

## PRESCRIBING INFORMATION

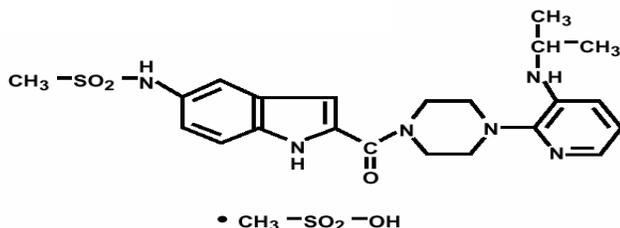
# RESCRIPTOR<sup>®</sup>

(delavirdine mesylate)

### Tablets

#### DESCRIPTION

RESCRIPTOR Tablets contain delavirdine mesylate, a synthetic non-nucleoside reverse transcriptase inhibitor (NNRTI) of the human immunodeficiency virus type 1 (HIV-1). The chemical name of delavirdine mesylate is piperazine, 1-[3-[(1-methyl-ethyl)amino]-2-pyridinyl]-4-[[5-[(methylsulfonyl)amino]-1H-indol-2-yl]carbonyl]-, monomethanesulfonate. Its molecular formula is  $C_{22}H_{28}N_6O_3S \cdot CH_4O_3S$ , and its molecular weight is 552.68. The structural formula is:



Delavirdine mesylate is an odorless white-to-tan crystalline powder. The aqueous solubility of delavirdine free base at 23°C is 2,942 mcg/mL at pH 1.0, 295 mcg/mL at pH 2.0, and 0.81 mcg/mL at pH 7.4.

Each RESCRIPTOR Tablet, for oral administration, contains 100 or 200 mg of delavirdine mesylate (henceforth referred to as delavirdine). Inactive ingredients consist of carnauba wax, colloidal silicon dioxide, croscarmellose sodium, lactose, magnesium stearate, and microcrystalline cellulose. In addition, the 100-mg tablet contains Opadry White YS-1-7000-E and the 200-mg tablet contains hypromellose and Opadry White YS-1-18202-A.

#### MICROBIOLOGY

**Mechanism of Action:** Delavirdine is an NNRTI of HIV-1. Delavirdine binds directly to reverse transcriptase (RT) and blocks RNA-dependent and DNA-dependent DNA polymerase activities. Delavirdine does not compete with template:primer or deoxynucleoside triphosphates. HIV-2 RT and human cellular DNA polymerases  $\alpha$ ,  $\gamma$ , or  $\delta$  are not inhibited by delavirdine. In addition, HIV-1 group O, a group of highly divergent strains that are uncommon in North America, may not be inhibited by delavirdine.

**In Vitro HIV-1 Susceptibility:** In vitro anti-HIV-1 activity of delavirdine was assessed by infecting cell lines of lymphoblastic and monocytic origin and peripheral blood lymphocytes with laboratory and clinical isolates of HIV-1.  $IC_{50}$  and  $IC_{90}$  values (50% and 90% inhibitory concentrations) for laboratory isolates (n = 5) ranged from 0.005 to 0.030  $\mu$ M and 0.04 to

39 0.10  $\mu\text{M}$ , respectively. Mean  $\text{IC}_{50}$  of clinical isolates ( $n = 74$ ) was 0.038  $\mu\text{M}$  (range: 0.001 to  
40 0.69  $\mu\text{M}$ ); 73 of 74 clinical isolates had an  $\text{IC}_{50} \leq 0.18 \mu\text{M}$ . The  $\text{IC}_{90}$  of 24 of these clinical  
41 isolates ranged from 0.05 to 0.10  $\mu\text{M}$ . In drug combination studies of delavirdine with  
42 zidovudine, didanosine, zalcitabine, lamivudine, interferon- $\alpha$ , and protease inhibitors, additive to  
43 synergistic anti-HIV-1 activity was observed in cell culture. The relationship between the in  
44 vitro susceptibility of HIV-1 RT inhibitors and the inhibition of HIV replication in humans has  
45 not been established.

46 **Drug Resistance:** Phenotypic analyses of isolates from patients treated with RESCRIPTOR  
47 as monotherapy showed a 50- to 500-fold reduced susceptibility in 14 of 15 patients by Week 8  
48 of therapy. Genotypic analysis of HIV-1 isolates from patients receiving RESCRIPTOR plus  
49 zidovudine combination therapy ( $n = 79$ ) showed resistance-conferring mutations in all isolates  
50 by Week 24 of therapy. In patients treated with RESCRIPTOR, the mutations in RT occurred  
51 predominantly at amino acid positions 103 and less frequently at positions 181 and 236. In a  
52 separate study, an average of 86-fold increase in the zidovudine susceptibility of patient isolates  
53 ( $n = 24$ ) was observed after 24 weeks of combination therapy with RESCRIPTOR and  
54 zidovudine. The clinical relevance of the phenotypic and the genotypic changes associated with  
55 therapy with RESCRIPTOR has not been established.

56 **Cross-Resistance:** RESCRIPTOR may confer cross-resistance to other NNRTIs when  
57 used alone or in combination. Mutations at positions 103 and/or 181 have been found in resistant  
58 virus during treatment with RESCRIPTOR and other NNRTIs. These mutations have been  
59 associated with cross-resistance among NNRTIs in vitro.

## 60 CLINICAL PHARMACOLOGY

61 **Pharmacokinetics: Absorption and Bioavailability:** Delavirdine is rapidly absorbed  
62 following oral administration, with peak plasma concentrations occurring at approximately  
63 1 hour. Following administration of delavirdine 400 mg 3 times daily ( $n = 67$ , HIV-1-infected  
64 patients), the mean  $\pm$ SD steady-state peak plasma concentration ( $C_{\text{max}}$ ) was  $35 \pm 20 \mu\text{M}$  (range: 2  
65 to 100  $\mu\text{M}$ ), systemic exposure (AUC) was  $180 \pm 100 \mu\text{M}\cdot\text{hr}$  (range: 5 to 515  $\mu\text{M}\cdot\text{hr}$ ), and  
66 trough concentration ( $C_{\text{min}}$ ) was  $15 \pm 10 \mu\text{M}$  (range: 0.1 to 45  $\mu\text{M}$ ). The single-dose  
67 bioavailability of delavirdine tablets relative to an oral solution was  $85\% \pm 25\%$  ( $n = 16$ , non-  
68 HIV-infected subjects). The single-dose bioavailability of delavirdine tablets (100-mg strength)  
69 was increased by approximately 20% when a slurry of drug was prepared by allowing  
70 delavirdine tablets to disintegrate in water before administration ( $n = 16$ , non-HIV-infected  
71 subjects). The bioavailability of the 200-mg strength delavirdine tablets has not been evaluated  
72 when administered as a slurry because they are not readily dispersed in water (see DOSAGE  
73 AND ADMINISTRATION).

74 Delavirdine may be administered with or without food. In a multiple-dose, crossover study,  
75 delavirdine was administered every 8 hours with food or every 8 hours, 1 hour before or 2 hours  
76 after a meal ( $n = 13$ , HIV-1-infected patients). Patients remained on their typical diet throughout  
77 the study; meal content was not standardized. When multiple doses of delavirdine were

78 administered with food, geometric mean  $C_{max}$  was reduced by approximately 25%, but AUC and  
79  $C_{min}$  were not altered.

80 **Distribution:** Delavirdine is extensively bound (approximately 98%) to plasma proteins,  
81 primarily albumin. The percentage of delavirdine that is protein-bound is constant over a  
82 delavirdine concentration range of 0.5 to 196  $\mu$ M. In 5 HIV-1–infected patients whose total daily  
83 dose of delavirdine ranged from 600 to 1,200 mg, cerebrospinal fluid concentrations of  
84 delavirdine averaged  $0.4\% \pm 0.07\%$  of the corresponding plasma delavirdine concentrations; this  
85 represents about 20% of the fraction not bound to plasma proteins. Steady-state delavirdine  
86 concentrations in saliva (n = 5, HIV-1–infected patients who received delavirdine 400 mg  
87 3 times daily) and semen (n = 5 healthy volunteers who received delavirdine 300 mg 3 times  
88 daily) were about 6% and 2%, respectively, of the corresponding plasma delavirdine  
89 concentrations collected at the end of a dosing interval.

90 **Metabolism and Elimination:** Delavirdine is extensively converted to several inactive  
91 metabolites. Delavirdine is primarily metabolized by cytochrome P450 3A (CYP3A), but in vitro  
92 data suggest that delavirdine may also be metabolized by CYP2D6. The major metabolic  
93 pathways for delavirdine are N-desalkylation and pyridine hydroxylation. Delavirdine exhibits  
94 nonlinear steady-state elimination pharmacokinetics, with apparent oral clearance decreasing by  
95 about 22-fold as the total daily dose of delavirdine increases from 60 to 1,200 mg/day. In a study  
96 of  $^{14}$ C-delavirdine in 6 healthy volunteers who received multiple doses of delavirdine tablets  
97 300 mg 3 times daily, approximately 44% of the radiolabeled dose was recovered in feces, and  
98 approximately 51% of the dose was excreted in urine. Less than 5% of the dose was recovered  
99 unchanged in urine. The parent plasma half-life of delavirdine increases with dose; mean  
100 half-life following 400 mg 3 times daily is 5.8 hours, with a range of 2 to 11 hours.

101 In vitro and in vivo studies have shown that delavirdine reduces CYP3A activity and inhibits  
102 its own metabolism. In vitro studies have also shown that delavirdine reduces CYP2C9,  
103 CYP2D6, and CYP2C19 activity. Inhibition of hepatic CYP3A activity by delavirdine is  
104 reversible within 1 week after discontinuation of drug.

105 **Special Populations: Hepatic or Renal Impairment:** The pharmacokinetics of delavirdine  
106 in patients with hepatic or renal impairment have not been investigated (see PRECAUTIONS).

107 **Age:** The pharmacokinetics of delavirdine have not been adequately studied in patients aged  
108 <16 years or >65 years.

109 **Gender:** Data from population pharmacokinetics suggest that the plasma concentrations of  
110 delavirdine tend to be higher in females than in males. However, this difference is not considered  
111 to be clinically significant.

112 **Race:** No significant differences in the mean trough delavirdine concentrations were  
113 observed between different racial or ethnic groups.

114 **Drug Interactions: (See also PRECAUTIONS: Drug Interactions.)**

115 Specific drug interaction studies were performed with delavirdine and a number of drugs.  
116 Table 1 summarizes the effects of delavirdine on the geometric mean AUC,  $C_{max}$ , and  $C_{min}$  of

117 coadministered drugs. Table 2 shows the effects of coadministered drugs on the geometric mean  
 118 AUC, C<sub>max</sub>, and C<sub>min</sub> of delavirdine.

119 For information regarding clinical recommendations, see CONTRAINDICATIONS,  
 120 WARNINGS, and PRECAUTIONS: Drug Interactions.

