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APPLICATION NUMBER:

22-116

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Number	22-116
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Submission Code	N
Letter Date	15 December 2006
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Reviewer Name	Yodit Belew, M.D.
Review Completion Date	June 14, 2007
Established Name	Fosamprenavir
Trade Name	Lexiva® Oral Suspension
Therapeutic Class	Anti-HIV-1 Protease Inhibitor
Applicant	GSK, Inc.
Priority Designation	P
Formulation	Oral Suspension
Dosing Regimen	FPV 30mg/kg BID (max 1400mg/day (age >2 years old) FPV 18mg/kg plus RTV 3mg/kg BID (max 1400/200 mg/day) (ages >6 years old)
Indication	Treatment of HIV-1 infection
Intended Population	Pediatric patients

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

This NDA seeking approval of Lexiva® (fosamprenavir, FPV) Oral Suspension for use in pediatric patients and patients with impaired hepatic function should be approved.

GlaxoSmithKline (the Applicant) submitted adequate data characterizing the pharmacokinetics of Lexiva Oral Suspension in pediatric patients that supports a dose of FPV 30 mg/kg BID (2-18 years old) and FPV18 mg/kg BID plus ritonavir 3 mg/kg BID (ages 6-18 years old). This conclusion is reached following review of the application containing safety and antiviral activity data from 144 HIV-1 infected pediatric patients aged 2 to 18 years treated with Lexiva® Oral Suspension or Lexiva Tablets in combination with other antiretroviral agents for at least 24 and up to 48 weeks. The data demonstrate comparable exposures (e.g., AUC) and efficacy (proportion with HIV RNA <400 c/mL and increases in CD4 cell counts) in pediatric patients compared to adult patients. However, emesis occurred substantially more frequently in pediatric patients compared to adults (38% versus 10%). The increased emesis was particularly noted in those pediatric subjects who received Lexiva Oral Suspension. Although the etiology remains unclear, most cases of emesis were mild with most patients being able to continue to take Lexiva Oral Suspension. In addition, there did not appear to be an increased incidence of development of resistance to Lexiva Oral Suspension in those subjects who experienced emesis.

1.2 Recommendation on Postmarketing Actions

Risk Management Activity

Lexiva Tablets have been marketed in the US since 2003 with a patient package insert. No post-marketing concerns have emerged. As such, no new risk management activity is required.

Required Phase 4 Commitments

- To address the remaining requirements of the Pediatric Written Request, the Applicant has committed to submit the results of an ongoing study of the pharmacokinetics, safety and antiviral activity of Lexiva in patients 0 (birth) to 2 years of age; the study report is due in December 2009.

Other Phase 4 Requests

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1.3 Summary of Clinical Findings

Brief Overview of Clinical Program

The clinical program to support approval of Lexiva Oral Suspension and Tablets in patients 2-18 years of age included two open-label single arm clinical studies (Studies APV29003 and APV20095) in which 144 HIV-1 infected pediatric patients received Lexiva (93 as Oral Suspension and 51 as Tablets) in combination with at least two other antiretroviral agents for at least 24 weeks. In addition, data were submitted from two clinical pharmacology studies that assessed bioavailability, food effect, and dose-ranging of Lexiva administered as the Oral Suspension and Tablet.

Efficacy

Overall, 63% of pediatric patients achieved and maintained HIV RNA <400 c/mL through 48 weeks (or 24 weeks for study APV20095) of therapy with 36% achieving HIV RNA <50 c/mL. Across all study participants, the median viral load reduction was -2.60 $\log_{10}$ c/mL, the median increase in CD4 cell counts was +200/mm^3. These results compare favorably with the efficacy of Lexiva-containing regimens in adults. However, since Lexiva was a component of triple drug regimens, and no comparator arms were utilized in any of the clinical trials, the absolute contribution of Lexiva to efficacy could not be determined.

There were no significant differences in efficacy outcomes based on formulation of Lexiva (Tablets or Oral Suspension) used. The response rates appeared to vary across the groups by age and by PI experience status; the subjects were not evenly distributed across the groups and the numbers involved were generally very limited.

Safety

Lexiva® is an approved product with a well characterized safety profile. There are two types of treatment-related adverse events which appear to have increased frequencies in pediatric patients compared to adult patients. Emesis (or gastrointestinal adverse events) and Infection and Infestations were more commonly observed in the pediatric studies.

The common adverse events in adult studies related to Lexiva included: diarrhea, nausea, vomiting, abdominal pain, headache, fatigue, rash, pruritis, oral and peripheral paresthesia, and depression. Common laboratory abnormalities included hepatic transaminitis, and increased cholesterol, triglycerides, and glucose levels. Co-administration of ritonavir led to increased incidence and severity of diarrhea, vomiting, fat redistribution, and increased glucose, cholesterol and triglyceride levels.

The most common adverse events reported in the pediatric studies were vomiting, diarrhea, infections and infestations, upper respiratory tract infection, headache, and nausea.

Emesis was reported in 38% (55/144) of pediatric patients compared to 10% (67/700) in adults. Emesis was more common in pediatric patients who received Oral Suspension. Most cases were considered mild in severity and most experienced resolution with continued dosing. The median duration of emesis was one day (range 1-62 days); four (3%) patients interrupted dosing and one discontinued from the studies due to emesis. The etiology of the emesis has not been fully elucidated, but may be related to one or more excipients in the Oral Suspension. Fortunately, despite the increased amount of emesis in the pediatric subjects, namely those who received Lexiva Oral Suspension, there appeared to be no decreased efficacy observed for that subpopulation.

Dosing Regimen and Administration

Lexiva: The proposed recommendations for FPV 30mg/kg BID dosage regimens in patients 2 to 18 years of age are based on results from Study APV29005 and the approved Agenerase (APV) pediatric dosage recommendations, which were largely based on PK and safety results from two APV pediatric studies PROB2004 and PROAB3004. In pediatric Study APV29005, 2 to 5 year old subjects received FPV 30mg/kg BID. Plasma APV exposures were consistent with the historical adult population receiving FPV 1400mg BID, with 11% lower plasma APV AUC(0-τ), similar Cmax, and 28% higher Cτ values. Similarly, converting the approved APV pediatric dosing recommendations into FPV-equivalent doses resulted in a 30mg/kg BID dosage regimen, up to the adult table dosage regimen of 1400mg BID.

Lexiva plus ritonavir: The proposed recommendations for ritonavir boosted FPV in pediatric patients 2-18 years of age is FPV 18 mg/kg plus RTV 3 mg/kg BID. This recommendation is based on FPV Studies APV29005 and APV20003 and a pediatric population PK analysis.

Drug-Drug Interactions

Drug-drug interaction studies were conducted during development of the Tablet formulation of fosamprenavir. Relevant drug-drug interaction information, including recommendations for dose adjustments of fosamprenavir or other agents, is included in the Lexiva Tablet label; these will also be included in the Lexiva® Oral Suspension label.

Special Populations

In addition to pediatric patients, Lexiva Oral Suspension could be used by adults who cannot take or tolerate Tablets and by patients with hepatic insufficiency. Pharmacokinetic data included in this NDA led to calculations that would allow Lexiva Oral Suspension to be administered to adult patients with mild, moderate and severe hepatic impairment. There are no data to support dosage of Lexiva with ritonavir for adult patients with severe hepatic impairment. There are no data to support dose adjustments for pediatric patients with hepatic impairment. It would be difficult for a sponsor to identify sufficient pediatric patients with HIV-1 infection and hepatic impairment to conduct such a study in that population. However, based on the adult data, it is likely that clinicians could use a similar dosing regimen in pediatric patients with hepatic impairment.

INTRODUCTION AND BACKGROUND

1.4 Product Information

Fosamprenavir ((Lexiva®, FPV) is a protease inhibitor (PI) approved for use in combination with other antiretroviral agents for treatment of adults with HIV-1 infection. The current application provides data to support the intended indication of treatment of pediatric patients with HIV-1 infection.

Fosamprenavir is the phosphate ester prodrug of amprenavir. Amprenavir is a selective inhibitor of the HIV-1 aspartyl protease. Fosamprenavir calcium is a single stereoisomer with the (*3*S)(*1*S,*2*R) configuration. Fosamprenavir is a calcium salt of amprenavir that is hydrolyzed to amprenavir and inorganic phosphate as it is absorbed through the epithelial lining of the gut.

Ritonavir (Norvir®, Abbott Laboratories) is one of the most potent inhibitors of CYP450 enzyme system and is increasingly being used to pharmacokinetically enhance concomitantly administered protease inhibitors. When co-administered with ritonavir, it is often possible to decrease in pill counts or frequency of dosing of the co-administered protease inhibitor.

1.5 Currently Available Treatment for Indications

There are currently over 25 drugs approved in the US for the treatment of HIV infection including the following: The nucleoside reverse transcriptase inhibitors (NRTIs) were the first class of compounds to exhibit anti-HIV efficacy. Currently there are 8 NRTI's marketed in the US: zidovudine (Retrovir®), didanosine (Videx®), zalcitabine (Hivid®), stavudine (Zerit®), lamivudine (Epivir®), abacavir (Ziagen®), emtricitabine (Emtriva™), and tenofovir (Viread®), sometimes also referred to as a nucleotide). Additional classes of antiretroviral agents include the non-nucleoside reverse transcriptase inhibitors (NNRTI), including delavirdine (Rescriptor®), nevirapine (Viramune®), and efavirenz (Sustiva®), protease inhibitors (PI), represented by indinavir (Crixivan®), ritonavir (Norvir®), saquinavir (Invirase® and Fortovase®), nelfinavir (Viracept®), amprenavir (Agenerase®), fosamprenavir (Lexiva®), atazanavir (Reyataz®), tipranavir (Aptivus®), darunavir (Prezista®) and lopinavir/ritonavir fixed dose combination (Kaletra®), and a GP41 fusion inhibitor, enfuvirtide (Fuzeon®).

