Darunavir/cobicistat
for the treatment of adult patients with COVID-19

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ITALIAN MEDICINES AGENCY

Given the absence of proven efficacy therapies for COVID 19, it is essential to provide clinicians with useful information to direct prescribing and to define, for each medicine used, the benefit-risk profile for each individual patients.

In the early phases of the pandemic, the off-label use of darunavir/cobicistat was allowed as an alternative to lopinavir/ritonavir, based on preliminary data available for the latter, only within the framework of the COVID-19 National Emergency Response Plan and in accordance with the elements described in the previous versions of this card. In light of the current evidence available in literature, as for lopinavir/ritonavir, **AIFA revoked the authorisation for off-label use outside of clinical trials**.

Framework Darunavir/cobicistat (Rezolsta® tablets 800 /150 mg) A Cobicistat-Boosted Protease Inhibitor. Cobicistat enhances its pharmacokinetic profile and by inhibiting cytochrome P450 3A4 isoenzyme, it decreases the metabolism of darunavir and increases its exposure. The combination has been proven to be effective in the context of ART for the treatment of HIV.	
Why do certain sources suggest darunavir/cobicistat as a medicine useful in the treatment of COVID-19?	***Rationale*** Several protease inhibitors currently used for HIV therapy (lopinavir – LPV – darunavir – DRV – atazanavir, – ATV-) can inhibit viral replication by binding and inactivating the proteases 3CLpro and PL2pro; Protease 3CLpro is also an essential molecular target for coronavirus replication. Animal models suggest that 3CLpro protease inhibition in animals under critical conditions is associated with improvements. Finally, previous experiences with SARS-CoV-1 and MERS infections suggest that Lopinavir may improve some clinical parameters of patients. Clinical experience with HIV has shown that these medicines are generally safe in the authorized indications, although variously tolerated and with numerous drug interactions.
What evidence of effectiveness and safety do we have available?	***Clinical Trials*** Evidence for its efficacy with respect to COVID-19 is only anectotal. A small study on darunavir/cobicistat is ongoing in China. The clinical benefit currently identified is its higher intestinal tolerability compared to lopinavi/ritonavir.

For which patients is it recommended?	***Guidance on therapeutic use*** **During this emergency phase, given the abovementioned premises, the therapeutic use of darunavir/cobicistat may be considered as an alternative to lopinavir/ritonavir (in the same setting i.e. within clinical trials) when the latter is not tolerated because of diarrhoea** The prescriber shall assess the benefit/risk balance on a case-by-case basis considering in particular: - ***Combinations of medications*** In particular, the combination with medicines metabolized by cytochrome P450. **Given the current state of knowledge, darunavr/cobicistat in combination with hydroxychloroquine and the possible addition of Azithromycin is not recommended.** This is supported by currently available safety data that further call for caution in case of use in combination with medicinal products that could enhance their toxicity, in absence of clear evidence demonstrating improved efficacy of the combination. There is no evidence that the addition of antibiotics (e.g. azithromycin) is safe and that it improves the evolution of the disease. ***Randomised clinical trials are necessary to assess the efficacy of the medicine across different the degrees of disease severity.***
Dosage, form and duration: how to prescribe?	***Dosage recommendations in Data sheet*** **darunavir/cobicistat** 800/150 mg capsules once daily, taken with food Ideal duration of treatment should be at least 5–7 days, according to clinical development. For special situations, please refer to the technical data sheet:https://www.ema.europa.eu/en/documents/product-information/rezolsta-epar-product-information_it.pdf

Who can prescribe the medicine for the treatment of COVID-19 during the emergency phase?	***Prescription Methods*** The medicinal product is subject, in its approved indications, to restricted medical prescription from an infectious disease specialist. The use of darunavir/cobicistat for the treatment of SARS-CoV-2 infection, as an alternative to lopinavir/ritonavir, should be restricted to clinical trials which are regulated by specific rules (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 approved indications** (from data sheet)**:** - severe hepatic impairment (Child-Pugh Class C); - Cobicistat has been shown to decrease estimated creatinine clearance, thus Rezolsta® should not be initiated in patients with creatinine clearance less than 70 mL/min in whom this parameter is used to guide aspects of their clinical management; - Drug interactions. The DRV/c combination should not be prescribed for HIV infected subjects, who shall be referred to a specialist. The use of darunavir/cobicistat is not recommended during pregnancy as treatment during the second and third trimester has been shown to result in low darunavir exposure.
Can it be prescribed in combination with other medicines?	**Main interactions in approved indications** (from data sheet)**:** Darunavir/cobicistat is an inhibitor of CYP3A, isoforms of cytochrome P450. Co-administration with medicinal products primarily metabolised by CYP3A may result in increased plasma concentrations of these medicinal products, increasing their therapeutic effect and adverse reactions. Given the numerous interactions related to cytochrome P450, P-glycoproteins and other mechanisms, in the case of polytherapy it is appropriate to consult the following website*:* https://www.covid19-druginteractions.org/
Ongoing studies in Italy	See dedicated section in AIFA website https://www.aifa.gov.it/documents/20142/1131319/covid-19_sperimentazioni_in_corso_27.03.2020.pdf/b2391bac-7920-0945-51a1-66db453053cf
Reference	Darunavir/cobicistat Data Sheet https://www.ema.europa.eu/en/documents/product-information/rezolsta-epar-product-information_it.pdf