

**Medical Officer Review of Supplemental Labeling Revisions
Prior Approval Recommendations for Pediatric
Patients Aged 4 to 6 Weeks
for
NDA 19-910/S-035 (SE5)
NDA 19-655/S-048 (SE5)
NDA 20-518/S-018 (SE5)**

Sponsor: GlaxoSmithKline
Product: Retrovir® (Retrovir, ZDV) Syrup 10 mg/kg, Capsule 100 mg, Tablet 300 mg
Date Submitted: May, 7 2009
Due Date: November 6, 2009
Medical Officer: Regina Alivisatos, MD
Acting MTL: Yodit Belew, MD
Project Manager: Robert Kosko, PharmD
Subject: Changes to Pediatric Dosing Recommendations for Pediatric Patients Aged 4 – less than 6 weeks
No changes to adult recommendations
Indication: Treatment of HIV Infections
Dosage Regimen: Please see label
Materials Reviewed: Electronic NDA 19910/ [REDACTED] (b) (4) submissions dated 05/07/09
MOR of SNDA 19-910/S-033 dated 09/17/08
References listed in Appendix
CDC Growth charts website

<http://www.cdc.gov/nchs/about/major/nhanes/growthcharts/datafiles.htm>

Review and Comments:

The product labeling (PL) submitted May 7, 2009 with S-035 for the cross referenced supplements was compared to that approved on September 17, 2008 by the PM (See PM Review).

In this supplemental NDA application the Applicant seeks approval to extend the age of patients in the lowest weight band (4 kg - < 9 kg) in the DOSAGE and ADMINISTRATION of the approved label from the current 6 weeks of age and greater, to include neonates of four weeks to less than six (4 - < 6) weeks of age.

Introduction:

The current submission includes proposed dosage modifications that provide for the treatment of HIV-1 infected pediatric patients aged four weeks to less than six weeks of age. The proposed changes include the lowering of the lower age limit from 6 weeks of age to 4 weeks of age and also propose a treatment regimen of 12 mg/kg twice daily (TDD 24 mg/kg day) as opposed to the four times daily regimen used for prophylactic therapy (1.5 mg/kg q8 IV or 2 mg/kg q6 PO, TDD range 6 – 8 mg/kg/day). These

supplemental applications include references to previously submitted data, as well as, pharmacokinetic modeling and simulations to support these changes. No new efficacy or safety data were included in this submission. This submission fulfills a postmarketing commitment imposed on the Applicant as a condition for approval of NDA supplement 19-910/S-033 on September 18, 2008.

Background:

Retrovir® (Retrovir 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 Retrovir 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 Applicant, GSK submitted a prior approval labeling supplement for NDA 19-910/S-033 on March 21, 2008 for revised pediatric dose recommendations for Retrovir Syrup for pediatric patients ages 6 weeks – 18 years of age. In addition, prior approval supplements were submitted on September 17, 2008 for the Retrovir Capsule NDA 19-655 and the Retrovir Tablet NDA 20-518. Approval for the revised labeling for all three submissions was granted on September 19, 2008. The revisions included modifying the pediatric dosing recommendations for Retrovir from a Body Surface Area (BSA) basis to body weight based (mg/kg) dosing and changing the dosing regimen from a three times daily to a twice or three times daily regimen.

As a condition of the approval, GSK received the following required Postmarketing Commitment:

1. Deferred pediatric study under PREA for the treatment of HIV-1 infection in pediatric patients ages 1 month to < 6 weeks of age. “Please assess Retrovir pharmacokinetic data in neonates and use pharmacokinetic modeling and simulation data to propose dosing recommendations for HIV-1 infected children between 1 month and < 6 weeks of age”.

The pediatric study requirement for neonates from birth to < 1 month of age was waived by the Agency because it was determined that necessary studies are impossible or highly impracticable to perform. In addition it is highly unlikely that neonates below the age of 4 weeks would be treated and therefore there is no real need to study treatments for this narrow age group.