A number of the above listed medications are approved for use in various pediatric populations, including: Retrovir®, Videx®, Zerit®, Epivir®, Ziagen®, Viramune®, Sustiva®, Norvir®, Viracept®, Agenerase®, Kaletra®, and Fuzeon®.

1.6 Presubmission Regulatory Activity

Fosamprenavir was initially developed as 700 mg tablet, and approved in the United States in 2003 for marketing for the treatment of adult HIV-1 infection (NDA 21-548).

On 26 December 2001, a Pediatric Written Request for Fosamprenavir (with subsequent amendments on 10 January 2003, 19 June 2003, and 14 June 2006) was issued requesting pharmacokinetic, antiviral activity and safety data in pediatric HIV-1 infected patients who have received the proposed dose(s) for marketing for at least 6 months.

A study evaluating the comparative bioavailability of the proposed commercial oral suspension formulation and the commercial tablet dosage form demonstrated equivalence between the two formulations under fasted conditions. However under fed conditions, the two formulations were shown to be not bioequivalent (i.e. the AUC and C_{max} for the suspension formulation decreased by 31% and 49% respectively).Therefore, the proposed pediatric dosages are 10% higher than that of Agenerase (30 mg/kg vs. 20 mg/kg, respectively) to account for decreased AUC and C_{max} under fed conditions.

The current application was submitted on 16 December 2006, and provides pharmacokinetic, safety and antiviral activity data that addresses the request for data in pediatric patients $\geq$ 2 years of age. A study evaluating fosamprenavir pharmacokinetics in the neonatal period and in children younger than 2 years of age (Study APV20002) is ongoing. The data from Study APV20002 will address the outstanding terms of the Pediatric Written Request and may permit a pediatric exclusivity determination. The information is currently planned for submission in December 2009.

1.7 Other Relevant Background Information

Fosamprenavir is a calcium salt of amprenavir that is hydrolyzed to amprenavir and inorganic phosphate as it is absorbed through the epithelial lining of the gut. Amprenavir (Agenerase®), Tablet and Oral Suspension were approved in the United States in 2003. The low aqueous solubility requiring a formulation that contains a high concentration of vitamin E, a high pill burden (8 Tablets BID, 16 total in adults), in addition to the significant gastrointestinal toxicities, lead to the development of a phosphate ester prodrug of amprenavir, which is more water soluble. A total of 2 tablets per day of fosamprenavir (Lexiva®) is equivalent to 16 tablets for adults.

Agenerase® is not recommended for pediatric population under 4 years of age due to the high content of Vitamin E and ethanol. It is approved for children older than 4 at the following doses: for adolescents (13 to 16 years), 1,200 mg (twenty- four 50-mg Tablets) twice daily in combination with other antiretroviral agents. For patients between 4 and 12 years of age or for patients 13 to 16 years of age with weight of <50 kg, the recommended oral dose of Agenerase®, Tablets is 20 mg/kg twice daily or 15 mg/kg 3 times daily (to a maximum daily dose of 2,400 mg) in combination with other antiretroviral agents.

2 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

2.1 CMC and Microbiology

For a detailed discussion of Chemistry, Manufacturing and Controls, please see Dr. Lunn's review.

Lexiva® Oral Suspension will be supplied as 50mg/ml. The composition of Lexiva Oral Suspension is provided below.

Table 1. Composition of Lexiva® Oral Suspension

Component	Function	Amount (mg/tablet)
Fosamprenavir calcium	Active	
Propylene glycol, USP		
Hypromellose NF		
Sucralose, NF		
Methylparaben, NF		
Propylparaben, NF		
Polysorbate 80, NF		
Calcium chloride dihydrate, USP		
Artificial grape bubblegum flavor		
Natural peppermint flavor		
Purified water, USP		

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For comparison, below is the composition of Lexiva tablet:

Table 2. Composition of Lexiva® Tablet

Component	Function	Amount (mg/tablet)
Fosamprenavir calcium	Active	
Microcrystalline cellulose, NF		
Croscarmellose sodium, NF		
Povidone K30, USP		
Magnesium stearate, NF		
Colloidal silicon dioxide, NF		
Target total weight		1174.2

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The process used to manufacture the commercial product is equivalent to the process used to manufacture the product used in the pivotal clinical studies. The regulatory specification for Lexiva Oral Suspension includes description, identification, assay, content uniformity, chromatographic impurity/degradation products, polymorphic form, dissolution, and microbial attributes, which were found to be generally acceptable.

2.2 Animal Pharmacology/Toxicology

All animal pharmacology/toxicology studies were conducted during development of Lexiva Tablet. There were no issues identified that would lead to a conclusion that Lexiva Oral Suspension would not be safe to administer to pediatric patients. Please refer to NDA 21-548 for a more detailed review.

3 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

3.1 Sources of Clinical Data

The clinical data submitted in this application was derived from two clinical studies conducted by the applicant.

3.2 Tables of Clinical Studies

Table 3 presents an overview of the pivotal pediatric clinical studies submitted to support the safety and efficacy of Lexiva® Oral Suspension.

Table 3. Pivotal Lexiva® Oral Suspension HIV Studies

Protocol No. Countries	**Start Date**	**Design Population**	**Treatment Regimens**	**No. Patients Treated Ages**
APV20003 U.S., Canada, Spain, Italy, Portugal, Netherlands Romania	June 10, 2002 Completed	Open-label HIV-1 Infected, Antiretroviral Naive and Experienced, Pediatric Subjects 2 to 18 Years Old	FPV/RTV QD: In addition to active 2 NRTI as background regimen FPV/RTV BID: In addition to active 2 NRTI as background regimen. Only PI experienced subjects were allowed to switch to BID regimen if preferred	2-5 Years: N=17 6-11 Years: N=17 12-18 Years: N= 35 Total: N= 69 ART naïve: 15 ART exp: 54 PI-naïve: 32 PI-exp: 37 QD: 69 BID: 10
APV20095 US, Panama, Mexico, South Africa	16 August 2004 Ongoing	Open-label HIV-1 Infected, Antiretroviral Naive and Experienced,	FPV/RTV BID: In addition to active 2 NRTI as background regimen	2-5 Years: N= 21 6-11 Years: N= 25

		Pediatric Subjects 2 to 18 Years Old	FPV BID : In addition to active 2 NRTI as background regimen Subjects are 2-<6 years old	12-18 Years: N= 29 Total: N=75 Boosted: 57 Unboosted:18 ART naïve: 18 ART exp: 57 PI-naïve: 21 PI-exp: 54
APV20002	Ongoing	Open-label		

3.3 Review Strategy

Studies 20003 and 20095 were reviewed in their entirety. There is very limited data on study APV20002. Only 13 subjects were enrolled in the study and received at least one dose at the time of application submission. The study is ongoing but at a slow rate due to what the Sponsor states "difficulty recruiting subjects". Study APV20002 will be reviewed in its entirety when more data is submitted.

3.4 Data Quality and Integrity

The submitted data appears to be with good quality and integrity. There was no issue in accessing any of the data sets.

3.5 Compliance with Good Clinical Practices

It appears that the three clinical trials were conducted in compliance with Good Clinical Practices and in accordance with acceptable ethical standards of the countries in which they were conducted.

4 CLINICAL PHARMACOLOGY

4.1 Pharmacokinetics

Bioequivalence, dose ranging in pediatric patients, and the impact of food on pharmacokinetics, were assessed in previous clinical pharmacology studies (1004, 1008, 20001). Please refer to the Clinical Pharmacology Review by Dr. Vikram Arya. In summary, according to the clinical pharmacology team, the Clinical Pharmacology and Biopharmaceutics Information pertaining to similarity in exposures between the suspension and tablet formulation is acceptable. The information provided supports the approval of the suspension. Further, the Clinical Pharmacology and Biopharmaceutics Information provided to support the dosing recommendations for subjects with different degrees of hepatic impairment is acceptable.

4.2 Pharmacodynamics

It is not ethical to administer Fosamprenavir for more than a couple of days as a monotherapy because of the rapid development of resistance. Fosamprenavir (with or without ritonavir) was used as a component of triple drug antiretroviral regimens, so it is not possible to determine its contribution to changes in HIV RNA.

4.3 Exposure-Response Relationships

For the reasons described above under 5.2, no Exposure-Response assessments were conducted.

5 INTEGRATED REVIEW OF EFFICACY

5.1 Indication

The proposed indication is "Lexiva Oral Suspension in combination with other antiretroviral agents is indicated for the treatment of patients >2 years of age with HIV-1 infection".

5.2 Methods

The two clinical studies, APV20003 and APV20095, were reviewed in their entirety.

5.3 General Discussion of Endpoints

Standard validated endpoints of proportion of patients with HIV RNA <400 and <50 c/mL and increases in CD4 cell counts through 24 or 48 weeks of anti-HIV therapy were utilized in the clinical studies. For Study APV20095, 24 week data was used as an endpoint; the 48 week data will be submitted in the future. These endpoints have been well validated and are utilized by sponsors, FDA, and clinicians to determine efficacy of anti-HIV drugs.

