HAUTE AUTORITÉ DE SANTÉ

NEUROLOGY
New indication
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TRANSPARENCY COMMITTEE OPINION SUMMARY

GILENYA (fingolimod), immunosuppressor

High clinical benefit in the treatment of highly active forms of relapsing-remitting multiple sclerosis in paediatric patients over the age of 10 years and minor clinical improvement in the therapeutic strategy

Main points

- GILENYA has been granted a marketing authorisation as a basic treatment for highly active forms of relapsing-remitting multiple sclerosis (RR-MS) in the following groups of paediatric patients aged 10 years and over:
  - patients presenting with a highly active form of the disease, despite a complete and well-conducted treatment involving at least one basic treatment for MS, or
  - patients presenting with severe and rapidly progressing RR-MS, defined by two or more incapacitating episodes over one year, combined with 1 or more lesions enhanced after injection of Gadolinium on the brain MRI, or with a significant increase in T2 lesion load compared to a previous recent MRI.
- Its efficacy was established on the annual rate of episodes and on the number of new or extended T2 lesions, through a comparative study versus intramuscular interferon β-1a, in a population suffering mainly from RR-MS at an early stage in terms of disease duration and inflammatory activity. Only post-hoc analyses in populations very similar to that of the marketing authorisation (highly active RR-MS) are available.
- Its impact on quality of life and its efficacy on the medium and long-term progression of the disability have not been established.
- Due to its safety profile, underlined in particular by significant risks of cardiac rhythm disorders, convulsions and skin cancer, patient monitoring is required.

Pre-existing indications*

- GILENYA has the same marketing authorisation in adults.

Therapeutic strategy

- As soon as the RR-MS diagnosis has been established, rapid initiation of basic treatment is recommended to reduce episode frequency and the progression of the disability in the short term. Several first-line therapeutic options may be proposed: beta interferons (only AVONEX, REBIF and BETAFERON have been granted a marketing authorisation for patients over the age of 12 years) and glatiramer acetate (COPAXONE) in the context of its off-label use. The choice of treatment should be made according to the safety profile of the medicinal products, their method of administration and to patient preference.
- When the disease's inflammatory activity, assessed by the clinic (number and severity of episodes) and by MRI criteria (T1 Gd+ lesions, T2 lesion load, etc.), becomes or remains high, despite first-line basic treatment, initiation of a more active treatment is recommended. In these situations of highly active RR-MS, GILENYA is the

* This summary does not cover this indication.

first medicinal product to be granted a marketing authorisation for the paediatric population. Thus far, in these situation, the use of medicinal products indicated for adults could be recommended after consultation with a reference centre (fingolimod and natalizumab in particular).

- **Role of the medicinal product in the therapeutic strategy**

  GILENYA is a first-line or second-line treatment for highly active forms of RR-MS in paediatric patients over the age of 10 years.

Clinical data

- The assessment of fingolimod in this indication extension is based on a phase III, randomised, double-blind, comparative study versus intramuscular interferon (IFN) β-1a. The study's inclusion criteria were broader than the marketing authorisation population, that was restricted to highly active forms of MS. Thus, of the 2015 randomised patients, only 108:
  - had received at least 1 basic MS treatment during the year preceding initiation of treatment and had at least 1 Gd+ T1 lesion upon inclusion and/or had presented with at least 1 episode during the year preceding inclusion (equivalent to highly active RR-MS despite basic treatment);
  - Or, had presented with at least 2 episodes during the year preceding inclusion and had at least 1 Gd+ lesion upon inclusion (equivalent to severe and rapidly progressing RR-MS).
- After no more than two years of treatment, in the study population, the annualised episode rate (primary endpoint) was higher in the IFN group (0.675; CI95% = [0.515; 0.885]) than in the fingolimod group (0.122; CI95% = [0.078; 0.192]), i.e. a ratio of 0.181; CI95% = [0.108; 0.303], p<0.001. The annualised number of new or extended T2 lesions (ranked secondary endpoint) was also higher in the IFN group (9.269; CI95% = [7.661; 11.214]) than in the fingolimod group (4.393; CI95% = [3.617; 5.336]), i.e. a ratio of 0.474; CI95% = [0.361; 0.622], p<0.001. The results of the post-hoc analyses in the sub-groups equivalent to the marketing authorisation population also suggest the superiority of fingolimod over IFN with respect to these two endpoints. The comparison of confirmed 3-month quality of life and disability progression scores was not included in the protocol.
- A higher number of treatment-related adverse events were reported in the IFN group (95.3%) than in the fingolimod group (88.8%). The numbers of serious adverse events and those of grade ≥3, on the other hand, were higher in the fingolimod group (17.8% versus 9.3% and 50.4% vs. 42.0% respectively). The major risks identified by the RMP remain: bradyarrhythmia, hypertension, increased transaminase levels, posterior reversible encephalopathy syndrome (PRES), macular oedema, reprotoxicity, bronchoconstriction, infections including opportunistic infections, skin cancer and convulsions.

Special prescription requirements

- Medicinal product subject to initial hospital prescription
- Prescription reserved for neurology specialists

Benefit of the medicinal product

- The actual clinical benefit* of GILENYA is high
- GILENYA provides minor clinical added value** (CAV IV) in the therapeutic strategy.
- Approved for non-hospital pharmacy reimbursement and for hospital treatment.

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This document was drafted on the basis of the Transparency Committee opinion dated 20 February 2019 (CT-17345 and 17542) available at **www.has-sante.fr**

* The actual clinical benefit (ACB) of a 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 ACB, which may be high, moderate, low, or insufficient for the medicinal product to be covered by public funding.

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