HAUTE AUTORITÉ DE SANTÉ

INFECTIOUS DISEASES
New indication
July 2018

TRANSPARENCY COMMITTEE OPINION SUMMARY

STRIBILD (emtricitabine, cobicistat, elvitegravir and tenofovir disoproxil fumarate), antiviral combination

Insufficient clinical benefit to justify its reimbursement for the treatment of HIV in adolescents aged 12 – 18 years-old

Main points

- STRIBILD now has MA for the treatment of HIV-1 infection in adolescents 12 to 18 years-old, weighing at least 35 kg, without known resistance mutation to one of the three antiretroviral agents contained in STRIBILD and having presented with toxicity preventing the use of other treatments not containing tenofovir disoproxil fumarate.
- It has no role in the therapeutic strategy for this population.

Pre-existing indication*

STRIBILD already has MA in adults from the age of 18.

Therapeutic strategy

- In adolescents over the age of 12, the combinations of at least 3 highly active agents are recommended in first-line. They include 2 nucleoside reverse transcriptase inhibitors (NRTI) + a third agent (protease inhibitor [PI], non-nucleoside reverse transcriptase inhibitor [NNRTI] or integrase inhibitor (INI).
- Two combinations of NRTIs (abacavir/lamivudine or emtricitabine/TAF) and three other alternative NRTI combinations (lamivudine/zidovudine, emtricitabine/zidovudine or abacavir/zidovudine) are recommended.
- In children and adolescents at least 12 years of age, it is recommended to combine two NRTIs with: a ritonavir-boosted protease inhibitor (darunavir or atazanavir) or an integrase inhibitor (dolutegravir or elvitegravir combined with cobicistat) or a non-nucleoside reverse transcriptase inhibitor (rilpivirine) .

Role of the medicinal product in the therapeutic strategy

STRIBILD has no role in the therapeutic strategy in adolescents due to:

- available pharmacokinetics data showing significant overexposure related to the use of the adult form which exposes this growing population to a risk of renal and bone toxicity,
- the presence of GENVOYA on the market (emtricitabine, cobicistat, elvitegravir and tenofovir alafenamide fumarate), with the same composition, the only difference being the tenofovir form, suggesting a better safety profile especially renal and phosphorus and calcium profile,
- the presence of therapeutic alternatives on the market, especially in the INI therapeutic class, such as dolutegravir and raltegravir, with a better safety profile, better drug interaction and resistance profile, especially for dolutegravir.

Clinical data

* This summary does not cover this indication.

- A phase II/III, non-comparative study included 50 treatment-naive patients aged 12 to 18 years-old. The primary objectives were to evaluate the pharmacokinetic profile of STRIBILD and its safety. One of the secondary objectives was to evaluate the antiretroviral activity of this drug after 48 weeks.
- In week 48, the virological response (HIV-1 RNA < 50 copies/mL) was 88% (44/50) and the average increase in CD4+ level between inclusion and week 48 was 229 ± 245.3 cells/mm^3, therefore an increase in average CD4 level of 8.1% ± 5.3%.
- The safety profile was favourable overall at 48 weeks. The adverse effects the most frequently reported included airway infections (28%), headaches (24%), vomiting (18%), diarrhea (14%), nausea (14%), vitamin D deficiency (12%), acne (12%), pharyngitis (10%) and a reduction in eGFR compared to inclusion of -15 mL/min/1.73m² in the 2nd week, of -14 mL/min/1.73m² in the 24th week and of -15 mL/min/1.73m² in the 48th week. A reduction in BMD was also observed.
  The plasma parameters (AUCtau, Cmax and Ctau) were higher in adolescents aged 12 to 18 years-old than in adults for all STRIBILD components, except for a lower residual concentration (Ctau) of emtricitabine. This overexposure raises the question of potential toxicity. To date, we do not have any data that can be used to confirm the safety of plasma over exposure of this magnitude, from the use of the adult dose of STRIBILD in children and adolescents aged 12 to 18 ≥ 35 kg. Also, higher exposure can occur chronically in the presence of other factors (intrinsic and extrinsic) which could lead to a greater increase in plasma parameters.
- With regard to a low number covered by the analyses and the short exposure time, these data are highly limited and cannot definitely conclude on clinical efficacy and safety among children and adolescents aged 12 to 18 years-old.

Special prescription requirements

- Medicinal product subject to initial annual hospital prescription

Benefit of the medicinal product

- The actual clinical benefit* of STRIBILD is insufficient to justify its reimbursement by public funding in this indication extension.
- Not approved for non-hospital pharmacy reimbursement or for hospital treatment.

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This document was drafted on the basis of the Transparency Committee opinion dated 25 July 2018 (CT-16834) available at **www.has-sante.fr**

* The actual clinical benefit (ACB) of a medicinal product consists of its benefit particularly on the basis of its clinical performances and the severity of the disease treated. The HAS Transparency Committee assesses the ACB, which may be high, moderate, low, or insufficient for the medicinal product to be covered by public funding.

** The clinical added value (CAV) consists of the clinical improvement offered by a medicinal product compared to existing treatments. The HAS Transparency Committee assesses the CAV rating from I, major, to IV, minor. A CAV rating of V (equivalent to "no CAV") denotes a "lack of clinical improvement"