# CLINICAL PHARMACOLOGY REVIEW

| | |
|---|---|
| NDA: 20-977 | REVIEWERS: Yuanchao (Derek) Zhang, Fang Li |
| TYPE: SE2 019 | TEAM LEADER: Kellie Reynolds |
| DRUG: Abacavir Scored Tablets (300 mg) | SUBMISSION DATE: 06-20-2008 |
| SPONSOR: GSK | |
| INDICATION: HIV Infection | |

## Executive Summary

The applicant is seeking approval for a scored abacavir 300 mg tablet and accompanying dosing regimens for pediatric patients. The scored tablet is identical to the unscored tablet except for the addition of the score line. Thus, all the relevant efficacy, safety and clinical pharmacology and biopharmaceutics data from the unscored tablet and oral solution can be directly applied to the scored tablet.

## Recommendations

The Office of Clinical Pharmacology (OCP) reviewed the information submitted and concluded that it is sufficient to support the proposed dosing regimens for pediatric patients weighing 14 kg or greater using the scored tablet.

The approved dose of abacavir in pediatric patients is 8 mg/kg BID using 20mg/mL solution and 300mg unscored tablets. We recommend approval of the following dosage regimens for various weight bands using 300 mg scored abacavir tablets as a new alternative for children who are able to swallow solid oral formulations.

| Weight range (kg) | Proposed Dosing of ZIAGEN Scored Tablet |
|---|---|
| 14 to 21 | Half tablet BID (150 mg BID) |
| >21 to <30 | Half tablet (150) in the morning plus full tablet (300 mg) in the evening |
| ≥30 | Full tablet BID (300 mg BID) |

For pediatric patients of body weight <14kg and who have difficulty in swallowing tablet, the recommended dose regimen is 8mg/kg BID using the oral solution.

**Summary of Clinical Pharmacology Findings**

There was no new clinical pharmacology study submitted in the application. The main clinical pharmacology objective was to evaluate the dosage regimens using 300 mg scored abacavir tablets proposed by the applicant compared to the currently approved dose (8 mg/kg BID) in the pediatric patients to avoid significant under dosing in order to minimize the risk for development of viral resistance and to avoid excessive doses that may be associated with toxicity.

The proposed dose regimens for the scored abacavir tablet in adolescent and pediatric patients are based on identification of appropriate weight bands for which administration of a scored tablet will result in a total daily abacavir dose that provide similar exposure compared to the approved 8mg/kg BID dose.

The total daily abacavir dose from the following proposed scored tablet dose regimens were compared to the total daily dose based on the currently approved weight-based regimen (8mg/kg BID): one-half tablet BID (equivalent to 300mg/day), one-half tablet in the morning and one full tablet in the evening (equivalent to 450mg/day), and one full tablet BID (equivalent to 600mg/day). Table 1 shows the percent difference in total daily abacavir dose for each potential dose regimen across the body weight band of 4 to 40kg. The highlighted areas indicate that the dose regimen meets the criteria of no more than a 40% higher dose or a 10% lower dose relative to the total daily dose for the currently approved 8 mg/kg BID regimen.

Table 1. Total Daily Dose (mg) from Currently Approved Abacavir Dose (8mg/kg BID) and % Difference Using Scored Abacavir Tablet

