

agomelatine, 25mg film-coated tablets (Valdoxan®) (No.564/09)
Servier Laboratories UK Ltd

09 October 2009

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

ADVICE: following a full submission

agomelatine (Valdoxan®) is not recommended for use within NHS Scotland for the treatment of major depressive episodes in adults.

When used in a flexible dosing schedule, agomelatine significantly reduced the symptoms of depression and increased the number of patients who responded to treatment compared with placebo. There are limited comparative data against existing antidepressants and the results of such comparisons are variable.

The manufacturer did not present a sufficiently robust economic analysis to gain acceptance by SMC.

The licence holder has indicated their intention to resubmit.

Overleaf is the detailed advice on this product.

**Chairman,
Scottish Medicines Consortium**

Indication

Treatment of major depressive episodes in adults.

Dosing information

Agomelatine 25mg daily taken orally at bedtime.

After two weeks of treatment, if there is no improvement of symptoms, the dose may be increased to 50mg once daily taken at bedtime.

Patients with depression should be treated for a sufficient period of at least 6 months to ensure that they are free of symptoms.

Product availability date

1 June 2009

Summary of evidence on comparative efficacy

Agomelatine has a novel pharmacological mechanism of action. It is an agonist at melatonin MT₁ and MT₂ receptors and has serotonin receptor (5-HT_{2C}) antagonist properties.

The clinical evidence presented assesses agomelatine in moderate to severe depression in mixed patient populations. Patients had both single and recurrent episodes and only some patients had received a selective serotonin reuptake inhibitor (SSRI) or other specific antidepressant treatment previously. However, the health economic case is based on using agomelatine as an alternative to venlafaxine in patients who had not responded to first-line treatment with SSRIs.

A total of 14 studies were included in the submission; one phase II dose ranging study, seven phase III studies (the main registration studies; two short term, placebo-controlled flexible dosing studies with optional 46-week extension, three short term placebo- and positive-controlled, fixed dose studies with optional 18 week extension period and two placebo-controlled long-term relapse studies); plus one recently completed active-comparator study. The primary outcome measure in all these studies was depression, measured using the Hamilton Rating Scale for Depression (HAM-D), a 17-item scale with score range 0 to 52 (higher scores indicating more severe depression). In addition four active-comparator studies (considered supportive registration studies, which did not have depression as their primary outcome) were included; one study with onset and quality of sleep as an outcome, one study with sexual function as an outcome, one study with rest/activity circadian rhythms as an outcome and one discontinuation study; plus one 'partial responder at week four' study.

Moderate and severe depression is a continuum and although there is no universally accepted threshold, scores ≥ 25 to 28 on the HAM-D scale are generally used as a measure of severe depression. The HAM-D scores were also used to calculate the secondary outcomes of response (defined as patients with a 50% or more decrease in the HAM-D score from baseline) and remission (defined as a HAM-D score < 6). The placebo-controlled studies included both in- and outpatients with a current episode (either single or recurrent) of moderate or severe major depressive disorder (MDD), minimum HAM-D score of 22 and requiring antidepressant treatment.

In the two 6-week, placebo-controlled, flexible-dosing studies, a total of 450 patients were randomised to placebo or agomelatine 25mg daily (with double-blind increase to 50mg daily at week 2 if response insufficient). Over 95% of patients were outpatients, and in both studies agomelatine significantly reduced the HAM-D score compared with placebo; treatment difference 3.44 (95% confidence interval [CI]: 1.63 to 5.26) and 2.30 (95%CI: 0.28 to 4.31). Significantly more patients achieved a response in the agomelatine group, (54% versus 35% and 49% versus 34%, for agomelatine and placebo respectively) with a quicker time to first response ($p=0.008$ and $p=0.032$).

In three, fixed-dose, double-blind, placebo-controlled, 6-week studies, fluoxetine and paroxetine, both 20mg daily, were used as an internal validators. The sensitivity of the studies was demonstrated by comparing the outcomes of agomelatine versus placebo to either fluoxetine or paroxetine versus placebo. The primary outcome was the HAM-D total score at week 6.

