

Lopinavir/ritonavir (Kaletra®)

Class:

Lopinavir/ritonavir is an HIV protease inhibitor.

Antiviral Activity:

Lopinavir/ritonavir has activity against HIV-1.

Mechanism of Action:

Lopinavir/ritonavir inhibits the HIV protease enzyme by forming an inhibitor-enzyme complex thereby preventing cleavage of the gag-pol polyproteins. Immature, non-infectious viral particles are subsequently produced.

Mechanism of Resistance:

Higher levels of protease inhibitor resistance result from the accumulation of multiple protease inhibitor-resistance mutations. There are many mechanisms of resistance. These include reduced binding affinity between the inhibitor and the protease enzyme, alterations in enzyme catalysis, effects on dimer stability, alterations in inhibitor binding kinetics, and re-shaping of the active site.

Pharmacodynamics:

Peripheral blood mononuclear cells transfected with six strains of wild type HIV in the absence of human serum expressed a mean EC₅₀ of 6.5 nM (range 4-11) for lopinavir.

Pharmacokinetics:

When taken while fasting, the AUCs for liquid and capsule formulations of lopinavir were 44% and 36% lower than compared to administration with food. Lopinavir is 98-99% protein bound to alpha-1-acid glycoprotein and albumin. Lopinavir is metabolized extensively by the CYP3A subfamily of enzymes. The majority of lopinavir/ritonavir is eliminated in the feces.

Adverse Effects:

Adverse effects are diarrhea, nausea, asthenia, abdominal pain, vomiting, headache, rash, hyperglycemia, uremia, hyperbilirubinemia, elevated AST or ALT, hypercholesterolemia, hypertriglyceridemia, elevated amylase, hypophosphatemia and neutropenia.

Dosage:

Capsule 133.3mg/33.3mg

Oral Solution 20mg/ml, 80mg/ml

The recommended dose for adult patients is 400/100mg (3 capsules or 5.0mL) twice daily administered with food.

For children ages 6 to 12 years, the dosing of lopinavir/ritonavir oral solution is based on body weight. For children 7 to <15kg and 15 to 40 kg, doses of 12/3 mg/kg and 10/2.5 mg/kg, respectively, should be given twice daily with food. A maximum of 400/100 mg

per dose for children >40 kg should be administered. It is recommended that calculations based on body weight be done for all pediatric patients.

A dose increase in lopinavir/ritonavir to 533/133mg twice daily with food should be implemented with concomitant efavirenz or nevirapine administration. Likewise, a 13/325 mg/kg and 11/2.75 mg/kg liquid dose should be given to children 7 to <15 kg and 15 to 45 kg, respectively who are on efavirenz or nevirapine.

Disease state based dosing:

Renal Impairment: no dose adjustment necessary

Hepatic Impairment: no dose adjustment but use caution in patients with hepatic insufficiency.

Contraindications/Warnings/ Precautions:

The liquid contains 42.4% (v/v) alcohol and should be used with caution in some patients.

Lopinavir/ritonavir is contraindicated with the following medications:

astemizole, terfenadine, dihydroergotamine, ergonovine, ergotamine, methylergonovine, cisapride, pimozide, midazolam and triazolam.

Drug Interactions:

In vitro, Lopinavir/ritonavir has been shown to be a substrate for, and inhibitor of, CYP3A. *In vivo*, lopinavir/ritonavir has shown autoinduction and induction of other drugs metabolized by CYP450 enzymes. Therefore, any medication metabolized through the CYP450 enzyme system may interact with lopinavir/ritonavir.

Pregnancy:

Category C: Risk unknown. Human studies inadequate.

Monitoring Requirements:

Blood glucose, LFTs, serum lipid profile

Brand names/Manufacturer:

Kaletra®/Abbott Pharmaceutical Product Division