

North of Tyne and Gateshead Area Prescribing Committee

Agomelatine - Information leaflet for primary care

Background information

Agomelatine is an antidepressant indicated for the treatment of major depressive episodes in adults. Agomelatine is a melatonin MT1 and MT2 receptor agonist, and antagonist at the serotonin 5-HT_{2C} receptor, thereby increasing levels of dopamine and noradrenaline in areas of the brain involved in mood control.

Current NICE guidance recommends the use of a generic SSRI antidepressant as first line treatment of patients with moderate to severe depression in primary care. Switching to another antidepressant should be considered if there has been no response after one month, or if the drug is poorly tolerated.

The limited data suggest that agomelatine has comparable efficacy to some commonly used antidepressants. Agomelatine is substantially more costly than many alternative antidepressant drugs and, on the basis of current evidence, it should not be used in preference to older, more established agents.

Agomelatine is recommended for the treatment of depression only following a lack of response to a trial of at least three alternative antidepressant drugs at adequate doses.

Prescribing should only be initiated by specialist mental health physicians who will prescribe for the first 12 weeks. If treatment is successful and is to be continued, prescribing will then be transferred to primary care.

The recommended monitoring of liver function tests will take place in secondary care before initiation, then at weeks 3, 6, 12 and 24 and thereafter when clinically indicated. At the final monitoring visit at week 24 a review of therapy should be undertaken by the specialist.

When increasing dosages, LFTs should be performed at the same frequency as initiation.

All patients prescribed agomelatine should be provided with a Patient Alert Card <https://www.medicines.org.uk/emc/RMM.68.pdf> (see Attachment 1 also) and the prescriber should explain the importance of the liver function monitoring to the patient.

North of Tyne + Gateshead formulary status Green Plus

Related NICE guidance NICE CG90 Managing Depression in Adults <https://www.nice.org.uk/guidance/cg90>

Licensed indication Treatment of major depressive episodes in adults

Dosage and administration The recommended dose is 25mg once daily, at bedtime. After two weeks of treatment, if there is no improvement of symptoms, the dose may be increased to 50mg daily, i.e. two 25mg tablets, taken together at bedtime.

Contraindications

- Hypersensitivity to the active substances or to any of the excipients
- Hepatic impairment (cirrhosis or active liver diseases) or serum transaminases exceeding 3x upper limit of normal
- Co-administration with potent CYP1A2 inhibitors (see drug interactions)

Cautions

- Agomelatine is not recommended for the treatment of depression in patients under 18 years of age.
- Only limited clinical data are available on the use of agomelatine in patients > 65 years old with major depression. As efficacy has not been clearly demonstrated in older patients (>75 years), caution should be exercised when prescribing agomelatine for these patients. Agomelatine should not be used for the treatment of major depressive disorder in elderly patients with dementia as safety and efficacy has not been established in this population.
- Combination with moderate CYP1A2 inhibitors
- Agomelatine should be used with caution in patients with a history of mania or hypomania and discontinued if a patient develops manic symptoms.
- As agomelatine tablets contain lactose, patients with hereditary problems of galactose intolerance, the LAPP lactase deficiency or glucose- galactose malabsorption should not take this medication.
- No clinical data on exposed pregnancies are available. Caution should be exercised when prescribing to pregnant women. There are no or limited amount of data (less than 300 pregnancy outcomes) from the use of agomelatine in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development. As a precautionary measure, it is preferable to avoid the use of agomelatine during pregnancy.
- The effects of agomelatine on the breast feeding infant have not been established. If treatment with agomelatine

is considered necessary, breast feeding should be discontinued.

- The combination of agomelatine and alcohol is not advisable, though this statement applies equally to many other CNS active substances.

Following several reports of liver injury, including hepatic failure, all available data on elevated transaminases and hepatotoxicity with agomelatine use have been reviewed and the MHRA issued updated advice in October 2012¹. The existing recommendations to perform liver function tests in all patients receiving agomelatine at treatment initiation and during treatment have been extended to include testing when the dose is increased.

Duration of treatment Patients with depression should be treated for a sufficient period of at least 6 months to ensure that they are free of symptoms.

