New Medicine Recommendation

Agomelatine 25 mg Tablets (Valdoxan®)
For the Treatment of Major Depressive Episodes in Adults

Recommendation: Red (using NHS Lancashire and South Cumbria Foundation Trust prior approval process).

- Medicine is supplied by the hospital for the duration of the treatment course.
- Primary care initiation or continuation of treatment is not recommended unless exceptional circumstances such as specialist GP.

Summary of supporting evidence:

- Uncertainty remains regarding the consistency and magnitude of efficacy for agomelatine. A Cochrane review stated the overall methodological quality of the studies was low, and, therefore, no firm conclusions could be drawn concerning the efficacy and tolerability of agomelatine.
- Both NICE and the SMC have not approved the use of agomelatine in the NHS.
- The authors of the Cochrane Review of agomelatine stated that the clinical significance of a 1.5-point improvement on the HAM-D scale was questionable.
- The cause of liver injury and raised transaminases in patients using agomelatine is unclear.
- There are several antidepressant agents already available as 2nd and 3rd line agents with established use (e.g. Mirtazapine) or stronger efficacy data from clinical trials (e.g. vortioxetine which has a positive NICE TA).
- Agomelatine is more expensive than the majority of marketed antidepressant agents and is approximately £30 per month more expensive than generic antidepressant preparations.
- Although agomelatine has not been associated with hyponatraemia in its clinical studies, its use in elderly patients is restricted (in over 75s and Alzheimer's patients) and alternative agents with low rates of hyponatraemia are already available (e.g. mirtazapine, TCAs, MAOIs).

Details of Review

Name of medicine (generic & brand name)**:** Agomelatine (Valdoxan®). [1]
Strength(s) and form(s): 25 mg tablets.
Dose 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. [1]

BNF therapeutic class / mode of action:

Antidepressant / melatonin receptor agonist and a selective serotonin-receptor antagonist.

Licensed indication(s):

The treatment of major depressive episodes in adults. [1]

Proposed use (if different from, or in addition to, licensed indication above):

Third line option for those who have not responded to other classes of antidepressants.

Intolerance of other antidepressants e.g. treatment option in antidepressant-induced hyponatraemia

Course and cost: £30 for 28 Valdoxan® tablets.

Annual cost of £391 - £767.

Current standard of care/comparator therapies:

Current treatment options following treatment failure/intolerance:

- Selective serotonin reuptake inhibitors (SSRIs) (citalopram, fluoxetine and sertraline tablets) – annual cost range depending on dose and choice agent: £11 to £34.
- Mirtazapine tablets – annual cost range depending on dose: £14 to £18.
- Venlafaxine tablets or m/r tablets - annual cost range depending on dose: £41 to £127.
- Vortioxetine - annual cost: £361

NB – Costs are based on the May 2019 Drug Tariff prices and prescribers selecting the most cost-effective preparations for each dose of drug.

Relevant NICE guidance:

The updated NICE clinical guideline “Depression in adults: treatment and management” is not expected to be published until February 2020.

The Current NICE clinical guideline CG90 Depression in adults: recognition and management [2] updated in April 2018 recommends the following:

1.5.2.2 When an antidepressant is to be prescribed, it should normally be an SSRI in a generic form because SSRIs are equally effective as other antidepressants and have a favourable risk–benefit ratio. Also take the following into account:

- SSRIs are associated with an increased risk of bleeding, especially in older people or in people taking other drugs that have the potential to damage the gastrointestinal mucosa or interfere with clotting. In particular, consider prescribing a gastroprotective drug in older people who are taking non-steroidal anti-inflammatory drugs (NSAIDs) or aspirin.
- Fluoxetine, fluvoxamine and paroxetine are associated with a higher propensity for drug interactions than other SSRIs.
- Paroxetine is associated with a higher incidence of discontinuation symptoms than other

SSRIs.

1.5.2.3 Take into account toxicity in overdose when choosing an antidepressant for people at significant risk of suicide. Be aware that:

- compared with other equally effective antidepressants recommended for routine use in primary care, venlafaxine is associated with a greater risk of death from overdose.
- tricyclic antidepressants (TCAs), except for lofepramine, are associated with the greatest risk in overdose.

