

PRODUCT MONOGRAPH

RESCRIPTOR[®]

(delavirdine mesylate)

Tablets - 100 mg

ANTIRETROVIRAL AGENT

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ANTIRETROVIRAL AGENT

ACTION AND CLINICAL PHARMACOLOGY

RESCRIPTOR (delavirdine mesylate) is a non-nucleoside reverse transcriptase inhibitor (NNRTI) of the human immunodeficiency virus-type 1 (HIV-1). Reverse transcriptase (RT) is located in the core of the HIV-1 virus and is released upon entry into the host cell. It uses the viral RNA as a template to form DNA. This is a pivotal step in the HIV-1 infection process.

Delavirdine mesylate (henceforth referred to as delavirdine) is a selective inhibitor of RT. It binds directly to 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 α , γ , or δ are not inhibited by delavirdine.

***In vitro* HIV-1 susceptibility**

The antiviral activity of delavirdine *in vitro* has been demonstrated in both acute and chronic HIV infections in lymphoblastic and monocytic cell lines and peripheral blood lymphocytes with laboratory and clinical isolates of HIV-1. IC₅₀ and IC₉₀ values (50% and 90% inhibitory concentrations) for laboratory isolates (N=5) ranged from 0.005 to 0.030 μ M and 0.04 to 0.10 μ M, respectively. Mean IC₅₀ of clinical isolates (N=74) was 0.038 μ M (range 0.001 to 0.69 μ M); 73 of 74 clinical isolates had an IC₅₀ \leq 0.18 μ M. The IC₉₀ of 24 of these clinical isolates ranged from 0.05 to 0.10 μ M. In drug combination studies of delavirdine with zidovudine, didanosine, zalcitabine, lamivudine, interferon- α and protease inhibitors, additive to synergistic anti-HIV-1 activity was

observed in cell culture. The relationship between the *in vitro* susceptibility of HIV-1 RT inhibitors and inhibition of HIV replication in humans has not been established.

Drug resistance

Phenotypic analysis of isolates from patients treated with delavirdine as monotherapy showed a 50-fold to 500-fold reduction in sensitivity in 14 of 15 patients by Week 8 of therapy. Genotypic analysis of HIV-1 isolates from patients receiving delavirdine plus zidovudine combination therapy (n=79) showed resistance conferring mutations in all isolates by Week 24 of therapy. In delavirdine treated patients the mutations in RT occurred predominantly at amino acid positions 103 and less frequently at position 181 and 236. In a separate study, an average of 86-fold increase in zidovudine susceptibility of patient isolates (n=24) was observed after 24-weeks of delavirdine and zidovudine combination therapy. The clinical relevance of the phenotypic and the genotypic changes associated with delavirdine therapy has not been established.

Cross-resistance

NNRTIs, when used alone or in combination, may confer cross-resistance to other NNRTIs.

Pharmacokinetics (see PHARMACOLOGY-Pharmacokinetics)

The pharmacokinetic properties of delavirdine have been studied in healthy volunteers and in HIV-1–infected patients after single oral doses of delavirdine ranging from 10 mg to 400 mg and after multiple oral doses ranging from 20 mg tid to 850 mg tid.

Pharmacokinetic parameters of delavirdine after multiple dosing of delavirdine tablets 400 mg tid are shown below.

Mean +/- Standard Deviation (Range) Steady-State Pharmacokinetic Parameters in HIV-1 Infected Patients (N=67) after 400 mg tid.

C _{min} (μM)	15± 10 (0.1-45)
C _{max} (μM)	35± 20 (2-100)
AUC (μM•hr)	180 ± 100 (5-515)
T _{max} (hr)	1.3 ± 0.7 (0.5-5)
T _{1/2} (hr)	5.8 ± 2.5* (2-13)

*n=54

Special Populations

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

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

Race: No significant differences in the pharmacokinetics of delavirdine were observed between different racial or ethnic groups.

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

Drug Interactions

Specific drug interaction studies were performed with delavirdine and a number of drugs. Table 1 summarizes the effect of delavirdine on the geometric mean AUC, C_{max} and C_{min} of coadministered drugs. Table 2 shows the effects of coadministered drugs on the geometric mean AUC, C_{max} and C_{min} of delavirdine.

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

Table 1. Pharmacokinetic Parameters for Coadministered Drugs in the Presence of Delavirdine

Coadministered Drug	Dose of Coadministered Drug	Dose of RESCRIPTOR	n	% Change in Pharmacokinetic Parameters of Coadministered Drug (90% CI)		
				Cmax	AUC	Cmin
HIV-Protease Inhibitors						
Nelfinavir	750 mg tid x 14 days	400 mg tid x 7 days	12	↑88 (↑66- ↑113)	↑107 (↑83 - ↑135)	↑136 (↑103- ↑175)
	750 mg tid x 28 days	400 mg tid x 28 days	22	↑63* (↑28 - ↑106)	↑74* (↑38 - ↑120)	↑83* (↑40 - ↑138)
Indinavir	600 or 800 mg tid x 7 days	0 or 400 mg tid x 7 days	28	↔**	↑53** (↑7 - ↑120)	↑298** (↑104 - ↑678)
	600 mg Single-Dose	400 mg tid x 10 days	14	↓18† (↓25 - ↓10)	↑45† (↑30 - ↑62)	-
Saquinavir	Hard gel capsule 600 mg tid x 21 days	400 mg tid x 14 days	13	↑317 (↑187- ↑504)	↑348 (↑215 - ↑535)	↑376 (↑256- ↑535)
	Soft gel capsule 1000 or 1200 mg tid x 28 days	0 or 400 mg tid x 28 days	20	↑98‡ (↑4- ↑277)	↑121‡ (↑14 - ↑340)	↑199‡ (↑37- ↑553)
Ritonavir	600 mg bid for >35 days	400 mg tid x 21 days	12	↑54 (↑24 - ↑91)	↓51 (↓24 - ↓83)	↑76 (↑50 - ↑105)
Nucleoside Reverse Transcriptase Inhibitors						
Zidovudine	200 mg tid for >38 days	100 mg qid to 400 mg tid for 8-10 days	34	↔	↔	-
Didanosine (buffered tablets)	125 or 250 mg bid x 28 days	400 mg tid x 28 days	9	↓20§ (↓44 - ↓15)	↓21§ (↓40 - ↓5)	-
Anti-infective Agents						
Rifabutin	300 mg od for 15-99 days	400-1000 mg tid for 45-129 days	5	↑128 (↑71 - ↑203)	↑230 (↑199 - ↑396)	↑452 (↑246 - ↑781)
Clarithromycin	500 mg bid x 15 days	300 mg tid x 30 days	6	-	↑100	-

↑Indicates increase ↓Indicates decrease ↔Indicates no significant change

*Percent change based on a comparison to historical data.

**Indinavir 600 mg tid plus RESCRIPTOR 400 mg tid relative to indinavir 800 mg tid without RESCRIPTOR.

†Indinavir 600 mg single-dose plus RESCRIPTOR 400 mg tid relative to indinavir 800 mg single-dose alone.

‡Saquinavir soft gel capsule 1000 mg tid plus RESCRIPTOR 400 mg tid relative to saquinavir soft gel capsule 1200 mg tid without RESCRIPTOR

§RESCRIPTOR taken with didanosine (buffered tablets) relative to doses of RESCRIPTOR and didanosine separated by at least 1 hr.

- Indicates no data is available.

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)		
				Cmax	AUC	Cmin
HIV-Protease Inhibitors						
Indinavir	600 mg Single-Dose	400 mg tid x 10 days	14	↔	↔	↔
	0 or 600 mg tid x 7 days	400 mg tid x 7 days	81	↔*	↔*	↔*
Nelfinavir	750 mg tid x 7 days	400 mg tid x 14 days	7	↓27 (↓49- ↑4)	↓31 (↓57- ↑10)	↓33 (↓70- ↑49)
	750 mg tid x 28 days	400 mg tid x 28 days	77	↓38* (↓57- ↓10)	↓35* (↓57- ↓1)	49* (↓70 - ↓12)
Ritonavir	0 or 600 mg bid for >35 days	400 mg tid for 7-21 days	25	↔*	↔*	↔*
Saquinavir	Hard gel capsule 600 mg tid x 14 days	400 mg tid x 28 days	7	↔*	↔*	↔*
	Soft gel capsule 0 or 1000 mg tid x 28 days	400 mg tid for 7-28 days	23	↔*	↔*	↔*
Nucleoside Reverse Transcriptase Inhibitors						
Zidovudine	0 or 200 mg tid for ≥ 7 days	400 mg tid for 7-14 days	42	↔*	↔*	↔*
Didanosine (buffered tablets)	125 or 250 mg bid x 28 days	400 mg tid x 28 days	9	↓32† (↓48- ↓11)	↓19† (↓37- ↑6)	↔†

Coadministered Drug	Dose of Coadministered Drug	Dose of RESCRIPTOR	n	% Change in Delavirdine Pharmacokinetic Parameters (90% CI)		
				Cmax	AUC	Cmin
Anti-infective Agents						
Clarithromycin	500 mg bid x 15 days	300 mg tid x 30 days	6	↔	↔	↔
Fluconazole	400 mg od x 15 days	300 mg tid x 30 days	8	↔	↔	↔
Ketoconazole	Various	200-400 mg tid	26	-	-	↑50‡
Rifampin	600 mg od x 15 days	400 mg tid x 30 days	7	↓90 (↓94 - ↓83)	↓97 (↓98- ↓95)	↓100
Rifabutin	300 mg od x 14 days	400 mg tid x 28 days	7	↓72 (↓61- ↓80)	↓82 (↓74- ↓88)	↓94 (↓90-↓96)
Sulfamethoxazole or Trimethoprim & Sulfamethoxazole	Various	200-400 mg tid	311	-	-	↔‡
Other						
Antacid (Maalox® TC)	20 mL	300 mg Single-Dose	12	↓52 (↓68 - ↓29)	↓44 (↓58 - ↓27)	-
Fluoxetine	Various	200-400 mg tid	36	-	-	↑50‡
Phenytoin, Phenobarbital, Carbamazepine	Various	300-400 mg tid	8	-	-	↓90‡

↑Indicates increase.

