OFFICE OF CLINICAL PHARMACOLOGY REVIEW

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| **NDA** | 19-910 SE5 035 |
| **Submission Date** | May 7, 2009 |
| **Brand Name** | RETROVIR® |
| **Generic Name** | Zidovudine |
| **OCP Division** | Division of Clinical Pharmacology 4 |
| **OND Division** | Division of Antiviral Products (DAVP) |
| **Sponsor** | GlaxoSmithKline |
| **Formulation; Strength** | Syrup; 50 mg/5 ml |
| **Indication** | Treatment of HIV-1 infection |
| **Current Pediatric Dosing Regimen** | For pediatric patients 6 weeks to 18 years of age, the doses are calculated according to the following weight bands:<br>4 kg to ≤9 kg: 12 mg/kg BID or 8 mg/kg TID<br>≥9 kg to <30 kg: 9 mg/kg BID or 6 mg/kg TID<br>≥30 kg: 300 mg BID or 200 mg TID<br>Alternatively:<br>For pediatric patients 6 weeks to 18 years of age: 480 mg/m$^2$/day in divided doses (240 mg/m$^2$ twice daily or 160 mg/m$^2$ three times daily) |
| **Reviewers** | Kevin M. Krudys, Ph.D.<br>Shirley K. Lu, Ph.D. |
| **Pharmacometrics Team Leader** | Pravin Jadhav, Ph.D. |
| **Clinical Pharmacology Team Leader** | Kellie S. Reynolds, Pharm. D. |

# 1 EXECUTIVE SUMMARY

Zidovudine (Retrovir®) is a nucleoside analogue reverse transcriptase inhibitor indicated for the treatment of HIV-1 infection in combination with other antiretroviral agents and for the prevention of maternal-fetal HIV-1 transmission. The current approved dosage regimens for the treatment of HIV-1 infection in pediatric patients (6 weeks to <18 years of age) are based on both body surface area (BSA) and body weight. The sponsor is seeking to expand the dosing regimens to include pediatric patients 4 weeks of age and older and weighing ≥4 kg.

The sponsor has not conducted any new clinical trials in support of this supplement. The scientific rationale for the change in recommended dosing comes from historical pediatric data, simulations and literature evidence. To obtain regulatory approval the data need to provide evidence that the expected zidovudine pharmacokinetic exposure in pediatric patients between 4 and 6 weeks of age will provide similar efficacy and safety as the currently approved dose.

## 1.1 Recommendations

The Office of Clinical Pharmacology reviewed the information submitted in this supplement and agrees that it supports the proposed dose of zidovudine (24 mg/kg/day or 480 mg/m$^2$/day) in pediatric patients between 4 and 6 weeks of age and weighing 4 to < 9 kg.

## 1.2 Phase 4 Commitments

None.

## 1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

Zidovudine is approved in pediatric patients 6 weeks to <18 years of age for the treatment of HIV-1 infection in combination with other antiretroviral agents according to the following dosing table:

| Body Weight (kg) | Total Daily Dose | Dosage Regimen and Dose | |
|---|---|---|---|
| | | b.i.d. | t.i.d. |
| 4 to <9 | 24 mg/kg/day | 12 mg/kg | 8 mg/kg |
| ≥9 to <30 | 18 mg/kg/day | 9 mg/kg | 6 mg/kg |
| ≥30 | 600 mg/day | 300 mg | 200 mg |

Alternatively, dosing for RETROVIR can be based on body surface area (BSA). The recommended oral dose of RETROVIR is 480 mg/m$^2$/day in divided doses (240 mg/m$^2$ twice daily or 160 mg/m$^2$ three times daily).

The sponsor is seeking to expand the dosing regimens to include pediatric patients 4 weeks of age and older and weighing ≥4 kg. In support of the application, the sponsor submitted published zidovudine pharmacokinetic data from four studies in a total of 82 pediatric patients ranging from one day to three months of age. The relationship between age and zidovudine clearance was modeled in order to predict zidovudine pharmacokinetics in the 4- to 6-week age range.

