CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

20-705 / S-009

Trade Name: Rescriptor

Generic Name: (delavirdine)

Sponsor: Agouron Pharmaceuticals Inc.

Approval Date: March 14, 2002

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20705 / S-009

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20705 / S-009

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-705/S-009

Agouron Pharmaceuticals Inc.
Attention: Stephen Sherman
Director, Regulatory Strategy
Worldwide Regulatory Affairs
10350 North Torrey Pines Road
La Jolla, CA 92037-1020

Dear Mr. Sherman:

Please refer to supplemental new drug application dated November 20, 2001, received November 21, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Rescriptor® (delavirdine) 100 mg and 200mg Tablets.

This "Special Supplement-Changes Being Effected" supplemental new drug application provides for new precautionary language concerning fat redistribution.

We have completed the review of this supplemental new drug application and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective for use as recommended in the final printed labeling dated November 20, 2001. We also acknowledge that the final printed labeling dated November 28, 2001 containing fat redistribution language is identical to the November 20, 2001 submission. Accordingly, the supplemental new drug application is approved effective on the date of this letter.

Please submit one market package of the product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81

If you have any question, call Sean Belouin, R.Ph., Regulatory Project Manager, at (301) 827-2335.

Sincerely,

{See appended electronic signature page}

Debra B. Birnkrant, M.D.
Division Director
Division of Antiviral Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Debra Birnkrant
3/14/02 04:34:00 PM
NDA 20-705 SLR 009

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

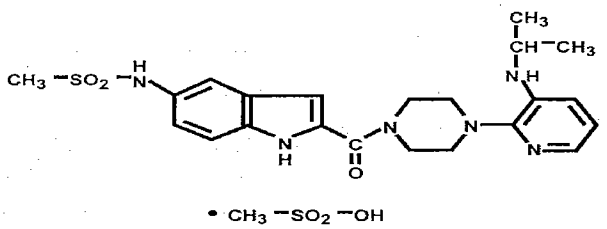
20705 / S-009

APPROVED LABELING

RESCRIPTOR®
brand of delavirdine mesylate tablets

DESCRIPTION

RESCRIPTOR Tablets contain delavirdine mesylate, a synthetic non-nucleoside reverse transcriptase inhibitor 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 2942 μg/mL at pH 1.0, 295 μg/mL at pH 2.0, and 0.81 μg/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 lactose, microcrystalline cellulose, croscarmellose sodium, magnesium stearate, colloidal silicon dioxide, and carnauba wax. In addition, the 100-mg tablet contains Opadry White YS-1-7000-E and the 200-mg tablet contains hydroxypropyl methylcellulose, Opadry White YS-1-18202-A and Pharmaceutical Ink Black.

MICROBIOLOGY

Mechanism of Action: Delavirdine is a non-nucleoside reverse transcriptase inhibitor (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 α, γ, or δ 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 μM and 0.04 to 0.10 μM, respectively. Mean IC_{50} of clinical isolates (N=74) was 0.038 μM (range 0.001 to 0.69 μM); 73 of 74 clinical isolates had an $IC_{50} \leq 0.18$ μM. The IC_{90} of 24 of these clinical isolates ranged from 0.05 to 0.10 μM. 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 the inhibition of HIV replication in humans has not been established.

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

Cross-resistance: RESCRIPTOR may confer cross-resistance to other non-nucleoside RT inhibitors when used alone or in combination. Mutations at positions 103 and/or 181 have been found in resistant virus during treatment with RESCRIPTOR and other non-nucleoside RT inhibitors. These mutations have been associated with cross-resistance among non-nucleoside RT inhibitors *in vitro.*

CLINICAL PHARMACOLOGY

Pharmacokinetics

Absorption and Bioavailability: Delavirdine is rapidly absorbed following oral administration, with peak plasma concentrations occurring at approximately one hour. Following administration of delavirdine 400 mg tid (n=67, HIV-1–infected patients), the mean ± SD steady-state peak plasma concentration (C_{max}) was 35 ± 20 μM (range 2 to 100 μM), systemic exposure (AUC) was 180 ± 100 μM • hr (range 5 to 515 μM • hr) and trough concentration (C_{min}) was 15 ± 10 μM (range 0.1 to 45 μM). The single-dose bioavailability of delavirdine tablets relative to an oral solution was 85 ± 25% (n=16, non-HIV–infected subjects). The single-dose bioavailability of delavirdine tablets (100 mg strength) was increased by approximately 20% when a slurry of drug was prepared by allowing delavirdine tablets to disintegrate in water before administration (n=16, non-HIV–infected subjects). The bioavailability of the 200 mg strength delavirdine tablets has not been evaluated when administered as a slurry, because they are not readily dispersed in water (see DOSAGE AND ADMINISTRATION).

