20-705/S-003

NDA 20-705/S-003

Pharmacia & UpJohn Company
Attention: James H. Chambers
Regulatory Manager, Regulatory Affairs
7000 Portage Road
Kalamazoo, MI 49001-0199

Dear Mr. Chambers:

Please refer to your supplemental application (NDA) dated March 15, 1999, received March 16, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for RESCRIPTOR® (delavirdine mesylate) Tablets, 200 mg.

We acknowledge receipt of your submissions dated:

March 16, 1999	July 2, 1999
May 17, 1999	July 9, 1999
May 28, 1999	

The supplemental application provides for a 200 mg tablet of RESCRIPTOR® (delavirdine mesylate).

We have completed our review of this supplemental application. The application is approved together with the negotiated changes in the WARNINGS and PRECAUTIONS sections regarding delavirdine-sildenafil and delavirdine-amprenavir interactions as indicated in the draft package insert dated July 9, 1999.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert, immediate container and carton labels). Marketing the product with FPL that is not identical to this draft labeling may render the product misbranded and an unapproved new drug.

Please submit 16 copies and a .pdf file of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten copies on heavy weight paper or similar material. For administrative purposes this submission should be designated "FINAL PRINTED LABELING" for approved NDA 20-705/S-003. Approval of this submission by FDA is not required before the labeling is used.

We remind you of your responsibility to comply with the requirements of 21 CFR §314.510 as indicated in the approval letter dated April 4, 1997.

We also 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 questions, contact Ms. Grace N. Carmouze, Regulatory Project Manager, at (301) 827-2335.

Sincerely,

Heidi M. Jolson, M.D., M.P.H.
Director
Division of Antiviral Drug Products
Office of Drug Evaluation IV

APPEARS THIS WAY
ON ORIGINAL

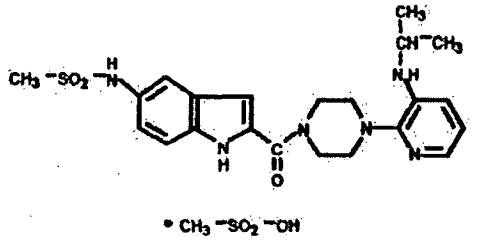
RESCRIPTOR®
brand of delavirdine mesylate tablets

WARNING: RESCRIPTOR Tablets are indicated for the treatment of HIV-1 infection in combination with appropriate antiretroviral agents when therapy is warranted. This indication is based on surrogate marker changes in clinical studies. Clinical benefit was not demonstrated for RESCRIPTOR based on survival or incidence of AIDS-defining clinical events in a completed trial comparing RESCRIPTOR plus didanosine with didanosine monotherapy (see DESCRIPTION OF CLINICAL STUDIES).

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

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 molecularweight 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 Tablets, 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 delavirdine as monotherapy showed a 50-fold to 500-fold reduction in sensitivity in 14 of 15 patients by week 8 of therapy. Genotypic analyses of HIV-1 isolates from patients receiving delavirdine plus zidovudine combination therapy (N=19) showed mutations in 16 of 19 isolates by week 24 of therapy. Mutations occurred predominantly at position 103 and less frequently at positions 181 and 236. In a separate study, an average 86-fold increase in the zidovudine sensitivity of patient isolates (N=24) was observed after 24 weeks on delavirdine and zidovudine combination therapy. The clinical relevance of the phenotypic and the genotypic changes associated with delavirdine therapy has not been determined.

Cross-resistance: Rapid emergence of HIV 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 mechanisms of action.

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. Following single-dose administration of delavirdine tablets with a high-fat meal (874 kcal, 57 g fat), mean C_{max} was decreased by 60% and mean AUC was decreased by 26%, relative to fasted administration (n=12, non-HIV–infected subjects). In a multiple-dose 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, mean C_{max} was reduced by 22% 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 apparent 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 and CYP2C19 activity. Inhibition of CYP3A 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 studied in patients <16 years or >65 years of age.

Gender: Following administration of delavirdine (400 mg every eight hours), median delavirdine AUC was 31% higher in female patients (n=12) than in male patients (n=55).
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)

Antacids: In a single-dose study in twelve healthy volunteers, simultaneous administration of 300 mg delavirdine with alumina and magnesia oral suspension resulted in a 41 ± 19% reduction in delavirdine AUC (see PRECAUTIONS-Drug Interactions).
Clarithromycin: In a study in six HIV-1–infected patients, coadministration of clarithromycin (500 mg bid) with delavirdine (300 mg tid) resulted in a 44 ± 50% increase in delavirdine AUC. Compared to historical data, clarithromycin AUC was increased by approximately 100% and 14-hydroxyclarithromycin AUC was decreased by 75%.
Didanosine: In a study in nine HIV-1–infected patients, simultaneous administration of didanosine (125 mg or 250 mg bid) with delavirdine (400 mg tid) for two weeks resulted in an approximately 20% decrease in both didanosine AUC and delavirdine AUC, relative to when administration of delavirdine and didanosine was separated by at least one hour (see PRECAUTIONS-Drug Interactions).
Fluconazole: In a study in eight HIV-1–infected patients, coadministration of fluconazole (400 mg once daily) with delavirdine (300 mg tid) did not significantly alter the pharmacokinetics of delavirdine. Compared to historical data, fluconazole pharmacokinetics were not altered by delavirdine.
Fluoxetine: Population pharmacokinetic data available for 36 patients suggest that fluoxetine increases trough plasma delavirdine concentrations by about 50%.
Indinavir: Preliminary data (n=14) indicate that delavirdine inhibits the metabolism of indinavir such that coadministration of a 400 mg single dose of indinavir with delavirdine (400 mg tid) resulted in indinavir AUC values slightly less than those observed following administration of an 800 mg dose of indinavir alone. Also, coadministration of a 600 mg dose of indinavir with delavirdine (400 mg tid) resulted in indinavir AUC values approximately 40% greater than those observed following administration of an 800 mg dose of indinavir alone. Indinavir had no effect on delavirdine pharmacokinetics (see PRECAUTIONS-Drug Interactions).
Ketoconazole: Population pharmacokinetic data available for 26 patients suggest that ketoconazole increases trough plasma delavirdine concentrations by about 50%.
Phenytoin, Phenobarbital, and Carbamazepine: Population pharmacokinetic data available for eight patients suggest that coadministration of phenytoin, phenobarbital, or carbamazepine with delavirdine results in a substantial reduction in trough plasma delavirdine concentrations (see PRECAUTIONS-Drug Interactions).
Rifabutin: In a study in seven HIV-1–infected patients, coadministration of rifabutin (300 mg once daily) with delavirdine (400 mg tid) resulted in an 80 ± 10% decrease in delavirdine AUC. Compared to historical data, rifabutin AUC was increased by at least 100% (see PRECAUTIONS-Drug Interactions).
Rifampin: In a study in seven HIV-1–infected patients, coadministration of rifampin (600 mg once daily) with delavirdine (400 mg tid) resulted in a 96 ± 4% decrease in delavirdine AUC (see PRECAUTIONS-Drug Interactions).

Ritonavir: Preliminary data (n=13) indicate that coadministration of delavirdine (400 mg or 600 mg bid) with ritonavir (300 mg bid) did not alter ritonavir pharmacokinetics. Coadministration of ritonavir (300 mg bid) with delavirdine (400 mg bid) did not significantly alter delavirdine pharmacokinetics (n=9). The pharmacokinetic interaction between delavirdine and ritonavir at their recommended doses has not been studied (see PRECAUTIONS-Drug Interactions).

Saquinavir: In 13 healthy volunteers, coadministration of saquinavir (600 mg tid) with delavirdine (400 mg tid) resulted in a five-fold increase in saquinavir AUC. In seven healthy volunteers, coadministration of saquinavir (600 mg tid) with delavirdine (400 mg tid) resulted in a 15 ± 16% decrease in delavirdine AUC (see PRECAUTIONS-Drug Interactions).