The sensitivity of two of these studies was not demonstrated, perhaps because in both studies the placebo relapse rate was unusually low. In the third study, fluoxetine was shown to be significantly better than placebo for the primary endpoint and therefore assay sensitivity was demonstrated. Although there was no significant difference between agomelatine 25mg and placebo at six weeks, there was a significant difference between both agomelatine and placebo and fluoxetine and placebo in the number of patients who were responders at six weeks but relapsed by week 24 (19%, 36% and 20% for agomelatine, placebo and fluoxetine).

In a meta-analysis including the five placebo-controlled studies described above plus the dose ranging study, an overall treatment effect of about 1.5 on the HAM-D total score in favour of agomelatine over placebo was observed. However, if only the two flexible dosing studies, which more closely reflect the licensed regimen for agomelatine, are combined there is an overall treatment effect of 2.9.

In the one phase III, double-blind, active comparator study measuring depression as a primary outcome, 504 severely depressed patients with HAM-D score of ≥ 25 were randomised to agomelatine 25mg daily (increased to 50mg daily at week 2 if required) or fluoxetine 20mg (increased to 40mg at week 4 if required) for eight weeks with an extension to 24 weeks in patients whose depression had improved. The aim of this study was to demonstrate the non-inferiority of agomelatine relative to fluoxetine using a fixed pre-defined non-inferiority margin of 1.5. If non-inferiority was demonstrated, the superiority of agomelatine was to be tested. The primary outcome, change from baseline in HAM-D total score at week 8, was -17.3 ± 7.3 and -16.0 ± 8.4 in the agomelatine and fluoxetine groups. Agomelatine was shown to be not only non-inferior to fluoxetine ($p < 0.001$) but also superior ($p = 0.03$) for the primary endpoint. There was no significant difference between the groups in the number of responders at week 8 (72% and 64%, for agomelatine and fluoxetine, respectively) or in the number of patients in remission.

The long-term efficacy was tested in two phase III, double-blind, placebo-controlled studies in patients with a HAM-D score of ≥ 22 . In both studies, patients were treated with open-label agomelatine for 8 to 10 weeks then responding patients were randomised to double-blind treatment with agomelatine or placebo for up to 24 weeks. In the first study, including 367 in- and outpatients, the primary outcome was the HAM-D total score, mainly expressed as time to relapse estimated using Kaplan Meier survival analysis. At week 34, there was no significant difference between agomelatine 25mg and placebo in the incidence of patients having a relapse over time (26% versus 24%). In a post hoc analysis of more severe patients (HAM-D > 25), agomelatine reduced the percentage of relapse compared to placebo (21% versus 31%) at 34 weeks and at 52 weeks this difference was significant ($p = 0.046$).

In the second study, including 339 outpatients, agomelatine dosing was flexible with patients able to increase their dose of agomelatine to 50mg at week 2, if required. To be eligible to be randomised at week 8 or 10, patients were required to have a HAM-D score of ≤ 10 and the primary outcome was relapse (defined as a HAM-D score of ≥ 16). The percentage of patients with a relapse was lower in the agomelatine group at 34 weeks (21% versus 41% for placebo), and the incidence and risk of relapse over time were significantly lower in the agomelatine group ($p=0.0001$).

Four active comparator studies looked at some alternative primary outcomes. In a phase III, double-blind study, 332 outpatients with MDD (HAM-D score ≥ 20) were randomised to either agomelatine 25mg to 50mg or venlafaxine 75mg to 150mg for six weeks. The primary outcome was the Leeds Sleep Evaluation Questionnaire (LSEQ) "getting to sleep" score completed during the first six weeks of the study but this primary analysis was only undertaken if the HAM-D scores were not significantly different between the groups at six weeks. No significant difference in any parameter of depression was noted at six weeks between treatments and therefore the analysis of sleep was undertaken. Over the six-week period the mean LSEQ "getting to sleep" improved in both groups with a significantly better improvement from week one onwards in the agomelatine group compared with the venlafaxine group (last post baseline value; 70.5 ± 16.8 mm versus 64.1 ± 18.2 mm, $p=0.001$). For the secondary outcome agomelatine reduced the HAM-D total score from 25.9 ± 3.2 to 9.9 ± 6.6 and venlafaxine from 26.0 ± 3.3 to 11.0 ± 7.4 with response rates of 76% and 71%, respectively.

