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Lopinavir/Ritonavir (LPV/r) 100/25 mg Tablet Developed for Pediatric Use: Bioequivalence to the LPV/r 200/50 mg Tablet at a Dose of 400/100 mg and Predicted Dosing Regimens in Children

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Abstract

Objectives: The currently available LPV/r 200/50 mg tablet eliminated the need for refrigeration and concurrent food intake. While this formulation decreased the number of dosing units/day for adults, it provides limited flexibility for pediatric use. A LPV/r 100/25 mg tablet was developed for HIV-1 infected pediatric patients to complement the marketed oral solution. The objectives of this study were to demonstrate bioequivalence of the LPV/r 100/25 mg tablets to the currently marketed 200/50 mg tablet at the same dose, and to predict dosing regimens for children of varying body surface area (BSA).

Methods: 45 healthy HIV-negative adults were enrolled in this 3-period, cross-over pharmacokinetic (PK) study. Each subject received a dose of LPV/r 400/100 mg under fasting conditions as the 200/50 mg tablet, 100/25 mg pale yellow tablet and 100/25 mg pale pink tablet with 7 days between each dose. Serial blood samples were drawn and PK parameters calculated. Two one- sided tests were used to compare each LPV/r 100/25 mg tablet to the 200/50 mg tablet. A previously established pediatric population PK model was used to predict concentrations following one to four LPV/r 100/25 mg tablets administered twice daily to patients with BSA from 0.3–1.4 m^2 and to compare to those observed with the oral solution.

Results: Both LPV/r 100/25 mg tablet formulations were bioequivalent to the marketed 200/50 mg formulation at the same dose as the 90% confidence intervals for the ratio of C_{max} and of AUC were within 0.8 and 1.25 for lopinavir (LPV) and ritonavir (RTV). Modeling/simulation suggest that the LPV/r 100/25 mg tablet will provide LPV exposure similar to the oral solution for children with BSA >0.4 m^2.

Conclusions: The LPV/r 100/25 mg tablet formulations are bioequivalent to the 200/50 mg tablet. These lower-strength tablets will allow for sufficient LPV/r dosing flexibility for pediatric patients who can swallow a tablet.

Introduction

- Lopinavir/ritonavir (LPV/r) is indicated for the treatment of HIV-1 infection in adult and pediatric populations age 2 years or greater.
- Pediatric dosing of LPV/r is based on body surface area (BSA) or body weight. Optimal dosing is achieved with a dosage form that can accommodate the spectrum of BSA or body weight encountered in this population.
- LPV/r (marketed as Kaletra® or Aluvia) has received regulatory approval worldwide and is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection.[1] In the United States and the European Union, LPV/r is available as 133.3/33.3 mg soft gelatin capsules (SGCs), 200/50 mg film-coated yellow tablets and as an (80 + 20) mg/mL liquid.
- A red version of the LPV/r 200/50 mg film-coated tablet has been manufactured for registration in developing countries to minimize the risk of diversion from these markets. A smaller-sized and lower-dose formulation of both the red and yellow tablets, LPV/r 100/25 mg, has been developed as an option for pediatric dosing.
- This study was designed to compare the bioavailability of the pale pink and pale yellow LPV/r 100/25 mg tablets relative to that of the marketed yellow (reference) LPV/r 200/50 mg tablet formulation.

Objectives

- To compare the single-dose bioavailability of two differently-colored LPV/r 100/25 mg tablets with that of the marketed (reference) LPV/r 200/50 mg yellow tablet formulation under fasting conditions.
- To predict dosing regimens for children of varying body surface area (BSA) or body weights.

Study Methods and Design — Crossover Study

- Healthy HIV-negative adults (N=45) were enrolled into this single-dose, fasting, open-label, three-period, randomized, complete-crossover design study if they met the following criteria:
  - General good health
  - No concomitant medication
  - Body mass index was between 18 and 29 kg/m^2.
- 44 were included in the PK analyses
  - One subject was discontinued prior to dosing in Period 2 due to a fungal infection.

