National Institute for Health and Clinical Excellence

Single Technology Appraisal (STA)

Agomelatine for the treatment of major depressive episodes

Response to consultee and commentator comments on the draft remit and draft scope (pre-referral)

Comment 1: the draft remit

Section	Consultees	Comments	Action
Appropriateness	British Association for Psychopharmacology	Yes. Agomelatine has been licensed in UK and European countries and thus its role within NHS care must be established.	Comment noted. This topic has been referred as a single technology appraisal of agomelatine for the treatment of major depressive episodes.
	Lundbeck	Yes since agomelatine was not reviewed as part of the recent update to the NICE Depression Guideline (CG90)	Comment noted. This topic has been referred as a single technology appraisal of agomelatine for the treatment of major depressive episodes.

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	Royal College of Psychiatrists	Yes, it is entirely appropriate to undertake an HTA of agomelatine for the treatment of depression. This is a newly licensed antidepressant with an entirely novel mechanism of action and unsual pharmacokinetics. It was not reviewed within the recent 2009 update of the Clinical Guideline for depression (CG23). As a result if not considered within an HTA, there will be a long lag before NICE reviews the drug as part of a subsequent further Clinical Guideline update. The drug has significant aquision costs compared to most currently routinely used antidepressants. The Health Care Economy is therefore in need of guidance from NICE as to the clinical place of agomelatine within the NHS.	Comment noted. This topic has been referred as a single technology appraisal of agomelatine for the treatment of major depressive episodes.
	Servier Laboratories Ltd	Given that agomelatine had previously been referred to NICE with a decision made not to conduct an appraisal, it would be preferable that an STA was not conducted. NICE have the opportunity to await the next update of the depression guidelines (CG 23) to consider the place of agomelatine in the management of depression. This would free up capacity for NICE to concentrate on those products and disease areas where local evaluation is really not an option (e.g. oncology, end of life, etc). Servier is not convinced that this is the best use of NICE resources.	Comment noted. Other consultees and commentators considered that an appraisal of agomelatine for major depressive episodes was appropriate. This topic has now been referred to NICE as a single technology appraisal.
Wording	British Association for Psychopharmacology	Yes	Comment noted. No actions required.
	Royal College Of Psychiatrists	Yes, the wording appears appropriate	Comment noted. No actions required.
	Servier Laboratories	Yes	Comment noted. No actions required.

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Timing Issues	British Association for Psychopharmacology	Not urgent	Comment noted. Agomelatine already has a marketing authorisation. This topic has been referred as a single technology appraisal of agomelatine for the treatment of major depressive episodes.
	Royal College Of Psychiatrists	This drug has a marketing authorisation. Because the CG23 update has only just been released (but didn't cover agomelatine) there will be a significant delay in providing advice the prescribers if this drug is not considered as an HTA before the next update.	Comment noted. See response above.
	Servier Laboratories	Servier do not believe there is any urgency to conduct this appraisal. Agomelatine is already available and a significant amount of NHS resource is already being dedicated to evaluating its position in therapy through regional and local groups. Whilst not benefiting from the depth of review available to NICE, local groups would perceive themselves as competent in the assessment of a new antidepressant for their local population. It is disappointing for Servier that an STA leading to NICE guidance will be produced approximately 2 years after the product has received marketing authorisation.	Comment noted. See response above.
Additional comments on the	British Association for Psychopharmacology	None	Comment noted. No action required.

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draft remit	Medtronic	General Comment: Deep Brain Stimulation has and is used off label for the treatment of Major Depression. However it is currently not CE marked for this indication, CE marking is anticipated in 2013.	Comment noted. Comparators were discussed at the scoping workshop. It was agreed that deep brain stimulation was not an appropriate comparator for agomelatine.
	Royal College Of Psychiatrists	In addition to considering the clinical and cost effectiveness of agomelatine in the treatment of major depressive epsiodes, the place of the drug in the clinical treatment pathways needs to be considered.	Comment noted. This topic has been referred to NICE as a single technology appraisal. Non- manufacturer consultees are invited to provide statements and the manufacturer is now invited to provide and evidence submission.
	Servier Laboratories	Servier do not believe this is a good use of public money; the single technology appraisal process should be reserved for those technologies that regional and local bodies are not technically competent and resourced to address.	Comment noted. See responses above: this topic has been referred to NICE as a single technology appraisal. The manufacturer is now invited to provide and evidence submission and non-manufacturer consultees are invited to provide statements.

