

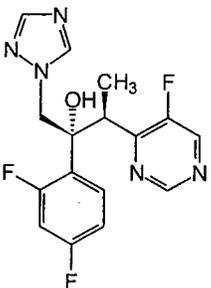
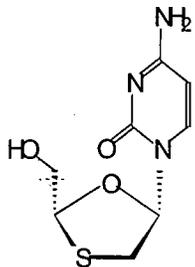
**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-652

PHARMACOLOGY REVIEW

PHARMACOLOGIST'S REVIEW

NDA NUMBER:	21-652
NUMBER/DATE/TYPER:	000/Oct-7-2003
VOL #	1 volume; EDR: \\CDSESUB1\N21652\000\2003-10-07\pharmtox
INFORMATION TO SPONSOR	Yes (x) No ()
SPONSOR	GlaxoSmithKline, Research Triangle Park, North Carolina 27709
DRUG MANUFACTURER	Same as above
REVIEWER NAME:	Kuei-Meng Wu
DIVISION NAME:	DAVDP
HFD #:	HFD-530
REVIEW COMPLETION	6/8/04
DRUG TRADE NAME:	Epzicom™
GENERIC NAME	Abacavir sulfate - Lamivudine
CODE NAME	Abacavir sulfate (1592U89 sulfate)-Lamivudine (GR109714X, 3TC)
CHEMICAL NAME	<u>Abacavir</u> : (1 <i>S</i> , <i>cis</i>)-4 <i>R</i> -[2-amino-6-(cyclopropylamino)-9 <i>H</i> -purin-9-yl]-2-cyclopentene-1-methanol sulfate (salt) (2:1) (enantiomer with 1 <i>S</i> , 4 <i>R</i> absolute configuration on the cyclopentene ring)
FORMULA/MW	<u>Lamivudine</u> : (2 <i>R</i> , <i>cis</i>)-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)(1 <i>H</i>)-pyrimidin-2-one Abacavir: (C ₁₄ H ₁₈ N ₆ O) ₂ ·H ₂ SO ₄ , MW: 670.74; CAS: 188062-50-2 Lamivudine: C ₈ H ₁₁ N ₃ O ₃ S, MW: 229.3; CAS: 134678-17-4
STRUCTURE	Abacavir:  Lamivudine: 
RELEVANT NDAS	Abacavir: NDA 20-977; Lamivudine: NDA 20-564
RELEVANT INDS	Abacavir: 45,331; Lamivudine: 40,916
DRUG CLASS:	Antiviral
INDICATION:	Treatment of HIV infection
CLINICAL FORMULATION:	Tablets (600mg Abacavir+300 mg Lamivudine); also contains microcrystalline cellulose, sodium starch glycolate, NF magnesium stearate NF ζ
ROUTE	Oral \supset USP with a coating of orange color, purified water, USP]

DISCLAIMER: Tabular and graphical information is from sponsor's submission unless stated otherwise.

COMMENTS

This NDA is a fixed-dose combination of abacavir and lamivudine. All preclinical information is cross-referenced to the original NDAs and INDs. No additional pharm/tox information is included in this NDA (please see EDR files at \\CDSESUB1\N21652\000\2003-10-07\pharmtox). No regulatory comments on pharm/tox are needed, except the following editings/rewrites on labeling changes proposed by the sponsor are provided.

REGULATORY RECOMMENDATIONS

From the Pharm/Tox perspectives, this NDA is recommended for approval. The Pharm/Tox portion of the labeling is commented (added text underlined) as below:

Carcinogenesis, Mutagenesis, Impairment of Fertility: Carcinogenicity:

Abacavir: Abacavir was administered orally at 3 dosage levels to separate groups of mice and rats in two-year carcinogenicity studies.

Results showed an increase in the incidence of malignant and non-malignant tumors. Malignant tumors occurred in the preputial gland of males and the clitoral gland of females of both species, and in the liver of female rats. In addition, non-malignant tumors also occurred in the liver and thyroid gland of female rats. These observations were made at systemic exposures in the range of 6 to 32 times the human exposure at the recommended dose.

Lamivudine: Long-term carcinogenicity studies with lamivudine in mice and rats showed no evidence of carcinogenic potential at exposures up to 10 times (mice) and 58 times (rats) those observed in humans at the recommended therapeutic dose for HIV infection.

It is not known how predictive the results of rodent carcinogenicity studies may be for humans.

Mutagenicity: Abacavir: Abacavir induced chromosomal aberrations both in the presence and absence of metabolic activation in an in vitro cytogenetic study in human lymphocytes. Abacavir was mutagenic in the absence of metabolic activation, although it was not mutagenic in the presence of metabolic activation in an L5178Y mouse lymphoma assay.

Abacavir was clastogenic in males and not clastogenic in females in an in vivo mouse bone marrow micronucleus assay.

Lamivudine: Lamivudine was mutagenic in an L5178Y mouse lymphoma assay and clastogenic in a cytogenetic assay using cultured human lymphocytes. Lamivudine was not mutagenic in a microbial mutagenicity assay, in an in vitro cell transformation assay, in a rat micronucleus test, in a rat bone marrow cytogenetic assay, and in an assay for unscheduled DNA synthesis in rat liver.

Impairment of Fertility:

Abacavir or lamivudine induced no adverse effects on the mating performance or fertility of male and female rats at doses producing systemic exposure levels approximately 8 or 130 times, respectively, higher than those in humans at the recommended dose based on body surface area comparisons.

Pregnancy: Pregnancy Category C. There are no adequate and well-controlled studies of _____ in pregnant women. Reproduction studies with abacavir and lamivudine have been performed in animals (see Abacavir and Lamivudine sections below). _____ should be used during pregnancy only if the potential benefits outweigh the risks.

Abacavir: Studies in pregnant rats showed that abacavir is transferred to the fetus through the placenta.

Kuei-Meng Wu, Ph.D.
Reviewing Pharmacologist
DAVDP
Concurrences:
HFD-530/PTL/JFarrelly
Wu/Pharm/6/8/04
Disk: HFD-530/PTL/JFarrelly

cc:
HFD-530 NDA 21-652(000)
HFD-530/Division File
HFD-530/CSO/
HFD-530/MO/
HFD-530/Pharm/
HFN-340

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/s/

Kuei Meng Wu
8/13/04 10:57:12 AM
PHARMACOLOGIST

James Farrelly
8/16/04 08:56:28 AM
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