↓Indicates decrease.

↔Indicates no significant change.

*Percent change based on a comparison to historical data.

†RESCRIPTOR taken with didanosine (buffered tablets) relative to doses of RESCRIPTOR and didanosine separated by at least 1 hr.

‡Population pharmacokinetic data from efficacy studies.

- Indicates no data is available.

INDICATIONS AND CLINICAL USE

RESCRIPTOR (delavirdine mesylate) is indicated for the treatment of HIV-1 infection in highly customized antiretroviral regimens, in patients who are likely to be intolerant to other non-nucleoside reverse transcriptase inhibitors (NNRTIs).

This indication is based on the modest antiretroviral efficacy shown in clinical trials in antiretroviral-naive patients, when RESCRIPTOR was used in combination with two other nucleoside reverse transcriptase inhibitors (NRTIs), compared to two NRTIs alone. There are insufficient data directly comparing RESCRIPTOR-containing antiretroviral regimens with currently preferred multi-drug regimens for treatment of HIV infection. There is no controlled clinical trial evidence for use of RESCRIPTOR in rescue-therapy regimens.

Resistant viruses emerge rapidly when RESCRIPTOR is used as monotherapy. Therefore, RESCRIPTOR should always be used in combination with at least two other appropriate antiretroviral agents. Non-nucleoside reverse transcriptase inhibitors, when used alone or in combination, may confer cross-resistance to other NNRTIs.

CONTRAINDICATIONS

RESCRIPTOR (delavirdine mesylate) is contraindicated in patients with previously demonstrated clinically significant hypersensitivity to any of the components of the formulation.

Coadministration of RESCRIPTOR is contraindicated with drugs that are highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or

life-threatening events. These drugs are listed in Table 3. **Also, see PRECAUTIONS, Table 4, Drugs That Should Not Be Coadministered With RESCRIPTOR.**

Table 3. Drugs That Are Contraindicated With RESCRIPTOR	
Drug Class	Drugs Within Class That Are Contraindicated With RESCRIPTOR
Ergot derivatives	Dihydroergotamine, ergonovine, ergotamine, methylergonovine
Neuroleptic	Pimozide
Sedative/hypnotics	Alprazolam, midazolam, triazolam

WARNINGS

Drug Interactions

Delavirdine may inhibit the metabolism of many different drugs (eg, antiarrhythmics, calcium channel blockers, sedative hypnotics, and others), **serious and/or life threatening drug interactions could result from inappropriate coadministration of some drugs with delavirdine.** In addition, some drugs may markedly reduce delavirdine plasma concentrations, resulting in suboptimal antiviral activity and subsequent emergence of drug resistance. All prescribers should become familiar with the following tables in this monograph: **Table 3, Drugs That Are Contraindicated With RESCRIPTOR; Table 5, Established and Other Potentially Significant Drug Interactions: Alteration in Dose or Regimen May Be Recommended Based on Drug Interaction Studies or Predicted Interaction.** Additional details on drug interactions can be found in Tables 1 and 2 under the CLINICAL PHARMACOLOGY section.

Concomitant use of lovastatin or simvastatin with RESCRIPTOR is not recommended. Caution should be exercised if RESCRIPTOR is used concurrently with other HMG-CoA reductase inhibitors (statins) that are also metabolized by the CYP3A4 pathway (e.g., atorvastatin) or CYP2C9 pathway (e.g., fluvastatin). The risk of myopathy including rhabdomyolysis may be increased when RESCRIPTOR is used in combination with these drugs.

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

Concomitant use of St. John's wort (*hypericum perforatum*) or St. John's wort containing products and RESCRIPTOR is not recommended. Coadministration of St. John's wort with non-nucleoside reverse transcriptase inhibitors (NNRTIs), including RESCRIPTOR, is expected to substantially decrease NNRTI concentrations and may result in suboptimal levels of RESCRIPTOR and lead to loss of virologic response and possible resistance to RESCRIPTOR or to the class of NNRTIs.

PRECAUTIONS

Hepatic Impairment:

Delavirdine is metabolized primarily by the liver. Therefore, caution should be exercised when administering RESCRIPTOR (delavirdine mesylate) to patients with impaired hepatic function.

Resistance/Cross-Resistance:

Non-nucleoside reverse transcriptase inhibitors, when used alone or in combination, may confer cross-resistance to other non-nucleoside reverse transcriptase inhibitors.

Skin Rash:

Patients may experience a skin rash, which is usually temporary. Skin rash attributable to RESCRIPTOR has occurred in 18% of all patients on combination regimens in phase II and III controlled trials who received RESCRIPTOR 400 mg tid. Dose titration does not significantly reduce the incidence of rash. Skin rash is more common in patients with lower CD4 cell counts and typically occurs within 1 to 3 weeks of treatment.

Severe and life threatening skin reactions have occurred on rare occasions in patients treated with RESCRIPTOR, including Stevens-Johnson syndrome and erythema multiforme. None of them were associated with fatalities. RESCRIPTOR must be discontinued in patients developing a severe rash or a rash accompanied by symptoms such as fever, blistering, oral lesions, conjunctivitis, swelling, muscle or joint aches, or general malaise. As there are currently insufficient data on patients who have had a skin reaction to nevirapine or efavirenz and were further treated with RESCRIPTOR, close monitoring of these patients is recommended. Symptomatic relief has been obtained using diphenhydramine hydrochloride, hydroxyzine hydrochloride, and/or topical corticosteroids.

Fat Redistribution:

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

Pregnancy:

No adequate and well-controlled studies in pregnant women have been conducted. Since delavirdine has been shown to be teratogenic in rats (see TOXICOLOGY), RESCRIPTOR should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Of 9 pregnancies reported in premarketing clinical studies and postmarketing experience, a total of 10 infants were

born (including 1 set of twins). Eight of the infants were born healthy. One infant was born HIV-positive but was otherwise healthy and with no congenital abnormalities detected, and 1 infant was born prematurely (34 to 35 weeks) with a small muscular ventricular septal defect that spontaneously resolved. The patient received approximately six weeks of treatment with delavirdine and zidovudine early in the course of pregnancy.

Antiretroviral Pregnancy Registry: To monitor maternal-fetal outcomes of pregnant women exposed to RESCRIPTOR and other antiretroviral agents, an Antiretroviral Pregnancy Registry has been established. Physicians are encouraged to register patients by calling (800) 258-4263 or via the internet at <http://www.apregistry.com>.

Nursing Mothers:

It is recommended that HIV-infected mothers not breast-feed their infants to avoid risking postnatal transmission of HIV. It is not known whether delavirdine is excreted in human milk. Since delavirdine has been found to be excreted in the milk of lactating rats (see TOXICOLOGY), mothers should be instructed not to breast-feed their babies if they are receiving RESCRIPTOR.

Pediatric Use:

Safety and effectiveness of RESCRIPTOR has not been established in HIV-1–infected individuals younger than 16 years of age.

Geriatric Use:

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

Drug Interactions (see also CONTRAINDICATIONS, WARNINGS, AND CLINICAL PHARMACOLOGY-Pharmacokinetics-Drug Interactions):

Delavirdine is an inhibitor of CYP3A4 isoform and other isoforms to a lesser extent, including CYP2C9, CYP2D6 and CYP2C19. Coadministration of RESCRIPTOR and drugs primarily metabolized by CYP3A (e.g., HMG-CoA reductase inhibitors, and sildenafil) may result in increased plasma concentrations of the coadministered drug that could increase or prolong both its therapeutic effect or adverse effects.

Delavirdine is metabolized primarily by CYP3A, but *in vitro* data suggest that delavirdine may also be metabolized by CYP2D6. Coadministration of RESCRIPTOR and drugs that reduce CYP3A, such as rifampin, may decrease delavirdine plasma concentrations and reduce its therapeutic effect. Coadministration of RESCRIPTOR and drugs that inhibit CYP3A may increase delavirdine plasma concentrations (See Table 4, Drugs That Should Not Be Coadministered With RESCRIPTOR, and Table 5, Established and Other Potentially Significant Drug Interactions: Alteration in Dose or Regimen May Be Recommended Based on Drug Interaction Studies or Predicted Interaction.)

Table 4. Drugs That Should Not Be Coadministered With RESCRIPTOR

Drug Class: Drug Name	<u>Clinical Comment</u>
Anticonvulsant Agents: phenytoin, phenobarbital, carbamazepine	May lead to loss of virologic response and possible resistance to RESCRIPTOR or to the class of non-nucleoside reverse transcriptase inhibitors.
Antimycobacterials: rifabutin*, rifampin*	May lead to loss of virologic response and possible resistance to RESCRIPTOR or to the class of non-nucleoside reverse transcriptase inhibitors or other coadministered antiviral agents.
Ergot Derivatives: 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.
Herbal Products: St. John's wort (hypericum perforatum)	May lead to loss of virologic response and possibly resistance to RESCRIPTOR or to the class of non-nucleoside reverse transcriptase inhibitors.
HMG-CoA Reductase Inhibitors: lovastatin, simvastatin	Potential for serious reactions such as risk of myopathy including rhabdomyolysis.
Neuroleptic: pimozide	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
Sedative/hypnotics: alprazolam, midazolam, triazolam	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as prolonged or increased sedation or respiratory depression.

*See CLINICAL PHARMACOLOGY for magnitude of interaction, Tables 1 and 2.