Comment 2: the draft scope

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Background information	British Association for Psychopharmacology	Yes	Comment noted. No action required.
	Royal College Of Psychiatrists	The discussion around treatment options in the background is based upon the old 2004 NICE CG23. However an update of this was published recently and so the text needs updating. It would be helpful to consider the poor response to antidepressants in naturalistic practice. For example, the large pragmatic Star*D study conducted in the USA showed that even with protocol driven treatment, first line therapy with an SSRI (citalopram) in over 2500 patients was associated with remission in only 30% and response (defined as a 50% decrease in symptom scores) in less than 50% of patients (Trivedi MH, et al. Evaluation of Outcomes With Citalopram for Depression Using Measurement-Based Care in STAR*D: Implications for Clinical Practice. Am J Psychiatry. 2006 January 1, 2006;163:28-40.). The background considers strategies to deal with non-response to first line agents. Again this is based on the 2004 version of the CG23. In addition, in clinical practice, lack of tolerability of the drug can be as big an issue as lack of response. While newer antidepressants such as SSRIs as better tolerated than older TCAs, they are associated with significant side effect burdens, with, for example, sexual side effect rates of at least 50%. Alternative antidepressants lacking sexual sides effects (e.g. mirtazepine) are associated with different problems (e.g. over sedation and weight gain).	Comment noted. The scope has been updated in line with the updated NICE clinical guideline for depression (CG90). A scope aims to briefly summarise the treatment pathway to give a context for the question that a technology appraisal aims to answer. Due to the complexity of the treatment pathway it is not possible to include details of all treatment recommendations listed in the guideline. There will be an opportunity to explore issues such as the place of agomelatine in the treatment pathway and unmet need during the technology appraisal.
	Servier Laboratories	The background data was not complete and needs context: The role of patient choice in selecting treatment options should be described as outlined in the Government policy document 'Our choices in mental health – a framework for improving choice for people who use mental health services and their carers'. This is referred to in the 'equality' section of this document	Comment noted. The scope has been updated in line with the updated NICE clinical guideline for depression (CG90). A scope aims to briefly summarise the

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		The recommendations of NICE Clinical Guidelines (CG23) (not guidance), which outline a lack of compelling evidence to inform treatment sequencing options should be more fully described. The need to profile the drug choice to the patient infers that all therapeutic options should be available to the clinician. The landmark STAR-D trial demonstrates that the likelihood of remission from depressive symptoms significantly decreases with 3rd and 4th line options. This should be described and should be considered by the appraisal committee if they are considering restricting any product to 3rd or 4th line use. It should be acknowledged in this section that there is an unmet need within depression - there exists a vast number of patients who either do not respond or do not achieve remission with currently available treatments and therefore remain at risk. It should be noted that there remains a lack of timely access to psychological services across most parts of the UK It should be noted from NICE clinical guidelines for depression in adults (CG 23) that the cost of medicines is only a very small part of the overall costs of treating Mental health problems The burden of depression on family and carers should be described even if this cannot be considered in this appraisal The economic burden to society, in terms of lost productivity and incapacity benefits payments, should be noted. The governments 'Fit to Work' and similar policies should be noted The importance of treating depression in a primary care setting by optimising the use of available pharmacological and psychological therapies should be should be noted. The secondary care environment should only be reserved for patients with severe depression or depression that has not responded to treatment in primary care based on use of the antidepressants available to the clinician prescribed in line with NICE guidelines. The significantly increased cost of treating depression in a secondary care setting should be noted	treatment pathway to give a context for the question that a technology appraisal aims to answer. Due to the complexity of the treatment pathway it is not possible to include details of all treatment recommendations listed in the guideline. Any appraisal will assess a technology within its licensed indication. There will be an opportunity to explore issues such as the place of agomelatine in the treatment pathway, setting, burden of disease and unmet need during the technology appraisal. This is important information to include in the submission for the appraisal.

