Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

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Lopinavir/Ritonavir (LPV/r, Kaletra)  (Last updated May 22, 2018; last reviewed May 22, 2018)

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

Formulations

Pediatric Oral Solution:
• [Kaletra] Lopinavir 80 mg plus ritonavir 20 mg/mL (contains 42.4% alcohol by volume and 15.3% propylene glycol by weight/volume

Film-Coated Tablets:
• [Kaletra] Lopinavir 100 mg plus ritonavir 25 mg
• [Kaletra] Lopinavir 200 mg plus ritonavir 50 mg

Dosing Recommendations

Neonatal Dose (Aged <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 due to potential toxicities.

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

Infant Dose (Aged 14 Days–12 Months):
• Once-daily dosing is not recommended.
• Lopinavir/ritonavir (LPV/r) 300 mg/75 mg per m² of body surface area per dose twice daily. This approximates LPV/r 16 mg/4 mg (both 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 and Adolescent Dose (Aged >12 Months to 18 Years):
• Once-daily dosing is not recommended.
• LPV/r 300 mg/75 mg per m² of body surface area per dose twice daily (maximum dose LPV/r 400 mg/100 mg twice daily, except as noted below). For patients weighing <15 kg, this approximates LPV/r 13 mg/3.25 mg (both per kg body weight) twice daily. For patients weighing ≥15 kg to 45 kg, this dose approximates LPV/r 11 mg/2.75 mg (both per kg body weight) twice daily. This dose is routinely used by many clinicians and is

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

• LPV/r tablets can be administered without regard to food; administration with or after meals may enhance GI tolerability.
• LPV/r tablets must be swallowed whole. Do not crush or split tablets.
• LPV/r oral solution should be administered with food because a high-fat meal increases absorption.
• The poor palatability of LPV/r oral solution is difficult to mask with flavorings or foods (see Pediatric Use).
• LPV/r oral solution can be kept at room temperature up to 77° F (25° C) if used within 2 months. If kept refrigerated (2° C to 8° C or 36° F to 46° F), LPV/r oral solution remains stable until the expiration date printed on the label.
• Once-daily dosing is not recommended
the preferred dose for treatment-experienced patients who could harbor virus with decreased lopinavir susceptibility (see text below).

- LPV/r 230 mg/57.5 mg per m² of body surface area per dose twice daily can be used in antiretroviral (ARV)-naive patients aged ≥1 year. For patients weighing <15 kg, this dose approximates LPV/r 12 mg/3 mg per kg body weight given twice daily. For patients weighing ≥15 kg to 40 kg, this dose approximates LPV/r 10 mg/2.5 mg per kg body weight given twice daily. This lower dose should not be used in treatment-experienced patients who could harbor virus with decreased lopinavir susceptibility.

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

<table>
<thead>
<tr>
<th>Dosing Target</th>
<th>Recommended Number of LPV/r 100 mg/25 mg Tablets Given Twice Daily</th>
</tr>
</thead>
<tbody>
<tr>
<td>15 kg to 20 kg</td>
<td>300 mg/m²/dose given twice daily</td>
</tr>
<tr>
<td>&gt;20 kg to 25 kg</td>
<td>2</td>
</tr>
<tr>
<td>&gt;25 kg to 30 kg</td>
<td>3</td>
</tr>
<tr>
<td>&gt;30 kg to 35 kg</td>
<td>3</td>
</tr>
<tr>
<td>&gt;35 kg to 45 kg</td>
<td>4*</td>
</tr>
<tr>
<td>&gt;45 kg</td>
<td>4* or 5*</td>
</tr>
</tbody>
</table>

* Four of the LPV/r 100 mg/25 mg tablets can be substituted with two tablets each containing LPV/r 200 mg/50 mg in children capable of swallowing a larger tablet.

In patients receiving concomitant nevirapine, efavirenz, fosamprenavir, or nelfinavir, weighing >45 kg, the Food and Drug Administration (FDA)-approved adult dose of LPV/r 500 mg/125 mg twice daily, given as a combination of two tablets of LPV/r 200 mg/50 mg and one tablet of LPV/r 100 mg/25 mg. Alternatively, three tablets of LPV/r 200 mg/50 mg can be used for ease of dosing.

