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Agomelatine (Valdoxan)

New contraindication for use and a reminder of the importance of liver function monitoring

Dear Healthcare Professional,

Servier, in agreement with the European Medicines Agency and Irish Medicines Board informed in October 2012 healthcare professionals on cases of severe liver toxicity related to the use of agomelatine and emphasized the importance of liver function monitoring. This letter is sent as a reminder and to inform of new recommendations for Agomelatine (Valdoxan) since further cases of severe hepatic adverse reactions have been reported

Summary

- **Cases of liver injury, including hepatic failure resulting in a fatal outcome or liver transplantation in patients with hepatic risk factors, have been reported in agomelatine-treated patients.**
- **Agomelatine is contra-indicated in patients with transaminases exceeding 3 times the upper limit of normal.**
- **Prescribers are reminded to perform liver function tests in all patients receiving agomelatine and agomelatine treatment should be discontinued if a patient presents with symptoms or signs of liver injury.**
- **Patients should be informed of the symptoms of potential liver injury, and should be advised to stop taking agomelatine immediately and to seek urgent medical advice if these symptoms appear.**

Elderly patient > 75 years:

- **The efficacy and safety of agomelatine (25-50 mg/day) have been established in elderly depressed patients (< 75 years). No significant effect is documented in patients ≥ 75 years. Therefore agomelatine should not be used by patients aged 75 years or more.**

The information in this communication has been agreed with the European Medicines Agency (EMA).

Further information on the safety concern

Agomelatine (Valdoxan) is authorised for the treatment of major depressive disorders in adult patients.

The risk of elevated transaminases in patients taking agomelatine has been known since marketing authorisation in February 2009. Cases of liver injury, including hepatic failure (a few cases resulted in a fatal outcome or liver transplantation in patients with hepatic risk factors), elevated liver enzymes exceeding 10 times the upper limit of normal, hepatitis and jaundice have been reported in patients treated with Valdoxan 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. When agomelatine was discontinued, the serum transaminases usually returned to normal levels.

Review of data from clinical studies showed that elevations of transaminases (>3 times the upper limit of the normal range) have been observed in patients treated with agomelatine, particularly those receiving a 50-mg dose (2.5% versus 1.4% with 25 mg). Some patients treated in daily practice presented with hepatic reactions following an increase in the dosage.
As the recommendations in the product information have not been strictly adhered to (liver function monitoring, risk factors for hepatic injury), the European Medicines Agency concluded that the benefits of agomelatine exceed the risks if further risk minimising measures are introduced. Consequently the product information should be strengthened by contraindicating the medicine in patients with transaminases exceeding 3 times the upper limit of normal range and that prescribers should be reminded of existing warnings related to liver function, as detailed above. Prescribers are therefore reminded to perform liver function tests in all patients receiving agomelatine:

- at initiation of treatment
- after 3 weeks and 6 weeks (end of acute phase), and after 12 weeks and 24 weeks (end of maintenance phase)
- at the same time intervals as above when increasing the dose of agomelatine
- whenever clinically indicated.

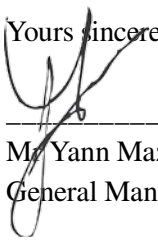
Any patient who develops increased serum transaminases should have their liver function test repeated within 48 hours.
Prescribers are also reminded that agomelatine is contraindicated in patients with hepatic impairment i.e. cirrhosis or active liver disease.
Additionally, considering the lack of significant benefit in very elderly patients (≥75 years) and the vulnerability of this age group, agomelatine should not be used in patients aged 75 years and above.

Call for reporting

Suspected adverse reactions should be reported to the Irish Medicines Board (IMB) using a Yellow Card obtained either from the IMB, or electronically via the website at www.imb.ie. Adverse reactions can also be reported to the IMB by calling (01) 676 4971

Communication information
For further inquiries concerning this information, and educational material please contact the Medical Information Department of Servier Laboratories Ireland Ltd. Block 2, West Pier Business Campus, Old Dunleary Road, Dun Laoghaire, Co. Dublin; Tel: 01-6638110.

Yours sincerely,



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