121  
 122 **Table 1. Pharmacokinetic Parameters for Coadministered Drugs in the Presence of**  
 123 **Delavirdine**

Coadministered Drug	Dose of Coadministered Drug	Dose of RESCRIPTOR	n	% Change in Pharmacokinetic Parameters of Coadministered Drug (90% CI)		
				C <sub>max</sub>	AUC	C <sub>min</sub>
<b><i>HIV-Protease Inhibitors</i></b>						
Indinavir	400 mg t.i.d. for 7 days	400 mg t.i.d. for 7 days	28	↓36 <sup>a</sup> (↓52 to ↓14)	↔ <sup>a</sup>	↑118 <sup>a</sup> (↑16 to ↑312)
	600 mg t.i.d. for 7 days	400 mg t.i.d. for 7 days	28	↔	↑53 <sup>a</sup> (↑7 to ↑120)	↑298 <sup>a</sup> (↑104 to ↑678)
Nelfinavir <sup>b</sup>	750 mg t.i.d. for 14 days	400 mg t.i.d. for 7 days	12	↑88 (↑66 to ↑113)	↑107 (↑83 to ↑135)	↑136 (↑103 to ↑175)
Saquinavir	Soft gel capsule 1,000 mg t.i.d. for 28 days	400 mg t.i.d. for 28 days	20	↑98 <sup>c</sup> (↑4 to ↑277)	↑121 <sup>c</sup> (↑14 to ↑340)	↑199 <sup>c</sup> (↑37 to ↑553)
<b><i>Nucleoside Reverse Transcriptase Inhibitors</i></b>						
Didanosine (buffered tablets)	125 or 250 mg b.i.d. for 28 days	400 mg t.i.d. for 28 days	9	↓20 <sup>d</sup> (↓44 to ↑15)	↓21 <sup>d</sup> (↓40 to ↑5)	-
Zidovudine	200 mg t.i.d. for >38 days	100 mg q.i.d. to 400 mg t.i.d. for 8 to 10 days	34	↔	↔	-
<b><i>Anti-infective Agents</i></b>						
Clarithromycin	500 mg b.i.d. for 15 days	300 mg t.i.d. for 30 days	6	-	↑100	-
Rifabutin	300 mg q.d. for 15 to 99 days	400 to 1,000 mg t.i.d. for 45 to 129 days	5	↑128 (↑71 to ↑203)	↑230 (↑119 to ↑396)	↑452 (↑246 to ↑781)

124 ↑ Indicates increase.

125 ↓ Indicates decrease.

126 ↔ Indicates no significant change.

127 - Indicates no data available.

128 <sup>a</sup> Relative to indinavir 800 mg t.i.d. without RESCRIPTOR.

- 129 <sup>b</sup> Plasma concentrations of the nelfinavir active metabolite (nelfinavir hydroxy-t-butylamide) were  
 130 significantly reduced by delavirdine, which is more than compensated for by increased nelfinavir  
 131 concentration.
- 132 <sup>c</sup> Saquinavir soft gel capsule 1,000 mg t.i.d. plus RESCRIPTOR 400 mg t.i.d. relative to saquinavir soft  
 133 gel capsule 1,200 mg t.i.d. without RESCRIPTOR.
- 134 <sup>d</sup> RESCRIPTOR taken with didanosine (buffered tablets) relative to doses of RESCRIPTOR and  
 135 didanosine (buffered tablets) separated by at least 1 hour.

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**Table 2. Pharmacokinetic Parameters for Delavirdine in the Presence of Coadministered Drugs**

Coadministered Drug	Dose of Coadministered Drug	Dose of RESCRIPTOR	n	% Change in Delavirdine Pharmacokinetic Parameters (90% CI)		
				C <sub>max</sub>	AUC	C <sub>min</sub>
<b><i>HIV-Protease Inhibitors</i></b>						
Indinavir	400 or 600 mg t.i.d. for 7 days	400 mg t.i.d. for 7 days	81	No apparent changes based on a comparison to historical data		
Nelfinavir	750 mg t.i.d. for 7 days	400 mg t.i.d. for 14 days	7	↓27 (↓49 to ↑4)	↓31 (↓57 to ↑10)	↓33 (↓70 to ↑49)
Saquinavir	Soft gel capsule 1,000 mg t.i.d. for 28 days	400 mg t.i.d. for 7 to 28 days	23	No apparent changes based on a comparison to historical data		
<b><i>Nucleoside Reverse Transcriptase Inhibitors</i></b>						
Didanosine (buffered tablets)	125 or 200 mg b.i.d. for 28 days	400 mg t.i.d. for 28 days	9	↓32 <sup>a</sup> (↓48 to ↓11)	↓19 <sup>a</sup> (↓37 to ↑6)	↔ <sup>a</sup>
Zidovudine	200 mg t.i.d. for ≥7 days	400 mg t.i.d. for 7 to 14 days	42	No apparent changes based on a comparison to historical data		
<b><i>Anti-infective Agents</i></b>						
Clarithromycin	500 mg b.i.d. for 15 days	300 mg t.i.d. for 30 days	6	↔	↔	↔
Fluconazole	400 mg q.d. for 15 days	300 mg t.i.d. for 30 days	8	↔	↔	↔
Ketoconazole	Various	200 to 400 mg t.i.d.	26	-	-	↑50 <sup>b</sup>
Rifabutin	300 mg q.d. for 14 days	400 mg t.i.d. for 28 days	7	↓72 (↓61 to ↓80)	↓82 (↓74 to ↓88)	↓94 (↓90 to ↓96)
Rifampin	600 mg q.d. for 15 days	400 mg t.i.d. for 30 days	7	↓90 (↓94 to ↓83)	↓97 (↓98 to ↓95)	↓100
Sulfamethoxazole or	Various	200 to 400 mg	311	-	-	↔ <sup>b</sup>

Trimethoprim & Sulfamethoxazole		t.i.d.				
<b>Other</b>						
Antacid (Maalox <sup>®</sup> TC)	20 mL	300 mg single dose	12	↓52 (↓68 to ↓29)	↓44 (↓58 to ↓27)	-
Fluoxetine	Various	200 to 400 mg t.i.d.	36	-	-	↑50 <sup>b</sup>
Phenytoin, Phenobarbital, Carbamazepine	Various	300 to 400 mg t.i.d.	8	-	-	↓90 <sup>b</sup>

138 ↑ Indicates increase.

139 ↓ Indicates decrease.

140 ↔ Indicates no significant change.

141 - Indicates no data available.

142 <sup>a</sup> RESCRIPTOR taken with didanosine (buffered tablets) relative to doses of RESCRIPTOR and didanosine (buffered tablets) separated by at least 1 hour.

144 <sup>b</sup> Population pharmacokinetic data from efficacy studies.

## 145 INDICATIONS AND USAGE

146 RESCRIPTOR Tablets are indicated for the treatment of HIV-1 infection in combination with  
147 at least 2 other active antiretroviral agents when therapy is warranted.

148 The following should be considered before initiating therapy with RESCRIPTOR in  
149 treatment-naïve patients. There are insufficient data directly comparing antiretroviral regimens  
150 containing RESCRIPTOR with currently preferred 3-drug regimens for initial treatment of HIV.  
151 In studies comparing regimens consisting of 2 nucleoside reverse transcriptase inhibitors  
152 (NRTIs) (currently considered suboptimal) to RESCRIPTOR plus 2 NRTIs, the proportion of  
153 patients receiving the regimen containing RESCRIPTOR who achieved and sustained an HIV-1  
154 RNA level <400 copies/mL over 1 year of therapy was relatively low (see DESCRIPTION OF  
155 CLINICAL STUDIES).

156 Resistant virus emerges rapidly when RESCRIPTOR is administered as monotherapy.  
157 Therefore, RESCRIPTOR should always be administered in combination with other  
158 antiretroviral agents.

## 159 DESCRIPTION OF CLINICAL STUDIES

160 For clinical Studies 21 Part II and 13C described below, efficacy was evaluated by the  
161 percentage of patients with a plasma HIV-1 RNA level <400 copies/mL through Week 52 as  
162 measured by the Roche Amplicor<sup>®</sup> HIV-1 Monitor (standard assay). An intent-to-treat analysis  
163 was performed where only subjects who achieved confirmed suppression and sustained it  
164 through Week 52 are regarded as responders. All other subjects (including never suppressed,  
165 discontinued, and those who rebounded after initial suppression of <400 copies/mL) are  
166 considered failures at Week 52. Results of an interim analysis of efficacy conducted for studies

167 21 Part II and 13C by independent Data and Safety Monitoring Boards (DSMBs) revealed that  
168 the triple-therapy arms in both studies produced significantly greater antiviral benefit than the  
169 dual-therapy arms, and early termination of the studies was recommended.

170 **Study 21 Part II:** Study 21 Part II was a double-blind, randomized, placebo-controlled trial  
171 comparing treatment with RESCRIPTOR (400 mg 3 times daily, zidovudine 200 mg 3 times  
172 daily, and lamivudine 150 mg twice daily versus RESCRIPTOR 400 mg 3 times daily and  
173 zidovudine 200 mg 3 times daily versus zidovudine 200 mg 3 times daily and lamivudine  
174 150 mg twice daily in 373 HIV-1–infected patients (mean age 35 years [range: 17 to 67], 87%  
175 male, and 60% Caucasian) who were antiretroviral treatment naive (84%) or had limited  
176 nucleoside experience (16%). Mean baseline CD4+ cell count was 359 cells/mm<sup>3</sup> and mean  
177 baseline plasma HIV-1 RNA was 4.4 log<sub>10</sub> copies/mL.

178 Results showed that the mean increases from baseline in CD4 cell counts at 52 weeks were  
179 111 cells/mL for RESCRIPTOR + zidovudine + lamivudine, 27 cells/mL for RESCRIPTOR +  
180 zidovudine, and 74 cells/mL for zidovudine + lamivudine.

181 The results of the intent-to-treat analysis of the percentage of patients with a plasma HIV-1  
182 RNA level <400 copies/mL are presented in Figure 1. HIV-1 RNA status and reasons for  
183 discontinuation of randomized treatment at 52 weeks are summarized in Table 3. Subjects who  
184 were never suppressed before discontinuation were placed in the discontinuation category.