Table 5. Established and Other Potentially Significant Drug Interactions: Alteration in Dose or Regimen May Be Recommended Based on Drug Interaction Studies or Predicted Interaction

Concomitant Drug Class: Drug Name	Effect on Concentration of Delavirdine or Concomitant Drug	Clinical Comment
<i>HIV-Antiviral Agents</i>		
Amprenavir	↑ Amprenavir	Appropriate doses of this combination, with respect to safety, efficacy and pharmacokinetics, have not been established.
Didanosine*	↓ Delavirdine ↓ Didanosine	Administration of didanosine (buffered tablets) and RESCRIPTOR should be separated by at least one hour.
Indinavir*	↑ Indinavir	A dose reduction of indinavir to 600 mg tid 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*	↑ 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*	↑ 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.
<i>Other Agents</i>		
Acid blockers: Antacids* H ₂ Receptor Antagonists: cimetidine, famotidine, nizatidine, ranitidine Proton Pump Inhibitors: omeprazole, lansoprazole	↓ Delavirdine	Doses of an antacid and RESCRIPTOR should be separated by at least one hour, because the absorption of delavirdine is reduced when coadministered with antacids.
		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.
Amphetamines	↑ Amphetamine	Use with caution.

Amiodarone, lidocaine (systemic), quinidine, flecainide, propafenone		Caution is warranted and therapeutic concentration monitoring is recommended, if available, for antiarrhythmics when coadministered with RESCRIPTOR.
Anticoagulant: warfarin	↑ Warfarin	It is recommended that INR (international normalized ratio) be monitored.
Anti-infective: clarithromycin*	↑ Clarithromycin	When coadministered with RESCRIPTOR, clarithromycin should be adjusted in patients with impaired renal function: –For patients with CL _{CR} 30 to 60 mL/min the dose of clarithromycin should be reduced by 50%. –For patients with CL _{CR} <30 mL/min the dose of clarithromycin should be reduced by 75%.
Dihydropyridine Calcium Channel Blockers: amlodipine, diltiazem, felodipine, nifedipine, nimodipine, verapamil	↑ Dihydropyridine calcium channel blockers	Caution is warranted and clinical monitoring of patients is recommended.
Corticosteroid: dexamethasone	↓ Delavirdine	Use with caution. RESCRIPTOR may be less effective due to decreased delavirdine plasma concentrations in patients taking these agents concomitantly.
Erectile Dysfunction Agent: sildenafil	↑ Sildenafil	Sildenafil should not exceed a maximum single dose of 25 mg in 48 hour period.
HMG-CoA Reductase Inhibitors: atorvastatin, 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.
Immunosuppressants: cyclosporine, tacrolimus	↑ Immunosuppressants	Therapeutic concentration monitoring is recommended for immunosuppressant agents when coadministered with RESCRIPTOR.
Narcotic Analgesic: methadone	↑ Methadone	Dosage of methadone may need to be decreased when coadministered with RESCRIPTOR.
Oral Contraceptives: ethinyl estradiol	↑ Ethinyl estradiol	Concentrations of ethinyl estradiol may increase. However, the clinical significance is unknown.

↑ Indicates increase

↓ Indicates decrease

*See CLINICAL PHARMACOLOGY for magnitude of interaction, Tables 1 and 2.

Information to be Provided to the Patient:

Patients should be informed that RESCRIPTOR is not a cure for HIV-1 infection, and that they may continue to acquire illnesses associated with HIV-1 infection, including opportunistic infections.

Treatment with RESCRIPTOR has not been shown to reduce the incidence or frequency of such illnesses, and patients should be advised to remain under the care of a physician when using RESCRIPTOR.

Patients should be advised that the use of RESCRIPTOR has not been shown to reduce the risk of transmission of HIV-1.

Patients should be instructed that the major toxicity of RESCRIPTOR is rash and should be advised to promptly notify their physician should a rash occur. The majority of rashes associated with RESCRIPTOR occur within 1 to 3 weeks after initiating treatment with RESCRIPTOR. The rash normally resolves in 3 to 14 days and may be treated symptomatically while therapy with RESCRIPTOR is continued. Any patient experiencing severe rash or rash accompanied by symptoms such as fever, blistering, oral lesions, conjunctivitis, swelling, muscle or joint aches should be advised to discontinue medication and consult a physician.

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

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

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

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

Because RESCRIPTOR may interact with certain drugs, patients should be advised to report to their doctor the use of any prescription and non-prescription medications or herbal products, particularly St. John's wort.

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

Patients taking RESCRIPTOR as a dispersion, should rinse the glass with water and swallow the rinse to ensure that the entire dose is consumed.

ADVERSE REACTIONS

The safety of RESCRIPTOR (delavirdine mesylate) alone and in combination with other antiretroviral therapies has been studied in patients in combination with nucleoside reverse transcriptase inhibitors (NRTIs) and protease inhibitors. The majority of adverse events were of mild or moderate intensity. The most frequently reported drug-related adverse event (i.e., an event considered by the investigator to be related to the blinded study medication, or an event with an unknown or missing causal relationship to the blinded medication) among patients receiving RESCRIPTOR was skin rash (see Table 6 and PRECAUTIONS-Skin Rash).

Table 6. Percent of Patients With Treatment-Emergent Rash in Pivotal Trials (Studies 21 Part II and 13C)*

Percent of Patients with:	Description of Rash Grade[§]	RESCRIPTOR 400 mg TID (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%)

*Includes rash reported regardless of causality.

[§]ACTG Toxicity Grading System; includes events reported as “rash”, “maculopapular rash” and “urticaria”.

Adverse events of moderate (ACTG grade 2) to severe (ACTG grade 3) intensity reported by at least 5% of evaluable patients in any treatment group in the pivotal trials, which includes patients receiving RESCRIPTOR in combination with zidovudine and/or lamivudine in Study 21 Part II for up to 98 weeks and in combination with zidovudine and either lamivudine, didanosine, or zalcitabine in Study 13C for up to 72 weeks are summarized in Table 7.

Table 7. Treatment-Emergent Adverse Events, Regardless of Causality, of Moderate-to-Severe or Life-Threatening Intensity Reported by at Least 5% of Evaluable* Patients in Any Treatment Group.

Adverse Events	Study 21 Part II			Study 13C	
	ZDV + 3TC (N=123)	400 mg tid RESCRIPTOR + ZDV (N=123)	400 mg tid RESCRIPTOR + ZDV + 3TC (N=119)	ZDV + ddI, ddC, or 3TC (N=172)	400 mg tid RESCRIPTOR + ZDV + ddI, ddC or 3TC (N=170)
	% of pts. (N)	% of pts. (N)	% of pts. (N)	% of pts. (N)	% of pts. (N)
<i>Body as a Whole</i>					
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)
<i>Digestive</i>					
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)
<i>Nervous</i>					
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)

Respiratory					
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)
Skin					
Rashes	3.3 (4)	19.5 (24)	13.4 (16)	7.6 (13)	18.8 (32)

*Evaluable patients in Study 21 Part II were those who received at least one dose of study medication and returned for at least one clinic study visit. Evaluable patients in Study 13C were those who received at least one dose of study medication.

Other adverse events that occurred in patients receiving RESCRIPTOR (in combination treatment) in all phase II/III studies, and considered possibly related to treatment and of at least ACTG grade 2 (moderate) in intensity are listed below by body system.

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

Cardiovascular: Abnormal cardiac rate and rhythm, cardiac insufficiency, cardiomyopathy, hypertension, migraine, pallor, peripheral vascular disorder, and postural hypotension.

Gastrointestinal: Anorexia, bloody stool, colitis, constipation, decreased appetite, diarrhea (*Clostridium difficile*), diverticulitis, dry mouth, dyspepsia, dysphagia, enteritis at all levels, eructation, fecal incontinence, flatulence, gagging, gastroenteritis, gastroesophageal reflux, gastrointestinal bleeding, gastrointestinal disorder, gingivitis, gum haemorrhage, hepatomegaly, increased appetite, increased saliva, increased thirst, jaundice, mouth or tongue inflammation or

ulcers, nonspecific hepatitis, oral/enteric monilia, pancreatitis, rectal disorder, sialadenitis, tooth abscess, and toothache.

Haemic and Lymphatic: Adenopathy, bruising, eosinophilia, granulocytosis, leukopenia, pancytopenia, purpura, spleen disorder, thrombocytopenia, and prolonged prothrombin time.

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

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

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

Respiratory: Chest congestion, dyspnea, epistaxis, hiccups, laryngismus, pneumonia, and rhinitis.

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

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

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

Postmarketing Experience: Adverse event terms reported from postmarketing surveillance that were not reported in the phase II and III trials are presented below by body system:

Digestive: Hepatic failure.

Hemic and Lymphatic: Hemolytic anemia.

Musculoskeletal: Rhabdomyolysis.

Skin Rash: Stevens-Johnson syndrome and erythema multiforme.

Urogenital: Acute kidney failure.

Laboratory Abnormalities:

Marked laboratory abnormalities observed in at least 2% of patients during therapy in Studies 21 Part II and 13C are summarized in Table 8. Marked laboratory abnormalities are defined as a two-gradeshift from baseline to a Grade 3 and 4 abnormality in a patient at any time during study.

Table 8. Marked Laboratory Abnormalities Reported by ≥ 2% of Patients

	Toxicity Limit	Study 21 Part II			Study 13C	
		ZDV + 3TC N=123	400 mg tid RESCRIPTOR + ZDV N=123	400 mg tid RESCRIPTOR + ZDV + 3TC N=119	ZDV + ddI, ddC or 3TC N=172	400 mg tid RESCRIPTOR + ZDV + ddI, ddC or 3TC N=170
		% pts.	% pts.	% pts.	% pts.	% pts.
Hematology						
Hemoglobin	<7 mg/dL	4.1	2.5	0.9	1.7	2.9
Neutrophils	<750/mm ³	5.7	4.9	3.4	10.4	7.6
Prothrombin time (PT)	>1.5 x ULN	0	0	1.7	2.9	2.4
Activated partial thromboplastin (APTT)	>2.33 x ULN	0	0.8	0	5.8	2.4
Chemistry						
Alanine aminotransferase (ALT/SGPT)	>5 x ULN	2.5	4.1	5.1	3.5	4.1
Amylase	>2 x ULN	0.8	2.5	2.6	3.5	2.9
Aspartate aminotransferase (AST/SGOT)	>5 x ULN	1.6	2.5	3.4	3.5	2.3
Bilirubin	>2.5 x ULN	0.8	2.5	1.7	1.2	0
Gamma glutamyl transferase (GGT)	>5 x 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	0.0

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

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Human experience of acute overdose with RESCRIPTOR is limited.

