Ipswich and East Suffolk Clinical Commissioning Group

Suffolk Mental Health Partnership NHS Trust
Drug & Therapeutics Committee
New Medicine Report (Adopted by the CCG until review and further notice)

Medicine	Agomelatine (Valdoxan, Servier)
Document status	Agreed at Suffolk D&T 18th February 2009
Date of last revision	22nd July 2009
Traffic light decision	Double Red - Prescribing not supported in either general practice or secondary/tertiary care
Prescribers rating	5 - Judgement reserved
Mechanism of action	Agomelatine is a synthetic analogue of the hormone melatonin, and strongly binds to and stimulates the activity of melatonin MT1 and MT2 receptors, normalising disturbed circadian rhythms and disrupted sleep-wake cycles. (Melatonin regulates circadian rhythms, including sleep-wake cycles.) Disturbances in circadian rhythms have been implemented in the development of mood disorders. Agomelatine is also a serotonin-receptor antagonist and binds to and inhibits the activity of serotonin 5HT-2C receptors. This antagonism is associated with antidepressant and anti-anxiety activity, and increases slow-wave sleep. Agomelatine does not affect the uptake of serotonin, noradrenaline or dopamine. The inhibition of 5HT-2C receptors increases noradrenaline and dopamine in the frontal cortex and may contribute to agomelatine's antidepressant activity.
Indication	Treatment of major depressive disorders in adults
Dosage	25mg increasing to 50mg daily
Treatment alternatives	SSRIs
Place in therapy	The summary of positive opinion for agomelatine granted by the European Medicines Agency in November 2008 states that the benefits with agomelatine are its superiority over placebo in the treatment of depression in both short-term and long-term studies, although not in all trials, as well as its different safety profile (lack of clinically relevant weight gain, low risk of sexual dysfunction, low incidence of gastro-intestinal reaction, absence of discontinuation symptoms and overall incidence rates of adverse events not different from placebo). Agomelatine showed statistically significant superiority over placebo in the short-term treatment of depression, although not in all trials. A meta-analysis of the six pivotal short-term studies resulted in an overall estimate of the difference between agomelatine and placebo of 1.5 on the HAM-D with a 95% confidence interval [0.80, 2.22]. Studies also showed that agomelatine 25 mg is probably less efficacious than other antidepressants. With regard to relapse prevention, one study failed to demonstrate a difference in time to relapse. The maintenance of antidepressant efficacy was demonstrated in a second relapse prevention study. Despite the large number of clinical trials with agomelatine in patients with moderate to severe depression, its place in therapy is not clear. Longer term

	studies are required to determine whether it has a consistently favourable effect on symptoms of depression, sleep and sexual dysfunction, and how it compares with the drugs of choice for depression, the SSRIs. Current NICE Guidance recommends the use of an SSRI antidepressant as first line treatment of patients with moderate to severe depression, as they are as effective as tricyclic antidepressants and less likely to be discontinued due to side effects. Generic versions, such as fluoxetine and citalopram, would be reasonable choices. This guidance was issued in April 2007 and does not include agomelatine: the expected review date for the guidance was December 2008. NICE Guidance recommends that when treating a patient with moderate-severe depression, the antidepressant dose should be titrated to the recognised therapeutic dose and the efficacy of this dose assessed over 4-6 weeks. If this is effective, treatment should be continued for a further 4-6 months, or longer in patients with recurrent depression, at the full treatment dose.
Future alternatives	None known
Evidence for use	A number of studies with agomelatine have been conducted in patients with moderate to severe depression: ♦ Three short term (6 week) placebo-controlled studies. ♦ One short term (6 week) comparator (sertraline)-controlled study. ♦ One long term (24 week plus 20 week) placebo-controlled study. ♦ One study evaluating discontinuation symptoms after 12 weeks, compared with those seen with paroxetine. ♦ One study of the effects on sexual function, compared with those seen with venlafaxine. ♦ Two studies of the effects of agomelatine on sleep, one placebo controlled, one compared with venlafaxine. Three short term (6 week studies) have compared the antidepressant effects of agomelatine with placebo. Significantly higher response rates were seen with agomelatine treatment (61.5%, 49.1% and 54.3%) compared with placebo (46.3%, 34.3% and 35.3% respectively). A response to agomelatine was seen as early as week two. One study was a dose-ranging study. In one of the shorter studies the symptoms of depression improved to a greater extent with agomelatine, as shown by lower HAMD scores at endpoint, compared with those treated with placebo, both in the intention-to-treat (ITT) population (14.1 vs. 16.5, p=0.026), those who had a dose increase (17.5 and 20.4, p=0.045), and those with severe depression (14.4 vs. 17.3, p=0.024). In another of the shorter studies, greater improvements were seen in those in the ITT population treated with agomelatine, with a between treatment difference in the HAMD total score at week 6 of 3.44 (p=<0.001). For those who were severely depressed the difference was 3.60, p=0.002. One short term study (6 weeks) compared the efficacy of agomelatine with sertraline. Both treatments significantly reduced symptoms of depression. By six weeks the HAMD scores had decreased from 26.1 to 10.3 in the agomelatine group and from 26.5 to 12.1 in the sertraline group (difference 1.68, p=0.031). There was no significant difference between the two