The daily zidovudine AUCs from the proposed 24 mg/kg/day dose in 4-week and 5-week old pediatric patients are predicted to be 16% and 7% higher, respectively, than in 6-week old patients. Safety data at these higher exposure levels are available from the 720 mg/m$^2$/day dose given in PACTG152 to pediatric patients from 3 months to 18 years of age. The equivalent weight-based dose of 720 mg/m$^2$/day for an average 4-week old male infant weighing 4 kg (BSA=0.233 m$^2$) is approximately 42 mg/kg/day. The 24 mg/kg/day dose in pediatric patients between 4- and 6-weeks of age is therefore expected to provide zidovudine exposures that will maintain efficacy without unanticipated safety concerns.

## 2 QUESTION BASED REVIEW

### 2.1 Regulatory background of the drug

Twice daily, body weight-based dosing of RETROVIR syrup, capsules and tablets in pediatric patients 6 weeks to <18 years of age for the treatment of HIV-1 infection in combination with other antiretroviral agents was approved on September 19, 2008. The Division of Antiviral Products requested an additional analysis to "assess zidovudine pharmacokinetic data in neonates and use pharmacokinetic modeling and simulation to propose dosing recommendations for HIV-1 infected children between 1 month and <6 weeks of age."

#### 2.1.1 What are the proposed dosage(s) and route(s) of administration?

The proposed dose of zidovudine for treatment of children ages 4 weeks and above and weighing 4 to <9 kg is 12 mg/kg administered orally twice daily or 8 mg/kg administered three times daily. Alternatively, 480 mg/m$^2$/day can be given in either two or three divided doses.

### 2.2 General clinical pharmacology

#### 2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

No new clinical studies were conducted in support of this supplement. Observed and simulated pharmacokinetic data from four studies in full-term infants aged 1 day to 3 months were used to support the proposed dosage (Table 1).

**Table 1: Summary of Published Zidovudine Pharmacokinetic Studies in Full Term Infants Aged 1 Day to 3 Months**

| Study | Age Range | ZDV Dosage Regimen | PK Sampling Strategy | ZDV PK Parameters Available |
|---|---|---|---|---|
| [Boucher, 1993] (PACTG049) | 1 day to 3 months (1 to 99 days)<br><br>N=32 | Group 1 (n=7):<br>2mg/kg IV infusion x 1h Days 1 & 14<br>2mg/kg PO single dose Days 2 & 15<br>2mg/kg PO q6h Days 16-46<br>Group 2 (n=25):<br>4mg/kg IV infusion x 1h Days 1 & 46<br>2-4mg/kg PO single dose Days 2 & 45<br>2-4mg/kg PO q6h Days 3-44 | Group 1: Days 1, 2, 14, 15<br>Group 2: Days 1, 2, 45, 46<br><br>IV: Pre, 1h, 2, 3, 4.5, 6, 8h<br>PO: Pre, 0.5, 1, 2, 3, 4.5, 6, 8h | Individual subject dose-normalized AUC(0-∞) presented by dose in Figure 2.<br><br>Mean ±SD Cmax, F, CL, t1/2 by dose or age group (≤ or >14days) |
| [Moodley, 1998] (NUCB2018) | 7 days<br><br>N=10 | 2mg/kg PO q6h x 7days<br>(in combination with 3TC 4mg/kg q12h x 7 days; Treatment B) | Day 7: Pre, 1, 3, 8, 12, 24h | Individual subject AUC(0-τ), Cmax and CL/F (Table 9 RM1997/00637/00)<br><br>Geometric mean (95% CI) AUC(0-τ), Cmax, CL/F, t1/2 |
| [Moodley, 2001] (ZDVB1003) | 7 days<br><br>N=16 | 4mg/kg PO q 12h x 7 days<br>(in combination with 3TC 2mg/kg PO q12h x 7 days | Day 1: Pre, 0.5, 1, 3, 8, 24h<br>Day 7: Pre, 0.5, 1, 3, 8, 24h | Individual subject AUC(0-τ), Cmax, CL/F & T1/2 (Listing 5 RM1999/00018/00)<br><br>Geometric mean (95% CI) AUC(0-τ), Cmax, CL/F, t1/2 |
| [Thaithumyanon, 1999] (COL10015) | 1 & 6 weeks<br><br>N=14 | 4mg/kg PO BID from birth to six weeks<br>(in combination with 3TC 2mg/kg BID) | Day 7: Pre, 1, 3, 8, 12h<br>Week 6 Pre, 1, 3, 8, 12, 24h | Geometric mean (95% CI)AUC(0-τ) and Cmax on Day 7 and Week 6 |

Source: Module 2.5 Clinical Overview, Table 2, Page 8.