Management of Overdosage:

Treatment of overdose with RESCRIPTOR (delavirdine mesylate) should consist of general supportive measures, including monitoring of vital signs and observation of the clinical status of the patient. There is no specific antidote for overdose with RESCRIPTOR. If indicated, elimination of unabsorbed drug should be achieved by emesis or gastric lavage. Since delavirdine is extensively metabolized by the liver and is highly protein bound, dialysis is unlikely to be beneficial in significant removal of the drug.

DOSAGE AND ADMINISTRATION

The recommended dosage for RESCRIPTOR (delavirdine mesylate) is 400 mg (four 100-mg tablets) three times daily administered in combination with other antiretroviral agents. The complete prescribing information for other antiretroviral agents should be consulted for information on dosage and administration.

RESCRIPTOR may be dispersed prior to consumption. To prepare a dispersion, add four tablets to at least 90 mL (3 ounces) of water, allow to stand for a few minutes, and then stir until a uniform dispersion occurs. The dispersion should be consumed promptly. (see PHARMACOLOGY- Pharmacokinetics, Absorption and Bioavailability). The glass should be rinsed and the rinse swallowed to insure the entire dose is consumed.

RESCRIPTOR may be administered with or without food (see PHARMACOLOGY- Pharmacokinetics, Absorption and Bioavailability). Patients with achlorhydria should take

RESCRIPTOR with an acidic beverage (eg. orange or cranberry juice). However, the effect of an acidic beverage on the absorption of delavirdine in patients with achlorhydria has not been investigated.

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

PHARMACEUTICAL INFORMATION

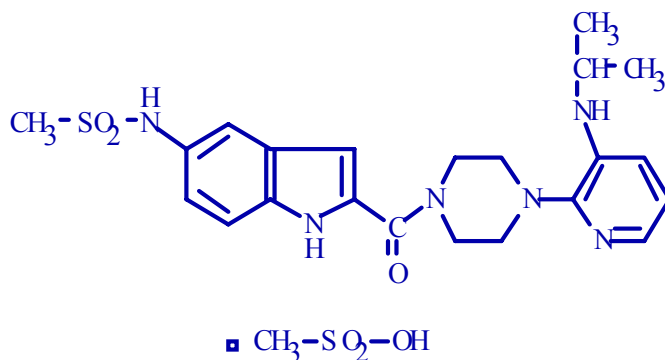
I. Drug Substance

Common Name: delavirdine mesylate

Chemical Name: piperazine, 1-[3-[(1-methyl-ethyl)amino]-2-pyridinyl]-4-[[5-[(methylsulfonyl)amino]-1*H*-indol-2-yl]carbonyl]-, monomethanesulfonate

Empirical Formula: C₂₂H₂₈N₆O₃S • CH₄O₃S

Structural Formula:



Molecular Weight: 552.68 (free base = 456.57)

Description: Delavirdine mesylate is an odourless white-to-tan crystalline powder. The aqueous solubility of delavirdine free base at 23°C is 2942 µg/mL at pH 1.0, 295 µg/mL at pH 2.0, and 0.81 µg/mL at pH 7.4. The melting point is 211-215°C and pK_a is 4.6 at 25°C. A 100 mg/mL solution of delavirdine mesylate in water gives an initial pH of 2.6, before precipitation of free base begins.

The measured octanol/water partition coefficient of delavirdine mesylate is pH dependent. At an intermediate range of pH (5 to 9), the partition coefficient (Log [PC]) is 2.98.

II. Composition

Non-medicinal ingredients consist of lactose, microcrystalline cellulose, croscarmellose sodium, colloidal silicon dioxide, magnesium stearate, propylene glycol, titanium dioxide and carnauba wax.

III. Stability and Storage Recommendations

Store at controlled room temperature (15-30°C). Keep container tightly closed. Protect from high humidity.

AVAILABILITY OF DOSAGE FORMS

Each RESCRIPTOR (delavirdine mesylate) tablet, for oral administration, contains 100 mg of delavirdine mesylate. It is available as 100 mg, white, film-coated, capsule-shaped tablets marked with "U 3761" in HDPE plastic, child resistant bottles with desiccants. Each 750 ml bottle contains 360 tablets.

INFORMATION FOR THE CONSUMER

PLEASE READ THIS PAMPHLET CAREFULLY BEFORE YOU START TAKING RESCRIPTOR® (delavirdine mesylate), even if you have just refilled your prescription, some of the information in the previous leaflet may have changed. It contains general information and directions about this medicine and should add to the advice from your doctor or pharmacist. If you have any questions or concerns after reading this pamphlet, please consult your doctor or other health care provider, such as nurse or pharmacist.

Keep this pamphlet with your medicine. You may need to read it again.

Why take anti-HIV therapy?

The goal of anti-HIV therapy is to reduce the amount of HIV in your body (viral load) to the lowest level possible. People with low viral loads are less likely to progress from HIV infection to acquired immune deficiency syndrome (AIDS).

By taking the correct dose of your HIV medicine at the correct time every day, you can keep your viral load down and keep your HIV infection under control. Keeping your viral load low can help protect your immune system and may prevent you from developing opportunistic infections that can occur in people with AIDS.

RESCRIPTOR, an antiretroviral, must always be combined with other antiretrovirals to fight HIV-1 disease. **It should never be used alone.**

What is RESCRIPTOR and how does it work?

RESCRIPTOR is the brand name of the antiviral agent delavirdine mesylate, produced by Agouron. It is a non-nucleoside reverse transcriptase inhibitor, or NNRTI. NNRTIs, like other groups of antiretrovirals (eg. protease inhibitors, nucleoside reverse transcriptase inhibitors) are an important part of your anti-HIV therapy and interfere with HIV's ability to reproduce. Each group does this in a different way. NNRTIs, such as RESCRIPTOR, work at an early point in the virus reproduction cycle, interfering with an important protein in the virus called reverse transcriptase.

Is RESCRIPTOR a cure for HIV/AIDS?

Like all other antiretrovirals, RESCRIPTOR is a treatment, not a cure for HIV-1 infection. You may continue to have illnesses associated with HIV-1 disease. Treatment with RESCRIPTOR has not been shown to reduce the frequency of such illnesses. Therefore, you should remain under the care of a doctor while using RESCRIPTOR.

Does RESCRIPTOR reduce the risk of passing HIV to others?

Treatment with RESCRIPTOR has not been shown to reduce the spread of HIV to others through sexual contact or blood contamination. Even when you are on anti-HIV medications and your HIV viral load is 'undetectable', you still have HIV in your body and you can still pass it to others. It is very important to practice safe sex and not use or share dirty needles.

Why has RESCRIPTOR been prescribed for you?

Many doctors who treat HIV/AIDS believe that an effective way to strike back at HIV is to use several drugs together. This is known as combination therapy. Since resistance to a *single* antiretroviral drug can develop more rapidly, the medical community has moved away from single drug therapy (monotherapy) to combination therapy. Therefore, RESCRIPTOR should always be used as part of a *combination* of therapies with other select antiretroviral agents that your doctor will prescribe.

RESCRIPTOR has been prescribed for you personally and should not be given to anyone else.

What conditions might affect your use of RESCRIPTOR?

Tell your doctor if you have any of the following conditions. Together with your doctor, you can decide whether RESCRIPTOR is right for you.

- **If you have problems with your liver or kidneys:** RESCRIPTOR has not been studied in people with liver or kidney disease.
- **If you are allergic to the active ingredient, delavirdine mesylate, in RESCRIPTOR or any of its other ingredients:** RESCRIPTOR also contains lactose, microcrystalline cellulose, croscarmellose sodium, colloidal silicon dioxide, magnesium stearate, propylene glycol, titanium dioxide and carnauba wax.
- **If you are pregnant, trying to become pregnant, or if you become pregnant:** the effect of RESCRIPTOR on pregnant women or their developing babies is not known.
- **If you are breast-feeding:** it is not known whether delavirdine is excreted in human milk. Also, if your baby does not already have HIV, there is a chance that HIV can be given to the baby by breast-feeding. **Women should not breast-feed if they have HIV.**

Can children take RESCRIPTOR?

The use of RESCRIPTOR has not been established in children under 16 years of age. Talk to your doctor and together you can decide whether this medication is right for your child.

Can you take RESCRIPTOR with other medications?

RESCRIPTOR may interact with other medicines, including those you take without a prescription. You must tell your healthcare provider about all medicines you are taking or planning to take before you take RESCRIPTOR. It is a good idea to keep a complete list of all the medicines that you take, including non-prescription medicines, herbal remedies and supplements and street drugs. Update this list regularly and give copies to all of your healthcare providers at every time you visit or fill your prescription.

