SUMMARY OF THE TRANSPARENCY COMMITTEE OPINION

DUPHALAC (lactulose), hypoammonaemic osmotic laxative

Moderate clinical benefit for hepatic encephalopathy and constipation

Main points

- DUPHALAC has been granted a marketing authorisation for hepatic encephalopathy and for the symptomatic treatment of constipation.
- In cases of constipation, it should only be envisaged after lifestyle and dietary measures have failed and in combination with such measures.
- In cases of hepatic encephalopathy, it is recommended in cases of minimal or subclinical encephalopathy as a first-line symptomatic treatment in the acute phase, supplementing triggering factor management, and for preventing recurrences, with a non-optimal level of evidence.

Therapeutic strategy

Constipation

- Medication-based treatment of constipation supplements lifestyle and dietary treatment including increasing dietary intake of plant-based fibre and beverages and advice on physical activity and defecation rehabilitation.
- To treat mild to moderate chronic constipation, it is recommended to increase daily fibre intake gradually over two weeks (so as to reduce adverse effects such as bloating and digestive discomfort). Waters enriched with minerals, particularly magnesium, also have a significant laxative effect.

Hepatic encephalopathy

- Treatment is based on identifying and correcting triggering factors: infection, bleeding of the digestive tract, excessive protein consumption, kidney failure, dehydration, electrolyte disorders, sedative medicines, digestive disorders such as constipation.
- Rifamixin (TARGAXAN; TIXTAR) is an antibiotic reserved for preventing relapses of recurrent clinical hepatic encephalopathy episodes, i.e. for adults having had at least 2 hepatic encephalopathy episodes after excluding the factors liable to trigger encephalopathy.
- In cases of severe encephalopathy (coma), artificial ventilation may be required. Liver transplantation may be required in cases of refractory and/or recurrent chronic hepatic encephalopathy, but it can only be carried out on a minority of patients.

Role of the medicinal product in the therapeutic strategy

Constipation

Where a laxative is required, osmotic laxatives (of which lactulose) remain, with bulk laxatives, first-line medicinal products. They must not be prescribed in cases of inflammatory colopathy or bowel obstruction.

Hepatic encephalopathy

Lactulose is recommended in cases of minimal or subclinical encephalopathy as a first-line symptomatic treatment in the acute phase, supplementing triggering factor management, and for preventing recurrences (secondary prevention) with a non-optimal level of evidence.

In cases of lactulose intolerance, lactitol may be an alternative to lactulose. Nevertheless, considerably less data in favour of its use are available. It is not cited in European and North American expert guidelines.

Clinical data

- For the treatment of constipation, no new clinical data in respect of efficacy or safety are available.
For the treatment of hepatic encephalopathy, in a meta-analysis of 9 studies, the efficacy of lactulose was compared to a placebo for minimal or subclinical hepatic encephalopathy in a total of 434 patients, with results demonstrating an improvement in neuropsychological tests after treatment; HR=0.52 (95% CI [0.44-0.62]). A Cochrane meta-analysis, based on 38 clinical studies of different levels of evidence, compared disaccharides (lactitol or lactulose) versus placebo or lack of treatment in patients with hepatic encephalopathy and cirrhosis. A total of 34 studies involved lactulose. The findings suggest a possible reduction in mortality, of hepatic encephalopathy and its complications compared to the placebo/or lack of treatment. Nevertheless, these endpoints were not primary endpoints and this benefit was not demonstrated in any of these studies. The level of evidence is moderate due to numerous bias factors (open-label study in particular). Furthermore, the clinical data remain limited for patients in the acute encephalopathy phase, in cases of chronic impairment. The data relating to patient quality of life are also limited.

Benefit of the medicinal product

- The actual clinical benefit* of DUPHALAC remains moderate for hepatic encephalopathy and for the symptomatic treatment of constipation.
- DUPHALAC does not provide any clinical added value** (CAV V) in the therapeutic strategy for these two conditions.
- Approval for retention of non-hospital pharmacy reimbursement and for hospital treatment.

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