Lopinavir/ritonavir in the treatment of adult patients with COVID-19

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ITALIAN MEDICINES AGENCY

Considering the absence of proven effective therapies for COVID-19, it is considered essential to provide clinicians with useful elements to guide the prescription and to define, for each medicine used, a relationship between the benefits and risks for the individual patient.

In the early stages of the epidemic, the off-label use of lopinavir/ritonavir was allowed, on the basis of the preliminary data available, only within the national COVID-19 emergency management plan and in compliance with the elements reported in the previous version of the card. In the light of current evidence in the literature, **AIFA decides to suspend the authorisation for the off-label use of the medicine outside clinical trials.**

Classification Lopinavir/ritonavir (Kaletra® 200/50 mg film-coated tablets; oral solution: (80 mg + 20 mg)/ml and equivalent medicines). It is a ritonavir-boosted protease inhibitor. Ritonavir improves its pharmacokinetic profile and by inhibiting cytochrome P450, isoenzyme 3A4, slows the metabolism of lopinavir and increases its pharmacological exposure. The association has proven effective in the context of ART for the treatment of HIV.	
Why do some sources indicate lopinavir/ritonavir as a useful medicine in the treatment of COVID-19?	***Rational*** Several protease inhibitors currently used for HIV therapy (lopinavir - LPV - darunavir - DRV - atazanavir, - ATV -) can inhibit viral replication by inactivating the 3CLpro and PL2pro proteases; the 3CLpro protease is an essential molecular target also for the replication of coronaviruses. Animal models suggest that inhibition of the 3CLpro protease in critically ill animals is associated with improvement. Finally, previous experiences with SARS-CoV-1 and MERS infection suggest that lopinavir can improve some clinical parameters of patients. Clinical experience with HIV has shown that in the authorised indications these medicines tend to be safe, even if variously tolerated and with numerous drug interactions.

What evidence of efficacy and safety do we have?	***Clinical studies*** Some efficacy data is available on small series (associated or not with ribavirin) on the coronavirus responsible for SARS or MERS. As regards COVID-19 pathology: - There are anecdotal evidence and case reports published on individual patients; a case report on 5 COVID-19 patients treated in Singapore shows that 3/5 had an apparent good and rapid response. - A review of the literature published in 2020 (in Chinese only) and reported in the LG just published in China seems to conclude that lopinavir/ritonavir is effective in the treatment of coronavirus infections in reducing mortality and consumption of glucocorticoids *if administered early*. - Numerous studies are ongoing involving lopinavir/ritonavir alone or in combination with other antivirals whose results are expected in the coming months. - An open-label RCT was published on March 18, 2020 comparing lopinavir/ritonavir added to usual care vs usual care only in patients (N = 199) hospitalised with COVID-19 pneumonia, a $SaO_2 \leq 94\%$, a $PaO_2/FiO_2 \leq$ 300 mg Hg and a median NEWS2 score of 5. Overall, the addition of the antiretroviral to usual care did not result in a clinical benefit in terms of a 2-point reduction on the 7-point category scale assessing health status of patients with severe respiratory disease or discharge (primary study outcome). A *post-hoc* analysis conducted to evaluate the efficacy of LPV/r vs usual care alone in the 2 subgroups of randomised patients within 12 days of symptom onset or more than 12 days of symptom onset does not indicate a clinical benefit of the antiretroviral in either of the two subgroups. Mortality (secondary outcome of the study, for which it was not potentiated) shows an absolute difference of 5.8% in favour of lopinavir which however does not reach statistical significance. Update July 17, 2020 - On June 29, 2020, through a press release, researchers from the ongoing RECOVERY study in Great Britain, which also included an LPV/r arm in patients with COVID19, announced the suspension of treatment. In the study, 1596 hospitalised patients were randomised to LPV/r and compared with 3376 treated with ordinary care only. A preliminary analysis showed that there was no significant difference in mortality at 28 days (22.1% LPV/r versus 21.3% for routine care; relative risk 1.04 [95% confidence interval 0, 91-1.18]; p = 0.58). These results were consistent with what was found in different subgroups of patients. There was also no evidence of advantages with the medicine regarding the risk of progression to mechanical ventilation or the length of hospital stay. The authors comment that these results are not transferable to mechanically ventilated patients because they are marginally present in the series. Furthermore, it is important to note that the series studied only concerns hospitalised patients.

	- There is an additional small (86 patients) randomised exploratory study (2:2:1) that evaluated the efficacy and safety of LPV/r or arbidol alone versus no antiviral for the treatment of patients with mild/moderate COVID-19. The results show no differences in primary outcomes (average positive to negative conversion time of SARS-CoV-2 nucleic acid and conversion rates at days 7 and 14), and secondary outcomes (antipyresis rates, alleviation of cough or improvement of thoracic TC at days 7 or 14). According to the authors, LPV/r or arbidol alone has no benefit in patients admitted to hospital with mild/moderate COVID-19 compared to supportive care. **Conclusion** While the first study questioned the use of lopinavir/ritonavir in COVID-19 patients with a severe and unstable clinical picture (SaO2 < 94%, need for oxygen therapy or mechanical ventilation techniques and who experienced symptoms of the disease for more than 12 days), the suspension of the treatment arm with this medicine in the RECOVERY study leads to a general reconsideration of its benefit-risk profile in all patients with COVID 19. In fact, at the moment the set of efficacy tests indicates that the administration of lopinavir/ritonavir is not associated with a clinical benefit compared to ordinary therapy. While not excluding the possible existence of specific subpopulations of patients who may somehow benefit from this treatment, the current framework of uncertainty suggests waiting for further results before recommending its use outside an experimental context.
For which patients is it recommendable?	***Guidelines for therapeutic use*** **In the current emergency phase, given the premises described above, the therapeutic use of lopinavir/ritonavir for COVID-19 can only be considered limited to patients included in clinical trials.** **In the current state of knowledge, the combination of lopinavir/ritonavir with hydroxychloroquine or the possible addition of azithromycin is not recommended.** This is supported by currently available safety data which further call for caution in the case of association with medicines that could enhance their toxicity in the absence of clear evidence of an improvement in efficacy following the combination. There is no evidence that the further addition of antibiotics (eg azithromycin) is safe and improves the evolution of the disease. ***Further randomised clinical trials are needed to evaluate the efficacy of the medicine at various levels of disease severity.***

