HAUTE AUTORITÉ DE SANTÉ

RARE DISEASE
New medicinal product
February 2019

TRANSPARENCY COMMITTEE OPINION SUMMARY

AMGLIDIA (glibenclamide), antidiabetic

High clinical benefit and minor clinical improvement in the therapeutic strategy for neonatal diabetes.

Main points

- AMGLIDIA has been granted marketing authorisation for the treatment of neonatal diabetes mellitus in newborns, infants and children.
- Two non-comparative, open-label studies have demonstrated the efficacy in neonatal diabetes of various sulphonylurea tablets (with glibenclamide in one of the studies) on maintaining blood sugar control as an insulin substitute, with acceptable safety.
- A non-comparative, open-label study assessed the acceptability and safety of changing from glibenclamide tablets to oral glibenclamide suspension (AMGLIDIA) in children with neonatal diabetes.
- The safety profile of AMGLIDIA appears to be favourable, but is based on a limited number of data.

Therapeutic strategy

- The initial aim of neonatal diabetes treatment is to restore balance to the carbohydrate metabolism and treatment should be initiated from diagnosis. It consists of striking a balance between calorie and carbohydrate intake required for moderate regular weight catch-up to prevent any risk of insulin resistance, and insulin therapy for obtaining metabolic balance. Diagnosed in cases presenting with ketoacidosis, it generally requires the initiation of intravenous insulin therapy with rehydration, until the metabolic disorders have been corrected. In the transient form of the disease, treatment may be discontinued from the first few weeks of the child's life up to 5 years of age. In its permanent form, lifetime treatment is needed.
- **Role of the medicinal product in the therapeutic strategy**

  AMGLIDIA is the first-line treatment for neonatal diabetes and should be initiated as early as possible, after metabolic balance has been restored in cases of onset of ketoacidosis, and without waiting for genetic confirmation of the diagnosis. The oral suspension dosage form of AMGLIDIA enables easier administration in the paediatric population.

Clinical data

- An uncontrolled, open-label study assessed the efficacy of substituting insulin by a sulphonylurea in tablet form (mostly glyburide, the name of glibenclamide in the United States) in neonatal diabetes (n=49) associated with KCNJ11 gene mutation. Insulin substitution by a sulphonylurea was effective in 44 of the 49 patients treated (90%) and failed in 5 patients (without specifying the sulphonylurea substance received by the patients subject to failure). The characteristics of these 5 patients subject to failure were: a high frequency of severe neurological disorders and an older age (6 to 35 years). For 44/49 patients, insulin substitution by a sulphonylurea was associated with a reduction in HbA1c of 1.7% CI95% [1.3- 2.1%] n=38, p<0.001) observed from week 12 and persisting for up to 1 year.
- A study assessed the efficacy of glibenclamide tablets on blood sugar control and certain associated neurological disorders in diabetes of neonatal or very early onset due to KCNJ11 or ABCC8 gene mutation. After 18 months of treatment with glibenclamide tablets, all 18 patients included had discontinued their insulin treatment. Remission resulting in glibenclamide being discontinued was observed in one patient after 12 months of treatment. Glibenclamide treatment was accompanied by a reduction in HbA1c of -1.55% [-3.8 to 0.1%] (p< 0.0001) and an increase in peptide-C baseline status and after glucagon stimulation, p<0.01. The neuropsychomotor assessment

findings after 1 year of treatment were variable according to the age and initial symptoms of the children included; however, no neuropsychomotor deterioration was observed under glibenclamide treatment.

- A phase II study assessed the acceptability and safety of changing from glibenclamide tablet treatment to AMGLIDIA in 10 children aged from 0.3 to 16.2 years (6 aged < 5 years). The median prior treatment duration was 2.3 years. After 4 months of treatment with the suspension, 4 of the children < 5 years were satisfied and one of the children > 5 years. Four of the parents of children < 5 years were very satisfied and 3 of the parents of children > 5 years. No difference was detected between the HbA1c levels measured when treated with glibenclamide tablets or AMGLIDIA (median 6.4% [6.0 - 7.2] versus 6.1% [5 - 6.2], p=0.07). No robust data are available on the impact on AMGLIDIA on the neurological symptoms of the disease.
- A total of 37 adverse events occurred in the 10 patients receiving AMGLIDIA, but none of the patients discontinued treatment due to an adverse event. No deaths occurred during the study. Hypoglycaemia (9 cases in 7 patients) and abdominal pain (4 cases in 2 patients) were the most frequently reported adverse events. Two serious adverse events (severe hypoglycaemia) were considered to be linked to AMGLIDIA and to disease progression. The safety profile of AMGLIDIA seemed favourable based, however, on the limited data available.

Special prescription requirements

- Medicinal product subject to initial annual hospital prescription.
- Prescription and repeat prescription reserved for specialists in paediatrics, or in endocrinology, diabetes and nutrition.

Benefit of the medicinal product

- The actual clinical benefit* of AMGLIDIA is high.
- AMGLIDIA provides minor clinical added value** (CAV IV) in the therapeutic strategy for neonatal diabetes in newborns, infants and children.
- 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 06 February 2019 (CT-17120) 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".