Drug interactions

- Agomelatine is metabolised mainly by cytochrome P450 1A2 (90%) and by CYP2C9/19 (10%). Medicinal products 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 a 60 fold (range 12-412) increase of agomelatine exposure. Consequently, co-administration of agomelatine with potent CYP1A2 inhibitors (e.g. fluvoxamine, ciprofloxacin) is contraindicated.
- Combination of agomelatine with oestrogens (moderate CYP1A2 inhibitors) results in a several fold increased exposure to agomelatine. Caution should be exercised when prescribing agomelatine with other moderate CYP1A2 inhibitors (e.g. propranolol,) until more experience has been gained.
- Rifampicin induces all three cytochromes involved in the metabolism of agomelatine and may decrease the bioavailability of agomelatine.
- Smoking induces CYP1A2 and has been shown to decrease the bioavailability of agomelatine, especially in heavy smokers (≥ 15 cigarettes/day)
- In clinical trials no evidence of pharmacokinetic or pharmacodynamic interaction noted with benzodiazepines, lithium, paroxetine, fluconazole and theophylline was noted.
- The combination of agomelatine and alcohol is not advisable.
- Animal studies have not shown that agomelatine has proconvulsant properties. Therefore, clinical consequences of ECT given concomitantly with agomelatine treatment are considered to be unlikely.

Side effects

Adverse reactions are usually mild or moderate and occur within the first two weeks of treatment, the most common adverse effects were nausea and dizziness.

Common	Headache, dizziness, somnolence, insomnia, abnormal dreams, diarrhoea, nausea, constipation, abdominal pain, back pain, fatigue, anxiety, increase in ALAT and ASAT
Uncommon	Parasthesia, blurred vision, eczema, confusion, agitation, suicidal thoughts/behaviours, aggression, nightmares, mania/hypomania, confusion, migraine, restless legs syndrome, tinnitus, raised GGT, hyperhidrosis, pruritis, urticaria, increased weight
Rare	Erythematous rash, hepatitis, hallucinations, akathisia, hallucinations, akathisia, increased AlkPhos, hepatic failure, jaundice, facial oedema and angioedema, urinary retention,

Monitoring

- Prescribers should perform liver function tests in all patients receiving agomelatine:
 - at initiation of treatment
 - at weeks 3, 6, 12, 24, and
 - periodically thereafter when increasing the dose of agomelatine (at the same time intervals as above)
 - whenever clinically indicated
- Any patient who develops increased serum transaminases should have their liver function tests repeated within 48 hours
- Agomelatine should be immediately discontinued if an increase in serum transaminases exceeds 3x ULN, or if patients present with symptoms or signs of potential liver injury, such as: dark urine; pale stools; jaundice; pain in the right upper abdomen; sustained new-onset and unexplained fatigue
- Patients should be informed of the symptoms of potential liver injury, and advised to stop taking agomelatine immediately and seek urgent medical advice if these symptoms appear.
- The balance of benefits and risks should be carefully considered before initiating treatment in patient with pre-treatment elevated transaminases levels or risk factors for hepatic injury, eg: obesity or being overweight, non-

¹ MHRA Drug Safety Update: Volume 6, Issue 3 October 2012

alcoholic fatty liver disease; substantial alcohol intake or use of concomitant medicines associated with risk of hepatic injury; diabetes. Extra vigilance is advised for such patients.
Agomelatine is contraindicated in patients with hepatic impairment, i.e. cirrhosis or active liver disease.

GP and specialist responsibilities

Clinicians are guided to the liver function monitoring scheme provided by the manufacturer of agomelatine <https://www.medicines.org.uk/emc/RMM.67.pdf> (see Attachment 2 also)

Specialist:

- Initiate treatment
- Prescribe for first 12 weeks
- Monitor response to treatment - if successful and is to be continued, prescribing will then be transferred to primary care
- Provide patients with a patient alert card <https://www.medicines.org.uk/emc/RMM.68.pdf>
- Inform patients of the importance of liver function tests and symptoms of potential liver injury, and advise to stop taking agomelatine immediately and seek urgent medical advice if these symptoms appear
- Monitor liver function and response to treatment as stated above

GP:

- Prescribe treatment as advised by specialist
- Undertake physical health monitoring (LFTs) as required after final monitoring visit
- Refer to specialist if any problems arise (lack of response or adverse effects)

Cost

Agomelatine 25 mg- 50mg once daily	NHS Cost/ 28 day's supply £30.00- £60.00
------------------------------------	--

1

UK15MDA0055B



Serravallo June 2016

2

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in the patient information leaflet. You can also report side effects directly via the Yellow Card Scheme, website: www.yhfrs.gov.uk/YellowCard.

By reporting side effects you can help provide more information on the safety of this medicine.

3

What to do to avoid liver problems during treatment

Have regular blood tests

Why?

Your doctor will check that your liver is working properly before starting the treatment by running blood tests. The results will tell her/him how your liver is working and whether Valdoxan is suitable for you.

During treatment with Valdoxan, some patients may experience increased levels of liver enzymes in their blood. The levels of these liver enzymes indicate whether your liver is working properly and are vital for the doctor when monitoring your treatment.