5.4 Study Design

Two open-label non-comparative studies provide the basis for the evaluation of efficacy of fosamprenavir in patients 2 to 18 years of age.

APV20003 is an open-label study of a once daily dose of fosamprenavir Tablets or Oral Suspension in combination with other antiretroviral agents in HIV-infected pediatric patients. The primary study objectives are: (1) to evaluate the safety and tolerability of FPV/RTV given once daily in combination with NRTI therapy for 48 weeks in HIV-1 infected, antiretroviral therapy (ART)-naïve and experienced, pediatric subjects 2 to ≤18 years of age; and (2) to characterize plasma APV PK following administration of FPV/RTV once daily and twice daily to pediatric subjects 2 to ≤18 years of age.

Enrollment was started on June 10, 2003. The last subject recruited completed Week 48 as of 16 February 2005. By the cut-of date for the Week 48 interim analysis, 69 subjects were enrolled in the study. Study 20003 was conducted at 38 sites: 13 in the United States, 2 in Canada, 9 in Spain, 8 in Italy, 3 in Portugal, 1 in Netherlands and 2 in Romania.

FPV 700mg tablets were available to subjects who were at least 12 years of age, weighed ≥50 kg and who were able to swallow whole tablets, at the discretion of the investigator. These subjects were to receive an adult dosage regimen of FPV 1400 mg QD in combination with RTV 200 mg QD. RTV 100 mg Tablets were made available to subjects who weigh ≥ 33 kg and who were able to swallow whole tablets, at the discretion of the investigator.

Subjects taking the FPV Oral Suspension would receive FPV 30 mg/kg (up to a maximum daily dose of 1800 mg QD) in combination with RTV 6 mg/kg QD (up to a maximum daily dose of 200 mg). FPV oral suspension doses were allowed to be adjusted for individual subjects based on PK assessments.

Enrolled subjects who were PI-experienced at Baseline/Day 1 and receiving FPV Tablets QD in combination with RTV QD who switched to the FPV/RTV BID regimen were to receive 700mg FPV BID in combination with RTV 100mg BID.

Subjects who were PI-experienced at Baseline/Day 1 and receiving the FPV Oral Suspension QD in combination with RTV QD who switched to FPV /RTV BID were to receive a starting dose FPV 20mg/kg or 15mg/kg BID (up to a maximum daily dose of 1800mg) in combination with RTV 3mg/kg or 4mg/kg BID.

The demographic and disease characteristics of patients enrolled in Study 20003 are listed in Tables 4 and 5.

Table 4. Demographic characteristics

	2-5 Years N=17	6-11 years N=17	12-18 years N=35	Total N=69
Age (median)	4 (2,5)	9 (6,11)	14 (12,17)	12 (2,17)

Sex Male Female	 7 (41) 10 (59)	 5 (29) 12 (71)	 18 (51) 17 (49)	 30 (43) 39 (57)
Weight, Kg (range)	17 (11,26)	25 (17,55)	51 (33,91)	34 (11,91)
Race (%)				
White	6 (35)	5(29)	24(69)	35(51)
Black	9 (53)	8(47)	7(20)	24(35)
Hispanic	2(12)	3(18)	3(9)	8(12)

Fifteen patients were treatment naïve while 54 had received some type of antiretroviral therapy prior to enrollment.

Table 5. Baseline characteristics based on treatment history

	Treatment-Naïve (n=15)	**Treatment-Experienced (n=54)**
Baseline Viral Load		
<400 c/mL	1 (3)	1(3)
500-<100,000	17(53)	17(46)
>100,000	12(37)	15(40)
Baseline CD4+ Cells		
<100/mm^3	4 (13)	5 (14)
100-<200	3 (9)	2 (5)
200-<500	17 (53)	14 (38)
>500	8 (25)	16 (43)

Thirty-five percent (24/69) received Tablets and 65% (45/69) received the Oral Suspension; exposure and disposition is described in Table 6.

Table 6. Exposure and disposition by formulation

	Tablet N= 24	**Suspension N= 45**
Exposure for ≥ 48 weeks	20 (83)	30 (66)
Discontinued ≤Week 48	6 (3)	16 (35)

Overall, 72% (50/69) of patients completed 48 weeks of therapy by the time of NDA submission. Two patients discontinued due to documented virologic failure, eight for adverse events, and two withdrew consent (e.g., decided to discontinue), and seven patients discontinued for "other" reasons, and are discussed in more detail below.

Study *APV20095* is an ongoing open-label study to evaluate the safety, tolerance, antiviral activity and pharmacokinetics of Fosamprenavir alone or in combination with ritonavir as twice-daily regimen in HIV-infected antiretroviral therapy naïve or experienced pediatric subjects 2 to 18 years of age. Patients who were ART naïve and <6 years of age were allowed to receive FPV without ritonavir. The primary study objectives are: (1) to define a boosted BID regimen that will achieve steady state PK exposure for 2-18 year old; (2) to analyze FPV BID dosing (unboosted) in age group 2-5 year old; and (3) to evaluate safety and tolerability of FPV (±RTV) given twice

daily in combination with NRTI therapy for 48 weeks in HIV-1 infected, antiretroviral therapy(ART)-naïve and experienced, pediatric subjects 2 to ≤18 years of age.

Enrollment was started on 16 August 2004 (first subject enrolled). The study is currently ongoing. The cut-off date for interim report (24 Week) was 22 May 2006. By the cut-of date for the Week 24 interim analysis, 75 subjects were enrolled in the study. Study 20095 is being conducted at 27 sites: 10 in the United States, 2 in Canada, 1 in Belgium, 9 in Spain, 3 in Russia, and 2 in Romania.

FPV 700 mg tablets were available to subjects who were at least 12 years of age, weighed ≥ 50kg and who were able to swallow whole tablets, at the discretion of the investigator. These subjects were to receive an adult dosage regimen of FPV 700 mg BID in combination with RTV 100 mg BID. RTV 100mg Tablets were made available to subjects who weigh ≥ 33 kg and who were able to swallow whole tablets, at the discretion of the investigator.

Subjects taking boosted FPV Oral Suspension received the following: Cohort 1B (2 to 5 years, FPV/RTV BID) subjects initiated dosing with FPV/RTV 20/4mg/kg BID. Only three subjects had been recruited as of the cut-off date therefore subjects are continuing to be enrolled into this cohort on the initial dose of FPV/RTV BID.

Cohort 2 (6 to 11 years, FPV/RTV BID) subjects initiated dosing with FPV/RTV 15/3 mg/kg BID. Steady-state PK data from the first eight subjects indicated a cohort dose revision to FPV/RTV 18/3 mg/kg BID regimen, and newly enrolled subjects initiated chronic dosing with this regimen.

For Cohort 3 (12 to 18 years, FPV/RTV BID), the majority of subjects in this age group are receiving the standard adult regimen of FPV/RTV 700/100 mg BID regimen whereas, a few received the FPV oral Suspension at a dose of FPV/RTV 15/3 mg/kg BID.

Subjects taking unboosted FPV oral suspension received the following: Cohort 1A (2 to 5 years, FPV BID) subjects initiated dosing with FPV 40 mg/kg BID. Steady-state PK data from the first 7/8 subjects indicated a cohort dose revision to FPV 30 mg/kg BID, and newly enrolled subjects initiated chronic dosing with this regimen.

Table 7. Baseline demographic characteristics

	2-5 Yrs		**6-11 yrs**	**12-18 yrs**	**Total**
	FPV N= 18	**FPV/RTV N=3**	**FPV/RTV N=25**	**FPV/RTV N=29**	**N=75**
Age (median)	2.5 (2,5)	5(3,5)	9(6,11)	15(12,18)	10(2,18)
Sex					
F	4(22)	1(33)	14 (56)	14 (48)	43 (57)
M	14(78)	2(67)	11(44)	15 (52)	32(43)
Weight Kg	14 (11,20)	14.8 (15.5,30)	40 (21,61)	69.8 (33,103)	
Race (%)					

White	18(100)	1(33)	15 (60)	17 (59)	51(68)
Black			8 (32)	10 (34)	18(24)
Hispanic		2 (67)			2 (3)
E. & S.E Asian				1(3)	1(1)
Other			2 (8)	1(3)	3(4)

Table 8. Baseline Disease Characteristics*

	FPV ART naive N=18 2-5 yo	**PI-naïve N=3 2-5 yo**	**FPV/RTV PI-naïve & Exp. N=54 6-18 yo**	**Total N=57**
Baseline Viral Load				
<5000	1 (6)	0	8 (15)	8 (14)
5000-<100,000	5 (27)	3 (100)	28 (46)	31 (57)
>100,000	12 (67)		17 (31)	17 (30)
Baseline CD4+ Cells				
<100				
100-<200			7 (13)	7 (12)
200-<500	4 (22)		21 (39)	21 (37)
>500	13 (72)	3 (100)	16 (30)	19 (33)

Baseline data incomplete*

In this study, 48 (64%) patients received Lexiva® Oral Suspension and 27 (36%) received Lexiva® Tablets: 91% (68/75) had completed at least 24 weeks of therapy by the time of NDA submission. Eight patients discontinued from the study after the Week 24 exposure: 1 patient due to documented virologic failure, two for adverse events, 3 for "other" reasons and two withdrew consent (e.g., decided to discontinue); these other reasons are discussed in more detail below.