Medicines You Should Not Take with RESCRIPTOR:

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

- midazolam (e.g., VERSED®)
- triazolam (e.g., HALCION®)
- alprazolam (e.g., XANAX®)
- Dihydroergotamine (e.g., MIGRANAL®), ergonovine, ergotamine (e.g., ERGOMAR®, CAFERGOT®), methylergonovine
- Pimozide (e.g., ORAP®)
- Cisapride
- Rifabutin (e.g. MYCOBUTIN®)

Do not take the following medicines when you take RESCRIPTOR. They may interact and cause the blood levels of RESCRIPTOR or the other drugs to increase or decrease. As a result, one of the drugs

may stop working or make you sick. Talk to your healthcare provider if you are currently taking these medicines because other medicines may have to be given to take their place:

- Rifampin (e.g. RIFADIN®, ROFACT®)
- Quinidine (e.g. QUINIDEX EXTEND TABS®)
- Clarithromycin
- Phenobarbital
- Phenytoin (e.g. DILANTIN®)
- Carbamazepine (e.g., TEGRETOL®)
- Dapsone (e.g. AVLOSULFON®)
- Warfarin
- Nifedipine (e.g. ADALAT®)
- Cimetidine (e.g. TAGAMET®)
- Nizatidine (e.g. AXID®)
- Ranitidine (e.g. ZANTAC®)
- Famotidine (e.g. PEPCID®)

Do not take RESCRIPTOR with St. John's wort (*hypericum perforatum*), an herbal product sold as a dietary supplement, or products containing St. John's wort. Taking St. John's wort may decrease RESCRIPTOR levels and lead to increased viral load and possible resistance to RESCRIPTOR or cross-resistance to other anti-HIV medicines.

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

Medicines that require dosage adjustment:

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

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

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

How should you take RESCRIPTOR?

Take RESCRIPTOR exactly as directed by your doctor. Do not increase or decrease the number of pills or doses per day or stop taking your anti-HIV medicines before speaking with your doctor, even if you are feeling better. The usual dose is four 100-milligram (mg) tablets three times a day for a total daily dose of 1200 mg.

Since RESCRIPTOR is taken in combination with other drugs, your doctor may need to adjust how and when you take your medicines.

The following statements apply to RESCRIPTOR unless otherwise prescribed by your physician:

- If you prefer, or are unable to swallow the tablets, RESCRIPTOR may be dissolved in water for easier swallowing and added convenience. Add four tablets to at least 90 mL (3 ounces) of water and allow to stand for a few minutes. Stir until the tablets have dissolved and then drink the mixture promptly. Add a little more water and swirl and then drink the remaining mixture to be sure that you took the entire dose.
- Your doctor may ask you to take RESCRIPTOR with an acidic drink like orange or cranberry juice.
- You can take RESCRIPTOR with or without food.
- Do not give RESCRIPTOR to others, or take medicines prescribed for someone else.
- It is important to ensure that you do not run out of your RESCRIPTOR because if you stop taking RESCRIPTOR, for even a short period of time, the amount of virus in your body can increase and it may then become harder to treat.

What should you do if you miss a dose of RESCRIPTOR?

Always take your medicine. Forgetting to take your medicine or not taking them properly may allow the amount of virus in your body to increase. HIV may then become resistant. Developing

resistance means that the virus in your body changes or mutates so that the drug can no longer protect you from the virus.

If you forget to take a dose of RESCRIPTOR at the time you normally take it, take the next dose as soon as possible. If you completely forget to take the dose, take your next dose when you normally would. Do not double the next dose. If you forget many doses, talk to your doctor about how you should continue taking your medicine.

What undesirable effects might you have with RESCRIPTOR?

Since each individual's body reacts differently to a drug, you may or may not experience side effects with RESCRIPTOR. Side effects may last for a short or long time, depending on how long it takes for your body to get used to the drug. Some people tolerate drugs better than others. If a medicine prescribed by your doctor can help improve your health, you may decide that you can tolerate its side effects. Before you start using RESCRIPTOR, talk to your doctor about what to expect and discuss ways to minimize side effects you may experience.

Skin rash

The most common side effect seen in patients using RESCRIPTOR has been a skin rash that usually lasts less than 2 weeks. In clinical studies, a skin rash occurred in 18% of patients receiving the 400 mg dose of RESCRIPTOR taken three times a day. Starting with a lower dose and gradually increasing the dose to 400 mg three times a day did not seem to reduce the chance of getting a rash. Reducing the dose after getting the rash also did not affect the management of the rash. Very few people in the clinical studies (3.3% to 3.5%) experienced a severe rash from taking RESCRIPTOR.

- **What is the rash like and when does it occur?** The rash affects mainly the upper body and upper arms, with decreasing intensity on the neck and face. The rash appears as a red, discoloured area on the skin with slight elevations, and it can be itchy. The rash tends to occur

early, usually within 1 to 3 weeks after you start taking RESCRIPTOR, and it usually lasts less than 2 weeks.

- **What should you do if you get a rash?** Watch your rash carefully. In most cases, the rash can be tolerated or treated with over-the-counter medicines without making any changes in the way you take RESCRIPTOR. As well, the body usually gets used to RESCRIPTOR and the rash disappears within 3 to 14 days. If your rash continues, or becomes bothersome, talk to your doctor. Some over-the-counter medicines that can be used are topical corticosteroids (eg. hydrocortisone) and oral antihistamines (eg. diphenhydramine hydrochloride).
- **What should you do if your rash is severe?** In a few patients the skin rash may be severe. You will know if the rash is severe because you will also have blistering, fever, sores in the mouth, inflammation of the eyes, swelling, or muscle and joint aches. This usually happens during the first 3 days of the rash. If you get a severe rash, you should stop taking RESCRIPTOR and speak with your doctor as soon as possible. Be prepared to tell your doctor where the rash is located, your temperature, and whether or not you have other symptoms.

Other side effects

Some patients taking RESCRIPTOR also get other side effects such as nausea, headache, diarrhea, vomiting, fatigue, and higher than normal amounts of liver enzymes. Be sure to talk with your doctor about side effects you may experience with RESCRIPTOR. In many instances, your doctor can help you with these symptoms.

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

How should you store RESCRIPTOR?

Store RESCRIPTOR at room temperature (between 15°C-30°C). Keep the container tightly closed and away from humid and moist places like your bathroom. Keep RESCRIPTOR out of the reach of children. Use before the expiry date on the label.

Important note to remember when taking RESCRIPTOR:

- The recommended dose of RESCRIPTOR is 400 mg (four 100 mg tablets) three times daily, in combination with other anti-HIV therapies.
- It is very important that you follow the instructions of your doctor when taking RESCRIPTOR.
- You can take RESCRIPTOR with or without food.

VIROLOGY

Antiviral Activity In Vitro: *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. IC₅₀ and IC₉₀ values (50% and 90% inhibitory concentrations) for laboratory isolates (N=5) ranged from 0.005 to 0.030 µM and 0.04 to 0.10 µM, respectively. Mean IC₅₀ values of clinical isolates (N=74) was 0.038 µM (range 0.001 to 0.69 µM); 73 of 74 clinical isolates had an IC₅₀ ≥ 0.18 µM. The IC₉₀ of 24 of these clinical isolates ranged from 0.05 to 0.10 µM. The potent inhibition of replication by delavirdine of both HIV-1 lymphotropic (H9,HIV-1_{IIIB} IC₉₀ = 0.045 µM) and monocytotropic (PBMC, HIV-1_{JRC5F} IC₅₀ = 0.039 µM) strains was comparable to, or exceeded, the antiviral activity of nucleoside or other non-nucleoside RT inhibitors. In drug combination studies of delavirdine with zidovudine, didanosine, zalcitabine, lamivudine, α-interferon, and protease inhibitors, additive to synergistic anti-HIV-1 activity was observed in cell culture.

Resistance: *In vitro* experiments have demonstrated that the predominant HIV-1 amino acid substitution attributable to delavirdine resistance was P236L. This substitution sensitizes other non-nucleoside RT inhibitors sevenfold to tenfold without influencing sensitivity to nucleoside analogue RT inhibitors. Although the RT amino acid substitutions K103N and Y181C, which confer cross-resistance to several non-nucleoside inhibitors, also decrease the potency of delavirdine, the drug retains significant *in vitro* activity against these mutant RTs. Mutations that induce resistance to one drug can induce sensitivity to a second drug. The Y181C mutation in zidovudine-resistant background has been shown to significantly suppress resistance to zidovudine. Similarly, the codon 184 mutation conferring resistance to lamivudine suppresses resistance to zidovudine. When delavirdine was administered in combination with zidovudine in HIV-1-infected patients, there was an average 86-fold increase in zidovudine sensitivity of all patient isolates after 24 weeks on the delavirdine and zidovudine therapy. Delavirdine had significant inhibitory activity against most nucleoside resistant forms of RT as well as non-nucleoside resistant forms of RT (Y181C and K103N).

In vitro analysis of isolates from 24 patients revealed that with delavirdine therapy, the predominant RT substitution was K103N. A spectrum of substitutions was identified including Y181C, K103N, K103N + Y181C, K103T, and P236L. However, treatment with delavirdine and zidovudine prevented the emergence of Y181C for at least 6 months. Complex interactions between one substitution and others have been shown to ameliorate susceptibility losses seen with single substitutions, suggesting that multiple drugs in combination may be able to maintain clinical benefit despite the emergence of mutations specific to any of the individual agents.

Cross Resistance: Rapid emergence of HIV-1 strains that are cross-resistant to certain NNRTIs has been observed *in vitro*. Mutations at positions 103 and 181 have been associated with resistance to

other NNRTIs. RESCRIPTOR may confer cross-resistance to other non-nucleoside reverse transcriptase inhibitors when used alone or in combination.

The potential for cross-resistance between delavirdine and protease inhibitors is low because of the different enzyme targets involved. The potential for cross-resistance between NNRTIs and nucleoside analogue RT inhibitors is low because of different sites of binding on the viral RT and distinct mechanism of action.

