Prescribing Information Sheet February 2019

**Agomelatine (Valdoxan ®) – third line for major depression**

**Formulary Status**

For the treatment of major depressive episodes in patients for whom other anti-depressants have not been efficacious or when potential or actual side effects of other anti-depressants prohibit use

GP may initiate or continue prescribing if initiated in secondary care

If initiated in secondary care then this service will continue to supply until all liver function tests have been completed. This will be 24 weeks following initiation or dose increase.

After that time point GPs will continue the prescription for the duration as advised by secondary mental health services

## Full prescribing guidance – Summary of Product Characteristics [www.emc.medicines.org.uk](http://www.emc.medicines.org.uk/)

**Indication and Dosage**

**Indication:** Agomelatine is licensed for the treatment of major depressive episodes in adults

**Presentation:** Tablet 25mg

**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, i.e. two 25 mg tablets, taken together at bedtime.

*Renal impairment:* No dose adjustment is required, however caution should be exercised when prescribing agomelatine to patients with moderate or severe renal impairment.

*Hepatic impairment:* Agomelatine is contraindicated in patients with hepatic impairment (see monitoring guidelines)

*Elderly:* Agomelatine should not be prescribed for patients 75 years of age or over

**CYP1A2 inhibitors**

Agomelatine is metabolised (90%) by CYP1A2.

Caution should be exercised when prescribing Agomelatine with moderate CYP1A2 inhibitors (e.g. propranolol, enoxacin) which may result in increased exposure of agomelatine.

Co-administration of Agomelatine with potent CYP1A2 inhibitors (e.g. fluvoxamine, ciprofloxacin) is contraindicated.

**Monitoring of liver function**

**Before starting treatment**

Treatment with Agomelatine should only be prescribed after careful consideration of benefit and risk in patients with hepatic injury risk factors e.g.:

- obesity/overweight/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.

Baseline liver function tests should be undertaken in all patients and treatment should not be initiated in patients with baseline values of ALT and/or AST >3 X upper limit of normal. Caution should be exercised when Agomelatine is administered to patients with pretreatment elevated transaminases (> the upper limit of the normal ranges and ≤3 times the upper limit of the normal range).

Patients should be supplied with an alert card, available on the eMC website: <https://www.medicines.org.uk/emc/rmm-directory/V>

**Frequency of liver function tests**

- before starting treatment

- and then:

- after around 3 weeks,

- after around 6 weeks (end of acute phase),

- after around 12 and 24 weeks (end of maintenance phase)

- and thereafter when clinically indicated.

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

Any patient who develops increased serum transaminases should have his/her liver function tests repeated within 48 hours.

**During treatment period**

Agomelatine treatment should be discontinued immediately if:

‐ patient develops symptoms or signs of potential liver injury (such as dark urine, light coloured stools, yellow skin/eyes, pain in the upper right belly, sustained new-onset and unexplained fatigue).

‐ the increase in serum transaminases exceeds 3 X upper limit of normal.

Following discontinuation of Agomelatine therapy liver function tests should be repeated until serum transaminases return to normal.

A chart summarising liver enzyme monitoring is available on the eMC website: <https://www.medicines.org.uk/emc/rmm-directory/V>

**End of treatment**

Agomelatine can be discontinued without down titration

**Adverse effects, special warnings and precautions for use (consult SPC for full list)**

**Pregnancy**

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.

**Breast-feeding**

It is not known whether agomelatine/metabolites are excreted in human milk. Available pharmacodynamic/toxicological data in animals have shown excretion of agomelatine/metabolites in milk (see section 5.3). A risk to the newborns/infants cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Agomelatine therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

**Bipolar disorder/ mania / hypomania**

Agomelatine should be used with caution in patients with a history of bipolar disorder, mania or hypomania and should be discontinued if a patient develops manic symptoms

**Suicide/suicidal thoughts**

Depression is associated with an increased risk of suicidal thoughts, self-harm and suicide (suicide-related events). This risk persists until significant remission occurs. As improvement may not occur during the first few weeks or more of treatment, patients should be closely monitored until such improvement occurs. It is general clinical experience that the risk of suicide may increase in the early stages of recovery.

Patients with a history of suicide-related events or those exhibiting a significant degree of suicidal ideation prior to commencement of treatment are known to be at greater risk of suicidal thoughts or suicide attempts, and should receive careful monitoring during treatment. A meta-analysis of placebo-controlled clinical trials of antidepressants in adult patients with psychiatric disorders showed an increased risk of suicidal behaviour with antidepressants compared to placebo, in patients less than 25 years old.

Close supervision of patients and in particular those at high risk should accompany treatment especially in early treatment and following dose changes. Patients (and caregivers of patients) should be alerted to the need to monitor for any clinical worsening, suicidal behaviour or thoughts and unusual changes in behaviour and to seek medical advice immediately if these symptoms present.

**Effects on ability to drive and use machines**

Agomelatine has minor influence on the ability to drive and use machines.

Considering that dizziness and somnolence are common adverse reactions, patients should be cautioned about their ability to drive or operate machines.

**Adverse reactions** were usually mild or moderate and occurred within the first two weeks of treatment. The most common adverse reactions were headache, nausea and dizziness.

## Drug Interactions (consult SPC for full list)

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 Valdoxan 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).

The combination of agomelatine and alcohol is not advisable.

**Continuation in patients > 75 years**

The SPC states that a placebo-controlled 8-week trial of agomelatine 25-50mg/day in elderly depressed patients (≥ 65 years, N=222, of which 151 on agomelatine) demonstrated a statistically significant difference of 2.67 points on HAM-D total score, the primary outcome. Responder rate analysis favoured agomelatine. No improvement was observed in very elderly patients (≥75 years, N= 69, of which 48 on agomelatine).

Tolerability of agomelatine in elderly patients was comparable to that seen in the younger adults.

If a patient is being successfully treated with agomelatine before they reach 75 years then it should be continued. If treatment becomes ineffective or no longer required then it should be stopped.

The patient can be referred back to KMPT for assessment if required.

Agomelatine should not be initiated in those over 75years of age.

**Contact details of Specialist team**

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