# New pediatric dosing information for Kaletra, patients 14 days to 6 months and 12-18 years of age and update information on coadministration with midazolam

The Kaletra (lopinavir/ritonavir) Tablet and Oral Solution labels were updated to include dosing recommendations for pediatric patients 14 days to 6 months of age and from 12 to 18 years of age. In addition, information regarding oral and parenterally administered midazolam was updated in the Contraindication and Drug Interactions section.

**Pediatric Patient Information:**

Dose selection in pediatric patients was based on the following. This information is also contained in section 14.4 Pediatric Studies

- Among patients 14 days to 6 months of age receiving 300/75 mg/m$^2$ twice daily without nevirapine, plasma concentrations were lower than those observed in adults or in older children. This dose resulted in HIV-1 RNA < 400 copies/mL in 55% of patients (70% in those initiating treatment at <6 weeks of age).
- Among patients 6 months to 12 years of age, the 230/57.5 mg/m$^2$ oral solution twice daily regimen without nevirapine and the 300/75 mg/m$^2$ oral solution twice daily regimen with nevirapine provided lopinavir plasma concentrations similar to those obtained in adult patients receiving the 400/100 mg twice daily regimen (without nevirapine). These doses resulted in treatment benefit (proportion of patients with HIV-1 RNA < 400 copies/mL) similar to that seen in the adult clinical trials.
- Among patients 12 to 18 years of age receiving 400/100 mg/m$^2$ or 480/120 mg/m$^2$ (with efavirenz) twice daily, plasma concentrations were 60-100% higher than among 6 to 12 year old patients receiving 230/57.5 mg/m$^2$. Mean apparent clearance was similar to that observed in adult patients receiving standard dose and in patients 6 to 12 years of age. Although changes in HIV-1 RNA in patients with prior treatment failure were less than anticipated, the pharmacokinetic data supports use of similar dosing as in patients 6 to 12 years of age, not to exceed the recommended adult dose.

    - For all age groups, the body surface area dosing was converted to body weight dosing using the actual patient dose

Dosing in children (14 days – 18 years of age) is based on body weight or body surface area (size). The Dosage and Administration section 2.2 Pediatric Patients was updated to include the following.

## 2.2 Pediatric Patients

KALETRA tablets and oral solution should not be administered once-daily in pediatric patients < 18 years of age.

Healthcare professionals should pay special attention to accurate calculation of the dose of KALETRA, transcription of the medication order, dispensing information and dosing instructions to minimize the risk for medication errors, overdose,and underdose.

Prescribers should calculate the appropriate dose of KALETRA for each individual child based on body weight (kg) or body surface area (BSA) and should not exceed the recommended adult dose.

Body surface area (BSA) can be calculated as follows:

$$* \text{BSA } (m^2) = \sqrt{\frac{\text{Ht (Cm)} \times \text{Wt (kg)}}{3600}}$$

The KALETRA dose can be calculated based on weight or BSA:

**Based on Weight:**

Patient Weight (kg) × Prescribed lopinavir dose (mg/kg) = Administered lopinavir dose (mg)

**Based on BSA:**

Patient BSA ($m^2$) × Prescribed lopinavir dose ($mg/m^2$) = Administered lopinavir dose (mg)

If KALETRA oral solution is used, the volume (mL) of KALETRA solution can be determined as follows:

Volume of KALETRA solution (mL) = Administered lopinavir dose (mg) ÷ 80 (mg/mL)

The dose of the oral solution should be administered using a calibrated dosing syringe.

Before prescribing KALETRA 100/25 mg tablets, children should be assessed for the ability to swallow intact tablets. If a child is unable to reliably swallow a KALETRA tablet, the KALETRA oral solution formulation should be prescribed.

*14 Days to 6 Months:*

In pediatric patients 14 days to 6 months of age, the recommended dosage of lopinavir/ritonavir using KALETRA oral solution is 16/4 mg/kg or 300/75 $mg/m^2$ twice daily. Prescribers should calculate the appropriate dose based on body weight or body surface area.