The approved mg/kg pediatric dosage recommendations for Retrovir (Retrovir) Syrup to be used in children ages 6 weeks to 18 years (NDA 19-910: S-033) are as follows:

Table 1: Recommended Pediatric Dosage of RETROVIR

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

Comment: As per the approved weight-based dosing recommendations for the treatment of HIV-1 infection a 4- 6 week old infant weighing 4 kg would receive 96 mg Retrovir daily (24 mg/kg divided into 2 doses (q 12 hours). The current approved chemoprophylactic dosing regimen for a 4 week old infant is 1.5(IV) – 2 (PO) mg/kg every 6 hours (TDD range 24 – 36 mg). Therefore the requested dose would be two - three times greater than the currently approved prophylactic dose for a 4 week old infant weighing 4 kg.

The approval of the weight based dosing recommendation was based on pharmacokinetic analyses and simulations provided by the Applicant that reasonably supported the change in approved pediatric dosing recommendations from a BSA based dosing to a weight based dosing regimen and from three times to twice daily and that showed that these changes would have little effect on antiviral activity and/or resistance development because the anticipated AUC (0- 24) ZDV values were comparable to the pediatric historical values and to approved adult twice daily data. There were some deviations in predicted exposures in the analyses used to support the twice daily mg/kg dosing recommendations compared to the approved BSA regimen (range 15% (Europe) - 36% (US) lower to 22% higher) however, it was determined from the available literature and PK modeling data that there was adequate safety to support the potential increase in exposure and further the potential decrease in total daily dose was not expected to adversely impact overall efficacy as numerous drug-drug interactions lead to a similar decreases in exposure without loss of efficacy (for example with ritonavir) and without the need for changes in dosing recommendations.

The approved mg/m² (BSA) dosing recommendations remained in the label for those situations where dosing on an 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 was included in the Dosage and Administration section of labeling.

Adequate safety information was available from pediatric trials where doses higher than the US approved dose were utilized that showed that the safety profile of Retrovir does not change at higher doses up to 240 mg/m² orally every six hours (TDD 960 mg/m²). It should be noted however that the data available to support total daily Retrovir doses of 720 – 960 mg/ m² are limited.

The efficacy and safety extrapolations of twice daily mg/kg dosing applied to subjects within the 5th -95th percentiles of CDC growth charts.

Financial Disclosure: The submitted package consisted only of previously reviewed studies, pharmacokinetic re-analyses, and literature references. As only previously reviewed studies were submitted for which GSK, the Applicant, adequately provided the required information regarding disclosed financial arrangements of the investigators and as this information was reviewed at the time of the original study reviews, no significant issues were raised regarding the integrity of the data presented in this NDA

ZDV Clinical Pharmacology Background in children:

In children over the age of 5 to 6 months, the pharmacokinetic profile of Retrovir is similar to that in adults. ZDV is well absorbed from the gut and, at all dose levels studied; its bioavailability was 60 to 74% with a mean of 65%. C_{max} levels were 4.45 micromole (1.19 micrograms/ml) following a dose of 120 mg/m² and 7.7 micromole (2.06 micrograms/ml) at 180 mg/m² (using Retrovir oral solution). With intravenous (i.v.) dosing, the mean terminal plasma half-life and total body clearance were 1.5 h and 30.9 mL/min/kg respectively. The data available on the pharmacokinetics in neonates and young infants indicate that glucuronidation of Retrovir is reduced with a consequent increase in bioavailability, reduction in clearance and longer half-life in infants less than 14 days old but thereafter the pharmacokinetics approach those reported in adults and stabilize after the 6 month age point.

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 primary question to the CP Review Team was “Does the maturation of clearance between 4 to 6 weeks warrant dose adjustment in this age group? Does clearance vary significantly between 4 and 6 weeks of age?”

Pharmacokinetic data from the following studies was used by the Applicant and the Agency review team to support the extension of the lower limit of the 12 mg/kg twice daily dose to pediatric patients ages 4 weeks to less than 6 weeks of age but who weigh between 4 – < 9 kilograms. Therefore only the age is modified but not the weight band.

Table 2 Summary of Published Zidovudine PK Studies in Full Term Infants

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

Individual Retrovir CL/F and dose-normalized AUC values were only available from five patients in the 4 to 6 week age range and summary PK data (geometric mean, 95% CI) were available from an additional fifteen 6-week old patients in COL10015

These analyses showed that Retrovir CL/F is low at birth and rapidly increases during the first two weeks of life. Patients in the 4 to 6 week age range have CL/F (and dose-normalized AUC) that are similar to older children (6 to 20 weeks). Similar trends were noted for Cmax although the available Cmax data were more limited.