In a 12 week comparison of agomelatine 50mg and venlafaxine 150mg daily in 277 severely depressed patients, there was no significant difference in stable remitted patients, in the total scores for sexual functioning between the agomelatine and venlafaxine groups. However, significantly more patients in the venlafaxine group reported a deterioration of at least one point in sexual functioning scores at 12 weeks (15.7% vs 7.3%).

Other data were also assessed but remain commercially confidential.*

Summary of evidence on comparative safety

Agomelatine has a different safety profile from other available antidepressants. In the placebo-controlled studies there was little or no difference between the adverse event rates reported for agomelatine and placebo within the individual trials, or when pooled and the majority of adverse events were mild to moderate. The most frequently reported included headache, nausea and dizziness.

There were no significant differences from placebo in blood pressure, heart rate, electrocardiogram and weight but in one study potentially significant hepatic changes were observed in two patients, compared to no patients in the placebo group. In the long term extension studies headache was the most frequently reported treatment-related adverse event.

Some comparative safety data are available for agomelatine with paroxetine and fluoxetine. In a 12-week double-blind safety study, discontinuation symptoms of patients treated with paroxetine and agomelatine were compared at one and two weeks after treatment cessation and were also compared with patients who had continued on treatment. There was no difference in discontinuation symptoms in patients who discontinued agomelatine and those who continued on treatment at one week. Discontinuation emergent symptoms were reported significantly more frequently at one week in the paroxetine group than the agomelatine group ($p<0.05$), including insomnia, dreaming, muscle aches, dizziness, nose

running, chills, nausea and diarrhoea. At two weeks there was no difference between treatments.

In the comparison with fluoxetine, the most frequent adverse events were gastrointestinal disorders (26.4% and 26.6% in the agomelatine and fluoxetine groups), nervous system disorders (24.0% and 20.2%) and infections/infestations (13.6% and 8.4%). In the agomelatine group, the most frequent emergent adverse events were headache, nausea and somnolence with a lower incidence than in the fluoxetine group for nausea (8.0% versus 11.4%, respectively) and higher for headache (16.0% versus 11.4%) and somnolence (6.0% versus 3.4%).

The major concern is the high frequency of elevated aminotransferases and is included in the Risk Management Plan agreed by the European Medicines Agency. The mechanism of agomelatine liver injury is unknown. Consequently, liver function tests should be performed in all patients: at initiation of treatment and then periodically after six weeks, after 12 and 24 weeks and thereafter when clinically indicated.

Summary of clinical effectiveness issues

Despite the clinical studies available, there are limited robust data comparing agomelatine with existing antidepressants using antidepressant efficacy as a primary outcome. There is one direct comparison with fluoxetine in which agomelatine was shown to be superior, although it should be noted that while agomelatine was titrated to its maximum dose fluoxetine was only titrated to 40mg daily. However, fluoxetine is an established first-line treatment, and first-line use is not the expected positioning of agomelatine so this study does little to help establish the position of agomelatine in therapy. In the study with venlafaxine on the effects of treatment on sleep parameters, depression was a secondary outcome and no significant difference was shown between treatments, but the dose of venlafaxine used in this study is at the lower end of the dosage range that might be expected in practice. This may have underestimated reported adverse events for venlafaxine but may also have underestimated its efficacy.

The study outcomes have been mixed with both positive and negative results against placebo. This is not an unusual result in studies of antidepressants as the additional monitoring, support and counselling inherent in clinical studies is an active treatment in itself and can, as observed in some agomelatine studies, lead to high placebo response.

