

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 20-977

20-978

CLINICAL PHARMACOLOGY and
BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

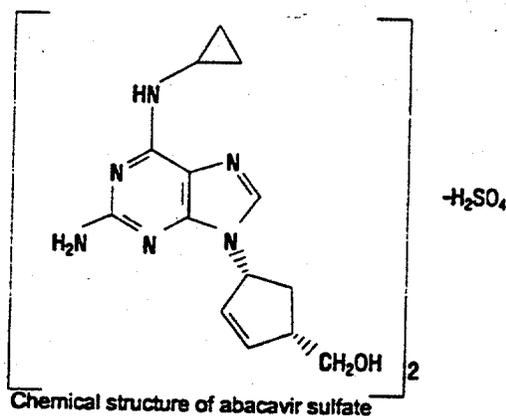
REVIEWER : Prabhu Rajagopalan, Ph. D.
NDA (FORMULATION) : 20977 (Tablet) and 20978 (Solution)
TYPE :
APPLICANT : GlaxoWellcome

DRUG (ROUTE OF ADMINISTRATION) : Abacavir (oral)
STRENGTH Tablet : 300 mg
Solution : 20 mg/mL

SUBMISSION DATE : June 24, 1998
DRAFT REVIEW : October 14, 1998
FINAL REVIEW : December 8, 1998

BACKGROUND

Abacavir ((1S-cis)-4-[2-amino-6-(cyclopropylamino)9H-purin-9-yl]-2-cyclopentene-1-methanol) is a synthetic nucleoside analog. *In vitro* studies indicate that abacavir is phosphorylated to abacavir monophosphate, which is then converted to carbovir mono-, di- and tri-phosphate. The anti-HIV activity of abacavir can be attributed to the inhibition of HIV reverse transcriptase by carbovir triphosphate. The intracellular half-life of carbovir triphosphate in CEM cells has been estimated to be approximately 3.3 hours. The Applicant proposes to market the sulfate salt of abacavir under the trade name ZIAGENTM.



The Applicant has evaluated the safety and efficacy of abacavir in the treatment of HIV infection in two Phase III studies. Study CNAAB3003 was conducted in treatment naïve adult HIV infected patients in North America and Europe. Patients were randomized to receive abacavir tablets (300 mg BID), zidovudine and lamivudine or placebo, zidovudine and lamivudine. Week 16 data and preliminary Week 24 data from this study are available at this time. Study CNAAB3006 was conducted in HIV infected children who have received at least 12 weeks of prior antiviral therapy. In this study, pediatric patients received abacavir solution (8 mg/kg BID), zidovudine and lamivudine or placebo, zidovudine and lamivudine. The Applicant is seeking approval for tablet and solution formulations of abacavir sulfate. The recommended dose of abacavir is 300 mg BID in adults and 8 mg/kg BID in pediatric patients.

SYNOPSIS

The important features in the pharmacokinetics and disposition of abacavir are presented in the synopsis. A detailed review begins on page 7. Unless specified otherwise, in all subsequent sections, the variation in the mean is represented by the standard deviation associated with the mean and is shown as mean \pm SD.

ABSORPTION

Following oral administration, abacavir was absorbed with a median t_{max} value of 0.5 hours. In 18 HIV infected patients receiving the proposed market tablet formulation of abacavir, the mean C_{max} and AUC_{∞} values were $2.64 \pm 0.61 \mu\text{g/mL}$ and $5.72 \pm 1.77 \mu\text{g}\cdot\text{h/mL}$, respectively, after a single oral dose of 300 mg. In these subjects, C_{max} values ranged from 1.1 to $4.1 \mu\text{g/mL}$. In 11 subjects receiving the proposed market solution formulation of abacavir, the mean C_{max} and AUC_{∞} values were $3.07 \pm 1.01 \mu\text{g/mL}$ and $5.75 \pm 1.78 \mu\text{g}\cdot\text{h/mL}$, respectively, after a single oral dose of 300 mg.

