Medical Officer Review of Supplemental Labeling Revisions (Prior approval) for
NDA 19-910/S-033 (SE2)
NDA 19-655/S-046 (SE2)
NDA 20-518/S-016 (SE2)

Sponsor:	GlaxoSmithKline
Product:	Retrovir® (Zidovudine, ZDV) Syrup 10 mg/kg
Date Submitted:	March 21, 2008
Date Received:	April 15, 2008
Date Review Completed:	September 17, 2008
Due Date:	September 18, 2008
Medical Officer:	Regina Alivisatos, MD
Medical Team Leader:	Kimberly Struble, PharmD
Project Manager:	Jaewon Hong, Project Manager
Subject:	Changes to Pediatric Doing Recommendations (Dosing and Administration section) and PLR formatting. No changes to adult recommendations.
Indication:	Treatment of HIV Infections
Dosage Regimen:	Please see label.
Cross Referenced NDAs:	• NDA 19-655/S-002 RETROVIR (zidovudine) Capsules • NDA 20-518/S-002 RETROVIR (zidovudine) Tablets
Materials Reviewed:	Electronic NDA 19910/S-033 SE2 submissions dated 03/21/08, 08/01/08 (pediatric waiver), 08/01/08, 9/11/08 (revised proposed labeling), 9/17 cross-references prior approval (PA) efficacy submissions for NDAs 19-655 and 20-518.

Review and Comments:

The product labeling (PL) submitted March 21, 2008 with S-033 and on September 17, 2008 for the cross referenced supplements was compared to that approved on November 20, 2006 by the PM (See PM Review).

A summary of labeling changes proposed by the Applicant are provided below in <u>double underline</u> font:

In this supplemental NDA application the Applicant seeks approval for the following changes to the DOSAGE and ADMINISTRATION section of the approved label:

Adults **(b) (4)**   The recommended oral dose of RETROVIR is 600 mg/day in divided doses in combination with other antiretroviral agents.
Pediatric Patients: The recommended dos<u>age in pediatric patients 6 weeks of age weighing ≥4 kg is provided in Table 1</u>. **(b) (4)**

(b) (4)   RETROVIR Syrup should be used to provide accurate dosage when whole tablets or capsules are not appropriate.

Table 1: Recommended Pediatric Dosage of RETROVIR

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

In addition the Retrovir® label for all US approved formulations was converted to PLR format and multiple changes were made throughout that were addressed in the labeling review section.

Introduction:

Despite the development of multiple antiretroviral drugs over the last decade and the use of highly active antiretroviral regimens (HAART), the management of HIV infection in children continues to present many challenges. A major issue is the lack of pediatric formulations as well as compliance issues associated with those antiretrovirals approved for pediatric use. Reasons that can lead to non-compliance include frequent dosing recommendations, large volumes, adverse events; primarily gastrointestinal, as well as logistical issues such as refrigeration needs etc. or even getting the treatments to resource poor areas. Within the context of the above, the Applicant, GSK, has undertaken to revise the pediatric dosing recommendations for Retrovir® both from a Body Surface Area (BSA) basis to body weight based (mg/kg) dosing and also to modify the dosing regimen from a TID to a BID OR TID regimen. Both of these measures will promote easier use of Retrovir® and the proposed BID dosing regimen will also be used to support the use of scored COMBIVIR® tables in children.

Background:

Retrovir® (Zidovudine or ZDV) is approved in the US for use in both adults and pediatric HIV-1 infected patients and is available for oral use as 100 mg capsules, 300 mg tablets, and a 10 mg/kg syrup. The efficacy and safety of ZDV have been evaluated in previous NDA submissions including:

- Retrovir® Capsule NDA 19-655 AP March 19, 1987
- Retrovir® Syrup NDA 19-910 AP September 28, 1989
- Retrovir® Infusion IV NDA 19-951 AP March 19, 1987
- Retrovir® Tablet NDA 20-518 AP December 19, 1995

The currently recommended adult ZDV dose is 600 mg QD in divided doses in combination with other antiretroviral agents. The current recommended US dose in children from 6 weeks to 12 years of age is 160 mg/m^2 every 8 hours in combination with other antiretrovirals. The maximum dose is 480 mg/m^2 per day and should not exceed 200 mg every 8 hours.

The approved US pediatric dosing regimen differs from that approved in Europe where the currently recommended dose in children from 3 months to 12 years of age is 360 to 480 mg/m^2 per day, in 3 or 4 divided doses in combination with other antiretroviral agents. The maximum dosage should not exceed 200 mg every 6 hours. Thus the regimens differ not only in the ages approved for use (6 weeks – 12 years US versus 3 months to 12 years Europe) and the dosing frequency (TID US versus TID OR QID Europe) but also in the total daily allowed doses. The reasons for the different dosing recommendations are not readily apparent as both approvals were based on the same clinical trials and the AUCs achieved by both the EU and US regimens appear to be within the range of the AUCs achieved by the approved adult dose of 300 mg BID.

Current dosing recommendation in both the US and Europe are based on BSA calculations (mg/m^2). There is a general worldwide trend to modify pediatric dosing to a weight based regimen in order to enable use in resource depleted areas. In addition, modifying the dosing regimen to BID from TID would also ease dosing. Issues with these changes are the avoidance of underdosing to minimize the risk for resistance development and to avoid excessive doses that could lead to increased toxicity as well as non-compliance.

This supplement contains pharmacokinetic rationale for pediatric dosing recommendations using a twice daily schedule and based upon mg/kg dosing calculations. No new efficacy or safety data are included. All data reviewed was previously submitted to the NDA or based on literature references.

Clinical Pharmacology:
NOTE: This review provides a summary of the proposed pharmacokinetic rationale. Defer to the Agency Clinical Pharmacology review for further analyses and comments. The Clinical Pharmacology review team concluded that "Overall, the empirical data and modeling support the dosing recommendations".

The conversion of the ZDV mg/m^2 regimen to a mg/kg regimen requires the determination of appropriate weight ranges where mg/kg doses provide acceptable approximations to the approved mg/m^2 doses. To support the proposed changes the Applicant submitted (after agreement with the Agency in pre-SNDA meeting dated November 14, 2007) the following:

- Different Calculation Methods for BSA [DuBois, 1917; Gehan, 1970; Haycock, 1978; Mosteller, 1987].

Comment: All of the equations yielded similar BSA values. Therefore calculations of BSA by one method or another in order to obtain weight based dosing guidelines will not differ significantly. Because of this the Applicant elected to use the simplest method of Mosteller. The Agency concurred with this position in the November, 2007 pre-SNDA meeting as well as in the Clinical Pharmacology review of the current submission.

The Applicant provided weight based dosing regimens by height (5th, 50th, and 95th percentiles for CDC growth charts and by using each of the formulas in order to ensure consistency of the proposed weight based ZDV dosage recommendation developed by using the Mosteller equation with results from BSA calculations based on the other formulas.
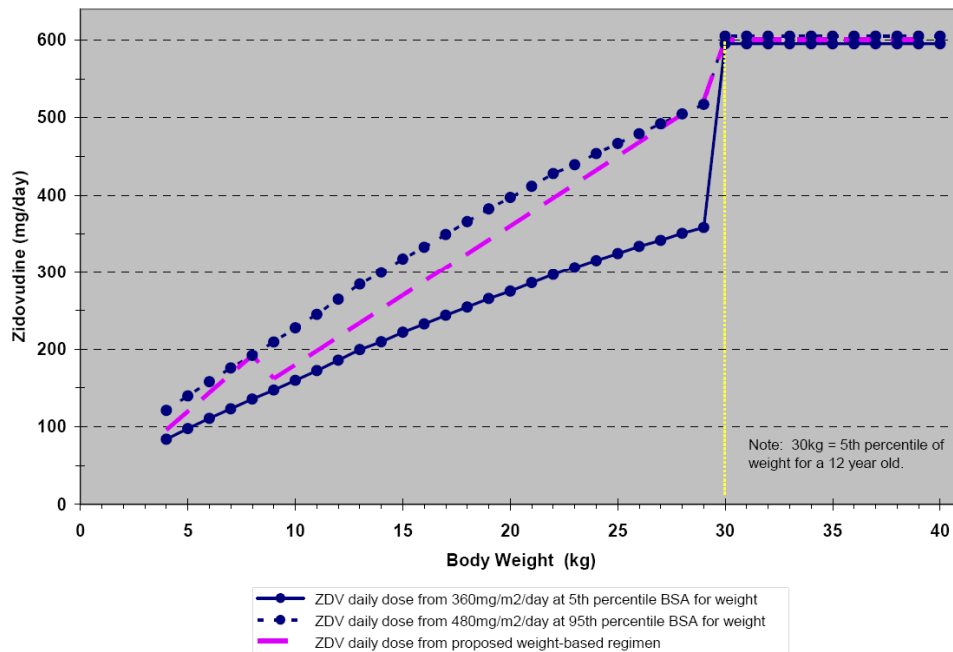
The proposed regimens (Mosteller equation based) are as follows:

Table 1: Recommended Pediatric Dosage of RETROVIR

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

The weight breakpoints for the proposed dose changes (i.e., specifically 9 and 30 kg) were chosen by the Applicant to provide a milligram total daily dose that is closer to the upper end of the mg/m^2 range while minimizing the number of breakpoints. In addition, the 30 kg breakpoint corresponds to the 5th percentile of body weight for 12 year olds, which is consistent with the upper age range of current pediatric dose recommendations. The lower weight of 4 kg was selected as this corresponds to approximately 80% of all 6-week old infants and essentially all 3-month old infants. The proposed 24 mg/kg/day dose starting from 4 kg is considered an appropriate dose as the ZDV total daily dose, 96 mg, is in the middle of the range based on the approved mg/m^2 dosing (83.9 to 121mg). Doses higher than 24 mg/kg/day will require more breakpoints while lower doses (< 22 mg/kg/day) would give ZDV total daily doses (in mg) closer to the lower end of the range based on the approved mg/m^2 dosing (83.9 mg) which may result in reduced efficacy through the development of viral drug resistance. Applicant's Figure 2 presents the total daily mg dose resulting from this proposal relative to the range of daily doses from approved mg/m^2 regimens.

Figure 2   ZDV Total Daily Dose (mg) vs. Body Weight from GSK-proposed Weight-Based Dosing and from FDA and EMEA Approved Product Labelling

Comment: The Applicant provided 4 scenarios for dosing recommendations based on different weight breakpoints and concluded that the proposed breakpoints are the most appropriate. The Agency Clinical Pharmacology Review Team stated (in the CP Review) that "In general, all of the scenarios including the proposed scenario are subjected to dose reductions. The derived dose irrespective of the scenario falls between the US and EU BSA based dosing recommendation. All of the above cut-offs are arbitrary and any given scenario does not offer any special advantage over any other scenarios".

However the reviewers also state that " On average, a daily dose from the proposed body weight based dosing was lower (~10%) than from the currently approved BSA based dosing (480 mg/m^2) in the US. The dose, however, on average was higher (~20%) from the currently approved BSA based dosing (360 mg/m^2) in the EU."

The proposed dosing regimens provide for ZDV concentrations that fall between the approved US and European dosing regimens. As noted in the introduction these regimens are not the same. The European dosing recommendations provide for lower ZDV daily doses as compared to the approved US regimen. Based on the Applicant's proposal most patients will receive a dose that falls between the approved regimens and can be expected to ensure ZDV dosing within the parameters necessary for both efficacy and safety for all proposed groups based on a reasonable understanding of the target concentrations. The proposal harmonizes the dosing recommendation between the US and Europe. Rarely will subjects receive a ZDV dose that leads to higher or lower concentrations. As per the CP review from their analyses of PACTG 152 the highest deviation leading to overexposure was 22% higher than the approved US dose and lowest deviation leading to underexposure was 15% lower than the approved European dose (or 36% less than the

*approved US dose). It should be noted however that underexposure was seen in only one
outlier subject in the Agency CP reanalyses of study ACTG 152. Please see the relevant
efficacy and safety sections of this review for further comments.*

In order to further support the conversion the Applicant provided a comparison of ZDV
PK exposures between the proposed weight based dose regimens and the approved BSA
based dose regimens. A number of analyses were performed comparing the predicted
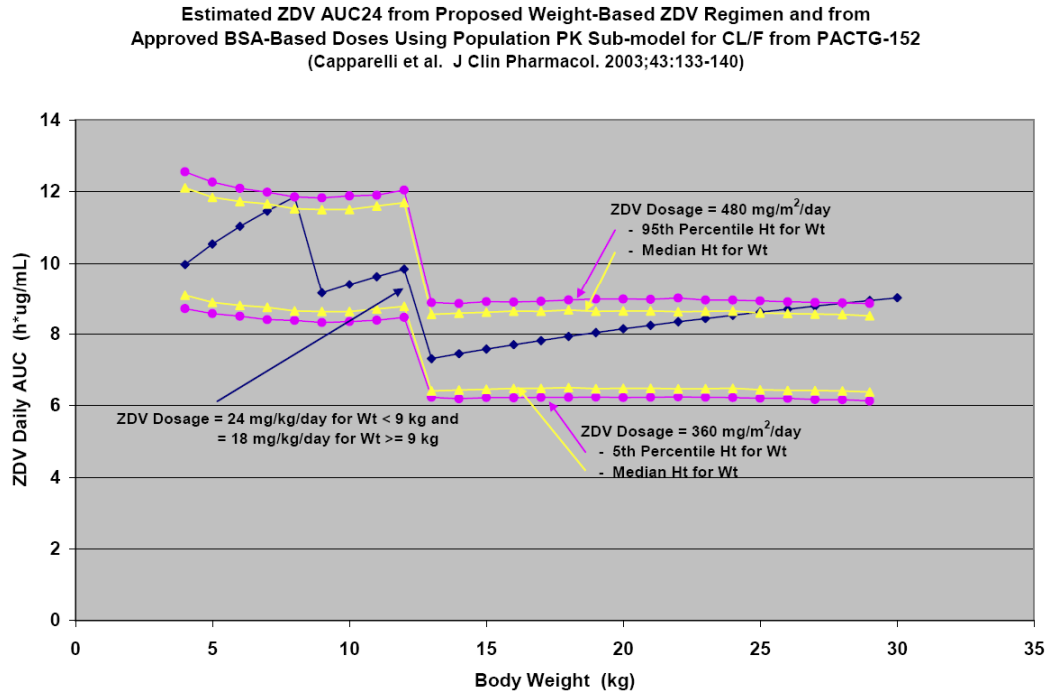plasma exposure of ZDV at the proposed mg/kg doses to the currently approved mg/m^2
doses:

• Estimation of ZDV daily AUC, AUC (0-24), using predicted CL/F from a
population PK model based on PACTG 152 PK data;

ZDV exposures (daily AUC) from both approved mg/m^2 TID and proposed mg/kg BID
dose regimens were calculated using weight-based clearance values from the population
PK analysis of PACTG 152 data published by Dr. Edmund Capparelli. ZDV exposures
from the proposed mg/kg dose given TID were also estimated for comparison to the BID
dosing.
Capparelli EV, Englund JA. Connor JD, JSpector SA, McKinney RE, Palumbo P, Baker
CJ, and PACTG 152 Team. Population Pharmacokinetics and Pharmacodynamics of
Zidovudine in HIV-Infected Infants and Children. J Clin Pharmacol 2003 43:133-140

Study PACTG 152 examined the use of ZDV 180 mg/m^2 every six hours, didanosine
(ddI) 120 mg/m^2 every 12 hours or a combination at reduced doses of both
ZDV (120 mg/m^2 q6h) and ddI (90 mg/m^2 q12h). Patients ranged from 3 months to 18
years of age, with a mean (± SD) age of 45.2 (± 45.0) months and body weight of 15.5 ±
(12.4) kg. A total of 394 HIV infected pediatric patients had ZDV plasma concentration
data available from sparse sampling for population PK analysis. As shown in the
Applicant's Figure 5 application of the population PK sub-model for CL/F derived from
ZDV dosing to children in PACTG-152 supports the conversion from currently approved
mg/m^2 dosing to the proposed mg/kg dosing on the basis of providing comparable daily
ZDV AUC.