Sulfamethoxazole and Trimethoprim/Sulfamethoxazole (TMP/SMX): Population pharmacokinetic data available for 311 patients suggest that the pharmacokinetics of delavirdine are not affected by sulfamethoxazole or TMP/SMX.

Zidovudine: Zidovudine and delavirdine do not alter one another's pharmacokinetics.

INDICATIONS AND USAGE

RESCRIPTOR Tablets are indicated for the treatment of HIV-1 infection in combination with appropriate antiretroviral agents when therapy is warranted. This indication is based on surrogate marker changes in clinical studies. Clinical benefit was not demonstrated for RESCRIPTOR based on survival or incidence of AIDS-defining clinical events in a completed trial comparing RESCRIPTOR plus didanosine with didanosine monotherapy (see DESCRIPTION OF CLINICAL STUDIES).

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

DESCRIPTION OF CLINICAL STUDIES

In two of the clinical studies described below (Study 0021, Part 1 and Study 0017), an experimental HIV nucleic acid amplification assay was used to estimate the level of circulating HIV RNA in plasma. In the clinical study ACTG 261, also described below, an approved HIV nucleic acid amplification assay was used.

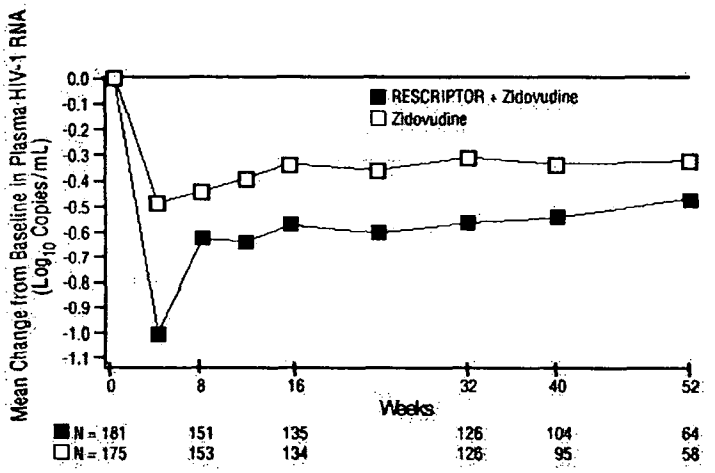
Figures 1-3 below present results for all patients with data available at the time points shown. The decrease in sample size reflects patients leaving the study, missed visits, and those who had not reached specified time points at data cutoff. In general, patients who left the study had lower CD4 cell counts and higher plasma HIV RNA values than patients remaining on study. Therefore, absolute changes from baseline are overstated in all treatment arms, increasingly so at later time points. However, the added effect of delavirdine treatment relative to the control arms does not appear to be significantly affected by patient dropout.

Study 0021, Part 1: RESCRIPTOR-Zidovudine Dual Therapy Trial

Study 0021, Part 1 was a randomized, double-blind trial comparing treatment with RESCRIPTOR plus zidovudine and zidovudine monotherapy in 718 HIV-1–infected patients (median age 34.3 years [range 17 to 70 years], 19% female, 32% non-Caucasian).

Patients were treatment naive or had received less than 6 months of prior zidovudine therapy. Mean baseline CD4 cell count was 334 cells/mm^3 (range 75 to 696 cells/mm^3) and mean baseline plasma HIV-1 RNA was 5.25 $\log_{10}$ copies/mL. Treatment doses were RESCRIPTOR 200 mg, 300 mg, or 400 mg tid plus zidovudine 200 mg tid or zidovudine monotherapy 200 mg tid. No statistically significant difference in CD4 cell count for the combination of RESCRIPTOR plus zidovudine compared with zidovudine monotherapy was observed in a planned analysis at 24 weeks. The mean change from baseline in $\log_{10}$ copies/mL plasma HIV-1 RNA is summarized in Fig 1 for RESCRIPTOR 400 mg tid plus zidovudine and zidovudine monotherapy. All patients had not completed 52 weeks at the time of this analysis.

Fig 1: Mean Change From Baseline in Plasma HIV-1 RNA*
Study 0021



* Clinical significance of changes in plasma HIV-1 RNA levels has not been established.

Study 0017 RESCRIPTOR-Didanosine Dual Therapy Trial

Study 0017 was a randomized, double-blind trial comparing treatment with RESCRIPTOR plus didanosine versus didanosine monotherapy in 1,190 HIV-1–infected patients (median age 37.4 years [range 19 to 78 years], 13% female, 32% non-Caucasian). Patients had received up to 4 months prior didanosine therapy; there were no restrictions on prior zidovudine use. Mean baseline CD4 cell count was 142 cells/mm^3 (range 0 to 541 cells/mm^3) and mean baseline plasma HIV-1 RNA was 5.77 $\log_{10}$ copies/mL. Treatment doses were RESCRIPTOR 400 mg tid plus didanosine or didanosine monotherapy. The dose of didanosine was adjusted by body weight (<60 kg, 125 mg bid; >60 kg, 200 mg bid). Mean changes from baseline in CD4 cell count and $\log_{10}$ copies/mL plasma HIV-1 RNA are summarized in Figs 2 and 3, respectively. All patients had not completed 52 weeks at the time of this analysis.

Fig 2: Mean Change From Baseline in CD4 Cell Counts
Study 0017

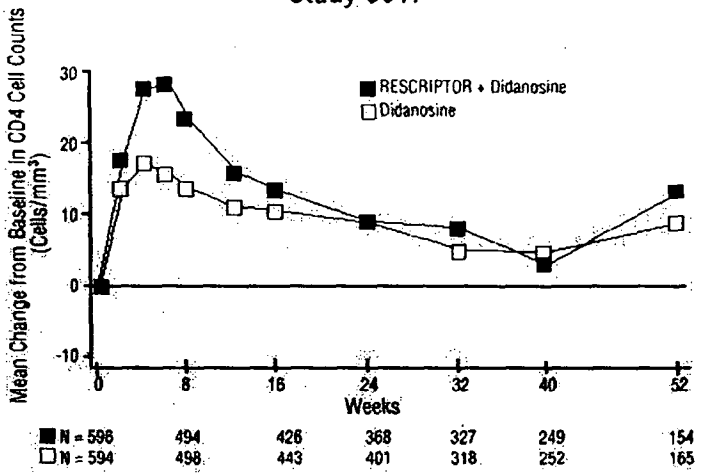
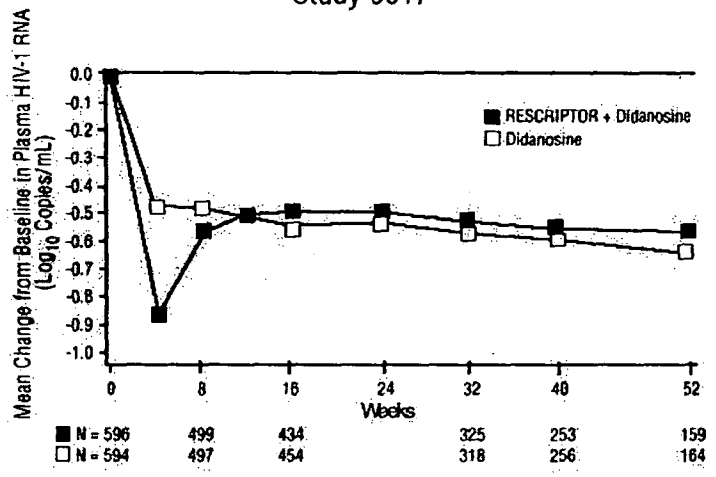


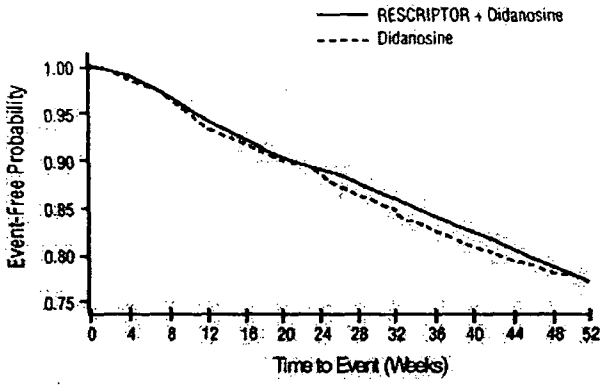
Fig 3: Mean Change From Baseline in Plasma HIV-1 RNA*
Study 0017



*Clinical significance of changes in plasma HIV-1 RNA levels has not been established.