PK simulations (Applicant Analyses): The distribution of predicted CL/F for 4-, 5-, and 6-week old infants based on the Monte Carlo simulations showed that there is considerable overlap in the distribution of CL/F expected for 4-, 5-, and 6-week old infants. The median CL/F for 4- and 5-week old infants were 13% and 6% lower, respectively, than the median CL/F for 6-week old infants suggesting that CL/F in 4- and 5-week old infant population is similar to CL/F in 6-week old infants. Therefore, 4- to 5-week old infants could receive the same mg/kg dose as 6 week old infants.

Table 5 Predicted CL/F (mL/min/kg) by Age (4-6 weeks)

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

Comment: The Agency Clinical Pharmacology Review Team agreed with the Applicant's analysis and determined that anticipated exposure in infants 4 weeks of age weighing 4 kg is not anticipated to differ greatly from that achieved in infants 6 weeks of age weighing 4 kg. As per the CP Review:

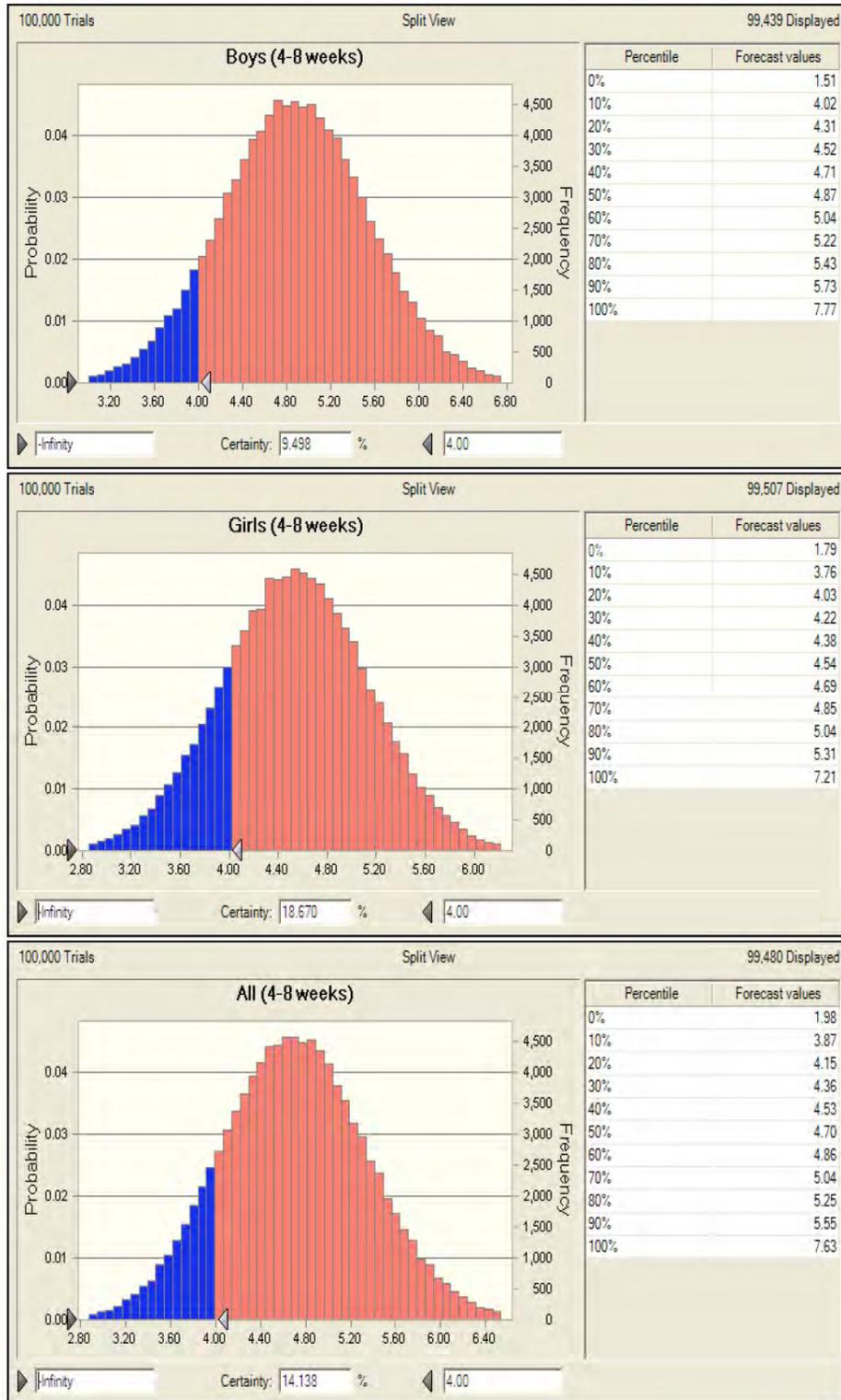
"The daily zidovudine AUCs from the proposed 24 mg/kg/day dose in 4-week and 5-week old pediatric patients are predicted to be 16% and 7% higher, respectively, than in 6 week old patients. ”.

