OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: 20-659 (oral solution) 20-945 (capsule)	Submission Date(s): 04-06-2005
Brand Name	Norvir
Generic Name	Ritonavir
Reviewer	Yuanchao (Derek) Zhang, Ph.D.
Team Leader	Kellie S. Reynolds, Pharm.D.
OCPB Division	Division of Pharmaceutical Evaluation III
OND Division	DAVDP
Sponsor	Abbott
Other NDA(s)	20-680 (original capsule, no longer marketed)
Relevant IND(s)	43-718
Submission Type; Code	SE5 (Pediatric Exclusivity); Priority
Indication	Treatment of HIV-1 infection

1 Executive Summary

1.1 Recommendations

The Office of Clinical Pharmacology and Biopharmaceutics (OCPB) has concluded that the clinical pharmacology information submitted to this NDA supplement is adequate to support the claim for Pediatric Exclusivity for Norvir and to make the relevant labeling revisions. Based on the submitted pharmacokinetic data, it is acceptable to expand the pediatric age range from > 2 years of age to > 1 month of age. The dosing regimen for HIV-infected pediatric patients does not change (350 to 400 mg/m^2 BID).

1.2 Post Marking Commitments

None

1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

Application Contents

Two studies provide pharmacokinetic data in HIV infected patients <2 years old of age.

Study PACTG 345 is the main study to support the Pediatric Exclusivity claim. The ritonavir dose regimens studied were 350 and 450 mg/m^2 BID. The number of subjects with pharmacokinetic data in each age group are as follows:

1 month to < 3 months:	18
3 months to < 6 months:	10
6 months to < 2 years:	13

Study PACTG 366 is a supportive study to the Pediatric Exclusivity claim. The ritonavir dose regimen studied was 350 mg/m^2 BID. The number of subjects with pharmacokinetic data in the age range of >6 months to 2 year was 9.

Pharmacokinetics of Ritonavir in Pediatric Patients

In Study PACTG 345, ritonavir exposures in infants and children < 2 years of age after 350 or 450 mg/m^2 BID dosing were similar to historical data in older children after 250 to 350 mg/m^2 BID dosing, with the exception that steady-state trough concentrations were lower in children < 2 years of age. There was high variability in ritonavir exposure. Higher ritonavir exposures were not evident with 450 mg/m^2 BID dose compared to the 350 mg/m^2 BID dose.

Table 1. Mean ± SD (Median) Pharmacokinetic Parameters of Ritonavir at Steady State Across Different Age Groups (All BID Regimens)

	1 month – 2 yrs		Children > 2 yrs				Adults	
	350 mg/m^2 (N = 14)	450 mg/m^2 (N = 27)	250 mg/m^2 (N = 7)	300 mg/m^2 (N = 9)	350 mg/m^2 (N = 11)	400 mg/m^2 (N = 10)	400 mg (N = 13)	600 mg (N = 10)
$C_{max,ss}$ (μg/mL)	10.1 ± 7.9 (5.6)	8.2 ± 6.8 (6.9)	9.7 ± 4.9 (9.6)	10.9 ± 3.7 (9.8)	11.4 ± 4.2 (12.4)	16.0 ± 9.9 (11.4)	7.1 ± 2.7 (6.0)	11.2 ± 3.6 (10.9)
$C_{trough,ss}$ (μg/mL)	1.4 ± 1.8 (0.86)	1.4 ± 1.9 (0.75)	3.3 ± 3.4 (2.3)	2.2 ± 1.4 (1.7)	2.1 ± 1.9 (2.0)	5.5 ± 4.0 (5.9)	1.8 ± 0.9 (1.5)	3.5 ± 2.5 (2.8)
AUCss (μg•h/mL)	61 ± 53 (40)	66 ± 54 (50)	58 ± 33 (56)	63 ± 27 (56)	60 ± 27 (52)	100 ± 64 (97)	49 ± 21 (46)	77 ± 32 (69)
CL/F (L/h)	3.0 ± 1.6 (2.9)	3.1 ± 2.0 (2.7)	--	--	--	--	9.5 ± 3.7 (8.7)	8.8 ± 3.2 (8.6)
CL/F (L/h/m^2)	8.4 ± 5.2 (7.8)	8.9 ± 5.7 (7.8)	6.0 ± 3.9 (4.4)	5.7 ± 2.7 (5.3)	7.4 ± 4.0 (6.8)	6.4 ± 5.2 (4.2)	5.2 ± 2.0* (4.8)	4.9 ± 1.7* (4.8)

Data for infants and children (1 month – 2 yrs.) are from the current study using Week 4 values.
Data for children > 2 yrs. are from Study M95-310 as previously submitted in NDA 20-659/S-008, approved 3/14/97.
Data for adults are from Study M93-112 as previously submitted in IND 43,718, Serial No. 99 in support of NDA 20-659, approved 3/1/96.
BSA of 1.818 m^2 was used to calculate the normalized values of CL/F (L/h/m^2)

In Study PACTG 366, ritonavir exposures in children ≤ 2 years of ago were lower than in older children receiving 350 mg/m^2 BID dose, and also were lower than those observed in the PACTG 345 study.

The data submitted with this sNDA adequately describe the RTV exposure in HIV-infected pediatric patients. It appears that increasing the RTV dose beyond 400 mg /m^2 will not lead to increased RTV concentrations.

Pending on the DSI's inspection results, Study 366 may need to be excluded from the review. However, it will have no impact on the overall conclusions of this review.

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/s/

Kellie Reynolds
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