CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA:	20-779 SE5 042, 20-778 SE5 022 and 21-503 SE5 001
Submission Dates:	06/19/2003, 08/01/2003, 09/25/2003, 10/23/2003, 10/30/2003 and 03/10/2004
Brand Name:	Viracept®
Generic Name:	nelfinavir mesylate
Formulation:	250 mg tablets, 625 mg tablets and 50 mg/g oral powder
Applicant:	Agouron Pharmaceuticals, Inc, A Pfizer Company
Reviewer:	Robert O. Kumi, Ph.D.
Team Leader:	Kellie Reynolds, Pharm.D.

EXECUTIVE SUMMARY

Viracept® (nelfinavir mesylate, tablets and oral powder) in combination with other antiretroviral agents is indicated for the treatment of HIV infection in children two years of age and older and in adults. Pharmacokinetic information was provided in NDAs 20-779 SE5 042, 20-778 SE5 022 and 21-503 SE5 001 to fulfill the Pediatric Exclusivity Written Request and a Phase IV Commitment. The listed NDA submissions provide the following pediatric information:

- Nelfinavir dosing for children < 2 years of age (birth to 2 years).
- New nelfinavir dosing recommendations for children between 2 and 13 years of age.
- Nelfinavir pharmacokinetics following twice daily administration of nelfinavir in children.

Six study reports were included in the current submission to support nelfinavir dosing recommendations in pediatric subjects: AG1343-524, AG1343-556, PACTG 725, PACTG 353, PENTA 7 and "German Study". The applicant sponsored only two of these studies, AG1343-524 and AG1343-556. In all studies the pharmacokinetics, safety and efficacy of nelfinavir were assessed to varying degrees.

A. Recommendation

The Office of Clinical Pharmacology and Biopharmaceutics has reviewed the information submitted to NDAs 20-779 SE5 042, 20-778 SE5 022 and 21-503 SE5 001. The NDA supplements provide adequate information to change the recommended nelfinavir dose for pediatric patients between 2 and 13 years of age **from 20 to 30 mg/kg TID with a meal to 25 to 35 mg/kg TID with a meal**. The submitted pharmacokinetic data do not support BID dosing for pediatric patients between 2 and 13 years of age; the nelfinavir exposure at the studied BID doses is higher than exposure achieved at approved doses in adults. The medical reviewer evaluated the safety data from study PACTG 377/725 to determine whether the label should include a BID dosing regimen for children between 2 and 13 years of age. The medical reviewer concluded that the safety data support a dose of 45-55 mg/kg BID. The submitted pharmacokinetic data do not support dosing recommendations for pediatric patients less than 2 years of age. None of the doses studied in this younger age group reliably achieved the target nelfinavir exposure associated with efficacy in adult studies (arithmetic mean AUC_{24} of 44 and 53 μg*hr/mL in two studies).

The label will be updated to include pharmacokinetic data for all pediatric age groups that were studied. The inclusion of these data will make health care providers aware of the high pharmacokinetic variability associated with nelfinavir use in young children.

Pediatric Exclusivity Determination

The FDA Pediatric Exclusivity Board granted the applicant Pediatric Exclusivity on September 4, 2003. The Board determined that the applicant had adequately fulfilled the terms of the Pediatric Written Request for Viracept.

Fulfillment of Phase IV Commitment

The applicant provided sufficient data to fulfill the Phase IV commitment to evaluate the pharmacokinetics of twice daily dosing of Viracept with the oral powder in pediatric patients. PACTG 353, PACTG 725, PENTA 7 and the German Study provide BID dosing information.

B. Phase IV Commitments

There are no phase IV commitments. The review team determined that additional pharmacokinetic data in pediatric patients less than 2 years of age are unlikely to allow selection of a dose for this age group, due to the high variability observed in the submitted studies.

C. Summary of Clinical Pharmacology Findings

NDAs 20-779 SE5 042, 20-778 SE5 022 and 21-503 SE5 001 provide information from six pediatric studies in which nelfinavir was coadministered with other antiretroviral agents. These studies were submitted to aid in nelfinavir dose selection across the pediatric age range of birth to 13 years of age. Currently, dosing information is available for children between 2 and 13 years of age: nelfinavir dose is 20 to 30 mg/kg TID. Pediatric subjects received nelfinavir as tablet, crushed tablet mixed with liquid, or oral powder mixed with liquids or food. Both BID and TID regimens were evaluated: TID doses ranged from 10 mg/kg to 35 mg/kg and BID doses ranged from 14 mg/kg to 75 mg/kg. The six studies are listed below; please refer to individual study reviews for additional study information. All studies were conducted in children born to HIV-infected mothers.

1) AG1343-524, TID dosing in children between 1.4 and 13 years of age (n = 17). This study was reviewed with original NDA.
2) AG1343-556, TID dosing in children between 0.6 to 12.7 years of age (n = 119).
3) PACTG 353, TID and BID dosing in children 0.02 to 0.1 years (1 week to 6 weeks) of age (n = 20).
4) PACTG 725, BID dosing in children between 3.4 and 11 years of age (n = 6).
5) PENTA 7, TID and BID dosing in children between 0.2 to 0.7 years (2.4 to 8.5 months) of age (n = 16).
6) "German Study", TID (n = 17) and BID (n = 18) dosing in children between 2 and 15 years of age.