In ten HIV infected subjects receiving abacavir 300 mg BID and zidovudine 300 mg BID, the mean steady-state C_{max} and AUC_{12} values were $3.15 \pm 0.41 \mu\text{g/mL}$ and $6.07 \pm 0.73 \mu\text{g}\cdot\text{h/mL}$, respectively. These values were not different from steady-state values observed in nine other subjects receiving abacavir 300 mg BID without zidovudine. These 19 subjects received abacavir succinate caplets.

When administered with a high fat breakfast, the mean fed to fasted ratios for abacavir C_{max} and AUC_{∞} were 0.74 (90% CI: [0.65 - 0.84]) and 0.97 (90% CI: [0.90-1.04]), respectively. The median t_{max} value increased from 0.5 hours under fasting condition to 1.5 hours under fed condition. Although peak abacavir concentration was affected by the presence of high fat meal in the gastrointestinal tract, the extent of absorption was not affected. Therefore, abacavir can be administered with or without food.

DOSE PROPORTIONALITY

The pharmacokinetics of abacavir were assessed after a single oral dose of abacavir (100 to 1200 mg) to HIV infected patients. The pharmacokinetic parameters were found to be dose proportional over a range of 600 - 1200 mg.

ABSOLUTE BIOAVAILABILITY

The absolute bioavailability of abacavir was assessed in 6 HIV infected male patients. The geometric mean absolute bioavailability was estimated to be 83%.

RELATIVE BIOAVAILABILITY

The relative bioavailability of the tablet formulation was assessed with respect to the solution formulation. The ratio of geometric mean C_{max} of the tablet to the solution formulation was 0.77 and that of AUC_{∞} was 1.04.

BIOEQUIVALENCY

The Applicant conducted a study to assess the bioequivalency between two formulations used in clinical trials. Abacavir caplets (100 mg) were used in Phase I and II studies. After a dose of 300 mg BID was chosen, the Applicant developed a tablet formulation containing 300 mg of abacavir sulfate per tablet. The tablet formulation has

been used in principal Phase III studies and is the proposed market formulation. The results of statistical analyses of the bioequivalency study are summarized below.

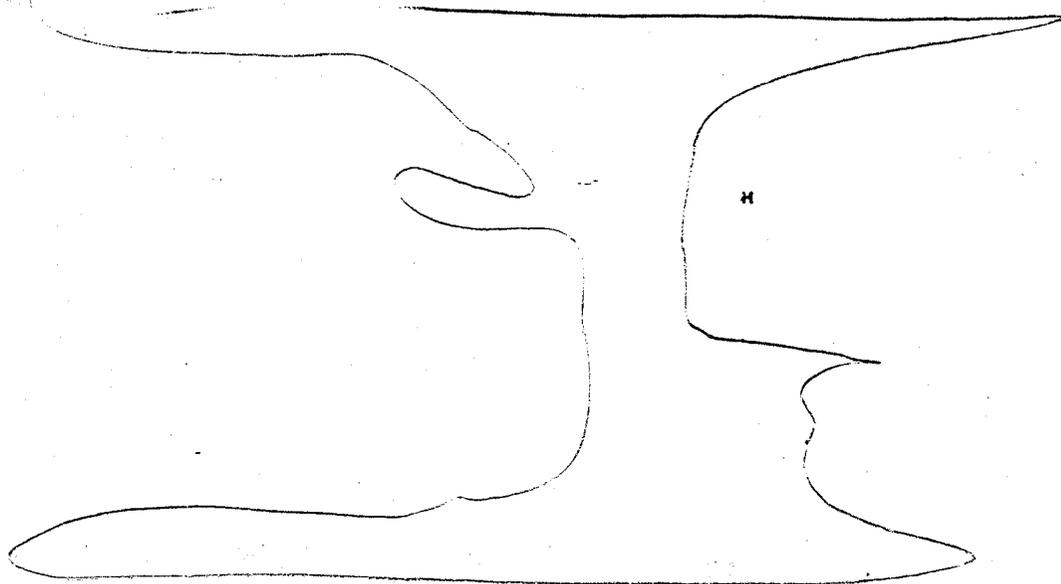
PK parameter	Formulation	Point estimate	90% CI
C_{max}	Abacavir succinate caplet (Reference)	100	
	Abacavir sulfate tablet	110	[97 - 124]
AUC_{∞}	Abacavir succinate caplet (Reference)	100	
	Abacavir sulfate tablet	95	[89 - 102]

The statistical analyses indicate that the two formulations are bioequivalent.

