HAUTE AUTORITÉ DE SANTÉ

RARE DISEASE
NEW MEDICINAL PRODUCT
January 2015

BRIEF SUMMARY OF THE TRANSPARENCY COMMITTEE OPINION

TRANSLARNA (ataluren), RNA interference agent

Minor improvement in the management of Duchenne muscular dystrophy

Main points

- TRANSLARNA has Marketing Authorisation in the treatment of Duchenne muscular dystrophy (DMD) resulting from a nonsense mutation in the dystrophin gene, in ambulatory patients aged 5 years and older.
- Available data suggest a potential benefit, poorly demonstrated and modest, in terms of slowing the loss of ambulation in some children with Duchenne muscular dystrophy, with acceptable safety.
- Efficacy has not been demonstrated in patients who have lost ambulation.

Therapeutic use

DMD treatment is essentially symptomatic. It includes, in France, orthopaedic treatment with physiotherapy and use of lower limb orthoses, spinal fusion at the onset of scoliosis, usually 2 years after the loss of ambulation. Preventive cardiology treatment combines ACE inhibitors and beta-blockers from 10 years of age. Respiratory treatment adapted to symptoms combines non invasive ventilation and cough assistance devices and, if necessary, tracheotomy and invasive ventilation, with gastrostomy in case of swallowing disorders. Symptomatic treatment extends life expectancy by several years (18 to 27 years in 30 years), but does not change motor impairment.
Only corticosteroids have shown partial efficacy. This treatment has numerous adverse effects in young children and in the long term can lead to behavioural disorders and weight gain.

Role of the medicinal product in the therapeutic strategy

TRANSLARNA is aimed at a highly targeted population of walking children, with DMD with a premature stop codon, from the age of diagnosis. It aims to slow the loss of ambulation. In this very small group, it would be included, without changes in the current treatment regimen.
The question of the place of this medicine in children from diagnosis as well as after the loss of ambulation is posed.

Clinical data

The efficacy and safety of ataluren was assessed in a Phase 2b placebo-controlled study in 174 boys aged 5 to 20 years, with DMD resulting from a nonsense mutation in the dystrophin gene, detected by sequencing. All patients were ambulatory at inclusion, which was defined as the ability to walk more than 75 metres without the aid of assistive devices during a 6-minute Walk Test (6MWT).

Two oral daily doses of ataluren (40 mg/kg or 80 mg/kg), divided into three doses (morning, afternoon, evening) for a period of 48 weeks, were evaluated in this study. The primary efficacy endpoint was change in distance walked in 6 minutes during the 6MWT test after 48 weeks of treatment.

The primary analysis, pre-defined in the protocol, showed no difference between the groups receiving ataluren and the placebo group:
- difference with ataluren 40 mg/kg versus placebo: 26.4 m (95% CI [-4.2; 57.1], not significant),
- difference with ataluren 80 mg/kg versus placebo: -0.1 m (95% CI [-30.4; 30.2], not significant)

A post-hoc analysis carried out in a modified ITT population (exclusion of 2 patients whose inclusion tests were considered invalid) suggested less degradation of the ability to walk in patients who received ataluren at 40 mg/kg

than with placebo. This potential difference compared with placebo was also observed in the secondary efficacy endpoints.

The most common adverse effects were nausea, vomiting and headaches. These adverse effects did not generally require medical intervention and none justified discontinuation of treatment.

The significant, identified or potential risks, monitored under the European Risk Management Plan associated with the Marketing Authorisation of TRANSLARNA, are: potentiation of aminoglycoside nephrotoxicity, modification of the lipid profile, hypertension with concomitant use of systemic corticosteroids, renal and hepatic toxicity, hibernoma and malignant tumours.

Benefit of the medicinal product

- The actual benefit* of TRANSLARNA is moderate.
- TRANSLARNA provides minor clinical added value** (CAV IV) in treatment.
- Recommends inclusion on the list of reimbursable products for supply by pharmacists and for hospital use.

HAS
HAUTE AUTORITÉ DE SANTÉ
This document was created on the basis of the Transparency Committee Opinion of 21 January 2015 (CT-13938) and is available at **www.has-sante.fr**

[i]

[i] ** 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.

** The clinical added value (CAV) describes the improvement in treatment provided by a medicinal product compared with existing treatments. The HAS Transparency Committee assesses the degree of CAV on a scale from I (major) to IV (minor). A level V CAV means "no improvement".