Figure 5   **Estimated ZDV AUC(0-24) from Proposed mg/kg Doses and from Approved mg/m^2 Doses Using Population PK Sub-model for CL/F from PACTG 152**

Estimated ZDV AUC24 from Proposed Weight-Based ZDV Regimen and from
Approved BSA-Based Doses Using Population PK Sub-model for CL/F from PACTG-152
(Capparelli et al. J Clin Pharmacol. 2003;43:133-140)

• Monte Carlo simulation using a population PK model based on PACTG 152 PK data;

Monte Carlo simulations were performed with Trial Simulator (Pharsight Corp, Mountain View, CA, Version 2.2) to predict ZDV exposures (daily AUC and steady-state Cmax) for the proposed weight-based (mg/kg) twice daily (BID, q12h) dose regimen in children using Dr. Capparelli's revised population PK model of data from PACTG 152. In addition, ZDV exposures for the proposed mg/kg dose given TID (q8h) were also predicted to compare with BID dosing.

Results from the Monte Carlo simulations are shown in Applicant Table 9, along with historical ZDV exposure at currently approved pediatric and adult dose regimens for comparison.

As per the Applicant the simulations demonstrate that the switch to weight-based BID dosing (mg/kg) will provide daily ZDV AUC (0-24) values that are similar to historical AUC (0-24) from BSA-based dosing (160 mg/m^2 TID), while simulated Cmax values for weight-based twice daily dosing were up to 122% higher than historical BSA-based data in pediatric patients, and up to 77% higher than historical adult exposure. It should be noted that the currently approved mg/m^2 dosing in children provides up to 46% higher

AUC (0-24) than that in adults at the approved adult dosage of 300 mg BID (q12h), which in part is due to the inherently larger variability observed in pediatric patients and the need to prevent sub-therapeutic exposures which can lead to the development of resistance.

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Table 9   Comparison of Simulated ZDV Exposures in Children Receiving Proposed Weight-Based Dosing

Study	Simulation 1	Simulation 2	Simulation 3	Simulation 4	Simulation 5	Simulation 6	Historical[1]	Historical[2]	
Population	Pediatric	Pediatric	Pediatric	Pediatric	Pediatric	Pediatric	Adults	Pediatric	
Range of Body Weight (kg)	4 to <9 kg	4 to <9 kg	9 to <13 kg	9 to <13 kg	9 to <30 kg	9 to <30 kg	69±11 kg	6-38 kg	
Age	< 2 years	< 2 years	< 2 years	< 2 years	> 2 years	> 2 years	19-36 years	6 months to 13 years	
Formulation/ dose/ frequency	Syrup/ 8mg/kg/ q8h	Syrup/ 12mg/kg/ q12h	Syrup/ 6mg/kg/ q8h	Syrup/ 9mg/kg/ q12h	Syrup/ 6mg/kg/ q8h	Syrup/ 9mg/kg/ q12h	Tablet/ 300mg/ q12h	Syrup/ 120mg/m²/ q8h	Syrup/ 160mg/m²/ q8h
# of Simulations or observations	1000	1000	1000	1000	1000	1000	24	28	28
AUC(0-24), h.µg/mL Geo Mean (CV%)	8.51 (42)	8.33 (42)	7.40 (43)	7.32 (41)	7.39 (43)	7.39 (42)	4.8 (29)	5.2 (51)	7.0 (51)
Cmax, µg/mL Geo Mean (CV%)	2.69 (46)	3.56 (50)	2.07 (47)	2.80 (49)	2.10 (48)	2.83 (49)	2.01[3](40)	1.2 (65)	1.6 (65)

1. Study NZTA1001 [GSK Document Number RM1997/00456/00]. Values are mean (CV%).
2. Study P53-04 [TBZZ/88/0051]. Values are geometric mean (CV%) and are dose-adjusted based on observed exposures at actual dose in the study.
3. Cmax = that from single dose; value is applicable due to short ZDV half-life and negligible accumulation with BID dosing.

• Re-analysis of historical PK data from Study P53-04.
Note: The Agency Clinical Pharmacology Review Team requested that GSK convert all available existing ZDV PK data (study P53-04) from mg/m² to mg/kg and provide a breakdown of the ages from that study.

Study P53-04 evaluated the intravenous and oral pharmacokinetics of ZDV in pediatric HIV infected patients with AIDS or ARC. Patients originally received 8 weeks of intravenous ZDV as 1-hour infusions every 6 hours at doses of either 80 or 160 mg/m² every six hours. This was followed by 4 weeks of oral solution dosing at 120 or 240 mg/m² every 6 hours. A subsequent protocol amendment allowed for indefinitely continued oral dosing, a reduction of the duration of intravenous therapy to 4 weeks, and the inclusion of an intermediate dose level of 120 mg/m² IV and 180 mg/m² orally. Serial blood samples were obtained for the first intravenous and oral doses, at time points prior to dosing and through 6 hours post dose. Standard pharmacokinetic parameter estimates were calculated for oral ZDV dosing using non-compartmental methods. A total of 36 patients were enrolled with ages ranging from 6 months to 13 years (mean 4.4 years), weight from 6.6 to 38.1 kg (mean 15.8 kg), and body surface area from 0.3 to 1.2 m2 (mean 0.64 m2). Twenty-eight of the subjects who received oral dosing had sufficient data for pharmacokinetic analysis and are used in the current analysis.

The doses used in Study P53-04 differed from the currently labeled regimens. In order to provide meaningful comparisons, the steady-state ZDV exposures were dose-adjusted to the currently approved 120 mg/m² TID (360 mg/m²/day) and 160 mg/m² TID (480 mg/m²/day) and proposed mg/kg dose regimens (both BID and TID) based on reported ZDV AUC (0-∞) and Cmax following the first oral administration of the studied doses, with the assumptions of dose proportional PK and no repeat-dose accumulation due to the short ZDV plasma half-life (<2hrs).

In addition, pediatric exposures were also compared to systemic exposure estimated from the approved adult dose regimen of ZDV 300 mg BID.

Table 10   Reanalysis of Study P53-04: Estimated ZDV Exposures, Geometric Mean (CV%), for Approved mg/m² Dose Regimens Compared to Those from Proposed mg/kg Dose Regimens (Overall, n=28)

Parameter	ZDV 360mg/m²/d (120 mg/m² TID)	ZDV 480 mg/m²/d (160 mg/m² TID)	ZDV mg/kg Dosing [1]	
AUC(0-24),h μg/mL	5.2 (51)	7.0 (51)	6.4 (54)	
			TID	BID
Cmax, μg/mL	1.2 (65)	1.6 (65)	1.5 (64)	2.2 (64)

1.   Weight range: 4-< 9 kg: 24 mg/kg/day (8mg/kg TID or 12 mg/kg BID); ≥9 to < 30 kg: 18 mg/kg/day (6 mg/kg TID or 9 mg/kg BID); ≥ 30 kg: 600 mg/day (200mg TID or 300mg BID).

Comment: The AUC of the proposed mg/kg regimens were within the AUC ranges of the approved BSA regimens. The proposed Cmax values for both the proposed mg/kg TID and BID regimens were either at the high end of the range of the Cmax for approved doses or higher for the BID dosing regimens relative to the TID and the approved regimens. These results were consistent when stratified by age and weight.

• Analysis using post hoc estimates of population PK model based on PACTG 152 PK data (see above).

Similar analyses to the above were provided in a post hoc analysis of data obtained from PACTG 152 Population PK Analysis.

Steady state AUC (0-24) and Cmax for individual subjects were calculated using the post-hoc parameter estimates for the following dose regimens:
1. approved BSA-based regimen, 120 mg/m2 TID (=360 mg/m2/day);
2. approved BSA-based regimen, 160 mg/m2 TID (=480 mg/m2/day);
3. proposed weight-based BID dose regimen;
4. proposed weight-based dose regimen given TID.

Comment: The results of these analyses both overall and when stratified by age and weight confirmed the reanalyses of P53-04 that is that the daily AUC from proposed mg/kg dosing is within the range obtained from dosing 360 to 480 mg/m²/day (120 to 160 mg/m² TID or the approved US and European dosing regimens. The Cmax values from proposed weight-based BID doses are higher than those obtained with the same daily dose given TID, but are similar to those obtained in adults from the approved 300 mg BID schedule (2.01 μg/mL). It should be noted that ZDV exposures in young children (<2 years old or weighing between 4 and 9 kg) are in general higher than in older children and this is true for both currently approved BSA-based and proposed weight-based dosing.