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The technology/ intervention	British Association for Psychopharmacology	Not really; the description of the pharmacology seems inaccurate	Comment noted. The description is based on the SPC.
	Royal College Of Psychiatrists	Yes	Comment noted. No action required.
	Servier Laboratories	Yes	Comment noted. No action required.
Population	British Association for Psychopharmacology	Analysis on more severe and treatment-resistant groups should be considered	Comment noted. The scope addresses patients with major depressive episodes in line with the licensed indication. It was agreed at the scoping workshop that moderate and severe sub-groups will be assessed if evidence allows.
	Royal College Of Psychiatrists	Yes in the first instance. It would be worth considering the effectiveness and cost-effectiveness in patients with chronic sub-syndromal symptoms meeting criteria for dysthymia although there is little or no data yet available in this area. In addition it would be helpful to consider sub populations of patients with major depression including the elderly, those with major sleep disturbance, those with marked comorbid anxiety, and those intolerant of other medications e.g. due to sexual dysfunction.	Comment noted. The scope addresses patients with major depressive episodes in line with the licensed indication. It was agreed at the scoping workshop that moderate and severe sub-groups will be assessed if evidence allows. For further detail on the analysis of data for patient subgroups, see the Guide to the Methods of Technology Appraisal, June 2008, section 5.10 (www.nice.org.uk)

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	Servier Laboratories	The population is defined appropriately, all adults with major depressive disorder. NICE Guidelines (CG 23) don't sub-group populations Local formularies and clinical practice doesn't typically sub group patients Although sub-groups of patients can be identified, there is unlikely to be significant evidence to robustly compare agents	Comment noted. The scope addresses patients with major depressive episodes in line with the licensed indication. It was agreed at the scoping workshop that moderate and severe sub-groups will be assessed if evidence allows. For further detail on the analysis of data for patient subgroups, see the Guide to the Methods of Technology Appraisal, June 2008, section 5.10 (www.nice.org.uk)
Comparators	British Association for Psychopharmacology	Yes but it should be matched with appropriate description of the group, for example SNRIs as second-line treatment rather than SNRIs in general. Comparisons with ECT would not be appropriate as there is no available drugs that would match ECT efficacy.	Comment noted. The comparators have been listed for the population as a whole and in line with the licensed indication. Following the scoping workshop, electroconvulsive therapy (ECT) has been excluded from the list of comparators.
	Royal College Of Psychiatrists	Yes, the comparators are reasonable and well help establish the place of agomelatine in the clinical pathway. Comparison should be with other antidepressant medication rather than with ECT	Comment noted. Following the scoping workshop, ECT has been excluded from the list of comparators.
	Servier Laboratories	No single one of the standard treatments could be described as the 'best alternative care' because the choice of antidepressant following initial treatment failure with an SSRI, according to NICE updated guideline CG23 (October 09), would be dependent on a multitude of criteria such as patient choice, side effects, suicide risk, discontinuation, etc. This makes the choice of	Comment noted. Relevant comparators are identified with consideration given specifically to routine and best practice in the NHS. A range

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		any one agent arbitrary For the purpose of this STA, the scoping committee should provide clarity about the decision rule that will be used to determine cost effectiveness. Is it appropriate that Servier demonstrate the cost effectiveness of agomelatine relative to just one of the currently used agents as an appropriate comparator? Servier propose to demonstrate cost effectiveness versus a number of SSRI and SNRI options in a primary care perspective. NICE should confirm that this is an acceptable approach. Comparison with other antidepressants should be limited to that in which the licensed flexible dose of all agents under consideration was available. Extra weight should be given to active comparator studies without a placebo arm – this represents the true patient in clinical practice Should best supportive care without pharmacological therapy be considered? Many patients with diagnosed MDD are untreated due to lack of access to psychological services and lack of access to an appropriate antidepressant. In consideration of agomelatine comparative data versus placebo (registration studies), only those trials in which the licensed flexible dosing schedule of agomelatine was used should be considered. In clinical trials, between 11% and 23% of patients require up-titration to the 50mg dose. The meta-analysis of dose finding studies and trials using the fixed dose of agomelatine versus placebo	of comparators have been listed reflecting the variety of treatments that may be provided in the NHS. At the scoping workshop best supportive care was not considered an appropriate comparator for this population and remained excluded from the list of comparators. The manufacturer is now invited to provide an evidence submission for the clinical and cost effectiveness of agomelatine. NICE will invite the manufacturer to attend a meeting to discuss the decision problem and to help ensure that it is specified appropriately. This meeting also provides an opportunity for the manufacturer to ask questions. For further details of factors that evidence providers should have due regard to when selecting comparator technologies for analyses in evidence submissions, see the Guide to the Methods of Technology Appraisal, June 2008, section 2.2.4 (www.nice.org.uk)