| Weight (kg) | Total daily dose (mg, based on 8mg/kg BID) | % difference (half tab BID, 300mg/day) | % difference (half tab [AM] and full tab [PM], 450mg/day) | % difference (full tab BID, 600mg/day) |
|---|---|---|---|---|
| 4 | 64 | 368.8 | 603.1 | 837.5 |
| 5 | 80 | 275.0 | 462.5 | 650.0 |
| 6 | 96 | 212.5 | 368.8 | 525.0 |
| 7 | 112 | 167.9 | 301.8 | 435.7 |
| 8 | 128 | 134.4 | 251.6 | 368.8 |
| 9 | 144 | 108.3 | 212.5 | 316.7 |
| 10 | 160 | 87.5 | 181.3 | 275.0 |
| 11 | 176 | 70.5 | 155.7 | 240.9 |
| 12 | 192 | 56.3 | 134.4 | 212.5 |
| 13 | 208 | 44.2 | 116.3 | 188.5 |
| 14 | 224 | 33.9 | 100.9 | 167.9 |
| 15 | 240 | 25.0 | 87.5 | 150.0 |
| 16 | 256 | 17.2 | 75.8 | 134.4 |
| 17 | 272 | 10.3 | 65.4 | 120.6 |
| 18 | 288 | 4.2 | 56.3 | 108.3 |
| 19 | 304 | -1.3 | 48.0 | 97.4 |
| 20 | 320 | -6.3 | 40.6 | 87.5 |
| 21 | 336 | -10.7 | 33.9 | 78.6 |
| 22 | 352 | -14.8 | 27.8 | 70.5 |
| 23 | 368 | -18.5 | 22.3 | 63.0 |
| 24 | 384 | -21.9 | 17.2 | 56.3 |
| 25 | 400 | -25.0 | 12.5 | 50.0 |
| 26 | 416 | -27.9 | 8.2 | 44.2 |
| 27 | 432 | -30.6 | 4.2 | 38.9 |
| 28 | 448 | -33.0 | 0.4 | 33.9 |
| 29 | 464 | -35.3 | -3.0 | 29.3 |
| 30 | 480 | -37.5 | -6.3 | 25.0 |
| 31 | 496 | -39.5 | -9.3 | 21.0 |
| 32 | 512 | -41.4 | -12.1 | 17.2 |
| 33 | 528 | -43.2 | -14.8 | 13.6 |
| 34 | 544 | -44.9 | -17.3 | 10.3 |
| 35 | 560 | -46.4 | -19.6 | 7.1 |
| 36 | 576 | -47.9 | -21.9 | 4.2 |
| 37 | 592 | -49.3 | -24.0 | 1.4 |
| 38 | 600 | -50.0 | -25.0 | 0.0 |
| 39 | 600 | -50.0 | -25.0 | 0.0 |
| 40 | 600 | -50.0 | -25.0 | 0.0 |

Table 2. Proposed Dosing Scheme of Abacavir Scored Tablet based on Weight Bands

| Weight range (kg) | Proposed Dosing of ZIAGEN Scored Tablet |
|---|---|
| 14 to 21 | Half tablet BID (150 mg BID) |
| >21 to <30 | Half tablet (150) in the morning plus full tablet (300 mg) in the evening |
| ≥30 | Full tablet BID (300 mg BID) |

For pediatric patients of body weight <14kg or who have difficulty in swallowing tablet, the recommended dose regimen is ZIAGEN solution at 8mg/kg BID.

The Applicant Analysis

The applicant also provided predicted abacavir plasma exposure data for the proposed dosing regimens using Monte Carlo simulations and re-analysis of abacavir pharmacokinetics data from three previously conducted pediatric studies (CNAA1001, ACTG 330/CNAA1013, and PENTA 13). The simulated abacavir exposure for abacavir scored tablet in pediatric patients with various weight bands were compared to those observed in adult and pediatric patients receiving currently approved abacavir dose regimens (historical controls) and reanalysis of historical pediatric pharmacokinetic data.

1. Monte Carlo simulations

Monte Carlo simulations were performed using Trial Simulator (Pharsight Corp, Mountain View, CA, Version 2.2) and a validated pediatric population PK model to predict abacavir daily AUC and Cmax values from the proposed dose regimens of scored abacavir tablets (Jullien and et. al., Abacavir pharmacokinetics in human immunodeficiency virus-infected children ranging in age from 1 month to 16 years: A population analysis. J Clin Pharmacol 2005; 45:257-264). This population PK model for abacavir is consistent with the known pharmacokinetics (distribution, metabolism and excretion) of the drug and developmental changes in children.

