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 abnormal liver function tests or clinical symptoms of hepatic dysfunction

– Patients with pretreatment elevated transaminases or hepatic injury risk factors

– Patients $\geq 75$ years

– Interaction with potent CYP1A2 inhibitors

Contact for further information

Please refer to the Summary of Product Characteristics for further information before prescribing

Prescribing Information can be found on the last page.
Valdoxan overview

- Valdoxan was registered in Europe in February 2009 and has been available in the UK since 2009 for the treatment of major depressive episodes in adults

Valdoxan and risk of hepatotoxicity

- Cases of liver injury, including hepatic failure\(^1\) (exceptionally with fatal outcome or liver transplantation in people 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 was predominantly hepatocellular.

- In clinical trials, an elevation in transaminases (>3 times the upper limit of normal) 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.

- In both clinical trials and post-marketing settings, elevated serum transaminases usually returned to normal levels when Valdoxan was discontinued.

- Valdoxan is contraindicated in patients with hepatic impairment (i.e. cirrhosis or active liver disease) or transaminases exceeding 3 times the upper limit of normal.

\(^1\) Frequency: rare (≥1/10,000 to <1/1,000)
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 or clinical symptoms of hepatic dysfunction during treatment with Valdoxan

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

- 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
- 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 instruct patients to seek urgent medical advice if symptoms or signs of potential liver injury are present.

**Initiation of Valdoxan in patients with pretreatment elevated transaminases or hepatic injury risk factors**

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.
Guidance for patients ≥75 years

- Valdoxan should not be initiated in patients ≥75 years, as no significant effect has been documented in this group.

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.

For Further information

Please contact the Medical Information Department of Servier in the UK.
Tel: 01753 666409
Email: Medical.Information@uk.netgrs.com

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Wexham Springs
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Liver function monitoring scheme with Valdoxan (agomelatine)

Licensed Indication: Treatment of major depressive episodes in adults (Ref: SPC)

- Valdoxan 25 mg
  - Initiation of 25mg: ALT .......... U/L
  - AST .......... U/L
  - Week 3: ALT .......... U/L
  - AST .......... U/L
  - Week 6: ALT .......... U/L
  - AST .......... U/L
  - Week 12: ALT .......... U/L
  - AST .......... U/L
  - Week 24: ALT .......... U/L
  - AST .......... U/L

Perform a test at any time if clinically justified

- If dose increased to 50mg, restart the monitoring scheme.
  - Initiation of 50mg: ALT .......... U/L
  - AST .......... U/L
  - Week 3: ALT .......... U/L
  - AST .......... U/L
  - Week 6: ALT .......... U/L
  - AST .......... U/L
  - Week 12: ALT .......... U/L
  - AST .......... U/L
  - Week 24: ALT .......... U/L
  - AST .......... U/L

Perform a test at any time if clinically justified

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Patient name: ____________________
Date of initiation: ________________

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**Symptoms or any sign of potential liver injury**: Discontinue the treatment
- Liver function tests (including transaminases) should be performed

**Serum transaminases (ALT, AST)**

1. Increased
   - ALT and/or AST > 3 times the upper limit of normal
   - Symptoms or any sign of potential liver injury
   - Discontinue the treatment
   - Liver function tests (including transaminases) should be performed

2. Normal
   - ALT and/or AST ≤ 3 times the upper limit of normal
   - No symptom or sign of liver injury
   - Repeat liver function tests within 48 hours

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ALT and/or AST > 3 times the upper limit of normal
- Symptoms or any sign of potential liver injury
- Discontinue the treatment
- Liver function tests (including transaminases) should be performed
- Continue the treatment
- Follow the time schedule for liver monitoring tests

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**Symptoms or any sign of potential liver injury**: Discontinue the treatment
- Liver function tests (including transaminases) should be performed

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

Provided by Servier Laboratories Ltd

Job Bag: UK13MDA025451
Date of Preparation: July 2014

Produced and provided by Servier Laboratories Ltd
Date of preparation: July 2014
VALDOXAN® 25mg tablets

Agomelatine

Refer to the Summary of Product Characteristics (SPC) before prescribing.