This increase is not anticipated to be clinically significant from an efficacy or a safety perspective and is generally lower than that observed with drug-drug interactions.

Expected Weight of Infants ages 4 - < 6 weeks of age:

Based on percentile data from the CDC Growth charts website (<http://www.cdc.gov/nchs/about/major/nhanes/growthcharts/datafiles.htm>), 85.9% of infants (combined male and female) 4 weeks of age or greater are expected to have a body weight of 4 kg or greater. Current dosing recommendations start at 4 kg. Therefore these recommendations can apply to at least 85.9% of infants ages 4 weeks and older (10th – 90th percentiles).

Figure 7 Distribution of Body Weight (kg) of Infants 4 to 8 Weeks of



1. Red indicates subjects with body weight $\geq 4\text{kg}$; blue indicates subjects with body weight $< 4\text{kg}$.

Efficacy:

No new efficacy data was submitted in support of this application. The efficacy of Retrovir is well-established in both adults and pediatric patients. The efficacy evaluation of the weight based twice daily regimen relied on previous findings from the original approval in pediatric patients receiving Retrovir three times daily (360 mg/m²/day – 640 mg/m²/day) and adults receiving Retrovir 600 mg total daily dose in divided doses and on pharmacokinetic assessments comparing the twice daily and three times daily regimens and conversion of mg/m² to mg/kg dosing. Trials comparing twice daily and three time daily dosing in children are not available. Given the similarity in Retrovir exposures between twice daily and three times daily dosing in adults and no discernable efficacy limitations of either regimen in adults, the extrapolation of adult conclusions of efficacy to the pediatric population was reasonable. The knowledge that Retrovir clearance and phosphorylation is similar between adults and children and that on average Retrovir exposures are higher in children compared to adults and reflect higher mg per kg dose in children compared to adults provided further support to the extrapolation argument. Although there may be some deviations in predicted exposures for the proposed twice daily mg/kg dosing recommendations in infants ages four to less than six weeks (approximately 7 - 16% higher for five and four week old infants respectively compared to approved mg/kg dosing), these deviations are anticipated to occur infrequently and for short periods as they will mostly occur in very young patients who are in periods of rapid growth. These deviations are not expected to adversely impact overall efficacy.

Safety:

Many years of safety data with Retrovir in adults and children at various doses and dosing regimens are available. The safety profile of Retrovir is well-characterized and includes gastrointestinal intolerance and hematologic abnormalities, specifically anemia and neutropenia. Limited data from studies in children evaluating 640 - 960 mg/m²/day show no discernable safety differences compared to the approved BSA dosing regimen of 480 mg/m²/day.

Retrovir twice daily in children has been used extensively off label worldwide for years and has been used in several clinical trials including CNAA3006 which supported approval for abacavir in children. This study was reviewed for the NDA 19-910/S-033 submission. No new or unexpected Retrovir -associated adverse events have been reported in recent years. Overall an adequate safety database exists, including safety data at higher doses and exposures than the currently approved regimen to support approval in children where potentially a 7 - 16% increase in Retrovir exposures is possible for a 4 kg five or four week old child.

Clinical Studies Used to Evaluate Safety

No new safety data were submitted. All data summarized were based on literature references.