Table 13   Re-analysis of PACTG 152: Comparison of Estimated ZDV Exposure, Geometric Mean (CV%), Based on Post-hoc Parameter Estimates Between mg/m^2 and mg/kg Dose Regimens (Overall, n=338)

Parameter	ZDV 360 mg/m²/d (120 mg/m² TID)	ZDV 480 mg/m²/d (160 mg/m² TID)	ZDV mg/kg Dosing [1]	
AUC(0-24), h.μg/mL	5.54 (43.1)	7.38 (43.1)	6.72 (45.1)	
			TID	BID
Cmax, μg/mL	1.13 (36.7)	1.51 (36.7)	1.38 (38.6)	2.06 (38.6)

1. Weight range: 4-< 9 kg: 24 mg/kg/day (8mg/kg TID or 12 mg/kg BID); ≥9 to < 30 kg: 18 mg/kg/day (6 mg/kg TID or 9 mg/kg BID); ≥ 30 kg: 600 mg/day (200mg TID or 300mg BID).

In support of the change in ZDV Dosing Frequency from TID to BID:

Comment: As the pharmacokinetics of ZDV when administered BID do not change in pediatric subjects, the clinical issues that need to be addressed are whether efficacy and safety with the proposed BID regimen are consistent with those obtained with the TID regimen in the pediatric population. It should be stressed that the change in the dosing regimen is likely to be associated with clinical benefit because of increased adherence. DHHS, WHO (2006) and PENTA groups advocate a twice daily regimen.

Although there is limited PK data to support the TID to BID change in pediatric subjects, (Bergshoeff 2004) there is a large volume of adult data that supported this change in the adult population. Further there is PK data to support the similarity of exposures (Cmax and AUC) between adult and pediatric subjects receiving the same relative dose. This data in conjunction with the safety data obtained from studies where higher total daily doses than those currently approved were utilized to support the proposed changes. These data are summarized below.

DHHS Recommendations:

Pediatric dose (age 6 weeks to 12 years):
Oral dosing: 160 mg per m^2 of body surface area every 8 hours. Although not FDA approved, twice daily dosing is routinely prescribed to improve adherence (180–240 mg per m^2 of body surface area every 12 hours).

Plasma ZDV has a terminal elimination half-life of approximately 1.5 hours for both adult and pediatric patients (excluding neonates). ZDV is sequentially phosphorylated intracellularly to the active moiety ZDV triphosphate with saturation occurring in conversion of the mono- to diphosphate [Stein, 2001]. This results in pooling of the monophosphate which may sustain anabolism to the triphosphate well after ZDV plasma concentrations have become low or non-quantifiable.

The Applicant submitted data from 2 studies of intracellular ZDV phosphorylation that show that the process is similar in adults and children and that it does not change with maturation.

Rodman (1999) assessed the systemic and intracellular pharmacokinetics of ZDV in 28 pregnant women and their newborns, a similar distribution of plasma ZDV, intracellular monophosphate (MP) and intracellular ZDV triphosphate (TP) concentrations were observed in the mothers at the time of delivery and the cord blood of the neonates
Rodman JH, Flynn PM, Robbins B, et al. Systemic pharmacokinetics and cellular pharmacology of zidovudine in human immunodeficiency virus type 1-infected women and newborn infants. J Infect Dis 1999;180:1844-1850.

Wintermeyer 1997: Conducted in 13 HIV-infected pediatric patients from 2 to 18 years of age who received ZDV doses from 264 to 720 mg/m^2/day, phosphorylated ZDV was assessed over a period of 180 to 394 days. Although intracellular phosphorylated ZDV showed considerable inter- and intra-patient variability, the authors noted that the range of concentrations was very similar to those in adults
Wintermeyer SM, Nahata MC, Brady MT, et al. Phosphorylated zidovudine concentrations in mononuclear cells in paediatric patients with human immunodeficiency virus infections. Pediatr AIDS HIV Infect 1997; 8(2):120-126.

Comment: It can be expected that the C_{trough} level will be lower when the drug is administered less frequently raising the question of consistent antiviral activity. The submitted literature data indicate that ZDV in the form of ZDV triphosphate is still active intracellularly when the ZDV plasma concentrations have become undetectable. This occurs in both adults and pediatric patients. There is no clear relationship between Cmin or trough levels and clinical efficacy thus the effect of less frequent dosing on these parameters is not of great import. More significant is the effect of BID dosing on the AUC or total exposure. In the Bergshoeff 2004 study in 6 HIV-infected children aged 2 – 13 years the plasma levels of ZDV 120 mg/m^2 TID were compared to ZDV 180 mg/m^2 BID. The AUC and Cmax were comparable between the doses and the C_{min} levels on both arms were undetectable.

Large comparative efficacy trials have not been conducted to assess BID versus TID dosing in pediatric patients. The Applicant submitted literature data or data from previously reviewed trials to support the proposed change from an efficacy and safety standpoint. The studies referenced can be seen in the following table:

Table of Studies and Literature Used to support Efficacy and Safety of Weight Based Retrovir Dosing in Pediatric Patients and Change in Dosing from TID to BID

Study ID	ZDV Treatment Regimens	Patient #	Ages/Weight	TOTAL Daily Dose	Efficacy	Safety	PK	Comments
ACTG 152	120 or 180 mg/m^2 q 6 DDI used both arms	120: n= 274 180 n = 276	3 mos- 18 yrs 15.5 ± 12.4 kg	480 or 720 mg/m^2		yes	Yes, sparse sampling and post hoc analyses	Supports BSA to mg/kg and TID to BID
ACTG 128	90 or 180 mg/m^2 q6	90: n = 216 180: n = 208	3 mos. – 12 yrs 15.5 ± 12.4 kg	360 or 640 mg/m^2	Yes	yes	No	Comparable safety high and low dose, more neutropenia high dose
P53-04	80 or 160 mg/m^2 IV q6 followed by 120 or 240 mg/m^2 q6 PO Amended to 120 and 180 mg/m^2	36	6 mos. – 13 yrs 6.6 kg – 38.1kg	360. 480, 640 or 960 mg/m^2 (approx. 12 received 640 TDD)		yes	28 PO had PK data Reanalysis to mg/kg TID and BID provided	Supports BSA to mg/kg and TID to BID
Bergshoeff	120 mg/m^2 TID Followed by 180 mg/m^2 BID	6	2 – 13 yrs.	360 mg/m^2	No	no	Yes, PK similar suggesting regimens bioequivalent	
CNAA3006	180 mg/m^2 BID + 3TC ± ABC	N= 205	0.6 mos- 13 yrs	360 mg/m^2	yes	yes	no	All regimens effective but greater efficacy for ABC regimens Comparable safety
PENTA5	ZDV + ABC vs ABC + 3TC vs ZDV + 3TC BID or TID	ZDV/ABC n = 45 3TC/ABC n = 47 ZDV/3TC	0.3 mos. – 16.5 yrs	360 mg/m^2	Yes	yes	no	All regimens effective but Greater efficacy for ABC regimens

		n = 36 TOTAL ZDV = 81						N for TID or BID not stated
ACTG 300	ZDV/3TC ZDV/3TC + DDI ZDV + DDI	N = 236 N= 235 N = 125	42 d – 15 yrs	480 mg/m^2	Yes	Yes	no	More neutropenia ZDV versus liver for other groups
Zhang	180 mg/m^2 BID (Cipla ZDV/3TC/NEV	N = 51 TN 32 TE	7 – 13 yrs	360 mg/m^2	Yes	Yes	No	Literature Acceptable safety and efficacy
Song	180 mg/m^2 BID ZDV/3TC/NEV	N = 29	2 – 16 yrs	360 mg/m^2	Yes	Yes	No	Literature Acceptable safety and efficacy
Bolton Moore	Not stated	N = 2938 (42% received ZDV)	291 aged < 18 mos		Yes	Yes	No	Literature Acceptable safety and efficacy

The pharmacokinetic parameters of the BID regimen were assessed in one small pilot pharmacokinetic (PK) study conducted to compare the BID and TID regimens [Bergshoeff, 2004].
Bergshoeff AS, Fraaij PLA, Verweij C, et al. Plasma levels of zidovudine twice daily compared with three times daily in six HIV-1-infected children. J Antimicrob Chemother 2004;54:1152-1154.

In six HIV infected children from 2 to 13 years of age, steady-state ZDV plasma pharmacokinetics were evaluated while subjects were receiving 120 mg/m^2 ZDV three times daily and again at least two weeks after switching to 180 mg/m^2 twice daily.