Table 9. Exposure and disposition by formulation

	Tablet N= 27	**Suspension N= 48**
Exposure for ≥ 24 weeks	25(93)	43(90)
Discontinued before or at the Week 24 visit	2(7)	6 (13)

5.5 Efficacy Findings

Efficacy in both studies was assessed as HIV RNA <400 c/mL (using the Roche Amplicor Monitor® Standard and <50 c/mL using the Ultrasensitive Test) and change from baseline in CD4 cell count through Week 48. Efficacy was calculated by the applicant using a various analytical approaches to confirm the applicant's findings. Patients who discontinued for any reason are summarized below (see Section 7.1.3.1).

Both studies are designed to have treatment duration of 48 weeks. Patients with HIV-1 RNA <400 c/mL at week 48 are allowed to continue to receive Oral Suspension until it is marketed, they met certain to switch to Tablet formulation, or they have virological failure.

Although both studies have allowed patients to continue on therapy beyond week 48, week 48 was chosen as the time point for analyses of efficacy as this was the original protocol-defined treatment duration for both studies. Week 48 data was submitted for Study APV20003 and 24 week data were submitted for Study APV20095; Week 48 data will be submitted for Study APV20095 once it is available. Table 10 shows the results of the applicant's efficacy analyses; the analyses were replicated and the conclusions confirmed by this clinical reviewer and the FDA statistical reviewer. Neither study was designed or powered for statistical analysis. Therefore all analysis is descriptive. Table 10 provides the overall antiviral activity results for the two trials; each trial will be discussed in more detail below.

Table 10. Efficacy outcomes (through 48 weeks Study APV20003, 24 weeks Study APV20095)

Efficacy Parameter	20003 (n=69)	20095 (n=75)	Overall (n=144)
Δ HIV-RNA (median) (range)	-2.41 $\log_{10}$ (-4.18, -0.00)	-2.78 $\log_{10}$ (-3.51, -1.21)	-2.60 $\log_{10}$ (-4.18, -0.00)
<400 c/mL	31(65%)	60(80%)	91 (63%)
<50 c/mL	26(38%)	26 (35%)	52 (36%)
Virologic failure[1]	20 (29%)	14 (19%)	24 (14%)
Δ CD4+ (median) (range)	+154/mm^3 (-692,+1386)	+245/mm^3 (-1032, +968)	+200/mm^3 (-692, +1386)

1: Defined as failure to achieve virologic suppression ((400 c/mL) or rebound after virologic suppression.

Study APV20003 The outcomes of treatment by ART experience are shown in Table 11. There were no significant differences in outcomes between PI-naïve and PI-experienced patients; ART naïve patients had a higher proportion achieving plasma HIV-1 RNA <400 c/mL at Week 48.

Table 11. Overall Outcomes, Study APV20003

	PI-naïve N=32		PI-experienced N=37	Total N=69
	ART Exp N=17	ART naïve N=15		
Outcome	n (%)	n(%)	n (%)	n (%)
Responders (<400copies/mL plasma HIV-1 RNA) <50 copies/mL	15 (29)	10 (67)	16 (43)	31 (45)
Virological failure	7 (41)	2(13)	11 (30)	20 (29)
Plasma HIV-1 RNA rebound	8 (25)		4 (11)	12 (17)
Never suppressed through Week 48	1 (3)		5 (14)	6 (9)

Insufficient viral load response	0		2 (5)	2 (3)
Discontinued due to Adverse event	2 (12)	2 (13)	4 (10)	8 (11)
Discontinued due to consent withdrawn	1 (6)		1 (3)	2 (3)
Discontinued due to other reasons*	2 (12)	1(7)	5 (14)	7 (10)
Missing HIV-1 RNA data at Week 48	1 (6)		0	1 (1)

*Adherence/compliance problems (3), poor taste (2), pregnancy (1), pharmacokinetic target not achieved (1)

The most common reason for failure was virologic failure in both groups (28% in PI-naïve, 30% in PI-experienced group). Plasma RNA rebound was the primary reason for virologic failure in the PI-naïve group, while not achieving suppression through week 48 was the primary reason for virologic failure in the PI-experienced group. Two ART naïve subjects experienced virological failure.

Subjects receiving the Tablet formulation had almost double the incidence of virologic failure when compared to the suspension group. This may be due to the nature of the subjects who were receiving the Tablet formulation, i.e. subjects were older and had experienced longer time of illness and ART treatment, which puts them at risk for the possibility of development of resistant strains. Slightly more subjects "Discontinuation due to other reasons" in the Oral Suspension group compared to the tablet group. It appears that taste and adherence may be contributing factors to "Discontinuation due to other reasons". Noted is also the one subject who did not achieve PK target who received suspension formulation. As discussed later (see Safety Section), emesis was a significant adverse event in the Oral Suspension group. This subject indeed experience significant amount of emesis. Although the reason for discontinuation is listed as other, this subject may also be considered to have left the study due to adverse event.

Table 12. Virologic Response by Formulation

	Suspension N=45	**Tablet N=24**
Virologic failure subjects	n=10 (22%)	n=10 (42%)
Viral load rebound	6 (13)	6 (25)
Never suppressed	4 (9)	2 (8)
Insufficient viral load response		2 (8)
Discontinue due to other reasons	n=5 (11%)	n=2 (8%)
Poor adherence	2 (4)	1 (4)
Poor taste	2(4)	
PK target not achieved	1 (2)	
Pregnancy		1(1)

The efficacy results appear to be similar to the comparable adult studies. Caution should be taken when interpreting the following table, as the pediatric studies were open label and not powered for statistical analyses.

Table 13. Virologic Response Compared to Adult Studies

	APV20003 ART-naïve	**APV30002 ART naïve adults**	**APV20003 PI-**	**APV30003 PI-experienced adults**

	pediatric	(boosted, QD)	experienced pediatric	(boosted, QD)
<400 at Week 48	10/15 (67%)	222/322 (69%)	16/47 (43%)	52/105 (50%)

The median increase in CD4+ cell count from Baseline to Week 48 showed a sustained rise; in the PI-naïve count was (+163 cells/mm3) and in the PI-experienced groups (+145 cells/mm3). At Week 48, the PI-experienced group had a median CD4+ cell count of 657 cells/mm3, and the PI-naïve group had a median CD4+ cell count of 520 cells/mm3.

Table 14 Immune (CD4+ Cell Count) Profiles

	PI-naïve N=32	n	PI-experienced N=37	n
CD4+ Cell Counts (cells/mm3)	520 (393, 623)	21	657 (456, 992)	24
CD4+ Cell Count Change from Baseline	163 (81, 302)	21	145 (45, 251)	24
% CD4+ Cell status	28 (22, 34)	21	27 (23, 35)	24
% CD4+ Cells Change from Baseline	10 (2, 12)	21	5 (2, 9)	24

Study APV20095: The proportion of PI-naïve subjects with plasma HIV-1 RNA <400copies/mL at Week 24 was similar in both boosted and unboosted groups: 67% (FPV) and 70% (FPV/RTV). The proportion of PI-experienced subjects with HIV-1 RNA <400 c/mL was lower at Week 24 (57%). This may be due to the fact that PI-experienced subjects may harbor resistant HIV-1 strain as they are likely to be more treatment experienced.

A similar proportion of PI-naïve subjects in the FPV and FPV/RTV treatment groups had virologic failure (11% in each). There were more subjects with virologic failure in the PI-experienced group (30%). Again this may be reflection of more difficult to treat population. Two of the virologic failures subjects were ART naïve. Of the 13 subjects who never achieved VL suppression (<400 c/mL) by Week 24, two eventually withdrew from the study (one subject who was PI-naïve and receiving FPV, withdrew due to insufficient viral load response; another subject who was PI-experienced withdrew due to compliance issues). Two subjects (both in FPV/RTV group) discontinued study drugs by Week 24 due to an AE. Discontinuation of study drug before achieving suppression due to "Other" reasons included: non-compliance (n=1), not taking study medication (n=1) and refusing liquid (n=1). All three subjects were receiving FPV oral suspension.

Six subjects did not have the opportunity to reach Week 24 by the data cut-off date of 22 May 2006 and were therefore regarded as non-responders ('Not discontinued but no data at ≥ Week 24') at the Week 24 analysis.

Table 15 Outcome study APV20095

Outcome at Week 24	FPV PI-naïve N=18	FPV/RTV PI-Naïve N=27	FPV/RTV PI-Exp. 30	FPV/RTV Total 57	Total N=75
Responders (<400copies/mL plasma HIV-1 RNA)	12 (67)	19(70)	17(57)	48(64)	6 0(80)
Virological failure	2 (11)	3(11)	9(30)	12(19)	14(19)
Plasma HIV-1 RNA rebound	0	1(4)	0	1(1)	1 (1)
Never achieved viral load suppression through Week 24	2 (11)	2(7)	9(30)	11(19)	13(17)
Discontinued due to an adverse event	0	1(4)	1(3)	2(3)	2(3)
Discontinued due to consent withdrawn	0	1(4)	1(3)	2(3)	2 (3)
Discontinued due to other reason*	1 (6)	1(4)	1(3)	2(3)	3 (4)
Not yet at Week 24	3(17)	1(4)	2(4)	3(4)	6(7)

Of the 14 subjects with virologic failure, six were receiving FPV tablets, and eight were receiving FPV oral suspension, suggesting that there was not a major difference in virologic response based on formulation. Significantly more subjects "Discontinuation due to other reasons" in the suspension group compared to the tablet group. It appears that taste and adherence may be contributing factors to "Discontinuation due to other reasons". The 'other' discontinuation reasons mentioned above [non-compliance (n=1), not taking study medication (n=1), refusing liquid (n=1)] occurred in the suspension group. These events, although small in number, raise the concern of tolerability of the suspension formulation.