Data from the historical pediatric studies (ACTG studies 152, 125, 300 and P53-04) as published in the literature were evaluated for safety to support the predicted up to 15% increases in exposures in children with the twice daily regimen. Further details of these studies can be found in the MOR of 19-910/S-033 dated September 18, 2008.

Table of Literature Based Studies Used to support Safety of Weight Based Twice Daily Dosing Regimens in Pediatric Patients

Study ID	ZDV Treatment Regimens	Patient #	Ages/Weight	TOTAL Daily Dose	Safety	Comments
ACTG 152	120 or 180 mg/m ² q6 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	TDD 720 mg/m ² exceeds proposed doses
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	Comparable safety high and low dose, more neutropenia high dose. TDD 720 mg/m ² exceeds proposed doses
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	TDD 960 mg/m ² exceeds proposed doses
ACTG 300	ZDV/3TC ZDV/3TC + DDI ZDV + DDI	N = 236 N= 235 N = 125	42 d – 15 yrs	360 mg/m ²	Yes	More neutropenia ZDV versus liver for other groups

The data from these studies however did not extend to infants less than 6 weeks of age. In order to assess for unexpected or serious safety issues in infants within the 4 – 6 week range, the pharmacokinetic studies submitted in support of the application were reviewed. In addition a search of ACTG trial data from PK studies in neonates was performed and the safety from the relevant publications was summarized. ODS was requested to search the Agency postmarketing safety database for serious safety adverse events including deaths occurring in infants of this age group attributable to Retrovir treatment.

Study ID	ZDV Treatment Regimens	Patient #	Ages/Weight	Discontinuations	Safety	Comments
Boucher 1993 (PACTG 049)	2 mg/kg IV SD days 1 and 14 then 2 mg/kg q6PO (N =7) OR 2 mg/kg IV days 1 and 46 then 2 mg/kg q6h PO days 3 – 44 (N = 25)	N = 32 26 ≤ 14 d 6 > 14 d	1 d – 3 mos Mean weight at entry: 3.46 kg (1.54 – 4.43)	6 DC anemia 1 DC irritability and neutropenia (2 wk old girl)	17/32 anemia between 3- 11 weeks of age at doses ≥3 mg/kg 9/17 neutropenia	Irritability one patient at 4 weeks. Resolved off ZDV Anemia spont. resolved 9/17. Neutropenia resolved spont. 7/9
Thailthumyanon 1999	4 mg/kg PO q 12 h	N = 14	No Info	No info	No info	PK only. Concluded that at wk 6 ZDV exposure at 4 mg/kg BID consistent with adult 300 BID dose
Moodley 1998	3TC 4 mg/kg BID PO alone or with ZDV 2 mg/kg QID for 7 days	N = 20	Not reported	None	No related SAEs. 4 reported SAEs (meconium aspiration, ARF. Gastroenteritis, jaundice). Not reported which arm	Retrovir elimination at 1 wk significantly increased compared to immediately after birth. Absorption in neonates variable because of irregular GI function and irregular feeding.
Moodley 2001	4 mg/kg ZDV q12 PO with 2 mg/kg 3TC PO for	N = 16	Median 3.2 kg (2.4 – 4.3 kg)	None	1 TR SAE: anemia 1 non TR death: acidosis 4 non TR events	PK CL/F increased by 2fold over 7 days. Cmax down by 37% compared

	7 days				(infection, diarrhea, hep/bil x 2) 12/16 had decrease in Hg Greatest decrease in neonates with highest Cmax and AUC day 1	to Day 1, AUC down by 52%
Mirochnink 1999 (Population PK from pooled data 6 studies)	Varied 2 – 4 mg/kg	N = 83 (26 weeks to full term)	0.71 – 6 kg	Not reported	Not reported	ZDV elimination slow immediately after birth but increases rapidly in term infants During 1st week. Plateau by 4 to 8 weeks of age. Increase in elimination slower in premature infants.
ACTG 076	2 mg/kg q 6 h for 6 weeks or placebo	N =206 ZDV 209 placebo	3160 gm (range 1040-5267 gm)	46 (22 ZDV, 24 placebo) including 11 on each arm due to AEs	Unspecified number of anemia with peak at 3 weeks of life 7 deaths before 6 weeks (3 ZDV/4 placebo) due to HIV or trauma	ZDV effective in reducing HIV 1 transmission
ACTG 250	2 mg/kg q 6 h for 6 weeks	N = 22	Not provided	Not stated	None	
ACTG 82	No dosing in infants	NA	NA	NA	NA	ZDV OK in mothers and neonates

The ODS review and conclusions are summarized below:

The ODS review provided an overview of adverse events in pediatric patients 28 to 60 days of age in association with zidovudine reported to FDA's Adverse Event Reporting System (AERS) as of August 28, 2009.