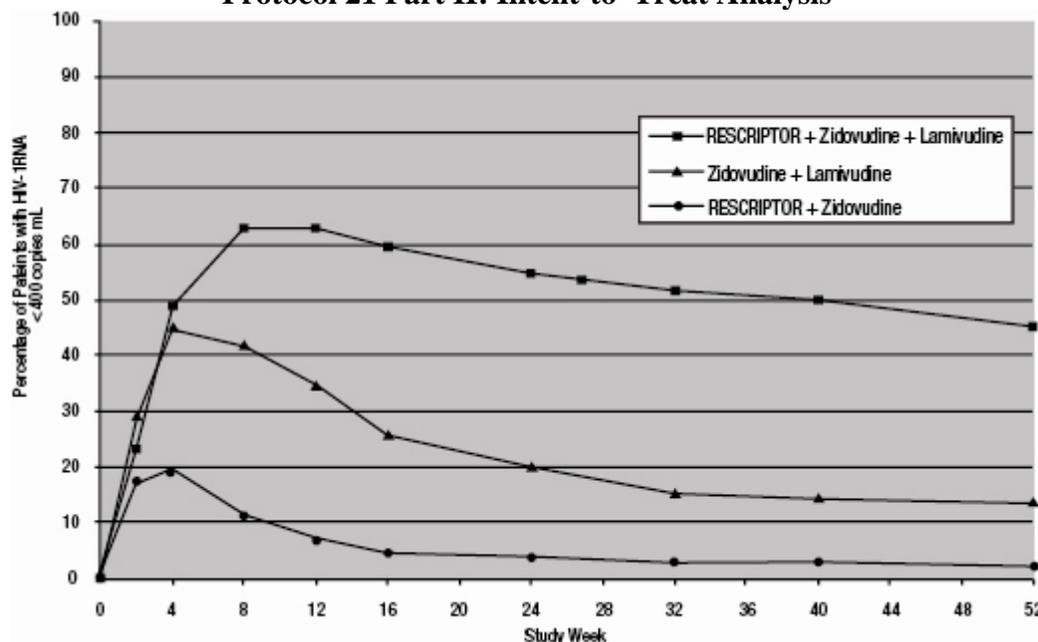
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**Figure 1. Percentage of Patients With HIV-1 RNA Below 400 copies/mL  
Standard PCR Assay  
Protocol 21 Part II: Intent-to-Treat Analysis**



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192 **Table 3. Outcomes of Randomized Treatment Through Week 52 for Protocol 21 Part II**

Outcome	Zidovudine + Lamivudine (n = 124) %	RESCRIPTOR + Zidovudine (n = 125) %	RESCRIPTOR + Zidovudine + Lamivudine (n = 124) %
HIV-1 RNA <400 copies/mL <sup>a</sup>	14	2	45
HIV-1 RNA ≥400 copies/mL <sup>b,c</sup>	64	52	31
Discontinued due to adverse events <sup>c</sup>	8	13	10
Discontinued due to other reasons <sup>c,d</sup>	14	33	14

193 <sup>a</sup> Corresponds to rates at Week 52 in proportion curve.

194 <sup>b</sup> Virologic failures at or before Week 52.

195 <sup>c</sup> Considered to be treatment failure in the analysis.

196 <sup>d</sup> Includes discontinuations due to consent withdrawn, loss to follow-up, protocol violations,  
197 non-compliance, pregnancy, never treated, and other reasons.

198

199 **Study 13C:** Study 13C was a double-blind, randomized, placebo-controlled trial comparing  
200 treatment with RESCRIPTOR 400 mg 3 times daily, zidovudine 200 mg 3 times daily or 300 mg  
201 twice daily, and either didanosine 200 mg twice daily, zalcitabine 0.75 mg 3 times daily, or  
202 lamivudine 150 mg twice daily versus zidovudine 200 mg 3 times daily or 300 mg twice daily  
203 and either didanosine 200 mg twice daily, zalcitabine 0.75 mg 3 times daily, or lamivudine  
204 150 mg twice daily in 345 HIV-1–infected patients (mean age 35.8 years [range: 18 to 72], 66%  
205 male, and 63% Caucasian) who were antiretroviral treatment naïve (63%) or had limited  
206 antiretroviral experience (37%). Mean baseline CD4+ cell count was 210 cells/mm<sup>3</sup> and mean  
207 baseline plasma HIV-1 RNA was 4.9 log<sub>10</sub> copies/mL.

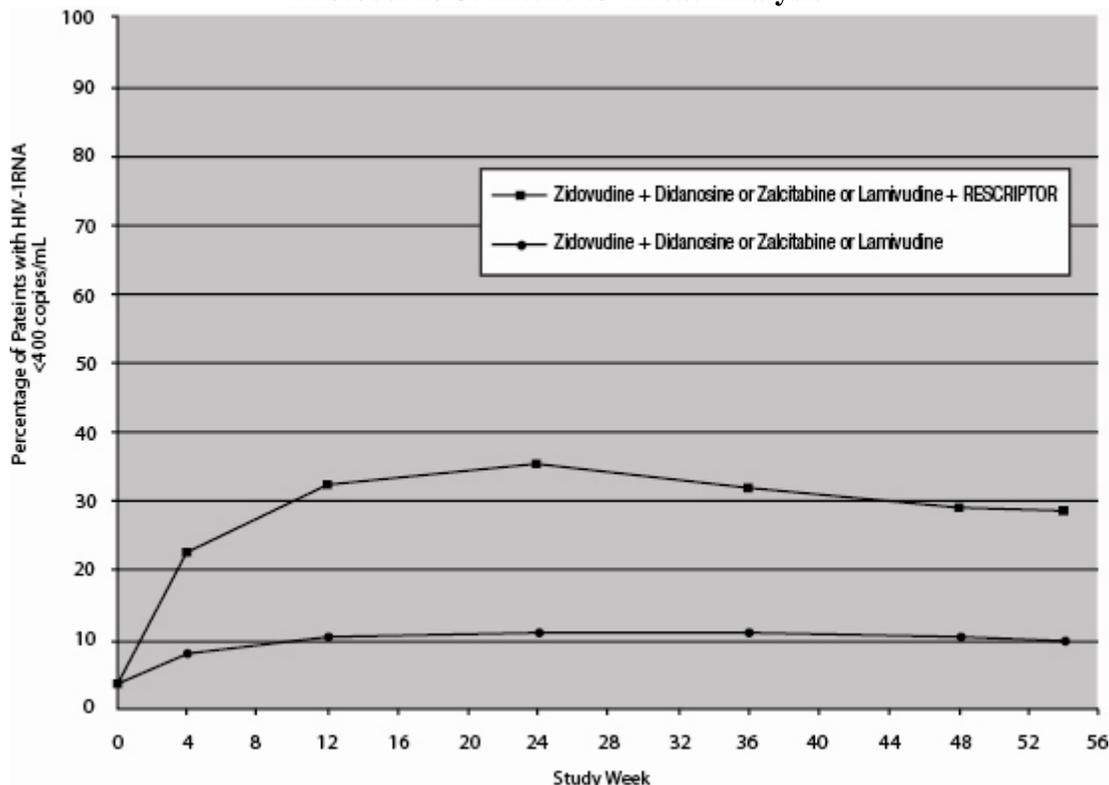
208 Results showed that the mean increases from baseline in CD4+ cell counts at 54 weeks were  
209 102 cells/mL for RESCRIPTOR + zidovudine + didanosine or zalcitabine or lamivudine, and  
210 56 cells/mL for zidovudine + didanosine or zalcitabine or lamivudine.

211 The results of the intent-to-treat analysis of the percentage of patients with a plasma HIV-1  
212 RNA level <400 copies/mL are presented in Figure 2. HIV-1 RNA status and reasons for  
213 discontinuation of randomized treatment at 54 weeks are summarized in Table 4. Subjects who  
214 were never suppressed before discontinuation were placed in the discontinuation category.

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**Figure 2. Percentage of Patients With HIV-1 RNA Below 400 copies/mL Standard PCR Assay Protocol 13C: Intent-to-Treat Analysis**



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**Table 4. Outcomes of Randomized Treatment Through Week 54 for Protocol 13C**

Outcome	Zidovudine + Didanosine or Zalcitabine or Lamivudine (n = 173) %	Zidovudine + Didanosine or Zalcitabine or Lamivudine + RESCRIPTOR (n = 172) %
HIV-1 RNA <400 copies/mL <sup>a</sup>	10	29
HIV-1 RNA ≥400 copies/mL <sup>b,c</sup>	69	42
Discontinued due to adverse events <sup>c</sup>	7	12
Discontinued due to other reasons <sup>c,d</sup>	14	17

222 <sup>a</sup> Corresponds to rates at Week 54 in proportion curve.  
 223 <sup>b</sup> Virologic failures at or before Week 54.  
 224 <sup>c</sup> Considered to be treatment failure in the analysis.  
 225 <sup>d</sup> Includes discontinuations due to consent withdrawn, loss to follow-up, protocol violations,  
 226 non-compliance, pregnancy, never treated, and other reasons.  
 227

228 Results from several smaller supportive studies evaluating the use of RESCRIPTOR in  
229 treatment-naïve patients suggest that it may have activity when used in combination with  
230 protease inhibitors and NRTIs in 3- or 4-drug combinations.

## 231 **CONTRAINDICATIONS**

232 RESCRIPTOR Tablets are contraindicated in patients with known hypersensitivity to any of  
233 its ingredients. Coadministration of RESCRIPTOR is contraindicated with drugs that are highly  
234 dependent on CYP3A for clearance and for which elevated plasma concentrations are associated  
235 with serious and/or life-threatening events. These drugs are listed in Table 5. **Also, see**  
236 **PRECAUTIONS, Table 6, Drugs That Should Not Be Coadministered With**  
237 **RESCRIPTOR.**

238  
239 **Table 5. Drugs That Are Contraindicated With RESCRIPTOR**

Drug Class	Drugs Within Class That Are Contraindicated With RESCRIPTOR
Antihistamines	Astemizole, terfenadine
Ergot derivatives	Dihydroergotamine, ergonovine, ergotamine, methylergonovine
GI motility agent	Cisapride
Neuroleptic	Pimozide
Sedative/hypnotics	Alprazolam, midazolam, triazolam

## 240 **WARNINGS**

241 **ALERT: Find out about medicines that should NOT be taken with RESCRIPTOR.** This  
242 statement is included on the product's bottle label.

243 **Drug Interactions:** Because delavirdine may inhibit the metabolism of many different drugs  
244 (e.g., antiarrhythmics, calcium channel blockers, sedative hypnotics, and others), **serious and/or**  
245 **life-threatening drug interactions could result from inappropriate coadministration of**  
246 **some drugs with delavirdine.** In addition, some drugs may markedly reduce delavirdine plasma  
247 concentrations, resulting in suboptimal antiviral activity and subsequent emergence of drug  
248 resistance. All prescribers should become familiar with the following tables in this package  
249 insert: **Table 5, Drugs That Are Contraindicated With RESCRIPTOR; Table 6, Drugs That**  
250 **Should Not Be Coadministered With RESCRIPTOR; and Table 7, Established and Other**  
251 **Potentially Significant Drug Interactions: Alteration in Dose or Regimen May Be**  
252 **Recommended Based on Drug Interaction Studies or Predicted Interaction.** Additional  
253 details on drug interactions can be found in Tables 1 and 2 under the CLINICAL  
254 PHARMACOLOGY section.