Delavirdine may be administered with or without food. In a multiple-dose, crossover study, delavirdine was administered every eight hours with food or every eight hours, one hour before or two hours after a meal (n=13, HIV-1–infected patients). Patients remained on their typical diet throughout the study; meal content was not standardized. When multiple doses of delavirdine were administered with food, geometric mean C_{max} was reduced by approximately 25%, but AUC and C_{min} were not altered.

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 μM. In 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% ± 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 (n=5, HIV-1–infected patients who received delavirdine 400 mg tid) and semen (n=5 healthy volunteers who received delavirdine 300 mg tid) were 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. Delavirdine is primarily metabolized by cytochrome P450 3A (CYP3A), but *in vitro* data suggest that delavirdine may also be metabolized by CYP2D6. The major metabolic pathways for delavirdine are N-desalkylation and pyridine hydroxylation. Delavirdine exhibits nonlinear steady-state elimination pharmacokinetics, with apparent oral clearance decreasing by about 22-fold as the total daily dose of delavirdine increases from 60 to 1200 mg/day. In a study of ^{14}C-delavirdine in six healthy volunteers who received multiple doses of delavirdine tablets 300 mg tid, approximately 44% of the radiolabeled dose was recovered in feces, and approximately 51% of the dose was excreted in urine. Less than 5% of the dose was recovered unchanged in urine. The parent plasma half-life of delavirdine increases with dose; 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 hepatic CYP3A activity by delavirdine is reversible within 1 week after discontinuation of drug.

Special Populations

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

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

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 mean trough delavirdine concentrations were observed between different racial or ethnic groups.

Drug Interactions (see also PRECAUTIONS: Drug Interactions)

Specific drug interaction studies were performed with delavirdine and a number of drugs. Table 1 summarizes the effects 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)		
				C_{max}	AUC	C_{min}
HIV-Protease Inhibitors						
Indinavir	400 mg tid × 7 days	400 mg tid × 7 days	28	↓36* (↓52-↓14)	↔*	↑118* (↑16-↑312)
	600 mg tid × 7 days	400 mg tid × 7 days	28	↔	↑53* (↑7-↑120)	↑298* (↑104-↑678)
Nelfinavir†	750 mg tid × 14 days	400 mg tid × 7 days	12	↑88 (↑66-↑113)	↑107 (↑83-↑135)	↑136 (↑103-↑175)
Saquinavir	Soft gel capsule 1000 mg tid × 28 days	400 mg tid × 28 days	20	↑98‡ (↑4-↑277)	↑121‡ (↑14-↑340)	↑199‡ (↑37-↑553)
Nucleoside Reverse Transcriptase Inhibitors						
Didanosine (buffered tablets)	125 or 250 mg bid × 28 days	400 mg tid × 28 days	9	↓20§ (↓44-↑15)	↓21§ (↓40-↑5)	-
Zidovudine	200 mg tid for >38 days	100 mg qid to 400 mg tid for 8-10 days	34	↔	↔	-
Anti-infective Agents						
Clarithromycin	500 mg bid × 15 days	300 mg tid × 30 days	6	-	↑100	-
Rifabutin	300 mg qd for 15-99 days	400-1000 mg tid for 45-129 days	5	↑128 (↑71-↑203)	↑230 (↑119-↑396)	↑452 (↑246-↑781)

