reported adverse events related to VIRAMUNE in pediatric patients were similar to those observed in adults, with the exception of granulocytopenia, which was more commonly observed in children receiving both zidovudine and VIRAMUNE (see **ADVERSE REACTIONS, Pediatric Patients**). The evaluation of the antiviral activity of VIRAMUNE in pediatric patients is ongoing.

Geriatric Use

Clinical studies 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.

ADVERSE REACTIONS

679 The most serious adverse reactions associated with VIRAMUNE (nevirapine) are
 680 hepatitis/hepatic failure, Stevens-Johnson syndrome, toxic epidermal necrolysis, and
 681 hypersensitivity reactions. Hepatitis/hepatic failure may be isolated or associated with signs of
 682 hypersensitivity which may include severe rash or rash accompanied by fever, general malaise,
 683 fatigue, muscle or joint aches, blisters, oral lesions, conjunctivitis, facial edema, eosinophilia,
 684 granulocytopenia, lymphadenopathy, or renal dysfunction (see **WARNINGS**).

685
 686 **Adults**

687 The most common clinical toxicity of VIRAMUNE is rash, which can be severe or life-threatening
 688 (see **WARNINGS**). Rash occurs most frequently within the first 6 weeks of therapy. Rashes are
 689 usually mild to moderate, maculopapular erythematous cutaneous eruptions, with or without
 690 pruritus, located on the trunk, face and extremities. In controlled clinical trials, Grade 1 and 2
 691 rashes were reported in 13.3% of patients receiving VIRAMUNE compared to 5.8% receiving
 692 placebo during the first 6 weeks of therapy. Grade 3 and 4 rashes were reported in 1.5% of
 693 VIRAMUNE recipients compared to 0.1% of subjects receiving placebo. Women tend to be at
 694 higher risk for development of VIRAMUNE associated rash.

695
 696 In controlled clinical trials, symptomatic hepatic events regardless of severity occurred in 4.0%
 697 (range 0% to 11.0%) of patients who received VIRAMUNE and 1.2% of patients in control groups.
 698 Female gender and higher CD4 counts (>250 cells/mm³ in women and >400 cells/mm³ in men)
 699 place patients at increased risk of these events (see **WARNINGS**).

700
 701 Asymptomatic transaminase elevations (AST or ALT > 5X ULN) were observed in 5.8% (range
 702 0% to 9.2%) of patients who received VIRAMUNE and 5.5% of patients in control groups. Co-
 703 infection with hepatitis B or C and/or increased liver function tests at the start of therapy with
 704 VIRAMUNE are associated with a greater risk of later symptomatic events (6 weeks or more after
 705 starting VIRAMUNE) and asymptomatic increases in AST or ALT.

706
 707 Treatment related, adverse experiences of moderate or severe intensity observed in >2% of
 708 patients receiving VIRAMUNE in placebo-controlled trials are shown in Table 5.

709
 710 **Table 5 Percentage of Patients with Moderate or Severe Drug Related Events in**
 711 **Adult Placebo Controlled Trials**

	Trial 1090 ¹		Trials 1037, 1038, 1046 ²	
	VIRAMUNE (n=1121)	Placebo (n=1128)	VIRAMUNE (n=253)	Placebo (n=203)
Median exposure (weeks)	58	52	28	28
Any adverse event	14.5%	11.1%	31.6%	13.3%
Rash	5.1	1.8	6.7	1.5
Nausea	0.5	1.1	8.7	3.9
Granulocytopenia	1.8	2.8	0.4	0
Headache	0.7	0.4	3.6	0.5
Fatigue	0.2	0.3	4.7	3.9
Diarrhea	0.2	0.8	2.0	0.5
Abdominal pain	0.1	0.4	2.0	0
Myalgia	0.2	0	1.2	2.0

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

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

717
 718 **Laboratory Abnormalities:** Liver function test abnormalities (AST, ALT) were observed more
 719 frequently in patients receiving VIRAMUNE than in controls (Table 6). Asymptomatic elevations in
 720 GGT occur frequently but are not a contraindication to continue VIRAMUNE therapy in the

721 absence of elevations in other liver function tests. Other laboratory abnormalities (bilirubin,
722 anemia, neutropenia, thrombocytopenia) were observed with similar frequencies in clinical trials
723 comparing VIRAMUNE and control regimens (see Table 6).