2. Re-analysis of abacavir pharmacokinetics data from three previously conducted pediatric studies

In addition to Monte Carlo simulations, the applicant retrieved abacavir pharmacokinetics data from three previously conducted pediatric studies (CNAA1001, ACTG 330/CNAA1013, and PENTA 13) (Studies described in Tables 3 and 4) and re-analyzed the data to estimate abacavir AUC and Cmax values from the proposed scored tablet dose regimens. Abacavir PK parameters (daily AUC and Cmax) for scored tablet were calculated by adjusting the reported individual abacavir PK parameters by the fold difference in the dose (mg) between the proposed abacavir scored tablet dose regimen and the original studied regimen assuming dose-proportional pharmacokinetics. However the assumption is not accurate in pediatric patients based on abacavir pharmacokinetic data in this population. The resulting individual PK parameters from all three studies were combined and summarized by weight band.

Table 3. Summary of Studies CNAA1001, ACTG 330 and PENTA13 used in PK Re-analysis

| Study | Age Range | Weight Range (kg) | ABC formulation/ dose/ frequency | N | PK Sampling Times |
|---|---|---|---|---|---|
| CNAA1001 | 3 months-13 years | 3.9-44.3 | Solution/ 4 and 8mg/kg/ single dose | 22 | 0, 0.5, 1, 1.5, 2, 2.5, 3, 5, and 8h |
| ACTG 330 | 0.6-12 years | 6.3-39.7 | Solution/4mg/kg/BID and Solution/8mg/kg/BID | 46 | 0, 1, 2, 3, and 5h |
| PENTA 13 | 2-12 years | 13.7-60.5 | Solution/8mg/kg/BID and Solution/16mg/kg/once daily | 14 | 0. 1, 2, 3, 4, 6,8, and 12 (BID) or 24h (once daily) |

N = number of subjects with ABC PK parameters reported

Table 4. Summary of Number of Subjects with Reportable Abacavir PK Parameters by Study and Weight Band

| | CNAA1001 | ACTG330 | PENTA-13 | All studies |
|---|---|---|---|---|
| <14kg | 13 | 11 | 2 | 26 |
| 14 to 21kg | 3 | 12 | 6 | 21 |
| >21 to <30kg | 3 | 17 | 4 | 24 |
| ≥30kg | 3 | 6 | 2 | 11 |
| Total | 22 | 46 | 14 | 82 |

***Appears This Way On Original***

The summary of predicted abacavir AUC and Cmax from Monte Carlo simulations and reanalysis of historical data are presented in Tables 5 and 6 and compared to historical control values in adults (approved dose of 300mg BID and 600mg once daily) and pediatrics (approved dose of 8mg/kg BID).

Table 5. Comparison of Predicted ABC Exposure following the Proposed Scored Abacavir Tablet Dose Regimen to Historical Data in Adult and Pediatric Patients

| Data Type | Simulation | | | Historical | |
|---|---|---|---|---|---|
| Population | Pediatric | Pediatric | Pediatric | Pediatric[1] | Adult[2] |
| Weight Range | 14 to 21kg | >21 to <30kg | ≥ 30 kg | 6.3-39.7kg | Not reported (age >13yrs) |
| Formulation/ Dose/ Frequency | Half Tab (150mg) q12h | Half Tab (150mg) AM and Full Tab (300mg) 12hrs later | Full Tab (300mg) q12h | Solution/ 8mg/kg/ q12h | Tablet/ 300mg q12h or 600mg q24h |
| **AUC(0-24), h.μg/mL, geometric mean(CV%)** | | | | | |
| Observed | NA | NA | NA | 19.6 (47%)[1,3] | 12.0 (29%)[2,3] (300mg BID), 13.3 (16)[2,4] (600mg once daily) |
| Monte Carlo simulations | 21.3 (32%) | 21.9 (33%) | 20.5 (30%) | NA | NA |
| Reanalysis of PK data | 14.2 (61%) | 19.8 (60%) | 18.9 (35%) | NA | NA |
| **Cmax, μg/mL, geometric mean (CV%)** | | | | | |
| Observed | NA | NA | NA | 3.71 (37%)[1] | 3.00 (30%)[2] (300mg BID), 4.95 (23%)[2,5] (600mg once daily) |
| Monte Carlo simulations | 3.69 (32%) | 4.53 (37%)[6] | 3.71 (31%) | NA | NA |
| Reanalysis of PK data | 3.17 (58%) | 5.29 (42%)[6] | 3.53 (43%) | NA | NA |

