Shared Care Protocol
Agomelatine in the treatment of patients with moderate to severe depression

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This shared care protocol (SCP) sets out details for the sharing of care for ***patients prescribed agomelatine for depression****. It should be read in conjunction with the latest Summary of Products Characteristics (SmPC) available at https://www.medicines.org.uk/emc*

As outlined in NHS England Guidance 2018 (07573), 'Responsibility for Prescribing Between Primary & Secondary/Tertiary Care': When a specialist considers a patient's condition to be stable or predictable, they may seek the agreement of the GP concerned (and the patient) to share their care.

This document provides information on drug treatment for the shared commitment between the specialist and GP concerned. GPs are invited to participate. If the GP is not confident to undertake these roles, then they are under no obligation to do so. In such an event, the total clinical responsibility for the patient for the diagnosed condition remains with the specialist. The doctor who prescribes the medication has the clinical responsibility for the drug and the consequences of its use.

N.B. If the GP decides not to participate in shared care for a particular patient, they must inform the relevant specialist in writing, within 2 weeks of receipt of a request to share care.

For further information please click on the links below or visit:

- Valdoxan 25 mg film-coated tablets - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk)
- NICE guideline on depression in adults: treatment and management (NG222)
- MHRA Drug Safety Update Dec 2014 Agomelatine (Valdoxan): risk of liver toxicity - GOV.UK (www.gov.uk)
- Valdoxan 25 mg film-coated tablets - Risk Management Materials - (emc) (medicines.org.uk)
- Agomelatine for the treatment of major depressive episodes (terminated appraisal) (nice.org.uk)

Introduction

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

Initiation of agomelatine is only recommended after an adequate trial, in terms of duration and dose, of at least two other antidepressants.

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. 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.

In October 2012, the MHRA published a drug safety update on the risk of dose-related hepatotoxicity and liver failure with agomelatine treatment. The MHRA published a reminder of the need to test liver function before starting agomelatine and regularly during treatment in November 2014.

This Shared Care Protocol is for adult patients aged 18 years and over.

Licensed indication:

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

Dose (posology & method of administration):

For full details see individual SmPCs at http://www.medicines.org.uk/emc/

- 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
- Agomelatine tablets may be taken with or without food
- Renal impairment: caution in moderate and severe impairment due to limited clinical data

Contra-indications:

For full details see individual SmPCs at http://www.medicines.org.uk/emc/

- 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)

Special warnings and precautions:

For full details see individual SmPCs at http://www.medicines.org.uk/emc/

MHRA/CHM advice:
Agomelatine (Valdoxan): risk of liver toxicity - GOV.UK (www.gov.uk)

- See **'Monitoring liver function'**

Drug interactions:

For full details see individual SmPCs at http://www.medicines.org.uk/emc/ and BNF https://bnf.nice.org.uk/interactions/

Agomelatine is metabolised mainly by cytochrome P450 1A2 (CYP1A2) (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 of agomelatine. While there was no specific safety signal in the 800 patients treated in combination with oestrogens, caution should be exercised when prescribing agomelatine with other moderate CYP1A2 inhibitors (e.g. **propranolol, enoxacin**) until more experience has been gained.
- **Rifampicin** an inducer of all three cytochromes involved in the metabolism of agomelatine 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) - dose adjustments might be necessary if smoking started or stopped during treatment.

Pregnancy and lactation:

Pregnancy - There is limited data on the use of agomelatine in pregnancy.
If planning a pregnancy, the patient should speak to their specialist to determine whether agomelatine is still the best option. Similarly, if an unplanned pregnancy occurs while taking agomelatine, the patient should be reviewed at the earliest opportunity by their specialist.

bumps - best use of medicine in pregnancy (medicinesinpregnancy.org)

USE OF AGOMELATINE IN PREGNANCY – UKTIS (UK Teratology Information Service)

Lactation – There is very limited data on the use of agomelatine in lactation. Its dopaminergic effects have the potential to affect a full milk supply establishing in the first 6 weeks (dopamine inhibits prolactin release). Its pharmacokinetic profile is somewhat favourable; however caution is advised - use specialist resources to discuss with parent if they would like to breastfeed.

Adverse effects & management:

For full details see individual SmPCs at http://www.medicines.org.uk/emc/

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.

See also **'Monitoring liver function'**

Any serious adverse reactions should be reported to the MHRA via the Yellow Card scheme www.mhra.gov.uk/yellowcard

Treatment Discontinuation:

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

Monitoring liver function

Liver function tests (**ALT & AST**) should be performed 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

Do not initiate treatment if:

- hepatic impairment (i.e. cirrhosis or active liver disease)
- or transaminases > 3 X ULN (Upper Limit of Normal)

Exercise caution in:

- patients with baseline values of ALT and/or AST > ULN and ≤ 3 X ULN

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

Summary of recommendations for liver function monitoring

Finding	Action needed
ALT and/or AST increase < 3 X ULN	Repeat the test within 48h
ALT and/or AST increase > 3 X ULN	Stop treatment immediately, repeat the blood tests until normalisation
Signs and symptoms of liver injury: dark urine, light coloured stools, yellow skin/eyes, right upper quadrant abdominal pain, sustained new-onset and unexplained fatigue	Stop treatment immediately, repeat the blood tests until normalisation