↑ Indicates increase
↓ Indicates decrease
↔ Indicates no significant change
* Relative to indinavir 800 mg tid without RESCRIPTOR
† Plasma concentrations of the nelfinavir active metabolite (nelfinavir hydroxy-t-butylamide) were significantly reduced by delavirdine, which is more than compensated for by increased nelfinavir concentration
‡ 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 (buffered tablets) separated by at least 1 hr
- Indicates no data 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)		
				C_{max}	AUC	C_{min}
HIV-Protease Inhibitors						
Indinavir	400 or 600 mg tid × 7 days	400 mg tid × 7 days	81	No apparent changes based on a comparison to historical data		
Nelfinavir	750 mg tid × 7 days	400 mg tid × 14 days	7	↓27 (↓49-↑4)	↓31 (↓57-↑10)	↓33 (↓70-↑49)
Saquinavir	Soft gel capsule 1000 mg tid × 28 days	400 mg tid for 7-28 days	23	No apparent changes based on a comparison to historical data		
Nucleoside Reverse Transcriptase Inhibitors						
Didanosine (buffered tablets)	125 or 200 mg bid × 28 days	400 mg tid × 28 days	9	↓32* (↓48-↓11)	↓19* (↓37-↑6)	↔*
Zidovudine	200 mg tid for ≥ 7 days	400 mg tid for 7-14 days	42	No apparent changes based on a comparison to historical data		
Anti-infective Agents						
Clarithromycin	500 mg bid × 15 days	300 mg tid × 30 days	6	↔	↔	↔
Fluconazole	400 mg qd × 15 days	300 mg tid × 30 days	8	↔	↔	↔
Ketoconazole	Various	200-400 mg tid	26	-	-	↑50†
Rifabutin	300 mg qd × 14 days	400 mg tid × 28 days	7	↓72 (↓61-↓80)	↓82 (↓74-↓88)	↓94 (↓90-↓96)
Rifampin	600 mg qd × 15 days	400 mg tid × 30 days	7	↓90 (↓94-↓83)	↓97 (↓98-↓95)	↓100
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
* RESCRIPTOR taken with didanosine (buffered tablets) relative to doses of RESCRIPTOR and didanosine (buffered tablets) separated by at least 1 hr
† Population pharmacokinetic data from efficacy studies
- Indicates no data available

INDICATIONS AND USAGE

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

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

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

DESCRIPTION OF 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 through Week 52 as measured by the Roche Amplicor® HIV-1 Monitor (standard assay). 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 < 400copies/mL) are considered failures at Week 52. Results of an interim analysis of efficacy conducted for studies 21 Part II and 13C 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.

Study 21 Part II: 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 naive (84%) or had limited nucleoside experience (16%). Mean baseline CD_4 cell count was 359 cells/mm^3 and mean baseline plasma HIV RNA was 4.4 $\log_{10}$ copies/mL.

Results showed that the mean increase from baseline in CD_4 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 results of the intent-to-treat analysis of the percentage of patients with a plasma HIV RNA level <400 copies/mL are presented in Figure 1. HIV-1 RNA status and reasons for discontinuation of randomized treatment at 52 weeks are summarized in Table 3. 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

