Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

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Lopinavir/Ritonavir (LPV/r, Kaletra) *(Last updated April 27, 2017; last reviewed April 27, 2017)*

For additional information see Drugs@FDA: [http://www.accessdata.fda.gov/scripts/cder/daf/](http://www.accessdata.fda.gov/scripts/cder/daf/)

### Formulations

- **Pediatric Oral Solution:** 80 mg/20 mg LPV/r per mL (contains 42.4% alcohol by volume and 15.3% propylene glycol by weight/volume)
- **Film-Coated Tablets:** 100 mg/25 mg LPV/r, 200 mg/50 mg LPV/r

### Dosing Recommendations

**Neonatal Dose (<14 Days):**
- No data on appropriate dose or safety in this age group. Do not administer to neonates before a post-menstrual age of 42 weeks and a postnatal age of at least 14 days because of potential toxicities.

**Dosing for Individuals not Receiving Concomitant Nevirapine, Efavirenz, Fosamprenavir, or Nelfinavir**

- **Infant Dose (14 Days–12 Months):**
  - Once-daily dosing **is not recommended**.
  - 300 mg/75 mg lopinavir/ritonavir per m² of body surface area twice daily (approximates 16 mg/4 mg lopinavir/ritonavir per kg body weight twice daily). **Note:** This dose in infants aged <12 months is associated with lower lopinavir trough levels than those found in adults; lopinavir dosing should be adjusted for growth at frequent intervals (see text below). Also see text for transitioning infants to lower mg per m² dose).

- **Pediatric Dose (>12 Months to 18 Years):**
  - Once-daily dosing **is not recommended**.
  - 300 mg/75 mg lopinavir/ritonavir per m² of body surface area per dose twice daily (maximum dose 400 mg/100 mg lopinavir/ritonavir twice daily except as noted below). For patients with body weight <15 kg, this approximates 13 mg/3.25 mg lopinavir/ritonavir per kg body weight twice daily; and for patients with body weight ≥15 to 45 kg this dose approximates 11 mg/2.75 mg lopinavir/ritonavir per kg body weight twice daily. This dose is routinely used by many clinicians and is the preferred dose for treatment-experienced patients who could harbor virus with decreased lopinavir susceptibility (see text below).

### Selected Adverse Events

- Gastrointestinal (GI) intolerance, nausea, vomiting, diarrhea, taste alteration
- Hyperlipidemia, especially hypertriglyceridemia
- Elevated transaminases
- Hyperglycemia
- PR interval prolongation
- QT interval prolongation and torsades de pointes
- Risk of toxicity—including life-threatening cardiotoxicity—is increased in premature infants (see Major Toxicities below).

### Special Instructions

- Lopinavir/ritonavir tablets can be administered without regard to food; administration with or after meals may enhance GI tolerability.
- Lopinavir/ritonavir tablets must be swallowed whole. Do not crush or split tablets.
- Lopinavir/ritonavir oral solution should be administered with food because a high-fat meal increases absorption.
- The poor palatability of lopinavir/ritonavir oral solution is difficult to mask with flavorings or foods (see Pediatric Use).
- Lopinavir/ritonavir oral solution can be kept at room temperature up to 77º F (25º C) if used within 2 months. If kept refrigerated (2º to 8º C or 36º to 46º F) lopinavir/ritonavir oral solution remains stable until the expiration date printed on the label.
- Once-daily dosing is not recommended because of considerable variability in plasma concentrations in children aged <18 years and higher incidence of diarrhea.
- Use of lopinavir/ritonavir once daily is specifically contraindicated if three or more of...
• 230 mg/57.5 mg lopinavir/ritonavir per m² of body surface area per dose twice daily can be used in antiretroviral (ARV)-naive patients aged >1 year. For patients <15 kg, this dose approximates 12 mg/3 mg lopinavir/ritonavir per kg body weight given twice daily and for patients ≥15 kg to 40 kg, this dose approximates 10 mg/2.5 mg lopinavir/ritonavir per kg body weight given twice daily. This dose should not be used in treatment-experienced patients who could harbor virus with decreased lopinavir susceptibility.