Table 16 Virologic Response of <400c/mL at Week 24 by Formulation

	Suspension N=48	Tablet N=28
Virologic failure subjects	n=8 (17%)	n=6 (21%)
Never suppressed by Week 24	8 (17)	6(21)
Discontinue Due to other reasons	n=9 (18%)	n=2 (8%)
Not yet at 24 weeks	5 (10)	1 (4)
AE	1(2)	1 (4)
Consent w/d	2 (3)	
Other	3 (4)	

The efficacy results appear to be similar to the comparable adult studies. Again, caution should be taken when interpreting the following table, as the pediatric studies were open label and not powered for statistical analysis. In addition, a 24 week data is being compared to a 48 week adult data.

Table 17 Virologic Response Compared to Adult studies*

	APV20095 ART naïve pediatric	Adult study APV30001 ART naïve (unboosted, BID)	APV20095 PI-Exp pediatric	Adult study APV30003 PI-Exp (boosted, BID)
VL <400	12/18 (67%)	110/166 (66%)	17/30 (57%)	62/107 (58%)

*The adult study was analyzed at 48 weeks; APV20095 was analyzed at week 24.

Younger children have higher absolute CD4+ cell counts than older children and adults, so the higher values reflected in the FPV group, may be driven by the young age of this cohort. Thus, interpretation of the data below is limited.

The median CD4+ cell increase from Baseline in the FPV treatment group was higher at Week 24 (353cells/mm3) compared to PI-naïve subjects receiving FPV/RTV treatment (131cells/mm3). This may be due to study populations and Baseline CD4+ cell count. In the FPV/RTV group, both PI-naïve and PI-experienced groups had comparable CD4+ cell count increases (131cells/mm3, 149cells/mm3, respectively).

Table 18 Immune Response at Week 24

	FPV		FPV/RTV					
	PI-naïve N=18	n	PI-naïve N=27	n	PI-exp N=30	n	FPV/RTV Total N=57	n
CD4+ Cell Counts Median (IQR)	1185 (1046, 1452)	13	371 (251, 652)	21	631 (393, 739)	24	585 (320, 672)	45
CD4+ Cell Count Change from Baseline Median (IQR)	353 (143, 643)	13	131 (71, 271)	21	149 (-3, 241)	24	136 (43, 256)	45
% CD4+ Cell status Median (IQR)	30 (23, 34)	13	20 (16, 36)	21	22 (17, 31)	24	22 (17, 33)	45
% CD4+ Cell Count Change from Baseline Median (IQR)	4 (2, 8)	13	8 (3, 10)	21	5 (1, 7)	24	6 (2, 9)	45

5.6 Clinical Microbiology

Please see Dr. Lalji Mishra for full review of Clinical Microbiology. No new mutations were identified among patients treated with Lexiva. Across the two trials, eight patients developed on-therapy APV-resistance associated mutations: V82A/T, I84V, L33F, L90M, L10F, D30N, M36I, L63P V77I, N88D, I50V/L, and I54M. Phenotypic analysis showed 3.0- to 38-fold reductions in susceptibility to amprenavir.

5.7 Efficacy Conclusions

The efficacy data support the conclusion that pediatric patients between 2 and 18 years of age who were treated with Lexiva Oral Suspension or Tablets as part of a multiple drug antiretroviral therapy combination attained antiviral and immunologic responses generally comparable to adult patients. Comparison of antiviral and immunologic response by formulation yielded no significant differences. However, the discontinuation rate due to "other" reasons, such as adherence, taste, and compliance occurred more often with the suspension formulation. There may well be a causal relationship between theses reasons and the AE (emesis) reported in those who received suspension. As discussed in the Safety section, the suspension group appears to have more adverse event (emesis) compared to the tablet group. Despite such findings, the efficacy of the suspension formulation does not appear to be affected. This conclusion should be interpreted with caution as the studies were open-label and without comparators. Finally, there was no new microbiology issues identified that require changes in the labeling for Lexiva Oral Suspension or Tablets or how it is used in clinical practice.

6 INTEGRATED REVIEW OF SAFETY

6.1 Methods and Findings

Deaths

There were no deaths reported during the study period.

Other Serious Adverse Events

Overall 23/144 (16%) patients experienced at least one serious adverse events. SAEs included: drug hypersensitivity (n=10), gastroenteritis, pneumonia, respiratory tract infection, urinary tract infection, pyrexia (n=2), flank pain, anxiety, bipolar disorder, borderline personality disorder, depression, impulse-control disorder, aggression, eye penetration, headache, hemoptysis, hepatitis, hyperglycemia, blood alkaline phosphatase increased, and anemia.

There were 10 subjects who experienced drug hypersensitivity. In study APV20003, 4 subjects experienced drug hypersensitivity reaction; all were attributed to abacavir, none discontinued from study or interrupted Lexiva. The AE resolved with discontinuation or interruption of abacavir. In study APV20095, 6 patients experienced drug hypersensitivity reaction. All were attributed to abacavir. Abacavir was discontinued in all cases; all but 1 recovered without discontinuation of study drug. Only one patient discontinued from study due to hypersensitivity. Concomitant medications for this patient included Abacavir sulphate, Co-trimoxazole, Combivir, and Lamivudine. Abacavir was thought to be the most likely cause of rash but Co-trimoxazole and Lexiva could not be completely ruled out.

Dropouts and Other Significant Adverse Events

Overall profile of dropouts

Thirty patients discontinued study medications prior to week 48 (or week 24 for study APV20095): 22 from study APV20003, and eight from study APV20095.

Reasons for discontinuations from study APV20003 included virologic failure (n=2), adverse events (n=8), withdrawal (n=2), protocol violation (n=1), and 'other' (n=6). Among the reasons listed as 'other' include: being unable to adhere to or tolerate the taste of FPV/RTV (n= 5), the plasma APV C_τ values were too low (n=2), very bad compliance for all antiretroviral drugs (n=1), and a pregnancy (n=1).

Reasons for discontinuations from study APV20095 included virologic failure (n=1), adverse events (n=2), withdrawal (n=2), and 'other' (n=3). Among the reasons listed as 'other' include: lack of adherence and palatability.

Adverse events associated with dropouts

Twelve patients discontinued the clinical studies due to adverse events: vomiting (4), nausea (2), nausea and stomach discomfort (1), hyperglycemia (SAE) (1), hypertriglyceridemia (1), elevated blood alkaline phosphatase (SAE) (1), hemoptysis (SAE) (1), and adverse drug reaction (SAE) (1).

More patients who received FPV Oral Suspension once daily with RTV discontinued due to an adverse event compared to twice daily administration: 10% versus 3%. The most common reason was vomiting.

Similarly, more patients discontinued who received the oral suspension compared to the tablet formulation due to vomiting.

Other significant adverse events

Grade 3 and 4 adverse events at least possibly related to study medications reported in the clinical trials included: vomiting, stomach discomfort, blood alkaline phosphatase increased, hypertriglyceridemia, hyperglycemia, ALT increased, hemoptysis, and drug hypersensitivity.

Common Adverse Events

Eliciting adverse events data in the development program

Safety was evaluated by collection of adverse events (AEs), HIV-1-related events, clinical laboratory testing (including hematology, clinical chemistry and serum lipase and lipids), physical examination, and vital signs measurements. Vital signs, physical examinations, concomitant medications, AE assessments and clinical laboratory evaluations were performed at Screening, Baseline, and every 2-4 weeks to week 24, and then every 12 weeks from weeks 24 to 48. Additional assessments of hepatitis status, and serum α-1 acid glycoprotein (AAG), were performed at specified study visits.

Appropriateness of adverse event categorization and preferred terms

All adverse events reported in studies in which patients received at least one dose of fosamprenavir were reviewed. In general, the review focused on known fosamprenavir associated adverse events that occurred in adults and reviewed in the adult NDA.

Incidence of common adverse events

The adverse event profile of fosamprenavir was well characterized in during the larger adults studies. The most common events are listed below.

During the two pediatric studies, gastrointestinal events (vomiting, diarrhea, nausea), headache, and infection were the most often reported adverse events; generally consistent with the known adverse event profile observed in adults. However, the number of events for vomiting and infections are significantly higher than those reported during the adult studies.

Common adverse event tables

The most common adverse events reported in the pediatric studies are compared to adults (see Table 19). With the exception of infection and vomiting the frequency of events occurring in pediatric patients was similar to the frequency reported in adults. Adverse events including fatigue and depression were reported in the adult studies as being >5%. These adverse events were less common in the pediatric studies. Adverse events reported at >5% frequency will be included in the label.

Table 19. Treatment emergent adverse events reported in pediatric patients compared to adults

	All Pediatric[1] (n=144)	Adults (n=700)
Infection	56%	-
Pyrexia	14%	-
Otitis media	7%	-
Upper respiratory infection	17%	-
Bronchitis	11%	-
Respiratory tract infection	6%	-
Nasopharyngitis	13%	-
Cough	17%	14%
Rhinorrhea	6%	12-18%
Nasal congestion	6%	-
Pharyngitis	6%	-
Nausea	15%	17%
Vomiting	38%	10%
Diarrhea	20%	22%
Abdominal pain	6%	5%
Rash	10%	11%
Headache	17%	11%

1. Selected adverse events reported in ≥5% of patients in pivotal studies APV20003 and APV20095

The incidence of infection is higher in the pediatric studies compared to the adult studies

The incidence of infection is higher in the pediatric studies compared to the adult studies. The most commonly reported infections included: upper respiratory infection, pharyngitis, and otitis media (see below under Infection).