1. ACTG 330 [RM1998/00100/00], values are mean (CV%), n=45 .
2. CNAA2001 [GM1997/00142/00], values are mean (CV%), n=20.
3. AUC(0-24), daily AUC, was calculated based on AUC(0-12) values reported in the original reports using the following formula: AUC(0-24) = 2 X AUC(0-12).
4. Based on reported AUC(0-τ) value from 600mg TID as there is no accumulation after multiple dose due to short half-life (~1.5hr).
5. Based on reported Cmax value from 600mg TID as there is no accumulation after multiple doses due to short half-life (~1.5hr).
6. Post evening dose (one full tablet).

**Appears This Way On Original**

Table 6. Comparison of Simulated Steady State ABC Exposures Post Morning and Evening Doses following BID Dosing in Children Taking Scored Abacavir Tablets

| Study | Simulation 1 | Simulation 2 | Simulation 3 | Historical | Historical |
|---|---|---|---|---|---|
| Population | Pediatric | Pediatric | Pediatric | Pediatric[1] | Adults[2] |
| Range of weight (kg) | 14 to 21 | 21 to 30 | 30 to 40 | 6.3 to 39.7 | >40 |
| Formulation/ ABC Dose/ Frequency | Half tab/ 150mg/q12h | Half tab/ 150mg AM and full tab/ 300mg 12 h later | Full Tab/ 300mg q12h | 8mg/kg q12h | 300mg q12h |
| N | 1000 | 1000 | 1000 | 46 | 20 |
| Post Morning Dose | | | | | |
| AUCτ, h.μg/mL | | | | | |
| Geo Mean (CV%) | 10.7[3] (32) | 7.9 (33) | 10.3[3] (30) | 8.8 (NR) | 5.8 (NR) |
| Mean (CV%) | 11.2[3] (31) | 8.3 (33) | 10.7[3] (30) | 9.8 (47) | 6.0 (29) |
| Median | 10.7[3] | 8.0 | 10.3[3] | 9.0 | 5.8 |
| Post Evening Dose | | | | | |
| AUCτ, h.μg/mL | | | | | |
| Geo Mean (CV%) | 10.7[3] (32) | 13.8 (33) | 10.3[3] (30) | 8.8 (NR) | 5.8 (NR) |
| Mean (CV%) | 11.2[3] (31) | 14.5 (32) | 10.7[3] (30) | 9.8 (47) | 6.0 (29) |
| Median | 10.7[3] | 13.9 | 10.3[3] | 9.0 | 5.8 |

NR = not reported, 1. ACTG 330, 2. CNAA2001, 3. AUCτ was calculated as one-half of the AUC(0-24) values reported in Table 5.

In general, similar results were obtained from the Monte Carlo simulations and re-analyses of historical data except for the predicted AUC(0-24) value in children 14 to 21kg receiving one-half tablet BID. The prediction based on Monte Carlo simulations (average AUC is 21.3 h-μg/mL) is close to the historical pediatric control (19.6 h-μg/mL). However, the predicted average AUC(0-24) based on reanalysis of PK data is 14.2 h-μg/mL, which is 28% lower than historical pediatric control (19.6 h-μg/mL), but were similar to or above adults controls (12.0 h-μg/mL at 300mg BID and 13.3 h-μg/mL at 600mg once daily).

On average, the applicant's predicted pharmacokinetic exposure data for scored abacavir tablet based on the proposed dosing regimens for various weight bands are comparable to the historical pediatric and adult pharmacokinetic data.