As shown in the following table, analysis of the within-subject ratios of systemic exposure parameters (daily AUC and Cmax) indicated that the pharmacokinetics of ZDV when administered every 12 hours (q12h) were numerically comparable to those from the every 8 hour (q8h) regimen, suggesting that the twice daily regimen was bioequivalent to the three times daily regimen when given the same total daily dose [Bergshoeff, 2004].

Table 7   Summary of ZDV PK Parameter Estimates and Within-Subject Parameter Ratios from ZDV Administration Twice Daily vs Three Times Daily [a]

ZDV PK Parameter	ZDV Dosage Regimen		Within-Subject q12h to q8h Ratio
	120mg/m^2 q8h	180mg/m^2 q12h	
AUC(0-24) (h.μg/mL)	5.24 (3.73 – 7.35)	4.72 (3.50 – 6.36)	0.90 (0.52 – 1.56)
Cmax (μg/mL)	0.96 (0.55 – 1.70)	1.04 (0.69 – 1.57)	1.08 (0.62 – 1.88)
t½ (h)	1.31 (0.99 – 1.72)	1.15 (0.90 – 1.47)	0.88 (0.71 – 1.10)

a.   All values denote geometric mean and 90% confidence interval

The Agency CP commented that" the AUC_{0-24} and Cmax exposures were not significantly different between the two treatments. Clearance and half-life estimates were also similar between patients receiving twice daily ZDV versus three times daily".

Comment: This small study (n =12) is the only study where the PK of the BID and TID regimens were directly compared in pediatric subjects. The comparison of the data from this trial to historical adult data is useful in that it confirms that the pharmacokinetics of ZDV do not change significantly between a TID and BID dosing regimen and therefore both efficacy and safety are not expected to change.

Other clinical studies that utilized a BID regimen in children included the CNAA3006 study and the PENTA study.
(NOTE: These studies did not collect PK data)

CNAA3006 evaluated the efficacy and safety of ZDV 180 mg/m^2 twice daily plus 3TC 4 mg/kg twice daily, with or without abacavir (ABC) 8 mg/kg twice daily, administered over 48 weeks in 205 children ranging at enrollment from 0.6 to 13 years of age. Regimens both with and without abacavir were safe, generally well tolerated, and

efficacious. Consistent with studies in adults, additional antiretroviral activity was observed in the ABC-containing regimen

Saez-Llorens X, Nelson RP, Emmanuel P, et al. A randomized, double-blind study of triple nucleoside therapy of abacavir, lamivudine, and zidovudine versus lamivudine and zidovudine in previously treated human immunodeficiency virus type 1-infected children. Paediatrics 2001;107;4

Comment: Efficacy from study CNAA3006 can be used to support the efficacy of the BID dosing regimen as the results from both study arms met the acceptable standard of efficacy at the time the study was performed thus indicating that a BID ZDV regimen results in efficacious drug exposure. As expected, the triple regimen arm was associated with greater efficacy. Safety was comparable between the treatment arms with GI events most frequently reported. These events did not lead to treatment discontinuations and generally resolved. It was concluded that the ZDV BID regimen of 180 mg/m^2 was not associated with significant adverse events.

PENTA: 48-week safety and efficacy study conducted in children from 0.3 to 16.5 years of age, found similar results regarding efficacy when ABC was part of a dual nucleoside regimen, either in combination with 3TC (N=47) or with ZDV (N=45), relative to a 3TC plus ZDV regimen (N = 36). The ZDV dosage regimen in this study was 360 mg/m^2/day, taken as divided doses two or three times daily. Of the 81 ZDV recipients, it was not reported how many received twice daily regimens versus three times daily regimens of ZDV. All three regimens were effective; however, greater efficacy was reported for the ABC-containing regimens.

PENTA-5 (Paediatric European Network for Treatment of AIDS). Comparison of dual nucleoside-analogue reverse-transcriptase inhibitor regimens with and without nelfinavir in children with HIV-1 who have not previously been treated: the PENTA 5 randomized trial. Lancet 2002;359: 733-740.
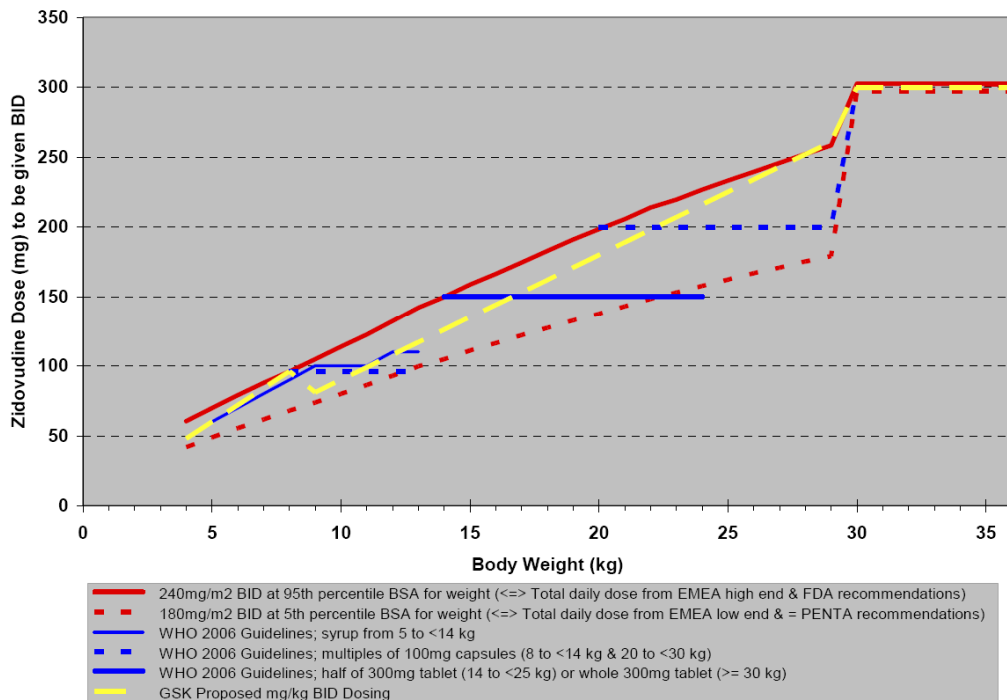
Comment: This study also shows the comparability of the ZDV BID and TID regimens with regards to efficacy. The submitted reference did not focus on safety however drug substitutions for toxicity occurred in only 1 subject on ZDV/3TC and in 5 on ZDV/ABC.

Based on the above, both the PENTA group and WHO advocate a BID ZDV dosing regimen based on a mg/kg basis. Other Agencies such as UNICEF also advocate BID dosing regimens.

The Applicant's proposed weight-based ZDV doses for twice daily regimens are based on maintenance of the same total daily dose (e.g. 240 mg/m^2 BID vs 160 mg/m^2 TID, or 180 mg/m^2 BID vs 120 mg/m^2 TID) and can be found in a table in the background section of this document.

A comparison of all current regimens or proposed regimens indicates that the Applicant's proposal is consistent with the dosing regimens recommended by WHO and EMEA.

**Figure 4   Comparison of GSK-Proposed Weight Based ZDV (mg) Twice Daily
Regimens and those from PENTA and WHO Treatment Guidelines**

*Efficacy conclusion: The pharmacokinetic data submitted by the Applicant to support
BID dosing has its limitations because of the high variability of ZDV pharmacokinetics
but in view of no discernible efficacy limitations (via extrapolation of adult data (Title IV)
or dose limiting toxicities in adults and children is deemed adequate to support the
approval of this application.*

