1. Indication

Use of agomelatine by Trust prescribers must be in line with the Product Licence. Agomelatine is licensed for the treatment of major depressive episodes in adults and is not approved for the treatment of any other psychiatric disorders.

2. Place in Treatment

Wherever possible, NICE guidance for the treatment of major depressive disorder (MDD) must be followed. This guidance does not include the use of agomelatine and therefore a local decision has been made regarding its place in therapy. (See also Section 9).

Agomelatine is only approved for use by Trust prescribers as third-line drug therapy. An SSRI antidepressant should be first-line and an alternative SSRI (or mirtazapine) should be second-line. If these are ineffective (or not tolerated) then agomelatine (or another alternative) may be tried. Only if first and second line treatments have failed, (or if the patient is intolerant of them), may agomelatine be used.

3. Dose Recommendations

Treatment should commence at 25mg nocte with a two week review date. After two weeks of treatment, in the absence of symptom improvement, the dose may be increased to 50mg nocte. This is the maximum licensed dose and no further dose increases should be made. Wherever possible, a CGI evaluation should be completed at baseline and at 4-week intervals during the first 12 weeks of treatment. Any discontinuation of agomelatine may take place without downward titration of dose as the drug is not associated with discontinuation symptoms.

4. Prescribing in Special Populations

4.1 Although agomelatine is not licensed for use in children and adolescents and no studies have reviewed its use in this patient group, the Trust has approved use in CAMHS provided strict monitoring and patient follow-up is undertaken. Prescribing in this care group must also be in accordance with named-patient protocols.

4.2 Agomelatine should not be used in pregnancy or during breast-feeding, due to insufficient safety data.

4.3 Agomelatine may be used with caution in elderly patients, although there is a lack of clinical data. However, it must not be used in those aged 75 years or over, or in those with dementia.

If you require this document in an alternative format, ie easy read, large text, audio, Braille or a community language please contact the Pharmacy Team on 01243 623349 (Text Relay calls welcome)
4.4 Agomelatine should not be used in patients with moderate or severe renal impairment.

4.5 Agomelatine must not be used in patients with any degree of hepatic impairment or in those with transaminase levels more than 3 times the upper limit of normal. (See section 5).

4.6 Agomelatine should be used with caution in patients who consume substantial quantities of alcohol or who are treated with other medicines associated with risk of hepatic injury.

4.7 Regular monitoring of liver transaminases is required in all patients. Agomelatine must be discontinued if the patient develops symptoms or signs of liver injury. (See below).

5. Monitoring of liver transaminases

Abnormalities of liver function tests (serum transaminases elevation to greater than 3x upper limit of normal [ULN]) are common (> 1%) in response to agomelatine therapy and there have been rare reports of cytolytic hepatitis and extensive transaminases elevation, (> 10xULN).

Liver function tests must be carried out for all patients at baseline, then after 3, 6, 12 and 24 weeks, if still on treatment, and thereafter whenever clinically indicated.

Liver function tests must be carried out at the same intervals as above following any increase in dose, and thereafter whenever clinically indicated.

Any patient who develops increased serum transaminases must have their LFTs repeated within 48 hours.

If patients present with symptoms or signs of potential liver injury, (eg. dark urine, pale stools, jaundice, right upper abdominal pain, unexplained fatigue), or if an increase in serum transaminases exceeds 3xULN then agomelatine therapy must be immediately discontinued and LFTs performed regularly until they return to within normal levels.

Any rise in ULN that leads to discontinuation must be reported to the CSM via the ‘yellow card scheme’ and to the patient’s GP to ensure that primary care records are complete.

6. Other Side Effects

6.1 Adverse events are usually mild or moderate and normally occur within the first two weeks of treatment. The most commonly reported effects are transient nausea and dizziness.

6.2 The following side effects have all been reported as common (>1 in 100, <1 in 10): Headache, dizziness, somnolence, insomnia, migraine, nausea, diarrhoea, constipation, upper abdominal pain, hyperhidrosis, back pain, fatigue, increases in serum transaminases, anxiety.

6.3 Significant side effects should be reported through the Yellow Card Scheme.
7. Significant Drug Interactions

7.1 Agomelatine must not be prescribed concomitantly with potent CYP1A2 enzyme inhibitors, such as fluvoxamine, ciprofloxacin, erythromycin and cimetidine.

7.2 Agomelatine should be used with caution alongside other inhibitors of CYP1A2 enzyme inhibitors, such as propranolol, paroxetine, grepafloxacin and enoxacin.

7.3 Agomelatine should be used with caution alongside combined hormonal contraceptives as they may increase plasma levels to a moderate degree.

8. Patient Information

All patients must be provided with written information on the use of agomelatine. They must also be specifically informed of the symptoms of potential liver injury, and be advised to stop taking agomelatine immediately and seek urgent medical advice if these symptoms appear.

9. Prescribing Costs & Transfer of Care

Agomelatine is very expensive when compared to SSRIs and mirtazapine in usual doses. Prescribers must also remain aware that they will be asked to retain full responsibility for prescribing agomelatine in newly initiated patients, and for associated costs, as local PCTs / CCGs have not approved the use of agomelatine in primary care.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Cost of 28 days treatment (NHS Drug Tariff – June 2018)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agomelatine tabs</td>
<td>25mg ON</td>
<td>£30</td>
</tr>
<tr>
<td>Agomelatine tabs</td>
<td>50mg ON (2x25mg)</td>
<td>£60</td>
</tr>
<tr>
<td>Citalopram tabs</td>
<td>20 - 40mg OD</td>
<td>£1 - £2</td>
</tr>
<tr>
<td>Escitalopram tabs</td>
<td>10 - 20mg OD</td>
<td>£1 - £2</td>
</tr>
<tr>
<td>Fluoxetine caps</td>
<td>20 - 60mg OD</td>
<td>£1 - £4</td>
</tr>
<tr>
<td>Paroxetine tabs</td>
<td>20 – 50mg OD</td>
<td>£2 - £10</td>
</tr>
<tr>
<td>Sertraline tabs</td>
<td>50 – 200mg OD</td>
<td>£1 - £2</td>
</tr>
<tr>
<td>Mirtazapine tabs</td>
<td>15 – 45mg OD</td>
<td>£2 - £3</td>
</tr>
<tr>
<td>Duloxetine caps</td>
<td>60mg OD</td>
<td>£12</td>
</tr>
<tr>
<td>Venlafaxine XL*</td>
<td>150-225mg OD</td>
<td>£4 - £30</td>
</tr>
</tbody>
</table>

* When prescribed as generic tablets.

This document provides only summary guidance for the use of agomelatine in major depressive disorder in adults. Please refer to the BNF and to the Summary of Product Characteristics (for Valdoxan®) for more detailed prescribing and safety information.

Jed Hewitt
Chief Pharmacist – Governance & Professional Practice
Version 1: November 2009 – Approved by Drugs & Therapeutics Group 26.10.09

Version 2: July 2011 – Approved by Drugs & Therapeutics Group 25.7.11

Version 3: June 2012 – Updated in response to manufacturers change in recommendation for monitoring liver transaminases. (Servier Laboratories communication, 4.5.12).


Version 5: December 2013 – Updated in response to healthcare professionals’ letter from Servier Laboratories Ltd, which further highlighted the risk of liver damage and the need to monitor liver function. (October 2013).

Version 6: June 2018 – Routine review and update. (Drug no longer has “black triangle” monitoring status).

Date of next scheduled review: June 2021