CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-226/S-002

21-251/S-002

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA	: 21-226/21-251 (SLR-002)	**REVIEWER**: Jooran S. Kim, Pharm.D.	
TYPE	: Labeling supplement	**SUBMISSION DATE**	: 01/02/01
DRUG	: lopinavir/ritonavir (capsules)	**DATE RECEIVED**	: 01/02/01
SPONSOR	: Abbott	**DRAFT REVIEW**	: 01/09/01

BACKGROUND: The applicant has proposed changes related to the pediatric dosing table in the Kaletra package insert. These changes address the concerns that children on the upper end of the weight range may be underdosed. This labeling supplement refers to the Kaletra Final Approved Labeling dated October 2000.

PROPOSED LABELING CHANGES:

The following highlighted changes were proposed by the applicant, under "DOSAGE ADMINISTRATION; Pediatric Patients" of the Kaletra package insert:

Weight (kg)	Dose (mg/kg)*	Volume of oral solution BID (80 mg lopinavir/20 mg ritonavir per mL)
Without nevirapine or efavirenz		
7 to <15kg	12 mg/kg BID	
7 to 10 kg		1.25 mL
>10 to <15 kg		1.75 mL
15 to 40 kg	10 mg/kg BID	
15 to 20 kg		2.25 mL
>20 to 25 kg		~~2.5~~ [redacted] mL
>25 to 30 kg		~~3.0~~ [redacted] mL
>30 to ~~40~~ [redacted] kg		~~3.5~~ [redacted] mL
[redacted]		[redacted]
>40 kg	Adult dose	5 mL (or 3 capsules)

* Dosing based on the lopinavir component of lopinavir/ritonavir solution (80 mg/20 mg per mL).
Note: Use adult dosage recommendation for children >12 years of age.

Concomitant therapy: Efavirenz or nevirapine: A dose increase of KALETRA oral solution to 13/3.25 mg/kg for those 7 to <15 kg and 11/2.75 mg/kg for those 15 to ~~50~~ [redacted] kg (approximately equivalent to 300/75 mg/m^2) twice daily taken with food, up to a maximum dose of 533/133 mg in children ~~>50~~ [redacted] kg twice daily should be considered when used in combination with efavirenz or nevirapine in treatment experienced children 6 months to 12 years of age in which reduced susceptibility to lopinavir is clinically suspected (by treatment history or laboratory evidence). The following table contains dosing guidelines for KALETRA oral solution based on body weight, when used in combination with efavirenz or nevirapine in children (see **CLINICAL PHARMACOLOGY – Drug Interactions** and/or **PRECAUTIONS** – Table 6).

Weight (kg)	Dose (mg/kg)*	Volume of oral solution BID (80 mg lopinavir/20 mg ritonavir per mL)
With nevirapine or efavirenz		
7 to <15 kg	13 mg/kg BID	
7 to 10 kg		1.5 mL
>10 to <15 kg		2.0 mL
15 to ~~50~~ [redacted] kg	11 mg/kg BID	
15 to 20 kg		2.5 mL
>20 to 25 kg		3.25 mL
>25 to 30 kg		4.0 mL
>30 to ~~40~~ [redacted] kg		4.5 mL
[redacted]		[redacted]
>40 to ~~50~~ [redacted] kg		~~5.0~~ [redacted] mL ~~(or 3 capsules)~~
~~>50~~ [redacted] kg	Adult dose	6.5 mL (or 4 capsules)

* Dosing based on the lopinavir component of lopinavir/ritonavir solution (80 mg/20 mg per mL).
Note: Use adult dosage recommendation for children >12 years of age.

CONCLUSIONS: With the proposed changes in weight ranges and volume of oral solution administered, doses achieved will be close to recommended mg/kg doses for each weight category. The proposed changes are, therefore, acceptable from a Clinical Pharmacology perspective.

COMMENTS TO THE SPONSOR:

In addition to your proposed changes, please add the following highlighted text (retaining the bold font) to the paragraph preceding the dosing tables:

"In children 6 months to 12 years of age, the recommended dosage of KALETRA oral solution is 12/3 mg/kg for those 7 to <15 kg and 10/2.5 mg/kg for those 15 to 40 kg (approximately equivalent to 230/57.5 mg/m^2) twice daily taken with food, up to a maximum dose of 400/100 mg in children >40 kg (5.0 mL or 3 capsules) twice daily. [redacted] the following table contains dosing guidelines for KALETRA oral solution based on body weight. When possible, dose should be administered using a calibrated dosing syringe."

Jooran S. Kim, Pharm.D.
Pharmacokinetics Reviewer, DPEIII

Concurrence: Kellie S. Reynolds, Pharm.D.
Pharmacokinetics Team Leader, DPEIII

/s/

Jooran Kim
1/17/01 04:20:20 PM
BIOPHARMACEUTICS

Kellie Reynolds
1/24/01 03:22:53 PM
BIOPHARMACEUTICS