Table 1. Demographics of Subjects Included in PK Analyses (N=44)

	Mean ± SD	Min – Max
Age (years)	39.5 ± 9.7	18 – 54
Weight (kg)	74.4 ± 11.5	49 – 97
Height (cm)	174.8 ± 7.9	159 – 190
BMI (kg/m^2)	24.2 ± 2.6	19 – 29
Sex	35 Males (80%), 9 Females (20%)	
Race	44 White (100%)	

Pharmacokinetic Analysis

- Blood samples were collected for lopinavir (LPV) and ritonavir (RTV) assay at pre-dose (0 hour) and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 18, 24, 30 and 36 hours after dosing on Study Day 1 in each period.
- Drug concentrations for LPV and RTV were measured by validated LC/MS/MS methods:
  - LPV lower limit of quantitation (LLOQ) = 5.00 ng/mL
  - RTV LLOQ = 1.00 ng/mL
- LPV and RTV PK parameters were calculated with standard non-compartmental analysis using WinNonlin v. 5.0.1 software (Pharsight Corp., Mountain View, CA) to estimate the maximum observed concentration (C_{max}), time to the maximum observed concentration (T_{max}), apparent terminal phase elimination rate constant (β), terminal phase elimination half-life ($t_{1/2}$), area under the plasma concentration time curve during a dosing interval (AUC_t), AUC from time 0 to infinite time (AUC_∞), apparent oral clearance value (CL/F, where F is the bioavailability) and apparent volume of distribution (V_d/F).

Statistical Analysis

- Analyses of variance (ANOVAs) were performed for C_{max} and AUC. Two one-sided tests were used to compare each of the LPV/r 100/25 mg tablets to the 200/50 mg tablet.

Safety Analysis

- Safety and tolerability were assessed throughout the study based on reported adverse events (AEs), vital signs and clinical laboratory measurements.

The regimens administered are presented in Table 2.

Table 2. Regimens Administered

	Regimen		
	Regimen A (test) Lopinavir/ritonavir	**Regimen B (test) Lopinavir/ritonavir**	**Regimen C (reference) Lopinavir/ritonavir**
Dosage Form	Tablet (pale pink)	Tablet (pale yellow)	Tablet (yellow)
Strength (mg)	100/25	100/25	200/50
# Tablets	4	4	2

There was a washout period of 7 days between each dose.

Selection of Doses in the Study

- The reference dose of 400/100 mg is the most commonly-administered dose of LPV/r and represents the dose used in previous bioequivalence studies for the approved 133/33 mg SGC, (80 + 20) mg/mL liquid and 200/50 mg tablet formulations of LPV/r.

Results — Crossover Study

Pharmacokinetics

- The observed plasma concentration vs. time profiles for LPV/r tablets are shown in Figure 1 for LPV and in Figure 2 for RTV.

Figure 1. LPV Plasma Concentration-Time Profile

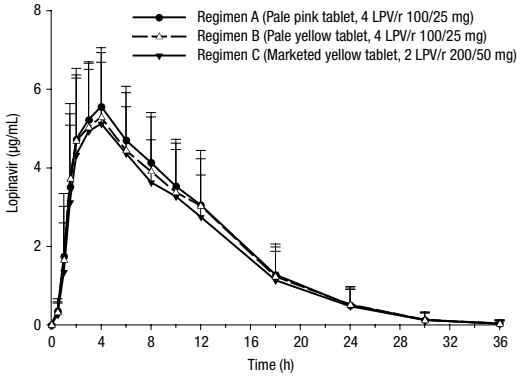
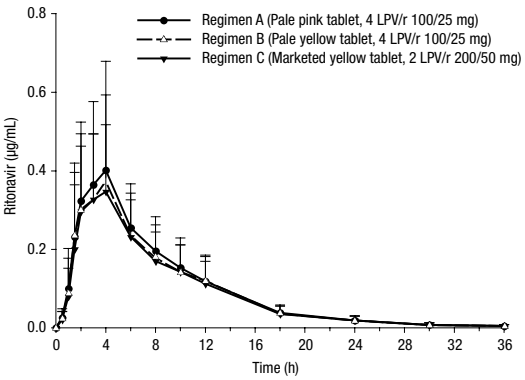


Figure 2. RTV Plasma Concentration-Time Profile



- Pharmacokinetic parameter estimates of LPV and RTV are shown in Table 3.

