Lopinavir/Ritonavir for the Treatment of COVID-19 (Abbreviated Monograph)

**DRUG NAME** Lopinavir and ritonavir (Brand name: Kaletra ®)

**CLINICAL PHARMACOLOGY**
Several existing drugs have been screened, using high-throughput assays, for in vitro activity against human coronaviruses, including MERS-CoV. Such screens have identified lopinavir/ritonavir, a drug approved for HIV treatment, as potentially active against beta coronaviruses. Lopinavir is an inhibitor of an HIV protease that cleaves viral protein precursors and allows maturation of viral particles. Ritonavir inhibits the CYP3A metabolism of lopinavir, allowing for increased plasma levels of lopinavir. It is hypothesized that lopinavir may also inhibit the COVID-19 protease (cysteine protease), albeit with less affinity than HIV protease. Additional unidentified host targets may also be a possibility.

**SUMMARY OF CLINICAL STUDIES**
- An RCT of 199 patients with COVID-19 disease failed to show that treatment with lopinavir/ritonavir reduced time to clinical improvement (primary end-point). Secondary endpoints were mixed: there was a non-statistically significant reduction in 28-day mortality, but higher SARS-CoV-2 viral loads in the lopinavir/ritonavir-treated group relative to the group that received standard of care. Larger trials are needed to determine if this negative result is due to true lack of benefit or because the study was insufficiently powered to detect a benefit.
- In vitro evidence suggests that lopinavir/ritonavir has antiviral activity against human coronavirus but may be less active compared to remdesivir.
- One study in marmosets (non-human primates) demonstrated improved outcomes in infection due to MERS-CoV, as measured by radiological and pathological findings and lower viral loads.
- Clinical data is limited to case reports and retrospective studies of small cohorts, often confounded by coadministration of other drugs such as ribavirin and interferon. One case report demonstrated a favorable outcome for in a single patient with MERS-CoV who received lopinavir/ritonavir monotherapy. A retrospective, matched cohort study (n=75) showed moderate improvement in overall survival and intubation rate when lopinavir/ritonavir was used as early therapy (with ribavirin), but no added benefit when used for as salvage therapy. This study is flawed by reliance on historical controls.

**PHARMACOKINETICS**
- Absorption: the absolute bioavailability of lopinavir co-formulated with ritonavir is not established.
- Metabolism: lopinavir is metabolized by CYP3A4 and may induce its own metabolism.
- Excretion: lopinavir is excreted through feces 20% as unchanged drug, and minimally excreted in urine (<3% as unchanged drug).
- Half-life elimination: 5-6 hours.

**DOSING AND ADMINISTRATION**
- Lopinavir/ritonavir 400mg/100 mg PO every 12 hours for 10 days.
- Generally, no adjustment is made in renal dysfunction.
- Crushing and administering tablets via a gastric tube may decrease absorption by ~50%. Decreased absorption is not expected to impact the activity of lopinavir against SARS-CoV.

**SAFETY AND MONITORING**
- Dermatologic (skin rash), GI upset (diarrhea, vomiting, nausea, abdominal pain), liver dysfunction (increased liver enzymes), CNS (headache, blurred vision, anxiety, insomnia), hematologic (thrombocytopenia, neutropenia, anemia), asymptomatic bradycardia, and metabolic disorders with longer duration (hypercholesterolemia, hypertriglyceridemia).
- Ritonavir is both a major substrate and strong inhibitor of CYP3A4, and a moderate induced of CYP2B6.
- In patients on tacrolimus, cyclosporine or other calcineurin inhibitors (CNI) for transplant immune suppression, level of CNI should be very carefully monitored to avoid toxicity.
REFERENCES