DISTRIBUTION

The distribution of abacavir was characterized in six HIV infected male subjects after intravenous infusion. The mean apparent volume of distribution was 0.86 ± 0.15 L/kg. Cerebrospinal fluid concentrations were measured in three subjects. The ratio of CSF to plasma AUC_{0-8} ranged from 0.27 to 0.33. *In vitro* studies indicate that the plasma protein binding of abacavir was independent of concentration and 50% of the drug was bound to human plasma proteins in the concentration range 0.03 to 10.3 $\mu\text{g/mL}$. Analysis of whole blood and plasma samples indicates that abacavir distributes into erythrocytes.

METABOLISM AND ELIMINATION



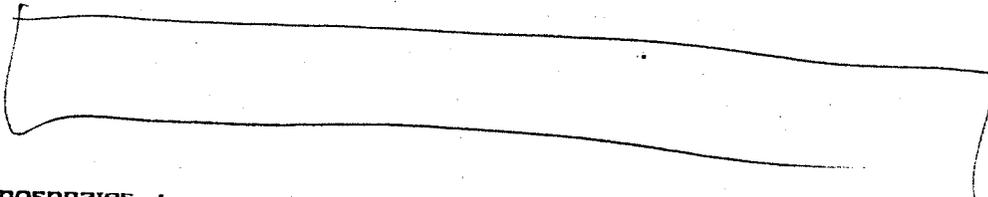
In the mass balance study, approximately 99% of the administered radioactivity

Abacavir (1.2%) and other minor metabolites in urine accounted for 3% of administered radioactivity. Fifteen percent of the administered radioactivity appearing in urine remains unidentified.

After an intravenous infusion of 150 mg of abacavir to six HIV infected male subjects, the mean total clearance was 0.80 ± 0.24 L/h/kg. The average plasma half-life in these subjects was 1 hour.

IN VITRO INTERACTION STUDIES

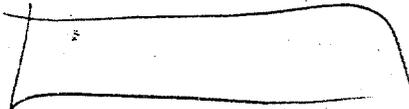
In vitro studies with human microsomal fractions indicate that the metabolism of abacavir is not mediated by cytochrome P450 enzymes. At clinically relevant concentrations, abacavir did not inhibit CYP2D6, CYP2C9 and CYP3A4 activity. At concentrations 5- fold and 1000- fold greater than typical C_{max} values, CYP3A4 activity was inhibited 13% and 100%, respectively. Incubations with human cytosolic fractions provided evidence for involvement of alcohol dehydrogenase in the metabolism of abacavir.



transformation. It

is considered the above study, however, it is

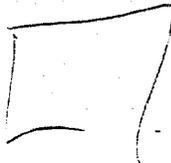
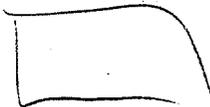
can be summarized in the following manner.



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DRUG INTERACTIONS

The Applicant evaluated the pharmacokinetic interaction between abacavir, AZT and 3TC in a single dose study. A clinically significant increase in abacavir exposure was not seen as a result of concomitant administration with AZT, 3TC or AZT and 3TC. When administered with abacavir, AZT and AZT-glucuronide AUC values were higher by approximately 10 and 40%, respectively. These changes are not considered to be clinically significant. When administered with abacavir, the mean lamivudine C_{max} values were 35% lower and mean AUC values were 15% lower. It should be noted that the Applicant has conducted a Phase III clinical trial with abacavir, AZT and 3TC.

The Applicant conducted a three-way crossover study to assess the pharmacokinetic interaction between abacavir and ethanol. When administered with ethanol, abacavir C_{max} and AUC increased by 15% and 40%, respectively. Concomitant administration of abacavir did not have an effect on the ethanol AUC.