An analysis of clinical efficacy end points (death, clinical progression defined as time to AIDS or death) was performed when all patients had completed at least 6 months in the trial. Comparable rates of deaths and AIDS progression between the didanosine monotherapy arm and the combination of RESCRIPTOR plus didanosine arm were observed. Refer to Fig 4.

Fig 4: Time to Clinical Progression or Death
Study 0017



ACTG 261: RESCRIPTOR-Zidovudine-Didanosine Triple Therapy Trial

AIDS Clinical Trials Group (ACTG) Protocol 261 was a randomized trial comparing the following four treatment regimens: RESCRIPTOR plus didanosine, RESCRIPTOR plus zidovudine, RESCRIPTOR plus didanosine and zidovudine, and zidovudine plus didanosine. The study enrolled 544 HIV-1–infected patients (median age 35 years, 18% female and 44% non-Caucasian patients) who were either nucleoside treatment naive or had prior treatment with zidovudine or didanosine (not both) for less than 6 months. Thirty-seven percent reported previous antiretroviral therapy (194 patients with zidovudine and 6 with didanosine). Mean baseline CD4 cell count was 296 cells/mm^3 (range 55 to 640 cells/mm^3). Median baseline plasma HIV-1 RNA level (available for 229 patients) was 4.45 $\log_{10}$ copies/mL (28,260 copies/mL). Treatment doses were RESCRIPTOR 400 mg tid, zidovudine 200 mg tid, and didanosine dose adjusted by body weight (<60 kg, 125 mg bid; >60 kg, 200 mg bid).

Preliminary results showed no statistically significant difference in CD4 cell count for the three drug combination of RESCRIPTOR, zidovudine, and didanosine compared with the combination of zidovudine plus didanosine. No statistically significant difference in plasma HIV-1 RNA for the three-drug combination of RESCRIPTOR, zidovudine, and didanosine compared with the combination of zidovudine plus didanosine was observed. The mean change from baseline in CD4 cell count is shown in Fig 5. The mean change from baseline in plasma HIV-1 RNA is displayed through week 32 due to the small number of subjects having HIV-1 RNA determinations at week 48 and is shown in Fig 6.

Fig 5: Mean Change From Baseline in CD4 Cell Counts
ACTG 261

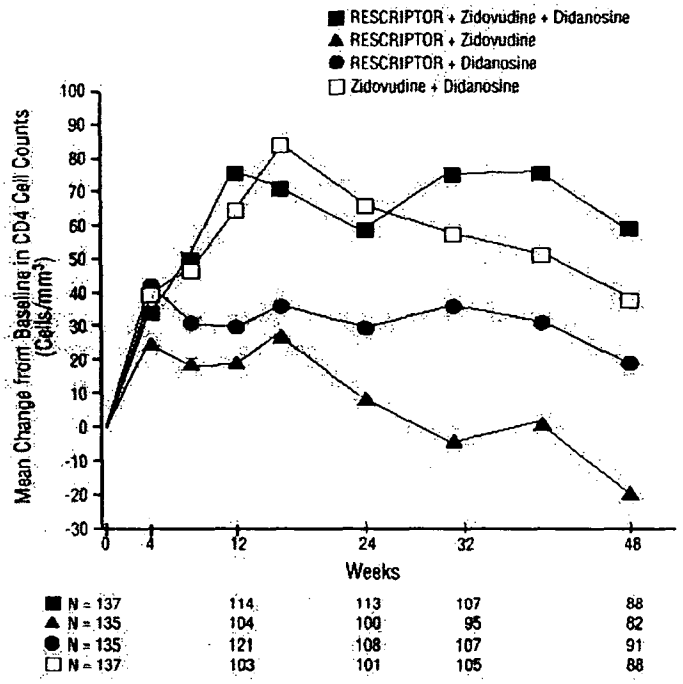


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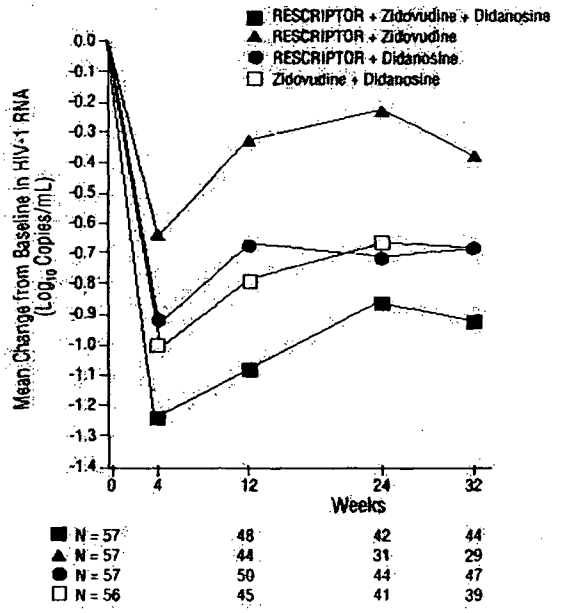
Fig 6: Mean Change From Baseline in
Plasma HIV-1 RNA*, ACTG 261



*Clinical significance of changes in plasma HIV-1 RNA levels has not been established.

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CONTRAINDICATIONS

RESCRIPTOR Tablets are contraindicated in patients with previously demonstrated clinically significant hypersensitivity to any of the components of the formulation.

WARNINGS

Coadministration of RESCRIPTOR Tablets with certain nonsedating antihistamines, sedative hypnotics, antiarrhythmics, calcium channel blockers, ergot alkaloid preparations, amphetamines, cisapride, and sildenafil, may result in potentially serious and/or life-threatening adverse events due to possible effects of RESCRIPTOR on the hepatic metabolism of certain drugs (see PRECAUTIONS section).

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.

Skin Rash: Skin rash attributable to RESCRIPTOR has occurred in 18% of all patients in combination regimens in phase II and III controlled trials who received RESCRIPTOR 400 mg tid. Forty-two percent to 50% of patients treated with RESCRIPTOR 400 mg tid in Studies 0021 and 0017 experienced rash compared with 24% to 32% of patients receiving monotherapy with zidovudine or didanosine, respectively. In Studies 0021 and 0017, 4.3% of patients treated with RESCRIPTOR 400 mg tid discontinued treatment due to rash.

Dose titration did not significantly reduce the incidence of rash. Rash was typically diffuse, maculopapular, erythematous, and often pruritic. Skin rash was more common in patients with lower CD4 cell counts and usually occurred within 1 to 3 weeks (median = 11 days) of treatment. Rash classified as severe was observed in 3.6% of patients in Studies 0021 and 0017. In most cases, the duration of the rash was less than 2 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. Erythema multiforme and Stevens-Johnson syndrome were rarely seen and resolved after withdrawal of RESCRIPTOR. Any patient experiencing severe rash or rash accompanied by symptoms such as fever, blistering, oral lesions, conjunctivitis, swelling, muscle or joint aches should discontinue RESCRIPTOR and consult a physician. Occurrence of a delavirdine-related rash after 1 month of therapy is uncommon unless prolonged interruption of treatment with RESCRIPTOR occurs. Symptomatic relief has been obtained using diphenhydramine hydrochloride, hydroxyzine hydrochloride, and/or topical corticosteroids.