255 Concomitant use of lovastatin or simvastatin with RESCRIPTOR is not recommended.  
256 Caution should be exercised if RESCRIPTOR is used concurrently with other HMG-CoA  
257 reductase inhibitors that are also metabolized by the CYP3A4 pathway (e.g., atorvastatin or

258 cerivastatin). The risk of myopathy including rhabdomyolysis may be increased when  
259 RESCRIPTOR is used in combination with these drugs.

260 Particular caution should be used when prescribing sildenafil in patients receiving  
261 RESCRIPTOR. Coadministration of sildenafil with RESCRIPTOR is expected to substantially  
262 increase sildenafil concentrations and may result in an increase in sildenafil-associated adverse  
263 events, including hypotension, visual changes, and priapism (see PRECAUTIONS: Drug  
264 Interactions and Information for Patients, and the complete prescribing information for  
265 sildenafil).

266 Concomitant use of St. John's wort (*Hypericum perforatum*) or St. John's wort-containing  
267 products and RESCRIPTOR is not recommended. Coadministration of St. John's wort with  
268 NNRTIs, including RESCRIPTOR, is expected to substantially decrease NNRTI concentrations  
269 and may result in suboptimal levels of RESCRIPTOR and lead to loss of virologic response and  
270 possible resistance to RESCRIPTOR or to the class of NNRTIs.

## 271 **PRECAUTIONS**

272 **General:** Delavirdine is metabolized primarily by the liver. Therefore, caution should be  
273 exercised when administering RESCRIPTOR Tablets to patients with impaired hepatic function.

274 **Immune Reconstitution Syndrome:** Immune reconstitution syndrome has been reported in  
275 patients treated with combination antiretroviral therapy, including RESCRIPTOR. During the  
276 initial phase of the combination antiretroviral treatment, patients whose immune systems respond  
277 may develop an inflammatory response to indolent or residual opportunistic infections (such as  
278 *Mycobacterium avium* infection, cytomegalovirus, *Pneumocystis jirovecii* pneumonia [PCP], or  
279 tuberculosis), which may necessitate further evaluation and treatment.

280 Autoimmune disorders (such as Graves' disease, polymyositis, and Guillain-Barré syndrome)  
281 have also been reported to occur in the setting of immune reconstitution; however, the time to  
282 onset is more variable, and can occur many months after initiation of treatment.

283 **Resistance/Cross-Resistance:** NNRTIs, when used alone or in combination, may confer  
284 cross-resistance to other NNRTIs.

285 **Fat Redistribution:** Redistribution/accumulation of body fat including central obesity,  
286 dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast  
287 enlargement, and "cushingoid appearance" have been observed in patients receiving  
288 antiretroviral therapy. The mechanism and long-term consequences of these events are currently  
289 unknown. A causal relationship has not been established.

290 **Skin Rash: Severe rash, including rare cases of erythema multiforme and**  
291 **Stevens-Johnson syndrome, has been reported in patients receiving RESCRIPTOR.**  
292 Erythema multiforme and Stevens-Johnson syndrome were rarely seen in clinical trials and  
293 resolved after withdrawal of RESCRIPTOR. Any patient experiencing severe rash or rash  
294 accompanied by symptoms such as fever, blistering, oral lesions, conjunctivitis, swelling, and  
295 muscle or joint aches should discontinue RESCRIPTOR and consult a physician. Two cases of

296 Stevens-Johnson syndrome have been reported through postmarketing surveillance out of a total  
297 of 339 surveillance reports.

298 In Studies 21 Part II and 13C (see DESCRIPTION OF CLINICAL STUDIES), rash  
299 (including maculopapular rash) was reported in more patients who were treated with  
300 RESCRIPTOR 400 mg 3 times daily (35% and 32%, respectively) than in those who were not  
301 treated with RESCRIPTOR (21% and 16%, respectively). The highest intensity of rash reported  
302 in these studies was severe (Grade 3), which was observed in approximately 4% of patients  
303 treated with RESCRIPTOR in each study and in none of the patients who were not treated with  
304 RESCRIPTOR. Also in Studies 21 Part II and 13C, discontinuations due to rash were reported in  
305 more patients who received RESCRIPTOR 400 mg 3 times daily (3% and 4%, respectively) than  
306 in those who did not receive RESCRIPTOR (0% and 1%, respectively).

307 In most cases, the duration of the rash was less than 2 weeks and did not require dose  
308 reduction or discontinuation of RESCRIPTOR. Most patients were able to resume therapy after  
309 rechallenge with RESCRIPTOR following a treatment interruption due to rash. The distribution  
310 of the rash was mainly on the upper body and proximal arms, with decreasing intensity of the  
311 lesions on the neck and face, and progressively less on the rest of the trunk and limbs.

312 Occurrence of a delavirdine-associated rash after 1 month is uncommon. Symptomatic relief  
313 has been obtained using diphenhydramine hydrochloride, hydroxyzine hydrochloride, and/or  
314 topical corticosteroids.

315 **Information for Patients:** A statement to patients and healthcare providers is included on the  
316 product's bottle label: **ALERT: Find out about medicines that should NOT be taken with**  
317 **RESCRIPTOR.** A patient package insert (PPI) for RESCRIPTOR is available for patient  
318 information.

319 Patients should be informed that RESCRIPTOR is not a cure for HIV-1 infection and that  
320 patients may continue to experience illnesses associated with HIV-1 infection, including  
321 opportunistic infections. Patients should be advised to remain under the care of a physician while  
322 taking RESCRIPTOR.

323 Patients should be advised to avoid doing things that can spread HIV-1 infection to  
324 others.

- 325 • **Do not share needles or other injection equipment.**
- 326 • **Do not share personal items that can have blood or body fluids on them, like**  
327 **toothbrushes and razor blades.**
- 328 • **Do not have any kind of sex without protection.** Always practice safe sex by using a latex or  
329 polyurethane condom to lower the chance of sexual contact with semen, vaginal secretions, or  
330 blood.
- 331 • **Do not breastfeed.** We do not know if RESCRIPTOR can be passed to your baby in your  
332 breast milk and whether it could harm your baby. Also, mothers with HIV-1 should not  
333 breastfeed because HIV-1 can be passed to the baby in the breast milk.

334 Patients should be instructed that the major toxicity of RESCRIPTOR is rash and should be  
335 advised to promptly notify their physician should rash occur. The majority of rashes associated

336 with RESCRIPTOR occur within 1 to 3 weeks after initiating treatment with RESCRIPTOR. The  
337 rash normally resolves in 3 to 14 days and may be treated symptomatically while therapy with  
338 RESCRIPTOR is continued. Any patient experiencing severe rash or rash accompanied by  
339 symptoms such as fever, blistering, oral lesions, conjunctivitis, swelling, and muscle or joint  
340 aches should discontinue medication and consult a physician.

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

344 Patients should be informed to take RESCRIPTOR every day as prescribed. Patients should  
345 not alter the dose of RESCRIPTOR without consulting their doctor. If a dose is missed, patients  
346 should take the next dose as soon as possible. However, if a dose is skipped, the patient should  
347 not double the next dose.

348 Patients with achlorhydria should take RESCRIPTOR with an acidic beverage (e.g., orange or  
349 cranberry juice). However, the effect of an acidic beverage on the absorption of delavirdine in  
350 patients with achlorhydria has not been investigated.

351 Patients taking both RESCRIPTOR and antacids should be advised to take them at least  
352 1 hour apart.

353 Because RESCRIPTOR may interact with certain drugs, patients should be advised to report  
354 to their doctor the use of any prescription, nonprescription medication, or herbal products,  
355 particularly St. John's wort.

356 Patients receiving sildenafil and RESCRIPTOR should be advised that they may be at an  
357 increased risk of sildenafil-associated adverse events, including hypotension, visual changes, and  
358 prolonged penile erection, and should promptly report any symptoms to their doctor.

359 **Drug Interactions:** (See also **CONTRAINDICATIONS, WARNINGS, and CLINICAL**  
360 **PHARMACOLOGY: Drug Interactions.**)

361 Delavirdine is an inhibitor of CYP3A isoform and other CYP isoforms to a lesser extent  
362 including CYP2C9, CYP2D6, and CYP2C19. Coadministration of RESCRIPTOR and drugs  
363 primarily metabolized by CYP3A (e.g., HMG-CoA reductase inhibitors and sildenafil) may  
364 result in increased plasma concentrations of the coadministered drug that could increase or  
365 prolong both its therapeutic or adverse effects.

366 Delavirdine is metabolized primarily by CYP3A, but in vitro data suggest that delavirdine  
367 may also be metabolized by CYP2D6. Coadministration of RESCRIPTOR and drugs that induce  
368 CYP3A, such as rifampin, may decrease delavirdine plasma concentrations and reduce its  
369 therapeutic effect. Coadministration of RESCRIPTOR and drugs that inhibit CYP3A may  
370 increase delavirdine plasma concentrations. (See **Table 6, Drugs That Should Not Be**  
371 **Coadministered With RESCRIPTOR, and Table 7, Established and Other Potentially**  
372 **Significant Drug Interactions: Alteration in Dose or Regimen May Be Recommended**  
373 **Based on Drug Interaction Studies or Predicted Interaction.**)

374

375 **Table 6. Drugs That Should Not Be Coadministered With RESCRIPTOR**

Drug Class: Drug Name	Clinical Comment
<b>Anticonvulsant agents:</b> Phenytoin, phenobarbital, carbamazepine	May lead to loss of virologic response and possible resistance to RESCRIPTOR or to the class of NNRTIs.
<b>Antihistamines:</b> Astemizole, terfenadine	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
<b>Antimycobacterials:</b> Rifabutin, <sup>a</sup> rifampin <sup>a</sup>	May lead to loss of virologic response and possible resistance to RESCRIPTOR or to the class of NNRTIs or other coadministered antiviral agents.
<b>Ergot Derivatives:</b> Dihydroergotamine, ergonovine, ergotamine, methylergonovine	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as acute ergot toxicity characterized by peripheral vasospasm and ischemia of the extremities and other tissues.
<b>GI motility agent:</b> Cisapride	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
<b>Herbal Products:</b> St. John's wort ( <i>Hypericum perforatum</i> )	May lead to loss of virologic response and possible resistance to RESCRIPTOR or to the class of NNRTIs.
<b>HMG-CoA reductase inhibitors:</b> Lovastatin, simvastatin	Potential for serious reactions such as risk of myopathy including rhabdomyolysis.
<b>Neuroleptic:</b> Pimozide	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
<b>Sedative/hypnotics:</b> Alprazolam, midazolam, triazolam	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as prolonged or increased sedation or respiratory depression.

376 <sup>a</sup>See CLINICAL PHARMACOLOGY for magnitude of interaction, Tables 1 and 2.