Weight-Band Dosing for 100 mg/25 mg Lopinavir/Ritonavir Pediatric Tablets for Children/Adolescents

<table>
<thead>
<tr>
<th>Body Weight (kg)</th>
<th>Recommended Number of 100-mg/25-mg Lopinavir/Ritonavir Tablets Given Twice Daily</th>
</tr>
</thead>
<tbody>
<tr>
<td>15 to 20 kg</td>
<td>2</td>
</tr>
<tr>
<td>&gt;20 to 25 kg</td>
<td>3</td>
</tr>
<tr>
<td>&gt;25 to 30 kg</td>
<td>3</td>
</tr>
<tr>
<td>&gt;30 to 35 kg</td>
<td>4a</td>
</tr>
<tr>
<td>&gt;35 to 45 kg</td>
<td>4a or 5b</td>
</tr>
<tr>
<td>&gt;45 kg</td>
<td>4a</td>
</tr>
</tbody>
</table>

a Four of the 100 mg/25 mg lopinavir/ritonavir tablets can be substituted with 2 tablets each containing 200 mg/50 mg lopinavir/ritonavir in children capable of swallowing a larger tablet.

b In patients receiving concomitant nevirapine, efavirenz, fosamprenavir, or nelfinavir, for body weight >45 kg, the Food and Drug Administration (FDA)-approved adult dose is 500 mg/125 mg lopinavir/ritonavir twice daily, given as a combination of 2 tablets of 200/50 mg lopinavir/ritonavir and 1 tablet of 100 mg/25 mg lopinavir/ritonavir. Alternatively, 3 tablets of 200/50 mg lopinavir/ritonavir can be used for ease of dosing.

Adult Dose (>18 Years):
• 800 mg/200 mg lopinavir/ritonavir once daily, or
• 400 mg/100 mg lopinavir/ritonavir twice daily.
• Do not use once-daily dosing in children or adolescents, or in patients receiving concomitant therapy with nevirapine, efavirenz, fosamprenavir, or nelfinavir, or in patients with three or more lopinavir-associated mutations (see Special Instructions for list).

The following lopinavir resistance-associated substitutions are present—L10F/I/R/V, K20M/N/R, L24I, L33F, M36I, I47V, G48V, I54L/T/V, V82A/C/F/S/T, and I84V—because higher lopinavir trough concentrations may be required to suppress resistant virus.

Metabolism/Elimination

• Cytochrome P (CYP) 3A4 inhibitor and substrate.
• Dosing of lopinavir/ritonavir in patients with hepatic impairment: Lopinavir/ritonavir is primarily metabolized by the liver. Caution should be used when administering lopinavir to patients with hepatic impairment. No dosing information is currently available for children or adults with hepatic insufficiency.
• In the co-formulation of lopinavir/ritonavir, the ritonavir acts as a pharmacokinetic enhancer, not as an ARV agent. It does this by inhibiting the metabolism of lopinavir and increasing lopinavir plasma concentrations.
In Patients with Three or more Lopinavir-Associated Mutations (see Special Instructions for list):

- 400 mg/100 mg lopinavir/ritonavir twice daily.

Dosing for Individuals Receiving Concomitant Nevirapine, Efavirenz, Fosamprenavir, or Nelfinavir:

**Note:** These drugs induce lopinavir metabolism and reduce lopinavir plasma levels; increased lopinavir/ritonavir dosing is required with concomitant administration of these drugs.

- Once-daily dosing should **not** be used.

Pediatric Dose (>12 Months to 18 Years):

- 300 mg/75 mg lopinavir/ritonavir per m² of body surface area per dose twice daily. See table for weight-band dosing when using tablets.

Adult Dose (>18 Years):

- FDA-approved dose is 500 mg/125 mg lopinavir/ritonavir twice daily, given as a combination of 2 tablets of 200/50 mg lopinavir/ritonavir and 1 tablet of 100 mg/25 mg lopinavir/ritonavir. Alternatively, 3 tablets of 200/50 mg lopinavir/ritonavir can be used for ease of dosing. Once-daily dosing should **not** be used.

Lopinavir/Ritonavir in Combination with Saquinavir Hard-Gel Capsules (Invirase) or in Combination with Maraviroc:

- Saquinavir and maraviroc doses may need modification (see the Saquinavir and Maraviroc sections for more information).

**Drug Interactions** (see also the Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents and http://hivdb.stanford.edu/DR/)

- **Metabolism:** CYP450 3A4 (CYP3A4) is the major enzyme responsible for metabolism. There is potential for multiple drug interactions.