1.5.2.4 When prescribing drugs other than SSRIs, take the following into account:

- The increased likelihood of the person stopping treatment because of side effects (and the consequent need to increase the dose gradually) with venlafaxine, duloxetine and TCAs.
- The specific cautions, contraindications and monitoring requirements for some drugs. For example:
  - the potential for higher doses of venlafaxine to exacerbate cardiac arrhythmias and the need to monitor the person's blood pressure.
  - the possible exacerbation of hypertension with venlafaxine and duloxetine.
  - the potential for postural hypotension and arrhythmias with TCAs.
  - the need for haematological monitoring with mianserin in elderly people.
- Non-reversible monoamine oxidase inhibitors (MAOIs), such as phenelzine, should normally be prescribed only by specialist mental health professionals.
- Dosulepin should not be prescribed.

1.8.1.2 When switching to another antidepressant, be aware that the evidence for the relative advantage of switching either within or between classes is weak. Consider switching to:

- initially a different SSRI or a better tolerated newer-generation antidepressant.
- subsequently an antidepressant of a different pharmacological class that may be less well tolerated, for example venlafaxine, a TCA or an MAOI.

Background and context

Depression is a broad and heterogeneous diagnosis. Central to it is depressed mood and/or loss of pleasure in most activities. Severity of the disorder is determined by both the number and severity of symptoms, as well as the degree of functional impairment. A formal diagnosis using the ICD-10 (International Classification of Diseases) classification system requires at least four out of ten depressive symptoms, whereas the DSM-IV (Diagnostic and Statistical Manual of Mental Disorders) system requires at least five out of nine for a diagnosis of major depression. Symptoms should be present for at least 2 weeks and each symptom should be present at sufficient severity for most of every day. Both diagnostic systems require at least one (DSM-IV) or two (ICD-10) key symptoms (low mood, loss of interest and pleasure or loss of energy) to be present. [2]

The severity and functional impact of the depression dictates the nature of the interventions that a patient may receive to manage their condition. NICE defines the following stepped care model of treatment:

Focus of the intervention	Nature of the intervention
STEP 4: Severe and complex[a] depression; risk to life; severe self-neglect	Medication, high-intensity psychological interventions, electroconvulsive therapy, crisis service, combined treatments, multiprofessional and inpatient care
STEP 3: Persistent subthreshold depressive symptoms or mild to moderate depression with inadequate response to initial interventions; moderate and severe depression	Medication, high-intensity psychological interventions, combined treatments, collaborative care[b] and referral for further assessment and interventions
STEP 2: Persistent subthreshold depressive symptoms; mild to moderate depression	Low-intensity psychosocial interventions, psychological interventions, medication and referral for further assessment and interventions
STEP 1: All known and suspected presentations of depression	Assessment, support, psychoeducation, active monitoring and referral for further assessment and interventions

[a] Complex depression includes depression that shows an inadequate response to multiple treatments, is complicated by psychotic symptoms, and/or is associated with significant psychiatric comorbidity or psychosocial factors.

[b] Only for depression where the person also has a chronic physical health problem and associated functional impairment (see depression in adults with a chronic physical health problem: recognition and management [NICE clinical guideline 91]).

When a patient requires an antidepressant to be prescribed NICE recommends a generic SSRI

as they are equally effective to other antidepressants and have a favourable risk-benefit ratio. When patients do not respond well to initial treatment NICE recommends prescribers to switch to either a different SSRI or better tolerated newer-generation antidepressant.

Summary of evidence

Summary of efficacy data in proposed use:

No published studies are available assessing the clinical efficacy of agomelatine following treatment failure/intolerance to two antidepressants. The majority of the clinical trial evidence relates to the use of agomelatine as a first-line agent versus placebo or other antidepressants. Not all patients included in the studies had previously been treated with another antidepressant.

