Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
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NHS SCOTLAND

agomelatine, 25mg film-coated tablets (Valdoxan®) SMC No. (564/09)

Servier Laboratories UK Ltd

06 August 2010

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 re-submission

agomelatine (Valdoxan®) is not recommended for use within NHS Scotland.

Indication under review: 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 no comparative data from clinical studies with existing second line antidepressants using depression as the primary outcome.

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 beincreased 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 mechanism of action. It is an agonist at melatonin MT_1 and MT_2 receptors and an antagonist at the serotonin receptor 5-HT_{2C}. It exerts its antidepressant effect without stimulating an increase in extra-cellular serotonin levels.

The company have proposed that SMC considers agomelatine when positioned after initial treatment failure with a selective serotonin reuptake inhibitor (SSRI). The clinical evidence base for agomelatine is in patients with moderate to severe depression, in both inpatients and outpatients, with both single and recurrent episodes but not all patients were previously treated with a selective serotonin reuptake inhibitor (SSRI) or other antidepressant.

A total of ten studies were included in the submission; two flexible dose placebo-controlled studies, two placebo-controlled long-term relapse studies and six active comparator studies. The primary outcome in the placebo-controlled studies, and one of the active comparator 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 the other five active comparator studies, depression was a secondary outcome with a number of different measures used as primary outcomes; two studies measured sleep parameters, one study sexual function, one study rest/activity circadian rhythms and one discontinuation study measured symptoms of withdrawal.

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 out-patients 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 an in-house meta-analysis of these two flexible dosing studies, an overall treatment effect of 2.93 on the HAM-D score in favour of agomelatine was observed.

In the one phase lll, 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.

Two phase lll, double-blind, placebo-controlled studies in patients with a HAM-D score of ≥22 tested the long-term efficacy of agomelatine and subsequent time to relapse following discontinuation of treatment. 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 inpatients and outpatients, the primary outcome was the HAM-D total score, 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 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 for randomisation 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 lll, 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 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% versus 7.3%).

In a 6 week double-blind study of agomelatine 25 to 50mg daily and sertraline 50 to 100mg daily in 313 outpatients with MDD, early changes in the rest/rhythm parameter led to a rapid improvement in sleep parameters in the agomelatine group. Agomelatine also reduced the secondary outcome of HAM-D score significantly more than sertraline (p=0.031).

*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 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 effects on blood pressure, heart rate, electrocardiogram and weight but in one study potentially significant hepatic changes were observed with agomelatine 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 in 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 at one week in patients who discontinued agomelatine and those who continued on treatment. 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, nervous system disorders and infections/infestations. In the agomelatine group, the most frequent 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 key safety issue is the higher frequency of elevated aminotransferases and this 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 6, 12 and 24 weeks and thereafter when clinically indicated.

Summary of clinical effectiveness issues

Agomelatine has a different mechanism of action from other antidepressants and has the potential to provide a better tolerability profile. The company has proposed that SMC considers the use of agomelatine in a subpopulation of the licensed population i.e. for use in both primary and secondary care after initial treatment failure with a generic SSRI. Despite the clinical studies available, there are limited robust data comparing agomelatine with second-line antidepressants using antidepressant efficacy as a primary outcome. There is one direct comparison with fluoxetine in which agomelatine was shown to be superior. However, fluoxetine is an established first-line treatment which can be prescribed generically as recommended in the National Institute for Health and Clinical Excellence (NICE): Clinical Guideline 90.

In the studies with venlafaxine, sertraline and escitalopram, all more appropriate comparators for the suggested positioning of agomelatine, the measure of depression was a secondary outcome. In each of these studies agomelatine was titrated to its maximum recommended dose when required, and although the comparator doses were increased, they were not titrated to the maximum recommended dose. This may have underestimated their reported adverse events but may also have underestimated their relative efficacy. An in-house meta analysis including three of the active comparator studies (fluoxetine, venlafaxine, sertraline), demonstrated that agomelatine significantly increased the probability of response compared with the pooled comparators (by 11%, p=0.0079) but this was a secondary analysis.

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 NICE required a difference of at least three points as a measure of clinical importance. In the in-house meta-analysis of the two placebo-controlled studies that represented the licensed indication and measured depression as the primary outcome, the reported difference between agomelatine and placebo was 2.93, which would suggest a borderline clinically significant outcome. However, other placebo-controlled studies, some of which did not have positive outcomes were excluded from this analysis, although arguably these studies were not representative of the licensed dose.