Information for Patients: 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 long-term effects of treatment with RESCRIPTOR are unknown at this time. They 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, muscle or joint aches should discontinue medication and consult a physician.

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 or over-the-counter medications.

Drug Interactions (see also CLINICAL PHARMACOLOGY-Pharmacokinetics-Drug Interactions)

General: Coadministration of RESCRIPTOR with certain nonsedating antihistamines, sedative hypnotics, antiarrhythmics, calcium channel blockers, ergot alkaloid preparations, amphetamines, cisapride, and sildenafil, may result in potentially serious and/or life-threatening adverse events. Due to the inhibitory effect of delavirdine on CYP3A and CYP2C9, coadministration of RESCRIPTOR with drugs primarily metabolized by these liver enzymes may result in increased plasma concentrations. Higher plasma concentrations of these drugs could increase or prolong both therapeutic and adverse effects (Table 1). Therefore, appropriate dose adjustments may be necessary for these drugs. Drugs that induce CYP3A may also reduce plasma delavirdine concentrations (Table 2). Physicians should consider using alternatives to drugs that induce CYP3A while a patient is taking RESCRIPTOR.

Table 1. Selected Drugs that are Predicted to Have Plasma Concentrations Increased by Delavirdine *

HIV protease inhibitors: indinavir, saquinavir
Antihistamines: terfenadine,† astemizole†
Antimicrobial agents: clarithromycin, dapsone, rifabutin
Anti-migraine agents: ergot derivatives
Benzodiazepines: alprazolam,† midazolam,† triazolam†
Calcium channel blockers: dihydropyridines, eg, nifedipine
GI motility agents: cisapride†
Other: sildenafil, quinidine, warfarin

* This table is not all inclusive.
† See WARNINGS.

Table 2. Selected Drugs that are Predicted to Decrease Plasma Delavirdine Concentrations ‡§

Anticonvulsants: carbamazepine, phenobarbital, phenytoin
Antimycobacterial agents: rifabutin, rifampin

‡ This table is not all inclusive.
§ RESCRIPTOR may not be effective when administered concomitantly with these drugs.

Antacids: 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.

Anticonvulsant Agents:

Phenytoin, phenobarbital, carbamazepine: Coadministration of delavirdine with these agents is not recommended, because limited population pharmacokinetic data indicate that a substantial reduction in plasma delavirdine concentrations may result (see CLINICAL PHARMACOLOGY-Pharmacokinetics).

Antimycobacterial Agents:

Rifabutin: Coadministration of delavirdine and rifabutin is not recommended, because rifabutin substantially decreases plasma delavirdine concentrations and delavirdine increases plasma concentrations of rifabutin (see CLINICAL PHARMACOLOGY-Pharmacokinetics).

Rifampin: Delavirdine should not be coadministered with rifampin, because rifampin reduces delavirdine systemic exposure (AUC) by almost 100% (see CLINICAL PHARMACOLOGY-Pharmacokinetics).

Erectile Dysfunction Agents:

Sildenafil: Caution should be used when prescribing sildenafil in patients receiving delavirdine, because delavirdine inhibits CYP3A4 which may result in an increase of sildenafil concentrations. Patients receiving delavirdine and sildenafil should be advised that they may be at an increased risk for sildenafil-associated adverse events, including hypotension, visual changes, and prolonged erection, and should report these symptoms

promptly to their physician. Currently, there are no safety and efficacy data available from the use of this combination. If delavirdine and sildenafil are used concomitantly, a single sildenafil dose of 25 mg in a 48-hour period should not be exceeded. This recommendation is based on data from a ritonavir/sildenafil drug-interaction study.

H_2Receptor Antagonists:

Cimetidine, famotidine, nizatidine, and ranitidine: 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 delavirdine is not recommended.

Nucleoside Analogue Reverse Transcriptase Inhibitors:

Didanosine: Administration of didanosine and delavirdine should be separated by at least one hour, because coadministration of didanosine and delavirdine resulted in reduced systemic exposure to both drugs by approximately 20% (see CLINICAL PHARMACOLOGY-Pharmacokinetics).

Protease Inhibitors (see CLINICAL PHARMACOLOGY-Pharmacokinetics)**:**

Amprenavir: Delavirdine has the potential to increase serum concentrations of amprenavir.

Indinavir: Due to an increase in indinavir plasma concentrations (preliminary results), a dose reduction of indinavir to 600 mg tid should be considered when delavirdine and indinavir are coadministered. Currently, there are no safety and efficacy data available from the use of this combination.

Ritonavir: No studies have been conducted with combination therapy of delavirdine and ritonavir at their recommended doses. Preliminary results indicate there is no evidence of an interaction at doses of delavirdine 400 mg to 600 mg bid and ritonavir 300 mg bid. Currently, there are no safety and efficacy data available from the use of this combination.

Saquinavir: Saquinavir AUC increased 5-fold when delavirdine (400 mg tid) and saquinavir (600 mg tid) were administered in combination. Currently, there are limited safety and no efficacy data available from the use of this combination. In a small, preliminary study, hepatocellular enzyme elevations occurred in 13% of subjects during the first several weeks of the delavirdine and saquinavir combination (6% grade 3 or 4). Hepatocellular enzymes (ALT/AST) should be monitored frequently if this combination is prescribed.

Carcinogenesis, Mutagenesis and Impairment of Fertility: Long-term carcinogenicity studies with delavirdine in animals have not been completed. 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 mutation assay in Chinese hamster ovary cells, and the micronucleus test in mice. The results were negative indicating delavirdine is not mutagenic.

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 7 unplanned pregnancies reported in premarketing clinical studies, 3 were ectopic pregnancies and 3 pregnancies resulted in healthy live births. One infant was born prematurely with a small muscular ventricular septal defect to a patient who received approximately six weeks of treatment with delavirdine and zidovudine early in the course of the pregnancy.

Nursing Mothers: The U.S. Public Health Services Centers for Disease Control and Prevention advises HIV-infected women not to breast-feed to avoid postnatal transmission of HIV to a child who may not yet be infected.

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.

ADVERSE REACTIONS

The safety of RESCRIPTOR Tablets alone and in combination with other therapies has been studied in 1,969 patients receiving RESCRIPTOR.

Adverse events of moderate or severe intensity reported in ≥ 2% of patients receiving RESCRIPTOR in combination with didanosine or zidovudine in Studies 0017 and 0021 are summarized in Table 3. The median duration of treatment in Studies 0017 and 0021 was 34 and 42 weeks (up to 107 weeks for both studies), respectively, at the time of the safety assessment. The most frequently reported drug-related medical event was rash (see PRECAUTIONS-Skin Rash).

Table 3. , Adverse Events of Moderate or Severe Intensity in ≥2% of Patients Receiving RESCRIPTOR*

Body System/ Adverse Event	Study 0017		Study 0021	
	Didanosine† 200 mg bid (n=591)	Delavirdine 400 mg tid + Didanosine† 200 mg bid (n=594)	Zidovudine 200 mg tid (n=271)	Delavirdine 400 mg tid + Zidovudine 200 mg tid (n=287)
Body as a Whole				
Headache	4.7	5.6	4.8	5.6
Fatigue	2.7	2.9	4.8	5.2
Digestive				
Nausea	3.4	4.9	6.6	10.8
Diarrhea	4.4	4.5	2.2	3.5
Vomiting	1.2	2.4	1.1	2.8
Metabolic and Nutritional				
Increased ALT (SGPT)	3.6	5.2	0.7	2.4
Increased AST (SGOT)	3.0	4.5	0.7	1.7
Skin				
Rash	3.0	9.8	1.5	12.5
Maculopapular rash	2.0	6.6	1.1	4.5
Pruritus	1.7	2.2	1.5	3.1

* Includes those adverse events at least possibly related to study drug or of unknown relationship and excludes concurrent HIV conditions.
† Dose adjusted body weight < 60 kg = 125 mg bid≥ 60 kg = 200 mg bid.