Table 3. LPV and RTV Pharmacokinetics

		Regimen[£]		
Pharmacokinetic Parameters	**(Units)**	**Regimen A (test) Pale Pink Tablets 4 LPV/r 100/25 mg (N=44)**	**Regimen B (test) Pale Yellow Tablets 4 LPV/r 100/25 mg (N=44)**	**Regimen C (reference) Yellow Tablets 2 LPV/r 200/50 mg (N=44)**
			Lopinavir	
T_{max}	(h)	3.3 ± 1.3	3.5 ± 1.7	3.6 ± 1.3
C_{max}	(µg/mL)	5.80 ± 1.54	5.66 ± 1.71	5.47 ± 1.67
AUC_t	(µg•h/mL)	68.5 ± 23.0*	66.6 ± 25.0	62.3 ± 22.0
AUC_∞	(µg•h/mL)	68.7 ± 23.2*	66.9 ± 25.4	62.6 ± 22.2
			Ritonavir	
T_{max}	(h)	3.1 ± 1.0	3.4 ± 1.8	3.3 ± 1.2
C_{max}	(µg/mL)	0.46 ± 0.29*	0.42 ± 0.22	0.40 ± 0.19
AUC_t	(µg•h/mL)	3.47 ± 1.57*	3.29 ± 1.40	3.14 ± 1.23
AUC_∞	(µg•h/mL)	3.51 ± 1.58*	3.33 ± 1.42	3.18 ± 1.24

£ All three regimens were administered as a single dose of LPV/r 400/100 mg.
* Statistically significantly different from reference regimen (Regimen C, ANOVA, $p<0.05$).

- The relative bioavailability of LPV and RTV is shown in Table 4.

Table 4. Relative Bioavailability of LPV and RTV

Regimens Test vs. Reference	Pharmacokinetic Parameter	Relative Bioavailability Point Estimate+	Relative Bioavailability 90% Confidence Interval
		Lopinavir	
A vs. C (Pale Pink Tablet vs. Reference)	C_{max}	1.075	1.012 – 1.143
	AUC_t	1.112	1.038 – 1.192
	AUC_∞	1.112	1.038 – 1.192
B vs. C (Pale Yellow Tablet vs. Reference)	C_{max}	1.025	0.964 – 1.090
	AUC_t	1.045	0.975 – 1.120
	AUC_∞	1.045	0.975 – 1.120
		Ritonavir	
A vs. C (Pale Pink Tablet vs. Reference)	C_{max}	1.125	1.023 – 1.237
	AUC_t	1.097	1.022 – 1.176
	AUC_∞	1.095	1.022 – 1.175
B vs. C (Pale Yellow Tablet vs. Reference)	C_{max}	1.036	0.943 – 1.139
	AUC_t	1.028	0.959 – 1.103
	AUC_∞	1.028	0.959 – 1.102

+ Antilogarithm of the difference (test minus reference) of the least square means for logarithms.

- Both test Regimen A (four LPV/r 100/25 mg pale pink tablets) and test Regimen B (four LPV/r 100/25 mg pale yellow tablets) were bioequivalent to the reference Regimen C (two LPV/r 200/50 mg marketed yellow tablets) because the 90% confidence intervals for log-transformed lopinavir and ritonavir C_{max}, AUC_t and AUC_∞ were contained within the 0.80 to 1.25 range.

Adverse Events — Crossover Study

- The regimens were generally safe and well tolerated. No differences were seen among regimens for their adverse event profiles.
- All AEs were mild (84%) or moderate (16%) in severity.
- One subject was discontinued from the study due to an AE of swelling and redness of the right forefoot and lower leg and swollen inguinal lymph nodes due to a fungal infection. The AE was judged to be not related to study drug.

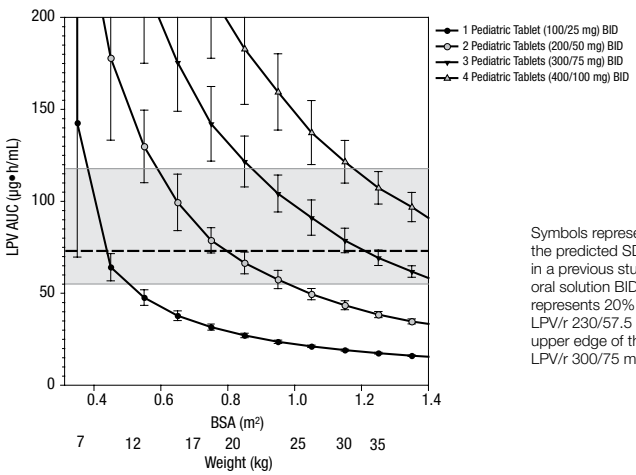
Study Methods and Design — Pediatric Model