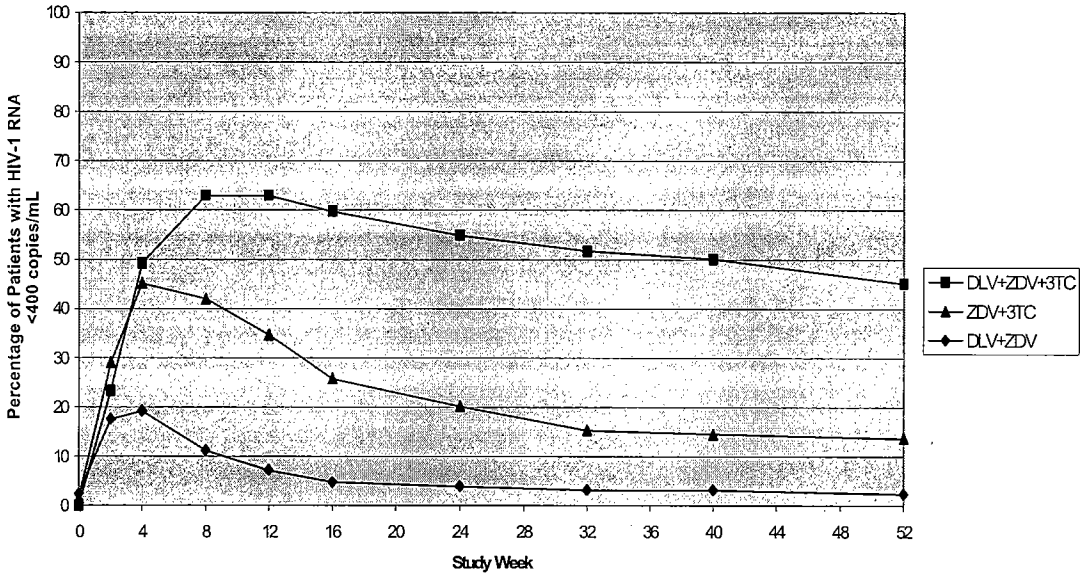


Table 3:
Outcomes of Randomized Treatment Through Week 52 for Protocol 21 Part 2

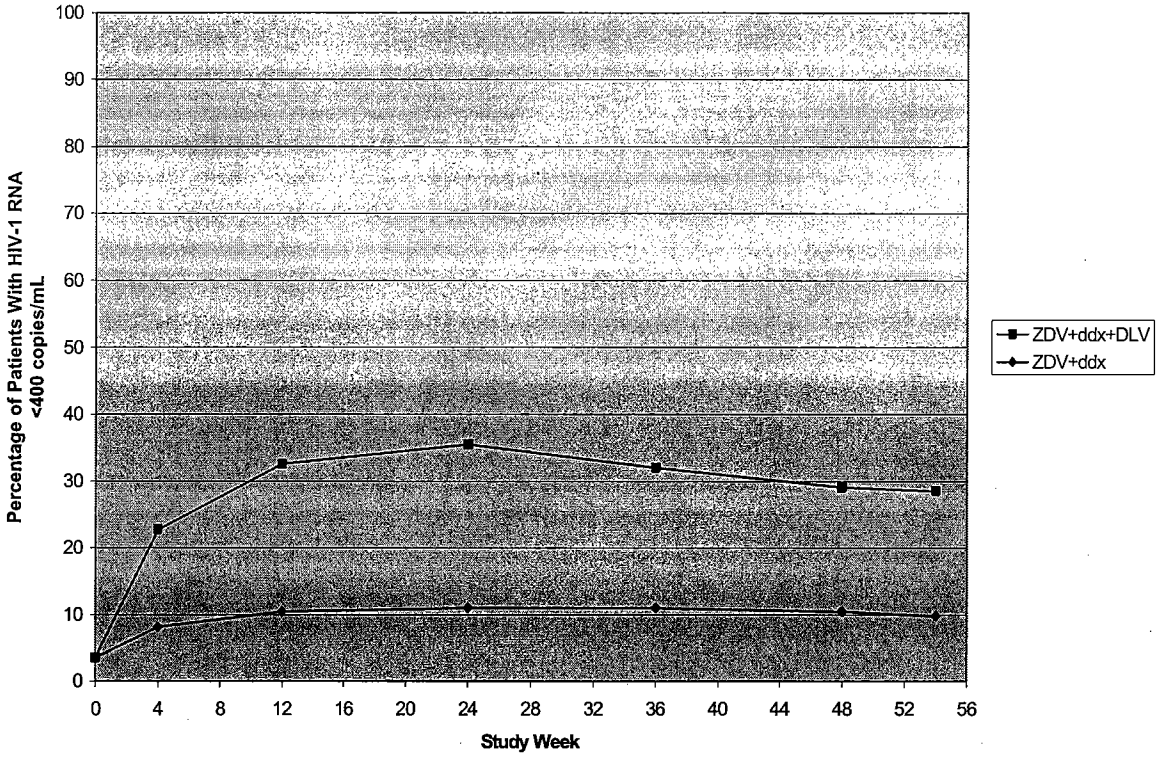
Outcome	ZDV + 3TC (N = 124) %	DLV + ZDV (N = 125) %	DLV + ZDV + 3TC (N = 124) %
HIV RNA <400 copies/mL*	14	2	45
HIV RNA ≥400 copies/mL†,‡	64	52	31
Discontinued due to adverse events‡	8	13	10
Discontinued due to other reasons‡,§	14	33	14

*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

Study 13C: Study 13C was a double-blind, randomized, placebo-controlled trial comparing treatment with RESCRIPTOR (400 mg tid), zidovudine (200 mg tid or 300 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 naive (63%) or had limited antiretroviral experience (37%). Mean baseline CD_4 cell count was 210 cells/mm^3 and mean baseline plasma HIV RNA was 4.9 $\log_{10}$ copies/mL.

Results showed that the mean increase from baseline in CD_4 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.

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



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

Table 4. 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

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

CONTRAINDICATIONS

RESCRIPTOR Tablets are contraindicated in patients with known hypersensitivity to any of its ingredients. 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 5. **Also, see PRECAUTIONS, Table 6, Drugs That Should Not Be Coadministered With RESCRIPTOR.**

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

WARNINGS

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

Drug Interactions

Because 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 package insert: **Table 5, Drugs That Are Contraindicated With RESCRIPTOR; Table 6, Drugs That Should Not Be Co-administered With RESCRIPTOR; and Table 7, 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 that are also metabolized by the CYP3A4 pathway (eg, atorvastatin or cerivastatin). 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

General: Delavirdine is metabolized primarily by the liver. Therefore, caution should be exercised when administering RESCRIPTOR Tablets 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.

