

Kaletra (lopinavir/ritonavir)



Kaletra tablets are light yellow-orange with the Abbott corporate logo and “KA” engraved on one side. Each tablet contains 200 mg of lopinavir and 50 mg of Norvir. A yellow-orange liquid formulation (42.4% alcohol) is also available, which contains 400 mg lopinavir and 100 mg Norvir per mL. Dosing may vary.



Background and description. On September 15, 2000, the US Food and Drug Administration (FDA) granted Abbott Laboratories accelerated approval for Kaletra. This combination product contains 2 protease inhibitors (PIs): lopinavir and Norvir (ritonavir); however, the antiviral activity of Kaletra is mainly because of the lopinavir. The addition of Norvir boosts levels of lopinavir in the blood. A tablet formulation was approved by FDA in October 2005, replacing the capsule formulation by March 2006.

Dose. Kaletra can be taken either once or twice a day, depending on a patient's situation. **Once-daily dosing of Kaletra is an option only for patients who have never before taken PIs**, otherwise Kaletra must be taken twice daily. The levels of Kaletra with this once-daily dose are only 60% of the twice-daily dosing, and patients reported more side effects such as diarrhea than with the twice-daily dose.

Kaletra tablets are dosed as either 2 tablets twice daily, or 4 tablets once daily. If taken by capsule, the correct dose of Kaletra is 3 capsules twice daily, or 6 capsules once daily. If taken by solution, the correct dose is 5 mL twice daily, for a total of 10 mL a day. When Kaletra is combined with either Sustiva (efavirenz) or Viramune (nevirapine) in treatment-experienced patients, once-daily dosing is not possible and the correct dose is 3 tablets twice daily, 4 capsules twice daily, or 6.5 mL of solution twice daily.

Food restrictions. Kaletra tablets can be taken with or without food. Kaletra capsules should be taken with a meal or snack.

Storage. Kaletra tablets do not need refrigeration. Both the capsules and solution should be refrigerated at 36°F to 46°F, but both formulations can be kept at a room temperature of up to 77°F if used within 2 months.

Patient assistance. Abbott Laboratories offers a patient assistance program for Kaletra. For more information, call 800.222.6885 (option 1).

Side effects. The side effects most commonly associated with Kaletra are nausea and diarrhea. The most common laboratory abnormalities are increases in some tests of liver function, as well as increases in triglycerides and total cholesterol. Patients with liver impairment should use Kaletra with caution. Elevated triglycerides are associated with a

risk of developing pancreatitis. Of note, during clinical trials of Kaletra, approximately 1 in 4 treatment experienced patients saw a serious or life-threatening laboratory abnormality. A small number of patients taking Kaletra may experience a severe skin rash ("Stevens Johnson Syndrome" and should see a healthcare provider immediately if any suspicious rash should appear. As a class, PIs are associated with metabolic (mainly sugar and lipid) and morphologic (body shape) changes, including the development or worsening of diabetes.

Drug interactions. Kaletra is metabolized in the liver by cytochrome P450 (CYP3A isoform). Other drugs that are metabolized by the same pathway (but not CYP2D6) should not be taken if with Kaletra. These drugs are: Hismanal (astemizole), Seldane (terfenadine), any ergot derivative (e.g. dihydroergotamine or DHE), Propulsid (cisapride), Orap (pimozide), Versed (midazolam), Halcion (triazolam), Voriconazole (VFEND), Mevacor (lovastatin), Zocor (simvastatin), Dilantin (phenytoin), fluticasone (an ingredient in Flonase), and St. John's wort (*Hypericum perforatum*).

When co-administered with Kaletra, dose reductions are required for Viagra (sildenafil), Cialis (tadalafil), and Levitra (vardenafil). HIV-infected women who are taking estrogen-based contraceptives should use additional or alternative contraceptives while on Kaletra. Important interactions between Kaletra and other agents, including Rifadin or Rimactane (rifampin), Mycobutin (rifabutin), Antabuse (disulfiram), Flagyl (metronidazole), methadone, Desyrel (trazodone), alfuzosin (for prostate problems), and corticosteroids, may require adjusted dosing of either drug.

Kaletra has the potential to reduce the plasma concentrations of Retrovir and Ziagen (also contained in Trizivir); however, the clinical significance of those reductions, if any, is unknown. When Kaletra and Videx are combined, Videx should be taken 1 hour before or 2 hours after Kaletra. Kaletra increases levels of Viread, so patients taking this combination should be monitored closely for Viread-related side effects. Because Kaletra contains Norvir, other protease inhibitors will require dose adjusting if given with Kaletra. Viracept doses should be decreased and Kaletra increased if given together. Finally, Kaletra should not be taken with Agenerase or Lexiva.

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Additional info:

Resistance and cross-resistance. Genomic point mutations associated with resistance to lopinavir/ritonavir have not yet been identified; however, isolates with reduced to susceptibility to Kaletra have been selected both *in vitro* and *in vivo*.

The relevance of resistance to other protease inhibitors (PIs) on the virologic success of Kaletra has not yet been fully characterized. In a study of 56 patients who had been treated with at least 2 other PIs, a Kaletra-containing regimen suppressed viral load below the limits of quantification (400 copies/mL) in 24 of 25 patients whose baseline virus contained 5 point mutations associated with resistance to PI therapy. However, these 25 patients, all of whom were naïve to non-nucleoside reverse transcriptase inhibitors (NNRTIs), were given Sustiva, a potent NNRTI, in addition to Kaletra and nucleoside reverse transcriptase inhibitors (NRTIs). Therefore, it is difficult to assess the relative contribution of Kaletra to the virologic success experienced by the patients in that study.

Clinical data in treatment-naïve patients. Study 863 is a double-blind trial in which investigators randomized 653 treatment-naïve patients to a regimen of Kaletra/Zerit/Epivir or Viracept/Zerit/Epivir. The participants, mostly Caucasian males, had an average baseline CD4 T cell count of 259 cells/mm³ and an average baseline viral load of approximately 79,000 copies/mL. After 24 weeks, 79% of participants in the Kaletra arm had viral loads less than 400 copies/mL, with 65% having viral loads less than 50 copies/mL. Participants saw an average CD4 T cell increase of 154 cells/mm³.

Importantly, 3 patients in the Kaletra arm and 3 patients in the Viracept arm experienced new AIDS-defining clinical events despite having viral loads below the limit of quantification. These data demonstrate that while a reduction in viral load greatly reduces the risk of disease progression on a population basis, even an unquantifiable viral load does not preclude the occurrence of AIDS-defining events in the individual.

Clinical data in treatment-experienced patients. Study 765 is a randomized, blinded trial using 2 doses of Kaletra, namely 400 mg of lopinavir and 100 mg of ritonavir or 400 mg of lopinavir and 200 mg of ritonavir. The participants, all of whom had taken 1 prior protease inhibitor but were naïve to NNRTIs, also took the NNRTI Viramune plus 2 NRTIs. The study volunteers were mostly Caucasian males with an average baseline CD4 T cell count of 372 cells/mm³ and an average baseline viral load of approximately 10,000 copies/mL.

After 72 weeks of treatment, 75% of volunteers in the 400 mg/100 mg arm had viral loads less than 400 copies/mL, with 58% having viral loads less than 50 copies/mL. The average CD4 T cell increase was 174 cells/mm³.

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To contact The Center for AIDS,
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