**Adult Dose (Aged >18 Years):**

- LPV/r 800 mg/200 mg once daily, or
- LPV/r 400 mg/100 mg 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

because of considerable variability in plasma concentrations in children aged <18 years and a higher incidence of diarrhea.

- Use of LPV/r once daily is specifically **contraindicated** if three or more of the following lopinavir resistance-associated substitutions are present: L10F/I/R/V, K20M/N/R, L24I, L33F, M36I, L47V, G48V, I54L/T/V, V82A/C/F/S/T, and I84V. This is because higher lopinavir trough concentrations may be required to suppress resistant virus.

**Metabolism/Elimination**

- Cytochrome P (CYP) 3A4 inhibitor and substrate.

**LPV/r Dosing in Patients with Hepatic Impairment:**

- LPV/r is primarily metabolized by the liver. Use caution 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 LPV/r, 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.
Drug Interactions (See also the Adult and Adolescent Guidelines and the HIV Drug Interaction Checker)

- **Metabolism:** Cytochrome P (CYP) 3A4 is the major enzyme responsible for metabolism. There is potential for multiple drug interactions with lopinavir/ritonavir (LPV/r).

- Before administration, a patient’s medication profile should be carefully reviewed for potential drug interactions with LPV/r. In patients treated with LPV/r, 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 dose adjustments or regimen change.

**Major Toxicities**

- **More common:** Diarrhea, headache, asthenia, nausea and vomiting, rash, insulin resistance, and hyperlipidemia, especially hypertriglyceridemia, possibly more pronounced in girls than boys. These adverse events may be exacerbated by the higher dose of ritonavir used for boosting with lopinavir (200 mg) compared with 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: LPV/r should not be used during 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,4 life-threatening bradyarrhythmias and cardiac dysfunction (including complete atrioventricular block, bradycardia, and cardiomyopathy),5–7 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%.7 Transient asymptomatic elevation in 17-hydroxyprogesterone levels has been reported in term newborns treated at birth with LPV/r.4

Resistance
The International Antiviral Society-USA (IAS-USA) maintains a list of updated resistance mutations and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation.

Pediatric Use
Approval
LPV/r is Food and Drug Administration (FDA)-approved for use in children. Because there is a risk of toxicity, LPV/r should not be administered to neonates before a postmenstrual age of 42 weeks and a postnatal age of at least 14 days. Ritonavir acts as a pharmacokinetic (PK) enhancer by inhibiting the metabolism of lopinavir and thereby increasing the plasma concentration of lopinavir.

Efficacy
Clinical trials of treatment-naive adults have shown that regimens containing LPV/r plus two nucleoside reverse transcriptase inhibitors (NRTIs) are comparable to a variety of other regimens including regimens that contain atazanavir, darunavir (at 48 weeks), fosamprenavir, saquinavir/ritonavir, or efavirenz. Studies have also shown that regimens containing LPV/r plus two NRTIs are superior to regimens containing nelfinavir and inferior to regimens containing darunavir (at 192 weeks).8–16 LPV/r has been studied in both antiretroviral (ARV)-naive and ARV-experienced children and has demonstrated durable virologic activity and acceptable toxicity.17–25

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 LPV/r 400 mg/100 mg, the appropriate pediatric dose would be approximately LPV/r 230 mg/57.5 mg 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 a C_trough similar 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 infants19,24,26 are compared to those in older children17 and adults27 in Table A below.
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Table A. Pharmacokinetics of Lopinavir/Ritonavir by Age

