HAUTE AUTORITÉ DE SANTÉ

RARE DISEASE
New indication
May 2018

TRANSPARENCY COMMITTEE OPINION SUMMARY

DELURSAN (ursodeoxycholic acid), bile acid

High clinical benefit for hepatobiliary disorders associated with cystic fibrosis in children over the age of 6 years, but no demonstrated clinical benefit in the management of this disease in this population.

Main points

- DELURSAN has been granted marketing authorisation for the treatment of hepatobiliary disorders associated with cystic fibrosis in children aged 6 to 18 years.
- The available clinical data confirm its effect, based exclusively on the drop in liver transaminases.
- Despite the lack of clinically-relevant data concerning the efficacy of ursodeoxycholic acid, particularly in the long-term, its use is associated with significant hindsight and acceptable safety.

Pre-existing indications*

DELURSAN has already been granted marketing authorisation for various types of cholestasis and lithiasis (for further details, see SPC).

Therapeutic strategy

To date, the treatment of cystic fibrosis is exclusively symptomatic and lifelong. Lung, or even liver, transplantation may be proposed as a last resort in advanced forms of the disease.
Symptomatic management is based on 4 complementary procedure types:
- respiratory management: physiotherapy, PULMOZYME (dornase alfa) or BRONCHITOL (mannitol) inhaled, antibiotic therapy,
- nutritional and digestive management,
- implementation of optimum prevention of lung infections in accordance with the immunisation schedule,
- patient therapeutic education.

Liver impairment is an early complication occurring in one quarter of patients suffering from cystic fibrosis and responsible for one third of deaths. The only available treatment is ursodeoxycholic acid (UDCA): it is the conventional treatment to be initiated as soon as hepatobiliary impairment is diagnosed in these patients (no age restriction).

- **Role of the medicinal product in the therapeutic strategy**
  Considering the significant hindsight with use, and despite the lack of clinical data of a high level of evidence, DELURSAN and the other ursodeoxycholic acid (UDCA) based medicinal products are first-line treatments to be initiated as soon as liver impairment associated with cystic fibrosis is diagnosed. This treatment is continued for life. Last resort treatment remains liver transplantation.

Clinical data

- An older, unpublished phase II, prospective, placebo-controlled, randomised, double-blind crossover study (one year of each treatment) evaluated the effect of UDCA on histological changes in 21 children with cystic fibrosis-related liver impairment. Upon inclusion, significant histological differences were observed between patients.

* This summary does not cover these indications.

At the end of the study, a deterioration in steatosis and portal fibrosis was noted in patients treated later with UDCA (group A, n=8) compared to group B patients (n=10) treated earlier. A significant improvement in transaminase levels was observed under UDCA treatment in both groups. This study did not make it possible to evaluate the effect of UDCA on liver histology. UDCA would appear to stabilise cholangitis, portal fibrosis or steatosis, if treatment is initiated sufficiently early in the progression of liver impairment associated with cystic fibrosis. It has no effect, however, on the progression of cirrhosis once established.

- These results can only be partially transposed into routine practice as in the study, a high proportion of patients suffered from advanced liver impairment upon inclusion, whereas in routine practice, initiation of UDCA is recommended as early as possible, as soon as hepatobiliary impairment associated with cystic fibrosis has been diagnosed, hence probably in patients with relatively premature hepatobiliary impairment.
- The known safety profile of this medicinal product is similar to that observed in other indications.

Benefit of the medicinal product

- The actual clinical benefit* of DELURSAN is high.
- DELURSAN does not provide any clinical added value (CAV V) in the management of hepatobiliary disorders associated with cystic fibrosis in children aged between 6 and 18 years, which already includes the ursodeoxycholic acid-based proprietary medicinal products URSOLVAN and CHOLURSO.
- 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 16 May 2018 (CT-16545_16546)
available at **www.has-sante.fr**

* The actual clinical benefit of a medicinal product (ACB) is 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"