BRIEF SUMMARY OF THE TRANSPARENCY COMMITTEE OPINION

TIXTAR (rifaximin), intestinal anti-infective agent

Minor improvement in the prevention of relapse of episodes of recurrent clinical hepatic encephalopathy with at least 2 prior episodes of hepatic encephalopathy and provided that triggers have been eliminated

Main points

- TIXTAR has Marketing Authorisation in the prevention of relapse of episodes of clinical 5eh° hepatic encephalopathy in adults.
- Its efficacy has been demonstrated versus placebo in terms of risk of onset of recurrent clinical hepatic encephalopathy, in combination with lactulose at 6 months with continued efficacy at 2 years.
- There are no data available related to the risk of selection of resistant bacteria.
- Considering the clinical data available, it should be reserved for recurrent clinical hepatic encephalopathies, i.e. adults who have had at least two prior episodes of hepatic encephalopathy and only after eliminating the factors likely to trigger the encephalopathy.

Therapeutic use

- Treatment is based on the identification and correction of triggering factors (infection, gastrointestinal bleeding, excessive consumption of proteins, renal failure, dehydration, electrolyte imbalance, sedative medicinal products, constipation-type gastrointestinal disorders).
- For clinical HE, preventive treatment of the encephalopathy is primarily based on the use of lactulose (DUPHALAC) or lactitol (IMPORTAL), oral or in enema, which aims to reduce ammonia levels, and the establishment of a low-protein diet. When the encephalopathy is severe (coma), artificial ventilation may be necessary. Finally, liver transplantation may be necessary in case of refractory and/or recurrent chronic hepatic encephalopathy, but it can be performed in only a small number of patients.

Role of the medicinal product in the therapeutic strategy

TIXTAR may be suggested in case of recurrent clinical hepatic encephalopathy, i.e. in adults with at least two prior episodes of hepatic encephalopathy, only after eliminating the triggering factors.

Clinical data

- In the phase III study, during 6 months of treatment, the risk of onset of hepatic encephalopathy was significantly reduced in the rifaximin group compared with placebo: HR 0.421, 95% CI [0.276; 0.641], p<0.0001.
- In an open-label follow-up study, after 2 years, episodes of hepatic encephalopathy were observed in 135/352 patients: 104/252 in the new patients group (41.3%) and 31/70 in the group of patients from the study mentioned above (44.3%).
  - A maintained Conn score compared with inclusion was observed in 216/322 (68.4%) of patients: 158/252 (64.2%) of new patients and 58/70 (82.9%) of those continuing with rifaximin.
  - An improved Conn score (from -1 to -2) was observed in 63/322 (19.6%) of patients: 60/252 (23.8%) and 3/70 (4.3%).
  - A worsening of the Conn score was observed in 11% of patients: 28/252 (11.1 %) and 9/70 (13%).
- These data demonstrate the efficacy of rifaximin 550 mg twice daily versus placebo in terms of risk of onset of recurrent clinical hepatic encephalopathy, in combination with lactulose at 6 months with continued efficacy at 2 years. No data is available on other forms of encephalopathies.
- According to the Marketing Authorisation, the most common adverse effects observed (>10%) were: ascites, nausea, peripheral oedema, vertigo, depression, headache, dyspnoea, abdominal pain, rash, pruritus, muscle spasms, arthralgia.
The Transparency Committee highlights the lack of available data related to the risk of selection of resistant bacteria.

**Benefit of the medicinal product**

- The actual benefit* of TIXTAR is:
  - substantial only in the prevention of relapse of episodes of recurrent clinical hepatic encephalopathy (with at least two prior episodes of hepatic encephalopathy) and after eliminating triggering factors.
  - Insufficient to justify its reimbursement by National Health Insurance in other patients.
- TIXTAR 550 mg provides minor clinical added value** (CAV IV) in the prevention of relapse of episodes of recurrent clinical hepatic encephalopathy with at least two prior episodes of hepatic encephalopathy and provided that triggers have been eliminated).
- Recommends inclusion on the list of reimbursable products for supply by pharmacists and for hospital use.

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*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 clinical added value".