<table>
<thead>
<tr>
<th></th>
<th>Adults27</th>
<th>Children17</th>
<th>Children17</th>
<th>Infants&lt;sup&gt;a&lt;/sup&gt; at 12 Months&lt;sup&gt;24&lt;/sup&gt;</th>
<th>Infants&lt;sup&gt;a&lt;/sup&gt; 6 Weeks–6 Months&lt;sup&gt;19&lt;/sup&gt;</th>
<th>Infants&lt;sup&gt;a&lt;/sup&gt; 14 Days to &lt;6 Weeks&lt;sup&gt;26&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dose LPV</strong></td>
<td>19</td>
<td>12</td>
<td>15</td>
<td>20</td>
<td>18</td>
<td>9</td>
</tr>
<tr>
<td><strong>AUC mcg-hr/mL</strong></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><strong>C&lt;sub&gt;max&lt;/sub&gt; mcg/mL</strong></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><strong>C&lt;sub&gt;trough&lt;/sub&gt; mcg/mL</strong></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><strong>C&lt;sub&gt;min&lt;/sub&gt; mcg/mL</strong></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>
</tbody>
</table>

<sup>a</sup> Data generated in a study that was 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 life<sup>28</sup> and with clearance slowing by age 2.3 years.<sup>29</sup> A study from the U.K. and Ireland compared outcomes of LPV/r treatment with either a 230 mg/m²/dose or a 300 mg/m²/dose in children aged 5.6 to 12.8 years at the time of LPV/r initiation. Study findings suggested that the higher doses were associated with improved long-term viral load suppression.<sup>30</sup>

**Pharmacokinetics and Dosing**

**12 Months to 12 Years (Without Concurrent Nevirapine, Efavirenz, Fosamprenavir, or Nelfinavir)**

Lower trough concentrations have been observed in children receiving LPV/r 230 mg/57.5 mg both per m² of body surface area when compared to LPV/r 300 mg/75 mg per m² of body surface area per dose twice daily (see table).<sup>16</sup> Therefore, some clinicians choose to initiate therapy in children aged 12 months to 12 years using LPV/r 300 mg/75 mg per m² of body surface area per dose twice daily (when given without nevirapine, efavirenz, fosamprenavir, or nelfinavir) rather than the FDA-recommended LPV/r 230 mg/57.5 mg per m² of body surface area per dose twice daily.

For infants receiving LPV/r 300 mg/75 mg 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” LPV/r 230 mg/57.5 mg per m² of body surface area per dose twice daily dose 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 LPV/r liquid formulation.

**14 Days to 12 Months (Without Concurrent Nevirapine, Efavirenz, Fosamprenavir, or Nelfinavir)**

The PK of the oral solution at approximately LPV/r 300 mg/75 mg per m² body surface area per dose twice daily was evaluated in infants aged <6 weeks<sup>26</sup> and infants aged 6 weeks to 6 months.<sup>19</sup> Even at this higher dose, C<sub>trough</sub> levels were highly variable but were lower in infants than in children aged >6 months. C<sub>trough</sub> levels were lower in infants aged ≤6 weeks than in infants aged 6 weeks to 6 months. By age 12 months, lopinavir area under the curve (AUC) was similar to that found in older children.<sup>24</sup> 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,<sup>20</sup> 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 C<sub>trough</sub> 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 LPV/r 230 mg/57.5 mg per m² body surface area per dose twice daily plus nevirapine, the mean lopinavir C_trough was 3.77 ± 3.57 mcg/mL.¹⁷ Not only are these trough plasma concentrations lower than those found in adults treated with standard doses of LPV/r, but the variability in concentration is much higher in children than in adults.¹⁷,³¹ In a study of 15 children with HIV aged 5.7 to 16.3 years who were treated with LPV/r 300 mg/75 mg 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 interindividual variation in lopinavir trough concentrations. Five of 15 children (33%) had lopinavir 12-hour trough concentrations less than 1.0 mcg/mL, the plasma concentration needed to inhibit wild-type HIV.³² A PK study in 20 children aged 10 to 16 years who were treated with LPV/r 300 mg/75 mg per m² body surface area twice daily plus efavirenz 350 mg/m² body surface area once daily showed only one patient (6.6%) with sub-therapeutic lopinavir trough concentrations,³³ perhaps because the trial used an efavirenz dose that was approximately 11 mg/kg body weight³³ instead of the 14 mcg/kg body weight dose used in the trial discussed above.³²