The incidence of rash was similar to that of the adult studies (14% vs. 11%). There was no significant difference between those subjects who received Lexiva QD (12%) and BID (16%); there was no significant difference between those who received Tablet (14%) or Oral Suspension (16%)

Identifying common and drug-related adverse events

Emesis

The most common adverse event reported in the pediatric NDA was vomiting. Compared to adults, the frequency of vomiting in pediatric patients was substantially higher. Yodit: put in the language we are putting in the label, but also include the QD data. The frequency and overall occurrence of vomiting appears to occur during the first few weeks of the study for many subjects.

In both pediatric studies, subjects who received the Oral Suspension formulation experienced more vomiting compared to those who received tablet formulation [46/93 (49%) vs. 9/51 (18%), respectively]. Further, emesis appears to be more common in the younger age group (2-5 years of age). In addition, subjects who received unboosted FPV (all suspension) had higher incidence of vomiting compared to those who received FPV/RTV (suspension) [33/75 (44%) vs. 10/18 (56%), respectively]; one patient discontinued due to vomiting. No subject who received unboosted study drug discontinued from the study.

The Applicant administered an Adherence Questionnaire at Weeks 2, 12, 24, 48 and Withdrawal, and collected the number of doses missed in the three days prior to the study visit. Percent adherence was calculated by dividing the number of doses taken over the three days prior to the study visit by the number of expected doses taken, and displayed as adherence <80% or ≥80%. Adherence ≥80% was achieved if no more than one dose was missed during the 3 days before each study visit.

Responses to questionnaire at both Week 2 and Week 24 were available for 6 of the 10 subjects in the 2 to 5 year old group receiving FPV without ritonavir who reported vomiting and all 6 subjects reported ≥80% adherence to FPV at both of these time points. Additional adherence data were also available for these subjects at other time points.

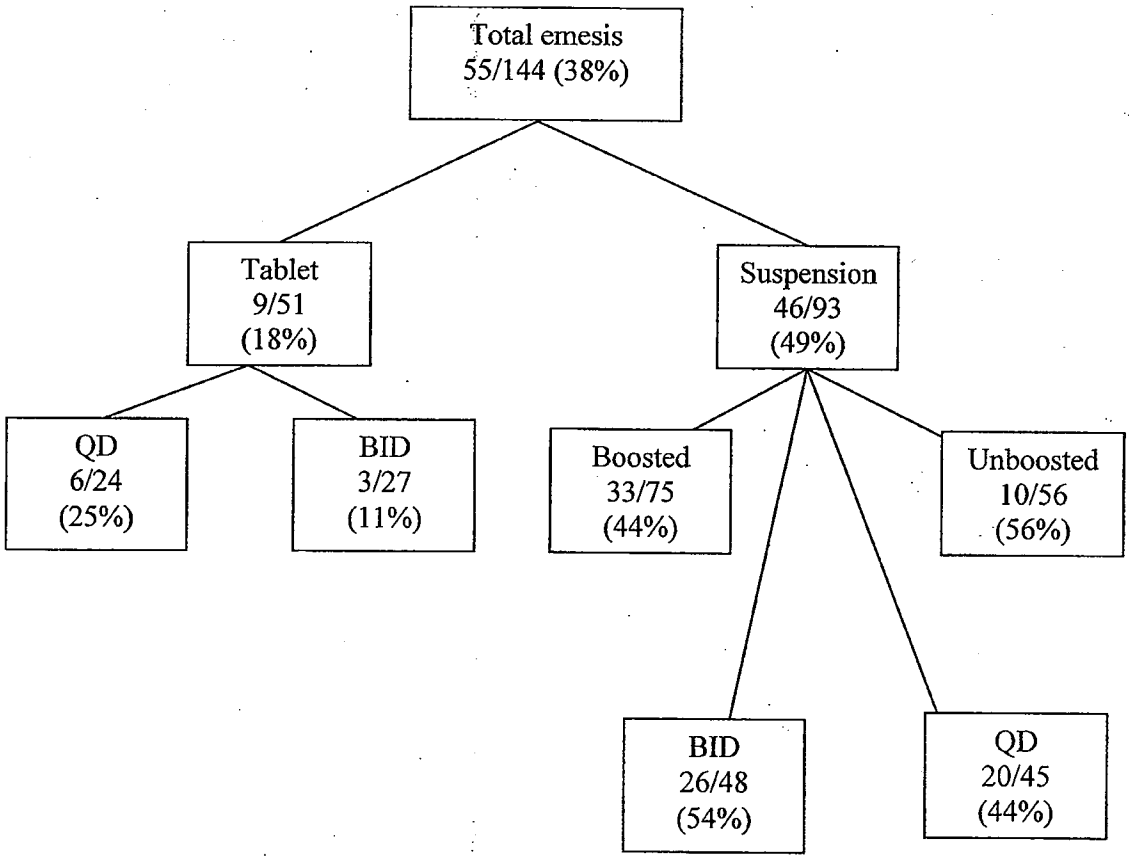
One patient who received FPV without RTV reported <80% adherence to FPV at Week 48 (why); however, the other five subjects in this group reported ≥80% adherence at all additional available time points.

For the remaining 4 subjects, one reported ≥80% adherence to FPV at Week 2 and Week 12; another subject reported ≥80% adherence to FPV at Week 12 and Week 24; a third subject

reported ≥80% adherence to FPV at Week 2 but <80% adherence at Week 12. The fourth reported <80% adherence to FPV at Week 48. These were the only time points at which adherence questionnaire were completed for these 4 patients.

Of the 10 subjects in the 2 to 5 year old group receiving unboosted FPV who reported vomiting, 7 subjects had completed a questionnaire, detailing reasons for non-adherence. "Taste, can't get it down" and "Child refuses" were reported as reasons for non-adherence by the caregivers of all of the 7 subjects at both Week 2 and Week 24, however in 6 of these subjects the frequency/intensity decreased at Week 24, e.g. response improved from "almost always a problem" at Week 2 to either "frequent problem" or "hardly ever a problem" at Week 24. In the remaining subject, "Taste, can't get it down" and "Child refuses" were each reported as a "frequent problem" at both Week 2 and Week 24. Interpretation of the adherence data is somewhat challenging given that these subjects who reported difficulties with adherence also reported that they took their medicine ≥80% of the time.

Below is a flow chart depicting the incidence of vomiting in the two pediatric studies:



Infections

In general, there were more infections reported in the pediatric studies when compared to the adult studies. The most commonly reported infections included: upper respiratory infection, pharyngitis, and otitis media.

Further, more pediatric patients experienced neutropenia (ANC <750/mm^3) compared to adults, 13% versus 3%. All the grade 3-4 neutropenia were reported among children in study APV20003 (see section 7.1.5). However, patients with neutropeina did not have more serious infections or hospitalization when compared to the rest of the pediatric patients who were in the study. Also, there was no difference in the incidence of serious infections between the pediatric patients and adults.

Laboratory Findings

All laboratory assessments, except viral genotyping and laboratory assessments that had to be performed at a local laboratory (e.g., arterial blood gases), were typically performed by a contract central laboratory designated by the applicant, to ensure standardization of results.

It is difficult to determine the absolute contribution of fosamprenavir to laboratory abnormalities because fosamprenavir was a component of triple drug regimens, and no comparator arms were utilized in any of the clinical trials. Following, however, is a discussion of what appear to be Lexiva-related laboratory abnormalities that were reported in the pediatric trials.

APV20003

The incidence of treatment-emergent Grade 3/4 clinical chemistry laboratory abnormalities was 9% over 48 weeks. Grade 4 treatment-emergent events included two patients with elevated alkaline phosphatase, one patient with elevated ALT and AST (patient has history of chronic hepatitis B), and one patient with elevated ALT. Grade 3 treatment-emergent events included two patients with elevated AST (one of these subjects also had the Grade 4 ALT), and one with Grade 3 triglycerides (non-fasting).

Table 20. Abnormalities in Clinical Chemistries, APV20003

Parameter	Grade	N	n	%
ALT (U/L)	All Grades	66	7	11
	Grades 3-4	66	2	3
AST (U/L)	All Grades	66	12	18
	Grades 3-4	66	1	2
Cholesterol (MG/DL)	All Grades	65	33	50
	Grade 3-4	65	0	0

Hyperglycemia	All Grades	66	19	29
	Grades 3-4	66	0	0
Hypoglycemia	All Grades	66	5	6
	Grades 3-4	66	0	0
Lipase (U/L)	All Grades	64	2	3
	Grades 3-4	64	1	2
Triglycerides (MG/DL)	All Grades	65	20	30
	Grades 3-4	65	1	2

There were 14 subjects who experienced Grade 3/4 hematologic adverse reactions. Of the 14 subjects with Grade 3/4 hematology toxicities, 13 subjects had Grade 3/4 neutropenia, and one had Grade 3/4 thrombocytopenia. Of those with Grade 3/4 neutropenia, five subjects had Grade 4 neutropenia, and 8 subjects had Grade 3 neutropenia. One patient had neutropenia (Grade 3) from baseline. Three patients were also on trimethoprim-sulfamethoxazole as a concomitant medication during the neutropenia. The Applicant believes that neutropenia reported for 4 patients may be due to an artifact (i.e. due to environmental factors such as sub zero temperature). All 4 were from Romania. It appears that the reference laboratory from these sites had shown degeneration of morphology of cells, limiting a 'reliable count'. The consulting hematologist at the reference laboratory reviewed all slides, and concluded that the neutropenia found in the samples may have been due to environmental factors. As a follow-up investigation, samples for 2 patients were repeated in 6 days and the white counts for the patients were shown to have increased (0.69 to 4.28 and 0.16 to 1.25).