FDA Analysis

To further evaluate the potential impact of unequal dosing (half tablet AM/whole tablet PM) on the safety and efficacy profiles of abacavir in children weighing >21 to <30kg, plasma abacavir exposure during each dosing interval (AUC0-12h and AUC12-24h) was re-estimated with Monte Carlo simulations using the same PK model and same Trial Simulator methods as the applicant but with the weight band increment of 1 kg. The summary of predicted plasma abacavir exposure during each dosing interval (AUC0-12h and AUC12-24h) and Cmax from Monte Carlo simulations are presented in Table 7.

Table 7. Monte Carlo Simulations of Abacavir Exposure in Pediatrics
Data presented as geometric mean (%CV)

| Dosing Regimen | Body Weight (kg) | $AUC_{ss,0-12}$ (µg.h.mL) | $AUC_{ss,12-24}$ (µg.h.mL) | $AUC_{ss,0-24}$ (µg.h.mL) | $C_{max,ss}$ (µg/mL) |
|---|---|---|---|---|---|
| Half tab/ (150 mg/q12) | 14 | 12.8 (31%) | 12.7 (31%) | 25.6 (28%) | 4.4 (27%) |
| | 15 | 12.0 (31%) | 12.0 (29%) | 24.2 (27%) | 4.2 (31%) |
| | 16 | 11.6 (34%) | 11.4 (35%) | 23.3 (32%) | 4.1 (29%) |
| | 17 | 10.6 (37%) | 10.6 (35%) | 21.4(32%) | 3.7 (29%) |
| | 18 | 10.3 (31%) | 10.3 (31%) | 20.8 (28%) | 3.7 (28%) |
| | 19 | 9.4 (28%) | 9.3 (30%) | 18.9 (24%) | 3.4 (29%) |
| | 20 | 9.2 (32%) | 9.1 (32%) | 18.5 (28%) | 3.3 (31%) |
| | 14-21 | 10.7 (34%) | 10.7 (34%) | 21.6 (31%) | 3.8 (32%) |
| Half tab/ 150 mg AM and full tab/ 300mg 12h later | 21 | 8.7 (27%) | 15.5 (33%) | 24.4 (28%) | 5.5 (42%) |
| | 22 | 8.8 (33%) | 15.6 (31%) | 24.5 (29%) | 5.1 (36%) |
| | 23 | 8.7 (30%) | 15.4 (30%) | 24.1 (28%) | 4.6 (37%) |
| | 24 | 8.1(34%) | 14.2 (35%) | 22.5 (31%) | 4.5 (38%) |
| | 25 | 8.0 (30%) | 13.5 (33%) | 21.7 (30%) | 4.6 (35%) |
| | 26 | 7.7 (33%) | 12.9 (36%) | 20.8 (32%) | 4.2 (37%) |
| | 27 | 7.5 (31%) | 12.7(31%) | 20.4 (28%) | 4.2 (32%) |
| | 28 | 7.1 (29%) | 12.1 (33%) | 19.3 (29%) | 4.1(37%) |
| | 29 | 6.8 (31%) | 12.0 (30%) | 19.0 (27%) | 4.1(32%) |
| | 21-30 | 7.9 (32%) | 13.7 (34%) | 21.7 (31%) | 4.5 (37%) |
| Full tab/ 300mg q12h | 30 | 12.0 (31%) | 12.1 (30%) | 24.3(27%) | 4.1(30%) |
| | 31 | 11.0 (32%) | 10.8 (33%) | 22.0 (29%) | 4.0 (30%) |
| | 32 | 11.2(27%) | 10.9 (25%) | 22.2(23%) | 4.0 (25%) |
| | 33 | 10.8 (33%) | 10.7 (29%) | 21.7(28%) | 3.9 (31%) |
| | 34 | 10.2 (34%) | 10.4 (35%) | 20.9 (31%) | 3.8 (30%) |
| | 35 | 10.3 (31%) | 10.6 (31%) | 21.1 (28%) | 3.8 (31%) |
| | 36 | 10.0 (30%) | 9.6 (30%) | 19.7 (26%) | 3.6 (27%) |
| | 37 | 9.1 (35%) | 9.0 (37%) | 18.3 (32%) | 3.4 (34%) |
| | 38 | 8.9 (38%) | 9.0 (33%) | 18.1 (33%) | 3.3 (25%) |
| | 39 | 9.1(34%) | 9.2 (31%) | 18.5 (29%) | 3.4 (30%) |
| | 30-40 | 10.2 (34%) | 10.2 (33%) | 20.6 (30%) | 3.7 (30%) |
| Pediatrics (8mg/kg b.i.d.) (Study ACTG 330) | | | | Mean (%CV) 19.6 (47) | Mean (%CV) 3.7 (37) |
| Pediatrics (16 mg/kg q.d.) (Study PENTA 13) | | | | GM (90%CI) 13.4 (11.8-15.1) | GM (90%CI) 4.8 (4.0-5.7) |
| Adults 600 mg t.i.d (Study CNAA2001) | | | | Mean (%CV) 40.0 (25) | Mean (%CV) 7.0 (42) |