Medical events occurring in less than 2% of patients receiving RESCRIPTOR (in combination treatment) in all phase II and III studies, 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 (generalized or localized), allergic reaction, asthenia, back pain, chest pain, chills, edema (generalized or localized), epidermal cyst, fever, flank pain, flu syndrome, lethargy, lip edema, malaise, neck rigidity, pain (generalized or localized), sebaceous cyst, trauma, and upper respiratory infection.

Cardiovascular System: Bradycardia, migraine, pallor, palpitation, postural hypotension, syncope, tachycardia, and vasodilation.

Digestive System: Anorexia, aphthous stomatitis, bloody stool, colitis, constipation, decreased appetite, diarrhea (Clostridium difficile), diverticulitis, duodenitis, dry mouth, dyspepsia, dysphagia, enteritis, esophagitis, fecal incontinence, flatulence, gagging, gastritis, gastroesophageal reflux, gastrointestinal bleeding, gastrointestinal disorder, gingivitis, gum hemorrhage, increased appetite, increased saliva, increased thirst, mouth ulcer, nonspecific hepatitis, pancreatitis, rectal disorder, sialadenitis, stomatitis, and tongue edema or ulceration.

Hemic and Lymphatic System: Anemia, bruise, ecchymosis, eosinophilia, granulocytosis, neutropenia, pancytopenia, petechia, prolonged partial thromboplastin time, purpura, spleen disorder, and thrombocytopenia.

Metabolic and Nutritional Disorders: Alcohol intolerance, bilirubinemia, hyperkalemia, hyperuricemia, hypocalcemia, hyponatremia, hypophosphatemia, increased gamma glutamyl transpeptidase, increased lipase, increased serum alkaline phosphatase, increased

serum amylase, increased serum creatine phosphokinase, increased serum creatinine, peripheral edema, and weight increase or decrease.

Musculoskeletal System: Arthralgia or arthritis of single and multiple joints, bone disorder, bone pain, leg cramps, muscular weakness, myalgia, tendon disorder, tenosynovitis, and tetany.

Nervous System: Abnormal coordination, agitation, amnesia, anxiety, change in dreams, cognitive impairment, confusion, decreased libido, depressive symptoms, disorientation, dizziness, emotional lability, hallucination, hyperesthesia, hyperreflexia, hypesthesia, impaired concentration, insomnia, manic symptoms, muscle cramp, nervousness, neuropathy, nightmares, nystagmus, paralysis, paranoid symptoms, paresthesia, restlessness, somnolence, tingling, tremor, vertigo, and weakness.

Respiratory System: Bronchitis, chest congestion, cough, dyspnea, epistaxis, laryngismus, pharyngitis, rhinitis, and sinusitis.

Skin and Appendages: Angioedema, dermal leukocytoclastic vasculitis, dermatitis, desquamation, diaphoresis, dry skin, erythema, erythema multiforme, folliculitis, fungal dermatitis, hair loss, nail disorder, petechial rash, seborrhea, skin disorder, skin nodule, Stevens-Johnson syndrome, urticaria, and vesiculobullous rash.

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

Urogenital System: Breast enlargement, calculi of the kidney, epididymitis, hematuria, hemospermia, impotence, kidney pain, metrorrhagia, nocturia, polyuria, proteinuria, and vaginal moniliasis.

Laboratory Abnormalities: The frequency of clinically important laboratory abnormalities observed during therapy in Studies 0017 and 0021 is summarized in Table 4. There was no significant difference in ACTG grades 3 and 4 laboratory abnormalities between treatment groups except a two-fold reduction in neutropenia in the delavirdine plus zidovudine combination group compared with the zidovudine monotherapy group in Study 0021.

536

Table 4. . Frequency (%)* of Clinically Important Laboratory Abnormalities

Laboratory Test	Study 0017		Study 0021	
	Didanosine† (n=591)	Delavirdine 400 mg tid + Didanosine† (n=594)	Zidovudine 200 mg tid (n=271)	Delavirdine 400 mg tid + Zidovudine 200 mg tid (n=287)
Neutropenia (ANC <750/mm³)	6.7	5.7	7.7‡	3.5
Anemia (Hgb <7.0 g/dL)	0.2	0.7	1.1	1.0
Thrombocytopenia (platelets <50,000/mm³)	1.4	1.5	0.0	0.0
ALT (>5.0 x ULN)	4.6	6.7	3.7	3.8
AST (>5.0 x ULN)	4.9	5.6	3.0	2.1
Bilirubin (>2.5 ULN)	0.7	0.5	0.4	1.0
Amylase (>2.0 ULN)	6.5	5.2	1.1	0.0

* Percentage was based on the number of patients for which data on that laboratory test was available.
† Dose adjusted by body weight <60 kg = 125 mg bid≥ 60 kg = 200 mg bid.
‡ Significant ($P<.05$) delavirdine + zidovudine vs zidovudine.
ANC = Absolute neutrophil count; ULN = upper limit of normal.

537 ## OVERDOSAGE

538 No reports of overdose with RESCRIPTOR Tablets are available in humans.
539 Several patients have received up to 850 mg tid for up to 6 months with no serious drug-
540 related medical events.
541 **Management of Overdosage:** Treatment of overdosage with RESCRIPTOR should
542 consist of general supportive measures, including monitoring of vital signs and observation
543 of the patient's clinical status. There is no specific antidote for overdosage with
544 RESCRIPTOR. If indicated, elimination of unabsorbed drug should be achieved by emesis
545 or gastric lavage. Since delavirdine is extensively metabolized by the liver and is highly
546 protein bound, dialysis is unlikely to result in significant removal of the drug.
547
548 ## DOSAGE AND ADMINISTRATION

549 The recommended dosage for RESCRIPTOR Tablets is 400 mg (four 100-mg or
550 two 200-mg tablets) three times daily. RESCRIPTOR should be used in combination with
551 other appropriate antiretroviral therapy. The complete prescribing information for other
552 antiretroviral agents should be consulted for information on dosage and administration.
553 The 100-mg RESCRIPTOR Tablets may be dispersed in water prior to
554 consumption. To prepare a dispersion, add four 100-mg RESCRIPTOR Tablets to at least
555 3 ounces of water, allow to stand for a few minutes, and then stir until a uniform
556 dispersion occurs (see CLINICAL PHARMACOLOGY-Pharmacokinetics-Absorption
557 and Bioavailability). The dispersion should be consumed promptly. The glass should be
558 rinsed with water and the rinse swallowed to insure the entire dose is consumed. **The 200-**
559 **mg tablets should be taken as intact tablets, because they are not readily dispersed**
560 **in water.** Note: The 200-mg tablets are approximately one third smaller in size than the
561 100-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 (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.

HOW SUPPLIED

RESCRIPTOR Tablets are available as follows:

100 mg: white, capsule-shaped tablets marked with "U 3761".
Bottles of 360 tablets NDC 0009-3761-03

200 mg: white, capsule-shaped tablets marked with "RESCRIPTOR 200 mg".
Bottles of 180 tablets NDC 0009-XXXX-XX

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 ($C_{min} \approx 15$ 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.