There are still a number of uncertainties around the use of agomelatine including the magnitude of the benefit compared with other second line antidepressant agents. However, the differing safety profile that agomelatine offers compared to other available antidepressants, including the lack of clinical weight gain, improved sleep quality, low risk of sexual dysfunction and absence of discontinuation symptoms, may provide an advantage for some patients.

There are still some concerns about the mechanism of liver injury and the number of patients who experience elevated transaminases with agomelatine treatment. Therefore the Summary of Product Characteristics recommends that liver function tests should be performed in all patients at initiation of treatment then periodically after 6 weeks (end of acute phase), 12 weeks and 24 weeks (end of maintenance phase) and thereafter when clinically indicated.

Summary of comparative health economic evidence

The manufacturer presented four cost-utility analyses comparing agomelatine with venlafaxine, fluoxetine, sertraline and escitalopram for the treatment of patients with major depressive episodes where an SSRI has been tried and failed. Each analysis was conducted using a common decision tree model over a 6 month time horizon. Clinical data used in the model related to the percentage of responders in each trial as measured by the change in HAM-D scores from baseline. Comparative trial data were available for each of the comparisons.

Resource use and utility values were measured from a burden of illness study involving 245 Scottish patients with moderate to severe MDD identified through primary care records. Patients in this study completed an EQ-5D and also provided details of their resource use. These data were used to conduct a regression analysis and establish the relationship between HAM-D scores, EQ-5D and resource use. For the fluoxetine comparison the utility values were taken from the literature as patients in the fluoxetine study had severe depression. Costs and disutilities associated with adverse events were included in the comparisons with venlafaxine (nausea) and sertraline (hyperhidrosis) as there was a statistically significant difference between treatments.

In the base case analysis the manufacturer estimated ICERs of £18,830 (increased cost of £152 and quality adjusted life year (QALY) gain of 0.008), £31,201 (increased cost of £246 and QALY gain of 0.008), £23,119 (increased cost of £227 and QALY gain of 0.0099) and £27,688 (increased cost of £137 and QALY gain of 0.005) for the comparisons with venlafaxine, fluoxetine, sertraline and escitalopram respectively.

The following issues were noted:

- There are some weaknesses with the clinical data used in the analysis. In particular, the majority of patients in the studies did not reflect the positioning of agomelatine and the data used in the economic analysis were derived from secondary endpoints where the differences between the treatments were not statistically significant.
- The sensitivity analysis showed that the results were sensitive to relatively small changes in the responder rates. Threshold analyses provided in the submission showed that the ICERs increased to over £30k per QALY when the response rates were changed by less than 3%.
- The inclusion of a range of comparators is helpful.. However, it should be noted that a number of other treatment options are available at a lower cost than agomelatine, such as citalopram and mirtazepine, and these comparators were not included in the economic analysis.
- Given the position sought by the manufacturer, the comparison with fluoxetine may not be relevant to Scottish practice as fluoxetine is an established first line treatment.
- The utility value for responders may be too high in comparison with the utility values identified in the literature. Also, the baseline utility value in the fluoxetine analysis may be too low. The sensitivity analysis showed the results were relatively sensitive to the utility values used, although the response rates are the key drivers of the model.

In order to address some of the weaknesses with the clinical data the manufacturer subsequently submitted a mixed treatment comparison (MTC) of agomelatine and a number of other antidepressants to support their case but for consideration only as a sensitivity analysis. The economic model was re-run using the efficacy and tolerability results from the MTC and this

produced ICERs of £10k, £14k, £17k and £13k per QALY for the comparisons with venlafaxine, fluoxetine, sertraline and escitalopram respectively. While the MTC appeared to be well conducted and showed agomelatine to have the highest response rate, the credible intervals are wide and overlap with the other drugs included in the MTC. Limited time was available to allow adequate appraisal of the mixed treatment methodology and thus to consider these ICERs, rather than the base-case analysis, as the basis for decision-making.

Due to weaknesses with the clinical data, the sensitivity of the base case results to changes in the response rates coupled with the relatively high incremental cost compared to the comparator treatments, plus the MTC having been supplied only as sensitivity analysis, the manufacturer has not presented a sufficiently robust economic analysis to gain acceptance by SMC.

Summary of patient and public involvement

A Patient Interest Group Submission was received from Depression Alliance.