724
725
726

Table 6 Percentage of Adult Patients with Laboratory Abnormalities

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

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

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

731

732 **Post Marketing Surveillance:** In addition to the adverse events identified during clinical trials,
733 the following events have been reported with the use of VIRAMUNE in clinical practice:

734 **Body as a Whole:** fever, somnolence, drug withdrawal (see **PRECAUTIONS: Drug**
735 **Interactions**), redistribution/accumulation of body fat (see **PRECAUTIONS, Fat**
736 **Redistribution**)

737 **Gastrointestinal:** vomiting

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

740 **Hematology:** anemia, eosinophilia, neutropenia

741 **Musculoskeletal:** arthralgia

742 **Neurologic:** paraesthesia

743 **Skin and Appendages:** allergic reactions including anaphylaxis, angioedema, bullous
744 eruptions, ulcerative stomatitis and urticaria have all been reported. In addition,
745 hypersensitivity syndrome and hypersensitivity reactions with rash associated with
746 constitutional findings such as fever, blistering, oral lesions, conjunctivitis, facial edema,
747 muscle or joint aches, general malaise, fatigue or significant hepatic abnormalities (see
748 **WARNINGS**) plus one or more of the following: hepatitis, eosinophilia, granulocytopenia,
749 lymphadenopathy and/or renal dysfunction have been reported with the use of
750 VIRAMUNE.

751

752 **Pediatric Patients**

753 Safety was assessed in trial BI 882 in which patients were followed for a mean duration of 33.9
754 months (range: 6.8 months to 5.3 years, including long-term follow-up in 29 of these patients in
755 trial BI 892). The most frequently reported adverse events related to VIRAMUNE in pediatric
756 patients were similar to those observed in adults, with the exception of granulocytopenia, which
757 was more commonly observed in children receiving both zidovudine and VIRAMUNE. Serious
758 adverse events were assessed in ACTG 245, a double-blind, placebo-controlled trial of
759 VIRAMUNE (n = 305) in which pediatric patients received combination treatment with
760 VIRAMUNE. In this trial two patients were reported to experience Stevens-Johnson syndrome or
761 Stevens-Johnson/toxic epidermal necrolysis transition syndrome. Cases of allergic reaction,
762 including one case of anaphylaxis, were also reported. In post-marketing surveillance anemia has
763 been more commonly observed in children although development of anemia due to concomitant
764 medication use cannot be ruled out.

765
766
767

768 **OVERDOSAGE**

769 There is no known antidote for VIRAMUNE (nevirapine) overdosage. Cases of VIRAMUNE
770 overdose at doses ranging from 800 to 1800 mg per day for up to 15 days have been reported.
771 Patients have experienced events including edema, erythema nodosum, fatigue, fever,
772 headache, insomnia, nausea, pulmonary infiltrates, rash, vertigo, vomiting and weight decrease.
773 All events subsided following discontinuation of VIRAMUNE.
774

775 **DOSAGE AND ADMINISTRATION**

776 **Adults**

777 The recommended dose for VIRAMUNE (nevirapine) is one 200 mg tablet daily for the first 14
778 days (**this lead-in period should be used because it has been found to lessen the**
779 **frequency of rash**), followed by one 200 mg tablet twice daily, in combination with other
780 antiretroviral agents. For concomitantly administered antiretroviral therapy, the manufacturer's
781 recommended dosage and monitoring should be followed.
782

783 **Pediatric Patients**

784 The recommended oral dose of VIRAMUNE for pediatric patients 2 months up to 8 years of age
785 is 4 mg/kg once daily for the first 14 days followed by 7 mg/kg twice daily thereafter. For patients
786 8 years and older the recommended dose is 4 mg/kg once daily for two weeks followed by 4
787 mg/kg twice daily thereafter. The total daily dose should not exceed 400 mg for any patient.
788

789 VIRAMUNE suspension should be shaken gently prior to administration. It is important to
790 administer the entire measured dose of suspension by using an oral dosing syringe or dosing
791 cup. An oral dosing syringe is recommended, particularly for volumes of 5 mL or less. If a dosing
792 cup is used, it should be thoroughly rinsed with water and the rinse should also be administered
793 to the patient.
794

795 **Monitoring of Patients**

796 Intensive clinical and laboratory monitoring, including liver function tests, is essential at baseline
797 and during the first 18 weeks of treatment with VIRAMUNE. The optimal frequency of monitoring
798 during this period has not been established. Some experts recommend clinical and laboratory
799 monitoring more often than once per month, and in particular, would include monitoring of liver
800 function tests at baseline, prior to dose escalation, and at two weeks post dose escalation. After
801 the initial 18 week period, frequent clinical and laboratory monitoring should continue throughout
802 VIRAMUNE treatment (see **WARNINGS**). In some cases, hepatic injury has progressed despite
803 discontinuation of treatment.
804