Presentation: Orange-yellow, oblong, film-coated tablets (with blue imprint of company logo on one side) containing 25mg of agomelatine. Indication: Treatment of major depressive episodes in adults. Dosage and Administration: Recommended daily dose is one 25 mg tablet taken orally at bedtime. After two weeks’ treatment, in the absence of symptom improvement, the dose may be increased to 50 mg once daily, taken as a single dose of two tablets at bedtime. Decision of dose increase has to be balanced with a higher risk of transaminases elevation. Any dose increase should be made on an individual patient benefit/risk basis and with strict respect of liver function test (LFT) monitoring. Patients with depression should be treated for at least 6 months to ensure freedom from symptoms. Valdoxan® may be taken with or without food. Children and adolescents below 18 years of age: Not recommended due to lack of data. Older people <75 years: safety and efficacy have been established; ≥75 years: No documented effect, therefore Valdoxan should not be used by patients in this age group. No dose adjustment required in relation to age. Patients with renal impairment: Caution in severe or moderate impairment due to limited clinical data. Patients with hepatic impairment: Contraindicated. Switching therapy from SSRI/SNRI antidepressant to agomelatine: Patients may experience discontinuation symptoms after cessation from an SSRI/ SNRI antidepressant. The SSRI/SNRI SPC should be consulted on how to withdraw the treatment to avoid this. Agomelatine can be started immediately while tapering the dosage of an SSRI//SNRI.Treatment discontinuation: No dosage tapering needed. Contraindications: Hypersensitivity to agomelatine or to excipients. Hepatic impairment or transaminases >3 times upper limit of normal. Concomitant potent CYP1A2 inhibitors i.e. fluvoxamine, ciprofloxacin. Precautions: Monitoring liver function: LFTs should be done at initiation or dosage increase and then again at approx. 3, 6, 12, 24 weeks after initiation or dosage increase, with further testing when clinically indicated. Repeat LFTs within 48 hours in any patient developing raised transaminases. Discontinue if transaminases >3 times the upper limit of normal and test regularly until they return to normal. Discontinue immediately if symptoms or signs of potential liver injury occur. Caution in patients with pre-treatment elevated transaminases (>upper limit of normal and ≤3 times upper limit of normal). Caution in patients with hepatic injury risk factors e.g. obesity/overweight/non-alcoholic fatty liver disease, diabetes, substantial alcohol intake or concurrent treatment associated with risk of hepatic injury. Older people with dementia: Do not use. Patients with history of bipolar disorder, mania or hypomania: Use with caution and discontinue if patient develops manic symptoms. Suicide/suicidal thoughts: Close supervision should accompany initial drug therapy. Carefully monitor patients with a history of suicide-related events. Lactose intolerance: Valdoxan® contains lactose – patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine. Pregnancy: As a precaution, not recommended. Breast-feeding: Discontinue breast-feeding if Valdoxan® treatment essential. Interactions: Co-administration with potent CYP1A2 inhibitors e.g. fluvoxamine, ciprofloxacin, is contra-indicated. Agomelatine bioavailability reduced by rifampicin and smoking. No evidence of interactions between Valdoxan® and the following: benzodiazepines, lithium, paroxetine, fluconazole or theophylline. As with all antidepressants, combining Valdoxan® and alcohol is not advisable. There is no evidence of concurrent use of Valdoxan® with electroconvulsive therapy. Side effects: Adverse reactions were usually mild or moderate and occurred within first two weeks. Common: nausea, dizziness, headache, somnolence, insomnia, migraine, diarrhoea, constipation, abdominal pain, vomiting, hyperhidrosis, back pain, fatigue, anxiety, increases in ASAT and ALAT. Uncommon: aggression, restless leg syndrome, tinnitus. Rare: mania/hypomania, hepatitis, increases in GGT and ALP, hepatic failure (exceptionally with fatal outcome or liver transplantation in patients with hepatic risk factors.), jaundice, facial oedema and angioedema. Frequency unknown: Suicidal thoughts or behaviour. Consult SPC for full list of side effects. NHS price: £30.00 - 28 tablets. Legal Category: POM Product Licence Number: EU/01/08/499/003. Further information: Servier Laboratories Ltd., Rowley, Wexham Springs, Slough SL3 6PJ Tel (01753) 666409. Date of Revision: June 2014.

Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard. Adverse events should also be reported to Servier Laboratories Ltd. Tel (01753) 666409

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