Key Clinical Pharmacology Findings

- Pharmacokinetic results from all pediatric studies were characterized by high inter-individual pharmacokinetic **variability,** as is observed in the adult population. In most pediatric studies, variability, measured by CV %, was > 50 %. The sources of variability were not identified, but are likely due to myriad factors, such as nominal vs. actual dose administered, varying absorption, dosing conditions (e.g. food type), compliance, and small numbers of patients. Data were most variable in Study 556, which employed a sparse sampling population pharmacokinetic approach.

- Numerically, the mean nelfinavir **apparent oral clearance**, normalized by body weight (CL/F_{BW}), appeared to be dependent on age. as shown in Table I.

Table I: Mean Nelfinavir CL/F_{BW} in children

		Mean ± SD NFV CL/F_{BW} (L/hr/kg)	
Age Category	Study ID	BID Regimen	TID Regimen
1 week old	353	2.17 ± 1.30 (n = 10)	Not evaluated
6 weeks old	353	2.89 ± 4.52 (n = 10)	Not evaluated
> 6 weeks < 1 year (2.4 to 8.5 months)	PENTA 7	4.23 ± 1.78 (n = 15)	3.36 ± 0.94 (n = 4)
3 – 11 years old	725	1.32 ± 0.65 (n = 6)	Not evaluated
2- 13 years old	524	Not evaluated	1.25 ± 0.55 (n = 14)
> 18 years old (adults)	Control	Not evaluated	0.72 ± 0.43 (n = 30)

- The tablet and oral powder had similar **bioavailability** in children; generally pediatric patients preferred receiving the intact or crushed tablet rather than the oral powder.

- Some of the pediatric dosing regimens evaluated (Table II), produced nelfinavir exposure that was comparable to that in adults receiving approved adult dosing regimens. The exposure in other pediatric age groups, who received varying nelfinavir doses, exceeded or was below the target adult exposure.

- The applicant attempted to show an exposure-response (population pharmacokinetic-pharmacodynamic) relationship for nelfinavir in Study 556; the applicant concluded that nelfinavir $AUC_{24} \geq 33$ μg·hr/mL (geometric mean) was associated with adequate efficacy and safety in pediatric patients. The Office of Clinical Pharmacology does not agree with the applicant's conclusion due to shortcomings of the exposure-response analyses.

- The data used to select dosing regimens for pediatric patients in the various age groups are summarized in Table II. For a majority of the age ranges, it is not possible to recommend a dose. Food increases nelfinavir exposure; thus, Viracept should be taken with food to optimize therapy.

Table II: Nelfinavir Steady State Exposure Measures in Adult and Pediatric Patients and Dosing Recommendations (Applicant vs. Clinical Pharmacology/Biopharmaceutics Reviewer)

Age group	**Study ID**	**Approximate Dose (mg/kg)**	**AUC_{24} (μg·hr/mL)**	**AUC Conclusion**	**Dosing Recommendation**	
Adults and older children				**Comment**	**Applicant's**	**Reviewer's**
> 18 years (n =10)	542	18 mg/kg BID^	52.8 ± 15.7	Target exposure	Not Applicable	Not Applicable
> 18 years (n = 11)	542	11 mg/kg TID^	43.6 ± 17.8	Target exposure	Not Applicable	Not Applicable
2 –13 years (n = 14)	524	22 ± 3 TID	56.1 ± 29.8	Acceptable	25 – 35 TID	25 – 35 TID
3 – 11 years (n = 6)	725	53 ± 4 BID	101.8 ± 56.1	High	50 – 60 BID	None
2 - 15 years (n = 18)	German	40 ± 9 BID	72.7#	High	Data were provided as supportive evidence.	
2 - 15 years (n = 17)	German	24 ± 5 TID	47.7#	Acceptable		
6 weeks to 2 years						
6 weeks to < 2 months	No studies conducted in this age group				40 – 50 TID	None
					60 – 75 BID	None
2 – 9 months (n = 12)	PENTA 7	66 ± 8 BID	37.2 ± 19.2	Low	60 – 75 BID	None
2 – 9 months (n = 4)	PENTA 7	39 ± 4 TID	33.8 ± 8.9	Low	40 – 50 TID	None
10 months to 2 years	PK data (Study 556) were not reliable for this age group				40 – 50 TID	None
					60 – 75 BID	None
Birth to 6 weeks						
6 weeks (n = 10)	353	37 ± 7 BID	44.1 ± 27.4	Acceptable, but highly variable	40 BID	None
6 weeks	TID regimen was not evaluated				None	None
1 week (n = 10)	353	29 ± 12 BID	45.8 ± 32.1	Acceptable, but highly variable	40 BID	None
1 week	TID regimen was not evaluated				None	None
Birth (0 weeks)	Neither the TID nor the BID regimen were evaluated				None	None

^ dose approximated by dividing 1250 mg by 70 kg or 750 mg by 70 kg

median values reported and range not available

Date_____

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Robert O. Kumi, Ph.D.,
Clinical Pharmacology Reviewer

Concurrence:

Date_____

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Kellie Reynolds, Pharm.D.
Clinical Pharmacology Team Leader

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/s/

Robert Kumi

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