Study PACTG049 was a phase 1 evaluation of zidovudine pharmacokinetics in infants and neonates given zidovudine IV and oral solution formulations (doses shown above in Table 1) as prophylaxis. The infants and neonates were between 1 day and 3 months (born at >34 weeks of gestational age) and were born to women with proven HIV infection. A total of 38 normalized oral zidovudine AUC values from 25 patients were extracted from Figure 2 in Boucher et al., 1993. Steady state AUC(0-τ) was assumed to be equal to AUC(0-∞) and CL/F was assumed to be the same under single and multiple dose conditions.

Study NUCB2018 was a phase 2 evaluation comparing lamivudine alone to lamivudine in combination with zidovudine in pregnant women infected with HIV-1 and their full-term neonates. Ten neonates were given lamivudine (4 mg/kg twice daily) in combination with zidovudine (2 mg/kg 4 times daily) as oral solution formulations. Individual AUC(0-τ), Cmax and CL/F values were available from the clinical study report.

Study ZDVB1003 was conducted to determine the pharmacokinetics of zidovudine and lamivudine coadministered orally every 12 hours in neonates whose mothers were infected with HIV-1. A total of 16 full-term neonates (median weight 3.2 kg) received 4 mg/kg zidovudine syrup and 2 mg/kg lamivudine solution every 12 hours for 1 week. Individual AUC(0- τ), Cmax and Cl/F values were available from the clinical study report.

Study COL10015 was a phase 1 evaluation of oral lamivudine (2 mg/kg twice daily) and oral zidovudine (4 mg/kg twice daily) in neonates over 6 weeks. Only mean pharmacokinetic parameters (n=14) are available at day 7 and week 6.

The reviewer also included data from Study PACTG152, an efficacy study comparing zidovudine, didanosine (ddI) and zidovudine+ddI in symptomatic HIV-infected infants and children aged 3 months to 18 years. Oral zidovudine alone was administered at 180

mg/m$^2$ every 6 hours and 120 mg/m$^2$ every 6 hours in combination with ddI. A total of 394 subjects had sparse plasma concentration data available for population pharmacokinetic analysis.

Within this set of studies, the sponsor identified individual zidovudine pharmacokinetic parameters from 5 patients in the relevant age range (3.9 to 6.6 weeks old) from Study PACTG049 and summary data from 15 patients at 6 weeks of age from Study COL10015 (Table 2). The pharmacokinetics of zidoviudine are dose-independent at oral dosing regimens between 2 mg/kg q8h and 10 mg/kg q4h. Thus it is reasonable to predict exposures in pediatric subjects from the lower dose data in infants.

The analysis of data from these studies is described in the pharmacometric review.

**Table 2: Oral Zidovudine Pharmacokinetic Parameters in Patients Aged 3.9 to 6.6 Weeks**

| Study | Dose (mg/kg) | Age (days) | CL/F (mL/min/kg) | Dose-Normalized[3] AUC(0-∞) or AUC(0-τ) (µg.h/mL) |
|---|---|---|---|---|
| [Boucher, 1993][1] | 3 | 27 | 28.5 | 0.59 |
| | 2 | 28 | 20.1 | 0.83 |
| | 2 | 29 | 30.9 | 0.54 |
| | 2 | 42 | 43.9 | 0.38 |
| | 4 | 46 | 25.3 | 0.66 |
| [Thaithumyanon, 1999][2] | 8 | 42 | 27.6 (17.5-34.6) | 0.61 (0.48-0.95) |

1. Individual patient values provided
2. Values represent geometric mean and 95% confidence intervals of N=15 patients at Week 6
3. AUC values normalized to a dose of 1mg/kg

Source: Module 2.5 Clinical Overview, Table 3, Page 9.

## 3 DETAILED LABELING RECOMMENDATIONS

The label is to be amended once in the HIGHLIGHTS OF PRESCRIBING INFORMATION section and twice in the DOSAGE AND ADMINISTRATION section to reflect the change in the lower age limit from 6 weeks to 4 weeks.

## 4 PHARMACOMETRIC REVIEW

### 4.1 Summary of Findings

#### 4.1.1 Key Review Question

The purpose of this review is to address the following key question

##### 4.1.1.1 Is the proposed zidovudine dose of 24 mg/kg/day (or 480 mg/m$^2$/day) acceptable in pediatric patients 4 weeks of age or older and weighing ≥4 kg?