Before administration, a patient’s medication profile should be carefully reviewed for potential drug interactions with lopinavir/ritonavir. In patients treated with lopinavir/ritonavir, fluticasone (a commonly used inhaled and intranasal steroid) should be avoided and an alternative used. **Drug interactions with anti-tuberculous drugs are common and may require dosage adjustments or regimen change.**

**Major Toxicities**

- **More common:** Diarrhea, headache, asthenia, nausea and vomiting, rash, and hyperlipidemia, especially hypertriglyceridemia,¹ possibly more pronounced in girls than boys.² In adults, lopinavir/ritonavir is associated with diarrhea, insulin resistance, and hyperlipidemia. These adverse events may be exacerbated by the higher dose of ritonavir used for boosting with lopinavir (200 mg) compared to atazanavir and darunavir (100 mg).
• **Less common (more severe):** Fat maldistribution

• **Rare:** New-onset diabetes mellitus, hyperglycemia, ketoacidosis, exacerbation of preexisting diabetes mellitus, hemolytic anemia, spontaneous and/or increased bleeding in hemophiliacs, pancreatitis, elevation in serum transaminases, and hepatitis (life-threatening in rare cases). PR interval prolongation, QT interval prolongation, and torsades de pointes may occur.

• **Special populations—neonates:** Lopinavir/ritonavir should not be used in the immediate postnatal period in premature infants because an increased risk of toxicity in premature infants has been reported. These toxicities in premature infants include transient symptomatic adrenal insufficiency, life-threatening bradyarrhythmias and cardiac dysfunction (including complete atrioventricular block, bradycardia, and cardiomyopathy), and lactic acidosis, acute renal failure, central nervous system depression, and respiratory depression. These toxicities may be from the drug itself and/or from the inactive ingredients in the oral solution, including propylene glycol 15.3%, and ethanol 42.4%. Transient asymptomatic elevation in 17-hydroxyprogesterone levels has been reported in term newborns treated at birth with lopinavir/ritonavir.

**Resistance**

The International Antiviral Society-USA (IAS-USA) maintains a list of updated resistance mutations (see http://iasusa.org/sites/default/files/tam/october_november_2015.pdf#page=10) and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation (see http://hivdb.stanford.edu/DR/).

**Pediatric Use**

**Approval**

Lopinavir/ritonavir is Food and Drug Administration (FDA)-approved for use in children. Ritonavir acts as a pharmacokinetic (PK) enhancer by inhibiting the metabolism of lopinavir and thereby increasing the plasma concentration of lopinavir.

**Efficacy**

In clinical trials of treatment-naive adults, regimens containing LPV/r plus two NRTIs have been demonstrated to be comparable to a variety of other regimens including atazanavir, darunavir (at 48 weeks), fosamprenavir, saquinavir/ritonavir, and efavirenz, superior to nelfinavir, and inferior to darunavir (at 192 weeks). LPV/r has been studied in both ARV-naive and ARV-experienced children and has demonstrated durable virologic activity and low toxicity.

**Pharmacokinetics**

**General Considerations**

Children have lower drug exposure than adults when treated with doses that are directly scaled for body surface area. The directly scaled dose approximation of the adult dose in children is calculated by dividing the adult dose by the usual adult body surface area of 1.73 m². For the adult dose of 400/100 mg lopinavir/ritonavir, the appropriate pediatric dose would be approximately 230/57.5 mg lopinavir/ritonavir per m². However, younger children have enhanced lopinavir clearance and need higher drug doses to achieve drug exposures similar to those in adults treated with standard doses. To achieve similar C₄₅₀ to that observed in adults, the pediatric dose needs to be increased 30% over the dose that is directly scaled for body surface area. Lopinavir exposures in infants are compared to those in older children and adults in the table below.
Pharmacokinetics of Lopinavir/Ritonavir by Age

<table>
<thead>
<tr>
<th></th>
<th>Adults 23</th>
<th>Children 16</th>
<th>Children 16</th>
<th>Infants a at 12 Months 23</th>
<th>Infants 6 weeks–6 months 18</th>
<th>Infants &lt;6 weeks 24</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>19</td>
<td>12</td>
<td>15</td>
<td>20</td>
<td>18</td>
<td>9</td>
</tr>
<tr>
<td>Dose LPV</td>
<td>400 mg</td>
<td>230 mg/m²</td>
<td>300 mg/m²</td>
<td>300 mg/m²</td>
<td>300 mg/m²</td>
<td>300 mg/m²</td>
</tr>
<tr>
<td>AUC mcg-hr/mL</td>
<td>92.6</td>
<td>72.6</td>
<td>116.0</td>
<td>101.0</td>
<td>74.5</td>
<td>43.4</td>
</tr>
<tr>
<td>Cmax mcg/mL</td>
<td>9.8</td>
<td>8.2</td>
<td>12.5</td>
<td>12.1</td>
<td>9.4</td>
<td>5.2</td>
</tr>
<tr>
<td>Ctrough mcg/mL</td>
<td>7.1</td>
<td>4.7</td>
<td>7.9</td>
<td>4.9</td>
<td>2.7</td>
<td>2.5</td>
</tr>
<tr>
<td>Cmin mcg/mL</td>
<td>5.5</td>
<td>3.4</td>
<td>6.5</td>
<td>3.8</td>
<td>2.0</td>
<td>1.4</td>
</tr>
</tbody>
</table>

a Data generated in study cited but not reported in final manuscript. Data in table source: personal communication from Edmund Capparelli, PharmD (April 18, 2012)

Note: Values are means; all data shown performed in the absence of non-nucleoside reverse transcriptase inhibitors (NNRTIs).