*The data show that the proposed BID regimen provides for an AUC similar to that of
approved TID regimens with Cmax values that are marginally higher than those seen
with TID regimens. As per the Agency CP Review Team the Applicant's proposals
provide for exposures that fall between the approved US (approximately 10% lower)and
European (approximately 20% higher) pediatric doses and serve to harmonize dosing
worldwide. This proposal is reasonable given the similarity in exposure data between
TID and BID dosing regimens in adults and the ability to extrapolate this data to
pediatric subjects. The worst case scenarios provide for doses up to 22% higher than the
US approved dose or up to 15% lower than the approved European dose or 36% less
than the US approved dose. The underexposure to ZDV (with possible resultant decrease
in efficacy) is not anticipated to occur frequently and indeed was seen in only one outlier
subject in the Agency reanalyses of study PACTG 152. In most cases the ZDV exposure
was as expected between the anticipated exposures achieved with the approved US and
European doses. It should be noted that both the US and European approved doses
provide for ZDV exposures consistent with exposures of the approved adult doses. As
noted above the lowest possible exposure would result in a 15% lower exposure than the
approved European dose. The European approval was based on the same efficacy data*

as the US and therefore based on efficacious clinical trials. It is unclear why the EMEA approved the lower dose but possibly this may have been due to a lower safety threshold at the time of the original approval relative to the US where the need for effective therapies was much greater at the time of the original approval. When the outlier was excluded in the CP analyses and the differences between the mg/kg twice daily regimen and the approved US mg/m^2 three times daily regimen were reassessed, it was found that with the proposed dosing regimen no patient would receive lower than the approved European dose and the greatest deviation from the approved US dose would be no greater than 22% lower than the approved dose. The potentially lower dose would occur only in subjects in the 9 kg range who would receive 171 mg twice daily compared to 211 mg by the current approved three times daily regimen. It was ultimately concluded that acceptance of the new dosing regimen is logical given its applicability to the overall pediatric population that falls within the 5th – 95% percentiles on CDC growth charts. The calculations of BSA of the outlier (s) were not consistent with those of the overall population. In the rare case that such patients receive ZDV and have resultant underexposure, that underexposure will not be > 15% the approved European dose and again consistent with a DI not requiring dose adjustment and without loss of efficacy.

The clinical trial data used for the original approval can be utilized to show that there is little possibility of reduced efficacy at the proposed doses as this data included studies where a lower ZDV dose than that approved in pediatric subjects in the US was utilized. This same data was used to support the European approval albeit at the approximately 25% less than the US dose, lower dose. In addition clinical trial data comparing abacavir and ZDV triple regimens to the standard of care at the time, dual ZDV regimens where dosing was BID revealed acceptable efficacy between the treatment arms although the triple regimens were more efficacious that the dual.

Finally a 22% decrease in zidovudine exposures in pediatric subjects is not likely to adversely affect efficacy. This decrease is similar to drug-drug interaction scenarios for antiretrovirals where a 25% decrease would not necessitate a dose adjustment and nether decreased efficacy or increased viral resistance would be expected (ZDV/RTV drug interaction study ZDV 200 mg q8 with RTV 300 mg q6 decreased ZDV concentrations by up to 25% without resultant decrease in efficacy).

A recommendation is made to approve the Applicant's proposal to convert to a weight based BID regimen in pediatric patients.

Safety: Retrovir® was the first antiretroviral approved for the treatment of adults and children with HIV infection and AIDS. Initial dosing recommendations were based on plasma levels of the drug and later evolved to take into account intracellular triphosphate levels.

In an effort to balance optimal anti-retroviral efficacy while minimizing toxicity, the dose of 300 mg BID was chosen for treatment of adults based on better tolerability compared to higher doses, and the observation that a steady state average plasma concentration higher than 0.7 micromolar was associated with appropriate intracellular triphosphate levels and better antiviral response [Capparelli, 2003].

Published data on the use of Retrovir® in pediatric patients are less extensive but concur with data in adult patients regarding safety and antiviral efficacy.

Retrovir® is generally well tolerated. The following adverse reactions are described in the **Boxed Warning** and/or **Warnings
and Precautions** section(s) of labeling:

• Hematologic toxicity, including neutropenia and anemia
• Symptomatic myopathy
• Lactic acidosis and severe hepatomegaly with steatosis
• Hepatic decompensation in patients co-infected with HIV-1 and hepatitis C.

ADRs that occur most frequently in adults and in children are from the GI tract including nausea and vomiting. Laboratory abnormalities that occur frequently include anemia, granulocytopenia, thrombocytopenia, and increased ALT and AST.

Additional supportive data:

In support of the safety of the proposed pediatric dosing regimens the Applicant summarized data from GSK sponsored trials as well as from the literature.

Comment: All submitted references were reviewed for accuracy of sponsor's summaries. The doses utilized in the submitted references included doses well above the proposed total daily doses.

CNAA3006: (see description in efficacy section of review). The most frequently reported adverse events were nausea and vomiting (46%) and cough (46%) in the ABC + 3TC + ZDV group and nausea and vomiting (30%) and cough (25%) in the 3TC + ZDV group. Grade 3 or 4 neutropenia and anemia were reported in 2% and <1% of subjects in the ABC + 3TC + ZDV group and in 8% and 3% in the 3TC + ZDV group, respectively. Adverse events were generally transient in nature and resolved within 3 weeks. Most adverse events were mild to moderate in intensity and few lead to treatment discontinuation: nausea and vomiting in 4 subjects, fever in 4 subjects and rash in two subjects.

PACTG300: 596 subjects were enrolled, aged 42 days – 15 years. 236 received ZDV/3TC, 235 received ZDV/3TC and DDI and 125 received ZDV/DDI. Total ZDV dose was 480 mg/m^2 day (160 mg/m^2 three times a day).

The most common adverse experiences reported were neutropenia (5.3%), fever (4.9%), and hepatic abnormalities (4.3%). In the ddI treatment group there were 15 occurrences of elevated serum aspartate aminotransferase, alanine aminotransferase, or bilirubin levels versus 5 for the ZDV/3TC treatment group and 4 cases of pancreatitis versus none for ZDV/3TC group. The incidence of nausea and vomiting was 8% in the ZDV/3TC group compared to 7% in the ddI group, while that of diarrhea was 8% versus 6%. Neutropenia occurred more frequently in the ZDV/3TC group (17 cases versus 8 for ddI).

There were no significant differences between the two treatment groups with respect to the rate of Grade 4 (life-threatening) toxicities and no patient was judged to have a treatment-related toxicity as the major cause of death.

PENTA 5 Study (see efficacy section). ZDV dosage was 360 mg/m^2/day in BID or TID doses. Most frequently reported events were neutropenia (n = 13) and thrombocytopenia (n = 3). As stated above little safety was reported.

Published Trials:

PACTG 152: This study examined the use of ZDV 180 mg/m^2 every six hours, didanosine (ddI) 120 mg/m^2 every 12 hours, or a combination of reduced doses of both ZDV (120 mg/m^2 q6h) and ddI (90 mg/m^2 q12h) [Capparelli, 2003]. Patients ranged from 3 months to 18 years of age, with a mean (± SD) age of 45.2 ± 45.0 months and body weight of 15.5 ± 12.4 kg. In this study no association was found between ZDV concentrations and negative study endpoints including growth failure, neuropsychological deterioration, HIV disease progression or death. Anemia was also more frequent in subjects receiving the higher dose compared to those receiving the lower dose of ZDV; Hb levels below 10 mg/dL occurred three times more frequently in subjects exposed to the higher dose and in infants (younger than 2 years of age, who were also less likely to obtain clinical benefit) compared to those exposed to the lower dose (23.4% vs. 7.6% in subjects with serum ZDV concentrations ≥ to 1.31μM [350 ng/mL, total daily AUC equivalent of 8.4 μg/hr/mL] compared to those below that level). The incidence of severe anemia, however, was uncommon (only 5 subjects), and no correlation with ZDV exposure or levels with neutropenia was found; neutropenia occurred in only 2% of participating subjects. Finally, serious events that resulted in discontinuation of study therapy were uncommon among the three groups (2.9%).

PACTG 128: This study examined the use of ZDV 180 mg/m^2 every six hours compared to a reduced dose of ZDV (90 mg/m^2 q6h) [Brady, 1996]. Patients ranged from 3 months to 12 years of age, with a mean (± SD) age of 3.9 ± 2.8 years and body weight of 15.5 ± 12.4 kg. A total of 426 HIV infected pediatric patients were enrolled in the study and 424 were evaluable, with a median exposure to ZDV of 25 and 36 months in the high and low dose groups, respectively. No differences in baseline characteristics were seen; 74% and 81% of subjects in the high dose vs. the low dose were still receiving full dose at 144 weeks. There were no differences in mortality, HIV disease progression or neurocognitive function between the two groups. Changes in CD4 cell counts and p24 antigen were also not significant. The safety profile of the two dosing regimens of ZDV was also comparable. Thirty-nine percent of subjects reported a grade 3 or 4 hematologic toxicity and no significant differences were identified between the two groups. There was a higher frequency of grade 3 or 4 neutropenia in the higher ZDV dose group (68% versus 54%, p=0.9), but few subjects discontinued therapy due to adverse events in the study. No differences in other laboratory abnormalities were observed. The authors concluded that the two groups (High dose vs. low dose) were comparable with respect to efficacy and safety and recommended that the lower dose be used in HIV infected children.