SPECIAL POPULATION:

Pediatric patients

The Applicant obtained single dose pharmacokinetic data from Study CNAA1001. HIV infected pediatric patients in the age range 3 months – 13 years received abacavir at a dose of 4 and 8 mg/kg separated by 14 days. At each dose level, the body weight normalized total clearance of abacavir was not found to be dependent on age in this study. However, at a dose of 4 mg/kg, it was noted that clearance values were 2- fold greater in pediatric patients when compared to historical data from adult patients receiving ~4 mg/kg.

The Applicant has conducted a multiple dose study in pediatric patients in collaboration with the AIDS Clinical Trials Group (ACTG 330). In general, patients received abacavir at a dose of 4 mg/kg BID for 6 weeks and at 8 mg/kg BID for another 6 weeks. Patients ranging from 3 months to 13 years were enrolled in this study. The mean steady-state AUC values were 30% lower and 50% higher at the 4 and 8 mg/kg dose levels when compared to AUC values in adults receiving a dose of 300 mg BID. The Applicant pursued a dose of 8 mg/kg for pediatric patients based on this study.

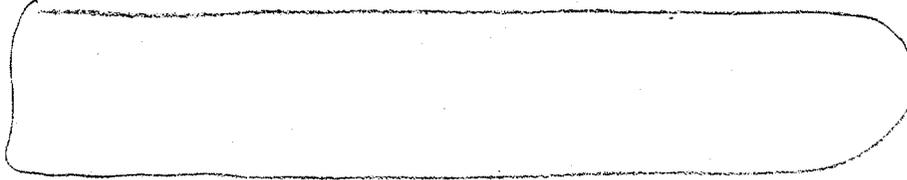
DOSE FINDING STUDIES

The Applicant conducted two dose finding studies to select an appropriate dose of abacavir for Phase III clinical trials. In Study CNAA2001, the Applicant studied abacavir at 200 mg TID, 400 mg TID, 300 mg BID and 600 mg TID, with or without zidovudine at 200 mg TID or 300 mg BID. In this 12 week study, the effect of abacavir (with or without zidovudine) on plasma HIV-RNA was examined. A clear dose-response relationship was not apparent in mean change in log(HIV-RNA) in this study. Inspection of the proportion of subjects below the limit of viral detection (400 copies/mL) in each cohort (noting that the data are derived from a small number of subjects, n = 7 to 10) indicates that:

- a) In general, combination therapy with abacavir and AZT is better when compared to monotherapy with abacavir
- b) Higher doses of abacavir with AZT were better when compared to abacavir 200 mg TID with AZT and
- c) At the same daily doses of abacavir and AZT, the BID regimen was better when compared to TID regimen.

The Applicant conducted another study, CNAB2002, to evaluate abacavir monotherapy at doses of 100 mg BID, 300 mg BID and 600 mg BID for 24 weeks. At Week 4, 300 mg BID and 600 mg BID dose levels were equally effective and superior to the 100 mg BID dose level. Based on these results, the lowest dose was abandoned. Limited Week 24 data appear to suggest no difference between the 300 mg BID (n = 8) and 600 mg BID (n = 7) dose levels. Therefore, the Applicant pursued a dose of 300 mg BID in adult patients in a principal Phase III clinical trial.

DISSOLUTION METHOD -



This dissolution method and the dissolution specification proposed by the Applicant are acceptable.

RECOMMENDATION

The human pharmacokinetic studies submitted under NDA 20977 and NDA 20978 provide an understanding of the pharmacokinetics of abacavir and fulfill the requirements of Section 320 of the Code of Federal Regulations (21 CFR). Adequate pharmacokinetic information has been provided to support approval of ZIAGEN™.

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS BRIEFING

The briefing was held on October 27, 1998 and was attended by Drs. Reynolds, Lazor, Bashaw, Ajayi, Sahajwalla, Collins, Huang, and Rajagopalan.

PHASE IV COMMITMENTS

- 1) Completion of the study (CNA1006) assessing the effect of hepatic impairment on the pharmacokinetics of abacavir.

/s/

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Division of Pharmaceutical Evaluation III, OCPB

/s/

Concurrence:

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cc: HFD-530 /NDA 20977
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/MO/Cvetkovich
/CSO/Truffa
HFD-880 /Rajagopalan
HFD-880 /TL/Reynolds
✓ HFD-880 /DPE III
✓ CDR /Barbara Murphy