Yes, the daily zidovudine AUC from the proposed dose in 4-week and 5-week old pediatric patients is predicted to be 16% and 7% higher, respectively, than in 6-week old patients (Table 3). Safety data at these exposure levels are available from the 720 mg/m$^2$/day dose given in PACTG152. The equivalent weight-based dose of 720 mg/m$^2$/day for an average 4-week old male infant weighing 4 kg (BSA=0.233 m$^2$) is

approximately 42 mg/kg/day. Thus, the 24 mg/kg/day dose in pediatric patients between 4- and 6-weeks of age is not expected to provide zidovudine exposures that would result in unexpected safety concerns.

**Table 3: Predicted CL/F and Daily Zidovudine AUC Assuming 24 mg/kg/day Dose***

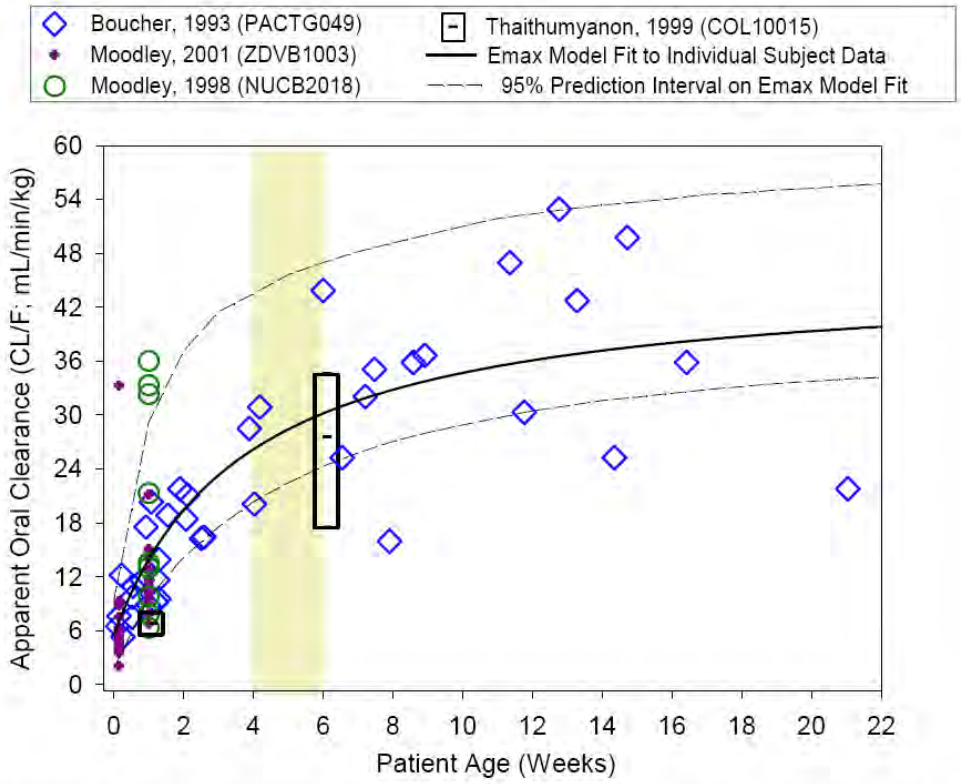
| Age | CL/F (ml/min/kg) [5th – 95th percentile] | Daily Zidovudine AUC (h.µg/ml) (24 mg/kg/day) [5th – 95th percentile] |
|---|---|---|
| 4 weeks | 29.4 [17.7 – 48.9] | 13.6 [8.2 – 22.6] |
| 5 weeks | 32.0 [19.2 – 52.0] | 12.5 [7.7 – 20.8] |
| 6 weeks | 34.2 [21.2 – 56.1] | 11.7 [7.1 – 18.8] |

*Reviewer-generated values

### 4.2 Results of Sponsor's Analysis

The sponsor used an $E_{max}$ model to describe the relationship between body weight adjusted CL/F and age within a narrow age range for patients in the pharmacokinetic database, where $E_0$ is the estimated baseline body weight adjusted CL/F (mL/min/kg) at birth, $EC_{50}$ is the age at which body weight adjusted CL/F is at 50% of its maximum value and $E_{max}$ is maximum body weight adjusted CL/F. A plot of body weight adjusted CL/F vs. age is shown in Figure 1 and parameter estimates are presented in Table 4. The model parameter estimates and associated standard errors were used to simulate confidence intervals around the model fit and to predict body weight adjusted CL/F for 4-, 5- and 6-week old pediatric patients (Table 5). Median body weight adjusted CL/F in 4- and 5-week old patients were predicted to be 13% and 6% lower, respectively, than in 6-week old patients.