P53-04: This study evaluated the intravenous and oral pharmacokinetics of ZDV in pediatric HIV infected patients with AIDS or ARC. Patients originally received 8 weeks of intravenous ZDV as 1-hour infusions every 6 hours at doses of either 80 or 160 mg/m^2 every six hours. This was followed by 4 weeks of oral dosing at 120 or 240 mg/m^2 every 6 hours. A subsequent protocol amendment allowed for indefinitely continued oral dosing, a reduction of the duration of intravenous therapy to 4 weeks, and the inclusion of an intermediate dose level of 120 mg/m^2 IV and 180 mg/m^2 orally. Serial blood samples were obtained around the first intravenous and oral dose predose through 6 hours post dose. Standard pharmacokinetic parameter estimates and measures of exposure were calculated for oral ZDV dosing using non-compartmental methods and pharmacokinetic relationships. A total of 36 patients were enrolled and ranged in age from 6 months to 13 years (mean 4.4 years), weighed from 6.6 to 38.1 kg (mean 15.8 kg), and had body surface areas from 0.3 to 1.2 m^2 (mean 0.64 m^2). A third of the subjects received a dose of 160 mg/m^2 every six hours. No substantial difference in tolerability of the different doses was reported.

Adverse Events in Pediatric Populations from the Developing World Using Fixed Dose Combination Tablets Potentially Delivering Higher Doses of Zidovudine
In addition to the data summarized above from published clinical trials, the Applicant provided a summary of safety from a number of cohorts from the developing world that generally follow WHO BID dosing recommendations similar to the ones being proposed in this submission.

Zhang et al described a cohort of 51 ART naïve and 32 ART experienced children with a median age (interquartile range; IQR) of 10 (7-13) years and 12 (8-13) years, respectively, and IQR for Z scores for weight of -2.4 to -1.3. Fifty percent of these children were treated with generic tablets containing ZDV, lamivudine and nevirapine (Cipla) with an intended ZDV dose of 180mg/m^2 BID. After one year of treatment there were significant improvements in virologic, immunologic and clinical parameters. Treatment was well tolerated and no discontinuation of therapy due to adverse events was reported. All children but two survived; the two deaths were not attributed to treatment effects.
Zhang F, Haberer J, Zhao Y; et al. Chinese Pediatric Highly Active Antiretroviral Therapy Observational Cohort. *J AIDS* 2007; 46:594-598.

Comment: Very little safety information was provided in this publication.

Song et al reported data from 29 children aged from 2 to 16 years in Mombasa, Kenya, who were treated with generic zidovudine, lamivudine and nevirapine. The intended zidovudine dose was 180mg/m^2/BID but some children were treated with adult tablets. The results showed excellent antiviral efficacy, immune recovery and weight gain in the majority of children. According to the investigators, the tolerability of the three drugs was good, with no unexpected adverse events that led to withdrawal or modification of therapy.
Song R, Jelagat J, Dzombo D, et al. Efficacy of Highly Active Antiretroviral Therapy in HIV-1 Infected Children in Kenya. *Pediatrics* 2007; 120:e856-e861.

Comment: Subjects in the Kenyan cohort were assessed every 2 – 4 weeks for AEs. One subject developed TB. There were no other reported AEs although the publication stated that there were no SAEs or AEs that led to discontinuation. Laboratory abnormalities were not reported.

Bolton-Moore et al reported data from 2938 children with a median age of 81 months (IQR: 36-125), including 291 children younger than 18 months, the majority with WHO stages III or IV. Approximately 42% of these children were treated with ZDV containing regimens, although ZDV was avoided in children with Hg levels lower than 10 g/dL. The doses of ZDV used during the reporting period was not described. ART was initiated based upon WHO guidelines (2003 and 2006) that were in place based upon a subject's enrollment into the study (May 1, 2004 through June 29, 2007). The authors conclude that scaling up of ART in sub-Saharan Africa is possible and leads to good outcomes including decreased mortality, immune reconstitution and weight gain, without any evidence of unexpected ZDV associated toxicity.
Bolton-Moore C, Mubiana-Mbewe M, Cantrell R, et al. Clinical Outcomes and CD4 Cell Response in Children Receiving Antiretroviral Therapy at Primary Health Care Facilities in Zambia. *JAMA* 2007; 298(16):1888-1899.

Comment: The data from pediatric cohorts in developing countries are primarily useful to show the efficacy benefits of a BID dosing regimen in resource poor areas of the world. Safety reporting in these studies is limited but essentially is notable for the absence of any unexpected AEs, SAEs, and AEs that lead to discontinuation when Retrovir® is used to treat children with HIV infection, even when doses higher than 360 to 480 $mg/m^2/day$ are used.

Pediatric Use data are also available from trials of Retrovir® for the Prevention of Maternal-Fetal Transmission. In a placebo-controlled trial, overall clinical adverse events and laboratory test abnormalities were similar for women in the Retrovir® and placebo groups. Hemoglobin concentrations in infants exposed to Retrovir® for this indication were marginally lower than in infants in the placebo group but transfusion was not required. Anemia resolved within 6 weeks after completion of Retrovir® therapy. Other clinical adverse events and laboratory test abnormalities were similar in the Retrovir® and placebo groups. It is unknown whether there are any long-term consequences of *in utero* and infant exposure to Retrovir®

Safety Conclusions: The safety profile of Retrovir® has been well-described in both adults and children and in view of the potential for up to a 22% increase in achievable ZDV concentrations there is adequate safety information available from trials where doses higher than the US approved dose were utilized that amply show that the safety profile of ZDV dose not change at higher doses up to 240 mg/m^2 PO Q6h. Such doses lead to concentrations much greater than those that could be achieved with the proposed regimens even in cases where higher than expected concentrations are achieved. No unexpected adverse events have been reported after extensive use of ZDV at doses above those approved in the US for dosing in children. BID dosing regimens have been used extensively worldwide and appear well tolerated and safe. There is adequate safety information available to support an approval of the proposed dosing regimens.

Other Regulatory Issues: Because the Applicant is proposing a new dosing regimen, PREA is triggered. ZDV is approved for the prevention of maternal/fetal transmission of HIV-1 in neonates up to 6 weeks of age but ZDV dosing is not available for treatment of HIV-1 infection in children < 6 weeks of age. The DHHS pediatric treatment guidelines support early diagnosis of HIV and switching from ZDV chemoprophylaxis dosing to treatment dosing as soon as possible. In addition, PREA commitments for other ARVs include dosing recommendations for 1 month and older for treatment of HIV-infection.

The ZDV dosing regimen for prevention in neonates is 2 mg/kg orally every 6 hours starting within 12 hours after birth and continuing through 6 weeks of age. Neonates unable to receive oral dosing may be administered RETROVIR intravenously at 1.5 mg/kg, infused over 30 minutes, every 6 hours. The PREA commitment for this application is to obtain dosing recommendations for children ages 1 month - < 6 weeks of age. GSK has agreed to use the applicable ZDV pharmacokinetic data in neonates and pharmacokinetic modeling and simulation to propose dose recommendations for this age range. Dosing recommendations will be twice daily regimen and mg/kg basis. GSK committed to submitting revised labeling within six months after issuance of an approval letter for the pending supplement 033.

No additional pediatric requirements are needed at this time. Dosing is available in neonates for prevention of maternal-fetal transmission and dosing is available for treatment of HIV infection in children 6 weeks to < 18 years of age.

Conclusions and Recommendations:

The pharmacokinetic analyses and simulations provided by the Applicant reasonably support their position that the proposed change in approved pediatric dosing recommendations from a BSA based dosing to a weight based dosing will have little effect on antiviral activity and/or resistance development because the anticipated AUC (0- 24) ZDV values are comparable to the pediatric historical values and to adult BID data. Viral load decline in adults on a BID regimen has been well established previously (Ruane) and this data can be extrapolated to pediatric subjects based on Title IV (see below).

