HAUTE AUTORITÉ DE SANTÉ

GASTROENTEROLOGY
New indication
February 2017

BRIEF SUMMARY OF THE TRANSPARENCY COMMITTEE OPINION

RELISTOR (methylnaltrexone), peripheral opioid receptor antagonist

No clinical advantage demonstrated in the management of opioid-induced constipation in adult patients who do not have advanced illness and are not palliative care patients

Main points

- RELISTOR has marketing authorisation in the treatment of opioid-induced constipation in adults who do not have advanced illness and are not palliative care patients, when response to conventional laxatives has been insufficient.
- Its efficacy has been demonstrated versus placebo. A moderate effect size was observed for an increase in the proportion of rescue-free bowel movements within 4 hours (in the very short term). This endpoint is poorly suited to this chronic situation.
- The population included in the studies does not match the marketing authorisation indication: only a small number of patients aged 65 years and over were included. The results observed in this subpopulation are not significant whereas an elderly population will be the main users of this medicine.
- The most common adverse effects in the studies were abdominal pain, whereas the purpose of treatment is to improve patients' quality of life.

Pre-existing indication*

RELISTOR has marketing authorisation in the treatment of opioid-induced constipation in adult palliative care patients with advanced illness, when response to conventional laxatives has not been sufficient. In this indication, the actual clinical benefit remains substantial.

Therapeutic use

- Opioid-induced constipation is managed with a 1st-line treatment that can be started at the same time as the opioid therapy. Increased dietary fibre intake (15 to 20 g/day) and psyllium are often poorly tolerated in this context. However, osmotic laxatives (macrogols or non-absorbable sugars) are still appropriate. If these fail, a higher dosage or additional treatment with a so-called stimulant laxative (e.g. bisacodyl, sodium picosulfate, prucalopride) should be offered. Evacuation disorders are very common in this context and should be screened for (rectal examination) and managed (suppositories or enemas).
- After these two lines of treatment, a peripheral opioid antagonist may be considered so that sufficient pain control can be maintained or obtained without the patient's quality of life noticeably deteriorating.

- To date, the following options are available:
  - replace the analgesic with TARGINACT (combined oxycodone and naloxone), which is indicated in cancer pain and certain types of non-cancer pain;
  - combine the opioid with RELISTOR (administered subcutaneously), in palliative care patients with advanced illness;
  - combine the opioid with MOVENTIG (administered orally), in patients with non-cancer pain.

- **Role of the medicinal product in the therapeutic strategy**
  RELISTOR has been shown to have moderate efficacy on opioid-induced constipation in non-palliative care patients who do not have advanced illness, when response to conventional laxatives is not sufficient (the new

* This summary does not cover this indication.

indication). Like MOVENTIG or TARGINACT, it may therefore be offered to patients with opioid-induced constipation who have had an insufficient response to optimised laxative therapy.

Clinical data

- In a randomised, double-blind study versus placebo-controlled study, after 4 weeks of treatment, an increased proportion of rescue-free bowel movements within 4 hours (the primary endpoint) was observed in the RELISTOR groups compared with the placebo group (p<0.001):
  - 33.3% (50/150) in the RELISTOR 12 mg/day group versus 9.9% (16/162) in the placebo group, difference = 23.5% [14.6; 32.3];
  - 35.1% (52/148) in the RELISTOR 12 mg every other day group versus 9.9% (16/162) in the placebo group, difference = 25.3% [16.3; 34.2].

  The percentage of RELISTOR injections that led to rescue-free bowel movements within 4 hours (co-primary endpoint) was 28.9% (26.2) in the RELISTOR 12 mg/day group and 30.2% (27.9) in the RELISTOR 12 mg every other day group, p<0.001 versus placebo. During the open-label follow-up phase, this percentage was 34.4%.
- A post-hoc analysis of data from this study, performed at the EMA's request, found a statistically significant difference versus placebo on the proportion of "responder" patients when the concept of bowel movements with a sensation of complete evacuation was added. This was observed in both RELISTOR groups, 12 mg/day (22.5% difference, p<0.001) and 12 mg every other day (8.7% difference, p=0.012).
- The main adverse effects observed during these 2 studies were abdominal pain, diarrhoea, nausea, psychiatric disorders, respiratory disorders and hyperhidrosis.

Benefit of the medicinal product

- The actual clinical benefit* is low in the new indication.
- In view of the following:
  - RELISTOR has efficacy on the proportion of rescue-free bowel movements within 4 hours of administration;
  - this efficacy was demonstrated versus placebo and in patients whose status regarding optimised laxative therapy has not been clearly determined;
  - the effect size observed is modest and short term;

  RELISTOR does not provide clinical added value** (CAV V) in the current therapeutic strategy for managing opioid-induced constipation in non-palliative care patients who do not have advanced illness, when response to conventional laxatives has not been sufficient.
- Recommends inclusion on the list of reimbursable products for supply by pharmacists and for hospital use.

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This document was created on the basis of the Transparency Committee Opinion of 22 February 2017 (CT-15883) and is available at **www.has-sante.fr**

* The actual clinical benefit (ACB) 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 ACB, 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".