European Medicines Agency Public Assessment Report

Agomelatine use in adults with major depressive episodes was approved by the EMEA in 2008. [3] The public assessment report concluded that short term efficacy (at 6 weeks) was demonstrated in three of six short-term pivotal trials to discriminate agomelatine from placebo. Data relating to comparative efficacy with other antidepressants was more limited. The EMEA concluded that the effect of agomelatine was in the same range as paroxetine in the dose finding trial; smaller than the efficacy of fluoxetine 20 mg in a separate trial; and superior to sertraline 50-100 mg in a trial primarily analysing agomelatine effect on the rest-activity cycle. Overall the data available to the EMEA from the short-term studies showed that agomelatine 25 mg is probably less efficacious than other antidepressants. [3]

Scottish Medicines Consortium (SMC)

The manufacturer submitted evidence to the SMC proposing the use of agomelatine after initial treatment failure with a SSRI. [4]

In the submitted studies with venlafaxine, sertraline and escitalopram, 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. [4]

The primary outcome in the placebo-controlled studies, and one of the active comparator studies submitted to the SMC 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). The SMC highlighted that 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. [4]

The SMC concluded that despite the clinical studies available, there was limited robust data comparing agomelatine with second-line antidepressants using antidepressant efficacy as a primary outcome. Following the submission of evidence to the SMC, agomelatine was not recommended for use in NHS Scotland as the manufacturer did not present a sufficiently robust economic analysis. [4]

NICE terminated technology appraisal

NICE published guidance in July 2011 advising that it was unable to recommend the use of agomelatine for the treatment of major depressive episodes because no evidence submission was received from the manufacturer or sponsor of the technology. [5]

Cochrane Review

A Cochrane review was performed to compare the efficacy of agomelatine versus other antidepressive agents for major depression and this review was published in December 2013. A total of 13 studies (4495 participants) were included in this review. Agomelatine was compared to SSRIs, namely paroxetine, fluoxetine, sertraline, escitalopram, and to the serotonin-noradrenaline reuptake inhibitor (SNRI), venlafaxine. Participants were followed up for six to 12 weeks. [6]

The authors concluded that the results of the review suggested that agomelatine does not offer any significant advantage over other new antidepressant agents (mirtazapine, reboxetine, bupropion) in the acute-phase treatment of major depression (with the exception of venlafaxine in terms of tolerability and acceptability). The reviewers found evidence that compared agomelatine with only a small number of other active antidepressive agents, and there were only a few trials for each comparison, which limited the generalisability of the results. Moreover, the overall methodological quality of the studies was low, and, therefore, no firm conclusions could be drawn concerning the efficacy and tolerability of agomelatine. [6]

In a separate publication relating to the Cochrane review written by the same authors, the authors state:

> "….*agomelatine is associated with a difference of 1.5 points on the HAM-D. This difference was statistically significant, although the clinical relevance of this small effect is questionable*." [7]

The authors also state:

> "*The extent of publication bias found in the present review was surprising. None of the negative trials were published, and the standardised effect size was more than three times higher in published than in unpublished trials……. The present review included unpublished data from 1908 patients and published data on 2022 patients randomised to short- or long-term trials of agomelatine. Thus, only about 50% of the data available was published*." [7]

Other efficacy data:

Functional outcomes for agomelatine

Data from two randomised, parallel, double-blind, placebo-controlled short-term agomelatine trials conducted by the manufacturer, one in adult and one in older patients, that evaluated the effect on social functioning, were pooled. The short-term effect of agomelatine on social functioning was assessed using the Sheehan Disability Scale (SDS). SDS measures the impact of depression on work/school, social life, and family life/home responsibilities. The total score is the sum of the three domain scores and may range from 0 to 30. A total score of 12 or less is considered a 'functional response', while a total score of 6 or less is a good indicator of 'functional remission'. In total, 633 patients (422 on agomelatine; 211 on placebo) were included in the analyses. At endpoint, there was a significant difference in favour of agomelatine vs placebo of 3.47 (0.62) (CI95% 2.26, 4.67; P<0.001) on the SDS total score. [8]

Comparison with vortioxetine

Patients non-responsive to SSRI/SNRI therapy were randomised (1:1) to vortioxetine (10–20 mg/day) or agomelatine (25–50 mg/day) in a double-blind 12-week study. The pre-defined primary efficacy endpoint was change from baseline to week 8 in Montgomery-Asberg Depression Rating Scale (MADRS) total score. MADRS consists of 10 questions and a maximum total of 60 points with higher scores indicative of greater depressive symptoms. In the overall population, vortioxetine (n=252) was significantly superior to agomelatine (n=241) by −2.2 MADRS points ($p < 0.01$) at week 8. [9]