US Patent No. 5,563,142

Pharmacia & Upjohn Company
Kalamazoo, Michigan 49001, USA

Revised XXXXX 1999 XXX XXX XXX
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CARMOUZE

JUL 7 1999

Medical Officer's Brief Review of Supplemental Application
NDA 20-705/S-003

Date received: 03/15/1999
Date completed: 05/27/1999

Drug: RESCRIPTOR® (delavirdine mesylate) 200 mg Tablets

Applicant: Pharmacia & Upjohn
7000 Portage Rd.,
Kalamazoo, MI 49001

1. Background Information

RESCRIPTOR® (delavirdine mesylate) 100-mg tablets were approved on 4 April 1997 for the treatment of HIV infection in combination with other antiretroviral agents. In this submission, the applicant provided the results of a single-dose bioequivalency study of a newly formulated 200-mg tablet compared to the currently marketed 100-mg tablet formulation in healthy volunteers for marketing approval and labeling change.

2. Study Summary

The study titled "Delavirdine mesylate (PNU-90152T): A bioequivalency evaluation of two 200-mg tablets and four 100-mg tablets in healthy volunteers" was conducted from 15 June 1998 to 22 June 1998 by P&U Clinical Research Unit, Kalamazoo, Michigan. This was an open-label, two-way crossover, single-dose design involving 30 healthy male and female volunteers. Each subject received a single, oral 400-mg dose of either two 200-mg tablets (treatment A) or four 100-mg tablets (treatment B) during each of two study periods with a 7-day washout between each period. Safety and pharmacokinetic parameters were monitored on day 1 of each study period.

3. Safety Evaluation

3.1. Clinical Adverse Events

Five (17%) of thirty subjects reported at least one adverse event during the study, and all events were of mild to moderate intensity. There were no deaths or serious adverse events. No subjects discontinued the study due to an adverse event. Adverse events are summarized in Table 3.1.

Table 1. Summary of Adverse Events[1]

Adverse events	Treatment	
	A (200-mg tablets)	B (100-mg tablets)
Asthenia	0	1
Headache	1	0
Pallor	1	0
Diarrhea	1	1
Dizziness	1	1
Pharyngitis	0	2
Rash	1	1

[1]Only one occurrence of maximum intensity per subject is tabulated.

3.2. Laboratory Abnormalities

A review of the laboratory data showed no clinically meaningful changes among all subjects in the study.

4. **Conclusions**

- Both formulations of delavirdine mesylate were well tolerated by subjects in this study. The adverse event profile associated with drug administration was consistent with those seen in other pharmacokinetic and clinical studies.

- According to biopharmaceutic review (please see Dr. Kumi's review), the two formulations are bioequivalent. The 200-mg tablets will allow reduction of pill burden for patients on delavirdine treatment.

5. **Regulatory Action**

The undersigned reviewer recommends that this Supplemental Application for RESCRIPTOR® Tablets, 200 mg (NDA 20-705/S-003) be approved under 21 CFR 314.50.

/S/

Tan T. Nguyen, MD, PhD
MO/DAVDP/ODEIV/CDER/FDA/HFD-530

Concurrence:

HFD-530/DivDir/Jolson /S/ 1/99
HFD-530/TL/Murray /S/ 1/9

cc:

Original NDA 20-705
HFD-530/Division File
HFD-530/TL/Murray
HFD-530/CSO/Carmouze
HFD-530/MO/Nguyen
HFD-530/Chem/Gu
HFD-530/Biopharm/Kumi

Addendum
(Entered: 07/13/1999)

During the review process, additional issues regarding drug-drug interactions were discussed with the applicant. As a result, the following changes to the label were also implemented:

"WARNINGS" section:

- Sildenafil is added to the list of medications that may potentially result in potentially serious and/or life threatening adverse events if taken concomitantly with delavirdine.

"PRECAUTIONS" section:

- Information on potential sildenafil-delavirdine interaction, risks, adverse events, and dosing recommendation on sildenafil is added.
- Information on potential amprenavir-delavirdine interaction is added.

/S/

Tan T. Nguyen, MD, PhD
MO/DAVDP/ODEIV/CDER/FDA/HFD-530

DIV

Clinical Pharmacology and Biopharmaceutics Review

NDA: 20-705 Supplement SCF-003 | **Reviewer**: Robert O. Kumi, Ph.D.
DRUG: Delavirdine mesylate (Rescriptor®) | **Submission Date**: 03/15/99
Formulation: Compressed Tablets (200 mg delavirdine) | **Draft Review**: 06/16/99
Applicant: Pharmacia & Upjohn

JUL - 6 1999

I. Background: This review summarizes the findings of studies submitted to Item 6 (Human Pharmacokinetics and Bioavailability) of NDA 20-705 SCF-003. An appendix containing pharmacokinetic and demographic data, graphs and dissolution profiles is included after the review. NDA 20-705 has been previously reviewed by the Division of Pharmaceutical Evaluation III. Delavirdine mesylate (DEL) is a non-nucleoside reverse transcriptase inhibitor approved for the treatment of HIV-1 in combination with other anti-retroviral agents. The recommended dosage regimen for Rescriptor® tablets is 400 mg (four 100-mg tablets) TID.

The applicant wishes to increase the tablet strength from 100 to 200 mg DEL per tablet, reducing the number of tablets per dose which will hopefully improve patient compliance. The composition of the marketed 100-mg formulation and new 200-mg formulation are presented in Table I. The composition of the tablet strengths is not proportional. Apart from the increased DEL content, the two main differences between the two formulations are:

1. two hundred mg formulation has one added component, hydroxypropyl methyl cellulose
2. decrease in amount of most ingredients per tablet that the two formulations have in common

The net effect of these formulation changes is a decrease in tablet size (200-mg tablet is about 1/3 smaller in size than the 100-mg tablet).

Table I : Composition of Delavirdine Mesylate Tablets

Core Tablet Component	Amount per Tablet (mg)	
	Rescriptor®	New Formulation
Delavirdine Mesylate	100	200
Microcrystalline Cellulose NF Coarse Powder		
Lactose NF Hydrous Spray Process Standard		
Hydroxypropyl Methylcellulose 2910 USP 3 CPS		
Croscarmellose Sodium NF		
Colloidal Silicon Dioxide NF		
Magnesium Stearate NF		
Film Coating/Polishing		
Opadry YS		
Purified Water USP		
Carnauba Wax NF		

II. Study Review

Document Number a0027639
CTN (Protocol Number) M/3331/0085
Investigator: L.A. Williams, MD, MPH. Pharmacia and Upjohn-Clinical Research Unit, Kalamazoo, MI.

Title: Delavirdine mesylate (PNU-90152T): A bioequivalency evaluation of two 200-mg tablets and four 100-mg tablets in healthy volunteers.

Objectives: To assess the bioequivalence of a newly formulated 200-mg tablet and the currently marketed 100-mg tablet formulation after administration of a single 400-mg dose in healthy volunteers

Subjects: Thirty healthy males and females (non-childbearing potential) from 18 to 55 years of age (inclusive) were enrolled in the study. The body mass index of each individual was between 18 and 29. Other inclusion and exclusion criteria were established and are satisfactory.

Demographic Factors of the subjects:
(1) Gender- 24 male and 6 female patients
(2) Race- all subjects were White
(3) Age- 18-53 years; Mean 33 years
(4) Weight- 55.8-92.5 kg; Mean 71.9 kg (BMI 23.6 ± 2.2)
The two groups (treatment sequences) did not differ significantly in race/ethnicity, age, or height. However, a gender imbalance occurred in the two groups.

Study Design: A single-dose, randomized, open-label, two-way crossover study design was employed to assess the bioequivalence (BE) of a 200-mg tablet and the marketed 100-mg tablet. The single dose was administered to 30 healthy male and female volunteers that were assigned to one of two treatment groups.

Dietary Compliance: Subjects fasted from 10 hours before dosing to 4 hours after dosing. A standardized meal was served 4-hours post-dosing and at dinner time on Day 1. Water was allowed *ad lib* during the fasting period.