- A previously established pediatric population PK model was used to predict concentrations following 1–4 LPV/r 100/25 mg tablets administered twice daily to patients with body surface area (BSA) from 0.3–1.4 m^2 and to compare to those observed with the oral solution.
- The PK parameters and associated variability estimated from NONMEM V.5 (Globomax, Ellicott City, MD) in the pediatric population as previously described[2] were added to the tablet absorption parameters in Clinical Trial Simulator (V.2.2, Pharsight, Mountain View, CA).
- Exposure to LPV following administration of one to four LPV/r 100/25 mg tablets (LPV/r 100/25 mg BID to LPV/r 400/100 mg BID) was simulated in 1000 pediatric patients (0.25 to 1.5 m^2 or 7 to 70 kg) and summarized by BSA/body weight.
- The model was replicated for concomitant administration with CYP3A-inducing antiretroviral (ARV) agents including efavirenz, nevirapine, amprenavir or fosamprenavir which have been demonstrated to increase LPV clearance approximately 20%.

Results — Pediatric Model

- The predicted values of LPV AUC administered in the absence of CYP3A-inducing ARV agents, by number of LPV/r 100/25 mg tablets administered and BSA/body weight, are shown in Figure 3.

Figure 3. Predicted LPV AUC in Pediatric Patients Following Administration of One to Four LPV/r 100/25 mg Tablets Compared to 230/57.5 mg/m^2 as the Oral Solution



Symbols represent the predicted mean LPV AUC, error bars represent the predicted SD. The dashed line represents the mean AUC seen in a previous study[2] for subjects receiving LPV/r 230/57.5 mg/m^2 oral solution BID without nevirapine. The lower edge of the grey box represents 20% lower exposure than observed for subjects receiving LPV/r 230/57.5 mg/m^2 oral solution BID without nevirapine and the upper edge of the grey box represents exposure at the higher dose, LPV/r 300/75 mg/m^2 without nevirapine.

- The predicted values of LPV AUC administered in the absence and presence of CYP3A-inducing ARV agents, by number of LPV/r 100/25 mg tablets administered and body weight, are shown in Table 5.

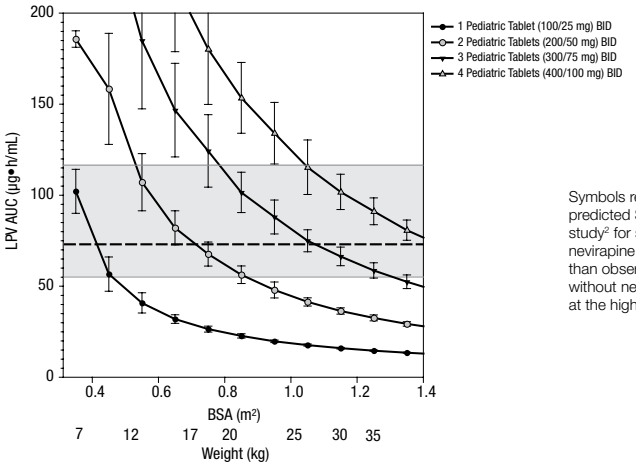
Table 5. Predicted LPV AUC Values by Body Weight for Pediatric Patients