377 **Table 7. Established and Other Potentially Significant Drug Interactions: Alteration in**  
 378 **Dose or Regimen May Be Recommended Based on Drug Interaction Studies or Predicted**  
 379 **Interaction**

Concomitant Drug Class: Drug Name	Effect on Concentration of Delavirdine or Concomitant Drug	Clinical Comment
<b><i>HIV-Antiviral Agents: Nucleoside Reverse Transcriptase Inhibitor</i></b>		
Didanosine <sup>a</sup>	↓Delavirdine ↓Didanosine	Administration of didanosine (buffered tablets) and RESCRIPTOR should be separated by at least 1 hour.
<b><i>HIV-Antiviral Agents: Non-nucleoside Reverse Transcriptase Inhibitors</i></b>		
NNRTI	↔Delavirdine ↑NNRTI	Combining NNRTIs has not been shown to be beneficial. RESCRIPTOR should not be coadministered with another NNRTI.
<b><i>HIV-Antiviral Agents: Protease Inhibitors</i></b>		
Indinavir <sup>a</sup>	↑Indinavir	A dose reduction of indinavir to 600 mg 3 times daily should be considered when RESCRIPTOR and indinavir are coadministered.
Lopinavir/Ritonavir	↑Lopinavir ↑Ritonavir	Appropriate doses of this combination with respect to safety, efficacy, and pharmacokinetics have not been established.
Nelfinavir <sup>a</sup>	↑Nelfinavir ↓Delavirdine	Appropriate doses of this combination with respect to safety, efficacy, and pharmacokinetics have not been established (see CLINICAL PHARMACOLOGY: Tables 1 and 2).
Ritonavir	↑Ritonavir	Appropriate doses of this combination with respect to safety, efficacy, and pharmacokinetics have not been established.
Saquinavir <sup>a</sup>	↑Saquinavir	A dose reduction of saquinavir (soft gelatin capsules) may be considered when RESCRIPTOR and saquinavir are coadministered (see CLINICAL PHARMACOLOGY: Table 1). Appropriate doses with respect to safety, efficacy, and pharmacokinetics have not been established.
<b><i>HIV-Antiviral Agents: CCR5 Inhibitor</i></b>		

Maraviroc	↑Maraviroc	Concomitant use of RESCRIPTOR and maraviroc has not been studied. However, RESCRIPTOR is a potent CYP3A4 inhibitor and the maraviroc dose should be reduced during coadministration. Refer to the full prescribing information for maraviroc (SELZENTRY) for dosing recommendations.
<b>Other Agents</b>		
<b>Acid blockers:</b> Antacids <sup>a</sup>	↓Delavirdine	Doses of an antacid and RESCRIPTOR should be separated by at least 1 hour, because the absorption of delavirdine is reduced when coadministered with antacids.
<b>Histamine H<sub>2</sub>-receptor antagonists:</b> Cimetidine, famotidine, nizatidine, ranitidine	↓Delavirdine	These agents increase gastric pH and may reduce the absorption of delavirdine. Although the effect of these drugs on delavirdine absorption has not been evaluated, chronic use of these drugs with RESCRIPTOR is not recommended.
<b>Proton pump inhibitors:</b> Omeprazole, lansoprazole	↓Delavirdine	These agents increase gastric pH and may reduce the absorption of delavirdine. Although the effect of these drugs on delavirdine absorption has not been evaluated, chronic use of these drugs with RESCRIPTOR is not recommended.
<b>Amphetamines</b>	↑Amphetamines	Use with caution.
<b>Antidepressant:</b> Trazodone	↑Trazodone	Concomitant use of trazodone and RESCRIPTOR may increase plasma concentrations of trazodone. Adverse events of nausea, dizziness, hypotension, and syncope have been observed following coadministration of trazodone and ritonavir. If trazodone is used with a CYP3A4 inhibitor such as RESCRIPTOR, the combination should be used with caution and a lower dose of trazodone should be considered.
<b>Antiarrhythmics:</b> Bepridil	↑Antiarrhythmics	Use with caution. Increased bepridil exposure may be associated with life-threatening reactions such as cardiac arrhythmias.

Amiodarone, lidocaine (systemic), quinidine, flecainide, propafenone		Caution is warranted and therapeutic concentration monitoring is recommended, if available, for antiarrhythmics when coadministered with RESCRIPTOR.
<b>Anticoagulant:</b> Warfarin	↑Warfarin	It is recommended that INR (international normalized ratio) be monitored.
<b>Anti-infective:</b> Clarithromycin <sup>a</sup>	↑Clarithromycin	When coadministered with RESCRIPTOR, clarithromycin should be adjusted in patients with impaired renal function: <ul style="list-style-type: none"> <li>• For patients with CL<sub>CR</sub> 30 to 60 mL/min the dose of clarithromycin should be reduced by 50%.</li> <li>• For patients with CL<sub>CR</sub> &lt;30 mL/min the dose of clarithromycin should be reduced by 75%.</li> </ul>
<b>Calcium channel blockers:</b> Amlodipine, diltiazem, felodipine, isradipine, nifedipine, nicardipine, nimodipine, nisoldipine, verapamil	↑Calcium channel blockers	Caution is warranted and clinical monitoring of patients is recommended.
<b>Corticosteroid:</b> Dexamethasone	↓Delavirdine	Use with caution. RESCRIPTOR may be less effective due to decreased delavirdine plasma concentrations in patients taking these agents concomitantly.
<b>Erectile dysfunction agents:</b> Sildenafil	↑Sildenafil	Sildenafil should not exceed a maximum single dose of 25 mg in a 48-hour period.
<b>HMG-CoA reductase inhibitors:</b> Atorvastatin, cerivastatin, fluvastatin	↑Atorvastatin ↑Cerivastatin ↑Fluvastatin	Use lowest possible dose of atorvastatin or cerivastatin, or fluvastatin with careful monitoring, or consider other HMG-CoA reductase inhibitors such as pravastatin in combination with RESCRIPTOR.
<b>Immunosuppressants:</b> Cyclosporine, tacrolimus, rapamycin	↑Immunosuppressants	Therapeutic concentration monitoring is recommended for immunosuppressant agents when coadministered with RESCRIPTOR.

<b>Inhaled/nasal steroid:</b> Fluticasone	↑Fluticasone	Concomitant use of fluticasone and RESCRIPTOR may increase plasma concentrations of fluticasone. Use with caution. Consider alternatives to fluticasone, particularly for long-term use.
<b>Narcotic analgesic:</b> Methadone	↑Methadone	Dosage of methadone may need to be decreased when coadministered with RESCRIPTOR.
<b>Oral contraceptives:</b> Ethinyl estradiol	↑Ethinyl estradiol	Concentrations of ethinyl estradiol may increase. However, the clinical significance is unknown.

380 ↑ Indicates increase.

381 ↓ Indicates decrease.

382 <sup>a</sup>The interaction between RESCRIPTOR and the drug was evaluated in a clinical study. All other  
383 drug interactions shown are predicted.

384

385 **Carcinogenesis, Mutagenesis, Impairment of Fertility:** Delavirdine was negative in a  
386 battery of genetic toxicology tests which included an Ames assay, an in vitro rat hepatocyte  
387 unscheduled DNA synthesis assay, an in vitro chromosome aberration assay in human peripheral  
388 lymphocytes, an in vitro mutation assay in Chinese hamster ovary cells, and an in vivo  
389 micronucleus test in mice.

390 Lifetime carcinogenicity studies were conducted in rats at doses of 10, 32, and 100 mg/kg/day  
391 and in mice at doses of 62.5, 250, and 500 mg/kg/day for males and 62.5, 125, and  
392 250 mg/kg/day for females. In rats, delavirdine was noncarcinogenic at maximally tolerated  
393 doses that produced exposures (AUC) up to 12 (male rats) and 9 (female rats) times human  
394 exposure at the recommended clinical dose. In mice, delavirdine produced significant increases  
395 in the incidence of hepatocellular adenoma/adenocarcinoma in both males and females,  
396 hepatocellular adenoma in females, and mesenchymal urinary bladder tumors in males. The  
397 systemic drug exposures (AUC) in female mice were 0.5- to 3-fold and in male mice 0.2- to  
398 4-fold of those in humans at the recommended clinical dose. Given the lack of genotoxic activity  
399 of delavirdine, the relevance of urinary bladder and hepatocellular neoplasm in delavirdine-  
400 treated mice to humans is not known.

401 Delavirdine at doses of 20, 100, and 200 mg/kg/day did not cause impairment of fertility in  
402 rats when males were treated for 70 days and females were treated for 14 days prior to mating.

403 **Pregnancy:** Pregnancy Category C. Delavirdine has been shown to be teratogenic in rats.  
404 Delavirdine caused ventricular septal defects in rats at doses of 50, 100, and 200 mg/kg/day  
405 when administered during the period of organogenesis. The lowest dose of delavirdine that  
406 caused malformations produced systemic exposures in pregnant rats equal to or lower than the  
407 expected human exposure to RESCRIPTOR ( $C_{min}$  15  $\mu$ M) at the recommended dose. Exposure  
408 in rats approximately 5-fold higher than the expected human exposure resulted in marked

409 maternal toxicity, embryotoxicity, fetal developmental delay, and reduced pup survival.  
410 Additionally, reduced pup survival on postpartum day 0 occurred at an exposure (mean  $C_{min}$ )  
411 approximately equal to the expected human exposure. Delavirdine was excreted in the milk of  
412 lactating rats at a concentration 3 to 5 times that of rat plasma.

413 Delavirdine at doses of 200 and 400 mg/kg/day administered during the period of  
414 organogenesis caused maternal toxicity, embryotoxicity, and abortions in rabbits. The lowest  
415 dose of delavirdine that resulted in these toxic effects produced systemic exposures in pregnant  
416 rabbits approximately 6-fold higher than the expected human exposure to RESCRIPTOR ( $C_{min}$   
417 15  $\mu$ M) at the recommended dose. The no-observed-adverse-effect dose in the pregnant rabbit  
418 was 100 mg/kg/day. Various malformations were observed at this dose, but the incidence of such  
419 malformations was not statistically significantly different from that observed in the control  
420 group. Systemic exposures in pregnant rabbits at a dose of 100 mg/kg/day were lower than those  
421 expected in humans at the recommended clinical dose. Malformations were not apparent at 200  
422 and 400 mg/kg/day; however, only a limited number of fetuses were available for examination as  
423 a result of maternal and embryo death.

424 No adequate and well-controlled studies in pregnant women have been conducted.  
425 RESCRIPTOR should be used during pregnancy only if the potential benefit justifies the  
426 potential risk to the fetus. Of 9 pregnancies reported in premarketing clinical studies and  
427 postmarketing experience, a total of 10 infants were born (including 1 set of twins). Eight of the  
428 infants were born healthy. One infant was born HIV-positive but was otherwise healthy and with  
429 no congenital abnormalities detected, and 1 infant was born prematurely (34 to 35 weeks) with a  
430 small muscular ventricular septal defect that spontaneously resolved. The patient received  
431 approximately 6 weeks of treatment with delavirdine and zidovudine early in the course of the  
432 pregnancy.