PHARMACOLOGY

Clinical Studies

For clinical studies 21 Part II and 13C described below, efficacy was evaluated by the percentage of patients with a plasma HIV RNA level < 400 copies/mL and < 50 copies/mL through Week 52 as measured by the Roche Amplicor Assay (> 400 copies/mL) or the Roche Ultrasensitive Assay (> 50 copies/mL). An intent-to-treat analysis was performed where only subjects who achieved confirmed suppression and sustained it through Week 52 are regarded as responders. All other subjects (including never suppressed, discontinued, and those who rebounded after initial suppression of < 400 copies/mL) are considered failures at Week 52. Results of an interim analysis of efficacy conducted for Studies 21 Part II and 13 C by independent Data and Safety Monitoring Boards (DSMBs) revealed that the triple therapy arms in both studies produced significantly greater antiviral benefit than the dual therapy arms, and early termination of the studies was recommended.

a. Studies in Antiretroviral Treatment Naïve Patients or in Patients with Limited Nucleoside Experience

Study 21 Part II: RESCRIPTOR + zidovudine + lamivudine versus RESCRIPTOR + zidovudine versus zidovudine + lamivudine

Study 21 Part II was a double-blind, randomized, placebo controlled trial comparing treatment with RESCRIPTOR (DLV; 400 mg tid), zidovudine (ZDV; 200 mg tid) and lamivudine (3TC; 150 mg bid) versus RESCRIPTOR (400 mg tid) and zidovudine (200 mg tid) versus zidovudine (200 mg tid) and lamivudine (150 mg bid) in 373 HIV-1 infected patients (mean age 35 years [range 17 to 67], 87% male and 60% Caucasian) who were antiretroviral treatment naïve (84%) or had limited nucleoside experience (16%). Mean baseline CD4 cell count was 359 cells/mm³ and mean baseline plasma HIV RNA was 4.412 log₁₀ copies/mL.

Results showed that the mean increase from baseline in CD4 count at 52 weeks was 111 cells/mL for RESCRIPTOR + ZDV+ 3TC, 27 cells/mL for RESCRIPTOR + ZDV, and 74 cells/mL for ZDV +3TC.

The intent-to-treat analyses of the percentage of patients with a plasma HIV RNA level < 400 copies/mL and 50 copies/mL are summarized in Figure 1. HIV-1 RNA status and reasons for discontinuation of randomized treatment at 52 weeks are summarized in Table 9. Subjects who were never suppressed before discontinuation were placed in the discontinuation category.

Figure 1
Percentage of Patients with HIV RNA Below 400 copies/mL
Standard PCR Assay
Protocol 21 Part 2
Intent-to-Treat Analysis

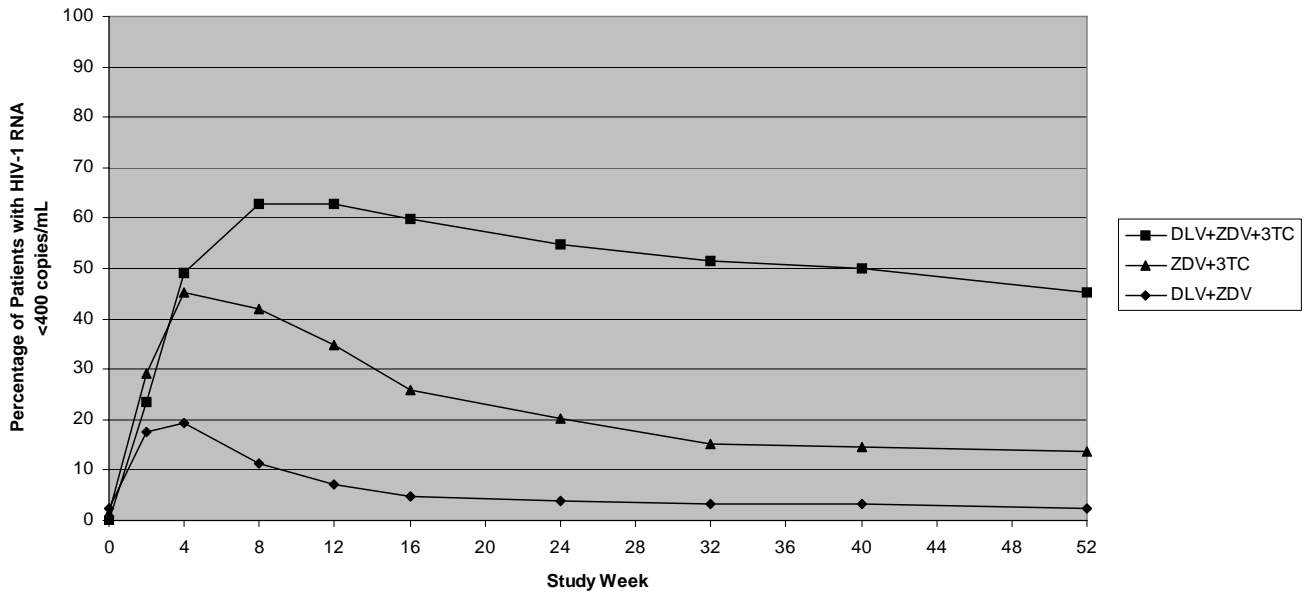


Table 9. Outcomes of Randomized Treatment Through Week 52 for Protocol 21 Part II

Outcome	ZDV + 3TC (N=124) %	DLV + ZDV (N=125) %	DLV + ZDV + 3TC (N=124) %
HIV RNA <400 copies/mL*	14	2	45
HIV RNA ≥ 400 copies/mL †,**	64	52	31
Discontinued due to adverse events ‡	8	13	10
Discontinued due to other reasons ‡,§	14	33	14

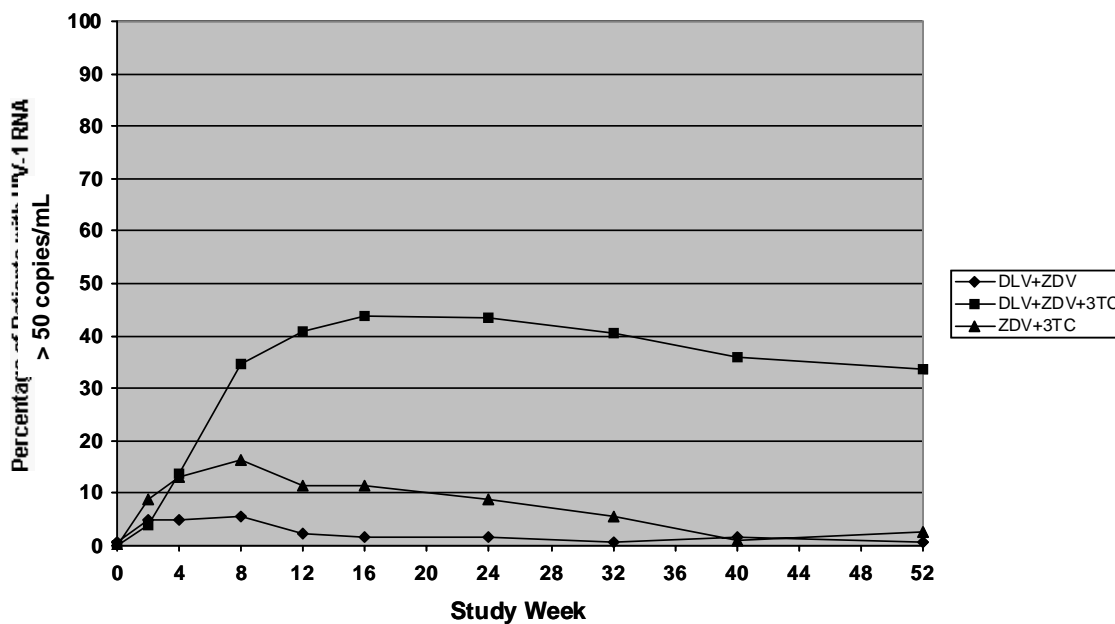
* Corresponds to rates at Week 52 in proportion curve.

** Virologic failures at or before Week 52.

‡ Considered to be treatment failure in the analysis.

§ Includes discontinuations due to consent withdrawn, loss to follow-up, protocol violations, non-compliance, pregnancy, never treated, and other reasons.

**Percentage of Patients with HIV RNA Below 50 copies/mL
Ultra Sensitive PCR Assay
Protocol 21 Part 2: Intent-to-Treat Patients
Intent-to-Treat Analysis: Noncompleters Assumed As Failures**



Study 13C: RESCRIPTOR + zidovudine + didanosine or zalcitabine or lamivudine versus zidovudine + didanosine/zalcitabine/lamivudine

Study 13C was a double-blind, randomized, placebo controlled trial comparing treatment with RESCRIPTOR (400 mg tid), zidovudine (200 mg tid or 300 mg bid) and either didanosine (ddI; 200 mg bid), zalcitabine (ddC; 0.75 mg tid) or lamivudine (150 mg bid) versus zidovudine (200 mg tid or 300 mg bid) and either didanosine (200 mg bid), zalcitabine (0.75 mg tid) or lamivudine (150 mg bid) in 345 HIV-1 infected patients (mean age 35.8 years [range 18 to 72], 66% male and 63% Caucasian) who were antiretroviral treatment naïve (63%) or had limited antiretroviral experience (37%). Mean baseline CD4 cell count was 210 cells/mm³ and mean baseline plasma HIV RNA was 4.855 log₁₀ copies/mL.

Results showed that the mean increase from baseline in CD4 count at 54 weeks was 102 cells/mL for RESCRIPTOR + ZDV + ddI or ddC or 3TC and 56 cells/mL for ZDV + ddI or ddC or 3TC.

The intent-to-treat analyses of the percentage of patients with a plasma HIV RNA level < 400 copies/mL and 50 copies/mL are summarized in Figure 2. HIV-1 RNA status and reasons for discontinuation of randomized treatment at 54 weeks are summarized in Table 10. Subjects who were never suppressed before discontinuation were placed in the discontinuation category.

