Valdoxan® (agomelatine) in the treatment of Major Depressive Episodes in Adults

Information for Healthcare Professionals

Recommendations regarding:

- **Risk of hepatotoxicity**
- **Liver function monitoring**
- **Guidance in the event of clinical symptoms of hepatic dysfunction**
- **Interaction with potent CYP1A2 inhibitors**

Valdoxan overview

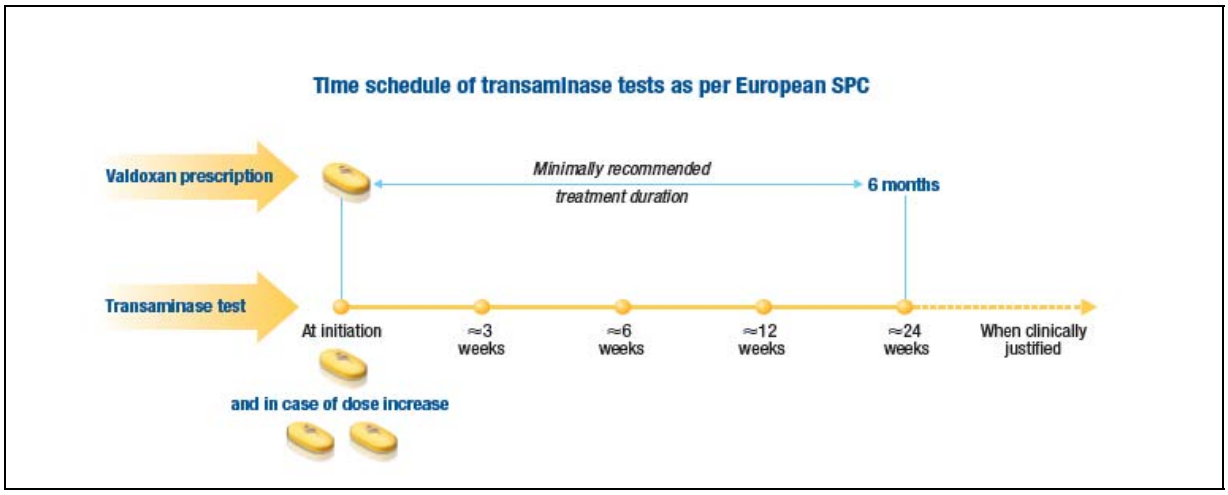
- Valdoxan was registered in Europe in February 2009 and is available in Malta since July 2009 for the treatment of major depressive episodes in adults.

Valdoxan and risk of hepatotoxicity

- Cases of liver injury, including hepatic failure, elevations of liver enzymes exceeding 10 times upper limit of normal, hepatitis and jaundice have been reported in patients treated with Valdoxan in the post-marketing setting. Most of them occurred during the first months of treatment. The pattern of liver damage was predominantly hepatocellular. When Valdoxan was discontinued in these patients, the serum transaminases usually returned to normal levels.
- In clinical trials, an elevation in transaminases (> 3 times ULN) was observed in 1.4% of patients on agomelatine 25 mg daily and 2.5 % on agomelatine 50 mg daily vs. 0.6% on placebo. When Valdoxan was discontinued in these patients, the serum transaminases usually returned to normal levels.
- Valdoxan is contraindicated in patients with hepatic impairment (i.e. cirrhosis or active liver disease).

Guidance for liver function monitoring

- Liver function tests (specifically alanine aminotransferase (ALAT) and aspartate aminotransferase (ASAT)) should be performed in all patients treated with Valdoxan at initiation of treatment, after around 3 weeks, 6 weeks (end of acute phase); after around 12 and 24 weeks (end of maintenance phase); and thereafter when clinically indicated.
- When increasing the dosage, liver function tests should again be performed at the same frequency as when initiating treatment.



Guidance in the event of abnormal liver function tests during treatment with Valdoxan

- Any patient who develops increased serum transaminases should have his/her liver function tests repeated within 48 hours.
- If symptoms or signs of potential liver injury (such as dark urine, light coloured stools, yellow skin/eyes, pain in the upper right belly, sustained new-onset and unexplained fatigue) are present, Valdoxan treatment should be discontinued immediately.
- If the increase in serum transaminases (ALAT and/or ASAT) exceeds 3 times the upper limit of normal:
  - ❑ Discontinue Valdoxan therapy, and

- ❑ Perform liver function tests regularly until serum transaminases return to normal

Guidance in the event of clinical symptoms of hepatic dysfunction during treatment with Valdoxan

- If the patient develops symptoms or signs of potential liver injury (such as dark urine, light coloured stools, yellow skin/eyes, pain in the upper right belly, sustained new-onset and unexplained fatigue):
  - ✓ Valdoxan treatment should be discontinued immediately.
  - ✓ Liver function tests (including transaminases) should be performed.

- Prescribers should ask patients to seek urgent medical advise if symptoms or signs of potential liver injury are present.

Caution for Valdoxan initiation in patients with specific conditions

Caution should be exercised when prescribing Valdoxan for patients with:

- Pretreatment elevated transaminases (> the upper limit of the normal ranges and ≤ 3 times the upper limit of the normal range).
- Hepatic injury risk factors e.g. obesity/overweight/non-alcoholic fatty liver disease, diabetes, substantial alcohol intake or concomitant medicinal products associated with risk of hepatic injury.

Valdoxan should not be initiated in patient with pretreatment elevated transaminases (> 3 X the upper limit of the normal ranges)

Interaction with potent CYP1A2 inhibitors

- Valdoxan is contraindicated with concomitant use of potent CYP1A2 inhibitors (e.g. fluvoxamine [Faverin®], ciprofloxacin [Aristin-C®, Ciproxin®, Ciprobay, Medociprin®, Sepcen®, Siprox®, Zindolin®, Viprolox®]).

- Agomelatine is metabolised mainly by cytochrome P450 1A2 (CYP1A2) (90%) and by CYP2C9/19 (10%). Medicines that interact with these isoenzymes may decrease or increase the bioavailability of agomelatine. Fluvoxamine, a potent CYP1A2 and moderate CYP2C9 inhibitor, markedly inhibits the metabolism of agomelatine resulting in an increase in agomelatine exposure.

- In vivo, agomelatine does not induce CYP450 isoenzymes. Agomelatine inhibits neither CYP1A2 in vivo nor the other CYP450 in vitro. Therefore, Valdoxan is not expected to modify exposure to medicinal products metabolised by CYP450.

Adverse events should be reported to the Medicines Authority Post-licensing Directorate, 203, Level 3, Rue D'Argens, Gżira GŻR 1368, MALTA, or at: http://www.medicinesauthority.gov.mt/pub/adr.doc

New Summary of Product Characteristics to be attached