At what dosages and in what forms do you prescribe it and for how long?	***Dosage recommended by technical data sheet*** **lopinavir/ritonavir** 200/50 mg tablets 2 tablets x 2/day taken with food (if necessary, use the oral solution: 5 ml x 2 orally) Ideally, the duration of treatment should be at least 5-7 days, to be established according to clinical evolution. For particular situations, see the technical sheet: https://www.ema.europa.eu/en/documents/product-information/kaletra-epar-product-information_it.pdf
Who can prescribe the medicine in this emergency phase for COVID-19 treatment?	***Method of prescription*** In the authorised indications, the medicine is subject to a restrictive prescription by the infectious disease specialist. The use of lopinavir/ritonavir for SARS-CoV-2 infection should be limited to clinical studies which are regulated by specific regulations (https://www.aifa.gov.it/web/guest/-/gestione-degli-studi-clinici-in-italia-in-corso-di-emergenza-covid-19-coronavirus-disease-19-).
What are the major risks in terms of adverse reactions?	**Warnings in the authorised therapeutic indications** (from the technical data sheet)**:** - Severe hepatic insufficiency (Child-Pugh Class C) - Drug interactions The LPV/r combination should not be prescribed for people with HIV infection, who should be referred to their treating specialist. The most common adverse events associated with lopinavir/ritonavir therapy in the initial phase of administration are diarrhoea and nausea (very common: ≥1/10), and vomiting (common: ≥1/100). The use of lopinavir/ritonavir tablets is not contraindicated in pregnancy. Kaletra® oral solution is contraindicated in pregnant women and children under the age of 14 days, due to the possible risk of toxicity of the excipient propylene glycol.
Can it be prescribed together with other medicines or not?	**Main interactions in the authorised therapeutic indications** (from the technical data sheet)**:** Lopinavir and ritonavir are both inhibitors of CYP3A, the cytochrome P450 isoform. Co-administration with other medicinal products metabolised primarily by CYP3A may result in increased plasma concentrations of the latter by increasing their effects or adverse events.

	Considering the numerous drug interactions related to cytochrome P450 and other mechanisms, in the case of polytherapy it is advisable to consult the site: https://www.covid19-druginteractions.org/.
Studies in progress in Italy	See the appropriate section on the AIFA website https://www.aifa.gov.it/documents/20142/1131319/covid-19_sperimentazioni_in_corso_27.03.2020.pdf/b2391bac-7920-0945-51a1-66db453053cf
References	Lopinavit/ritonavir technical sheet: https://www.ema.europa.eu/en/documents/product-information/kaletra-epar-product-information_it.pdf Kim Y et Al: Reversal of the Progression of Fatal Coronavirus Infection in Cats by a Broad-Spectrum Coronavirus Protease Inhibitor¸PLoS Pathog. 2016 30;12(3. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4814111/pdf/ppat.1005531.pdf Young B E et Al Epidemiologic Features and Clinical Course of Patients Infected With SARS-CoV-2 in Singapore March 2020 https://jamanetwork.com/journals/jama/fullarticle/2762688 Jaegyun Lim et Al. Case of the Index Patient Who Caused Tertiary Transmission of Coronavirus Disease 2019 in Korea: the Application of Lopinavir/Ritonavir for the Treatment of COVID-19 Pneumonia Monitored by Quantitative RT-PCR February 2020 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7025910/ Ying-Hui Jin et al. A rapid advice guideline for the diagnosis and treatment of 2019 novel coronavirus (2019-nCoV) infected pneumonia. Military Medical Research 2020, https://doi.org/10.1186/s40779-020-0233-6 Cao B et al. A Trial of Lopinavir–Ritonavir in Adults Hospitalized with Severe Covid-19. NEJM 2020, march 18 DOI: 10.1056/NEJMoa2001282. https://www.nejm.org/doi/pdf/10.1056/NEJMoa2001282?articleTools=true (NCT04381936).RECOVERY Trial. Randomised Evaluation of COVID-19 Therapy. Available from https://www.recoverytrial.net/news/no-clinical-benefit-from-use-oflopinavir-ritonavir-in-hospitalised-covid-19-patients-studied-in-recovery on 01/07/2020; Yueping Li, et al. An exploratory randomized, controlled study on the efficacy and safety of lopinavir/ritonavir or arbidol treating adult patients hospitalized with mild/moderate COVID-19 (ELACOI). Pre-print https://www.medrxiv.org/content/10.1101/2020.03.19.20038984v2.full.pdf