**Figure 1: Relationship between Zidovudine CL/F and Age**




Individual subject CL/F as calculated from AUC(0-∞) values shown for [Boucher, 1993] study. Individual subject CL/F shown for [Moodley, 1998] and [Moodley, 2001] studies. Boxes indicate geometric mean CL/F and 95% CI as calculated by AUC(0-τ) data presented by [Thaithumyanon, 1999].

Solid black line indicates fit of Emax model through individual subject CL/F versus Age data [Boucher, 1993; Moodley, 1998; Moodley, 2001]. Dashed line indicates 95% confidence interval on the model fit.

Shaded rectangle indicates 4 to 6 week age range of interest.

Source: Module 2.5 Clinical Overview Figure 3, Page 12.

**Table 4: $E_{max}$ Model Parameter Estimates**

| Parameter | Estimate | Standard Error (SE) | CV% |
|---|---|---|---|
| Emax | 45.733738 | 5.334996 | 11.67 |
| EC50 | 3.786437 | 1.561586 | 41.24 |
| E0 | 5.520398 | 2.020120 | 36.59 |

Source: Module 2.5 Clinical Overview, Table 4, Page 9.

**Table 5: Predicted CL/F (mL/min/kg) by Age**

| Age | Mean | Median | SD | CV% | Percentile | | |
|---|---|---|---|---|---|---|---|
| | | | | | 25% | 50% | 75% |
| 4 week | 30.39 | 29.19 | 7.69 | 25% | 26.0 | 29.2 | 33.9 |
| 5 week | 32.74 | 31.70 | 6.77 | 21% | 28.5 | 31.7 | 36.3 |
| 6 week | 34.62 | 33.75 | 6.42 | 19% | 30.4 | 33.8 | 38.3 |

Source: Module 2.5 Clinical Overview, Table 5, Page 12.

*Reviewer's Comments: The sponsor's approach provides a reasonable account of zidovudine pharmacokinetics in pediatric patients between 4 and 6 weeks of age. Ideally, individual data, including zidovudine concentrations, body weight and age would have been used to develop a population pharmacokinetic model to determine the influence of maturation of clearance in the pediatric population. Given the limitations in the data, there are a few qualities of the model that require further inspection to ensure the conclusions drawn from it are robust, namely:*

- *From the sponsor's database, it is not evident that the maximum body weight adjusted CL/F has been reached. There are only 8 data points above 10 weeks of age, where $E_{max}$ is expected to be achieved.*
- *There appears to be a discrepancy between the best fit line in Figure 1 and the predictions from the parameters in Table 4. For example, using the model parameters, CL/F at 6 weeks is predicted to be 33.5 ml/min/kg. Inspection of the model fit line in Figure 1 suggests a value of 30 ml/min/kg. Based on the reviewer's analysis, it appears the best fit line in Figure 1is not an accurate representation of the modeling results.*
- *$EC_{50}$ is poorly estimated. This may be due to the lack of observations between 2 and 6 weeks. Also, $EC_{50}$ may be strongly correlated with $E_{max}$. Given the relative lack of data, it may not be possible to estimate both parameters with high degrees of precision.*
- *The confidence interval around the model fit provides a measure of parameter uncertainty, but does not necessarily reflect the between-subject variability expected in the population. Between-subject variability in clearance has been previously established to be ~30% in a pediatric population and should be considered in simulation analyses.*

### 4.3 Reviewer's Analysis

An independent analysis was conducted to:

1. Further explore the relationship between zidovudine pharmacokinetics and age to test the robustness of the sponsor's analysis to reliably predict zidovudine clearance between 4 and 6 weeks of age.
2. Determine the need for and the feasibility of dosing recommendations for pediatric patients ≥ 4 weeks of age but weighing less than 4 kg

### 4.3.1 Methods

#### 4.3.1.1 Data Sets

Data sets used are summarized in Table 6. The zidovudine pharmacokinetic data submitted by the sponsor was supplemented with population pharmacokinetic data (n=394) from PACTG152, an efficacy study in symptomatic HIV-infected infants and children aged 3 months to 18 years.

