Agomelatine

Traffic light classification- Amber 2
Information sheet for Primary Care Prescribers

Licensed Indications[1]

- Agomelatine is licensed for the treatment of major depression in adults
- Agomelatine is not licensed in patients ≥ 75 years of age
- Agomelatine is not recommended in patients < 18 years of age

Therapeutic Summary

Agomelatine is a melatonin receptor agonist and a selective serotonin-receptor antagonist; it does not affect the uptake of serotonin, noradrenaline, or dopamine[1,2].

Medicines Initiation

Agomelatine is a fourth line option in the treatment of major depression where other antidepressants have failed or not been tolerated. Treatment should be initiated and stabilised by the specialist (e.g. consultant psychiatrist or appropriately qualified non-medical prescriber) before prescribing is transferred to primary care.

Treatment with agomelatine should only be initiated after careful consideration of benefit and risk in patients with hepatic injury risk factors such as:

- Obesity, overweight, non-alcoholic fatty liver disease, diabetes
- Alcohol use disorder and/or substantial alcohol intake
- Receiving concomitant medicines associated with risk of hepatic injury

Products Available

Agomelatine 25mg tablets. Cost x 28 tablets = £30.05[3]

Dosages and Route of Administration[1,2]

- Initiation, titration and stabilisation of the dose will be performed by the specialist
- The starting dose is 25mg once daily at bedtime
- Dose to be increased, if necessary, after at least 2 weeks to 50mg once daily at bedtime
- Agomelatine tablets may be taken with or without food
- Renal impairment: caution in moderate and severe impairment due to limited clinical data

Duration of Treatment

NICE guideline 222[4] advises to support and encourage a person who has benefited from taking an antidepressant to continue medication for at least six months after remission of an episode of depression; this greatly reduces the risk of relapse. Review the need for continued antidepressant treatment beyond six months after remission considering the likelihood of relapse and the potential risks of continuing with antidepressants long term. For people who have been assessed as being at higher risk of relapse, consider continuing with antidepressant medication maintaining the dose that led to full or partial remission, unless there is good reason to reduce it. Review treatment with antidepressant medication at least every six months thereafter.

Treatment Discontinuation

No dose tapering is needed on treatment discontinuation[1]. Unlike other antidepressants, agomelatine has not been associated with discontinuation symptoms.

Monitoring of Liver Function

Liver toxicity is a side effect of agomelatine; hepatic failure, elevations of liver enzymes exceeding 10 times upper limit of normal, hepatitis and jaundice have been reported in the post-marketing setting[1]. Most cases occurred during the first few months of treatment. The pattern of liver damage is predominantly hepatocellular with increased serum transaminases usually returning to normal levels on cessation of agomelatine[1].

In December 2014, the MHRA reminded healthcare professionals to test liver function before and regularly during treatment (see schedule below)[5].

Pathology Services at all three of our local Acute Trusts (NUH, SFH and DBH) will only routinely report ALT levels if "LFTs" are requested. The agomelatine SPC[1] requires both ALT and AST levels are checked so clinicians are requested to state "LFTs, including AST" on the blood form.

Liver Function Monitoring Requirements and Responsibilities (ALT and AST)[1]

When increasing the dose, liver function tests should again be performed at the same frequency as when initiating treatment

	Baseline	3 weeks	6 weeks	12 weeks	24 weeks	Annually at review of maintenance treatment	Any time when clinically justified
Secondary Care	√	√	√	√			√
Primary Care					√ (unless already performed by secondary care)	√ (see notes below)	√

√ = Remember to specifically state "LFTs, including AST" on the blood form

Important points for practice:

- Treatment should not be initiated if baseline liver function tests transaminases (ALT and/or AST) exceed 3 X upper limit of normal.
- Treatment should be discontinued immediately if patients present with symptoms or signs of potential liver injury such as: dark urine, pale stools, jaundice, pain in the right upper abdomen or sustained new onset and unexplained fatigue.
- Treatment should be discontinued if transaminases (ALT and/or AST) exceed 3 X upper limit of normal at any point.
- In the event of raised serum transaminases and/or signs of potential liver injury see the Manufacturers Liver Function Monitoring Scheme[1] for advice on management.
- Although not included in the manufacturer's liver function monitoring scheme, it may be appropriate to check liver function tests at the same time as maintenance treatment is reviewed in primary care (annually is recommended).
- See the following links for further information:
  Agomelatine Prescriber Guide[1]

Side effects

Side effects are generally mild or moderate and occur within the first 2 weeks of treatment. The most common side effects are headache, nausea and dizziness; they are usually transient[1].
For a comprehensive list of side effects, refer to the SPC[1].

Contraindications[1]

- Hypersensitivity to the active substance or to any of the excipients
- Hepatic impairment (i.e. cirrhosis or active liver disease) or transaminases exceeding 3 X upper limit of normal
- Concomitant use of potent CYP1A2 inhibitors (e.g. fluvoxamine, ciprofloxacin)

Precautions[1,2]

- Alcoholism / excessive alcohol consumption
- Non-alcoholic fatty liver disease
- Obesity
- Diabetes
- Bipolar disorder/mania/hypomania
- History of suicide-related events or a current significant degree of suicidal ideation
- Concomitant use of moderate CYP1A2 inhibitors (e.g. propranolol)

Clinically Relevant Medicine Interactions and Their Management[1,2]

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.

- Contraindicated with potent CYP1A2 inhibitors (fluvoxamine and ciprofloxacin) – risk of significantly increased agomelatine exposure.
- Cautioned with moderate CYP1A2 inhibitors (propranolol, enoxacin and oestrogens) – risk of increased agomelatine exposure.
- Rifampicin may decrease the bioavailability of agomelatine.
- Smoking induces CYP1A2 and has been shown to decrease bioavailability of agomelatine (especially in heavy smokers, ≥15 cigarettes per day). Caution if stopping smoking – risk of increased agomelatine exposure.
- Caution with concomitant use of medicines associated with hepatic injury.

For a comprehensive list of interactions, refer to the SPC[1] and BNF[2].

Patient information

- Patients must 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. There is a useful Patient Alert Card and Information Sheet on liver side-effects and blood testing under agomelatine product Risk Materials on the emc website.[1]
- Patient information leaflet for agomelatine - https://www.mind.org.uk/information-support/drugs-and-treatments/antidepressants-a-z/agomelatine/

Pharmacy Contacts - Nottinghamshire Healthcare NHS Foundation Trust

Mental Health Medicines Pharmacist Advice Line: 0300 3035808
Wells Road Centre Pharmacy 01159 555 357
Email MI@nottshc.nhs.uk

References and Version Control

1. Agomelatine Aristo 25mg film-coated tablets - Aristo Pharma Limited. Summary of Product Characteristics and Risk Materials (last updated 22 May 2023). http://www.medicines.org.uk [Accessed on 10/07/2024].

2. Joint Formulary Committee. *British National Formulary* (online). London: BMJ Group and Pharmaceutical Press. https://www.medicinescomplete.com/mc/bnf/current/. [Accessed on 10/07/2024].
3. The Electronic Drug Tariff https://www.drugtariff.nhsbsa.nhs.uk/#/00798052-DC/DC00798043/Home [Accessed on 10/07/2024].
4. Depression in Adults: Treatment and Management. NICE Guideline 222 (June 2022). https://www.nice.org.uk/guidance/ng222 [Accessed on 10/07/2024].
5. Agomelatine (Valdoxan): Risk of Liver Toxicity. MHRA Drug Safety Update. December 2014. Available at: https://www.gov.uk/drug-safety-update/agomelatine-valdoxan-risk-of-liver-toxicity [Accessed on 24/07/24].