PHARMACOLOGY REVIEW(S)
PHARMACOLOGIST'S REVIEW

NDA 21-205.000
Date Submitted: December 20, 1999
Date Assigned: February 7, 2000
Date Completed: February 16, 2000
Assigned Reviewer: Pritam Verma, Ph.D.
DAVDP
HFD-530

SPONSOR: Glaxo Wellcome, Inc.
Five Moore Drive
Research Triangle Park, NC 27709

INFORMATION TO SPONSOR: Yes

DRUG: Trizivir™ Tablets
(Abacavir Sulfate 300 mg/Lamivudine 150 mg/Zidovudine 300 mg tablets)

1. ZIAGEN™ (abacavir)

Dosage and administration: The recommended oral dose of ZIAGEN for adults is 300 mg twice daily in combination with other antiviral agents.

Adolescents and pediatric patients: The recommended oral dose of Ziden for adolescents and pediatric patients 3 months to up to 16 years of age is 8 mg/kg twice daily (up to a maximum of 300 mg twice daily) in combination with other antiretroviral agents.

2. EPIVIR® (lamivudine)

Dosage and administration: Adults and adolescents (12 to 16 years): The recommended oral dose of lamivudine for adults and adolescents is 150 mg twice daily (300 mg/day) administered in combination with Retrovir (zidovudine). Dose Adjustment: It is recommended that doses of EpiVir be adjusted in accordance with renal function in patients older than age 16 years. Pediatric patients: the recommended oral dose of lamivudine for 3
months to up to 12 yr of age is 4 mg/kg (up to a maximum of 150 mg twice a day) administered in combination with Retrovir.

3. RETROVIR® (zidovudine)

Dosage and administration: For adults, the recommended total oral daily dose is 600 mg per day in divided doses in combination with other antiretroviral agents and 500 mg (100 mg every 4 hr while awake) or 600 mg per day in divided doses for monotherapy. Pediatric patients: the recommended dose in 3 months to 12 yr of age patients is 180 mg/m² every 6 hr, not to exceed 200 mg every 6 hr.

ROUTE OF ADMINISTRATION: Oral

RELATED INDs & NDAs: 19-655; 20-977; 20-798; 20-564; 20-596; 19-655; 20-518

INDICATION: Treatment of HIV infection.

INTRODUCTION AND DRUG HISTORY:

The sponsor is developing a fixed-dosage combination formulation consisting of abacavir sulfate 300 mg, lamivudine 150 mg and zidovudine 300 mg in an oral tablet (trizivir). Trizivir has been shown to be effective antiretroviral therapy in the treatment of HIV in adults and children. Results of a bioequivalence study (AZL10001) indicate that trizivir tablet is bioequivalent relative to Cmax and AUC to abacavir, lamivudine and retrovir when given as separate tablets. The fixed-dosage tablet is to be administered as a twice daily regimen that should offer a less complicated and more convenient dosing schedule for HIV-infected patients taking abacavir 300 mg daily, lamivudine 150 mg twice daily and zidovudine 200 mg thrice daily. Presently, the sponsor submitted a NDA requesting accelerated approval of trizivir tablets.
TOXICOLOGY AND PHARMACOKINETICS:

Abacavir sulfate, lamivudine and zidovudine are approved drug products and have been reviewed in the division. For pharm/tox studies, please see the respective reviews.

LABEL:

On line 530, the sponsor should change the number ——— to "approximately 3700."

Starting line 544, the two sentences starting with ——— should be deleted.

CONCLUSIONS:

There are no pharm/tox issues associated with this NDA.

Pritam S. Verma, Ph.D.
Reviewing Pharmacologist
Concurrences:
HFD-530/WDempsey 3/17/82
HFD-530/JFarrelly 3/17/82
HFD-530/PVerma

Disk:
HFD-530/JFarrelly

cc
HFD-530/NDA 21-205
HFD-340
HFD-530/PVerma
HFD-530/JMartin
HFD-530/KRao
HFD-530/LConnors
HFD-530/MTruffa
PHARMACOLOGIST'S REVIEW

NDA 21-205
Date Submitted: September 13, 2000
Date Assigned: November 13, 2000
Date Completed: November 13, 2000
Assigned Reviewer: Pritam Verma, Ph.D.
DAVDP
HFD-530

SPONSOR: Glaxo Wellcome, Inc.
Five Moore Drive
Research Triangle Park, NC 27709

INFORMATION TO SPONSOR: No

DRUG: Trizivir™ Tablets
(Abacavir Sulfate 300 mg/Lamivudine 150 mg/Zidovudine 300 mg tablets)

1. ZIAGEN™ (abacavir)

   Dosage and administration: The recommended oral dose of ZIAGEN for adults is 300 mg twice daily in combination with other antiviral agents.

2. EPIVIR® (lamivudine)

   Dosage and administration: Adults and adolescents (12 to 16 years): The recommended oral dose of lamivudine for adults and adolescents is 150 mg twice daily (300 mg/day) administered in combination with other antiretroviral agents.

3. RETROVIR® (zidovudine)

   Dosage and administration: For adults, the recommended total oral daily dose is 600 mg per day in divided doses in combination with other antiretroviral agents and 500 mg (100-mg every 4 hr while awake) or 600 mg per day in divided doses for monotherapy.

APPEARS THIS WAY ON ORIGINAL

BEST POSSIBLE COPY
ROUTE OF ADMINISTRATION: Oral

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INDICATION: Treatment of HIV infection.

INTRODUCTION AND DRUG HISTORY:

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TOXICOLOGY:

LABEL:

The label has been reviewed and there are no issues associated with the label.

CONCLUSIONS:

There are no pharm/tox issues associated with the label.
Concurrences:

HFD-530/WDempsey
HFD-530/JFarrelly
HFD-530/PVerma
HFD-530/PVerma

Disk:
HFD-530/JFarrelly
cc
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HFD-530/LMishra
HFD-530/KRao
HFD-530/TCvetkovich
HFD-530/MTruffa

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Pritam S. Verma, Ph.D.
Reviewing Pharmacologist