805 **Dosage Adjustment**

806 **VIRAMUNE should be discontinued if patients experience severe rash or a rash**
807 **accompanied by constitutional findings (see WARNINGS). Patients experiencing rash**
808 **during the 14-day lead-in period of 200 mg/day (4 mg/kg/day in pediatric patients) should**
809 **not have their VIRAMUNE dose increased until the rash has resolved (see PRECAUTIONS,**
810 **Information for Patients).**
811

812 **If a clinical (symptomatic) hepatic event occurs, VIRAMUNE should be permanently**
813 **discontinued. Do not restart VIRAMUNE after recovery (see WARNINGS).**
814

815 Patients who interrupt VIRAMUNE dosing for more than 7 days should restart the recommended
816 dosing, using one 200 mg tablet daily (4 mg/kg/day in pediatric patients) for the first 14 days
817 (lead-in) followed by one 200 mg tablet twice daily (4 or 7 mg/kg twice daily, according to age, for
818 pediatric patients).
819

820 An additional 200 mg dose of VIRAMUNE following each dialysis treatment is indicated in
821 patients requiring dialysis. Nevirapine metabolites may accumulate in patients receiving dialysis;

822 however, the clinical significance of this accumulation is not known (see **CLINICAL**
823 **PHARMACOLOGY, Pharmacokinetics in Special Populations: Renal Impairment**). Patients
824 with CrCL \geq 20 mL/min do not require an adjustment in VIRAMUNE dosing.
825

826 **HOW SUPPLIED**

827 VIRAMUNE (nevirapine) Tablets, 200 mg, are white, oval, biconvex tablets, 9.3 mm x 19.1 mm.
828 One side is embossed with "54 193", with a single bisect separating the "54" and "193". The
829 opposite side has a single bisect. VIRAMUNE Tablets are supplied in bottles of 60 (NDC 0597-
830 0046-60).

831
832 VIRAMUNE (nevirapine) Oral Suspension is a white to off-white preserved suspension containing
833 50 mg nevirapine (as nevirapine hemihydrate) in each 5 mL. VIRAMUNE suspension is supplied
834 in plastic bottles with child-resistant closures containing 240 mL of suspension (NDC 0597-0047-
835 24).

836
837 **Store at 25°C (77°F); excursions permitted to 15°–30°C (59°–86°F)** [see USP Controlled
838 Room Temperature]. Store in a safe place out of the reach of children.

839
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849 **ATTENTION PHARMACISTS: Detach “[Medication Guide](#)” and dispense with the**
850 **product.**
851



852
853

854 **MEDICATION GUIDE**

855

856 **VIRAMUNE® (VIH-rah-mune) Tablets**

857 **VIRAMUNE® Oral Suspension**

858

859 **Generic name: nevirapine tablets and oral suspension**

860

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

867

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

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

872

873 **Liver Reactions**

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

881

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

885

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

- 889
- 890 • general ill feeling or “flu-like” symptoms
 - 891 • tiredness
 - 892 • nausea (feeling sick to your stomach)
 - 893 • lack of appetite
 - 894 • yellowing of your skin or whites of your eyes
 - 895 • dark urine (tea colored)
 - 896 • pale stools (bowel movements)
 - 897 • pain, ache, or sensitivity to touch on your right side below your ribs

894

895 Your doctor should check you and do blood tests often to check your liver function during the first
896 18 weeks of therapy. Checks for liver problems should continue regularly during treatment with
897 VIRAMUNE.

898

899

900

901 **Skin Reactions**

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

- 906 • general ill feeling or “flu-like” symptoms • blisters
907 • fever • mouth sores
908 • muscle or joint aches • swelling of your face
909 • conjunctivitis (red or inflamed eyes, like “pink eye”) • tiredness
910 • any of the symptoms of liver problems discussed above

911

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

914

915 These are not all the side effects of VIRAMUNE. See the section "**What are the possible side**
916 **effects of VIRAMUNE?**" for more information. Tell your doctor if you have any side effects from
917 VIRAMUNE.