433 **Antiretroviral Pregnancy Registry:** To monitor maternal-fetal outcomes of pregnant  
434 women exposed to RESCRIPTOR and other antiretroviral agents, an Antiretroviral Pregnancy  
435 Registry has been established. Physicians are encouraged to register patients by calling (800)  
436 258-4263.

437 **Nursing Mothers: The Centers for Disease Control and Prevention recommend that**  
438 **HIV-infected mothers not breastfeed their infants to avoid risking postnatal transmission**  
439 **of HIV.** Because of both the potential for HIV transmission and any possible adverse reactions in  
440 nursing infants, **mothers should be instructed not to breastfeed if they are receiving**  
441 **RESCRIPTOR.**

442 **Pediatric Use:** Safety and effectiveness of delavirdine in combination with other antiretroviral  
443 agents have not been established in HIV-1-infected individuals younger than 16 years of age.

444 **Geriatric Use:** Clinical studies of RESCRIPTOR did not include sufficient numbers of subjects  
445 aged 65 and over to determine whether they respond differently from younger subjects. In  
446 general, caution should be taken when dosing RESCRIPTOR in elderly patients due to the  
447 greater frequency of decreased hepatic, renal, or cardiac function and of concomitant disease or  
448 other drug therapy.

449 **ADVERSE REACTIONS**

450 The safety of RESCRIPTOR Tablets alone and in combination with other therapies has been  
 451 studied in approximately 6,000 patients receiving RESCRIPTOR. The majority of adverse events  
 452 were of mild or moderate (i.e., ACTG Grade 1 or 2) intensity. The most frequently reported  
 453 drug-related adverse event (i.e., events considered by the investigator to be related to the blinded  
 454 study medication or events with an unknown or missing causal relationship to the blinded  
 455 medication) among patients receiving RESCRIPTOR was skin rash (see Table 8 and  
 456 PRECAUTIONS: Skin Rash).

457  
 458 **Table 8. Percent of Patients With Treatment-Emergent Rash in Pivotal Trials (Studies 21**  
 459 **Part II and 13C)<sup>a</sup>**

Percent of Patients With:	Description of Rash Grade <sup>b</sup>	RESCRIPTOR 400 mg t.i.d. (n = 412)	Control Group Patients (n = 295)
Grade 1 rash	Erythema, pruritus	69 (16.7%)	35 (11.9%)
Grade 2 rash	Diffuse maculopapular rash, dry desquamation	59 (14.3%)	17 (5.8%)
Grade 3 rash	Vesiculation, moist desquamation, ulceration	18 (4.4%)	0 (0.0%)
Grade 4 rash	Erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, necrosis requiring surgery, exfoliative dermatitis	0 (0.0%)	0 (0.0%)
Rash of any grade		146 (35.4%)	52 (17.6%)
Treatment discontinuation as a result of rash		13 (3.2%)	1 (0.3%)

460 <sup>a</sup> Includes events reported regardless of causality.

461 <sup>b</sup> ACTG Toxicity Grading System; includes events reported as “rash,” “maculopapular rash,”  
 462 and “urticaria.”

463  
 464 Adverse events of moderate to severe intensity reported by at least 5% of evaluable patients in  
 465 any treatment group in the pivotal trials, which includes patients receiving RESCRIPTOR in  
 466 combination with zidovudine and/or lamivudine in Study 21 Part II for up to 98 weeks and in  
 467 combination with zidovudine and either lamivudine, didanosine, or zalcitabine in Study 13C for  
 468 up to 72 weeks are summarized in Table 9.

469

470 **Table 9. Treatment-Emergent Events Regardless of Causality, of Moderate-to-Severe or**  
471 **Life-Threatening Intensity Reported by at Least 5% of Evaluable<sup>a</sup> Patients in Any**  
472 **Treatment Group**

Adverse Events	Study 21 Part II			Study 13C	
	Zidovudine + Lamivudine (n = 123)	400 mg t.i.d. RESCRIPTOR + Zidovudine (n = 123)	400 mg t.i.d. RESCRIPTOR + Zidovudine + Lamivudine (n = 119)	Zidovudine + Didanosine, Zalcitabine, or Lamivudine (n = 172)	400 mg t.i.d. RESCRIPTOR + Zidovudine + Didanosine, Zalcitabine, or Lamivudine (n = 170)
	% of pts. (n)	% of pts. (n)	% of pts. (n)	% of pts. (n)	% of pts. (n)
<b>Body as a Whole</b>					
Abdominal pain, generalized	2.4 (3)	3.3 (4)	5.0 (6)	1.7 (3)	2.4 (4)
Asthenia/fatigue	16.3 (20)	15.4 (19)	16.0 (19)	8.1 (14)	5.3 (9)
Fever	2.4 (3)	1.6 (2)	3.4 (4)	6.4 (11)	7.1 (12)
Flu syndrome	4.9 (6)	7.3 (9)	5.0 (6)	5.2 (9)	2.4 (4)
Headache	14.6 (18)	12.2 (15)	16.8 (20)	12.8 (22)	11.2 (19)
Localized pain	4.9 (6)	5.7 (7)	5.0 (6)	2.9 (5)	1.8 (3)
<b>Digestive</b>					
Diarrhea	8.1 (10)	2.4 (3)	4.2 (5)	8.1 (14)	5.9 (10)
Nausea	17.1 (21)	20.3 (25)	16.8 (20)	9.3 (16)	14.7 (25)
Vomiting	8.9 (11)	4.9 (6)	2.5 (3)	4.1 (7)	6.5 (11)
<b>Nervous</b>					
Anxiety	1.6 (2)	2.4 (3)	6.7 (8)	4.1 (7)	3.5 (6)
Depressive symptoms	6.5 (8)	4.9 (6)	12.6 (15)	3.5 (6)	5.9 (10)
Insomnia	4.9 (6)	4.9 (6)	5.0 (6)	2.9 (5)	1.2 (2)
<b>Respiratory</b>					
Bronchitis	4.1 (5)	6.5 (8)	6.7 (8)	3.5 (6)	3.5 (6)
Cough	9.8 (12)	4.1 (5)	5.0 (6)	5.2 (9)	3.5 (6)
Pharyngitis	6.5 (8)	1.6 (2)	5.0 (6)	4.1 (7)	3.5 (6)
Sinusitis	8.9 (11)	7.3 (9)	5.0 (6)	2.3 (4)	1.2 (2)
Upper respiratory infection	11.4 (14)	6.5 (8)	7.6 (9)	8.7 (15)	4.7 (8)
<b>Skin</b>					
Rashes	3.3 (4)	19.5 (24)	13.4 (16)	7.6 (13)	18.8 (32)

473 <sup>a</sup>Evaluable patients in Study 21 Part II were those who received at least 1 dose of study  
474 medication and returned for at least 1 clinic study visit. Evaluable patients in Study 13C were  
475 those who received at least 1 dose of study medication.  
476

477 **Other Adverse Events in Phase II/III Studies:** Other adverse events that occurred in  
478 patients receiving RESCRIPTOR (in combination treatment) in all Phase II and III studies,  
479 considered possibly related to treatment, and of at least ACTG Grade 2 in intensity are listed  
480 below by body system.

481 **Body as a Whole:** Abdominal cramps, abdominal distention, abdominal pain (localized),  
482 abscess, allergic reaction, chills, edema (generalized or localized), epidermal cyst, fever,  
483 infection, infection viral, lip edema, malaise, *Mycobacterium tuberculosis* infection, neck  
484 rigidity, sebaceous cyst, and redistribution/accumulation of body fat (see PRECAUTIONS: Fat  
485 Redistribution).

486 **Cardiovascular System:** Abnormal cardiac rate and rhythm, cardiac insufficiency,  
487 cardiomyopathy, hypertension, migraine, pallor, peripheral vascular disorder, and postural  
488 hypotension.

489 **Digestive System:** Anorexia, bloody stool, colitis, constipation, decreased appetite,  
490 diarrhea (*Clostridium difficile*), diverticulitis, dry mouth, dyspepsia, dysphagia, enteritis at all  
491 levels, eructation, fecal incontinence, flatulence, gagging, gastroenteritis, gastroesophageal  
492 reflux, gastrointestinal bleeding, gastrointestinal disorder, gingivitis, gum hemorrhage,  
493 hepatomegaly, increased appetite, increased saliva, increased thirst, jaundice, mouth or tongue  
494 inflammation or ulcers, nonspecific hepatitis, oral/enteric moniliasis, pancreatitis, rectal disorder,  
495 sialadenitis, tooth abscess, and toothache.

496 **Hemic and Lymphatic System:** Adenopathy, bruising, eosinophilia, granulocytosis,  
497 leukopenia, pancytopenia, purpura, spleen disorder, thrombocytopenia, and prolonged  
498 prothrombin time.

499 **Metabolic and Nutritional Disorders:** Alcohol intolerance, amylase increased,  
500 bilirubinemia, hyperglycemia, hyperkalemia, hypertriglyceridemia, hyperuricemia,  
501 hypocalcemia, hyponatremia, hypophosphatemia, increased AST (SGOT), increased gamma  
502 glutamyl transpeptidase, increased lipase, increased serum alkaline phosphatase, increased serum  
503 creatinine, and weight increase or decrease.

504 **Musculoskeletal System:** Arthralgia or arthritis of single and multiple joints, bone  
505 disorder, bone pain, myalgia, tendon disorder, tenosynovitis, tetany, and vertigo.

506 **Nervous System:** Abnormal coordination, agitation, amnesia, change in dreams, cognitive  
507 impairment, confusion, decreased libido, disorientation, dizziness, emotional lability, euphoria,  
508 hallucination, hyperesthesia, hyperreflexia, hypertonia, hypesthesia, impaired concentration,  
509 manic symptoms, muscle cramp, nervousness, neuropathy, nystagmus, paralysis, paranoid  
510 symptoms, restlessness, sleep cycle disorder, somnolence, tingling, tremor, vertigo, and  
511 weakness.

512 **Respiratory System:** Chest congestion, dyspnea, epistaxis, hiccups, laryngismus,  
513 pneumonia, and rhinitis.

514 **Skin and Appendages:** Angioedema, dermal leukocytoclastic vasculitis, dermatitis,  
515 desquamation, diaphoresis, discolored skin, dry skin, erythema, erythema multiforme, folliculitis,  
516 fungal dermatitis, hair loss, herpes zoster or simplex, nail disorder, petechiae, non-application  
517 site pruritus, seborrhea, skin hypertrophy, skin disorder, skin nodule, Stevens-Johnson syndrome,  
518 urticaria, vesiculobullous rash, and wart.