Body Weight (kg)	One 100/25 mg Tablet BID	Two 100/25 mg Tablets BID	Three 100/25 mg Tablets BID	Four 100/25 mg Tablets BID
		LPV/r 100/25 mg Tablets		
7 to 10	76.9 ± 15.9	200.5 ± 41.6	309.8 ± 50.6	406.4 ± 57.9
10 to 15	45.4 ± 6.2	138.5 ± 117.6	217.8 ± 50.9	306.7 ± 63.4
15 to 20	32.5 ± 3.1	82.7 ± 13.6	150.1 ± 27.0	217.9 ± 36.6
20 to 25	25.1 ± 1.7	60.1 ± 6.2	110.1 ± 14.6	168.4 ± 24.9
25 to 30	20.6 ± 1.1	47.7 ± 3.8	86.3 ± 8.4	131.7 ± 14.7
30 to 35	17.6 ± 0.7	39.2 ± 2.5	70.2 ± 5.9	108.6 ± 10.8
35 to 40	15.4 ± 0.6	32.6 ± 1.7	57.6 ± 4.3	89.5 ± 8.0
		LPV/r 100/25 mg Tablets + Concomitant CYP3A-inducing ARA		
7 to 10	62.0 ± 10.4	170.7 ± 35.3	286.7 ± 74.6	494.0 ± 146.9
10 to 15	38.5 ± 5.1	99.2 ± 18.3	187.5 ± 47.9	263.2 ± 74.6
15 to 20	27.0 ± 2.3	70.3 ± 10.5	125.7 ± 19.9	184.0 ± 33.2
20 to 25	21.0 ± 1.4	51.7 ± 5.4	93.1 ± 12.9	142.0 ± 19.5
25 to 30	17.2 ± 0.9	40.2 ± 3.4	73.7 ± 7.4	110.2 ± 13.1
30 to 35	14.7 ± 0.6	32.6 ± 2.2	58.9 ± 5.3	91.3 ± 8.8
35 to 40	12.8 ± 0.5	27.4 ± 1.4	48.6 ± 3.2	74.5 ± 6.0

AUC data presented as predicted mean ± standard deviation (µg•h/mL).

- The predicted values of LPV AUC, summarized by number of LPV/r 100/25 mg tablets concomitantly administered with efavirenz or nevirapine and by BSA/body weight are shown in Figure 4.

Figure 4. Predicted LPV AUC in Pediatric Patients Following Administration of One to Four LPV/r 100/25 mg Tablets BID with a Concomitant CYP3A-inducing Antiretroviral Agent Compared to 230/57.5 mg/m² BID as the Oral Solution



Symbols represent the predicted mean LPV AUC, error bars represent the predicted SD. The dashed line represents the mean AUC seen in a previous study[2] for subjects receiving LPV/r 230/57.5 mg/m² oral solution BID without nevirapine. The lower edge of the grey box represents 20% lower exposure than observed for subjects receiving LPV/r 230/57.5 mg/m² oral solution BID without nevirapine and the upper edge of the grey box represents exposure at the higher dose, LPV/r 300/75 mg/m² without nevirapine.

- Pediatric dosing recommendations for the LPV/r 100/25 mg tablet administered in the absence and presence of CYP3A-inducing ARV agents, by body weight, are shown in Table 6.

Table 6. Pediatric Dosing Recommendations for the LPV/r 100/25 mg Tablet, by Body Weight

Pediatric Dosing Guidelines	
Body Weight (kg)	Recommended Number of 100/25 mg Tablets Twice Daily
7 to 10	1 tablet (100/25 mg)
>10 to 25	2 tablets (200/50 mg)
>25 to 35	3 tablets (300/75 mg)
>35	4 tablets (400/100 mg)
Pediatric Dosing Guidelines with Concomitant Efavirenz, Nevirapine, or (fos) Amprenavir	
Body Weight (kg)	Recommended Number of 100/25 mg Tablets Twice Daily
7 to 10	1 tablet (100/25 mg)
>10 to 20	2 tablets (200/50 mg)
>20 to 30	3 tablets (300/75 mg)
>30	4 tablets (400/100 mg)

- Modeling/simulation suggest that the LPV/r 100/25 mg tablet will provide LPV exposure similar to the oral solution for children with BSA > 0.4 m² or body weight > 7 kg.

Overall Conclusions

- The LPV/r 100/25 mg tablet formulations are bioequivalent to the LPV/r 200/50 mg tablet.
- These lower-strength tablets will allow for sufficient LPV/r dosing flexibility for pediatric patients who can swallow an intact tablet.

References

1. Kaletra® package insert, October 2005.
2. Liu W et al. Predicted pharmacokinetics of lopinavir after multiple-dose administration of lopinavir/ritonavir tablet to pediatric patients. Poster 366, 8th International Congress on Drug Therapy in HIV. 12–16 November 2006. Glasgow, UK.

The LPV/r 100/25 mg tablet formulation is currently under regulatory review. These tablets should not be crushed, broken or chewed.