

## **Agomelatine (Valdoxan)-Reminder of the importance of liver function monitoring to reduce the risk of serious hepatic adverse reactions**

Agomelatine\* is a melatonergic agonist (MT<sub>1</sub> and MT<sub>2</sub> receptors) and 5-HT<sub>2C</sub> antagonist, indicated in the treatment of major depressive episodes in adults. It was first authorised for use across the EU since 2009 on the basis of studies showing that the medicine has comparable effects to other antidepressants. Since agomelatine has a different mode of action and a different safety profile to existing antidepressants, it was concluded that, as long as their liver function is tested regularly, agomelatine could be a valuable treatment for some patients. In the post marketing setting, hepatic adverse reactions have continued to be reported and an EU level review has recently been finalised which concluded that the benefit risk balance for agomelatine remains positive. However there is a need to reiterate the importance of liver monitoring, which is the cornerstone for the safe use of this product.

A risk of hepatic adverse effects has been known to be associated with agomelatine since it was first authorised and the product information has included warnings about these risks and the requirement for regular monitoring of liver function tests during treatment with agomelatine. In December 2012 and December 2013, the HPRA highlighted the risk of hepatotoxicity in its Drug Safety Newsletter (51<sup>st</sup> and 57<sup>th</sup> edition) and emphasised the importance of liver function monitoring.

The EMA's Pharmacovigilance Risk Assessment Committee (PRAC) recently concluded its regular benefit-risk assessment (known as a periodic safety update report or PSUR) of agomelatine. As part of this assessment, the PRAC considered cumulative data on severe hepatic adverse effects associated with agomelatine and recommended further reinforcement of measures to minimise the risk of hepatotoxicity.

Reports of hepatic failure included a small number of cases which resulted in a fatal outcome or liver transplantation in patients with hepatic risk factors. Elevations of liver enzymes exceeding 10 times the upper limit of normal, hepatitis and jaundice have also been reported in patients treated with agomelatine in the post-marketing setting. The majority of these abnormalities occurred during the first months of treatment. The pattern of liver damage appears mainly hepatocellular.

Extra vigilance is advised for patients with risk factors for hepatic injury. The balance of benefits and risks should be carefully considered before initiating treatment in a patient with risk factors for hepatic injury e.g. obesity/overweight/ non-alcoholic fatty liver disease, diabetes, substantial alcohol intake and in patients receiving concomitant medicinal products

associated with hepatic injury. Caution should be exercised when Valdoxan is administered to patients with pretreatment elevated transaminases.

Efficacy has not been demonstrated in patients ≥75 years and use of agomelatine is not recommended for patients in this age group. Prescribers are reminded that agomelatine is contraindicated in patients with hepatic impairment i.e. cirrhosis or active liver disease and in patients with transaminases exceeding 3 times the upper limit of normal. Elevations of transaminases (>3 times the upper limit of the normal range) occur more frequently in patients treated with 50mg compared to 25mg. For some patients treated in clinical practice, hepatic reactions occurred following an increase in dose.

### **Advice for Healthcare Professionals**

- Baseline liver function tests should be performed in every patient and treatment should not be started in patients with transaminases exceeding 3 times the upper limit of normal.
- Liver function must be monitored regularly during treatment, at 3, 6, 12 and 24 weeks and regularly thereafter when clinically indicated.
- Treatment must be discontinued immediately if the increase in serum transaminases exceeds 3 times the upper limit of normal, or if patients present with symptoms or signs of potential liver injury.
- Patients should be informed of the symptoms of potential liver injury and the importance of liver function monitoring, and should be advised to stop taking Valdoxan immediately and to seek urgent medical advice if these symptoms appear.

### **Key Message**

- Cases of liver injury, including hepatic failure, where a small number of cases have resulted in a fatal outcome or liver transplantation, in patients with hepatic risk factors have been reported in association with post-marketing use of agomelatine.
- Liver function tests (LFTs) should be monitored in all patients before and during treatment, in line with the recommendations described in the approved product information.

*\*Product information for agomelatine is available at [www.hpria.ie](http://www.hpria.ie)*