Liver function monitoring scheme with Valdoxan (agomelatine)
Licensed Indication: Treatment of major depressive episodes in adults (Ref: SPC)

- **Valdoxan 25 mg**
  - Before 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.

**Serum transaminases (ALT, AST)**

- 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
- ALT and/or AST ≤ 3 times the upper limit of normal
  - Increased
    - ALT and/or AST ≤ 3 times the upper limit of normal
      - Normal
        - No symptom or sign of liver injury
          - Repeat liver function tests within 48 hours
        - ALT and/or AST > 3 times the upper limit of normal
          - Discontinue the treatment
          - Continue the treatment
            - Follow the time schedule for liver monitoring tests
          - Repeat liver function tests regularly until serum transaminases return to normal

* Such as dark urine, light coloured stools, yellow skin/eyes, right upper quadrant abdominal pain, sustained new-onset and unexplained fatigue

Patient name: _______________________
Date of initiation: ____________________

Provided by Servier Laboratories Ltd
Job Bag: UK14MDA0128f
Date of preparation: December 2014
Prescribing Information
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. Perform LFTs in all patients before starting treatment. Do not initiate treatment if transaminases exceed 3 X upper limit of normal. Exercise caution before starting treatment and maintain close surveillance throughout treatment, especially if hepatic injury risk factors or concomitant medicinal products associated with risk of hepatic injury are present. 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 X upper limit of normal. Concomitant potent CYP1A2 inhibitors i.e. fluvoxamine, ciprofloxacin. **Precautions:** **Monitoring liver function:** Perform baseline LFTs in all patients and do not initiate treatment in patients with baseline values of ALT and/or AST >3 X upper limit of normal. Perform LFTs before starting treatment 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 immediately if symptoms or signs of potential liver injury occur (such as dark urine, light coloured stools, yellow skin/eyes, right upper quadrant abdominal pain, sustained new-onset and unexplained fatigue). Discontinue if transaminases >3 X upper limit of normal and test regularly until they return to normal. Caution in patients with pre-treatment elevated transaminases (>upper limit of normal and ≤3 X upper limit of normal). Exercise 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 experience 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 AST and ALT. **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:** November 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.