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Outcomes	British Association for Psychopharmacology	Yes. Hospitalisation is not a relevant outcome as it is a very rare event for depression within current NHS practice.	Comment noted. Following the scoping workshop, hospitalisation has been included as it relates to costs in the economic evaluation.
	Royal College Of Psychiatrists	The major outcomes should be: "Change from baseline severity of depression"; "Remission of symptoms"; "Health-related quality of life". "Time to relapse" for those continuing on agomelatine is also important since this provides evidence of the prophylactic effect of the drug post acute episode. "Adverse effects of treatment" is an absolutely critical outcome measure in relation to this drug since its major advantage over other current treatments appears to be one of significantly greater tolerability. The draft includes "mortality". While of obvious importance, it is unlikely that this will be a useful outcome measures since most studies will not have sufficient power to be able to determine this. The draft includes "Anxiety". This is a worthwhile outcome measure, as is "quality of sleep", but it is unclear why these two symptoms of depression have been pulled out from others.	Comment noted. Mortality has remained in the list of outcomes as cost per QALY measures incorporate both quality and quantity of life. At the scoping workshop sleep and anxiety were considered particularly relevant symptoms and have been included as separate items. Time to relapse has also been included as an outcome.
	Servier Laboratories	The outcomes listed in the draft scoping document will NOT fully capture the most important health benefits associated with this technology: Change from baseline severity of depression - does this infer response rate? Clinical trials of depression typically report results in terms of responder rates which are based on the accepted 50% reduction from baseline assessment score on a validated rating scale (HAMD-D, MADRS) Is mortality a valid outcome for inclusion and if so could more clarity be provided? Is it inferring suicidality? Agomelatine is not indicated for the treatment of anxiety disorder therefore there is limited available clinical data relating to effect of agomelatine on anxiety symptoms If considering ‘quality of sleep’, should we also consider the important measures of day time vigilance?	Comment noted. Following the scoping workshop response rate and time to response (as a measure of speed of onset) have been added to the list of outcomes and mortality has remained in the list of outcomes as cost per QALY measures incorporate both quality and quantity of life. Sleep and anxiety were considered particularly relevant symptoms and have been included as

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		Speed of onset should be an outcome – many patients discontinue treatment in the early weeks due to delay in antidepressant efficacy Is sexual dysfunction considered to be an adverse event of treatment? If not, this should be listed as an outcome. Discontinuation symptoms on withdrawal of treatment should be considered as an outcome measure. Discontinuation for any reason should be an outcome measure. The draft scope appears to be focusing on the sleep outcome as a particular feature of agomelatine (possibly following inappropriate comments from the consideration panel meeting?), there are 10 core symptoms described on the HAM-D rating scale, including work and activities, etc, against all of which agomeltine is effective. Sleep should not be separated from its overall efficacy profile Weight gain should be considered Use in patients with co morbid CV disease should be considered NICE should provide more guidance on its definition of adverse events and side effects as outcome measures	separate items. The scope aims to broadly outline the outcomes to be included and does not aim to define the detailed approach to be taken by the manufacturer in the submission. Adverse events are not normally defined in the scope and may include weight gain or sexual dysfunction. The scope has been amended so that adverse events associated with treatment discontinuation are included.
Economic analysis	British Association for Psychopharmacology	None	Comment noted. No action required.
	Royal College Of Psychiatrists	This seems approriate.	Comment noted. No action required.

