NHS Surrey Prescribers Information Leaflet: Agomelatine (Valdoxan®) 25 mg film-coated tablets. – Updated October 2014

Surrey Area Prescribing Committee Recommendation:

NHS Surrey Area Prescribing Committee reviewed agomelatine on January 7th 2011.
The committee members recommended the prescribing of agomelatine to be given GREEN status.
GREEN status drugs are those that can be initiated and continued in primary, secondary or tertiary care.

The committee approved green status on the basis that an information sheet is provided for prescribers recommending the place in therapy of agomelatine, and information on monitoring requirements.

Licenced Indication:

Treatment of major depressive episodes in adults.

Place in Treatment Recommended by Surrey Area Prescribing Committee:

Recommendations for agomelatine prescribing falls inline with NICE (Clinical Guidelines 90, (October 2009), Depression: the treatment and management of depression in adults (partial update of NICE clinical update 23)) and also as per NHS Surrey Depression and Anxiety Spectrum Disorders Web Care Pathway:
www.sabp.nhs.uk/moodhive

If first line treatment for depression (usually an SSRI with lowest acquisition cost such as citalopram, fluoxetine or sertraline) fails:

- *Due to Lack of Efficacy*: Dose of generic SSRI should be maximised **or** changed to a different antidepressant in same class (i.e. a different SSRI)
- *Due to Adverse Effect*: Change to different antidepressant in same class. ***OR***
- Change to antidepressant in different class dependent on patient acceptability of profile (see side effects section).
  Agomelatine is one of the options as an antidepressant in a different class.

Therefore agomelatine is recommended as a treatment option in the following circumstances:

- 2nd line where patients have not adhered to initial treatment because they have experienced side effects such as sexual dysfunction, weight gain, sleep disorders or other side effects.
- 3rd line where a patient's symptom of depression has not improved after taking at least two SSRIs or two antidepressants from different classes e.g. an SSRI and SNRI

Mode of action:

Agomelatine is a novel antidepressant, which should improve sleep without causing daytime sedation. Agomelatine works by re-synchronising circadian rhythms which are often disrupted in patients suffering with depression, and by simultaneously increasing noradrenalin and dopamine release specifically in the frontal cortex. Agomelatine has no influence on the extracellular levels of serotonin and therefore is not associated with serotonin side effects.

Written by: Pharmacy Department, Surrey and Borders Mental Health Partnership

Date: October 2014 Review Date: October 2017

Recommended Doses:

Adult over 18 years: 25mgs at bedtime. Increase if necessary after two weeks to 50 mgs at bedtime.

Decision of dose increase has to be balanced with a higher risk of transaminases elevation. Any dose increase to 50 mg should be made on an individual patient benefit/risk basis and with strict respect of LFT monitoring.

Older people: The efficacy and safety of agomelatine (25 to 50mg/day) have been established in elderly depressed patients (<75years). No effect is documented in patients ≥75 years. Therefore agomelatine should not be used by patients in this age group. No dose adjustment is required in relation to age.

Dosing Information:

Agomelatine should be taken at bedtime with or without food. Shift-workers should take agomelatine at their bedtime. If there is no improvement in symptoms after two weeks, the prescriber may consider increasing the dose to 50mgs (two tablets) at bedtime. Agomelatine is not known to be addictive.

Patients should be treated for at least six months after they are free of symptoms of depression.

Side Effects

Adverse reactions were usually mild or moderate and occurred within the first two weeks of treatment. The most common adverse reactions were nausea, dizziness, headache, somnolence, insomnia, migraine, diarrhoea, constipation, upper abdominal pain, anxiety, hyperhidrosis, back pain and fatigue. These adverse reactions were usually transient and did not generally lead to cessation of therapy.

Comparison of side effects of medication used for depression and anxiety spectrum disorders can be found at http://www.surreyhealth.nhs.uk/SERVICES/PROFESSIONALS/dpc/Documents/D3.3a3.pdf

Patient Monitoring:

The EMEA/ SPC require patients to have liver function monitoring. Monitoring should take place at baseline when treatment starts, then after at three, six, 12 and 24 weeks of treatment, and then when increasing the dose at the same time intervals as already stated. Increases in LFTs are rare. If LFTs do rise >3x upper level of normal, treatment should be discontinued. Monitor LFTs until they return to normal.

Agomelatine should be immediately discontinued 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, or if an increase in serum transaminases in liver function tests exceeds 3 times the upper limit of normal. 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-alcoholic fatty liver disease; substantial alcohol intake or use of concomitant medicines associated

Can agomelatine be stopped suddenly?

Agomelatine maybe stopped abruptly if necessary or if switching to alternative treatment (refer to stopping and swapping document http://www.surreyhealth.nhs.uk/SERVICES/PROFESSIONALS/dpc/Documents/D3.31a.pdf)

Interactions:

Agomelatine has few clinically relevant drug interactions.

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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. Potent CYP1A2 inhibitors, e.g. fluvoxamine and ciprofloxacin should not be prescribed with agomelatine.

Combination with potent CYP1A2 inhibitors is contraindicated. Caution should be exercised when prescribing agomelatine with moderate CYP1A2 inhibitors (*e.g.* propranolol, grepafloxacin, enoxacin) which may result in increased exposure of agomelatine.

Please refer to Summary of Product Characteristics for full details:
http://www.medicines.org.uk/EMC/medicine/21830/SPC/Valdoxan/

The Depression and Anxiety Spectrum Care pathway has been developed jointly between NHS Surrey (PCT) and Surrey and Borders NHS Foundation Trust. It is a web based pathway.

The pathway has been developed to improve the management of depression and anxiety spectrum disorders (generalised anxiety, panic, social phobia, post-traumatic stress and obsessive compulsive disorders). The main purposes of developing this pathway were to:

- Improve recognition and diagnosis
- Educate about appropriate treatment choices and management of lack of efficacy and/or tolerability issues
- Improve the overall management to remission of symptoms and restoration of normal function
- Improve the appropriateness of referrals to secondary care

The website can be accessed at: http://www.sabp.nhs.uk/moodhive