The HAM-D rating score used to measure the primary outcome of depression in most studies has a scale of 0 to 52. There is no consensus as to what constitutes a clinically significant difference between treatments, although the National Institute for Health and Clinical Excellence (NICE) required a difference of at least three points as a measure of clinical importance. The outcomes in the agomelatine studies fall between two and four points. While the meta-analysis of all the placebo-controlled studies reported a difference of 1.5 when only the two flexible dosing studies were combined the difference was 2.9. In addition, the number of responders in both these studies falls within the NICE definition of clinical importance for this outcome.

In a meta-analysis combining the secondary outcome of depression in the three active comparator studies which used agomelatine within its licensed regimen, the relative risk of response in agomelatine patients compared with venlafaxine, sertraline and fluoxetine patients, favoured agomelatine. However it should be noted that while agomelatine was titrated to the maximum licensed dose, the comparators in these studies were not.

There are still a number of uncertainties around the use of agomelatine including the lack of consistently demonstrated clinical benefit, the magnitude of that benefit, whether increasing the dose to 50mg offers additional benefit - as in the partial responder study there was no significant difference in the 25mg and 50mg groups in the number of responders at the end of the double-blind period and in one of two relapse studies no difference was shown between agomelatine and placebo.

The differing safety profile that agomelatine offers compared to other available antidepressants, the lack of clinical weight gain, low risk of sexual dysfunction and absence of discontinuation symptoms may provide a real advantage for some patients but there is still a concern over the high frequency of elevated aminotransferases and the mechanism of liver injury.

Summary of comparative health economic evidence

The manufacturer presented a cost-utility analysis over a 24 week time horizon comparing agomelatine with venlafaxine in patients with MDD after initial treatment failure. Clinical data on response to treatment, as measured by change in HAM-D from baseline, were taken from a comparative study of agomelatine and venlafaxine. Resource use and utility values were estimated from a burden of illness study of 245 patients with MDD in Scotland. Quality of life data were collected in the burden of illness study using EQ-5D and severity of depression was assessed using HAM-D. Resource use and utility values were then estimated for responders, non-responders and baseline according to the average HAM-D scores for each group. Response was measured after 6 weeks and responders were assumed to remain on treatment for the duration of the model and non-responders moved to subsequent treatment with mirtazapine. The base case cost per QALY was estimated to be £26,382 based on an increased cost of £122 and a QALY gain of 0.005.

There were some weaknesses with the clinical data used in the economic evaluation. In particular, the use of the secondary endpoint of change in HAM-D scores from baseline, where the difference between the two treatment groups did not reach statistical significance but there was a numerical difference in response rate, was the basis of the QALY gain in the model. In addition, a large proportion of patients in the clinical trial did not reflect the patient population specified in the niche i.e. having failed on an SSRI, and the dose of venlafaxine in the study may be lower than used in practice.

The sensitivity analysis showed the results were particularly sensitive to changes in the responder rates used in the model. This was important given the weaknesses with the clinical data outlined above. Using the upper 95% confidence interval for venlafaxine responders in the scenario increased the ICER to £1.3m/QALY. When the lower 95% confidence interval for agomelatine responders was used, venlafaxine was the dominant treatment. When the response rates were equalised, the ICER was £231k/QALY.

The only comparator drug considered in the economic analysis was venlafaxine. This is just one of a number of medicines which could be introduced following failure of first-line therapy, most of which are considered as clinically of similar efficacy and many of which are cheaper than venlafaxine. The true cost-effectiveness of agomelatine at this stage of therapy would require options other than venlafaxine to be considered.

The utility value for responders may be on the high side. This could overestimate the utility gain from patients responding to treatment, which may bias the analysis in favour of agomelatine. The results were relatively sensitive to changes in the responder utility value.

However, no adverse event costs or quality of life loss were included in the model which may be a conservative assumption.

Given the weaknesses with the economic analysis, the economic case was not demonstrated.