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	Servier Laboratories	More guidance is required for efficacy estimates beyond first line treatments. Almost all trials of antidepressants are in treatment naïve patients. NICE guidelines (CG23) use a response rate of 20% for third line treatment option – is this appropriate for this appraisal? More guidance is required on the use of the economic model developed by NICE in depression guidelines CG23. Is this an appropriate model for this appraisal? More guidance is required on time horizon. Modelling more than one depressive episode or even a lifetime horizon will amplify the cost effectiveness of treatment, however, the availability of long term data is limited	The scope does not aim to define the economic model or the detailed approach to be taken by the manufacturer in the submission. NICE will invite the manufacturer to attend a meeting to discuss the decision problem and to help ensure that it is specified appropriately. This meeting also provides an opportunity for the manufacturer to ask questions. Please refer to the NICE guide to the methods of technology appraisal (2008) for guidance on approaches to economic evaluation and the reference case.
Equality and Diversity	British Association for Psychopharmacology	None	Comment noted. No action required.
	Royal College Of Psychiatrists	No concerns	Comment noted. No action required.
	Servier Laboratories	Servier would like to draw the attention of NICE to the following government policy document relating to Mental Health: "Our choices in mental health – a framework for improving choice for people who use mental health services and their carers". This policy outlines the Government's plans to create a modern mental health system which is designed to rise to these demands "*by improving access to effective treatment and care, reducing unfair variation, raising standards, and providing prompt, convenient, high quality services. Increased choice also means that service users and carers are able to be*	Comment noted. It is important that any information which could be relevant to promotion of equality and elimination of unlawful discrimination is reflected in the submission of evidence made for the appraisal.

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		treated at home instead of hospital, and have access to a wide range of services more easily." With regard to medication this document states that "*it is also crucial that people should be given information to make informed choices about the medication that might be recommended for them, particularly what side-effects certain drugs might have on their physical health.*" Consideration to the principles of this document, particularly relating to the setting for treatment and access to information about all available medicines will ensure that patients are not discriminated against. There is evidence suggesting that the evident varying levels of antidepressant prescribing across the UK may be a proxy measure for access to care rather than an indicator of a differing prevalence of disease. In these areas where access to care is strained an antidepressant therapy for which there is less resource intensive follow up for patients may be of added value. (compared to the comparators such as venlafaxine, TCA's etc)	
Other considerations	British Association for Psychopharmacology	This could be jointly assessed with other newer antidepressants such as quetiapine	Comment noted. This was discussed at the scoping workshop and an STA of agomelatine was considered appropriate due to potentially different indications.
	Medtronic	Deep Brain Stimulation is currently used in the treatment of Major Depression however this is off label usage. Should this figure in the evaluation scope?	Comparators were discussed at the scoping workshop and deep brain stimulation was not considered an appropriate comparator in this population and has not been included in the scope.

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	Royal College Of Psychiatrists	Examining the effect of the drug stratified by baseline depression severity is relevant. As described above, issues around tolerability of the drug are critical to this evaluation	Comment noted. Following the scoping workshop, moderate and severe sub-groups have been included in the scope if evidence allows.
	Servier Laboratories	The problem of placebo response when conducting depression studies should be described	Comment noted. This detail is not required in the scope of an appraisal. This information should be reflected in the submission of evidence made for the appraisal.
Questions for consultation	British Association for Psychopharmacology	None	Comment noted. No action required.
	Royal College Of Psychiatrists	Place of agomelatine in clinical treatment pathway: SSRIs are likely to remain first line choices of antidepressants. Agomelatine may be appropriate for patients who fail to respond to first and/or second line treatments (e.g. alternate SSRI, SNRI, mirtazepine). Agomelatine may also be appropriate for patients suffering from unacceptable side effects on other medication (e.g. sexual dysfunction, weight gain). Appropriate comparators - should ECT be included? No - see above. Outcomes, should hospitalisation be included: See above re outcomes in general. Hospitalisation is costly element of the potential care package and hence this may be very relevant for the economic analysis. However this is a rarely reported outcome in clinical trials, so it is unlikely to be a useful outcome. Subgroups: See above. It would be worthwhile to consider in those with major sleep dysfunction given the melatonergic effects of the drug. It is also important to consider for patients intolerant (and hence non-adherent) to current treatments. Could agomelatine be considered together with quetiapine in an MTA? The	NICE appraises technologies within their licensed indications. Following the scoping workshop, ECT was not seen as an appropriate comparator and has been excluded. Hospitalisation has been included in the scope. Sleep is listed as an outcome in the scope. An STA was considered appropriate due to potentially different indications with quetiapine.

