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APPLICATION NUMBER:

20-705 / S-008

MICROBIOLOGY REVIEW

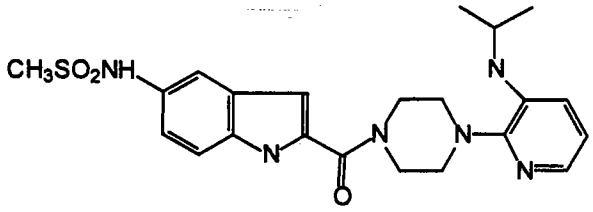
Microbiology Review
Division of Antiviral Drug Products (HFD-530)

NDA: 21-705	Serial #: SE7-008 and S7-008/BL	**Reviewer:**	N. Battula
Date submitted:	July 12, 2000	**Date received:**	July 17, 2000
Date assigned:	January10, 2001	**Date reviewed:**	May 10, 2001

Sponsor: Agouron Pharmaceuticals, Inc.
10350 North Torrey Pines Road
La Jolla, CA 92037

Product name(s):
Proprietary: Rescriptor®
Non-proprietary: Delavirdine mesylate
Chemical: 1-[3-{(1-Methylethyl)amino}-2-pyridinyl}-4-{{5-{methyl-sulfonyl}amino}-1H-indol-2-yl}carbonyl}-piperazine, methanesulfonate.
Mol. Formula= $C_{22}H_{28}N_6O_3S$ Mol.Wt. = 456.57

Structural formula:



Dosage form/route of administration: Tablets/ Oral

Indication: Treatment of HIV infection

Related documents: [redacted]

Background and **Summary**: Rescriptor® (delavirdine mesylate) is a non-nucleoside reverse transcriptase inhibitor of HIV-1. On April 4, 1997, Rescriptor® received accelerated approved by the FDA for the treatment of HIV-1 infection in combination with appropriate antiretroviral agents. The accelerated approval was based on changes in HIV-1 RNA and $CD4^+$ T-cell counts at 24 weeks in clinical studies 0021 Part1, 0017 and ACTG 261.

In this supplemental NDA the applicant provided reports of pivotal clinical studies 0021 Part II and 0013C, and additional supportive clinical studies on the use of Rescriptor® in combination with other antiretroviral agents. In the clinical studies the antiviral efficacy was evaluated by monitoring the changes in the patient's plasma HIV-1 RNA and $CD4^+$ T-cell counts.

With the sNDA, the applicant has not provided a microbiology submission or revisions to the microbiology portion of the package insert. Therefore, the microbiology reviewer made a request to the applicant to submit an amendment to the package insert reflecting the current understanding of the microbiology of Rescriptor® that is available in the open literature and the data from their clinical studies. The applicant submitted an amendment (#SE7-008/BL) to the package insert along with the supporting materials.

The submitted microbiology amendment and appropriate publications in the open literature were reviewed and the package insert was revised. The revised version of the microbiology portion of the package insert to Rescriptor® is presented below.

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. IC50 and IC90 values (50% and 90% inhibitory concentrations) for laboratory isolates (N=5) ranged from 0.005 to 0.030 μM and 0.04 to 0.10 μM, respectively. Mean IC50 of clinical isolates (N=74) was 0.038 μM (range 0.001 to 0.69 μM); 73 of 74 clinical isolates had an IC50 ≤ 0.18 μM. The IC90 of 24 of these clinical isolates ranged from 0.05 to 0.10 μM. 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 has 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.

Recommendations: With respect to microbiology the sNDA for the indication stated in the package insert is supported.

Narayana Battula

Concurrence:
HFD 530Assoc. Dir. HFD 530/TLMicro
Distribution:
Original IND HFD-530/MO

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/s/

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Delavirdine NDA

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