HAUTE AUTORITÉ DE SANTÉ

GASTROENTEROLOGY / ONCOLOGY
New medicinal product
January 2019

TRANSPARENCY COMMITTEE OPINION SUMMARY

XERMELO (telotristat), antidarrhoeal agent

Low clinical benefit in the event of severe diarrhoea due to carcinoid syndrome but no demonstrated clinical added value in the therapeutic strategy.

Main points

- XERMELO has a marketing authorisation in the treatment of carcinoid syndrome diarrhoea in combination with somatostatin analogue (SSA) therapy in adults inadequately controlled by SSA therapy.
- The efficacy/adverse effects ratio has not been adequately established: low effect size compared to placebo, and no clinical relevance for the reduction in average bowel movement frequency after 12 weeks, no effect on flushing and abdominal pain, and a safety profile determined in the short term and in a limited number of patients.
- Additional data suggest that a more clinically relevant reduction in the number of bowel movements may be possible in "responder" patients, without it being able to identify these patients in advance. It is essential that use of the treatment be reassessed after the first 12 weeks, at the latest.
- It is a second-line treatment in the event of severe diarrhoea resistant to SSA therapy.

Therapeutic strategy

- When a well-differentiated neuroendocrine tumour (NET) causes carcinoid syndrome, the objectives of treatment are to improve quality of life by reducing incapacitating symptoms, including diarrhoea and flushing, and to prevent the development of long-term complications, in particular carcinoid heart disease.
- Curative surgical resection is rarely possible due to the presence of metastases, generally already present at the time of diagnosis. It is only considered in cases of grade G1 and G2 NET.
- Prolonged-release and parenteral somatostatin analogues (SSA: lanreotide or octreotide) are the conventional first-line treatment to control symptoms, including severe diarrhoea. They are effective in the majority of patients.
- In the event of SSA therapy failure, there is no consensus with respect to management. Subcutaneous short-acting octreotide, in the event of intercurrent symptoms, supportive treatments (anti-diarrhoeal agents, pancreatic enzymes, bile salt chelating agents) and lifestyle and dietary measures are used in addition to antisecretory therapy. Another alternative is to prescribe another SSA or increase the dosage of the SSA.
- If medicinal products with a specific antisecretory effect are ineffective, the only other option is anti-tumour therapy.
- **Role of the medicinal product in the therapeutic strategy**

  The initiation of a treatment is decided upon on following a multidisciplinary review meeting, as part of the nationwide NET network, RENATEN. XERMELO is a second-line treatment for severe carcinoid syndrome diarrhoea in adults. Its prescription should be considered in combination with SSA therapy if diarrhoea is not controlled despite SSA therapy at an optimal dose.

  The prescription must be reassessed at most 12 weeks after the initiation of treatment. The prescription should only be renewed if the patient achieves the treatment objectives set in terms of a reduction in the number of bowel movements per day and an improvement in quality of life, and in the absence of serious adverse reactions.

Clinical data

- A randomised, double-blind, placebo-controlled comparative study was conducted in adults with well-differentiated metastatic NET and carcinoid syndrome. The patients were randomised into one of the following three groups: 250 mg x3/d or 500 mg x3/d (off-label) of telotristat or placebo. After 12 weeks of treatment, of the 135 patients randomised, 117 (86% of the population) completed the comparative phase: 41/45 (91%) in the telotristat 250 mg x3/d group, 38/45 (82.6%) in the telotristat 500 mg, 3 times daily (off-label) group, and 38/45 (84.4%) in the placebo group. Despite SSA therapy, the average daily bowel movement frequency was 5.2 to 6.1 depending on the groups (severe diarrhoea). At inclusion, 39% of patients had at least two episodes of flushing per day and 39% had an abdominal pain severity score of ≥ 3 (on a scale of 10). The patients had been treated with prolonged-release SSA therapy for an average of 3 years.
- On average, over the 12-week treatment period, the reduction in mean bowel movement frequency was 0.81 bowel movements/day ($CI_{97.5\%}$: [- 1.26; - 0.29]) in the telotristat 250 mg group compared to the placebo group, p<0.001. The clinical relevance of this effect, less than the expected minimum difference of - 1.5 bowel movements/day, was low. No difference was demonstrated between the two groups for the incidence of flushing and abdominal pain.
- The most common adverse reactions reported with telotristat, generally of mild or moderate intensity, were abdominal pain (26%), elevated gamma-glutamyl transferase (11%) and fatigue (10%). The most frequently reported adverse reaction leading to discontinuation of telotristat was abdominal pain in 7.1% of patients (5/70). XERMELO can cause constipation, with a risk of faecaloma.

Special prescription requirements

- Medicinal product subject to initial annual hospital prescription. Unrestricted repeat prescription.

Benefit of the medicinal product

- The actual clinical benefit* of XERMELO is low.
- XERMELO does not provide any clinical added value** (CAV V) in the treatment of carcinoid syndrome diarrhoea.
- 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 23 January 2019 (CT-16851) 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".