Key to Acronyms: AUC = area under the curve; LPV = lopinavir

Models suggest that diet, body weight and postnatal age are important factors in lopinavir PK, with improved bioavailability as dietary fat increases over the first year of life26 and with clearance slowing by age 2.3 years.27 A study from the UK and Ireland in children ages 5.6 to 12.8 years at the time of lopinavir/ritonavir initiation that compared outcomes in children treated with 230 mg/m²/dose versus 300 mg/m²/dose suggests that the higher doses were associated with improved long-term viral load suppression.28

Pharmacokinetics and Dosing

12 Months to 12 Years (Without Concurrent Nevirapine, Efavirenz, Fosamprenavir, or Nelfinavir)
Lower trough concentrations have been observed in children receiving 230 mg/57.5 mg lopinavir/ritonavir per m² of body surface area when compared to 300 mg/75 mg lopinavir/ritonavir per m² of body surface area per dose twice daily (see table).16 Therefore, some clinicians choose to initiate therapy in children aged 12 months to 12 years using 300 mg/75 mg lopinavir/ritonavir per m² of body surface area per dose twice daily (when given without nevirapine, efavirenz, fosamprenavir, or nelfinavir) rather than the FDA-recommended 230 mg/57.5 mg lopinavir/ritonavir per m² of body surface area per dose twice daily.

For infants receiving 300 mg/75 mg lopinavir/ritonavir per m² of body surface area per dose twice daily, immediate dose reduction at age 12 months is not recommended; many practitioners would allow patients to “grow into” the 230 mg/57.5 mg lopinavir/ritonavir per m² of body surface area per dose twice daily dosage as they gain weight over time. Some would continue the infant dose (300 mg/m² of body surface area per dose twice daily) while on lopinavir/ritonavir liquid formulation.

Younger Than 6 Weeks to 12 Months (Without Concurrent Nevirapine, Efavirenz, Fosamprenavir, or Nelfinavir)
The PK of the oral solution at approximately 300 mg/75 mg lopinavir/ritonavir per m² body surface area per dose twice daily was evaluated in infants younger than age 6 weeks24 and infants aged 6 weeks to 6 months.18 Even at this higher dose, pre-dose (Ctrough) levels were highly variable but were lower in infants than in children older than age 6 months and were lowest in the youngest infants aged 6 weeks or younger compared with those aged 6 weeks to 6 months. By age 12 months, lopinavir area under the curve (AUC) was similar to that found in older children.23 Because infants grow rapidly in the first months of life, it is important to optimize lopinavir dosing by adjusting the dose at frequent intervals. Given the safety of doses as high as 400 mg/m² body surface area in older children and adolescents,19 some practitioners anticipate rapid infant growth and prescribe doses somewhat higher than the 300 mg/m² body surface area dose to allow for projected growth between clinic appointments.

Pharmacokinetics and Dosing with Concurrent Nevirapine, Efavirenz, Fosamprenavir, or Nelfinavir
In both children and adults, the lopinavir Ctrough is reduced by concurrent treatment with non-nucleoside...
reverse transcriptase inhibitors (NNRTIs) or concomitant fosamprenavir, or nelfinavir. Higher doses of lopinavir are recommended if the drug is given in combination with nevirapine, efavirenz, fosamprenavir, or nelfinavir. In 14 children treated with 230 mg/57.5 mg lopinavir/ritonavir per m² body surface area per dose twice daily plus nevirapine, the mean lopinavir C_{trough} was 3.77 ± 3.57 mcg/mL. Not only are these trough plasma concentrations lower than those found in adults treated with standard doses of lopinavir/ritonavir, but the variability in concentration is much higher in children than in adults. In a study of 15 children with HIV aged 5.7 to 16.3 years treated with the combination of 300 mg/75 mg lopinavir/ritonavir per m² body surface area per dose twice daily plus efavirenz 14 mg/kg body weight per dose once daily there was a 34-fold inter-individual variation in lopinavir trough concentrations, and 5 of 15 (33%) children had lopinavir 12-hour trough concentrations less than 1.0 mcg/mL, the plasma concentration needed to inhibit wild-type HIV. A PK study in 20 children aged 10 to 16 years treated with the combination of lopinavir/ritonavir 300 mg/75 mg per m² body surface area twice daily plus efavirenz 350 mg/m² body surface area once daily showed only 1 (6.6%) patient with sub-therapeutic lopinavir trough concentrations, perhaps because of the use of a lower efavirenz dose of approximately 11 mg/kg body weight compared with efavirenz 14 mg/kg body weight in the Bergshoeff trial.