Summary of patient and public involvement

Patient Interest Group Submission: Depression Alliance Scotland

Additional information: guidelines and protocols

The National Institute for Health and Clinical Excellence (NICE): Clinical Guideline 23, Depression: management of depression in primary and secondary care (2007).

This guideline makes recommendations for the identification, treatment and management of depression for adults aged 18 years and over, in primary and secondary care. The guideline recommends that for routine care of moderate to severe depression in primary care, a selective serotonin reuptake inhibitor should be used, in particular a generic form. Switching to another antidepressant should be considered if there has been no response after a month or in situations where an antidepressant is poorly tolerated. These guidelines also highlight special considerations for switching to particular drugs; if switching to mirtazapine clinicians and patients should be aware that it can cause sedation and weight gain. For venlafaxine, cardiac and blood pressure monitoring is required and pre-existing hypertension needs to be properly controlled.

The guideline predates the availability of agomelatine.

Additional information: comparators

NICE published The Management of Depression in Primary and Secondary Care (clinical guideline 23) in December 2004 and it was updated in May 2007. It recommends the use of SSRIs for the first-line treatment of moderate to severe depression in primary care. Second line choices, in patients where there has been a limited response to initial treatment including a gradual increase in dose, are a different SSRI or mirtazapine. Alternatives include moclobemide, reboxetine, tricyclic antidepressants (except dosulepin), and venlafaxine, which may be considered in patients who have failed two adequate trials of alternative antidepressants.

Cost of relevant comparators

Drug	Dose regimen	Cost per year (£)
Agomelatine	25 to 50mg daily	501 to 1002
Duloxetine	60 to 120mg daily	360 to 721
Venlafaxine	75 to 375mg daily	243 to 976
Venlafaxine XL	75 to 225mg daily	292 to 878
Reboxetine	8 to 12mg daily	229 to 344
Mirtazepine	15 to 45mg daily	145
Paroxetine	20 to 50mg daily	34 to 110
Citalopram	20 to 60mg daily	16 to 49
Sertraline	50 to 200mg daily	18 to 43
Fluoxetine	20 to 60mg daily	12 to 37

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 8 and 30 June 2009.

Additional information: budget impact

Based on an estimated 150 patients receiving a course of 24 weeks treatment in year 1 rising to 749 patients in year 5, the manufacturer estimated the gross drug budget impact at £29k in year 1 rising to £186k in year 5. Assuming that venlafaxine would be the treatment displaced, the net drug budget impact was estimated to be £13k in year 1 and £84k in year 5.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

This assessment is based on data submitted by the applicant company up to and including 01 October 2009.

Drug prices are those available at the time the papers were issued to SMC for consideration. These have been confirmed from the eVadis drug database.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal: <http://www.scottishmedicines.org.uk/>*

The undernoted references were supplied with the submission. The reference shaded grey is additional to those supplied with the submission.

Lemoine P, Guilleminault C, Alvarez E. Improvement in subjective sleep in major depressive disorder with a novel antidepressant, agomelatine: randomized, double-blind comparison with venlafaxine. *J Clin Psychiatry*. 2007 Nov;68(11):1723-32.

Montgomery SA, Kennedy SH, Burrows GD, Lejoyeux M, Hindmarch I. Absence of discontinuation symptoms with agomelatine and occurrence of discontinuation symptoms with paroxetine: a randomized, double-blind, placebo-controlled discontinuation study. *Int Clin Psychopharmacol*. 2004 Sep;19(5):271-80.

Kennedy SH, Rizvi S, Fulton K, Rasmussen J. A double-blind comparison of sexual functioning, antidepressant efficacy, and tolerability between agomelatine and venlafaxine XR. *J Clin Psychopharmacol*. 2008 Jun;28(3):329-33.

The European Medicines Agency (EMA). European Public Assessment Report (EPAR) for agomelatine (Valdoxan®), 20/11/08 EMA/H/C/000915. www.emea.europa.eu