European Medicines Agency
Pre-Authorisation Evaluation of Medicines for Human Use

London, 24 April 2008
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COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE
SUMMARY OF POSITIVE OPINION*
for
RELISTOR

International Nonproprietary Name (INN): ***methylnaltrexone bromide***

On 24 April 2008 the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion,** recommending to grant a marketing authorisation for the medicinal product Relistor, 12mg/0.6 ml (20mg/ml), solution for injection intended for treatment of opioid-induced constipation in advanced illness patients who are receiving palliative care when response to usual laxative therapy has not been sufficient.
The applicant for this medicinal product is Wyeth Europa Limited.

The active substance of Relistor is methylnaltrexone bromide, a quaternary derivative of the well known μ-opioid antagonist, naltrexone *(ATC Code not yet assigned)*. Whereas naltrexone is used to counteract the CNS related effects of opioid treatment (and overdose), Relistor was designed to potentially block the undesired peripheral side effects of opioids without interfering the central analgesic effects. Relistor acts as an antagonist preferentially at the μ-opioid receptor (K_i=28 nM), exhibits less potency at the k-receptor and shows no action at the δ-opioid receptor or at any other receptor investigated in a broad screen. The methylation in Relistor causes greater polarity and lower lipid solubility of the molecule, and hence, Relistor is restricted from crossing the blood-brain barrier in animals and in humans at clinically relevant doses. Relistor is intended for application via the s.c. route only.

The benefits with Relistor are its clear superiority over placebo in the induction of prompt laxation in patients that are already treated with laxatives for opioid induced constipation and have ongoing difficulties with defecation. Laxation within 4 hours after the first dose of study drug was observed in 48.4% (CI = 35.9-60.8) of patients in the Relistor group versus 15.5% (CI = 7.1-23.9) of patients in the placebo group. The proportion of patients with ≥ 2 laxations within 4 hours after dose administration over the first 4 doses was 51.6% (CI = 39.2-64.1) in the Relistor group and 8.5% (CI = 2.0-14.9) in the placebo group. In addition, there was some indication that the compound relieves defecation complaints and improves stool consistency over the short term in the more severely affected patients, leading to an overall patient satisfaction that is clearly distinct from placebo.
Adverse events that were reported in the methylnaltrexone group at a higher rate than in the placebo group were within the system organ classes 'Gastrointestinal disorders' and 'Nervous system disorders' i.e. abdominal pain, flatulence, diarrhoea, nausea, and dizziness.

* Summaries of positive opinion are published without prejudice to the Commission Decision, which will normally be issued within 67 days from adoption of the Opinion.

** Applicants may request a re-examination of any CHMP opinion, provided they notify the EMEA in writing of their intention to request a re-examination within 15 days of receipt of the opinion.

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A pharmacovigilance plan for Relistor as for all medicinal products, will be implemented as part of the marketing authorisation.

The approved indication is: “Treatment of opioid-induced constipation in advanced illness patients who are receiving palliative care when response to usual laxative therapy has not been sufficient.” Relistor will be available by prescription only.

Detailed recommendations for the use of this product will be described in the Summary of Product Characteristics (SPC) which will be published in the European Public Assessment Report (EPAR) and will be available in all official European Union languages after the marketing authorisation has been granted by the European Commission.

The CHMP, on the basis of quality, safety and efficacy data submitted, considers that there is a favourable benefit to risk balance for Relistor and therefore recommends the granting of the marketing authorisation.