

**BRIEF SUMMARY OF THE TRANSPARENCY COMMITTEE OPINION****GLYBERA** (alipogene tiparvovec), gene therapy

**Insufficient clinical benefit because of the moderate, heterogeneous and unsustained effect on the blood triglyceride level and the prevention of pancreatitis and because of the uncertainties about its short- and medium-term safety**

**Main points**

- ▶ GLYBERA has Marketing Authorisation in the treatment of adult patients with familial lipoprotein lipase (LPL) deficiency who have severe or multiple pancreatic crises despite a low-fat diet.
- ▶ A moderate effect on triglycerides and on episodes of pancreatitis has been observed but this effect was not sustained in the medium- and long-term (return to the baseline triglyceride level 1 year after the injection) and inter-patient heterogeneity of the treatment response.
- ▶ Uncertainties about the short- and medium-term safety of this gene therapy, which cannot be re-administered because of its action mechanism, remain.

**Therapeutic use**

- The treatment of familial LPL deficiency is based on a low-fat diet (10 to 20% of the calorie intake); that is to say, less than 40 g per day for an intake of 2000 Cal, compared with less than 40% in a normal diet, for life.
- **Role of the medicinal product in the therapeutic strategy**  
GLYBERA is the first proprietary medicinal product (gene therapy) intended for the treatment of homozygous LPL deficiency to be put on the market. This medicinal product must be combined with a strict low-fat diet. The mode of administration of GLYBERA is complex: it is based on a series of > 40 intramuscular injections in the buttocks and the thighs. The efficacy of the treatment must be checked by measuring the neutralising antibodies and the T-lymphocyte response in the initial examination and the response obtained 6 and 12 months after treatment. On the basis of the efficacy data obtained, GLYBERA does not have a role in the treatment strategy for patients with symptomatic LPL deficiency.

**Clinical data**

- In the available interventional studies, a median reduction in the plasma TG level after 12 weeks of treatment of  $\geq 40\%$  compared with baseline was observed in:
  - 3/8 patients (1 at a low dose, 2 at a high dose), but these reductions were not sustained beyond 12 weeks,
  - 7/14 patients. This reduction was sustained for 26 weeks in 6 patients (secondary endpoint), but not beyond 52 weeks.
  - 2/5 patients (study CT-AMT-011-02). This reduction was not sustained at 1 year.
- A post-hoc analysis of the incidence and severity of pancreatitis in a sample of the patients presenting LPL deficiency with severe or multiple episodes of pancreatitis from the three interventional studies was carried out on the basis of 12 patients. A pre-/post-treatment comparison showed:
  - of the 6/12 patients who presented episodes of pancreatitis in the pretreatment phase, 3 took part in the treatment phase (monitored for 3 years).
  - of the 5/12 patients who presented episodes of pancreatitis before treatment, 5 took part in the treatment phase (monitored for 5 years).

- The available data show a reduction in the median plasma TG level of  $\geq 40\%$  compared with baseline (descriptive analysis) in some patients after 12 weeks, but the results were not maintained beyond 1 year. The clinical relevance of the chosen primary efficacy endpoint (reduction in the triglyceride level) is debatable.
- Taking into account the methodology of these studies (open, before/after), the low number of patients included compared with the number of patients likely to be treated and the absence of a sustained effect beyond 1 year, the benefit of GLYBERA cannot be established.

The absence of precise information about the dietary regime followed, the simple fact of receiving the treatment could have led patients to improve their compliance with their dietary regimen, leading to a reduction in the triglyceride level.

The data on the incidence and severity of the episodes of pancreatitis in the interventional studies, obtained from 12 patients who were selected retrospectively, do not provide proof that GLYBERA has an impact in the prevention of pancreatitis.

## Special prescribing conditions

- Orphan medicinal products, gene therapy product
- Medicine for hospital prescription, restricted to certain specialists and requiring special monitoring during the treatment.

## Benefit of the medicinal product

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



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This document was created on the basis of the Transparency Committee Opinion of 04 November 2015 (CT-14224) and is available at [www.has-sante.fr](http://www.has-sante.fr)

<sup>i</sup> \* 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.