**Table 6: Analysis Data Sets**

| File Name | Description | Location in \\cdsnas\pharmacometrics\ |
|---|---|---|
| 2.fit | Zidovudine posthoc parameter estimates from PACTG152 | \\cdsnas\pharmacometrics\Retrovir_NDA19910SE5035_KK\PPK Analyses\Shared Analysis Data\2.fit |
| data.csv | Zidovudine pharmacokinetic parameters provided by the sponsor | \\cdsnas\pharmacometrics\Retrovir_NDA19910SE5035_KK\Sponsor Data and Reports\data.csv |

#### 4.3.1.2 Software

Nonlinear least squares regression, simulation and plotting were all performed using R.

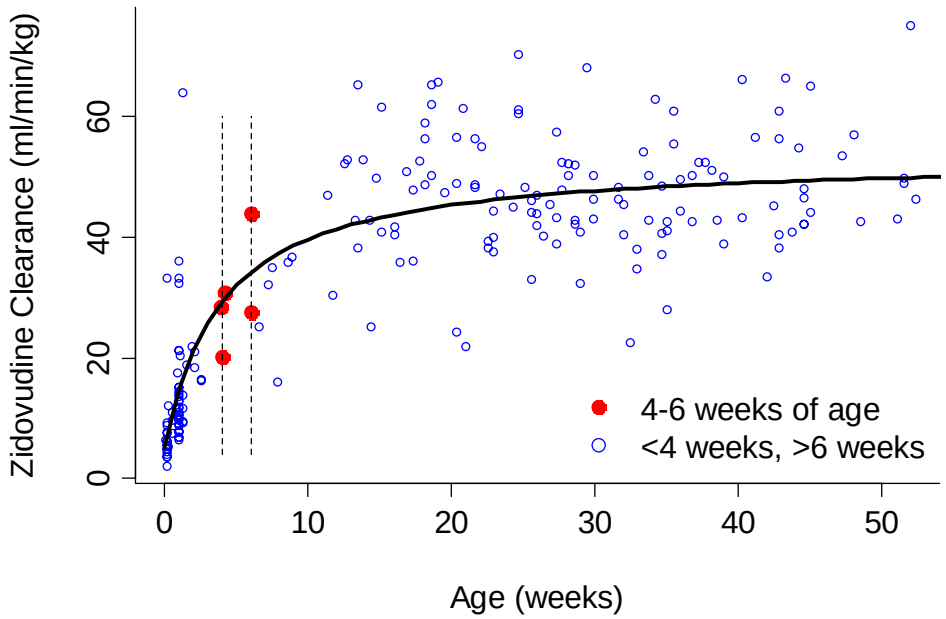
#### 4.3.1.3 Relationship between Zidovudine Pharmacokinetics and Age

Data from 119 subjects less than one year of age from PACTG152 were combined with the 82 data points from the sponsor's database. Only subjects younger than one year of age were included in the analysis because metabolic pathways are believed to mature over the first year of life. The same $E_{max}$ model used by the sponsor was applied to the augmented database. A comparison of the sponsor's and reviewer's parameter estimates is presented in Table 7. The reviewer's model parameter estimates were very similar to the sponsor's. As expected, the precision of $E_{max}$ was improved, as was that of $EC_{50}$. The precision of the $E_0$ parameter worsened. The plot of the data with the model fit is shown in Figure 2 and clearly shows the maximum body weight adjusted CL/F being reached at an age of approximately 20 weeks.

