NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Single Technology Appraisal

Agomelatine for the treatment of major depressive episodes

Final scope

Remit/appraisal objective

To appraise the clinical and cost effectiveness of agomelatine within its licensed indication for the treatment of major depressive episodes (MDE) in adults.

Background

Depression refers to a range of mental health conditions characterised by the absence of positive affect (loss of interest and enjoyment in ordinary activities), low mood and a range of associated emotional, cognitive, physical and behavioural symptoms.

Diagnosis is based on severity, duration and course of the disease. According to the DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition) the person must have five or more out of a list of nine symptoms which must include depressed mood or loss of interest and pleasure. The other symptoms are fatigue or loss of energy, a feeling of worthlessness or excessive guilt, recurrent thoughts of death or suicide (or attempted suicide), diminished concentration or decisiveness, activity disturbance (psychomotor agitation or retardation), sleep disturbance (insomnia or hypersomnia), and significant appetite or weight disturbance (weight gain or loss). The diagnostic system requires symptoms to have been present for at least two weeks and the symptoms must result in impairment of functioning. Episodes can be single or recurrent. Severity ranges from mild to severe based on the number of symptoms and level of functional impairment. Some depression rating scales and questionnaires indicate severity ranges but there is a lack of consensus and variable correlation between measures.

The estimated point prevalence for depressive episodes among 16 to 74 year-olds in the UK in 2000 was 2.6% (2.3% in men and 2.8% in women). However, the figure is much higher (11.4%) when ‘mixed depression and anxiety’ is included. The risk of relapse is 50%, 70% and 90% after the first, second and third episodes of major depression respectively. Persistent or chronic depression is present in 10% of patients.

MDE are treated with a range of pharmacological and non-pharmacological interventions depending on severity, previous disease course, response to interventions, adverse effects and patient preference. According to NICE clinical guideline 90, routine use of antidepressants is not recommended for sub-threshold depressive symptoms or mild depression except for people with a past history of moderate or severe depression, 2 years or more of sub-

threshold depressive symptoms, or persistent sub-threshold depressive symptoms or mild (to moderate) depression after other interventions. Moderate and severe depressions are routinely treated with selective serotonin reuptake inhibitors (SSRIs) and high-intensity psychological interventions (cognitive behavioural therapy (CBT) and interpersonal therapy (IPT)).

If there is inadequate response to antidepressants, increasing the dose may be considered. If the patient experiences side effects, prefers to change drug or still has inadequate response, switching to another antidepressant may be considered. Initially a different SSRI or a better tolerated newer-generation antidepressant is recommended and, subsequently, an antidepressant of a different class that may be less well tolerated (such as venlafaxine, a tricyclic antidepressant, or a reversible monoamine oxidase inhibitor [MAOI]) may be considered. Antidepressants may then be augmented with other pharmacological treatments.

The technology

Agomelatine (Valdoxan, Servier) is a melatonergic agonist (MT1 and MT2 receptors) and 5-HT2C antagonist. Agomelatine increases noradrenaline and dopamine release specifically in the frontal cortex and has no influence on the extracellular levels of serotonin. Agomelatine is taken orally.

Agomelatine has a marketing authorisation applicable in the UK for the treatment of MDE in adults (18 years and over).

Intervention(s)	Agomelatine
Population(s)	Adults with major depressive episodes (MDE)
Comparators	• Selective serotonin reuptake inhibitors (SSRIs) – such as citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline • Tricyclic antidepressants – such as clomipramine, doxepin, imipramine, lofepramine, nortriptyline, trimipramine, amitriptyline • Tricyclic-related antidepressants – such as mianserin, trazodone • Serotonin and noradrenaline reuptake inhibitors – such as venlafaxine, duloxetine • Other antidepressant drugs – such as mirtazapine, reboxetine

Outcomes	The outcome measures to be considered include: • change from baseline severity of depression • mortality • time to relapse (maintenance of effect) • response rate • time to response • remission of symptoms • anxiety • sleep • hospitalisation • health-related quality of life • adverse effects (including those associated with treatment and treatment discontinuation)
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.
Other considerations	If evidence allows the following subgroups by the severity of depression (moderate or severe) will be considered. Guidance will only be issued in accordance with the marketing authorisation.
Related NICE recommendations	Related Technology Appraisals: Technology Appraisal No.97, Feb 2006, Computerised cognitive behaviour therapy for depression and anxiety (Review of Technology Appraisal 51). Updated as part of clinical guideline No. CG90. Technology Appraisal No. 59, Apr 2003, The clinical effectiveness and cost effectiveness of electroconvulsive therapy (ECT) for depressive illness, schizophrenia, catatonia and mania. The recommendations related to depression have been

	updated in clinical guideline No. CG90. Related Guidelines: Clinical guideline No. CG 38, Jul 2006, The management of bipolar disorder in adults, children and adolescents, in primary and secondary care. Expected review date: July 2011. Clinical Guideline No. CG 28, Sept 2005, Depression in children and young people: identification and management in primary, community and secondary care. Expected review date: February 2011. Clinical Guideline No. CG90, October 2009, Depression: the treatment and management of depression in adults (update of CG23). Expected review date: to be confirmed. Clinical Guideline No. CG91, October 2009, The treatment and management of depression in adults with chronic physical health problems (partial update of CG23). Expected review date: to be confirmed. Related Interventional Procedures: IPG 242, Nov 2007, Transcranial magnetic stimulation for severe depression. Review date: NA IPG 330, Dec 2009, Vagus nerve stimulation for severe depression. Review date: NA