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

Information for Healthcare Professionals

Recommendations regarding:

- **Liver function monitoring**
- **Interaction with potent CYP1A2 inhibitors**

Valdoxan overview

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

Valdoxan and risk of hepatotoxicity

Cases of liver injury, including hepatic failure (few cases were exceptionally reported with fatal outcome or liver transplantation in patients with hepatic risk factors), 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 is predominantly hepatocellular with serum transaminases which usually return to normal levels on cessation of Valdoxan.

Recommendations for liver function monitoring

- ***Do not use Valdoxan in case of***

  - **Hepatic impairment** (i.e. cirrhosis or active liver disease) **or transaminases > 3ULN**

- ***Before starting treatment***

  - **Caution for Valdoxan initiation in patients with hepatic injury risk factors**

Valdoxan should be **prescribed after careful consideration of benefit and risk**:

- in patients with **hepatic injury risk factors** e.g. obesity/overweight/non-alcoholic fatty liver disease, diabetes, substantial alcohol intake,

- in patients receiving **concomitant** medicinal products associated with risk of hepatic injury.

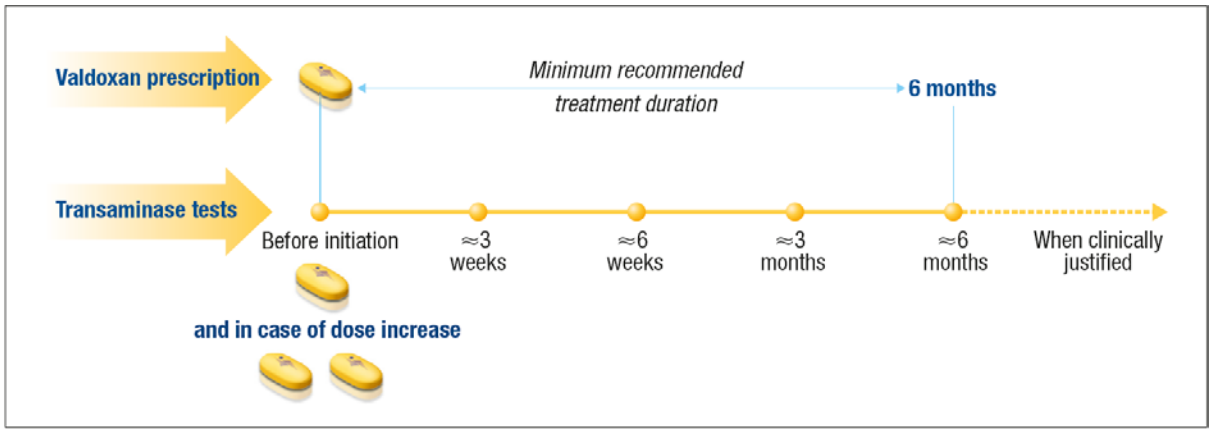
  - **Checking for patient liver function tests**

Baseline liver function tests should be **undertaken in all patients before starting treatment:**

- treatment should **not be initiated in patients with baseline values of ALT and/or AST>3 ULN.**

- caution should be exercised in patients with baseline values of ALT and/or AST > ULN and ≤ 3 ULN.

- ***Prescribe transaminases tests (ALT/AST) to your patients***



When increasing the dosage, liver function tests should again be performed at the same frequency as when initiating treatment.

Any patient who develops increased serum transaminases should have his/her liver function tests repeated within 48 hours.

- ***During treatment period***

Valdoxan treatment **should be discontinued** immediately if:

- 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**),

- the increase in **serum transaminases exceeds 3X ULN.**

Following discontinuation of Valdoxan therapy liver function tests should be repeated until serum transaminases return to normal.

Inform your patients about:

- the importance of liver function monitoring and,
- the vigilance about signs and symptoms of liver injury.

Reminder :

What to do in case of:

ALT and /or AST increase ≤ 3 ULN	Repeat the test within 48h
ALT and/or AST increase > 3 ULN	Stop the treatment immediately , repeat the blood tests until normalization
Signs and symptoms of liver injury*	Stop the treatment immediately, repeat the blood tests until normalization

* dark urine, light coloured stools, yellow skin/eyes, pain in the upper right belly, sustained new-onset and unexplained fatigue

Interaction with potent CYP1A2 inhibitors

- Valdoxan is contraindicated with concomitant use of potent CYP1A2 inhibitors (e.g. fluvoxamine [Faverin], ciprofloxacin [Ciproxin])

- 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.

New Summary of Product Characteristics to be attached