The AERS search identified 123 reports (crude count) in association with zidovudine as in patients 28 to 60 days of age. Adverse events with MedDRA preferred term crude counts of ≥ 4 were compared with the current zidovudine label. The majority of adverse events with MedDRA preferred term crude counts of ≥ 4 involve labeled events (such as neutropenia, anemia). No unusual pattern or trend is noted in the unlabeled events with crude counts of ≥ 4 with the exception of six cases reporting the same medication error: 10-fold dosing errors in which the zidovudine dose was administered in mLs instead of mg. Adverse events reported in the 10-fold overdose cases include labeled events such as anemia, neutropenia, increased LFTs, fever, constipation and unlabeled events included pneumopathy, septic staphylococcus aureus infection, severe poor feeding, lethargy, pallor and heart murmur. The unlabeled events may be due to sequelae of zidovudine induced neutropenia (pneumopathy, septic staphylococcus aureus infection) or anemia (pallor, poor feeding, lethargy, heart murmur).

Sixteen unduplicated cases with an outcome of death were identified. The majority of cases with an outcome of death provide insufficient information to assess causality (such as HIV status or cause of death), however zidovudine may have contributed to 4 deaths that report known adverse events associated with zidovudine: one death involving hyperlactatemia in an infant reported to be HIV negative at birth, two deaths in patients with unknown HIV status who experienced neutropenia and one death in a patient with unknown HIV status who had epilepsy in conjunction with hyperlactatemia.

The ODS review concluded that "Based on the AERS overview no labeling recommendations are suggested at this time".

Comment: The Clinical Review Team agreed with the ODS recommendations. The deaths were reviewed and similar conclusions were drawn. That is that a direct attribution of causality to Retrovir could not be made although the contributory effects of Retrovir in 4 of the deaths was a possibility.

All of the adverse events associated with Retrovir usage in the four to less than six week old age group are currently labeled. Of concern is the increased incidence of overdoses due to dosing errors with resultant increased incidence of adverse events. It is recommended that ODS continue to monitor for these occurrences and if they continue, further action may be indicated.

Safety from the literature studies are summarized below.

Boucher 1993: Multicenter, phase 1 study of the PK and safety of Retrovir in infants born to HIV infected women. Thirty-two symptom-free infants less than 3 months of age were

enrolled. The pharmacokinetics of Retrovir were evaluated in each infant after single intravenously and orally administered doses of Retrovir and during long term oral administration of the drug for four to six weeks. As new patients were enrolled doses of Retrovir were progressively increased from two to four mg/kg. Therapy was continued for up to 12 months in seven of the infants that proved to be infected with HIV. Of the 32 infants enrolled six were older than 14 days at the time of study start and 13 did not complete the study. There were seven (7) discontinuations due to AEs including six due to anemia and one due to irritability and neutropenia. 17 developed anemia while on the study. An additional three had evidence of anemia before Retrovir was started, nine developed neutropenia during the study. These events usually resolved spontaneously (9/17 anemia and 7/9 neutropenia). Retrovir was generally well tolerated. There were no deaths or SAEs reported.

Comment: Overall the percentage of infants developing anemia (> 50%) is higher than usually reported. A similar comment can be made regarding neutropenia. Three infants required transfusions however, in most case the hematologic events resolved spontaneously.

Thailthumyanon 1999: A phase 1, pharmacokinetic (PK) Study of 3TC and Retrovir administered to children born to HIV-1 Infected Pregnant Women. The objective of this Phase 1 study was to measure serum PK of 3TC (2 mg/kg q 12 h) and Retrovir (4 mg/kg q 12h) administered orally in combination. All newborns (N = 14) received this regimen for 6 weeks, No safety was provided.

