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

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COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE
SUMMARY OF POSITIVE OPINION*
for
VALDOXAN

International Nonproprietary Name (INN): ***agomelatine***

On 20 November 2008 the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion,** recommending to grant a marketing authorisation for the medicinal product Valdoxan, 25 mg, film-coated tablet, intended for: treatment of major depressive episodes in adults.

The applicant for this medicinal product is Les Laboratoires Servier.

The active substance of Valdoxan is agomelatine, an antidepressant medicinal product (ATC Code: N06AX22) which has shown to be a melatonin agonist (MT_1 and MT_2 receptors) and a serotonin 5-HT_{2C} antagonist, although with low affinity.

The benefits with Valdoxan are its superiority over placebo in the treatment of depression in both short-term and long-term studies, although not in all trials, as well as its different safety profile (lack of clinically relevant weight gain, low risk of sexual dysfunction, low incidence of gastro-intestinal reaction, absence of discontinuation symptoms and overall incidence rates of adverse events not different from placebo). Valdoxan showed statistically significant superiority over placebo in the short-term treatment of depression, although not in all trials.
Six placebo controlled trials have been performed to investigate the short term efficacy of Valdoxan in major depressive disorder: two flexible dose studies and four fixed dose studies. At the end of treatment (over 6 or 8 weeks), significant efficacy of agomelatine 25-50 mg was demonstrated in 3 of the six short-term double-blind placebo-controlled studies.
A meta-analysis of the six pivotal short-term studies resulted in an overall estimate of the difference between agomelatine and placebo of 1.5 on the HAM-D with a 95% confidence interval [0.80, 2.22]. Studies also showed that agomelatine 25 mg is probably less efficacious than other antidepressants.

With regard to relapse prevention, one study failed to demonstrate a difference in time to relapse. The maintenance of antidepressant efficacy was demonstrated in a second relapse prevention study. Patients responding to 8/10-weeks of acute treatment with open-label Valdoxan 25-50 mg once daily were randomised to either Valdoxan 25-50 mg once daily or placebo for further 6-months. Valdoxan 25-50 mg once daily demonstrated a statistically significant superiority compared to placebo on the primary outcome measure, the prevention of depressive relapse, as measured by time to relapse. The incidence of relapse during the 6-months double-blind follow up period was 22% and 47% for Valdoxan and placebo, respectively.

The most common side effects observed are headache, dizziness, somnolence, insomnia, migraine, nausea, diarrhoea, constipation, upper abdominal pain, hyperhydrosis, back pain, fatigue and anxiety. Of note, abnormalities of liver function tests (transaminase elevation > 3xULN), were also common.

* 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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Hepatitis (cytolytic) and transaminase elevation > 10 x ULN have been rarely reported. Therefore, monitoring of liver function tests is required during treatment at all doses.

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

The approved indication is: “Treatment of major depressive episodes in adults”.

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 Valdoxan and therefore recommends the granting of the marketing authorisation.