HAUTE AUTORITÉ DE SANTÉ

INFECTIOLOGY
New medicinal product
January 2016

BRIEF SUMMARY OF THE TRANSPARENCY COMMITTEE OPINION

REZOLSTA (darunavir/cobicistat), antiretroviral

Insufficient clinical benefit as an alternative to darunavir/ritonavir

Main points

- REZOLSTA contains 800 mg of darunavir and 150 mg of cobicistat (pharmacokinetic enhancer). It has Marketing Authorisation in combination with other antiretroviral medicinal products for the treatment of Human Immunodeficiency Virus (HIV-1) in adults aged 18 years and older.
- Its benefit as an alternative to darunavir/ritonavir is not established; REZOLSTA has not demonstrated benefit in terms of efficacy, safety or adherence and exposes patients to a potential risk of drug interactions or abstention from treatment, while the combination darunavir/ritonavir has demonstrated its efficacy and good safety. Consequently, it has no role in the therapeutic strategy.

Therapeutic use

- The aim of antiretroviral treatment, regardless of the therapeutic situation (firstline, further lines, including after multiple failure), should be to achieve and maintain a plasma viral load < 50 HIV-1 RNA copies/ml and a CD4 lymphocyte count > 500/mm3. Six classes of anti-HIV medicinal products with different mechanisms of action are available for the treatment of patients infected with HIV: nucleo(side/tide) reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), fusion inhibitors (FIs), integrase inhibitors (INIs) and CCR5 receptor antagonists.
- At the present time, therapeutic combinations combining at least three highly active agents are recommended. First-line triple therapy remains a combination of two NRTIs with a third agent (1 PI,1 NNRTI or 1 INI).
- Darunavir (PREZISTA) is a PI active on numerous viral strains, including strains resistant to other PIs. Considering its antiretroviral efficacy and its safety, it is currently recommended, in combination with ritonavir (pharmacokinetic enhancer), for the treatment of all phases of HIV infection. In adults, it must be administered:
  - either at a dose of 800 mg x 1/day in combination with ritonavir 100 mg, in ARV treatment-naïve patients or in patients previously treated with no darunavir resistance-associated mutations and having a plasma HIV-1 RNA level < 100,000 copies/ml and a CD4+ cell count ≥ 100 cells × 10^6/l,
  - or at a dose of 600 mg x 2/day in combination with ritonavir 100 mg morning and evening, in patients previously treated who have already developed protease gene mutations.
- **Role of the medicinal product in the therapeutic strategy**

  REZOLSTA is intended to be taken once a day in naïve patients or in patients previously treated whose HIV has no protease gene mutation, It has demonstrated no benefit in the Marketing Authorisation indication due to the lack of comparative efficacy and safety data and a higher potential risk of drug interactions than darunavir enhanced by ritonavir. As for the fixed-dose combination, this proprietary medicinal product does not allow the dose adaptations that are necessary in some situations (in particular in cases of resistance to darunavir or when resistance testing is not available, high viral load, low CD4 level or creatinine clearance below 70 mL/min). It is also impossible to adapt the posology of the treatment according to the measurement of residual plasma concentration when this is recommended. Note that in pharmacokinetic bioequivalence studies, the residual concentration of darunavir was approximately 30% lower with cobicistat than with ritonavir (enhancer).
  Therefore, REZOLSTA has no role in the therapeutic strategy of patients with HIV-1 infection.

Clinical data

- No study has compared the efficacy and safety of treatment with darunavir enhanced by cobicistat to treatment with darunavir enhanced by ritonavir.

- In a non-comparative study, 295 (94%) treatment-naïve patients with HIV-1 infection and 18 (6%) previously treated patients received treatment with darunavir (2 x 400 mg) enhanced by cobicistat (150 mg) for 48 weeks. The primary objective was to evaluate safety after 24 weeks of treatment. The assessment of efficacy was part of the secondary objectives. After 24 weeks of treatment, 83.7% (247/295) of treatment-naïve patients and 61.1% (11/18) of previously treated patients had an undetectable viral load (< 50 copies/mL). These results were respectively 82.7% (244/295) and 50% (9/18) after 48 weeks of treatment. The mean increase in CD4+ was 145 cells/mm^3 in treatment-naïve patients and 99 cells/mm^3 in previously treated patients.
- The adverse effects observed are compatible with the known safety profile of the medicinal products studied. However, the data are very limited, especially in previously treated patients, women, elderly subjects and in patients at an advanced stage of the disease.
- Furthermore, although the potential for drug interactions with darunavir/cobicistat seems different or even more significant with cytochrome P3A inducers than that of the darunavir/ritonavir combination, no drug interaction studies have been conducted. The SmPC of PREZISTA states that "*darunavir and cobicistat are metabolised by CYP3A, and co-administration with CYP3A inducers may therefore result in subtherapeutic plasma exposure to darunavir. Darunavir boosted with cobicistat is more sensitive to CYP3A induction than ritonavir-boosted darunavir*", which may favour the selection of darunavir-resistant virus.
- In conclusion, the data available do not allow the therapeutic benefit or the efficacy/adverse effects ratio of REZOLSTA to be assessed in the indication of its Marketing Authorisation.

Prescribing conditions

- Initial annual hospital prescription
- Prescription reserved for certain specialists

Benefit of the medicinal product

- The actual benefit* of REZOLSTA is insufficient to justify reimbursement by National Health Insurance.
- Does not recommend inclusion on the list of reimbursable products for supply by pharmacists and for hospital use.

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This document was created on the basis of the Transparency Committee Opinion of 20 January 2016 (CT-14430) and is available at **www.has-sante.fr**

[i] * The actual benefit (AB) of a proprietary medicinal product describes its benefit primarily in terms of its clinical efficacy and the seriousness of the condition being treated. The HAS Transparency Committee assesses the AB, which can be substantial, moderate, low or insufficient for reimbursement for hospital use.

** The clinical added value (CAV) describes the improvement in treatment provided by a medicinal product compared with existing treatments. The HAS Transparency Committee assesses the degree of CAV on a scale from I (major) to IV (minor). A level V CAV means "no clinical added value".