Advice to patients/carers:

- Tell patients to watch out for the symptoms and signs of liver injury (eg, jaundice, dark urine, bruising). Explain the importance of regular liver function monitoring.
- Advise patients to stop taking agomelatine and to get medical help immediately if they have any signs or symptoms of liver injury.
- Provide patients with an Agomelatine Patient Alert Card

Further information:

- Agomelatine Liver Function Monitoring Scheme
- Agomelatine Prescriber Guide

Shared Care Responsibilities

Responsibilities of the Psychiatric Service

- Diagnosis of condition and ensuring other treatment options have been fully explored.
- Initiation of agomelatine is only considered after an adequate trial, in terms of duration and dose, of at least two other antidepressants, where treatments have been ineffective or have not been tolerated due to weight gain, sexual dysfunction or sleep disturbance.
- Check liver function (ALT & AST) prior to starting agomelatine
- Carefully evaluate risk factors for hepatic injury (i.e. obesity, overweight, non-alcoholic fatty liver disease, diabetes, alcohol use disorder, concomitant medication).
- Counsel the patient with regard to the benefits and risks of treatment and provide the patient with any relevant information and advice, including patient information leaflets on individual medicines.
- Initiate treatment with agomelatine, ensuring patient/carer has a basic understanding of what the drug is, how and when it should be taken, why it is being used, and an awareness of potential side effects.
- Inform patients of the symptoms 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) and advising them to stop taking agomelatine immediately and seek urgent medical advice if these symptoms appear.
- Notify the patient's GP that agomelatine has been initiated and report progress following each clinic review.
- In line with NICE guidelines, review the patient 1 or 2 weeks after drug initiation dependent on suicide risk, and then see them regularly (i.e. every 2 to 4 weeks) for the first 3 months.
- Monitor patient for adverse drug reactions (ADRs) and tolerance during titration period.
- Ensure LFTs are monitored at 3, 6, 12 and 24 weeks after initiation or if dose is increased.
- Supply patient with an Agomelatine Patient Alert Card (can be printed here)
- After six months, and once the specialist considers the patient's condition is stable on a dose effective for symptom control, a request can be made to the patient's GP to 'share' the patient's care.
- The patient/carer should be informed of arrangements for further prescriptions.
- All patients will remain under the ongoing care of the psychiatric service.
- The psychiatric service will provide support if problems occur using the contact details provided.
- The psychiatric service will give directions as to when treatment should be discontinued
- Notify the GP promptly and in writing of any changes in medication regime.
- Accept responsibility for prescribing back should problems arise that cannot be readily corrected.

General Practitioner Responsibilities

- Accept request to take on prescribing of agomelatine once the specialist considers a patient's condition is stable and the patient is stabilised on a tolerated dose effective for symptom control, no sooner than six months after initiation
- Reinforce educational points provided by the specialist.
- Repeat prescribing of agomelatine no sooner than six months after initiation, and once stable.
- Referral back to the psychiatric service if any problems arise related to antipsychotic medication or the patients psychiatric condition, for a review of medication and consideration of change where indicated.
- Monitoring the patient's overall health and wellbeing and observing patient for evidence of ADRs/abnormalities and raising with specialist if necessary.
- Report suspected adverse events to the specialist and the MHRA.
- If dose is increased (under specialist advice & guidance only) restart LFT monitoring schedule i.e. at start, 3, 6, 12 and 24 weeks. Any patient who develops increased serum transaminases should have his/her liver function tests (LFT) repeated within 48 hours – **see 'Monitoring liver function'**
- After the 24 week test further tests are only indicated if clinically indicated, i.e. there are signs or symptoms of potential liver injury (for example dark urine, light-coloured stools, yellow skin/eyes, right upper quadrant abdominal pain, sustained new-onset and unexplained fatigue or itching).
- **Discontinuing therapy if patient presents with symptoms or signs of potential liver injury OR the increase in serum transaminases exceeds three times the upper limit of normal. Liver function tests should be performed regularly until serum transaminases return to normal – see 'Monitoring liver function'**
- Complying with any national advice on agomelatine.
- Ensuring advice is sought from the specialist if there is any significant change in the patient's physical health status.
- Contact the psychiatric service for management advice as required.
- Reducing/stopping treatment in line with specialist's original request.

Patient/Carer Responsibilities

- After counselling, to be willing to take / administer prescribed medication as directed at home.
- To attend blood tests, clinic appointments and any other appointments needed for monitoring of medication and possible side effects.
- Report any adverse effects, concordance issues, or warning symptoms to the GP or specialist.
- To inform the Psychiatric Service or GP if they have stopped taking their medication.

Further advice and support

- Further support can be accessed via the patient's specialist or the local Community Mental Health Team
- Medicines Management Team, Somerset NHS Foundation Trust, Cheddon Lodge: 01823 368265 MedicinesManagement@somersetft.nhs.uk
- Prescribing & Medicines Management Team, NHS Somerset: 01935 384123

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