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.

Skin Rash: Severe rash, including rare cases of erythema multiforme and Stevens-Johnson syndrome, has been reported in patients receiving RESCRIPTOR. Erythema multiforme and Stevens-Johnson syndrome were rarely seen in clinical trials and resolved after withdrawal of RESCRIPTOR. Any patient experiencing severe rash or rash accompanied by symptoms such as fever, blistering, oral lesions, conjunctivitis, swelling, and muscle or joint aches should discontinue RESCRIPTOR and consult a physician. Two cases of Stevens-Johnson syndrome have been reported through postmarketing surveillance out of a total of 339 surveillance reports.

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

In most cases, the duration of the rash was less than two weeks and did not require dose reduction or discontinuation of RESCRIPTOR. Most patients were able to resume therapy after rechallenge with RESCRIPTOR following a treatment interruption due to rash. The distribution of the rash was mainly on the upper body and proximal arms, with decreasing intensity of the lesions on the neck and face, and progressively less on the rest of the trunk and limbs. Occurrence of a delavirdine-associated rash after 1 month is

uncommon. Symptomatic relief has been obtained using diphenhydramine hydrochloride, hydroxyzine hydrochloride, and/or topical corticosteroids.

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

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 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, and muscle or joint aches should 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 (e.g., 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 1 hour apart.

Because RESCRIPTOR may interact with certain drugs, patients should be advised to report to their doctor the use of any prescription, nonprescription medication 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.

Drug Interactions (see also CONTRAINDICATIONS, WARNINGS, and CLINICAL PHARMACOLOGY: Drug Interactions)

Delavirdine is an inhibitor of CYP3A isoform and other CYP 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 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 induce 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 6, Drugs That Should Not Be Coadministered With RESCRIPTOR, and Table 7, Established and Other Potentially Significant Drug Interactions: Alteration in Dose or Regimen May Be Recommended Based on Drug Interaction Studies or Predicted Interaction.)**

Table 6. Drugs That Should Not Be Coadministered With RESCRIPTOR

Drug Class: Drug Name	Clinical Comment
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.
Antihistamines: astemizole, terfenadine	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
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.
GI motility agent: cisapride	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
Herbal Products: St. John's wort (hypericum perforatum)	May lead to loss of virologic response and possible 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 7. 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
HIV-Antiviral Agents		
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.
Other Agents		
Acid blockers: antacids*	↓ 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.
H_2Receptor antagonists: cimetidine, famotidine, nizatidine, ranitidine Proton pump inhibitors: omeprazole, lansoprazole		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	↑ Amphetamines	Use with caution.

Antiarrhythmics: bepridil	↑ Antiarrhythmics	Use with caution. Increased bepridil exposure may be associated with life-threatening reactions such as cardiac arrythmias.
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, isradipine, nifedipine, nicardipine, nimodipine, nisoldipine, 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 a 48 hour period.
HMG-CoA reductase inhibitors: 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.
Immunosuppressants: cyclosporine, tacrolimus, rapamycin	↑ 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.

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

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 12 (male rats) and 9 (female rats) times human exposure at the recommended clinical dose. In mice, delavirdine produced significant increases in the incidence of hepatocellular adenoma/adenocarcinoma in both males and females, hepatocellular adenoma in females, and mesenchymal urinary bladder tumors in males. The systemic drug exposures (AUC) in female mice were 0.5- to 3-fold and in male mice 0.2- to 4-fold of those in humans at the recommended clinical dose. Given the lack of genotoxic activity of delavirdine, the relevance of urinary bladder and hepatocellular neoplasm in delavirdine-treated mice to humans is not known.

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

Pregnancy: Pregnancy Category C: Delavirdine has been shown to be teratogenic in rats. Delavirdine caused ventricular septal defects in 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 RESCRIPTOR (C_{min} 15 μM) at the recommended dose. Exposure in rats approximately 5-fold higher than the expected human exposure resulted in marked maternal toxicity, embryotoxicity, fetal developmental delay, and reduced pup survival. Additionally, reduced pup survival on postpartum day 0 occurred at an exposure (mean C_{min}) approximately equal to the expected human exposure. Delavirdine was excreted in the milk of lactating rats at a concentration three to five times that of rat plasma.