Because no data exists for dosage when administered with efavirenz, nevirapine, (fos)amprenavir, or nelfinavir, it is recommended that KALETRA not be administered in combination with these drugs in patients < 6 months of age.

*6 Months to 18 Years:*

*Without Concomitant Efavirenz, Nevirapine, (Fos)amprenavir or Nelfinavir*

In children 6 months to 18 years of age, the recommended dosage of lopinavir/ritonavir using KALETRA oral solution without concomitant efavirenz, nevirapine, (fos)amprenavir or nelfinavir is 230/57.5 mg/$m^2$ given twice daily, not to exceed the recommended adult dose. If weight-based dosing is preferred, the recommended dosage of lopinavir/ritonavir for patients < 15 kg is 12/3 mg/kg given twice daily and the dosage for patients ≥ 15 kg to 40 kg is 10/2.5 mg/kg given twice daily.

Table 1 provides the dosing recommendations for pediatric patients 6 months to 18 years of age based on body weight or body surface area for KALETRA tablets.

**Table 1. Pediatric Dosing Recommendations for Patients 6 Months to 18 Years of Age Based on Body Weight or Body Surface Area for KALETRA Tablets Without Concomitant Efavirenz, Neviraprine, (Fos)amprenavir, or Nelfinavir**

| Body Weight (kg) | Body Surface Area ($m^2$)* | Recommended number of 100/25 mg Tablets Twice-Daily |
|---|---|---|
| 15 to 25 | ≥0.6 to < 0.9 | 2 |
| >25 to 35 | ≥ 0.9 to < 1.4 | 3 |
| >35 | ≥ 1.4 | 4 (or two 200/50 mg tablets) |

*KALETRA oral solution is available for children with a BSA less than 0.6 $m^2$ or those who are unable to reliably swallow a tablet.

*Concomitant Therapy: Efavirenz, Nevirapine, (Fos)amprenavir, or Nelfinavir*

A dose increase of KALETRA to 300/75 mg/$m^2$ is needed when co-administered with efavirenz, nevirapine, (fos)amprenavir, or nelfinavir in children (both treatment-naïve and treatment-experienced) 6 months to 18 years of age, not to exceed the recommended adult dose. If weight-based dosing is preferred, the recommended dosage for patients <15 kg is 13/3.25 mg/kg given twice daily and the dosage for patients ≥15 kg to 45 kg is 11/2.75 mg/kg given twice daily.

Table 2 provides the dosing recommendations for pediatric patients 6 months to 18 years of age based on body weight or body surface area for KALETRA tablets when given in combination with efavirenz, nevirapine, (fos)amprenavir, or nelfinavir.

| Table 2. Pediatric Dosing Recommendations for Patients 6 Months to 18 Years of Age Based on Body Weight or Body Surface Area for KALETRA Tablets With Concomitant Efavirenz†, Nevirapine, (Fos)amprenavir† or Nelfinavir† | | |
|---|---|---|
| **Body Weight (kg)** | **Body Surface Area ($m^2$)*** | **Recommended number of 100/25 mg Tablets Twice-Daily** |
| 15 to 20 | ≥0.6 to < 0.8 | 2 |
| >20 to 30 | ≥ 0.8 to < 1.2 | 3 |
| >30 to 45 | ≥ 1.2 to <1.7 | 4 (or two 200/50 mg tablets) |
| >45 | ≥ 1.7 | 4 or 6 (or two or three 200/50 mg tablets) See Dosage and Administration, Adult Patients (2.1) |

*KALETRA oral solution is available for children with a BSA less than 0.6 $m^2$ or those who are unable to reliably swallow a tablet.
†Please refer to the individual product labels for appropriate dosing in children

The following information was added to section 6 Adverse Reactions subsection 6.2 Pediatric Patients - Clinical Trials Experience

KALETRA oral solution dosed at 300/75 mg/$m^2$ has been studied in 31 pediatric patients 14 days to 6 months of age. The adverse reaction profile in Study 1030 was similar to that observed in older children and adults. No adverse reaction was reported in greater than 10% of subjects. Adverse drug reactions of moderate to severe intensity occurring in 2 or more subjects included decreased neutrophil count (N=3,) anemia (N=2), high potassium (N=2), and low sodium (N=2).