	treatments in response rates, though a higher responder rate was seen with agomelatine treatment (70%) than sertraline (61.5%). The time to falling asleep was reduced with agomelatine (from 22.5 to 18.9 minutes) but increased with sertraline (from 23.48 to 27.75 minutes), and sleep efficiency favoured agomelatine (78.85% compared with 75.70% with sertraline). Improvements in sleep measurements were seen as early as after one week of treatment with agomelatine. The clinical benefits of these differences following longer term treatment have not been studied. There is one longer term, placebo-controlled study which studied the efficacy of agomelatine on preventing relapse. An initial open label 8-10 week phase determined the agomelatine dose, during which the HAMD scores fell from 27 to ~6. This was followed by a 24 week placebo-controlled phase. After this treatment period patients could continue with agomelatine treatment for another 20 weeks. The difference seen after 24 weeks of treatment in the proportion of patients who suffered with a relapse (21.7% on agomelatine vs. 46.6% on placebo, p=0.0001) was sustained after 10 months of treatment (23.9% vs. 49.9%, p<0.001), indicating continued efficacy of agomelatine. Discontinuation symptoms after 12 weeks of treatment occurred to a significantly lower extent with agomelatine compared with paroxetine. Both treatments were stopped abruptly in a proportion of patients in each treatment group after 12 weeks of therapy. Discontinuation symptoms occurring over the first and second week after stopping treatment were compared within each group. After the first week, no statistically significant difference in the number of emergent discontinuation symptoms between patients continuing or discontinuing agomelatine were seen (3.0 vs. 4.4, p+0.25), whilst significant differences were seen in the number of symptoms reported by those discontinuing or continuing paroxetine (7.3 vs. 3.5, p<0.001). No differences were seen after the second week. Stopping paroxetine abruptly after this length of treatment is well known to result in discontinuation symptoms, which is why slow withdrawal is recommended. The effects of agomelatine on sexual function were compared with those of venlafaxine. What the trial results indicate is that treatment-emergent sexual dysfunction was significantly less prevalent among sexually-active patients who received agomelatine compared with venlafaxine. The main differences were in the percentage of patients with reduced desire and orgasm: 4.3% and 9.1% with agomelatine and 21.2% and 18.5% with venlafaxine. This reflects the pharmacological differences between the two treatments: dopamine and noradrenaline can cause diminished feelings of desire and arousal. It should be noted that, as for other antidepressant trials, no sexually related adverse events were recorded, but instead they were reported via indirect questioning. Two studies have analysed the effects of agomelatine on sleep. One open label, 6-week study used polysomnography to monitor sleep waves. These results show that agomelatine can increase sleep efficiency (from 88% to 93%) and slow-wave sleep, as shown by the increase in the amount of stage 3-4 sleep (from 15.9% to 19.4%), though it has no effect on REM sleep, which can be poor in patients with depression, stage 1 or 2 sleep and time to sleep onset. Total sleep time increased by 30 minutes. The second sleep study compared the effects of agomelatine to venlafaxine on subjective sleep variables over 6 weeks. The main assessment tool was