Cut out the alert card from the printed sheet and fold in half



Fold in half again



Cut line



Fold line

4

Provided by Serravallo Laboratories Ltd

5

YOUR BLOOD TEST APPOINTMENTS

REMEMBER
When taking Valdoxan, it is important that you have regular blood tests.
The table below helps you to track your blood test appointments.

VALDOXAN 25 mg – Treatment start	Date
Blood tests for liver enzymes	
2 nd test (after 2 weeks)	
3 rd test (after 3 weeks)	
4 th test (after 4 weeks)	
5 th test (after 5 weeks)	
6 th test (after 6 weeks)	
7 th test (after 7 weeks)	
8 th test (after 8 weeks)	
9 th test (after 9 weeks)	
10 th test (after 10 weeks)	
11 th test (after 11 weeks)	
12 th test (after 12 weeks)	
13 th test (after 13 weeks)	
14 th test (after 14 weeks)	
15 th test (after 15 weeks)	
16 th test (after 16 weeks)	
17 th test (after 17 weeks)	
18 th test (after 18 weeks)	
19 th test (after 19 weeks)	
20 th test (after 20 weeks)	
21 st test (after 21 weeks)	
22 nd test (after 22 weeks)	
23 rd test (after 23 weeks)	
24 th test (after 24 weeks)	
25 th test (after 25 weeks)	
26 th test (after 26 weeks)	
27 th test (after 27 weeks)	
28 th test (after 28 weeks)	
29 th test (after 29 weeks)	
30 th test (after 30 weeks)	
31 st test (after 31 weeks)	
32 nd test (after 32 weeks)	
33 rd test (after 33 weeks)	
34 th test (after 34 weeks)	
35 th test (after 35 weeks)	
36 th test (after 36 weeks)	
37 th test (after 37 weeks)	
38 th test (after 38 weeks)	
39 th test (after 39 weeks)	
40 th test (after 40 weeks)	
41 st test (after 41 weeks)	
42 nd test (after 42 weeks)	
43 rd test (after 43 weeks)	
44 th test (after 44 weeks)	
45 th test (after 45 weeks)	
46 th test (after 46 weeks)	
47 th test (after 47 weeks)	
48 th test (after 48 weeks)	
49 th test (after 49 weeks)	
50 th test (after 50 weeks)	

Your doctor will decide if any further tests should be taken. Remember to bring this card with you when you visit your doctor.

6

What to do before taking Valdoxan

Tell your doctor if you know that you have liver problems: do not take Valdoxan if this is the case. There could be other reasons why Valdoxan may not be suitable for you.

Ask your doctor for advice on the following:

- if you have ever had liver problems
- if you are obese or overweight
- if you are diabetic
- if you drink alcohol
- if you are taking other medicines (some are known to affect the liver)

7

Why?

Be vigilant about signs of liver problems

If you observe any of the following, your liver may not be working properly:

- yellow skin/eyes
- darkening of the urine
- light coloured stools
- pain in the upper right abdomen (belly)
- unusual fatigue (especially associated with other symptoms listed above)

Seek urgent advice from a doctor who may advise you to stop taking Valdoxan.

Attachment 2: Liver function monitoring scheme with Valdoxan® (agomelatine)

<https://www.medicines.org.uk/emc/RMM.67.pdf>

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
ALTU/L
ASTU/L

Week 3
ALTU/L
ASTU/L

Week 6
ALTU/L
ASTU/L

Week 12
ALTU/L
ASTU/L

Week 24
ALTU/L
ASTU/L

Perform a test at any time if clinically justified.

If dose increased to 50mg, restart the monitoring scheme.

Initiation of 50mg ALTU/L
ASTU/L

Week 3 ALTU/L
ASTU/L

Week 6 ALTU/L
ASTU/L

Week 12 ALTU/L
ASTU/L

Week 24 ALTU/L
ASTU/L

Perform a test at any time if clinically justified.

Patient name: _____

Date of initiation: _____

Serum transaminases (ALT, AST)

Symptoms or any sign of potential liver injury*

ALT and/or AST > 3 times the upper limit of normal

Normal

Symptoms or any sign of potential liver injury*

Increased 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

ALT and/or AST > 3 times the upper limit of normal

ALT and/or AST ≤ 3 times the upper limit of normal

Discontinue the treatment

- Liver function tests (including transaminases) should be performed

Discontinue the treatment

- Repeat liver function tests regularly until serum transaminases return to normal

Continue the treatment

- Follow the time schedule for liver monitoring tests

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

Provided by Servier Laboratories Ltd Job Bag : UK16MDA0102b Date of preparation June 2016