519 **Special Senses:** Blepharitis, blurred vision, conjunctivitis, diplopia, dry eyes, ear pain,  
520 parosmia, otitis media, photophobia, taste perversion, and tinnitus.

521 **Urogenital System:** Amenorrhea, breast enlargement, calculi of the kidney, chromaturia,  
522 epididymitis, hematuria, hemospermia, impaired urination, impotence, kidney pain,  
523 metrorrhagia, nocturia, polyuria, proteinuria, testicular pain, urinary tract infection, and vaginal  
524 moniliasis.

525 **Postmarketing Experience:** Adverse event terms reported from postmarketing surveillance  
526 that were not reported in the Phase II and III trials are presented below.

527 **Digestive System:** Hepatic failure.

528 **Hemic and Lymphatic System:** Hemolytic anemia.

529 **Musculoskeletal System:** Rhabdomyolysis.

530 **Urogenital System:** Acute kidney failure.

531 **Laboratory Abnormalities:** Marked laboratory abnormalities observed in at least 2% of  
532 patients during Studies 21 Part II and 13C are summarized in Table 10. Marked laboratory  
533 abnormalities are defined as any Grade 3 or 4 abnormality found in patients at any time during  
534 study.

535

536 **Table 10. Marked Laboratory Abnormalities Reported by  $\geq 2\%$  of Patients**

Adverse Events/Toxicity Limits	Study 21 Part II			Study 13C	
	Zidovudine + Lamivudine (n = 123) % pts.	400 mg t.i.d. RESCRIPTOR + Zidovudine (n = 123) % pts.	400 mg t.i.d. RESCRIPTOR + Zidovudine + Lamivudine (n = 119) % pts.	Zidovudine + Didanosine, Zalcitabine, or Lamivudine (n = 172) % pts.	400 mg t.i.d. RESCRIPTOR + Zidovudine + Didanosine, Zalcitabine, or Lamivudine (n = 170) % pts.
<b>Hematology</b>					
Hemoglobin <7 mg/dL	4.1	2.5	0.9	1.7	2.9
Neutrophils <750/mm <sup>3</sup>	5.7	4.9	3.4	10.4	7.6
Prothrombin time (PT) >1.5 × ULN	0	0	1.7	2.9	2.4
Activated partial thromboplastin (APTT) >2.33 × ULN	0	0.8	0	5.8	2.4
<b>Chemistry</b>					
Alanine aminotransferase (ALT/SGPT) >5 × ULN	2.5	4.1	5.1	3.5	4.1
Amylase >2 × ULN	0.8	2.5	2.6	3.5	2.9
Aspartate aminotransferase (AST/SGOT) >5 × ULN	1.6	2.5	3.4	3.5	2.3
Bilirubin >2.5 × ULN	0.8	2.5	1.7	1.2	0
Gamma glutamyl transferase (GGT) >5 × ULN	N/A	N/A	N/A	4.1	1.8
Glucose (hypo-/hyperglycemia) <40 mg/dL >250 mg/dL	4.1	0.8	1.7	1.2	0

537 N/A = not applicable because no predose values were obtained for patients.

## 538 **OVERDOSAGE**

539 Human experience of acute overdose with RESCRIPTOR is limited.

540 **Management of Overdosage:** Treatment of overdose with RESCRIPTOR should consist  
541 of general supportive measures, including monitoring of vital signs and observation of the  
542 patient's clinical status. There is no specific antidote for overdose with RESCRIPTOR. If  
543 indicated, elimination of unabsorbed drug should be achieved by emesis or gastric lavage. Since  
544 delavirdine is extensively metabolized by the liver and is highly protein-bound, dialysis is  
545 unlikely to result in significant removal of the drug.

## 546 **DOSAGE AND ADMINISTRATION**

547 The recommended dosage for RESCRIPTOR Tablets is 400 mg (four 100-mg or two 200-mg  
548 tablets) 3 times daily. RESCRIPTOR should be used in combination with other antiretroviral  
549 therapy. The complete prescribing information for other antiretroviral agents should be consulted  
550 for information on dosage and administration.

551 The 100-mg RESCRIPTOR Tablets may be dispersed in water prior to consumption. To  
552 prepare a dispersion, add four 100-mg RESCRIPTOR Tablets to at least 3 ounces of water, allow  
553 to stand for a few minutes, and then stir until a uniform dispersion occurs (see CLINICAL  
554 PHARMACOLOGY: Pharmacokinetics: Absorption and Bioavailability). The dispersion should  
555 be consumed promptly. The glass should be rinsed with water and the rinse swallowed to insure  
556 the entire dose is consumed. **The 200-mg tablets should be taken as intact tablets, because**  
557 **they are not readily dispersed in water.** Note: The 200-mg tablets are approximately one-third  
558 smaller in size than the 100-mg tablets.

559 RESCRIPTOR Tablets may be administered with or without food (see CLINICAL  
560 PHARMACOLOGY: Pharmacokinetics: Absorption and Bioavailability). Patients with  
561 achlorhydria should take RESCRIPTOR with an acidic beverage (e.g., orange or cranberry  
562 juice). However, the effect of an acidic beverage on the absorption of delavirdine in patients with  
563 achlorhydria has not been investigated.

564 Patients taking both RESCRIPTOR and antacids should be advised to take them at least  
565 1 hour apart.

## 566 **HOW SUPPLIED**

567 RESCRIPTOR Tablets are available as follows:

568 100-mg: white, capsule-shaped tablets marked with "U 3761"

569 Bottles of 360 tablets - NDC 49702-209-24.

570 200-mg: white, capsule-shaped tablets marked with "RES200"

571 Bottles of 180 tablets - NDC 49702-225-17.

572 Store at controlled room temperature 20° to 25°C (68° to 77°F) [see USP]. Keep container  
573 tightly closed. Protect from high humidity.

574 **ANIMAL TOXICOLOGY**

575 Toxicities among various organs and organ systems in rats, mice, rabbits, dogs, and monkeys  
576 were observed following the administration of delavirdine. Necrotizing vasculitis was the most  
577 significant toxicity that occurred in dogs when mean nadir serum concentrations of delavirdine  
578 were at least 7-fold higher than the expected human exposure to RESCRIPTOR ( $C_{\min}$  15  $\mu\text{M}$ ) at  
579 the recommended dose. Vasculitis in dogs was not reversible during a 2.5-month recovery  
580 period; however, partial resolution of the vascular lesion characterized by reduced inflammation,  
581 diminished necrosis, and intimal thickening occurred during this period. Other major target  
582 organs included the gastrointestinal tract, endocrine organs, liver, kidneys, bone marrow,  
583 lymphoid tissue, lung, and reproductive organs.

584

585

586 Manufactured for



587

588 ViiV Healthcare

589 Research Triangle Park, NC 27709

590

591 by

592 Pfizer Pharmaceuticals LLC

593 Vega Baja, Puerto Rico 00693

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597 August 2012

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## PATIENT INFORMATION

### **RESCRIPTOR<sup>®</sup>** **(ree-SKRIP-tor)** **(delavirdine mesylate) Tablets**

Generic name: delavirdine mesylate (de-LAH-vur-deen MESS-ihl-ate)

**ALERT: Find out about medicines that should NOT be taken with RESCRIPTOR.** Please also read the section "**MEDICINES YOU SHOULD NOT TAKE WITH RESCRIPTOR.**"

Read this information carefully before taking RESCRIPTOR. Also, read this leaflet each time you renew the prescription, just in case anything has changed. This is a summary and not a replacement for a careful discussion with your healthcare provider (doctor, nurse, pharmacist). You and your healthcare provider should discuss RESCRIPTOR when you start taking this medication and at regular checkups. You should remain under a doctor's care when taking RESCRIPTOR and should not change or stop treatment without first talking with your healthcare provider.

#### **What is RESCRIPTOR and how does it work?**

RESCRIPTOR is a medicine used in combination with other anti-HIV medicines to treat people with HIV-1 infection. Infection with HIV-1 leads to the destruction of infection-fighting immune system cells (called CD4+ cells or T cells), which are important to the immune system. After a large number of CD4+ cells have been destroyed, the infected person develops acquired immune deficiency syndrome (AIDS).

RESCRIPTOR helps to block HIV-1 reverse transcriptase, a chemical the virus uses to make more copies of itself. The main goals of anti-HIV medicines like RESCRIPTOR are to decrease the amount of virus in your blood (called viral load) and to increase the number of CD4+ cells as much as possible for as long as possible.

RESCRIPTOR, when taken with other anti-HIV medicines, lowers the HIV-1 viral load in patients. Patients who took RESCRIPTOR as part of combination therapy for HIV-1 also had increases in their CD4+ cell count.

638

639 **General information about RESCRIPTOR**

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

643

644 Avoid doing things that can spread HIV-1 infection.

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

651

652 **How should I take RESCRIPTOR?**

- 653 • You should stay under a healthcare provider's care when taking RESCRIPTOR. Do  
654 not change your treatment or stop treatment without first talking with your  
655 healthcare provider.
- 656 • You must take RESCRIPTOR every day exactly as your healthcare provider  
657 prescribes it. Follow the directions from your healthcare provider, exactly as  
658 written on the label.
- 659 • **The usual dose of RESCRIPTOR is two 200-mg tablets 3 times a day or**  
660 **four 100-mg tablets 3 times a day, in combination with other anti-HIV-1**  
661 **medicines. Either way, your total daily dose of RESCRIPTOR remains the**  
662 **same.**
- 663 • You can take RESCRIPTOR with or without food.
- 664 • If you have trouble swallowing tablets, the 100-mg RESCRIPTOR tablets may be  
665 dissolved in water. Place 4 tablets in at least 3 ounces of water and allow the  
666 tablets to sit in the water for a few minutes. Then, stir the water until the tablets  
667 have dissolved and drink the mixture right away. Add a little more water, swirl,  
668 and then drink the rest of the mixture to be sure that you get all the medicine.  
669 **The 200-mg tablets must be swallowed whole. They cannot be dissolved**  
670 **in water.**
- 671 • Many people find it easier to take their RESCRIPTOR with breakfast, lunch, and  
672 dinner, since food does not interfere with RESCRIPTOR. It is a good idea to get  
673 into the habit of taking RESCRIPTOR on a regular schedule to make it easier to  
674 remember. Figure out things that happen every day at pill-taking time and take  
675 your tablets then. By taking your medicine along with activities you do every day,  
676 such as getting up in the morning, brushing your teeth, eating lunch, coming

- 677 home from work in the evening, or watching a favorite TV show, you will find it  
678 easier to remember to take every dose.
- 679 • When your supply of RESCRIPTOR starts to run low, get more from your  
680 healthcare provider or pharmacy. This is very important because the amount of  
681 virus in your blood may increase if the medicine is stopped for even a short time.  
682 The virus may develop resistance to RESCRIPTOR and become harder to treat.
  - 683 • Only take medicine that has been prescribed specifically for you. Do not give  
684 RESCRIPTOR to others or take medicine prescribed for someone else.