In summary, although neutropenia may be explained by environmental condition for possibly 4 subjects and by abnormal baseline for a second subject, 8 out of the 13 had no clear explanation for the neutropeina. Although 3 subjects were taking concomitant trimethoprim-sulfamethoxazole, they had been on the medication prior to enrollment into the study and did not have Grade 3 or 4 neutropenia at baseline.

Table 21. Hematologic Abnormalities, APV20003

Parameter	Grade	N	n	%
Hemoglobin (G/DL)	All Grades	66	9	14
	Grades 3-4	66	0	0
Neutrophils (GI/L)	All Grades	66	30	46
	Grades 3-4	66	8	12
Platelets (GI/L)	All Grades	66	4	6
	Grades 3-4	66	1	2
WBC Count (GI/L)	All Grades 1	66	17	26
	Grades 3-4	66	1	2

APV20095

The overall incidence of Grade 3/4 chemistry laboratory abnormalities was 11% (8/73) over 24 weeks; 6% (1/18) in the FPV group and 13% (7/55) in the FPV/RTV Group. None of the

treatment-emergent chemistry Grade 3/4 laboratory abnormalities occurred in the FPV group. Two subjects experienced treatment-emergent Grade 3/4 laboratory abnormalities which were considered to be clinically significant; one Subject had a Grade 3 increase in sodium and another subject had a Grade 4 increase in CPK .

Table 22. Abnormalities in Clinical Chemistries, APV20095

Parameter	Grade	N	n	%
ALT (U/L)	Grades 3-4	55	0	0
AST (U/L)	Grades 3-4	55	0	0
Cholesterol (MG/DL)	Grade 3-4	23	2	9
LDL	Grade 3-4	23	3	13
hypoglycemia	Grades 3-4	25	0	0
Triglycerides (MG/DL)	Grades 3-4	23	0	0

Two subjects in the FPV/RTV group had treatment-emergent Grade 3 neutropenia: One subject had a Grade 1 abnormality at Baseline and by Week 60, count had decreased to Grade 3. A second subject experienced transient neutropenia to Grade 3 and then returned to normal and remained normal through Week 48.

Table 23. Hematologic Abnormalities, APV20095

Parameter	Grade	N	n	%
Hemoglobin (G/DL)	Grades 3-4	54	1	2
Neutrophils (GI/L)	**Grades 3-4**	53	2	4
Platelets (GI/L)	Grades 3-4	54	1	2
WBC Count (GI/L)	Grades 3-4	53	0	
	Grades 3-4			

Overall, the incidence of laboratory adverse events (Grade 3/4) is similar to that seen in adult studies, with the exception of increased frequency of neutropeina in one of the pediatric study.

Vital Signs

In general, there were no significant changes in vital signs identified.

Human Carcinogenicity

The non-clinical carcinogenicity studies have demonstrated that fosamprenavir is not oncogenic.

Special Safety Studies

Gender and Race Assessments

Analyses conducted by the Applicant revealed no clinically relevance differences in safety between gender and race. However the number of subjects is small enough that limited conclusions can be made. Further, the studies were not powered for statistical comparisons based on gender or race.

Withdrawal Phenomena and/or Abuse Potential

There is no withdrawal phenomenon or abuse potential with fosamprenavir.

Human Reproduction and Pregnancy Data

Fosamprenavir is classified as Pregnancy Category C. There are no data on use of fosamprenavir during pregnancy. To monitor fetal outcomes of pregnant women exposed to fosamprenavir, an Antiretroviral Pregnancy Registry has been established, and healthcare providers are encouraged to register patients; this will be included in the Lexiva Oral Suspension/Tablet label.

Assessment of Effect on Growth

The Applicant did not conduct any assessments on the effects of Lexiva on growth and development. Information on growth would have provided assurance that the emesis experienced by many subjects was not growth limiting. Nonetheless, because the majority of the subjects had short number of days with emesis, it should have no major impact on their growth and development. Thus, there is no significant concern about the lack of data on assessment of growth.

Overdose Experience

There is no information on overdoses in pediatric patients. The Lexiva labeling describes one case of overdose in an adult, that here is no known antidote for Lexiva, and that it is not known whether amprenavir can be removed by peritoneal dialysis or hemodialysis.

Post marketing Experience

Fosamprenavir has been marketed for treatment of HIV-1 infected adults in the US since 2003 as Lexiva Tablets. No new safety signals have been identified in adult patients.

6.2 Adequacy of Patient Exposure and Safety Assessments

The Applicant submitted safety data on 144 patients between 2 and 18 years of age who received Lexiva Oral Solution or Tablets for at least six months. The number of pediatric patients and duration of treatment with fosamprenavir represents adequate database upon which to determine safety and efficacy for some of the proposed doses that will be included in the label. The study types, designs, demographics, extent of exposure, postmarketing experience, adequacy of clinical experience, and clinical testing have been summarized above, and support the safety findings.

7. ADDITIONAL CLINICAL ISSUES

7.1 Dosing Regimen and Administration

The Applicant proposed the following dosing regimens of Lexiva® Oral Suspension in pediatric patients:

Patient Population	Age	Lexiva* Twice daily	Lexiva/Ritonavir†	
			Once-Daily	Twice-Daily
Therapy-Naive	2-5 years	30 mg/kg	[redacted]	b(4)
	≥6 years	30 mg/kg	[redacted]	LEXIVA 18 mg/kg Ritonavir 3 mg/kg
Protease Inhibitor-Naive	2-5 years	NA	[redacted]	b(4)
	≥6 years	NA	[redacted]	LEXIVA 18 mg/kg Ritonavir 3 mg/kg
Protease Inhibitor-Experienced	2-5 years	NA	NA	[redacted] b(4)
	≥6 years	NA	NA	LEXIVA 18 mg/kg Ritonavir 3 mg/kg

*Maximum dose not to exceed the recommended adult dose. The adult regimen of LEXIVA Tablets 1,400 mg twice daily may be used for pediatric patients weighing at least 47 kg.
†Maximum dose not to exceed the recommended adult dose. When administered in combination with ritonavir, LEXIVA Tablets may be used for pediatric patients weighing at least 39 kg; ritonavir capsules may be used for pediatric patients weighing at least 33 kg.

The Applicant's proposal consisted of a number of different doses of FPV/RTV based on the doses studied in the clinical trials. In some cases, the proposed dose is different than what was actually administered to patients; the Applicant modeled higher than studied doses in an attempt to realign expected pharmacokinetics. For example, a regimen of FPV 30 mg/kg plus RTV 6 mg/kg QD resulted in a 30% less than expected AUC exposure when compared to the historical adult population. The Applicant estimated that a ~30% increase in FPV dose (i.e. increasing from 30 to 40 mg/kg QD) would result in comparable adult AUC exposure. [redacted] b(4)

[redacted] b(4)

The proposed doses for children older than 6 years were FPV 18 mg/kg plus RTV 3 mg/kg BID [redacted] The BID dosing regimen of 18/3 mg/kg led to AUC exposure that was 26% higher than the historical adult data. This rests within an acceptable range of difference between the pediatric and adult AUC. The Applicant also studied a regimen of FPV 30 mg/kg plus RTV 6 mg/kg QD which resulted in a 27% lower AUC compared to the historic adult data. Based on these findings the Applicant assumed that an additional 6 mg of FPV would increase the AUC to expected levels. b(4)

[redacted] b(4)

Based on review the data contained in the NDA, the dosing for pediatric patients to be included in the approved labeling will read as follows:

Pediatric Patients (≥2 to 18 years of age)

The recommended dosage of LEXIVA in patients ≥2 years of age should be calculated based on body weight (kg) and should not exceed the recommended adult dose. **The data are insufficient to recommend: (1) once-daily dosing of LEXIVA alone or in combination with ritonavir, and (2) any dosing of LEXIVA in therapy-experienced patients 2 to 5 years of age.**

- Therapy-naive 2 to 5 years of age: LEXIVA Oral Suspension 30 mg/kg twice daily, not to exceed the adult dose of LEXIVA 1,400 mg twice daily.

- Therapy-naive >6 years of age: either LEXIVA Oral Suspension 30 mg/kg twice daily not to exceed the adult dose of LEXIVA 1,400 mg twice daily or LEXIVA Oral Suspension 18 mg/kg plus ritonavir 3 mg/kg twice daily not to exceed the adult dose of LEXIVA 700 mg plus ritonavir 100 mg twice daily.

- Therapy-experienced ≥6 years of age: LEXIVA Oral Suspension 18 mg/kg plus ritonavir 3 mg/kg administered twice daily not to exceed the adult dose of LEXIVA 700 mg plus ritonavir 100 mg twice daily.

When administered without ritonavir, the adult regimen of LEXIVA Tablets 1,400 mg twice daily may be used for pediatric patients weighing at least 47 kg.
When administered in combination with ritonavir, LEXIVA Tablets may be used for pediatric patients weighing at least 39 kg; ritonavir capsules may be used for pediatric patients weighing at least 33 kg.

7.2 Drug-Drug Interactions

Drug-drug interactions have been well characterized and important interactions are summarized in the Lexiva label.