Delavirdine at doses of 200 and 400 mg/kg/day administered during the period of organogenesis caused maternal toxicity, embryotoxicity and abortions in rabbits. The lowest dose of delavirdine that resulted in these toxic effects produced systemic exposures in pregnant rabbits approximately 6-fold higher than the expected human exposure to RESCRIPTOR (C_{min} 15 μM) at the recommended dose. 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.

No adequate and well-controlled studies in pregnant women have been conducted. 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 the 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.

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

Pediatric Use: Safety and effectiveness of delavirdine in combination with other antiretroviral agents have 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.

ADVERSE REACTIONS

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

Table 8. 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 epideral 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 events reported regardless of causality
†ACTG Toxicity Grading System; includes events reported as "rash" , "maculopapular rash", and "urticaria".

Adverse events of moderate to severe 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 9.

Table 9. Treatment-Emergent Events, Regardless of Causality, of Moderate-to-Severe or Life-Threatening Intensity Reported by at Least 5% of Evaluable* Patients in any Treatment Group

	Study 21 Part II			Study 13C	
Adverse Events	**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)
Body as a Whole					
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)
Digestive					
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)
Nervous					
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 1 dose of study medication and returned for at least 1 clinic study visit. Evaluable patients in Study 13C were those who received at least 1 dose of study medication.

Other adverse events that occurred in patients receiving RESCRIPTOR (in combination treatment) in all phase II and III studies, and considered possibly related to treatment and of at least ACTG grade 2 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, sebaceous cyst, and redistribution/accumulation of body fat (see **PRECAUTIONS, Fat Redistribution**).
Cardiovascular System: Abnormal cardiac rate and rhythm, cardiac insufficiency, cardiomyopathy, hypertension, migraine, pallor, peripheral vascular disorder, and postural hypotension.
Digestive System: 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 hemorrhage, hepatomegaly, increased appetite, increased saliva, increased thirst, jaundice, mouth or tongue inflammation or ulcers, nonspecific hepatitis, oral/enteric moniliasis, pancreatitis, rectal disorder, sialadenitis, tooth abscess, and toothache.
Hemic and Lymphatic System: 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 System: Arthralgia or arthritis of single and multiple joints, bone disorder, bone pain, myalgia, tendon disorder, tenosynovitis, tetany, and vertigo.
Nervous System: 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 System: Chest congestion, dyspnea, epistaxis, hiccups, laryngismus, pneumonia, and rhinitis.
Skin and Appendages: Angioedema, dermal leukocytoclastic vasculitis, dermatitis, desquamation, diaphoresis, discolored skin, dry skin, erythema, erythema multiforme, folliculitis, fungal dermatitis, hair loss, herpes zoster or simplex, nail disorder, petechiae, non-application site pruritus, seborrhea, skin hypertrophy, skin disorder, skin nodule, Stevens-Johnson syndrome, urticaria, vesiculobullous rash, and wart.
Special Senses: Blepharitis, blurred vision, conjunctivitis, diplopia, dry eyes, ear pain, parosmia, otitis media, photophobia, taste perversion, and tinnitus.
Urogenital System: 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.

Digestive System: Hepatic failure.

Hemic and Lymphatic System: Hemolytic anemia.

Musculoskeletal System: Rhabdomyolysis.

Urogenital System: Acute kidney failure.

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

Table 10. Marked Laboratory Abnormalities Reported by ≥2% of Patients

		Study 21 Part II			Study 13C	
Adverse Events	**Toxicity Limit**	**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 × ULN	0	0	1.7	2.9	2.4
Activated partial thromboplastin (APTT)	>2.33 × ULN	0	0.8	0	5.8	2.4
Chemistry						
Alananine 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	0.0

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

OVERDOSAGE

Human experience of acute overdose with RESCRIPTOR is limited.

Management of Overdosage: Treatment of overdosage with RESCRIPTOR should consist of general supportive measures, including monitoring of vital signs and observation of the patient's clinical status. There is no specific antidote for overdosage 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 result in significant removal of the drug.

DOSAGE AND ADMINISTRATION

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

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

RESCRIPTOR Tablets may be administered with or without food (see **CLINICAL PHARMACOLOGY: Pharmacokinetics-Absorption and Bioavailability**). Patients with achlorhydria should take RESCRIPTOR with an acidic beverage (e.g., 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.