Additional information: guidelines and protocols

National Institute of Health and Clinical Excellence (NICE) Clinical Guideline 90, October 2009. Depression. Treatment and management of depression in adults. This is a partial update of the NICE Clinical Guideline 23. These updated guidelines recommend:
Normally choose an SSRI in generic form but when choosing an agent consider both the patient's history and adverse event profile of the different drugs. When prescribing drugs other than SSRIs, take into account the increased likelihood of stopping treatment because of side effects, and the consequent need to increase the dose gradually and the specific cautions, contraindications and monitoring requirements for some drugs.

The British Association for Psychopharmacology published evidence-based guidelines for treating depressive disorders with antidepressants: a revision of the 2000 guidelines in January 2008. These guidelines recommend that the choice of antidepressant should be matched to individual patient requirements as far as possible, taking into account short and long term effects. In the absence of special factors the antideressant that is better tolerated and safer in overdose should be considered; SSRIs and other newer antidepressants are first line choices.

Additional information: comparators

In October 2009, NICE published: Depression. Treatment and management of depression in adults. It recommends the use of an SSRI in generic form for the first-line treatment of moderate to severe depression. Second line choices, in patients where there has been a limited response to initial treatment include a different SSRI, mirtazapine, moclobemide, reboxetine, tricyclic antidepressants (except dosulepin), and venlafaxine.

Cost of relevant comparators

Drug	Dose Regimen	Cost Per Year (£)
Agomelatine	**25 to 50mg daily**	**569 to 1138**
Venlafaxine XL	75 to 225mg daily	292 to 780
Fluoxetine	20 to 60mg daily	30 to 833
Duloxetine	60 to 120mg daily	360 to 721
Reboxetine	8 to 12mg daily (in divided doses)	229 to 344
Escitalopram	10 to 20mg daily	194 to 328
Venlafaxine	75 to 375mg daily (in 2 divided doses)	55 to 212
Paroxetine	20 to 50mg daily	32 to 78
Mirtazepine	15 to 45mg daily	63 to 71
Sertraline	50 to 200mg daily	19 to 44
Citalopram	20 to 60mg daily	18 to 38

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 7.6.10

Additional information: budget impact

The manufacturer estimated a net budget impact of £37.8k in year 1 rising to £189k.in year 5 based on 148 patients in year 1 and 740 in year 5. To estimate patient numbers the manufacturer assumed that the number of patients was based on 10% of the patient population treated with venlafaxine rising to 50% in year 5, but that displacement of market share came equally from each of the comparator drugs.

References

The undernoted references were supplied with the submission. The reference shaded in 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: randomised, double-blind comparison with venlafaxine. J Clin Psychiatry. 2007 Nov;68(11):1723-32.

Servier. Study CL3-20098-035. Efficacy of agomelatine (25 mg with potential adjustment at 50 mg) given orally versus venlafaxine on subjective sleep evaluation of patients with Major Depressive Disorder. A randomised double-blind parallel groups study. 6-week treatment plus optional continuation for 18 weeks. Data on file. 2005.

Servier. Study CL3-20098-046. Efficacy of agomelatine (25 mg/day with potential adjustment to 50 mg) given orally on rest/activity circadian rhythms in outpatients with Major Depressive Disorder. A randomized, double-blind international study with parallel groups versus sertraline (50 mg/day with potential adjustment to 100 mg/day). Data on file. 2004.

Olie JP, Kasper S. Efficacy of agomelatine, a MT1/MT2 receptor agonist with 5-HT2C antagonistic properties, in major depressive disorder. Int J Neuropsychopharmacol. 2007 Oct;10(5):661-73.

Kennedy SH, Emsley R. Placebo-controlled trial of agomelatine in the treatment of major depressive disorder. Eur Neuropsychopharmacol. 2006 Feb;16(2):93-100.

Servier. Study CL3-20098-021. Maintenance of efficacy of agomelatine (25 mg given orally once a day) for prevention of relapse in out- or in-patients with recurrent depression. A randomised double-blind, placebo-controlled, parallel group, 6-month study, following a 2-month open treatment period. Optional 4-month double-blind, extension period. Data on file. 2004.

Servier. Study CL3-20098-041. A study to determine the maintenance of efficacy of agomelatine (25 to 50 mg) in order to prevent relapses in out-patients with Major Depressive Disorder. A 8 or 10 weeks open period treatment with agomelatine (25 to 50 mg), followed by 24 weeks randomised double-blind period, placebo-controlled, parallel groups and 20 weeks of optional double-blind treatment period. Data on file. 2007.

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.

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

This assessment is based on data submitted by the applicant company up to and including 16 July 2010

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. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that

can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

**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/*

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.