7.3 Special Populations

Fosamprenavir is metabolized by hepatic enzymes. Therefore, liver impairment can impact the pharmacokinetics of fosamprenavir. A pharmacokinetic study evaluating fosamprenavir in adults with mild and moderate hepatic impairment was submitted and reviewed under this NDA. The following findings and recommendations were made for adults with hepatic impairment:

- Mild Hepatic Impairment (Child-Pugh score ranging from 5 to 6): LEXIVA should be used with caution at a reduced dosage of 700 mg twice daily without ritonavir (therapy-naive) or 700 mg twice daily plus ritonavir 100 mg once daily (therapy-naive or PI-experienced).

- Moderate Hepatic Impairment (Child-Pugh score ranging from 7 to 9): LEXIVA should be used with caution at a reduced dosage of 700 mg twice daily (therapy-naive) without ritonavir, or 450 mg twice daily plus ritonavir 100 mg once daily (therapy-naive or PI-experienced).

- Severe Hepatic Impairment (Child-Pugh score ranging from 10 to 12): LEXIVA should be used with caution at a reduced dosage of 350 mg twice daily without ritonavir (therapy-naive). There are no data on the use of LEXIVA in combination with ritonavir in patients with severe hepatic impairment.

7.4 Pediatrics

This is primarily a pediatric NDA and the majority of the above information applies to pediatric patients.

7.5 Postmarketing Risk Management Plan

Lexiva has been marketed in the US since 2003. No post-marketing safety issues have been identified, and no new post-marketing risk management plan is necessary for the Oral Suspension.

8 OVERALL ASSESSMENT

8.1 Conclusions

Based on the safety, pharmacokinetic and antiviral activity reviewed in this NDA, the application is recommended for approval. Clinical pharmacokinetic, safety and efficacy data from 144 HIV-1 infected pediatric patients aged 2 to 18 years treated with Lexiva® Oral Suspension or Lexiva® Tablets in combination with other antiretroviral agents for at least 24- 48 weeks demonstrated comparable exposures (e.g., AUC) at the doses that will be approved, general safety profile and efficacy (proportion with HIV RNA <400 c/mL and increases in CD4 cell counts) in pediatric compared to adult patients.

However, emesis occurred substantially more frequently in pediatric patients compared to adults (38% versus 10%). The increased emesis was particularly noted in those pediatric subjects who received Oral Suspension. Although the etiology remains unclear, most cases of emesis were mild with most patients being able to continue to take Lexiva. In addition, there did not appear to be an increased incidence of development of resistance to Lexiva in those subjects who experienced emesis. Therefore, the Oral Suspension should be approved for used in the pediatric population as it provides an alternative protease-inhibitor treatment for pediatric patients.

With respect use of fosamprenavir in patients with hepatic impairment, pharmacokinetic data submitted in this NDA provided an opportunity to estimate dosing of the oral Suspension in adult patients with mild to moderate hepatic impairment.

8.2 Recommendation on Regulatory Action

From a clinical perspective, the NDA for Lexiva® Oral Suspension should be approved.

8.3 Recommendation on Postmarketing Actions

- The Applicant is continuing to enroll subjects for study APV20095 to assess the pharmacokinetics, safety, tolerability and efficacy of Fosamprenavir with ritonavir in subjects 2 to 5 years of age.
- The Applicant is also continuing to enroll and submit the results of an ongoing study of the pharmacokinetics, safety and antiviral activity of fosamprenavir in patients 0 (birth) to 2 years of age. The report of this study is due in December 2009.

Risk Management Activity

The current labeling of Lexiva adequately describes the Warnings, Contraindications and Precautions related to fosamprenavir. As such, no additional post-approval risk management activities are required.

Required Phase 4 Commitments

There are no new required Phase 4 requests. The Sponsor will continue with Studies APV20095 and APV20002 to their completion.

Other Phase 4 Requests

There are no additional Phase 4 requests.

8.4 Labeling Review

The Lexiva Tablet label will be revised to include salient information about the new oral Suspension formulation including pediatric pharmacokinetic, efficacy and safety data with a specific discussion on the higher frequency of emesis observed in pediatric patients compared to adults. A section describing hepatic dosing of Lexiva Oral Suspension will also be included in the product labeling.

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/s/

Yodit Belew
6/14/2007 08:15:10 PM
MEDICAL OFFICER

Russell Fleischer
6/15/2007 09:15:36 AM
MEDICAL OFFICER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Silver Spring, MD 20993

DATE: June 14, 2007

TO: NDA 22-116 (Lexiva® Oral Suspension)

FROM: Russell Fleischer, PA-C, MPH
Senior Clinical Analyst, DAVP

RE: Team Leader Memorandum

BACKGROUND

Pursuant to a Written Request, GlaxoSmithKline (the Applicant) submitted pharmacokinetic, safety and antiviral activity data to support use of Lexiva® (fosamprenavir, FPV) Oral Suspension with and without ritonavir in pediatric patients. In addition, the NDA contains data from a study to support Lexiva Oral Suspension dosing in patients with impaired hepatic function.

PEDIATRICS

The pharmacokinetic, safety and antiviral activity data to support pediatric dosing of Lexiva Oral Suspension was derived from 144 HIV-1-infected patients between 2-18 years of age who received Lexiva Oral Suspension (n=93) or Tablets (n=51) with (n=126) and without (n=18) ritonavir once (n=69) or twice (n=75) per day for at least six months.

Dosing and Administration

The Applicant's initial proposal consisted of a number of different doses of Lexiva Oral Suspension that were different than those studied. The Applicant modeled higher than studied doses in an attempt to realign expected pharmacokinetics. Unfortunately, none of the modeled doses had been administered to enough pediatric patients, and as such there were no or limited pharmacokinetic or safety data available for review; [

b(4)

Based on a thorough review of these complex data sets, the data support the following doses of Lexiva Oral Suspension for inclusion in the label:

- Therapy-naive 2 to 5 years of age: LEXIVA Oral Suspension 30 mg/kg twice daily
- Therapy-naive ≥6 years of age: either LEXIVA Oral Suspension 30 mg/kg twice daily or LEXIVA Oral Suspension 18 mg/kg plus ritonavir 3 mg/kg twice daily
- Therapy-experienced ≥6 years of age: LEXIVA Oral Suspension 18 mg/kg plus ritonavir 3 mg/kg administered twice-daily.

In all cases, the pediatric dose is not to exceed the adult dose of LEXIVA plus ritonavir. When administered without ritonavir, the adult regimen of LEXIVA Tablets 1,400 mg twice daily may be used for pediatric patients weighing at least 47 kg. When administered in combination with ritonavir, LEXIVA Tablets may be used for pediatric patients weighing at least 39 kg; ritonavir capsules may be used for pediatric patients weighing at least 33 kg.

Antiviral and Immunologic Activity

Antiviral activity was assessed as the proportion with HIV-1 RNA <400 c/mL and increases from baseline in CD4 cell counts were comparable to adults.

Safety

With the exception of vomiting, neutropenia and infection, the types, frequency and severity of adverse reactions was similar in pediatric and adult patients

Vomiting occurred substantially more often in pediatric patients compared to adults (overall 38% versus 10%). Among pediatric patients receiving Lexiva twice-daily with ritonavir, the rate was 30% (patients 2-18 years of age) and 56% (patients 2-5 years of age) compared to adults: 10% and 16% with and without ritonavir, respectively. The increased emesis was particularly noted in those pediatric subjects who received Lexiva Oral Suspension.

Although the etiology remains unclear, most cases of emesis were mild with most patients being able to continue to take Lexiva Oral Suspension. In addition, there did not appear to be an increased incidence of development of resistance to Lexiva Oral Suspension in those subjects who experienced emesis. The median duration of drug-related vomiting episodes was 1 day (range 1 to 62 days). Vomiting required temporary dose interruptions in 3 pediatric patients and was treatment-limiting in one pediatric patient, all of whom were receiving Lexiva twice-daily with ritonavir.

Neutropenia was reported in 13% of pediatric patients compared to 3% of adults.

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The etiology remains unclear, but the Applicant claims they were due to lab and

sample storage problems. This may explain some cases, but not all. ⌐

b(4)

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Infections were reported at a greater rate than in adults. However the type and severity were comparable. Pediatric patients experienced more infections typical of young children, such as upper respiratory tract infections and otitis media. There was no correlation between the occurrence of infections and neutropenia.

HEPATIC IMPAIRMENT

The applicant also submitted the results of a Hepatic Impairment study conducted in HIV-1 infected patients with mild, moderate and severe hepatic insufficiency. No safety issues were identified. The results support recommendations for dosing of Lexiva Oral Suspension or Tablets with and without ritonavir in patients with varying degrees of impaired hepatic function.

CONCLUSIONS

The data contained in this complicated to review NDA support the described twice-daily dosing of Lexiva either as the Oral Suspension or Tablets in pediatric patients 2-18 years of age. ⌐

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Further, in order to fulfill the requirements of the Pediatric Written Request, the Applicant must submit data gathered in patients 0-2 years of age; these data are due to be submitted in December 2009.

The proposed dosing for patients with varying degrees of hepatic impairment are supported by data reviewed in this NDA.

The labeling has been reformatted to be consistent with the requirements of PLR and includes salient information on dosing, adverse reactions and the results of clinical studies in pediatric patients as well as dosing for patients with degrees of hepatic impairment.

Therefore, I agree with the conclusions reached by the reviewers, Dr. Yodit Belew (Medical) and Dr. Vikram Ayra (Clinical Pharmacology), that is application should be approved.

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/s/

Russell Fleischer
6/14/2007 12:40:19 PM
MEDICAL OFFICER