SERVIER INTERNATIONAL

19.03.2014

Agomelatine (Valdoxan)

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

Dear Healthcare Professional,

In 01.2013, Servier informed Health care professionals (HCPs) of serious liver toxicity in association with agomelatine (Valdoxan®) and recommended liver function monitoring. This letter is to inform of new recommendations for the safe use of Agomelatine since further cases of severe hepatic adverse reactions have been reported and to remind you of the importance of liver function monitoring.

Summary

- Cases of liver injury, including rare 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.
- 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**.
- Inform patients of the symptoms of potential liver injury, and advise to stop taking agomelatine immediately and to seek urgent medical advice if these symptoms appear.

Elderly patient ≥ 75 years:

- **Agomelatine should not be used by patients aged 75 years or more,** as no significant effect has been documented in this patient group.

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 its marketing authorisation. It has been shown in clinical studies, elevations of transaminases (>3 times the upper limit of the normal range) 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.
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.

Merci d'adresser toute correspondance au :
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In order to reinforce the precautions for use, the Valdoxan product information has been strengthened by contraindicating the medicine in patients with transaminases exceeding 3 times the upper limit of normal range. Prescribers should be reminded of existing warnings related to liver function, as detailed above.
The benefit of taking agomelatine still outweighs the risk if the Prescribers consider the following:
They should 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.

The Summary of Product Characteristics (SPC) and patient leaflet of Valdoxan in *Saudi Arabia* will be updated accordingly the soonest possible to strengthen the safety of treated patients.

This information has been agreed with the Saudi Food and Drug Authority.

Call for reporting

As a reminder, there is a need to report any suspected adverse reactions to the National Pharmacovigilance and Drug Safety Centre or pharmacovigilance department in Servier, according to the following;

By e-mail: npc.drug@sfda.gov.sa
Or by fax: +966 11 2057662
Or by online: https://ade.sfda.gov.sa/

Pharmacovigilance department in Servier:
LPV: Fawaz Al-Anazi
E-mail: Fawaz.al-anazi@sa.netgrs.com
Fax no. : +966 (11) 2886814

Communication information

For further inquiries concerning this information and educational material please contact the Medical Information Department of Servier (+966 12 6976997) and at: samy.sinnuqrut@sa.netgrs.com.

Yours sincerely,

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