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DARUNAVIR/COBICISTAT

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Description of the drug

Darunavir/cobicistat (Rezolsta® tablet 800/150 mg) is an antiviral drug used to treat patients with human immunodeficiency virus type 1 (HIV-1), a virus that causes acquired immune deficiency syndrome (AIDS). It is given in combination with other medicines for treating adults and adolescents from 12 years of age and weighing at least 40 kg.

Pharmacokinetic characteristics

The pharmacokinetics of darunavir/cobicistat has been evaluated in a single-arm, open-label, phase III clinical trial (GS-US-216-130) of 313 patients with HIV treated with oral dose of darunavir 800 mg/cobicistat 150 mg once a day for 48 weeks. Darunavir/cobicistat absorption was rapid following oral administration, based on observed achieving maximum plasma concentrations in 0.3 to 4.5 hours. The drug is extensively metabolized by CYP3A4. The terminal elimination half-life of darunavir was approximately 15 hours, while that of cobicistat was approximately 3-4 hours. Darunavir/cobicistat are generally eliminated from the body by renal excretion [**1**].

Mechanism of action and pharmacodynamic characteristics

Darunavir is an inhibitor of the dimerization and of the catalytic activity of the HIV-1 protease. Cobicistat is an inhibitor of cytochromes P450 of the CYP3A subfamily.

Rationale for the use of the drug in the treatment of SARS-CoV-2 infection

The rationale for the use of darunavir/cobicistat in the treatment of COVID-19 is based on experience of a Chinese research team that carried out an open-label, randomized clinical trial at Shanghai Public Health Clinical Center (SPHCC) on 30 patients with COVID-19. This phase III trial (NCT04252274) aims to evaluate the efficacy and safety of darunavir/cobicistat for the treatment of pneumonia caused by SARS-Co V-2. The end of this study is estimated on December 31, 2020 [**2**]. At this stage, its use can represent an alternative to treatment with lopinavir/ritonavir as it has shown greater intestinal tolerability. However, the manufacturing company Johnson&Johnson states that there is no evidence to support the use of darunavir/cobicistat for the treatment of COVID-

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19. Therefore, an evaluation *in vitro* is currently ongoing to verify potential antiviral properties of the drug against SARS-COV-2 [**3**].
In Italy darunavir/cobistat is marketed by Janssen-Cilag S.p.a. and can only be obtained with a prescription. The Italian Medicine Agency (AIFA) has published in the Official Gazette (no. 69 of 17.03.2020) the reimbursement by the National Health Service and has approved darunavir/cobicistat for an *off-label* use. However, based on current knowledge is not recommended co-administering with hydroxychloroquine and azithromycin [**4-5**].

Treatment scheme in COVID-19 patients
According to the protocol of the ongoing clinical trial, subjects will take darunavir/cobicistat one tablet daily for 5 days in combination with standard treatments [**2**].
Inclusion criteria:
- Patients for all age groups;
- Patients were diagnosed as pneumonia caused by COVID-19;
- Written the informed consent.

Exclusion criteria:
- Hypersensitivity to darunavir, cobicistat or any excipients;
- Patients with severe liver injury (Child-Pugh Class C);
- Concomitant medications that are highly dependent on CYP3A clearance and are associated with serious or life-threatening events;
- Subjects were considered to be unable to complete the study or not suitable for the study.

Toxicity monitoring
The most common side effects with darunavir/cobicistat are diarrhea, nausea, headache and rash [**6**]. The most serious side effects were diabetes, Stevens-Johnson syndrome and immune reconstitution syndrome [**7**]. Cases of overdose with darunavir/cobicistat are limited. Darunavir/cobicistat is not recommended for use in pediatric patients and should not be used during pregnancy because it may be associated with an increased risk of treatment failure and an increased risk of HIV transmission to the child.

Potential interactions
Life-threatening and fatal drug interactions have been reported in patients treated with colchicine and strong inhibitors of CYP3A and P-glycoprotein. Co-administration of darunavir/cobicistat and other medicinal products that inhibit

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CYP3A may decrease (e.g. azole antifungals such as clotrimazole) or increase (e.g efavirenz) the clearance of darunavir/cobicistat [**1**].

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