CENTER FOR DRUG EVALUATION AND RESEARCH

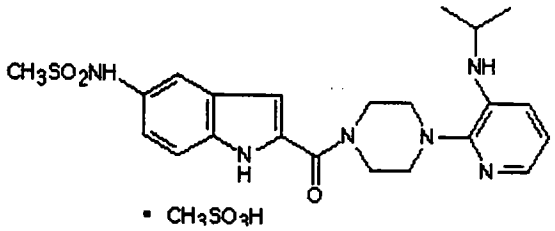
APPLICATION NUMBER:

20-705 / S-008

PHARMACOLOGY REVIEW

PHARMACOLOGIST'S REVIEW

NDA 20-705 Supplement 008 (Traditional Approval)
Date Submitted: 7/17/00
Date Assigned: 7/18/00
PDUFA Date: 5/17/01



SPONSOR Agouron Pharmaceuticals
La Jolla, California

DRUG RESCRIPTOR®, U-90152S; 1-{3-{(1-Methylethyl)amino}-2-pyridinyl}-4-{{5-{methylsulfonyl)amino}-1H-indol-2-yl}carbonyl}-piperazine, monomethanesulfonate; $C_{22}H_{28}N_6O_3S \cdot CH_4O_3S$; MW: 552.68

FORMULATION Tablets (100 mg)

INDICATION AIDS, AIDS-related complex and asymptotic HIV positives

INTRODUCTION

Delavirdine mesylate (RESCRIPTOR®) is a NNRTI for use, under accelerated approval, in the treatment of AIDS. The present submission included clinical data in support of a traditional approval of this drug and no other nonclinical safety reports were submitted. It included a new version of labeling. The preclinical pharmacology/toxicology portion of the new label as attached below reflects comments provided on labeling changes (related to the rat and mouse carcinogenicity findings) directed to submission 6. No further comments about this portion of the contents will be provided. There are no issues from the perspective of pharmacology/toxicology that would preclude traditional approval of this drug.

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 0.5-3 fold and in male mice 0.2-4 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.

Kuei-Meng Wu, Ph.D.
Reviewing Pharmacologist
DAVDP

Concurrences:
HFD-530/TL/JFarrelly
Wu/Pharm/4/26/01

cc:
HFD-530 NDA 20-705 (008)
HFD-530/Division File
HFD-530/CSO/
HFD-530/Pharm/KWu
HFD-345/

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

/s/

Kuei Meng Wu
5/8/01 09:20:58 AM
PHARMACOLOGIST

James Farrelly
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