KALETRA oral solution and soft gelatin capsules dosed at higher than recommended doses including 400/100 mg/$m^2$ (without concomitant NNRTI) and 480/120 mg/$m^2$ (with concomitant NNRTI) have been studied in 26 pediatric patients 7 to 18 years of age in Study 1038. Patients also had saquinavir mesylate added to their regimen at Week 4. Rash (12%), blood cholesterol abnormal (12%) and blood triglycerides abnormal (12%) were the only adverse reactions reported in greater than 10% of subjects. Adverse drug reactions of moderate to severe intensity occurring in 2 or more subjects included rash (N=3), blood triglycerides abnormal (N=3), and electrocardiogram QT prolonged (N=2). Both subjects with QT prolongation had additional predisposing conditions such as electrolyte abnormalities, concomitant medications, or pre-existing cardiac abnormalities.

The following information was added to Section 8 Use in Specific Populations subsection 8.4 Pediatric Use

The safety, efficacy, and pharmacokinetic profiles of KALETRA in pediatric patients below the age of 14 days have not been established. KALETRA once-daily has not been evaluated in pediatric patients.

An open-label, multi-center, dose-finding trial was performed to evaluate the pharmacokinetic profile, tolerability, safety and efficacy of KALETRA oral solution containing lopinavir 80 mg/mL and ritonavir 20 mg/mL at a dose of with 300/75 mg/m$^2$ twice daily plus two NRTIs in HIV-infected infants ≥14 days and < 6 months of age. Results revealed that infants younger than 6 months of age generally had lower lopinavir $AUC_{12}$ than older children (6 months to 12 years of age), however, despite the lower lopinavir drug exposure observed, antiviral activity was demonstrated as reflected in the proportion of subjects who achieved HIV-RNA <400 copies/mL at Week 24.

Safety and efficacy in pediatric patients > 6 months of age was demonstrated in a clinical trial in 100 patients. The clinical trial was an open-label, multicenter trial evaluating the pharmacokinetic profile, tolerability, safety, and efficacy of KALETRA oral solution containing lopinavir 80 mg/mL and ritonavir 20 mg/mL in 100 antiretroviral naïve and experienced pediatric patients ages 6 months to 12 years. Dose selection for patients 6 months to 12 years of age was based on the following results. The 230/57.5 mg/m$^2$ oral solution twice-daily regimen without nevirapine and the 300/75 mg/m$^2$ oral solution twice-daily regimen with nevirapine provided lopinavir plasma concentrations similar to those obtained in adult patients receiving the 400/100 mg twice-daily regimen (without nevirapine).

A prospective multicenter, open-label trial evaluated the pharmacokinetic profile, tolerability, safety and efficacy of high-dose KALETRA with or without concurrent NNRTI therapy (Group 1: 400/100 mg/m$^2$ twice daily + ≥ 2 NRTIs; Group 2: 480/120 mg/m$^2$ twice daily + ≥ 1 NRTI + 1 NNRTI) in children and adolescents ≥ 2 years to < 18 years of age who had failed prior therapy. Patients also had saquinavir mesylate added to their regimen. This strategy was intended to assess whether higher than approved doses of KALETRA could overcome protease inhibitor cross-resistance. High doses of KALETRA exhibited a safety profile similar to those observed in previous trials; changes in HIV-1 RNA were less than anticipated; three patients had HIV-1 RNA <400 copies/mL at Week 48. CD4+ cell count increases were noted in the eight patients who remained on treatment for 48 weeks.