Dosing

Once Daily

Once-daily dosing of lopinavir/ritonavir 800 mg/200 mg administered as a single daily dose is FDA-approved for treatment of HIV in therapy-naive adults older than age 18 years. However, once-daily administration cannot be recommended for use in children in the absence of therapeutic drug monitoring (TDM). There is high inter-individual variability in drug exposure and trough plasma concentrations below the therapeutic range for wild-type virus as demonstrated in studies of antiretroviral (ARV)-naive children and adolescents. Compared with the soft-gel formulation of lopinavir/ritonavir, the tablet formulation has lower variability in trough levels. An international, randomized, open-label trial designed to demonstrate noninferiority in viral suppression between once daily vs. twice daily LPV/r dosing in children (median [IQR] age of 11 [9–14] years) was unsuccessful, and more children on once daily dosing had viral load ≥50 copies/ml within 48 weeks.

Dosing and Its Relation to Efficacy

Lopinavir/ritonavir is effective in treatment-experienced patients with severe immune suppression, although patients with greater prior exposure to ARVs may have slower reductions in viral load to undetectable concentrations and less robust response in CD4 T lymphocyte (CD4) percentage. Twice daily doses of lopinavir used in this cohort were 230 to 300 mg/m² body surface area in 39% of patients, 300 to 400 mg/m² body surface area in 35%, and greater than 400 mg/m² body surface area per dose in 4%. More important than viral resistance to lopinavir is the relationship of the drug exposure (trough plasma concentration measured just before a dose, or C_{trough}) to the susceptibility of the HIV-1 isolate (EC_{50}). The ratio of C_{trough} to EC_{50} is called the inhibitory quotient (IQ), and in both adults and children treated with lopinavir/ritonavir, viral load reduction is more closely associated with IQ than with either the C_{trough} or EC_{50} alone.

A study of the practical application of the IQ to guide therapy using higher doses of lopinavir/ritonavir in children and adolescents to reach a target IQ of 15 showed the safety and tolerability of doses of 400 mg/100 mg lopinavir/ritonavir per m² body surface area per dose twice daily (without fosamprenavir, nelfinavir, nevirapine, or efavirenz) and 480 mg/120 mg lopinavir/ritonavir per m² body surface area per dose twice daily (with nevirapine or efavirenz). Results of a modeling study suggest that standard doses of lopinavir/ritonavir may be inadequate for treatment-experienced children and suggest the potential utility of TDM when lopinavir/ritonavir is used in children previously treated with protease inhibitors.

Formulations

Palatability

The poor palatability of the lopinavir/ritonavir oral solution can be a significant challenge to medication adherence for some children and families. Numbing of the taste buds with ice chips before or after administration of the solution, masking of the taste by administration with sweet or tangy foods, chocolate

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syrup, or peanut butter, for example, or by having the pharmacist flavor the solution prior to dispensing, are examples of interventions that may improve tolerability. Alternative pediatric formulations are currently being developed.46,47

Do Not Use Crushed Tablets

Lopinavir/ritonavir tablets must be swallowed whole. Crushed tablets are slowly and erratically absorbed, and result in significantly reduced AUC, C\textsubscript{max}, and C\textsubscript{trough} compared with swallowing the whole tablet. The variability of the reduced exposure with the crushed tablets (5% to 75% reduction in AUC) means that a dose modification cannot be relied on to overcome the reduced absorption. Crushed tablets cannot be recommended for use.48 In a PK study using a generic adult formulation of lopinavir/ritonavir manufactured in Thailand, 21 of 54 children were administered cut (not crushed) pills and had adequate lopinavir C\textsubscript{trough} measurements.36

Toxicity

Weight Gain

Compared with children treated with NNRTI-based regimens, those treated with lopinavir/ritonavir may have less robust weight gain and smaller increases in CD4 percentage.21,49-51 The poor weight gain associated with lopinavir/ritonavir is not understood, but may be related to aversion to the taste of the liquid formulation or decreased appetite.

References


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