SERVIER

SERVIER LABORATORIES (IRELAND) LTD. Reg. in Ireland No. 46172
Block 2, West Pier Business Campus, Old Dunleary Road, Dún Laoghaire, Co. Dublin.

Tel: (01) 663 8110
Fax: (01) 663 8120

Date: 9th October 2012

Direct Healthcare Professional Communication on the risk of hepatotoxicity with agomelatine (Valdoxan)

Dear Healthcare Professional,

This letter is to inform you of new reports of serious hepatotoxicity associated with agomelatine (Valdoxan), and to remind you of the importance of monitoring liver function when treating patients with agomelatine.

Summary

- **There have been several serious cases of hepatotoxicity reported with agomelatine (Valdoxan) since its marketing in 2009. These cases include six reports of hepatic failure**
- **Prescribers are reminded to perform liver function tests in all patients receiving agomelatine:**
  - **at initiation of treatment**
  - **periodically at 3 weeks, 6 weeks (end of acute phase), 12 weeks, 24 weeks (end of maintenance phase) and thereafter**
  - **when increasing the dose of agomelatine at the same time intervals that apply to initiation**
  - **whenever clinically indicated**
- **Any patient who develops increased serum transaminases should have their liver function tests repeated within 48 hours**
- **Agomelatine should be immediately discontinued if an increase in serum transaminases exceeds 3 times the upper limit of normal, or if patients present with symptoms or signs of potential liver injury, such as: dark urine; light coloured stools; yellow skin/eyes; pain in the right upper belly; sustained new-onset and unexplained fatigue**
- **Inform patients of the symptoms of potential liver injury, and advise them to stop taking agomelatine immediately and to seek urgent medical advice if these symptoms appear.**
- **Exercise caution when prescribing agomelatine to patients with pre-treatment elevated transaminases levels or hepatic injury risk factors, eg: obesity/overweight/non-alcoholic fatty liver disease; substantial alcohol intake or use of concomitant medicines associated with risk of hepatic injury; diabetes.**

The information in this communication has been agreed with the European medicines Agency (EMA).
The product information has been amended to reflect these changes.

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, elevations of liver enzymes exceeding 10 times the upper limit of normal, hepatitis and jaundice have been reported in patients treated with Valdoxan/Thymanax 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.

The CHMP (the EMA's Committee on Medicinal Products for Human Use) has reviewed all data available from clinical trials and the post-marketing setting on elevated transaminases with agomelatine use. The review showed that in clinical studies, 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.

The CHMP concluded that agomelatine product information should be strengthened by including new warnings, additional monitoring of liver function tests when increasing the dosage and a reminder of existing warnings relative to liver function, as detailed above. Prescribers are also reminded that agomelatine is contraindicated in patients with hepatic impairment, ie, cirrhosis or active liver disease.

Reporting suspected adverse reactions

Irish Medicines Board, Earlsfort Centre, Earlsfort Terrace, Dublin 2.

Tel: 01-6764971

www.imb.ie

Communication information

For further inquiries concerning this information, 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,

Yann Mazeman, PharmD

General Manager