Health and Social Care Board

Department of Health
An Roinn Sláinte
Männystrie O Poustie
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Interface Pharmacist Network
Specialist Medicines

Agomelatine Shared Care Guideline

Note: Amber status only normally applies to cover the required monitoring during the first 24 weeks of treatment (see below)

Specialist Details	Patient Identifier
Name: _____	
Location: _____	
Tel: _____	**Date:** _____

Introduction

Licensed indications: treatment of major depressive disorder in adults.

Use of agomelatine may be considered an option in cases of treatment failure or non-tolerance to a minimum of two or more other antidepressants.

Scope of shared care

- Amber status only applies to cover periods of treatment where monitoring of LFTs is required (e.g. during the first 24 weeks of treatment, following dose increases or other scenarios where monitoring period is extended).
- Once monitoring has been completed, agomelatine is no longer considered to be an amber list specialist medicine and shared care arrangements will no longer apply.
- **Specialists must remain available for urgent referral / advice in the event problems arise during treatment beyond the first 24 weeks**.

Adult dosage and administration

The recommended dose is 25 mg once daily taken orally at bedtime.
After two weeks of treatment, if there is no improvement of symptoms, the dose may be increased to 50 mg once daily taken at bedtime.

Available as: Agomelatine 25 mg film-coated tablets

Hospital specialist responsibilities

- Diagnose the condition and assess if the patient is suitable for treatment with agomelatine.
- Carefully evaluate the risk factors for hepatic injury and communicate the outcome of the risk assessment to the GP. Risk factors include:
  - obesity/overweight/non-alcoholic fatty liver disease
  - diabetes
  - alcohol use disorder and/or substantial alcohol intake
  - concomitant medication associated with risk of hepatic injury.
- Undertake baseline tests as indicated in the monitoring table and communicate to the GP that these have been done and evaluated. Do not initiate treatment if baseline values of ALT and/or AST > 3 X ULN.
- Arrange shared care with the patient's GP.
- Advise GP on dose to prescribe.
- Re-evaluate hepatic risk factors prior to increasing dose to 50mg and advise patient and GP of need to recommence LFT monitoring schedule
- Provide the patient/carer with relevant written information on use, side effects and need for monitoring of medication. A patient alert card is available to download at: http://www.medicines.org.uk
- Monitor response to treatment and need to continue therapy for the duration of the shared care arrangement.
- Continue to review the patient at agreed specified intervals for the duration of the shared care arrangement, sending a written summary to the GP whenever the patient is reviewed.
- Provide any other advice or information for the GP if required.
- Remain available for urgent referral if any concerns arise at any stage during treatment

GP responsibilities

- Prescribe agomelatine.
- Arrange and record on-going monitoring as advised by specialist (see monitoring table), ensuring practice systems are in place to recall patients for monitoring blood tests.
- Manage any liver abnormalities as detailed below.
- If patient is not compliant with monitoring, contact specialist urgently.
- Refer back to specialist if any concerns arise during treatment, including when the shared-arrangement no longer applies.
- Report adverse drug reactions to initiating specialist and the usual bodies (e.g. CHM, MHRA)
- Ensure no significant drug interactions with other medicines.

Monitoring

	Hospital Specialist	GP	
Test	Pre-Treatment Baseline	During Treatment	
		First 24 weeks	Thereafter
LFTs	✓	3, 6, 12 and 24 weeks	When clinically justified

- Perform additional LFTs at any time if clinically justified.
- If the dose is increased, perform liver function tests at the same frequency as when initiating treatment. Dose reductions do not warrant any change in the monitoring schedule.

Management of liver abnormalities

Signs of liver injury	Action required
Symptoms or any sign of potential liver injury (such as dark urine, light coloured stools, yellow skin/eyes, right upper quadrant abdominal pain, sustained new-onset and unexplained fatigue) ⇨	• Stop agomelatine immediately • Contact initiating specialist • Check LFTs • **Seek urgent medical advice**
AST or **ALT** is **more than 3 times** upper limit of normal ⇨	• Stop agomelatine immediately • Contact initiating specialist • Repeat LFTs within 48 hours • Continue to monitor LFTs regularly until return to normal
AST or **ALT** is greater than upper limit of normal but **less than 3 times** upper limit of normal ⇨	• Continue agomelatine • Contact Specialist • Repeat LFTs within 48 hours • Treatment can continue if AST / ALT remain < 3 x ULN
If repeat LFTs are required, they must be carried out within 48 hours (if necessary via out-of-hours services)	

Adverse effects, precautions and contraindications

Contraindications:

- Concomitant use of potent CYP1A2 inhibitors (e.g. fluvoxamine, ciprofloxacin).
- Hepatic impairment or patients with baseline values of ALT and/or AST > 3 X ULN
- Patients ≥75 years
- Patients with dementia
- Hypersensitivity to the active substance or to any of the excipients

Liver impairment. Cases of liver injury, including hepatic failure have been reported in patients treated with agomelatine. Most of them occurred during the first months of treatment and serum transaminases usually return to normal levels on cessation of agomelatine. **Caution** is advised in patients who are obese, overweight, have non-alcoholic fatty liver disease, diabetes, alcohol use disorder and /or substantial alcohol intake and in patients receiving concomitant medicinal products associated with risk of hepatic injury. Caution is advised in patients with pre-treatment elevated transaminases (> the upper limit of the normal ranges and ≤3 times the upper limit of the normal range). **Discontinuation**. Dose tapering is not required when stopping treatment. Discontinuation symptoms are not known to be induced after abrupt treatment cessation.

Cautions:
Bipolar disorder/ mania / hypomania. Use with caution in patients with a history of bipolar disorder, mania or hypomania and should be discontinued if a patient develops manic symptoms

Renal Impairment. Use with caution in moderate to severe impairment.

Suicidal behaviour and antidepressant therapy. The use of antidepressants in general has been linked with suicidal thoughts and behaviour; children, young adults, and patients with a history of suicidal behaviour are particularly at risk. Where necessary patients should be monitored for suicidal behaviour, self-harm, or hostility, particularly at the beginning of treatment or if the dose is changed.

Commonly reported adverse reactions include: anxiety, abnormal dreams, gastrointestinal disorders e.g. nausea, diarrhoea, constipation, abdominal pain; headache, dizziness, somnolence, insomnia, fatigue, back pain, weight gain, increased liver transaminases.

Pregnancy: as a precautionary measure**,** it is preferable to avoid the use of agomelatine during pregnancy.
Breast feeding: Agomelatine may be excreted in human breast milk and a risk to babies/infants cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue agomelatine therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Common drug interactions

Agomelatine is contraindicated in combination with:

- Potent CYP1A2 inhibitors (e.g. fluvoxamine, ciprofloxacin).

Use agomelatine with caution in association with:

- Phenytoin, fosphenytoin, rifampicin or ritonavir – may decrease exposure to agomelatine
- Oestrogens (moderate CYP1A2 inhibitors) - results in a several fold increased exposure of agomelatine.
- Other moderate CYP1A2 inhibitors (e.g. propranolol).
- Drugs associated with hepatic injury
- Smoking - induces CYP1A2 and has been shown to decrease the bioavailability of agomelatine, especially in heavy smokers (>15 cigarettes/day)

Communication

For any queries relating to this patient's treatment with agomelatine, please contact the specialist named at the top of this document.

This information is not inclusive of all prescribing information and potential adverse effects.
Please refer to full prescribing data in the SPC at www.medicines.org.uk or the BNF

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