HOW SUPPLIED

RESCRIPTOR Tablets are available as follows:

100 mg: white, capsule-shaped tablets marked with "U 3761".
Bottles of 360 tablets NDC 63010-020-36
200 mg: white, capsule-shaped tablets marked with "RESCRIPTOR 200 mg".
Bottles of 180 tablets NDC 63010-021-18

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

Rx only

ANIMAL TOXICOLOGY

Toxicities among various organs and organ systems in rats, mice, rabbits, dogs, and monkeys were observed following the administration of delavirdine. Necrotizing vasculitis was the most significant toxicity that occurred in dogs when mean nadir serum

concentrations of delavirdine were at least 7-fold higher than the expected human exposure to RESCRIPTOR (C_{min} 15 μM) at the recommended dose. 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. Other major target organs included the gastrointestinal tract, endocrine organs, liver, kidneys, bone marrow, lymphoid tissue, lung, and reproductive organs.

Agouron Pharmaceuticals, Inc.
La Jolla, CA 92037, USA

RESCRIPTOR is a registered trademark of Pharmacia & Upjohn Company.

L416-0001 Rev. 06/08/01
7 Dec2001 FPL for Traditional Approval and Lipodystrophy CBE Approved 20Nov2001.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20705 / S-009

MEDICAL REVIEW

Medical Officer Comments
NDA 20-705, SLR 009
(Special Supplement, Changes being effected)

Date submitted: 11/20/01
Date received: 11/21/01
Date reviewed: 2/13/02

Sponsor: Agouron Pharmaceuticals, Inc.
10350 North Torry Pines Road
La Jolla CA 92037-1020

Drug: Delavirdine 100 or 200 mg tablets

Indication: Treatment of HIV infection in adults

Brief Review:
In response to a request from the Division, this supplement contains revised precautionary language regarding fat redistribution associated with antiretroviral therapy in the package insert and patient package insert. The suggested package insert changes were incorporated verbatim and presented in final printed label as requested in our letter dated 7/24/01. There are no additional comments.

Linda L. Lewis, M.D.
Medical Officer, HFD-530

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Linda Lewis
2/14/02 08:43:36 AM
MEDICAL OFFICER

Jeffrey Murray
2/22/02 04:33:21 PM
MEDICAL OFFICER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20705 / S-009

ADMINISTRATIVE DOCUMENTS AND CORRESPONDENCE

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Rockville, MD 20857

Memorandum of Project Manager's Review: Supplemental Labeling Review

NDA: **20-705/S-009**

Date submitted: **November 20, 2001**
Date received: **November 21, 2001**
Date completed: **February 6, 2002**

Sponsor: **Agouron Pharmaceuticals, Inc.**
10350 North Torrey Pines Road
La Jolla, CA 92307-1020

Product: **Rescriptor® (delavirdine mesylate) 100mg and 200mg Tablets**

Materials Reviewed:

1. Supplement: Changes Being Effected dated November 20, 2001.
2. Final Printed Labeling dated November 28, 2001

Background
The applicant submitted the Final Printed Label (FPL) November 28, 2001 in response to the approval letter dated May 16, 2001 for Rescriptor® traditional approval, NDA 20-705/S-008. Additionally, precautionary language concerning fat redistribution, requested by the Division of Antiviral Drug Products in a letter dated July 24, 2001, was also incorporated into the FPL.

Revisions

Deleted text is reflected as a ~~strike~~ and new text is <u>underlined.</u> The following was added to PI and PPI for 200mg tablets:

1. Format changes were incorporated throughout the FPL, which included grammatical and font changes. These changes were incorporated without altering the content of the FPL. For example: ~~action:~~ changed to <u>Action</u>, a semi-colon was between precautions and drug, e.g. PRE~~CAUTIONS Drug~~ changed to **<u>PRECAUTIONS: Drug</u>.**

2. Under the **Drug Interaction** subsection of the **WARNINGS** section in the PI, the following changes were made to the title of

   Table 5, Drugs That Are Contraindicated ~~with~~With RESCRIPTOR; Table 6, Drugs That Should Not Be Co-administered With RESCRIPTOR; and Table 7, Established and Other Potentially Significant Drug ~~Interactions for Which~~Interactions: Alteration in Dose or Regimen May Be ~~Recommended.~~ Recommended Based on Drug Interaction Studies or Predicted Interaction.

3. Under the **Resistance/Cross-Resistance** subsection of **PRECAUTIONS** section in the PI, the following paragraph regarding fat redistribution was incorporated:

   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.