Moodley 1998: Single center (Durban, South Africa), phase 2, open-label, repeat-dose, randomized, two-way, parallel-group study. Two groups of 10 women received either lamivudine alone (300 mg twice daily) or lamivudine (150 mg twice daily) with Retrovir (300 mg twice daily) before delivery (from 38 weeks gestation), intrapartum, and for 1 week after delivery. At the onset of labor, the women received either a single 300-mg lamivudine dose or 150 mg of lamivudine with 300 mg of Retrovir orally. Lamivudine oral dosing was continued every 12 h during labor. Women assigned to combination therapy also were given 300 mg of Retrovir orally every 3 h until delivery. In the absence of any life-threatening condition or severe laboratory abnormality, neonates were treated for 1 week in accordance with their mother's randomization, commencing 12 h after delivery. Neonates were given lamivudine orally—alone (4 mg/kg twice daily) or in combination with Retrovir (2 mg/kg 4 times/day).

Both lamivudine and lamivudine plus Retrovir were well tolerated. No woman or neonate discontinued treatment because of an AE, and no SAEs were considered related to study medication. Two neonates died at ages five and six months during follow-up; neither death was considered related to study drug. Four neonates experienced SAEs; however, after investigation, these were not considered treatment-related: acute renal failure, meconium aspiration, gastroenteritis, and jaundice.

Two neonates had “nonserious” AEs that may have been treatment-related. One neonate, who received combination therapy, had a rash on day 6 of therapy, which resolved

in 2 days. Another, who received lamivudine alone, had mild anemia (hemoglobin: 9.1 g/dL) at age 6 weeks, which resolved. Other unrelated adverse events were mainly ear, nose, and throat and lower respiratory tract infections.

Comment: No SAEs were attributed to Retrovir in this study.

Moodley 2001: Phase 1, repeat-dose, open-label study conducted to determine the PK and safety of Retrovir and lamivudine co-administered PO q 12 hours, in 16 neonates whose mothers were infected with HIV-1. Neonatal treatment was initiated 12 hours following birth with 4 mg/kg of Retrovir suspension plus 2 mg/kg of 3TC solution q12h for 1 week. Between days 1 and 7 of neonatal treatment, the neonatal clearance (CL/F of Retrovir and lamivudine increased by 2-fold and 1.6-fold, respectively reflecting hepatic and renal function maturation occurring during the first week of life. The every 12 hour regimen provided similar exposures to an every 6 hour regimen of ZDV. Both ARVs well tolerated. There was one SAE (anemia in one neonate). There was one non-treatment related death due to accidental acidosis associated with gastroenteritis. There were four non serious non- drug related adverse events in the neonates including two hepatobiliary events (not specified), one infection, and one diarrhea. Clinical laboratory was notable for decrease in mean serum hemoglobin from 15.4 g/dL to 10.3 g/dL by week 12 of life. The decreases were greater in six neonates including three with the greatest C_{max} values and three with the greatest AUC values on day 1.

Mirochnink 1999: Population Analysis of Retrovir PK in neonates through five months across studies. Included data from ACTG 049 (N = 29, 2 – 4 mg/kg), ACTG 076 (N = 2. 1.5 mg/kg), ACTG 082 (N = 18, no dosing of neonates), ACTG 239 (N = 12, 2 mg/kg q6 with DDI through 6 weeks) and ACTG 250 (N = 22, 2 mg/kg q6 through 6 weeks). No safety was provided.

ACTG 076: Double-blind, placebo-controlled, randomized study that enrolled pregnant, HIV-infected women and treated them with Retrovir (100 mg five times daily antepartum or intrapartum 2 mg/kg over 1 hour then 1 mg/kg per hour until delivery) or placebo. All infants born to these women were treated with Retrovir 2 mg/kg every 6 hours for six weeks. 477 women were enrolled and there were 415 live born infants. Twelve infants (5 Retrovir and 7 placebo) did not receive treatment for a number of reasons unrelated to Retrovir. 206 infants were randomized to ZDV and 209 to placebo. Forty six infants discontinued (22 Retrovir, 24 placebo) treatment before six weeks including 11 on each arm due to AEs. Mean birth weight was 3160 gm (range 1040-5267 gm). Short term toxicities included lower hemoglobin levels in newborns of Retrovir treated mothers but by 12 weeks of age the hemoglobin values between the two treatment arms were similar. There were eight fetal/neonatal deaths, none attributed to study treatment (5 Retrovir, 3 placebo) and there were 7 deaths beyond the neonatal period (2 Retrovir, 4 placebo). Two Retrovir and 4 placebo deaths were due to HIV infection and one Retrovir death was due to trauma.