Analytical Methodology: The concentrations of DEL and its N-desalkyl metabolite, PNU-96183, in plasma samples were quantified by a validated reverse phase HPLC method with fluorescence detection. The lower limit of quantitation (LLOQ) was 25.0 ng/mL. The assay performance was acceptable. The N-desalkyl metabolite concentration data are not provided in this submission. These results are not necessary for the determination of bioequivalence.

Formulation: Two different formulations were used in the study.

- Treatment A **TEST**: Delavirdine mesylate 200-mg tablets x 2 (400-mg dose) Packaging Lot 28,269 and Manufacturing Lot 38,284
- Treatment B **REFERENCE**: Delavirdine mesylate 100-mg tablets x 4 (400-mg dose) (Rescriptor®) Lot PM,9544

Dosing Regimen: A single, oral 400-mg dose of the DEL was administered to each subject during each of the two study periods. Room temperature water (180 mL) was administered with each treatment. There was a 7-day washout period in between each period.

Pharmacokinetic Analysis: Pharmacokinetic parameters of DEL were determined by noncompartmental methods using the (_____ _____ . The pharmacokinetic parameters determined were C_{max}, t_{max}, AUC, λ_z and $t_{1/2}$ (terminal).

Blood Sampling
Blood samples were collected pre-dose (-10 minutes) and 0.25, 0.5, 0.75, 1, 1.25, 1.5, 2, 3, 4, 6, 8, 10, and 12 hours post-dose. Twenty-three blood samples were drawn at a time later than the specified time (range 1-13 minutes late). The impact of these deviations on pharmacokinetic

analysis is not significant as the deviation was ≤ 4 minutes late for all samples except one (13 minutes late for 4 hour sample). According to the sponsor, scheduled times were used in calculating pharmacokinetic parameters.

Statistical Analysis: ANOVA was conducted on the pharmacokinetic parameters using the —— software. The fixed effects for ANOVA were group, period and treatment, whereas the random effect was subject within group. The confidence interval approach (based on the two one-sided t-tests procedure) was used to analyze pharmacokinetic parameters for possible differences between treatments. In addition, regression analysis and Wilcoxon rank sum tests were conducted.

III. RESULTS

A. Pharmacokinetics

1. Bioequivalence and Comparison of Pharmacokinetic Parameters of Tablets

The mean DEL pharmacokinetic parameters in healthy subjects after administration of DEL tablets are summarized in Table II. The two formulations are bioequivalent, based on the ninety-percent log-transformed confidence intervals. The confidence intervals for the 200-mg tablet AUC and C_{max}, relative to the 100-mg reference tablet, fall within the acceptable range of 80-125 %. AUC and C_{max} of the 200-mg formulation are 5-10 % lower than that of the 100-mg tablet, although these differences were not statistically significant.

Table II Mean ± SD Delavirdine Pharmacokinetic Parameters in Healthy Patients

Parameter	Treatment A DLV 200 mg Tablets x 2	Treatment B DLV 100 mg Tablets x 4	(A-B x 100)/B Observed Difference (%)	90 % Confidence Intervals Log-Transformed (%)	
				Lower Limit	Upper Limit
AUC_{∞} (μM·h)*	18.1 ± 12.9	20.1 ± 12.7	-9.95	84	104
AUC_{0-12} (μM·h)	17.7 ±12.5	19.4± 12.2	-8.76	85	105
C_{max} (μM)	6.7 ± 3.5	7.0 ± 4.0	-4.28	91	112
t_{max} (h)	1.0 ± 0.3	0.8 ± 0.4	25.0		
λ_z (h^{-1})	0.36 ± 0.12	0.34 ± 0.14	5.88		
Half-life (h)	2.2 ± 0.9	2.4 ± 1.1	-8.33		

* AUC units reported in NDA (μM·h/mL)* were a typographical according to the sponsor

2. Statistical Analyses

No significant treatment effects were observed for AUC_{∞}, C_{max}, AUC_{0-12}, λ_z, and $t_{1/2}$. A significant group effect was observed for the primary pharmacokinetic parameters. Exploratory analyses were performed to explain the group effect. It was noted that the lighter body mass group had mean AUC_{∞}, AUC_{0-12} and C_{max} values that were approximately 60 % higher than those in the heavier group. However, regression analyses of AUC_{∞} for each treatment against body mass did not show a statistically significant correlation. The sponsor attributes these group differences to subject randomization (Refer to variability section 3) into groups rather than due to sequence or carryover effects. It is unlikely that a carryover effect is present because the washout period is adequate ($t_{1/2}$ < 3 h).

3. Variability

Delavirdine pharmacokinetic parameters exhibited large inter-subject variability in the current study. Inter-subject AUC differences were as high as 10-fold (see Appendix). Similar variability has been observed in previous studies. The sponsor attributes this variability to large inter-subject variability in CYP3A activity. CYP3A is the P450 enzyme primarily involved in DEL clearance. In addition, results from previous studies suggest that reduced gastric acidity (elevated pH) decreases DEL bioavailability. CYP2D6 activity may be an additional source of variability, because it exhibits genetic polymorphism and may play a role in DEL metabolism (*in vitro* studies). None of these possible sources of variability were monitored in this study. The sponsor should continue to investigate the sources of inter-patient variability. It may be possible to individualize dosing by determining delavirdine concentrations following a test dose.

B. SAFETY RESULTS

No serious adverse events occurred with either treatment and no subjects dropped out of the study due to a medical event. Five subjects reported adverse events during the study.

C. DISSOLUTION STUDIES

Approved dissolution conditions (T/A 2508) for the Rescriptor® 100-mg tablets are:

- [redacted]
- [redacted]
- [redacted]

Dissolution studies were carried out by the Sponsor on the new 200-mg DEL tablets. Bulk particle size did not have a significant effect on the dissolution of the tablets (see Appendix). According to the Sponsor, test conditions for dissolution testing of the 100 mg strength (Rescriptor®) tablet are applicable to the 200-mg tablet as a weak *in vitro-in vivo* correlation exists and the 100-mg and 200-mg tablets are bioequivalent. The assumption of similarity in test conditions, based on these two observations, is not valid; formulation changes (different components and proportions) require (re)establishment of dissolution conditions in various media. The sponsor acknowledges that the correlation can not be used to set specifications, as the correlation is weak, and tested the new formulation in various media.

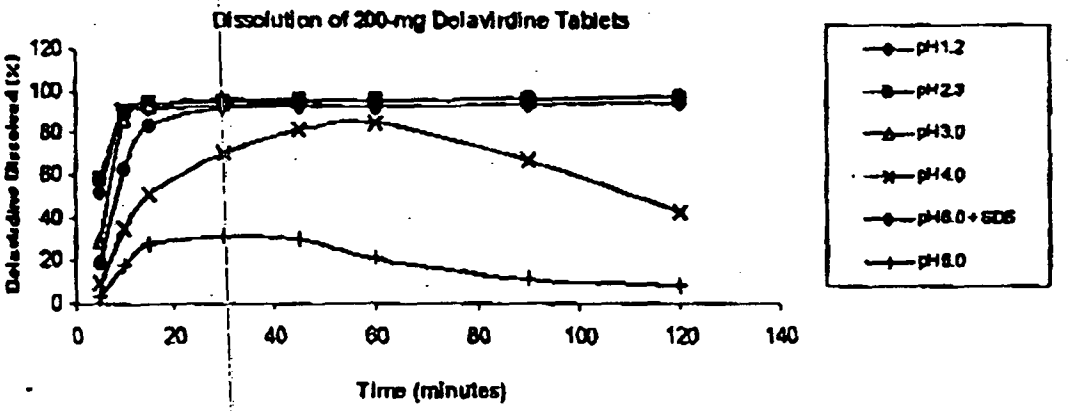
Table III: Dissolution of DEL 200-mg Tablets in various media

	Mean* Percent of Delavardine Label Dissolved in Various Media					
Time (min	pH 1.2	pH 2.3	pH 3.0	pH 4.0	pH 6.0	pH 6.0 + SDS
5	52.2	58.0	29.2	9.4	3.3	19.0
10	89.9	91.1	86.6	34.9	18.2	62.6
15	91.8	93.8	93.6	51.2	27.2	83.7
30	92.9	95.2	96.4	70.8	31.8	92.8
45	93.3	95.6	96.5	81.5	30.4	94.7
60	93.6	95.9	96.6	85.0	21.0	95.6
90	94.2	96.6	96.8	67.1	11.5	97.1
120	94.9	97.3	97.0	42.8	7.8	97.8

* standard deviations associated with all values were < 13 % of mean value
Dissolution profiles were generated in different media using Lot number 38,282. In pH 4 and 5, DEL precipitates leading to decreased dissolution.