Summary of safety data:

According to the EPAR, 4738 patients irrespective of the studied disorder received agomelatine. The mean treatment duration under agomelatine (all doses) was 4.2 ± 3.6 months (i.e. about 16 weeks), ranging from 1 day to 19 months. When considering the target population of depressed patients, a total of 3956 patients were exposed to agomelatine. Among these patients, 1030 had 6-month of exposure to agomelatine. 368 patients received agomelatine 25 mg and 32 patients received agomelatine 50 mg for 350 days or more. [3]

Agomelatine is an antidepressant with a different safety profile compared to the SSRI/SNRIs group (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 that are not different from placebo). The adverse events associated with agomelatine are listed in the table below:

System organ class	Frequency	Preferred Term
Psychiatric	Common (≥1/100 to <1/10)	Anxiety, abnormal dreams*
	Uncommon (≥1/1,000 to <1/100)	Suicidal thoughts or behaviour, agitation and related symptoms* (such as irritability and restlessness), aggression*, nightmares*, mania/hypomania*, confusional state*
	Rare (≥1/10,000 to <1/1,000)	Hallucinations*
Nervous system	Very common (≥1/10)	Headache
	Common (≥1/100 to <1/10)	Dizziness, somnolence, insomnia
	Uncommon (≥1/1,000 to <1/100)	Migraine, paraesthesia, restless leg syndrome*
	Rare (≥1/10,000 to <1/1,000)	Akathisia*
Eyes	Uncommon (≥1/1,000 to <1/100)	Blurred vision
Ear and labyrinth	Uncommon (≥1/1,000 to <1/100)	Tinnitus*
Gastrointestinal	Common (≥1/100 to <1/10)	Nausea, diarrhoea, constipation, abdominal pain, vomiting*
Hepato- biliary	Common (≥1/100 to <1/10)	Increased ALT and/or AST (in clinical trials, increases >3 times the upper limit of the normal range for ALT and/or AST were seen in 1.2% of patients on agomelatine 25 mg daily and 2.6% on agomelatine 50 mg daily vs. 0.5% on placebo).
	Uncommon (≥1/1,000 to <1/100)	Increased gamma-glutamyltransferase* (GGT) (>3 times the upper limit of the normal range)
	Rare (≥1/10,000 to <1/1,000)	Hepatitis, increased alkaline phosphatase* (>3 times the upper limit of the normal range), hepatic failure*, Jaundice*
Skin and subcutaneous tissue	Uncommon (≥1/1,000 to <1/100)	Hyperhidrosis, eczema, pruritus*, urticaria*
	Rare (≥1/10,000 to <1/1,000)	Erythematous rash, face oedema and angioedema*
Musculoskeletal and connective tissue	Common (≥1/100 to <1/10)	Back pain
Renal and urinary	Rare (≥1/10,000 to <1/1,000)	Urinary retention*
General disorders and admin site conditions	Common (≥1/100 to <1/10)	Fatigue

Investigations	Common (≥1/100 to <1/10)	Weight increased*
	Uncommon (≥1/1,000 to <1/100)	Weight decreased*

* Frequency estimated from clinical trials for adverse reactions detected from spontaneous report

Hepatic effects

The key safety issue is the higher frequency of elevated aminotransferases and this is included in the Risk Management Plan agreed by the EMEA. The mechanism of agomelatine liver injury is unknown. Consequently, liver function tests (LFTs) should be performed in all patients, at initiation of treatment and then periodically after 6, 12 and 24 weeks and thereafter when clinically indicated. [4] The SPC for agomelatine carries the following warning:

> "**Caution should be exercised before starting treatment and close surveillance should be performed throughout the treatment period in all patients, especially if hepatic injury risk factors or concomitant medicinal products associated with risk of hepatic injury are present**." [1]

Agomelatine is contraindicated in patients with hepatic impairment.

