HAUTE AUTORITÉ DE SANTÉ

INFECTIOUS DISEASES
New indication
July 2018

TRANSPARENCY COMMITTEE OPINION SUMMARY

GENVOYA (emtricitabine, cobicistat, elvitegravir and tenofovir alafenamide), antiviral combination

High clinical benefit but no clinical benefit demonstrated in the treatment strategy for HIV-1 in children aged 6 – 12.

Main points

- GENVOYA now has MA in the treatment of HIV-1 infection in children aged 6 to 12, weighing at least 25kg, in whom other treatments cannot be used due to toxicity.
- No study has evaluated its efficacy in this population.
- The pharmacokinetic data available show significant overexposure in children when the adult form is used. This exposes this growing population to a high risk of renal and bone toxicity.
- It is a last resort therapeutic option in the treatment of HIV-1 infection with no known integrase inhibitor (elvitegravir, dolutegravir or raltegravir), emtricitabine or tenofovir resistance mutation.

Pre-existing indication*

GENVOYA already has MA in adults and adolescents from the age of 12.

Therapeutic strategy

- In children aged 6 to 12 years-old, the preferred tritherapies combine 2 nucleoside reverse-transcriptase inhibitors (abacavir/lamivudine or abacavir/emtricitabine) and 1 protease inhibitor combined with ritonavir (darunavir/r or atazanavir/r) or 1 integrase inhibitor (dolutegravir).
- Treatment prescription must be guided by a resistance genotyping test, given the possibility of primary resistance of the virus transmitted by the mother or acquired during perinatal prophylactic treatment. This test is also essential in children from endemic areas and already exposed to antiretroviral treatment.
- **Role of the medicinal product in the therapeutic strategy**

  GENVOYA is a last resort therapeutic option in the treatment of HIV-1 infection with no integrase inhibitor, emtricitabine or tenofovir resistance mutation, in children aged 6 to 12, weighing at least 25kg, in whom other treatments cannot be used due to toxicity.

Clinical data

- A phase II/III, non-comparative study evaluated the pharmacokinetic profile of GENVOYA and its safety. One of the secondary objectives was to evaluate the antiretroviral activity of this drug after 48 weeks. It included 24 patients aged 6 to 12 years-old, pretreated and virologically suppressed for 6 months and not presenting with resistance mutation to any of the components of GENVOYA.
- After 24 weeks of treatment, all the patients maintained a viral load of < 50 copies/mL. Average CD4 levels in the 24th week were 816 ± 175.2 cells/mm^3 versus 966 ± 201.7 cells/mm^3 on inclusion, and the median percentage of CD4 was 37.5% [33.3; 41.6] versus 38.8% [36.1; 44.3] on inclusion, therefore a 2.1% reduction. The data at 48 weeks are not available.

* This summary does not cover this/these indication(s).

- The safety profile at 24 weeks was favourable overall and consistent with the results previously reported in the older cohort and in adults. The adverse effects the most commonly reported were abdominal pain, vomiting, respiratory infections, reduction in eGFR, increase in lipid parameters (total cholesterol and LDL cholesterol). The plasma parameters (AUCtau, Cmax and Ctau) were higher in children aged 6 to 12 years-old than in adults for all GENVOYA components, except for a lower residual concentration (Ctau) of elvitegravir. This over-exposure 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 GENVOYA in children aged 6 to 12 > 25kg. Also, even 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 aged 6 to 12 years-old.

Special prescription requirements

- Medicinal product subject to initial annual hospital prescription

Benefit of the medicinal product

- The actual clinical benefit* of GENVOYA is high in children aged 6 to 12 years-old.
- GENVOYA does not provide clinical added value** (CAV V) in the treatment strategy for children aged 6 to 12 years-old.
- 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-16929) 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"