NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Proposed Health Technology Appraisal

Agomelatine for the treatment of major depressive episodes

Draft scope (Pre-referral)

Draft 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 patient 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. Major Depressive Disorder (MDD) is characterised by MDE. 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 episode among 16 to 74 year-olds in the UK in 2000 was 2.6% (males 2.3%, females 2.8%). 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. 10% of patients have persistent or chronic depression.

MDE is treated with a range of pharmacological and non-pharmacological interventions depending on severity, previous disease course, response to interventions, adverse effects and patient preference. The current NICE guidance for depression recommends mild depression is initially treated with watchful waiting or low-intensity psychological interventions such as computerised cognitive behavioural therapy (CBT), guided self-help, brief

psychological interventions, counselling and/or supervised exercise programmes. Moderate and severe depressions are routinely treated with selective serotonin reuptake inhibitors (SSRIs) and psychological interventions (mainly CBT).

Where response to initial treatment is low, the dose may be increased, the patient switched to alternative antidepressant treatments or other high-intensity psychological interventions prescribed including CBT, interpersonal therapy or couples therapy. For treatment-resistant depression, antidepressants may be augmented with other pharmacological treatments or combined with further psychological interventions. Electroconvulsive therapy (ECT) may also be used.

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 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 MDE
Comparators	• selective serotonin reuptake inhibitors (SSRIs) - citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline • tricyclic antidepressants – clomipramine, doxepin, imipramine, lofepramine, nortriptyline, trimipramine, amitriptyline • tricyclic-related antidepressants – mianserin, trazodone • reversible monoamine oxidase inhibitors (MAOIs) - moclobemide • serotonin-norepinephrine reuptake inhibitors (SNRIs) - venlafaxine, duloxetine • other antidepressant drugs - mirtazapine, reboxetine, phenelzine
Outcomes	The outcome measures to be considered include: • change from baseline severity of depression • mortality • time to relapse • remission of symptoms • anxiety • quality of sleep • health-related quality of life • adverse effects of treatment
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 the evidence allows subgroups will be considered by the severity of depression. 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). To be updated as part of the clinical guideline No. CG23. 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 Depression: management of depression in primary and secondary care (CG23). Proposed Technology Appraisal, The clinical effectiveness and cost effectiveness of quetiapine for the treatment of depression. Earliest anticipated date of publication: to be confirmed. Related Guidelines: Clinical guideline No. CG 3, Jul 2006, The management of bipolar disorder in adults, children and adolescents, in primary and secondary care. Review date: July 2010. Clinical Guideline No. CG 28, Sept 2005, Depression in children and young people: identification and management in primary, community and secondary care. Review date: September 2009. Clinical Guideline No. GG 23, Dec 2004, Depression: management of depression in primary and secondary care. Clinical guideline in preparation, Update of guideline CG23. Depression: the treatment and management of depression in adults (update). Earliest anticipated date of publication Oct 2009. Clinical guideline in preparation, The treatment and management of depression in adults with chronic physical health problems (partial update of CG23). Earliest anticipated date of publication Sept 2009.

	Related Interventional Procedures: IPG 242, Nov 2007, Transcranial magnetic stimulation for severe depression. Review date: TBC. Guideline in preparation, Vagus nerve stimulation for severe depression. Earliest anticipated date of publication Spring 2009.

Questions for consultation

What is the likely place of agomelatine in the clinical treatment pathway?

Have the most appropriate comparators for agomelatine been included in the scope? Should electroconvulsive therapy (ECT) be included?

Have the appropriate outcomes been included? Should hospitalisation due to depression also be included?

Are the subgroups suggested in the 'other considerations' section appropriate? Are there any other subgroups of patients in whom the technology is expected to be more clinically effective and cost effective or other groups that should be examined separately?

Are there any issues that require special attention in light of the duty to have due regard to the need to eliminate unlawful discrimination and promote equality?

NICE intends to appraise this technology through its Single Technology Appraisal (STA) Process. We welcome comments on the appropriateness of appraising this topic through this process. (Information on the Institute's Technology Appraisal processes is available at http://www.nice.org.uk/aboutnice/howwework/devnicetech/technologyappraisalprocessguides/technology_appraisal_process_guides.jsp)

Could agomelatine and quetiapine be appraised together in a multiple technology appraisal?