Hyponatraemia

Antidepressant-induced hyponatraemia occurs particularly frequently in elderly patients and is predominantly recognised in female elderly patients. It has been suggested that age alone is not an independent risk factor, but that the increased incidence of hyponatraemia seen in the elderly can be explained by higher rates of co-morbidities and co-prescribed medicines. [10] The SPC for agomelatine notes that 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 or patients with dementia. Therefore, agomelatine should not be used in these patient groups. [1]

A Q&A document produced by the UKMI summarises that hyponatraemia is most associated with the use SSRIs and venlafaxine. The document also highlights that no cases of agomelatine induced hyponatraemia have been documented. The document goes on to summarise that in patient developed hyponatraemia whilst on an SSRI or venlafaxine, clinicians should consider changing to tricyclic antidepressants (TCAs) or a monoamine oxidase inhibitor (MAOI). Mirtazapine may also be considered due to its low reported incidence of hyponatraemia. [10]

Potential interactions

Co-administration of agomelatine with potent CYP1A2 inhibitors (e.g. fluvoxamine, ciprofloxacin) is contraindicated. Caution should be exercised when prescribing agomelatine with moderate CYP1A2 inhibitors (e.g. oestrogens, propranolol). Rifampicin 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.

Strengths and limitations of the evidence:

Strengths

- Agomelatine has a favourable safety profile (lack of weight gain, improved sleep quality, low risk of sexual dysfunction and absence of withdrawal symptoms) compared to other antidepressants that are the current standard care for major depressive episodes.
- The EMEA concluded that the magnitude of efficacy of agomelatine was sufficient to provide a clinically valuable alternative to other antidepressants.

- A pooled analysis found that agomelatine improved functional outcomes compared to placebo. [8]
- No cases of hyponatraemia have been documented for agomelatine.

Limitations

- Uncertainty remains regarding the consistency and magnitude of efficacy for agomelatine. A Cochrane review stated the overall methodological quality of the studies was low, and, therefore, no firm conclusions could be drawn concerning the efficacy and tolerability of agomelatine. [6]
- Both NICE and the SMC have not approved the use of agomelatine in the NHS. [4] [5]
- The authors of the Cochrane Review of agomelatine stated that the clinical significance of a 1.5-point improvement on the HAM-D scale was questionable.
- The cause of liver injury and raised transaminases in patients using agomelatine is unclear. The SPC for agomelatine recommends that baseline LFTs should be performed, then LFTs should be performed periodically thereafter.
- There are several antidepressant agents already available as 2nd and 3rd line agents with established use (e.g. Mirtazapine) or stronger efficacy data from clinical trials (e.g. vortioxetine which has a positive NICE TA).
- Agomelatine is more expensive than the majority of marketed antidepressant agents and is approximately £30 per month more expensive than generic antidepressant preparations.
- Although agomelatine has not been associated with hyponatraemia in its clinical studies, its use in elderly patients is restricted (in over 75s and Alzheimer's patients) and alternative agents with low rates of hyponatraemia are already available (e.g. mirtazapine, TCAs, MAOIs).

Summary of evidence on cost effectiveness:

The SMC received four cost utility analyses from the manufacturer. [4]

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 mirtazapine, 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.

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

Prescribing and risk management issues:

LFTs should be performed in all patients before starting treatment. Treatment should not be initiated if transaminases exceed 3 X upper limit of normal. 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.

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

Commissioning considerations:

Comparative unit costs:

Drug	Example regimen	Pack cost	Cost per patient per year (ex VAT)
Agomelatine (Valdoxan®) tablets	**25mg at night**	**£30 for 28**	**£391**
SSRIs	Citalopram 20mg daily Fluoxetine 20mg daily Sertraline 100mg daily	£0.88 for 28 £0.93 for 30 £1.08 for 28	£11.47 £11.32 £14.08
Mirtazapine	30mg daily	£1.07 for 28	£13.95
Venlafaxine	225mg daily	£6.50 for 30 x 75mg and 150mg m/r tablets	£79.08
Vortioxetine	10mg daily	£27.72	£361
Costs based on drug tariff list prices May 2019. This table does not imply therapeutic equivalence of drugs or doses.			

Innovation, need and equity implications of the intervention:

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 does not affect the uptake of serotonin, noradrenaline or dopamine. The safety profile is favourable relative to currently available antidepressant agents.