In particular, we looked at the following two scenarios:

1. At the higher end of the (21 – 30 kg) weight band, the predicted lowest mean $AUC_{0-12h}$ following administration of the half tablet in the morning was 7.0 h-μg/mL, about 30% lower than that of historical pediatric control ($AUC_{0-12h}$: 9.8 h-μg/mL at 8 mg/kg), but was slightly higher than the adults controls ($AUC_{0-12h}$: 6.0 h-μg/mL at 300mg BID). The $AUC_{0-24h}$ at 600 mg once daily in adults is 13.3 h-μg/mL. Because the half-life of abacavir is about 1-1.5 hours, in the 600 mg once daily dosing, the $AUC_{12-24h}$ should be much less than 50% of the $AUC_{0-24h}$, i.e., the $AUC_{12-24h}$ value is much less than 6.7 h-μg/mL. Based on the similar efficacy observed in once daily and twice daily dosing in adults, the worst case scenario of 30% lower mean $AUC_{0-12h}$ receiving half tablet in the morning (7.0 h-μg/mL) is not expected to reduce efficacy.
   The approved dose regimens for adults are 300 mg BID and 600 mg QD. The approved pediatric dose regimen (8 mg/kg) has higher plasma exposure than those of adult dose regimens.

2. At the lower end of the (21 – 30 kg) weight band, the predicted highest mean $AUC_{12-24h}$ following administration of the full tablet in the afternoon was 15.5 h-μg/mL, about 50% higher than that of historical pediatric control ($AUC_{12-24h}$: 9.8 h-μg/mL at 8 mg/kg), but was much lower than the adults controls ($AUC_{0-24h}$: 40.0 h-μg/mL at 600 mg TID, Study CNAA2001 (N= )). Based on the acceptable safety profile observed in adults receiving 600 mg TID dosing, the worst case scenario of 50% higher mean $AUC_{12-24h}$ receiving full tablet in the afternoon (15.5 h-μg/mL) is not expected to cause unacceptable safety issues.

Overall, the proposed dosage regimens for various weight bands (>14 kg < 40 kg) using 300 mg scored abacavir tablets are acceptable.

Please refer to Medical Officer, Dr. Yodit Belew's review for safety and efficacy assessment.

Yuanchao (Derek) Zhang, Ph.D.
Clinical Pharmacology Reviewer, DCP IV
Office of Clinical Pharmacology

Fang Li, Ph.D.
Pharmacometrics
Office of Clinical Pharmacology

Concurrence:

Kellie S. Reynolds, Pharm. D.
Clinical Pharmacology Team Leader, DCP IV
Office of Clinical Pharmacology

---

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

---

/s/
---
Derek Zhang
12/1/2008 10:47:30 AM
BIOPHARMACEUTICS

Kellie Reynolds
12/2/2008 02:09:29 PM
BIOPHARMACEUTICS