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-HT2C 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 a 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 2012[1].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:

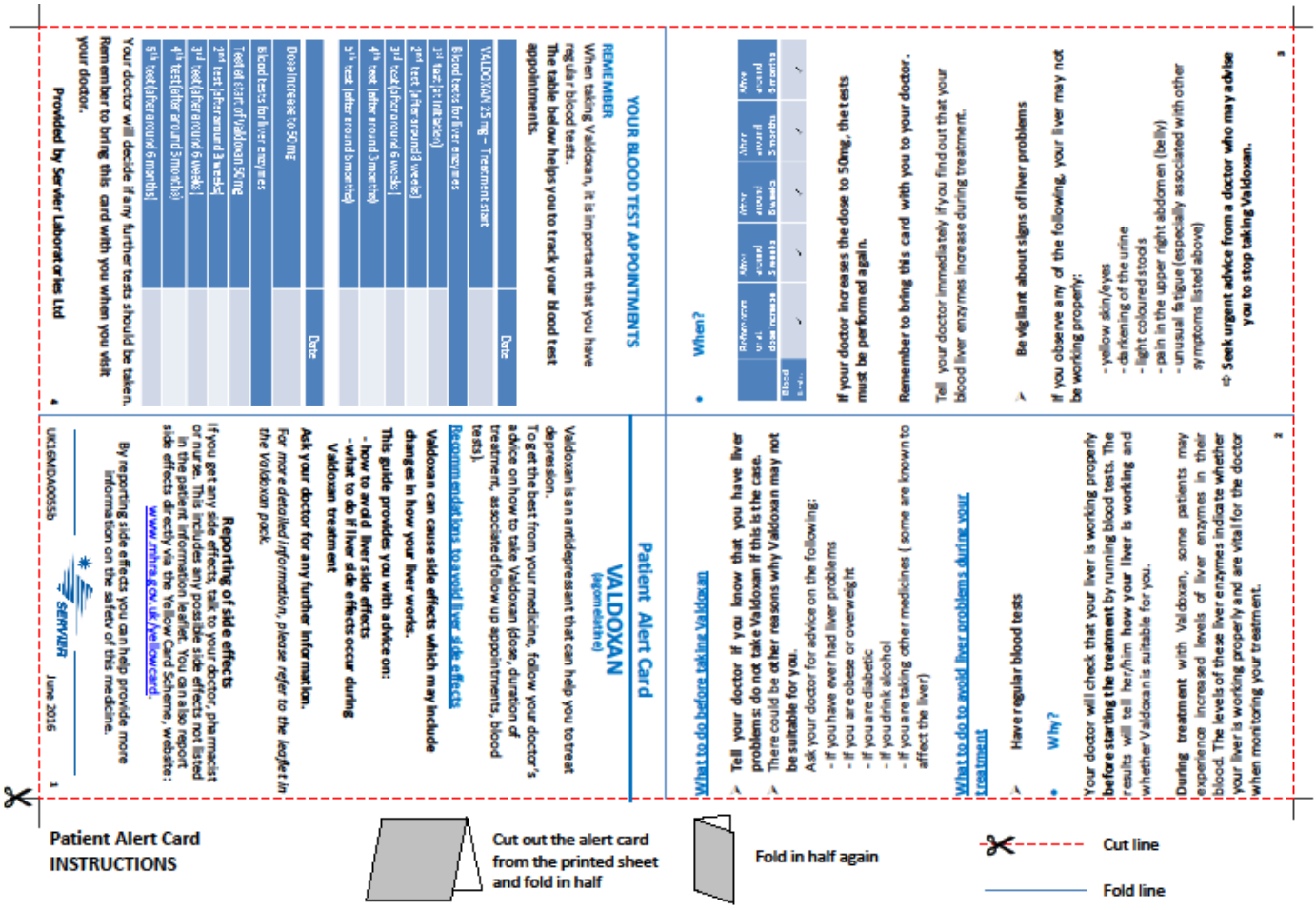
- Prescribe treatment as advised by specialist
- Undertake physical health monitoring (LFTs) as required after final monitoring visit
- Refer to specialist if any problems arise (lack of response or adverse effects)

Cost

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

Attachment 1: Patient Alert Card Valdoxan®(agomelatine)

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



Patient Alert Card INSTRUCTIONS

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

Fold in half again

Cut line

Fold line

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

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