**Table 7: Comparison of sponsor's and reviewer's $E_{max}$ model parameters**

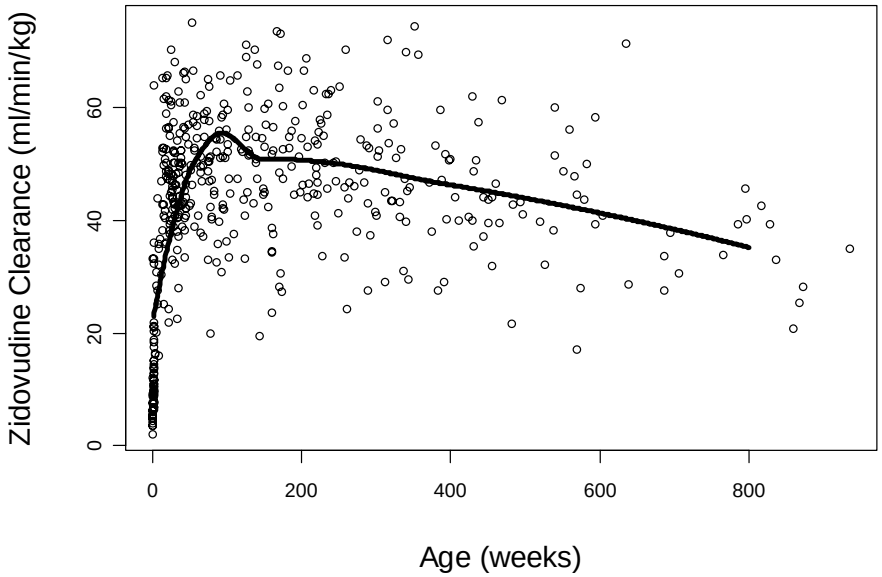
| | Sponsor's model | | | Reviewer's model | | |
|---|---|---|---|---|---|---|
| **Parameter** | **Estimate** | **Standard Error** | **%CV** | **Estimate** | **Standard Error** | **%CV** |
| Emax | 45.7 | 5.33 | 11.7% | 48.3 | 2.06 | 4.27% |
| $EC_{50}$ | 3.79 | 1.56 | 41.2% | 3.94 | 1.05 | 26.7% |
| $E_0$ | 5.52 | 2.02 | 36.6% | 5.00 | 2.25 | 45.0% |

**Figure 2: Relationship between Zidovudine CL/F and Age (Reviewer).** The solid line represents the model fit to the data. The vertical dashed lines demarcate 4 to 6 weeks of age.




For completeness, all 394 body weight adjusted CL/F estimates from PACTG152 were combined with the sponsor's dataset to produce Figure 3. The data show an increase in body weight adjusted clearance over the first year of life followed by a decrease with age to reach adult levels in adolescence. This pattern is expected when clearance is expressed per kilogram.

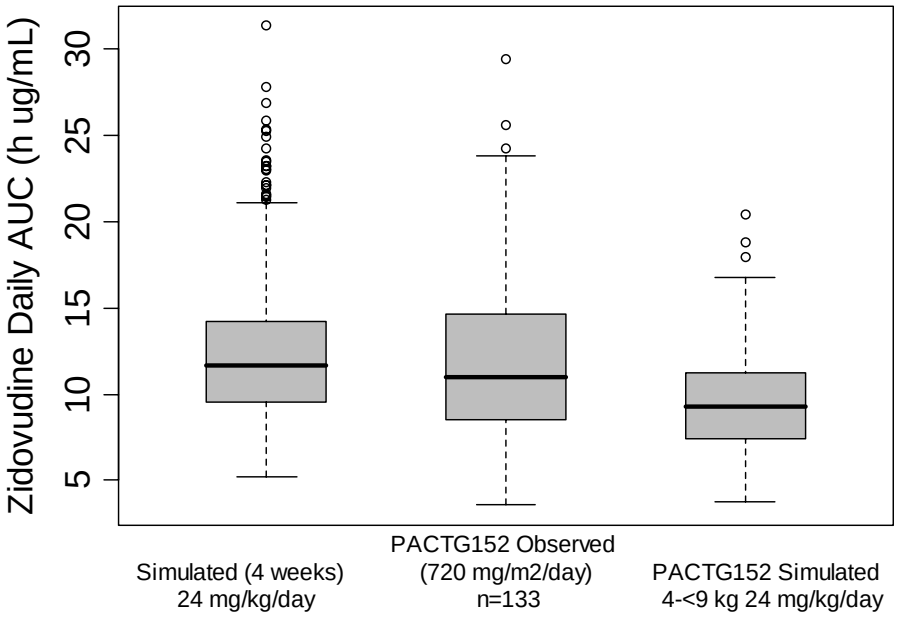
**Figure 3 Relationship between Zidovudine CL/F and Age (0 – 18 years).** The bold line represents a LOESS fit to the data.