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		issues around these two medications are extremely different. Quetiapine is more likley than not to be used in combination with current antidepressants for non-response. Agomelatine is likely to be mainly for monotherapy. The major issue around the use of quetiapine is its risk/benefit ratio due to its not inconsiderable side effect profile. Agomelatine has an extremely good side effect profile. As a result, separate STA's may be most appropriate, though the background would be common to both.	
	Servier Laboratories	In line with the therapeutic strategy outlined in the updated NICE guidelines CG 23, agomelatine is likely to be positioned as a newer generation, better tolerated antidepressant for use in moderate to severe depression in primary care for patients who have failed to respond or tolerate initial treatment with an SSRI Further clarity is required about the appropriate comparator for the purpose of this STA. It would create an unjustifiable burden for Servier to model against every potential listed comparator. NICE updated guideline (CG23) for depression in adults (October 09) currently recommends that the clinician selects an appropriate antidepressant from the range of available options after initial SSRI failure. In order to be endorsed as cost effective by NICE, agomelatine should only need to demonstrate its cost effectiveness against one of the commonly prescribed antidepressants (e.g. duloxetine). If a cost effectiveness demonstration is required against more than one antidepressant, NICE should provide a rationale for this and offer guidance on which are the appropriate comparators. With reference to NICE TA 59, ECT is not an appropriate comparator based on its current NICE recommendation. ECT would be used in a different setting, in different patient groups with a view to achieving rapid but only short term improvements. This is not the therapeutic objective when using agomelatine.	NICE must appraise technologies within their licensed indication. The manufacturer is now invited to provide an evidence submission for the clinical and cost effectiveness of agomelatine. Relevant comparators are identified with consideration given specifically to routine and best practice. At the scoping workshop it was confirmed that this could include a range of treatments. For further details of factors that evidence providers should have due regard to when selecting comparator technologies for analyses in evidence submissions, see the Guide to the Methods of Technology Appraisal, June 2008, section 2.2.4 (www.nice.org.uk). NICE will invite the

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		Comments on sub-groups are referred to in an earlier section	manufacturer to attend a meeting to discuss the decision problem and to help ensure that it is specified appropriately. This meeting also provides an opportunity for the manufacturer to ask questions.
		To eliminate discrimination, special consideration should be given to the policy document 'Our choices in mental health – a framework for improving choice for people who use mental health services and their carers'. The scope should also state that PCTs make their own arrangements for the funding of agomelatine whilst NICE guidance is prepared. Modelling cost effectiveness Conducting an MTA of agomelatine and quetiapine together is not an option. They have different indications.	It is important that any information which could be relevant to promotion of equality and elimination of unlawful discrimination is reflected in the submission of evidence made for the appraisal.
Additional comments on the draft scope.	British Association for Psychopharmacology	None	Comment noted. No action required.
	Lundbeck	The 'related guidelines' lists the update and partial update to CG23 as due for publication in September 2009 and October 2009. These guidelines are now fully published.	Comment noted. The scope has been updated in line with the revised NICE clinical guideline for depression (CG90).

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	Servier Laboratories	Servier would encourage NICE to fully consider the immense burden that depression has on patients, their carers, their family, and on society, looking beyond the simple perspective of the NHS and PSS.	The appraisal will be conducted in accordance with the published process and methods. The NICE guide to the methods of technology appraisal (2009) specifies that NHS and PSS costs should be included as the reference case as well as cost per QALY.
		Agomelatine has a distinctly different profile than any other antidepressant and is the first new class of antidepressant to be made available to UK patients in over a decade. The scope should allow the limitations of current treatment options to be fully described such that the significantly reduced risk of discontinuation that is evident throughout agomelatine's clinical trial dossier is not overlooked because it is not fully captured within a cost per QALY calculation.	Comment noted. All important differences in costs and outcomes between technologies being compared should be captured in the evidence base for the appraisal.

The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope

NHS Quality Improvement Scotland
Novartis
GSK
RICE - Research Institute for the Care of Older People
Royal College of Nursing
Welsh Assembly Government
NPHS - Wales