 Independent analyses of the data by the Agency Clinical Pharmacology Review team confirmed the Applicant's conclusions although they also pointed out that the Applicant's proposals provide for exposures that fall between the approved US (approximately 10% lower) and European doses (approximately 20% higher) and serve to harmonize dosing worldwide. The worst case scenarios provide for doses up to 22% higher than the US approved dose or up to 15% lower than the approved European dose (or up to 36% lower than the US approved dose). The over or underexposure to ZDV is not anticipated to occur frequently and indeed was seen infrequently in the Agency reanalyses of study PACTG 152. In most cases the observed ZDV exposures fell between the anticipated exposures of the approved US and European doses and were fully consistent with previously documented exposures achieved with the adult regimen as well as the US and

European pediatric regimens. When only subjects between the 5th and 95th percentiles on CDC growth charts were taken into account as representative of the overall population, and the differences between the mg/kg twice daily regimen and the approved US mg/m² three times daily regimen were reassessed, it was found that with the proposed dosing regimen no patient would receive lower than the approved European dose and the greatest deviation from the approved US dose would be no greater than 22% lower than the approved dose. The potentially lower dose and exposure could infrequently occur only in subjects in the 9 kg range. However, even if this underexposure did occur, efficacy should not be adversely affected because similar exposures to those achieved with the approved adult dose would still be anticipated. In the rare instance that underexposure did occur it would not be anticipated to be greater than that seen in drug interaction scenarios where even a 25% decrease usually doses not necessitate a dose adjustment and as has been seen in clinical trials, neither decreased efficacy or increased viral resistance have occurred (DI ZDV/RTV 200 mg q8/300 mg q6 results in a 25% decrease in ZDV concentrations. Acceptable efficacy can be expected with a range of doses. An example of this is that the US and European approvals were based on efficacy studies that utilized a range of ZDV doses (360 – 480 mg/m2 TD QD) and led to the approval of different but equally effective regimens because both the US and European approved pediatric regimens provided for ZDV exposures fully consistent with the exposures achieved with the approved adult dose.

It was ultimately concluded by the Agency Review Team that acceptance of the new dosing regimen is logical given its applicability to the overall pediatric population that falls within the 5th – 95% percentiles on CDC growth charts. It was also determined that the previously approved mg/m² dosing recommendations would remain in the label for those situations where dosing on a mg/kg basis is not reasonable. As an individual subject's dose may be different depending on which dosing method is used, a statement to this effect will also be included in the Dosage and administration section on labeling.

There is adequate safety information available from pediatric trials where doses higher than the US approved dose were utilized that amply show that the safety profile of ZDV dose not change at higher doses up to 240 mg/m² PO Q6h.

Safety has also been shown to be comparable between the TID and BID regimens despite differences in Cmax values.

Based on the submitted pharmacokinetic data, the multiple publications regarding safety and efficacy and reanalyses of the submitted data, it is recommended that an approval be granted for this prior approval labeling supplement. The risks of underexposure and resultant lack of adequate antiviral activity or overexposure and toxicity are very low compared to the anticipated benefit of a harmonized dosing regimen which will ease dosing and therefore compliance of subjects receiving ZDV containing antiretroviral regimens.

For specific labeling recommendations including PLR format, please see attached label.

APPENDIX 1

References:

Working Group on Antiretroviral Therapy and Medication Management of HIV-infected children. Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection. February 28, 2008 1 – 134. http://aidsinfo.nih.gov/content files/PediatricGuidelines.pdf

Bolton-Moore C, Mubiana-Mbewe M, Cantrell R, et al. Clinical Outcomes and CD4 Cell Response in Children Receiving Antiretroviral Therapy at Primary Health Care Facilities in Zambia. *JAMA* 2007; 298(16):1888-1899.

Song R, Jelagat J, Dzombo D, et al. Efficacy of Highly Active Antiretroviral Therapy in HIV-1 Infected Children in Kenya. *Pediatrics* 2007; 120:e856-e861.

Zhang F, Haberer J, Zhao Y; et al. Chinese Pediatric Highly Active Antiretroviral Therapy Observational Cohort. *J AIDS* 2007; 46:594-598.

PENTA-5 (Paediatric European Network for Treatment of AIDS). Comparison of dual nucleoside-analogue reverse-transcriptase inhibitor regimens with and without nelfinavir in children with HIV-1 who have not previously been treated: the PENTA 5 randomized trial. Lancet 2002;359: 733-740.

Saez-Llorens X, Nelson RP, Emmanuel P, et al. A randomized, double-blind study of triple nucleoside therapy of abacavir, lamivudine, and zidovudine versus lamivudine and zidovudine in previously treated human immunodeficiency virus type 1-infected children. Paediatrics 2001;107;4

Bergshoeff AS, Fraaij PLA, Verweij C, et al. Plasma levels of zidovudine twice daily compared with three times daily in six HIV-1-infected children. J Antimicrob Chemother 2004;54:1152-1154.

Rodman JH, Flynn PM, Robbins B, et al. Systemic pharmacokinetics and cellular pharmacology of zidovudine in human immunodeficiency virus type 1-infected women and newborn infants. J Infect Dis 1999;180:1844-1850.

Wintermeyer SM, Nahata MC, Brady MT, et al. Phosphorylated zidovudine concentrations in mononuclear cells in paediatric patients with human immunodeficiency virus infections. Pediatr AIDS HIV Infect 1997; 8(2):120-126.

Capparelli EV, Englund JA. Connor JD, JSpector SA, McKinney RE, Palumbo P, Baker CJ, and PACTG 152 Team. Population Pharmacokinetics and Pharmacodynamics of Zidovudine in HIV-Infected Infants and Children. J Clin Pharmacol 2003 43:133-140

Brady M, McGrath, N, Brouwers P, et al. Randomized Study of the Tolerance and Efficacy of High- versus Low-Dose Zidovudine in Human Immunodeficiency Virus infected Children with Mild to Moderate Symptoms (AIDS Clinical Trial Group 128). *J Infect Dis* 1996; 173(5):1097-1106.

Title IV: New efficacy data for the change from TID to BID dosing in children has not been submitted. However the efficacy (and safety) of BID dosing in adults is well established. The extrapolation of efficacy for ARVs are based on the assumption that the course of HIV disease and the effects of the drugs are sufficiently similar in adult and pediatric patients (21 CFR 201.57 (f) (9) (iv), Sec. 505B 21 USC 355c). DAVP agrees that HIV disease in pediatric patients is similar but not identical to adult HIV disease (Domachoske JB; Pediatric Human Immunodeficiency Virus Infection October 1996; Cl. Microbiol. Rev. 9 (4) 448- 468), although the route of transmission may be different. Vertical transmission from mother to child is the predominant means for children less that 12 years of age in contrast to adolescent and adult patients in whom sexual contact or IV drug use are the primary modes of transmission. The pathophysiology of immune system destruction is similar in adult and pediatric patients. Consequently infectious complications of pediatric HIV disease consist of both severe manifestations of common pediatric infections and also opportunistic infections like those seen in adults.

In pediatric patients and adults, treatment of HIV disease is monitored by the same two markers, CD4 counts and HIV RNA load. Antiretroviral drugs including nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs) have been shown to loser HIV RNA, improve CD4 counts (or percentage) and improve general clinical outcome in all ages and treatment recommendations are very similar across all ages (see Working Group on Antiretroviral Therapy and Medication Management of HIV-infected children. Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection. February 28, 2008 1 – 134. available at http://aidsinfo.nih.gov/content files/PediatricGuidelines.pdf for a review of studies and references.

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[1] TITLE IV—PEDIATRIC RESEARCH EQUITY ACT OF 2007 ''(B) SIMILAR COURSE OF DISEASE OR SIMILAR EFFECT OF DRUG OR BIOLOGICAL PRODUCT.— (i) IN GENERAL.—If the course of the disease and the effects of the drug are sufficiently similar in adults and pediatric patients, the Secretary may conclude that pediatric effectiveness can be extrapolated from adequate and well-controlled studies in adults, usually supplemented with other information obtained in pediatric patients, such as pharmacokinetic studies. (ii) EXTRAPOLATION BETWEEN AGE GROUPS.—A study may not be needed in each pediatric age group if data from one age group can be extrapolated to another age group. (iii) INFORMATION ON EXTRAPOLATION.—A brief documentation of the scientific data supporting the conclusion under clauses (i) and (ii) shall be included in any pertinent reviews for the application under section 505 of this Act or section 351 of the Public Health Service Act (42 U.S.C. 262).

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