Financial implications of the intervention:

No prevalence data is available to identify the number of patients with depression in Lancashire and South Cumbria.

Approximations from Lancashire Care NHS Foundation trust indicate that a maximum of 12 patients are using agomelatine in any financial year, with approximately 3 initiation requests per quarter. Given this it is estimated that approximately 25 patients may be prescribed agomelatine. The annual acquisition cost of £391 for agomelatine.

The annual cost difference of treating 25 patients with agomelatine versus comparator antidepressants is outlined below:

- Agomelatine cost versus fluoxetine: (391-11) X 25 = £9,500
- Agomelatine cost versus mirtazapine: (391-14) X 25 = £9,425
- Agomelatine cost versus venlafaxine (most cost-effective 225mg dose): (391-79) X 25 = £7,800
- Agomelatine cost versus vortioxetine: (391-361) X 25 = £750

ePACT data for the number of patients in Lancashire and South Cumbria prescribed comparator antidepressants in the year to March 2019 are shown in the table with the cost of 0.1% of these patients being switched to agomelatine below:

BNF Chemical Substance	Identified Patient Count	0.1% patient count	Cost if 0.1% of patients switched to agomelatine
Citalopram Hydrobromide	65221	65	£24,700
Fluoxetine Hydrochloride	32681	33	£12,540
Mirtazapine	43488	43	£16,211
Sertraline Hydrochloride	70904	71	£26,767
Venlafaxine	10794	11	£3,432
Vortioxetine	653	1	£30

Service Impact Issues Identified:

Agomelatine is not currently approved by the LMMG for use in Lancashire and South Cumbria. Amending the RAG status for agomelatine may result in an increased workload (LFT monitoring and prescribing) for either primary and secondary care services depending on the RAG classification.

Equality and Inclusion Issues Identified:

No equality issues have been identified for the provision of agomelatine, as other treatment options are already available for the management of major depressive episodes.

Cross Border Issues Identified:

Agomelatine is not currently recommended by Greater Manchester Medicines Management Group or Pan Mersey APC. Approving the use of agomelatine in Lancashire may lead to local equality issues.

Legal Issues Identified:

N/A

Media/ Public Interest:

N/A

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[2] National Institute for Health and Care Excellence, "Depression in adults: recognition and management," April 2018. [Online]. Available: https://www.nice.org.uk/guidance/cg90. [Accessed May 2019].

[3] European Medicines Agency, "CHMP Assessment Report For Valdoxan," 17 March 2009. [Online]. Available: https://www.ema.europa.eu/en/documents/assessment-report/valdoxan-epar-public-assessment-report_en.pdf. [Accessed 16 May 2019].

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[6] G Guaiana et al, "Agomelatine versus other antidepressive agents for major depression," 17 December 2013. [Online]. Available: https://www.cochrane.org/CD008851/DEPRESSN_agomelatine-versus-other-antidepressant-medication-for-depression. [Accessed 15 May 2019].

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[8] SH Kennedy et al, "Effect of agomelatine 25-50 mg on functional outcomes in patients with major depressive disorder," *Journal of Affective Disorders,* vol. 238, pp. 122-128, 2018.

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[10] UKMI, "If antidepressant-induced hyponatraemia has been diagnosed how should depression be treated?," 16 February 2017. [Online]. Available: https://www.sps.nhs.uk/articles/if-antidepressant-induced-hyponatraemia-has-been-diagnosed-how-should-the-depression-be-treated-2/. [Accessed 20 May 2019].

Grading of evidence (based on SORT criteria):

Levels	Criteria	Notes
Level 1	Patient-oriented evidence from: • high quality randomised controlled trials (RCTs) with low risk of bias • systematic reviews or meta-analyses of RCTs with consistent findings	High quality individual RCT= allocation concealed, blinding if possible, intention-to-treat analysis, adequate statistical power, adequate follow-up (greater than 80%)
Level 2	Patient-oriented evidence from: • clinical trials at moderate or high risk of bias • systematic reviews or meta-analyses of such clinical trials or with inconsistent findings • cohort studies • case-control studies	
Level 3	Disease-oriented evidence, or evidence from: • consensus guidelines • expert opinion • case series	Any trial with disease-oriented evidence is Level 3, irrespective of quality