Section 12.3 Pharmacokinetics was updated as follows

The pharmacokinetics of KALETRA oral solution at approximately 300/75 mg/m$^2$ twice-daily have also been evaluated in infants at approximately 6 weeks of age (n = 9) and between 6 weeks and 6 months of age (n = 18) in Study 1030. The mean steady-state lopinavir $AUC_{12}$, $C_{max}$, and $C_{12}$ were 43.4 ± 14.8 µg• h/mL, 5.2 ± 1.8 µg/mL and 1.9 ± 1.1 µg/mL, respectively, in infants at approximately 6 weeks of age, and 74.5 ± 37.9 µg• h/mL, 9.4 ± 4.9 and 3.1 ± 1.8 µg/mL, respectively, in infants between 6 weeks and 6 months of age after KALETRA oral solution was administered at approximately 300/75 mg/m$^2$ twice-daily without concomitant NNRTI therapy.

The pharmacokinetics of KALETRA soft gelatin capsule and oral solution (Group 1: 400/100 mg/$m^2$ twice daily + 2 NRTIs; Group 2: 480/120 mg/$m^2$ twice daily + ≥ 1 NRTI + 1 NNRTI) have been evaluated in children and adolescents age ≥ 2 years to < 18 years of age who had failed prior therapy (n=26) in Study 1038. KALETRA doses of 400/100 and 480/120 mg/$m^2$ resulted in high lopinavir exposure, as almost all subjects had lopinavir $AUC_{12}$ above 100 μg•h/mL. Both groups of subjects also achieved relatively high average minimum lopinavir concentrations.

KALETRA once-daily has not been evaluated in pediatric patients.

Section 14 Clinical Studies subsection 14.4 Pediatric Studies was also updated with the following study results.

Study 1030 was an open-label, multicenter, dose-finding trial evaluating the pharmacokinetic profile, tolerability, safety and efficacy of KALETRA oral solution containing lopinavir 80 mg/mL and ritonavir 20 mg/mL at a dose of 300/75 mg/$m^2$ twice daily plus 2 NRTIs in HIV-1 infected infants ≥14 days and <6 months of age.

Ten infants, ≥14 days and <6 wks of age, were enrolled at a median (range) age of 5.7 (3.6-6.0) weeks and all completed 24 weeks. At entry, median (range) HIV-1 RNA was 6.0 (4.7-7.2) $log_{10}$ copies/mL. Seven of 10 infants had HIV-1 RNA <400 copies/mL at Week 24. At entry, median (range) $CD4^+$ percentage was 41 (16-59) with a median decrease of 1% (95% CI: -10, 18) from baseline to week 24 in 6 infants with available data.

Twenty-one infants, between 6 weeks and 6 months of age, were enrolled at a median (range) age of 14.7 (6.9-25.7) weeks and 19 of 21 infants completed 24 weeks. At entry, median (range) HIV RNA level was 5.8 (3.7-6.9) $log_{10}$ copies/mL. Ten of 21 infants had HIV RNA <400 copies/mL at Week 24. At entry, the median (range) $CD4^+$ percentage was 32 (11-54) with a median increase of 4% (95% CI: -1, 9) from baseline to week 24 in 19 infants with available data.

**Midazolam Information:**

Orally administered midazolam is contraindicated for use with Kaletra. This change is reflected in section 4 Contraindications.

Section 7 Drug Interactions Table 9 Established and Other Potentially Significant Drug Interactions was updated to include information on parenterally administered midazolam and includes the following statement.

Midazolam is extensively metabolized by CYP3A4. Increases in the concentration of midazolam are expected to be significantly higher with oral than

parenteral administration. Therefore, KALETRA should not be given with orally administered midazolam [see *Contraindications (4)*]. If KALETRA is coadministered with parenteral midazolam, close clinical monitoring for respiratory depression and/or prolonged sedation should be exercised and dosage adjustment should be considered.