Figure 2
Percentage of Patients with HIV RNA Below 400 copies/mL
Standard PCR Assay
Protocol 13C
Intent-to-Treat Analysis

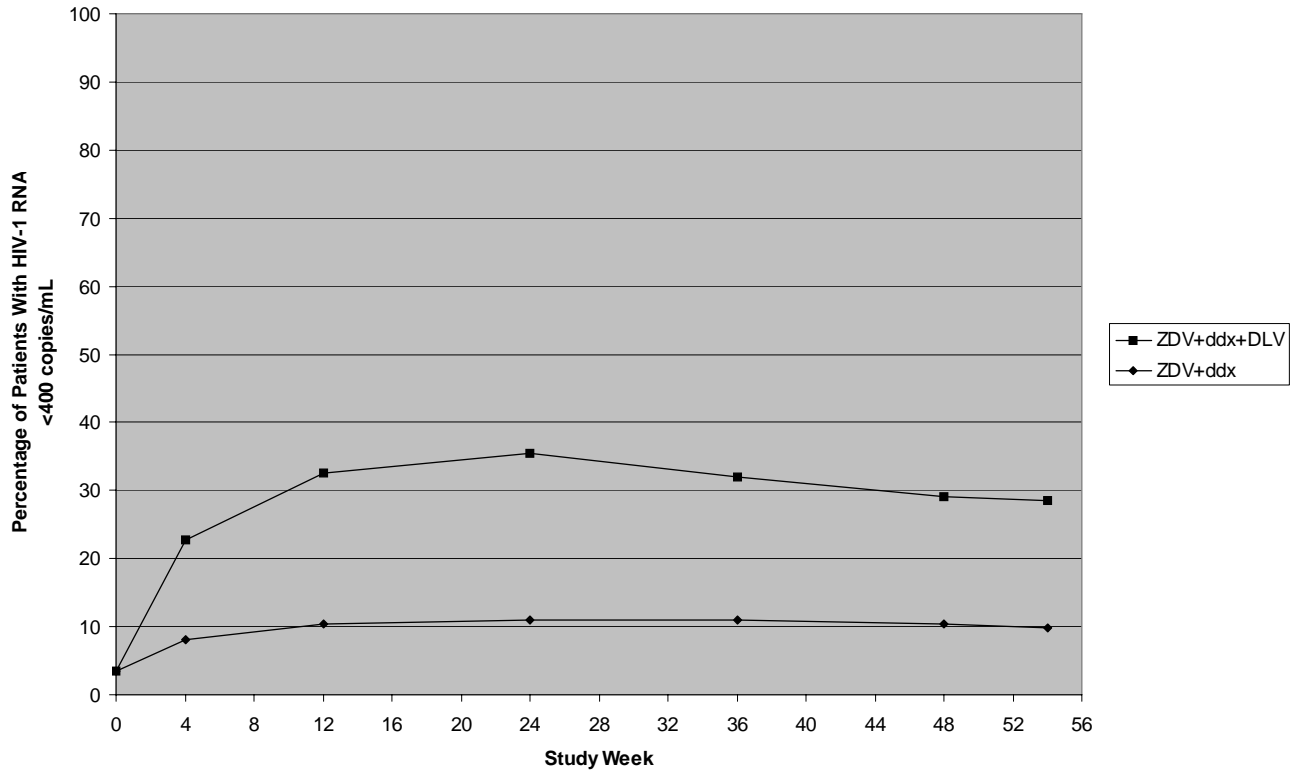


Table 10. Outcomes of Randomized Treatment Through Week 54 for Protocol 13C.

Outcome	ZDV + ddX[#] (N=173) %	ZDV + ddX + DLV N= 172) %
HIV RNA <400 copies/mL*	10	29
HIV RNA ≥ 400 copies/mL §,‡	69	42
Discontinued due to adverse events §	7	12
Discontinued due to other reasons §,**	14	17

* Corresponds to rates at Week 54 in proportion curve.

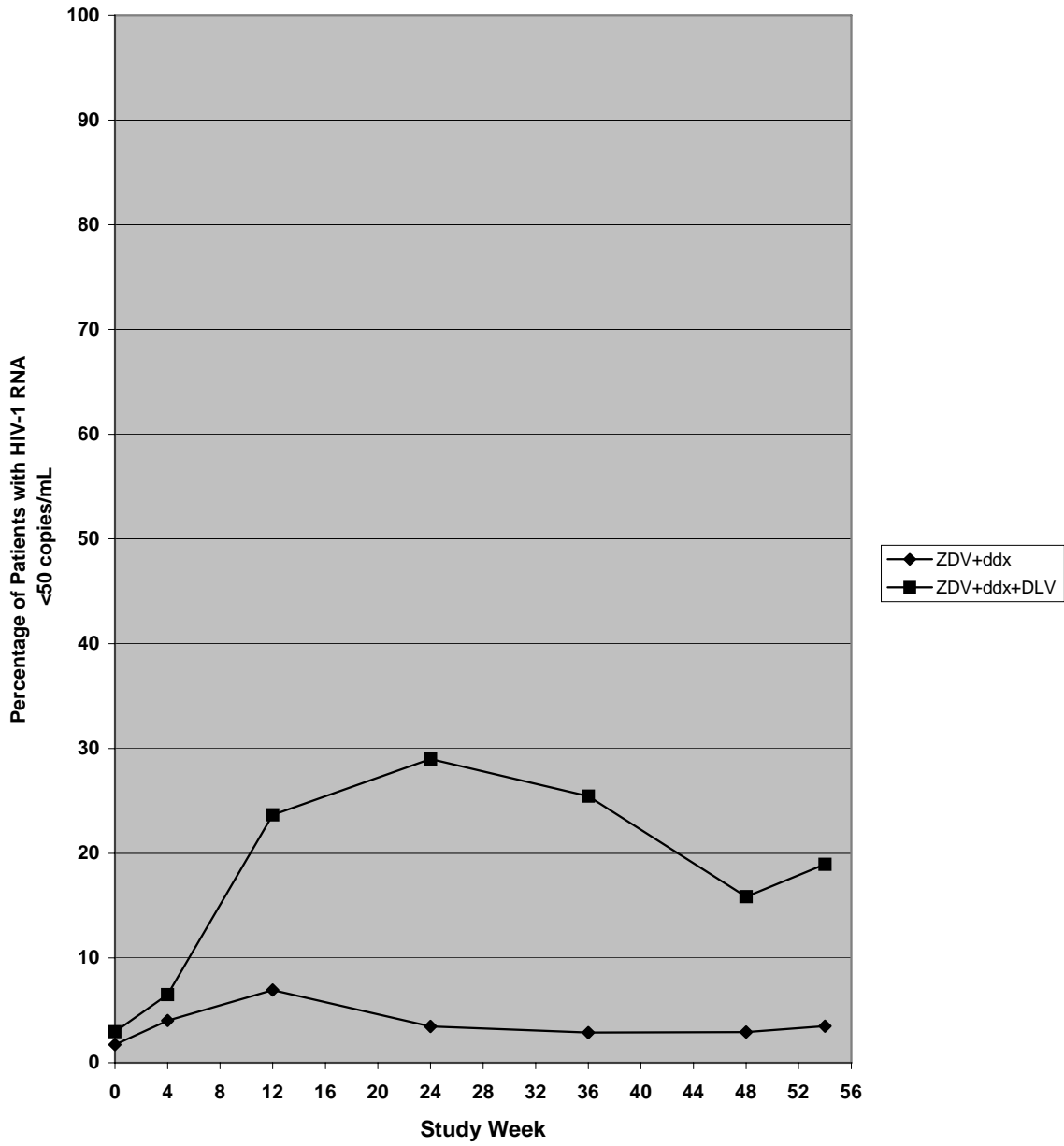
ddX = ddI or ddC or 3TC.

‡ Virologic failures at or before Week 54.

§ Considered to be treatment failure in the analysis.

**Includes discontinuations due to consent withdrawn, loss to follow-up, protocol violations, non-compliance, pregnancy, never treated, and other reasons.

Percentage of Patients with HIV RNA Below 50 copies/mL
Ultra Sensitive PCR Assay
Protocol 13C: Intent-to-Treat Patients
Intent-to-Treat Analysis: Noncompleters Assumed As Failures



Preliminary findings from an additional small controlled study in naïve adults (Study 74) using indinavir plus two reverse transcriptase inhibitors supports the efficacy of RESCRIPTOR in combination with indinavir plus two RT inhibitors through 24 weeks of treatment.

Pharmacokinetics

Absorption and Bioavailability: Delavirdine is rapidly absorbed following oral administration of delavirdine tablets to healthy volunteers and HIV-1–infected patients, with peak plasma concentrations occurring at about 1 hour. The extent of drug absorption is at least 50% based on urinary recovery of a radiolabeled dose of a delavirdine solution. The single-dose bioavailability of delavirdine tablets relative to an equivalent dose of oral solution averaged $85\% \pm 25\%$ (mean \pm SD) in 16 healthy volunteers. The effect of food on delavirdine was studied in 13 HIV-1–infected patients who took delavirdine tablets 400 mg tid for 14 days with meals and for 14 days under fasted conditions (1 hour before or 2 hours after food). The peak plasma delavirdine concentration (C_{max}) was decreased by about 22%, the time to peak (T_{max}) was unchanged, and the extent of absorption as measured by the area under the plasma concentration versus time curve (AUC) and C_{min} was unaltered when delavirdine was taken with meals compared with drug administration in the fasted state. Thus, delavirdine tablets may be taken either on an empty stomach or with meals. Single-dose bioavailability of delavirdine is about 20% higher when a slurry of drug is prepared by allowing delavirdine tablets to disintegrate in water before administration.