918

919 **What is VIRAMUNE?**

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

922

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

929

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

933

934 **Who should not take VIRAMUNE?**

- 935 • Do not take VIRAMUNE if you are allergic to VIRAMUNE or any of its ingredients. The active
936 ingredient is nevirapine. Your doctor or pharmacist can tell you about the inactive ingredients.
937 • Do not restart VIRAMUNE after you recover from serious liver or skin reactions that
938 happened when you took VIRAMUNE.
939 • Do not take VIRAMUNE if you take certain medicines. (See "**Can I take other medicines**
940 **with VIRAMUNE?**" for a list of medicines.)
941 • Do not take VIRAMUNE if you are not infected with HIV.

942

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

944 Before starting VIRAMUNE, tell your doctor about all of your medical conditions, including if you:

- 945 • have problems with your liver or have had hepatitis
946 • are undergoing dialysis
947 • have skin conditions, such as a rash
948 • are pregnant, planning to become pregnant, or are breast feeding

949

950 **How should I take VIRAMUNE?**

- 951 • Take the exact amount of VIRAMUNE your doctor prescribes. The usual dose for adults is
952 one tablet daily for the first 14 days followed by one tablet twice daily. Starting with one dose
953 a day lowers the chance of rash, which could be serious. Therefore, it is important to strictly
954 follow the once daily dose for the first 14 days. Do not start taking VIRAMUNE twice a day if

- 955 you have any symptoms of liver problems or skin rash. See the first section "**What is the**
956 **most important information I should know about VIRAMUNE?**".
- 957 • The dose of VIRAMUNE for children is based on their age and weight. Children's dosing also
958 starts with once a day for 14 days and then twice a day after that.
 - 959 • You may take VIRAMUNE with water, milk, or soda, with or without food.
 - 960 • If you or your child uses VIRAMUNE suspension (liquid), shake it gently before use. Use an
961 oral dosing syringe or dosing cup to measure the right dose. After drinking the medicine, fill
962 the dosing cup with water and drink it to make sure you get all the medicine. If the dose is
963 less than 5 mL (one teaspoon), use the syringe.
 - 964 • Do not miss a dose of VIRAMUNE, because this could make the virus harder to treat. If you
965 forget to take VIRAMUNE, take the missed dose right away. If it is almost time for your next
966 dose, do not take the missed dose. Instead, follow your regular dosing schedule by taking the
967 next dose at its regular time.
 - 968 • If you stop taking VIRAMUNE for more than 7 days, ask your doctor how much to take before
969 you start taking it again. You may need to start with once-a-day dosing.
 - 970 • If you suspect that you have taken too much VIRAMUNE, contact your local poison control
971 center or emergency room right away.

972 **Can I take other medicines with VIRAMUNE?**

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

987 **What should I avoid while taking VIRAMUNE?**

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

993
994 The Centers for Disease Control and Prevention advises mothers with HIV not to breast feed so
995 they will not pass HIV to the infant through their milk. Ask your doctor about the best way to feed
996 your infant.

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

998
999 VIRAMUNE can cause serious liver damage and skin reactions that can cause death. Any
1000 patient can experience such side effects, but some patients are more at risk than others. See
1001 "**What is the most important information I should know about VIRAMUNE?**" at the beginning
1002 of this Medication Guide.

1003
1004 Other common side effects of VIRAMUNE include nausea, fatigue, fever, headache, vomiting,
1005 diarrhea, abdominal pain, and myalgia. This list of side effects is not complete. Ask your doctor
1006 or pharmacist for more information.

1007
1008

1009 Changes in body fat have also been seen in some patients taking antiretroviral therapy. The
1010 changes may include increased amount of fat in the upper back and neck (“buffalo hump”),
1011 breast, and around the trunk. Loss of fat from the legs, arms, and face may also happen. The
1012 cause and long-term health effects of these conditions are not known at this time.
1013

1014 **How do I store VIRAMUNE?**

1015 Store VIRAMUNE at room temperature, between 59° to 86°F (15° to 30°C).

1016 Throw away VIRAMUNE that is no longer needed or out-of-date.

1017 **Keep VIRAMUNE and all medicines out of the reach of children.**

1018

1019 **General information about VIRAMUNE**

1020 Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide.

1021 Do not use VIRAMUNE for a condition for which it was not prescribed. Do not give VIRAMUNE to
1022 other people, even if they have the same condition you have. It may harm them.
1023

1024 This Medication Guide summarizes the most important information about VIRAMUNE. If you
1025 would like more information, talk with your doctor. You can ask your pharmacist or doctor for
1026 information about VIRAMUNE that is written for health professionals, or you can visit
1027 www.viramune.com or call 1-800-542-6257 for additional information.
1028

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