4. Under the *Information for the Patient* subsection of **PRECAUTIONS** section in the PI, the following paragraph regarding fat redistribution was added:

   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.

5. Under *Body as a Whole* subsection under **ADVERSE REACTIONS** section in the PI, the following statement was added to the end of the paragraph to emphasize the fat redistribution warning:

   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,~~and~~ sebaceous ~~cyst.~~cyst, and redistribution/accumulation of body fat (see **PRECAUTIONS, Fat Redistribution**).

6. Under *Urogenital System* subsection of the **ADVERSE REACTIONS** section in the PI, the following change was made in the paragraph:

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

7. Under the **Laboratory Abnormalities** subsection of the **ADVERSE REACTIONS** section, N-values from Study 21 Part II and Study 13c were incorporated into Table 10 similar to Table 9 without changing the data.

8. Under the question "What is RESCRIPTOR and how does it work?", in the PPI the following changes were implemented:

   RESCRIPTOR is a medicine used in combination with other anti-HIV medicines to treat people with HIV nfection. Infection with HIV leads to the destruction of ~~CD4 cells,~~infection-fighting immune system cells (called CD_4 cells or T cells), which are important to the immune system. After a large number of CD_4 cells have been destroyed, the infected person develops acquired immune deficiency syndrome (AIDS).

   RESCRIPTOR helps to block HIV reverse transcriptase, a chemical the virus uses to make more copies of tself. 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~~infection-fighting immune system cells (called~~ CD_4 cells~~orT cells)~~ as much as possible for as long as possible.

9. Under the section **Medicines you should not take with RESCRIPTOR** in the PPI, the following changes were made:

   - Versed® (midazolam) Injection and ~~syrup (sedative hypnotics)~~Syrup (for sedation)

10. Under section What are the possible side effects of RESCRIPTOR the following paragraph was added regarding fat redistribution:

    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"), breast, 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.

Conclusions/Recommendations

The revisions to the Package Insert (PI) and the Patient Package Insert (PPI) are acceptable, and the additional revisions to the **WARNINGS, PRECAUTIONS, ADVERSE REACTIONS** sections as well as the PPI are also acceptable. Additionally, please see the Medical Officer memorandum for concurrence. An approval letter based on the Final Printed Label will be issued to the applicant.

Vasavi Reddy, R.Ph.
Regulatory Project Manager
Division of Antiviral Drug Products

Grace Carmouze
Regulatory Health Project Manager
Division of Antiviral Drug Products

Anthony W. DeCicco, R.Ph.
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Attachments:
Document Comparison
November 21, 2001 Final Printed Labeling

WITHHOLD 14 PAGE(S)

Draft Labeling
B4

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Vasavi Reddy
3/14/02 02:35:41 PM
CSO
PM SLR for Rescriptor/Hard-Copy Sign-off/TD 2/22/02
PM SLR for Rescriptor/Hard-Copy Sign-off/TD 2/22/02

Tony DeCicco
3/15/02 03:47:27 PM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-705/S-009

CBE-0 SUPPLEMENT

Agouron Pharmaceuticals, Inc.
Attention: Stepen W. Sherman
Director, Regulatory Strategy
10350 North Torrey Pines Road
La Jolla, CA 92037-1020

Dear Mr. Sherman:

We have received your supplemental drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: RESCRIPTOR® (delavirdine mesylate) Tablets 100mg and 200 mg.

NDA Number: 20-705

Supplement number: S-009

Date of supplement: November 20, 2001

Date of receipt: November 21, 2001

This supplemental application was submitted as a "Supplement - Changes Being Effected." The appropriateness of reporting the proposed change(s) as changes being effected is under review.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on January 20, 2002 in accordance with 21 CFR 314.101(a).

All communications concerning this supplement should be addressed as follows:

U.S. Postal Service:
Center for Drug Evaluation and Research
Division of Antiviral Drug Products, HFD-530
Attention: Division Document Room
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Antiviral Drug Products, HFD-530
Attention: Document Room
9201 Corporate Blvd.
Rockville, Maryland 20850

If you have any questions, please call Grace M. Carmouze, Regulatory Project Manager, at (301) 827-2335.

Sincerely yours,

Anthony W. DeCicco, R.Ph
Chief, Project Management Staff
Center for Drug Evaluation and Research
Division of Antiviral Drug Products

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Tony DeCicco
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