### 685 **What should I do if I miss a dose of RESCRIPTOR?**

687 If you forget to take a dose of RESCRIPTOR, take it as soon as possible. However, if  
688 you skip the dose entirely, do not double the next dose. If you forget a lot of doses,  
689 talk to your healthcare provider about how you should continue taking your  
690 medicine.

### 691 **Who should not take RESCRIPTOR?**

693 Together with your healthcare provider, you need to decide whether RESCRIPTOR is  
694 right for you.

- 695 • **Do not take RESCRIPTOR if you are taking certain medicines.** These could  
696 cause serious side effects that could cause death. Before you take RESCRIPTOR,  
697 you must tell your healthcare provider about all the medicines you are taking or  
698 are planning to take. These include other prescription and nonprescription  
699 medicines and herbal supplements.

700 For more information about medicines you should not take with RESCRIPTOR,  
701 please read the section titled "**MEDICINES YOU SHOULD NOT TAKE WITH**  
702 **RESCRIPTOR.**"

- 703 • **Do not take RESCRIPTOR if you have an allergy to RESCRIPTOR.** Also tell  
704 your healthcare provider if you have any known allergies to other medicines,  
705 foods, preservatives, or dyes.
- 706 • **Tell your healthcare provider if you are pregnant or plan to become**  
707 **pregnant.** The effects of RESCRIPTOR on pregnant women or their unborn babies  
708 are not known.
- 709 • If you are breastfeeding, **do not breastfeed.** We do not know if RESCRIPTOR  
710 can be passed to your baby in your breast milk and whether it could harm your  
711 baby. Also, mothers with HIV-1 should not breastfeed because HIV-1 can be  
712 passed to the baby in the breast milk. Talk with your healthcare provider about  
713 the best way to feed your baby.
- 714 • **Talk with your healthcare provider if you have liver or kidney disease.**  
715 RESCRIPTOR has not been studied in people with liver or kidney disease.

- 716 • **Certain medical problems may affect the use of RESCRIPTOR.** Be sure to  
717 tell your healthcare provider of any other medical problems you may have.  
718

719 **Can I take RESCRIPTOR with other medicines?**

720 RESCRIPTOR may interact with other medicines, including those you take without a  
721 prescription. You must tell your healthcare provider about all medicines you are  
722 taking or planning to take before you take RESCRIPTOR. It is a good idea to keep a  
723 complete list of all the medicines that you take, including nonprescription  
724 medicines, herbal remedies and supplements, and street drugs. Update this list  
725 when medicines are added or stopped. Give copies of this list to all of your  
726 healthcare providers **every** time you visit or fill a prescription.  
727

728 **MEDICINES YOU SHOULD NOT TAKE WITH RESCRIPTOR**

729  
730 **Do not take the following medicines with RESCRIPTOR because they can**  
731 **cause serious problems or death if taken with RESCRIPTOR:**

- 732 • VERSED<sup>®</sup> (midazolam) Injection and Syrup (for sedation)
- 733 • HALCION<sup>®</sup> (triazolam) Tablets (for sleep problems)
- 734 • XANAX<sup>®</sup> (alprazolam) Tablets (for anxiety)
- 735 • D.H.E. 45<sup>®</sup> Injection, ERGOMAR<sup>®</sup>, MIGRANAL<sup>®</sup>, WIGRAINE<sup>®</sup>, and CAFERGOT<sup>®</sup> (for  
736 migraine headaches)
- 737 • METHERGINE<sup>®</sup> (for bleeding after childbirth)
- 738 • ORAP<sup>®</sup> (pimozide) Tablets (for seizures)
- 739 • PROPULSID<sup>®</sup> (cisapride) Tablets and Suspension (for heartburn)
- 740 • HISMANAL<sup>®</sup> (astemizole) Tablets (for allergies)
- 741 • SELDANE<sup>®</sup> (terfenadine) Tablets (for allergies)

742  
743 Do not take the following medicines when you take RESCRIPTOR. They may reduce  
744 the levels of RESCRIPTOR in the blood and make it less effective. Talk with your  
745 healthcare provider if you are currently taking these medicines because other  
746 medicines may have to be given to take their place:

- 747 • Rifampin (also known as RIMACTANE<sup>®</sup>, RIFADIN<sup>®</sup>, RIFATER<sup>®</sup>, RIFAMATE<sup>®</sup>) (to  
748 treat tuberculosis)
- 749 • Phenobarbital (for seizures)
- 750 • DILANTIN<sup>®</sup> (phenytoin) (for seizures)
- 751 • TEGRETOL<sup>®</sup> (carbamazepine) (for seizures)

752  
753 Do not take RESCRIPTOR with St. John's wort (*Hypericum perforatum*), an herbal  
754 product sold as a dietary supplement, or products containing St. John's wort. Talk  
755 with your healthcare provider if you are taking or planning to take St. John's wort.

756 Taking St. John's wort may decrease levels of RESCRIPTOR and lead to increased  
757 viral load and possible resistance to RESCRIPTOR or cross-resistance to other anti-  
758 HIV medicines.

759

760 Do not take RESCRIPTOR with cholesterol-lowering medicines MEVACOR®  
761 (lovastatin) or ZOCOR® (simvastatin) because of possible serious reactions. There  
762 is also an increased risk of drug interactions between RESCRIPTOR and LIPITOR®  
763 (atorvastatin), BAYCOL® (cerivastatin), and LESCOL® (fluvastatin); talk to your  
764 healthcare provider before you take any of these cholesterol-reducing medicines  
765 with RESCRIPTOR.

766

767 **Medicines that require dosage adjustments:**

768 It is possible that your healthcare provider may need to increase or decrease the  
769 dose of other medicines when you are taking RESCRIPTOR. Remember to tell your  
770 healthcare provider all the medicines you are taking or planning to take.

771

772 **Before you take VIAGRA® (sildenafil) with RESCRIPTOR, talk to your**  
773 **healthcare provider about problems these 2 medicines can cause when**  
774 **taken together. You may get increased side effects of VIAGRA, such as low**  
775 **blood pressure, vision changes, and penis erection lasting more than 4**  
776 **hours. If an erection lasts longer than 4 hours, get medical help right away**  
777 **to avoid permanent damage to your penis. Your healthcare provider can**  
778 **explain these symptoms to you.**

- 779 • **If you are taking both VIDEX® (didanosine, ddi) and RESCRIPTOR:** Take  
780 VIDEX (buffered tablets) 1 hour before or 1 hour after you take RESCRIPTOR.  
781 Taking them together causes lower amounts of RESCRIPTOR in the blood, making  
782 both medicines less effective.
- 783 • **Protease inhibitors:** A number of healthy volunteers and HIV-1-infected  
784 patients were studied while taking RESCRIPTOR with one of these protease  
785 inhibitors: CRIXIVAN® (indinavir), INVIRASE® and FORTOVASE® (saquinavir),  
786 NORVIR® (ritonavir), or VIRACEPT® (nelfinavir). RESCRIPTOR was shown to  
787 increase the amount of these protease inhibitors in the blood. RESCRIPTOR is  
788 expected to increase the amount of AGENERASE® (amprenavir) and KALETRA®  
789 (lopinavir + ritonavir) in the blood. **As a result, your healthcare provider may**  
790 **choose to lower the dose of one of these medicines or monitor certain lab**  
791 **tests if these protease inhibitors are taken in combination with**  
792 **RESCRIPTOR.**
- 793 • **Antacids** should be taken at least 1 hour before or 1 hour after you take  
794 RESCRIPTOR because they can slow the absorption of RESCRIPTOR.

795 Based on your history of taking other anti-HIV medicine, your healthcare provider  
796 will direct you on how to take RESCRIPTOR and other anti-HIV medicines. These  
797 drugs should be taken in a certain order or at specific times. This will depend on  
798 how many times a day each medicine should be taken. It will also depend on  
799 whether the medicines should be taken with or without food.

800

### 801 **What are the possible side effects of RESCRIPTOR?**

- 802 • This list of side effects is not complete. If you have questions about side effects,  
803 ask your doctor, nurse, or pharmacist. You should report any new or continuing  
804 symptoms to your healthcare provider right away. Your healthcare provider may  
805 be able to help you manage these side effects.
- 806 • The most important common side effect seen in people taking RESCRIPTOR has  
807 been a skin rash. The rash occurs mainly on the upper body and upper arms, and  
808 sometimes on the neck and face. The rash appears as a red area on the skin with  
809 slight bumps, and it can be itchy. The rash tends to occur early, usually within 1  
810 to 3 weeks after you start taking RESCRIPTOR, and it usually lasts less than  
811 2 weeks. Watch your rash carefully and talk to your healthcare provider about  
812 how to treat it. If the rash is going to be serious or severe (with fever, blistering,  
813 sores in the mouth, redness or swelling of the eyes, or muscle and joint aches),  
814 you and your healthcare provider will usually realize it during the first 3 days of  
815 the rash. If you have symptoms of a severe rash, you should stop taking  
816 RESCRIPTOR and speak with your healthcare provider as soon possible. Be  
817 prepared to explain where the rash is, your temperature, and whether or not you  
818 have other symptoms.
- 819 • Other side effects include headache, nausea, diarrhea, and tiredness. Of these,  
820 nausea was the most common.
- 821 • Changes in body fat have been seen in some patients taking antiretroviral  
822 therapy. These changes may include increased amount of fat in the upper back  
823 and neck ("buffalo hump"), breast, and around the trunk. Loss of fat from the  
824 legs, arms and face may also happen. The cause and long-term health effects of  
825 these conditions are not known at this time.
- 826 • Before you start using any medicine, talk with your healthcare provider about  
827 what to expect and discuss ways to reduce the side effects you may have.

828

### 829 **How do I store RESCRIPTOR?**

- 830 • Keep RESCRIPTOR and all other medicines out of the reach of children. Keep the  
831 bottle closed and store at room temperature (between 68°F and 77°F) away from  
832 sources of moisture such as a sink or other damp place. Heat and moisture may  
833 reduce the effectiveness of RESCRIPTOR.

- 834 • Do not keep medicine that is out of date or that you no longer need. Be sure that  
835 if you throw any medicine away, it is out of the reach of children.

836

837 **General advice about prescription medicines:**

838 Discuss all questions about your health with your healthcare provider. If you have  
839 questions about RESCRIPTOR or any other medicines you are taking, ask your  
840 healthcare provider. You can also call 1-877-844-8872 toll free.

841

842 AGENERASE and RESCRIPTOR are registered trademarks of ViiV Healthcare.

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845 of ViiV Healthcare. The makers of these brands are not affiliated with and do not  
846 endorse ViiV Healthcare or its products.

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860 August 2012

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