The modeling results were used to predict CL/F and daily zidovudine AUC values in 4-, 5- and 6-week old patients receiving the proposed 24 mg/kg/day dose. One thousand new subjects were simulated based on the model predicted value of CL/F at 4, 5 and 6 weeks of age. Between-subject variability in clearance was assumed to be 30%, as estimated from a previous population pharmacokinetic analysis (see Dr. Pravin Jadhav's review for NDA19-910 SE2 033). The results are presented in Table 3 and predict a 16% and 7% increase in daily zidovudine AUC in patients 4-weeks and 5-weeks of age, respectively, compared to patients 6-weeks of age. These results are in excellent agreement with those generated from sponsor's approach (Table 5) and therefore provide a greater degree of confidence in their predictions.

Safety data are available from the 720 mg/m$^2$/day dose given in PACTG152, which provides higher exposures than that of the approved dose (480 mg/m$^2$/day). The simulated daily zidovudine AUCs from a 24 mg/kg/day dose in 4-week old patients are comparable to the observed daily zidovudine AUC from all patients (mean body weight: 15.5 kg) receiving the 720 mg/m$^2$/day dose in PACTG152 (Figure 4). For further context, the rightmost box in Figure 4 shows the slightly lower daily zidovudine AUCs expected if those subjects weighing between 4 and 9 kg from PACTG152 had received the 24 mg/kg/day dose.

**Figure 4: Comparison of Predicted Daily Zidovudine AUC (24 mg/kg/day) to Observations from PACTG152 (720 mg/m$^2$/day)**




#### 4.3.1.4 Dosing recommendations for pediatric patients ≥ 4 weeks of age but weighing < 4 kg

The reviewer investigated the possibility of removing the 4 kg lower weight limit because the expected percentage of pediatric patients older than 4 weeks of age but weighing less than 4 kg was significant (Table 8). The proportion may be even larger in HIV-infected patients since they are not healthy infants. However, there is no existing pharmacokinetic data in pediatric patients older than 4 weeks of age and weighing less than 4 kg. Given the limitations in the existing database and the inability of the pharmacokinetic model to incorporate weight independently of age effects, zidovudine exposures could not reliably be extrapolated for lower weights. Therefore, dosing will not be extended to patients weighing less than 4 kg. To overcome these limitations, a model of clearance incorporating age and weight independently could be developed to predict zidovudine clearance at these margins. Alternatively, pharmacokinetic data from infants older than 4 weeks of age but weighing less than 4 kg could be collected. It should be noted, however, that under an allometric scaling model of clearance, to maintain a given level of exposure as weight decreases, a higher per mg dose is required. A total daily dose of 24 mg/kg/day would therefore not be expected to give rise to unsafe zidovudine exposures in pediatric patients older than 4 weeks of age but weighing less than 4 kg.

**Table 8: Percentage of Pediatric Patients Expected to Weigh Less than 4 kg by Age**

| Age | Percentage of Boys < 4 kg | Percentage of Girls < 4 kg |
|---|---|---|
| 4 weeks | 24% | 38% |
| 5 weeks | 16% | 27% |
| 6 weeks | 10% | 18% |
| 8 weeks | 3% | 8% |

Source: CDC Growth Charts

## 4.4 Listing of Analyses Codes and Output Files

| File Name | Description | Location in \\cdsnas\pharmacometrics\ |
|---|---|---|
| make.clvsage.R | Reviewer's Emax model | \\cdsnas\pharmacometrics\Retrovir_NDA19910SE5035_KK\PPK Analyses\CLvsAge |
| make.comparison.R | Reviewer's calculation of zidovudine exposure and comparison to PACTG152 | \\cdsnas\pharmacometrics\Retrovir_NDA19910SE5035_KK\PPK Analyses\ExposureComparison |

| Application Type/Number | Submission Type/Number | Submitter Name | Product Name |
|---|---|---|---|
| NDA-19655 | PMR/PMC-1 | GLAXOSMITHKLINE | RETROVIR (ZIDOVUDINE) CAPSULES |
| NDA-19910 | PMR/PMC-1 | GLAXOSMITHKLINE | RETROVIR SYRUP |
| NDA-20518 | PMR/PMC-1 | GLAXOSMITHKLINE | RETROVIR (ZIDOVUDINE) TABS 200MG/300MG |

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