Results from dissolution testing of the 200-mg tablets, in various media and in pH 6.0 with SDS dissolution medium, are presented in Tables III and IV. Dissolution profiles for the 200-mg strength in various media are depicted in figure 1.

Figure 1 Dissolution of 200 mg Delavirdine Tablets in Various Media



Previously, in the development of the 100-mg tablet dissolution method, the sponsor claimed that the pH 6.0 with SDS medium was more discriminating among formulations than the pH 1.2 simulated gastric fluid without enzymes. Consequently, the pH 6.0 with SDS medium was approved as an acceptable dissolution medium (T/A 2508). Under the same conditions (paddle speed and bath temperature), dissolution profiles for the 200-mg tablets are similar to profiles for the 100-mg tablets in a given medium (pH 1.2, 2.3, 3.0, 4.0, 6.0 or 6.0 with SDS). The similarity in dissolution characteristics of the two tablet strengths suggests that the dissolution medium used for the 100-mg tablet is acceptable for the 200-mg tablet.

Table IV: Dissolution of Rescriptor® 200-mg tablets using method

	Mean* Percent of Label Dissolved for Individual Tablets (Range)		
Time (minutes)	15	30	60
Lot Number^			
38,282	82 (72-93)	91 (81-98)	94 (86-100)
38,283	81 (63-89)	88 (75-95)	91 (81-97)
38,284♦	79 (61-88)	89 (76-95)	92 (82-96)
38,285	67 (60-75)	84 (74-92)	89 (78-97)

* coefficients of variation associated with all values were < 11 %

^ lot size was half-scale) that of the typical manufacturing size

♦Lot 38,284 was used in bioequivalence study

The dissolution results in Table IV indicate that the dissolution specification for the 100-mg tablets (Q = is appropriate for the new 200-mg tablets.

D. Dispersion of 100-mg and 200-mg Tablets in Water

Data from the original NDA indicate that the 100-mg tablets form a slurry when dispersed in water. This slurry is 20 % more bioavailable than the intact tablets. According to the sponsor, the 200-mg tablets are not readily dispersed in water. This finding suggests that the solubility in water of the 200-mg tablets is less than that of the 100-mg tablets. The proposed labeling indicates that the 200 mg tablets should be administered as intact tablets rather than as a slurry.

IV. Conclusions

1. The bioequivalency study shows that the new 200-mg delavirdine tablet is bioequivalent to the 100-mg marketed (reference) tablet. This conclusion is based on the confidence interval approach. The 90 % confidence intervals for AUC_∞ and C_{max} were 84-104 % and 91-112%, respectively, which meet the acceptance criteria of 80-125 %.

2. The dissolution conditions and specifications for the 100-mg tablets are suitable for the 200-mg formulation. The method and specification for the 200-mg delavirdine tablets are:
   - [redacted]
   - [redacted]

V. Labeling

The sponsor proposes minor changes to the current label to account for the new tablet strength. Comments regarding labeling in the Clinical Pharmacology and Dosage and Administration Sections have been forwarded to the sponsor. The final version of the label is included in the appendix.

VI. Recommendation

The pharmacokinetic and bioequivalency information provided in NDA 20-705 SCF-003 by the sponsor is sufficient to support approval of the new 200 mg strength delavirdine mesylate tablet.

/S/

Robert O. Kumi, Ph.D.
Reviewer, Pharmacokinetics
Division of Pharmaceutical Evaluation III

Concurrence: /S/

for Kellie Schoolar Reynolds, Pharm.D.
Team Leader, Antiviral Drug Products Section

HFD-530 /NDA20-705
/MO/TNguyen
/PM/GCarmouze

HFD-880 /Kumi, R.
/TL/Reynolds

HFD-340 /Viswanathan
CDR /Barbara Murphy

APPEARS THIS WAY
ON ORIGINAL

CARMOUZE

JUL 12 1999

SUPPLEMENTAL NDA CHEMIST'S REVIEW	1. ORGANIZATION HFD-530	2. NDA NUMBER 20,705
3. NAME AND ADDRESS OF APPLICANT *(City and State)* Pharmacia & Upjohn 7000 Portage Road Kalamazoo, MI 49001-0199		4. AF NUMBER 5. DOCUMENT(S) NUMBER(S) SCF-003 DATE(S) 3/16/99
6. NAME OF DRUG RESCRIPTOR	7. NONPROPRIETARY NAME Delavirdine Mesylate	
8. SUPPLEMENT(S) PROVIDES FOR: Introduction of a new strength (200 mg) tablet of delavirdine mesylate.		9. AMENDMENTS AND OTHER **Amendment #1 & #2** **DATES** **5/17/99 and 5/28/88**
10. PHARMACOLOGICAL CATEGORY Anti-viral	11. HOW DISPENSED |X| Rx | | OTC	12. RELATED IND/NDA/DMF(S) —
13. DOSAGE FORM(S) compressed tablets	14. POTENCY(IES): 200 mg, bottles of 180 tablets	
15. CHEMICAL NAME AND STRUCTURE Piperazine, 1-[3-[(1-methyl-ethyl)amino]-2-pyridinyl]-4-[[5-[(methyl-sulfonyl)amino]-1*H*-indol-2-yl]carbonyl]-, monomethanesulfonate		16. MEMORANDA

17. COMMENTS

This supplement provides a 200-mg tablet of delavirdine mesylate, which is designed to improve patient acceptance and compliance for delavirdine mesylate treatment of HIV-1 infection.

The 200-mg strength is a white to off-white, film coated tablet with 30% delavirdine mesylate. The composition and purpose of the inactive ingredients included in the formulation are similar to 100-mg tablet except the addition of — hydroxypropyl methylcellulose as a binder. The quantity of most inactive ingredients in 200-mg tablet is reduced in order to achieve a smaller tablet (approximately two-thirds as large as the 100 mg tablet). The manufacturing, processing, bulk packaging, and control operations are same as for the 100-mg strength and are performed by Pharmacia & Upjohn.

The proposed specifications and test methods for 200-mg drug product are adequate and the same as for the 100-mg tablet (——————). Six months of stability data under the conditions c —————— H are provided from three batches (Lot #38283, #38284, #38285) of drug products packaged i —————— The data indicated that these drug products are stable under the testing conditions. An adequate stability commitment for the 200-mg tablet is also provided.

18. CONCLUSIONS AND RECOMMENDATIONS

The chemistry, manufacturing and controls information provided in this application is adequate for the 200 mg tablet of delavirdine mesylate. This supplement is therefore recommended for approval from the chemistry perspective.

19. REVIEWER

NAME	SIGNATURE	DATE COMPLETED
Zi-Qiang Gu, Ph.D.	/S/	July 9, 1999

20. CONCURRENCE: HFD-530/SMiller /S/ 7/12/99

DISTRIBUTION							
	X	Orig. NDA	X	Div. File	X	HFD-830/CChen
	X	HFD-530/SMiller	X	HFD-530/TNguyen	X	HFD-530/GCarmouze
	X	HFD-530/ZGu	X		X	