Distribution: Delavirdine is extensively bound (approximately 98%) to plasma proteins, primarily albumin. The percentage of delavirdine that is protein bound is constant over a delavirdine concentration range of 0.5 to 196 μ M. The erythrocyte-to- plasma ratio of delavirdine-related radioactivity averaged 0.14 ± 0.02 in human samples collected from a 14 C-delavirdine mesylate study in six healthy volunteers. In a study of five HIV-1–infected patients whose total daily dose of delavirdine ranged from 600 to 1200 mg, cerebrospinal fluid concentrations of delavirdine averaged $0.4\% \pm 0.07\%$ of the corresponding plasma delavirdine concentrations; this represents about 20% of the fraction not bound to plasma proteins. Steady-state delavirdine concentrations in saliva and semen are about 6% and 2%, respectively, of the corresponding plasma delavirdine concentrations collected at the end of a dosing interval.

Metabolism and Elimination: Delavirdine is extensively converted to several inactive metabolites. The major metabolic pathways for delavirdine are N-desalkylation and pyridine hydroxylation.

Delavirdine is primarily metabolized by cytochrome P450 3A (CYP3A), but *in vitro* data suggest that delavirdine may also be metabolized by cytochrome P450 2D6 (CYP2D6). In a study of ¹⁴C-delavirdine in six healthy volunteers who received multiple doses of delavirdine tablets 300 mg tid, about 44% of the radiolabeled dose was recovered in feces, with the pyridine-cleaved product and the N-desalkyl metabolite accounting for approximately 29% and 28%, respectively, of fecal recovery. About 51% of the dose was excreted in urine; approximately 85% of the urinary recovery was the N-desalkyl metabolite; and about 5% was unchanged drug. Renal clearance of unchanged drug is, therefore, a minor route of elimination for delavirdine. Delavirdine exhibits nonlinear steady-state elimination pharmacokinetics, with oral clearance decreasing by about 22-fold as the total daily dose of delavirdine increases from 60 to 1200 mg/day. The apparent plasma half-life of delavirdine varies with dose; the mean half-life following 400 mg tid is 5.8 hours, with a range of 2 to 11 hours.

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

TOXICOLOGY

Numerous preclinical toxicity studies were conducted with delavirdine administered by systemic (mainly oral) routes. Durations of exposure of up to 3 months in mice and cynomolgus monkeys, 6 months in rats and 1 year in dogs were investigated. *In vitro* and *in vivo* genetic toxicology tests were completed and carcinogenicity studies in rats and mice are in progress. The results of these studies indicate that delavirdine mesylate affects multiple organ systems of animals and that toxicity is more closely correlated with serum drug concentrations rather than dose administered. Target organs affected by delavirdine in animals include blood vessels, gastrointestinal tract, endocrine system, liver, kidneys, bone marrow, lymphoid tissue, lung, and reproductive system.

Acute and Long-Term Toxicity Studies

Single oral doses of delavirdine mesylate or delavirdine free base given to rats at doses of 5000 mg/kg or less (250 times the recommended human dose) were not lethal and were practically nontoxic providing a wide margin of safety if the total daily dose were inadvertently consumed as a single dose.

Drug-related mortalities (deaths/unscheduled sacrifices) in repeated-dose toxicity studies were associated with high nadir serum concentrations of delavirdine. In rats, drug-related death/unscheduled sacrifice was attributed to multiple organ toxicity at high mean nadir serum concentrations of delavirdine of $> 160 \mu\text{M}$. In dogs and monkeys, the main cause of death/unscheduled sacrifice was gastrointestinal toxicity (erosions/ulcers). Nadir serum concentrations of delavirdine at the time of gastrointestinal toxicity were $> 180 \mu\text{M}$ in dogs and $> 190 \mu\text{M}$ in monkeys.

Vasculitis in arteries occurred in dogs when mean nadir serum concentrations of delavirdine were at least 7-fold higher, than the expected human exposure (mean $C_{\text{min}} = 15 \mu\text{M}$) when administered at

the recommended dosage. Vasculitis in dogs was not reversible during a 2.5-month recovery period; however, partial resolution of the vascular lesion characterized by reduced inflammation, diminished necrosis, and intimal thickening occurred during this period. The dog is the only species for which there is a defined association between treatment with delavirdine and the development of vasculitis/perivasculitis.

Numerous endocrine-related changes were observed in the repeated-dose toxicity studies with delavirdine mesylate, including increased organ weights and hypertrophy of the thyroid gland, adrenal gland, pituitary gland, and reproductive organs. Mechanistic studies in rats demonstrated that these effects were likely secondary to delavirdine's ability to alter hormone levels by enhancing their clearance (thyroxine) or by inhibiting their synthesis (corticosterone). Organ hypertrophy was therefore considered to be compensatory in nature, involving normal regulatory mechanisms attempting to maintain normal hormone levels. Based on species-specific differences in hormone clearance pathways, the human safety profile of other drugs which cause similar effects in rodents and/or the lack of effects of delavirdine mesylate in clinical trials, it is unlikely that similar endocrine-related changes will occur in humans. Pseudopregnancy was observed in mice, in association with the formation of a unique metabolite of delavirdine with a high affinity for the dopamine-D2 receptor, resulting in increased blood prolactin levels. Because of the species-specific nature of the formation of this metabolite, similar effects would not be anticipated in humans.

Deposition of delavirdine crystals with or without associated inflammation has been observed in tissues of rats (oral) and dogs (intravenous) and is likely related to prolonged exposure (≥ 3 months) to high maximum serum concentrations (rats: $\geq 130 \mu\text{M}$; dogs: $\geq 270 \mu\text{M}$) of delavirdine and the relative insolubility of delavirdine in the serum of these species. Based on the relatively higher *in vitro* solubility of delavirdine in human serum and the low serum concentrations of delavirdine achieved with therapeutic doses of delavirdine mesylate in humans, it is unlikely that deposition of delavirdine crystals in tissues will occur in humans.

The liver, kidney, lung and peripheral blood were target organs in the rat at low serum concentrations of delavirdine (mean nadir serum concentrations of delavirdine $\geq 5.12 \mu\text{M}$). Some kidney, liver and peripheral blood changes were not reversible after a 2-month recovery period in rats which had a mean nadir serum concentration of $37.6 \mu\text{M}$ or more. Similarly, increased serum cholesterol values in rats, mice and dogs and liver changes in mice were observed at low serum concentrations of delavirdine. The relevance of these findings to human safety is not known.

Reproduction and Teratology Studies

Reproduction studies revealed no impairment of fertility in rats.

Delavirdine caused interventricular septal defects in pregnant rats at doses of 50, 100, and 200 mg/kg/day when administered during the period of organogenesis. The lowest dose of delavirdine that caused malformations produced systemic exposures in pregnant rats equal to or lower than the expected human exposure to delavirdine ($C_{\text{min}} = 15 \mu\text{M}$) after treatment at the recommended dosage. Exposure in rats to concentrations approximately 5-fold higher than the expected human exposure resulted in marked maternal toxicity during late gestation/parturition, embryotoxicity, delay of fetal development, and reduced pup survival. Additionally, reduced pup survival occurred on postpartum day 0 at an exposure (mean C_{min}) approximately equal to the expected human exposure.

In rabbits, delavirdine at doses of 200 and 400 mg/kg/day when administered during the period of organogenesis caused marked maternal toxicity and embryotoxicity at an exposure (based on median C_{min} concentrations of delavirdine) approximately 6-fold higher than the expected human exposure ($C_{\text{min}} = 15 \mu\text{M}$). The no-observed-adverse-effect dose in the pregnant rabbit was 100 mg/kg/day. Various malformations were observed at this dose, but the incidence of such malformations was not statistically significantly different from those observed in the control group. Systemic exposures in pregnant rabbits at a dose of 100 mg/kg/day were lower than those expected in humans at the recommended clinical dose. Malformations were not apparent at 200 and 400 mg/kg/day; however,

only a limited number of fetuses were available for examination as a result of maternal and embryo death.

Excretion of delavirdine occurred in the milk of lactating rats at a concentration 3 to 5 times that of rat serum.

Carcinogenicity and Mutagenicity Studies

Lifetime carcinogenicity studies were conducted in rats at doses of 10, 32 and 100 mg/kg/day and in mice at doses of 62.5, 250 and 500 mg/kg/day for males and 62.5, 125 and 250 mg/kg/day for females. In rats, delavirdine was noncarcinogenic at maximally tolerated doses that produced exposures (AUC) up to 17 times human exposure at the recommended clinical dose. In mice, submucosal mesenchymal urinary bladder tumours and hepatocellular adenomas/carcinomas were observed in high-dose (500 mg/kg/day) males at an exposure level (AUC) approximately 4 times that in humans at the recommended clinical dose. The C_{max} value reported for high dose males was approximately twice the targeted human C_{max}. In female mice, hepatocellular adenomas were observed in all delavirdine treatment groups at levels of exposure (AUC) ranging from 0.5 to 3 times human exposure at the recommended clinical dose. C_{max} values in delavirdine-treated females approximated 0.4 to 2 times the human targeted C_{max}. The urinary bladder tumours in males were associated with a species-specific metabolite of delavirdine and are considered unlikely to be of relevance to humans. Given the frequent occurrence of liver tumours in mouse carcinogenicity studies, the unique genetic susceptibility of many mouse strains to the development of both spontaneous and clinically induced liver tumours, and the lack of genotoxic activity of delavirdine, the relevance to hepatocellular neoplasms in delavirdine-treated mice to humans is unknown.

A battery of genetic toxicology tests was conducted with delavirdine, including the Ames assay, *in vitro* unscheduled DNA synthesis (UDS) assay, an *in vitro* cytogenetics (chromosome aberration) assay in human peripheral lymphocytes, a mammalian cell mutation assay in Chinese hamster ovary

cells, and the micronucleus test in mice. The results were negative, indicating delavirdine is not mutagenic.

Local Tolerance Studies

Local tolerance studies indicate that delavirdine mesylate is a primary eye and dermal irritant. However, since delavirdine mesylate is administered orally as a tablet, eye contamination and skin irritation are considered remote consequences of drug therapy and not a health concern. Delavirdine mesylate was practically nontoxic when administered intratracheally to rats at a dose of 25 mg/kg.

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