Dosing

Once Daily

Once-daily dosing of LPV/r 800 mg/200 mg administered as a single daily dose is FDA-approved for treatment of HIV in therapy-naive adults aged >18 years. However, once-daily administration cannot be recommended for use in children in the absence of therapeutic drug monitoring (TDM), although this approach may be successful in select, closely monitored children.³⁴ There is high interindividual variability in drug exposure and trough plasma concentrations below the therapeutic range for wild-type virus, as demonstrated in studies of ARV-naive children and adolescents.³⁵-³⁸ The currently available tablet formulation of LPV/r has lower variability in trough levels than the previously used soft-gel formulation.³⁸,³⁹ An international, randomized, open-label trial designed to demonstrate noninferiority in viral suppression between once-daily and twice-daily LPV/r dosing in children (median [IQR] age of 11 years [with a range of 9–14 years]) was unsuccessful, and more children on once-daily dosing had viral loads ≥50 copies/mL within 48 weeks.⁴⁰

Dosing and Its Relation to Efficacy

LPV/r is effective in treatment-experienced patients with severe immune suppression,⁴¹,⁴² although patients with greater prior exposure to ARVs may be slower to reach undetectable viral load concentrations⁴²,⁴³ and may have less-robust CD4 T lymphocyte (CD4) percentage responses.⁴⁴ Twice daily doses of lopinavir used in treatment-experienced patients were 230 mg to 300 mg/m² body surface area in 39% of patients, 300 mg to 400 mg/m² body surface area in 35%, and greater than 400 mg/m² body surface area per dose in 4%.⁴⁴

More important than viral resistance to lopinavir is the relationship of the drug exposure to the susceptibility of the HIV-1 isolate (EC₅₀). The ratio of C_trough to EC₅₀ is called the inhibitory quotient (IQ), and in both adults and children treated with LPV/r, viral load reduction is more closely associated with IQ than with either the C_trough or EC₅₀ alone.⁴⁵-⁴⁷ A study of the practical application of the IQ to guide therapy using higher doses of LPV/r in children and adolescents to reach a target IQ of 15 showed the safety and tolerability of doses of LPV/r 400 mg/100 mg per m² body surface area per dose twice daily (without fosamprenavir, nelfinavir, nevirapine, or efavirenz) and LPV/r 480 mg/120 mg per m² body surface area per dose twice daily (with nevirapine or efavirenz).²⁰ Results of a modeling study suggest that standard doses of LPV/r may be inadequate for treatment-experienced children and suggest the potential utility of TDM when LPV/r is used in children previously treated with protease inhibitors.⁴⁸ A lopinavir plasma concentration of ≥1 mcg/mL is cited as a minimum target trough concentration,⁴⁹,⁵¹ but this concentration may not adequately control viremia in patients with multiple lopinavir mutations.⁵²,⁵³

Formulations

Palatability

The poor palatability of the LPV/r 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 (e.g., chocolate syrup or peanut butter), or having the pharmacist flavor the solution prior to dispensing are examples of interventions that may improve tolerability. Alternative pediatric formulations are currently being developed.⁵⁴,⁵⁵
Do Not Use Crushed Tablets

LPV/r 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.\textsuperscript{56} In a PK study using a generic adult formulation of LPV/r manufactured in Thailand, 21 of 54 children were administered cut (not crushed) pills and had adequate lopinavir C\textsubscript{trough} measurements.\textsuperscript{39}

Toxicity

Children treated with LPV/r may have less-robust weight gain and smaller increases in CD4 percentage than children treated with NNRTI-based regimens.\textsuperscript{22,57-61} However, one study did not observe this difference in the effect of LPV/r on CD4 cell count,\textsuperscript{62} and another study found that the difference did not persist after a year of therapy.\textsuperscript{63,64} Some studies found no differences in the weight gain of children treated with LPV/r versus efavirenz.\textsuperscript{60,61} Switching to efavirenz-based ART at or after age 3 years removed the risk of lopinavir-associated metabolic toxicity, with no loss of virologic control (see Table 16 of Modifying Antiretroviral Regimens in Children with Sustained Virologic Suppression on Antiretroviral Therapy).\textsuperscript{60,61} Bone mineral density improved when children were treated with efavirenz-containing ART instead of LPV/r-containing ART.\textsuperscript{64}

References


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