	the Leeds Sleep Evaluation Questionnaire, which uses a visual analogue scale: all scores are in 'mm'. Significant between-group differences in a number of items at the last visit were in favour of agomelatine compared with venlafaxine, such as the getting to sleep score (70.5 vs. 64.1), the quality of sleep score (72.5 vs. 66.9), the sleep awakening score (66.9 vs. 62.0) and the integrity of behaviour score (66.2 vs. 62.0). However, the lack of baseline data makes it difficult to know whether the improvements seen as early as week 1 were due to the treatment effect or because of a difference in the groups at baseline. The authors do not make any comments on the changes from week 1 for the within-group scores: similar improvements in the quality of sleep score were seen in both groups (11.3mm increase for agomelatine vs. 11.2mm increase for venlafaxine); the improvements in sleep awakening scores were slight better with agomelatine (9.5mm vs. 8.2mm) whilst the integrity of behaviour scores were improved by a greater extent with venlafaxine (12.6mm vs. 7.6mm). The venlafaxine dose was not titrated above 150mg/day so it is possible that some patients were not adequately treated. Longer studies are necessary to determine whether the effects of agomelatine on sleep are sustained.
Points for consideration	There has been an increase in the response to placebo in antidepressant trials, which could reflect a tendency for the trials to be carried out on people with mild depression that may spontaneously resolve. The difference between the drug and the placebo is thought to be greater with increasing degrees of severity of depression. This can be difficult to demonstrate with mean changes in depression rating scale scores, as the ranges may overlap. NICE considers a weighted mean between-group difference of at least three points or a standardised mean difference of at least 0.5 in the Hamilton Depression (HAMD) rating scores to demonstrate clinical efficacy. The overall effect of new-generation antidepressants, based on both published and unpublished data, has been shown to be below the NICE recommended criteria for clinical significance, in all but the most severely depressed patients (HAMD scores ≥28). Efficacy only reached clinical significance in trials involving extremely depressed patients, and this was due to a decrease in the response to placebo rather than an increase in the response to the medication.
Cautions / side effects	Agomelatine is metabolised primarily by cytochrome P450 -1A2 (CYP1A2). Drugs which inhibit CYP1A2 such as fluvoxamine will decrease the metabolism of agomelatine and cause high serum concentrations. Drugs which induce CYP1A2, such as omeprazole, could be expected to decrease agomelatine concentrations but the clinical significance of this is unclear. No difference between dosing, effectiveness or safety of agomelatine between older and younger adults has been reported from trials. There are limited data on the use of agomelatine in children, and no specific data have been reported on the safety of it during pregnancy, though animal studies have reported no risks. The most common side effects observed are headache, dizziness, somnolence, insomnia, migraine, nausea, diarrhoea, constipation, upper abdominal pain, hyperhydrosis, back pain, fatigue and anxiety. Of note, abnormalities of liver function tests (transaminase elevation > 3xULN), were also common. Hepatitis (cytolytic) and transaminase elevation > 10 x ULN have been rarely reported. Therefore, monitoring of liver function tests is required during treatment at all doses.

<table>
<tr><td></td><td>A pharmacovigilance plan for agomelatine, as for all medicinal products, will be implemented as part of the marketing authorisation.</td></tr>
<tr><td colspan="2"></td></tr>
<tr><td>Costs</td><td>The cost of agomelatine is not yet known.
Cost of SSRIs is set out below. Prices are for generic drugs unless otherwise stated.
<table>
<tr><td>Drug</td><td>Dose</td><td>Cost
(Drug Tariff Dec 2008)</td></tr>
<tr><td>Amitriptyline</td><td>75mg, increased to 150-200mg daily</td><td>28x25mg: £0.97
28x50mg: £1.12</td></tr>
<tr><td>Citalopram</td><td>20mg, increased to 60mg daily</td><td>28x20mg: £1.25
28x40mg: £1.46</td></tr>
<tr><td>Escitalopram</td><td>10mg, increased to 20mg daily</td><td>28x10mg: £14.91 (Cipralex)
28x20mg: £25.20 (Cipralex)</td></tr>
<tr><td>Fluoxetine</td><td>20mg, increased to 60mg daily</td><td>30x20mg: £1.02
30x60mg: £55.72</td></tr>
<tr><td>Fluvoxamine</td><td>50-100mg, increased to 300mg daily</td><td>30x50mg: £6.80
30x100mg: £8.34</td></tr>
<tr><td>Paroxetine</td><td>20mg, increased to 50mg daily</td><td>28x20mg: £2.92
28x30mg: £6.46</td></tr>
<tr><td>Sertraline</td><td>50mg, increased to 100mg daily</td><td>28x50mg: £1.37
28x100mg: £1.80</td></tr>
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<tr><td>Potential number of patients in Suffolk PCT</td><td></td></tr>
<tr><td></td><td>Suffolk population >18 years = 457,718

The point prevalence for major depression among 16–65-year-olds in the UK is estimated to be 21/1000 (males 17/1000, females 25/1000). If the less specific and broader category of 'mixed depression and anxiety' is included, these figures rise dramatically to 98/1000 (males 71/1000, females 124/1000)

Applying the point prevalence above to the adult population in Suffolk, there could be 9612 people with major depression.</td></tr>
<tr><td colspan="2"></td></tr>
<tr><td>Comments sought from</td><td>No comments sought prior to meeting</td></tr>
<tr><td colspan="2"></td></tr>
<tr><td>Decision review date</td><td>TBC</td></tr>
</table>

References

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