ACTG 250: Assessment of PK and safety in nevirapine in pregnant women. All women and infants received standard Retrovir treatment (2 mg/kg q 6) for an unspecified period. No specific AEs were reported in the 22 infant that received Retrovir.

ACTG 82: PK assessment of Retrovir in mothers and newborns. No infants treated.

Safety Conclusions: Although the available safety database for neonates aged 4 – less than 6 weeks of age is limited in the number of patients it appears that the safety profile of Retrovir remains unchanged in this age group. This conclusion is also reflected in current labeling (section 6.1) from trials performed in support of the prophylaxis indication. Primary adverse events were hematologic (anemia, neutropenia) or gastrointestinal. In general these events appeared to occur more frequently in the younger patients however they did not lead to treatment discontinuations or transfusions. The frequency of overdose due to dosing errors should be monitored and if increased further actions will need to be discussed.

Use for the Prevention of Maternal-Fetal Transmission of HIV-1: In a randomized, double-blind, placebo-controlled trial in HIV-1-infected women and their neonates conducted to determine the utility of RETROVIR for the prevention of maternal-fetal HIV-1 transmission, RETROVIR Syrup at 2 mg/kg was administered every 6 hours for 6 weeks to neonates beginning within 12 hours following birth. The most commonly reported adverse reactions were anemia (hemoglobin <9.0 g/dL) and neutropenia (<1,000 cells/mm³). Anemia occurred in 22% of the neonates who received RETROVIR and in 12% of the neonates who received placebo. The mean difference in hemoglobin values was less than 1.0 g/dL for neonates receiving RETROVIR compared with neonates receiving placebo. No neonates with anemia required transfusion and all hemoglobin values spontaneously returned to normal within 6 weeks after completion of therapy with RETROVIR. Neutropenia in neonates was reported with similar frequency in the group that received RETROVIR (21%) and in the group that received placebo (27%). The long-term consequences of in utero and infant exposure to RETROVIR are unknown.

Pediatrics: Because the Applicant is proposing a new dosing regimen, PREA is triggered. Retrovir is approved for the prevention of maternal/fetal transmission of HIV-1 in neonates up to 6 weeks of age. Retrovir dosing for treatment of HIV-1 infection in children between four and less than 6 weeks of age is proposed in this supplement. The DHHS pediatric treatment guidelines support early diagnosis of HIV and switching from Retrovir 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 Retrovir dosing regimen for prevention in neonates is 2 mg/kg orally every 6 hours starting within 12 hours after birth and continuing through six 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 addressed in this application is to obtain dosing recommendations for children ages four weeks to less than six weeks of age. GSK has used Retrovir pharmacokinetic data in neonates and

pharmacokinetic modeling and simulation to propose twice daily weight-based dose recommendations for this age range.

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.

Risk/Benefit:

Retrovir is a preferred NRTI component of a first line anti HIV-1 treatment regimens for infants and children and is currently approved as a twice daily weight based dosing regimen for children ages six weeks or older or who weigh four kg or greater. The benefits of the twice daily weight based regimen included increased adherence and greater accuracy of dosing. Similar benefits exist for extending this regimen to patients ages four to less than six weeks who weigh between four and less than nine kg. Based on pharmacokinetic simulations no differences in efficacy or safety are predicted in the four to less than six week age group. At the lower end of the range (infants 4 to 5 weeks) there may be increases in C_{max} of up to 15%. The known safety profile of Retrovir in conjunction with limited clinical trial data support dosing of up to 960 mg/m² daily. In a worst case scenario 15% higher than expected exposures may be achieved. These possible increases would be balanced by the more rapid clearance of Retrovir in this age group.

Recommendation: An approval is recommended for extending the lower age limit for pediatric dosing recommendation for the treatment of HIV-1 infection with Retrovir to 4 weeks of age.

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

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/s/

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09/28/2009

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