National Institute for Health and Clinical Excellence

Single Technology Appraisal (STA)

Quetiapine for the treatment of generalised anxiety disorder

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	AstraZeneca	AstraZeneca would welcome the opportunity to discuss the appropriateness of an STA for quetiapine prolonged release in GAD at the scheduled scoping workshop. Discussions are currently ongoing with the regulatory authorities regarding the indication and appropriate positioning for Seroquel XL for the treatment of patients with GAD, versus available treatment guidelines. Commercial in confidence information removed	Comment noted. This topic has been referred to NICE as an STA.
	British Association for Psychopharmacology	yes, it is certainly appropriate to appraise the evidence relating to the efficacy and tolerability of quetiapine in the management of patients with generalised anxiety disorder (GAD). GAD is a common and imparing disorder; associated with many other problems; the existing treatment approaches are not ideal; and quetiapine is already being used 'off-label' for this indication.	Comment noted. No changes to the draft scope required
	Royal College of Psychiatrists	Yes, it is certainly appropriate to appraise the evidence relating to the efficacy and tolerability of quetiapine in the management of patients with generalised anxiety disorder (GAD). GAD is a common and imparing disorder; associated with many other problems; the existing treatment approaches are not ideal; and quetiapine is already being used 'off-label' for this indication.	Comment noted. No changes to the draft scope required
Wording	AstraZeneca	AstraZeneca suggests a minor rewording of the remit to: To appraise the clinical and cost effectiveness of quetiapine for the treatment of generalised anxiety disorder (GAD) within its licensed indication.	The remit from the Department of Health is as stated on the scope.
	British Association for Psychopharmacology	The wording seems appropriate.	Comment noted. No changes to the draft scope required

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	Royal College of Psychiatrists	The wording seems appropriate.	Comment noted. No changes to the draft scope required
Timing Issues	AstraZeneca	There has been no suggested timing for submission of evidence made by NICE on the covering letter. Consideration should be given to alignment with ongoing regulatory discussions.	Comment noted. This will be scheduled into the work programme accordingly.
	British Association for Psychopharmacology	The granting of a market authorisation for quetiapine for treatment of GAD would undoubtedly be followed by marketing efforts and it seems timely to produce guidance for primary and secondary care doctors.	Comment noted.
	Royal College of Psychiatrists	The granting of a market authorisation for quetiapine for treatment of GAD would undoubtedly be followed by marketing efforts and it seems timely to produce guidance for primary and secondary care doctors.	Comment noted.
Additional comments on the draft remit	British Association for Psychopharmacology	It would be worth considering whether the efficacy and tolerability data suggest the place of quetiapine in overall management - for example, after non-response to a licensed SSRI or SNRI or after unsuccessful treatment with CBT.	Attendees at the Scoping Workshop suggested that quetiapine would be a potential treatment in both of these positions in the treatment pathway. Therefore, the scope has been amended to include SSRIs, SNRIs and CBT as comparators. The decision problem may need to be interpreted in line with the licensed indication once it is known.

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	Royal College of Psychiatrists	It would be worth considering whether the efficacy and tolerability data suggest the place of quetiapine in overall management - for example, after non-response to a licensed SSRI or SNRI or after unsuccessful treatment with CBT.	Attendees at the scoping workshop suggested that quetiapine would be a potential treatment in both of these positions in the treatment pathway. Therefore, the scope has been amended to include SSRIs, SNRIs and CBT as comparators. The decision problem may need to be interpreted in line with the licensed indication once it is known.

Comment 2: the draft scope

Section	Consultees	Comments	Action
Background information	AstraZeneca	No comments	Comment noted.
	British Association for Psychopharmacology	The epidemiology of GAD is rather more certain than is suggested here. The systematic review of mental health problems in EU community samples of people aged 18-65 years reported by Wittchen and Jacobi (2005) provides reliable data on both the 12-month and lifetime prevalence of GAD.	Scope amended accordingly
	North Tyneside PCT	OK	Comment noted.
	Royal College of Psychiatrists	The epidemiology of GAD is rather more certain than is suggested here. The systematic review of mental health problems in EU community samples of people aged 18-65 years reported by Wittchen and Jacobi (2005) provides reliable data on both the 12-month and lifetime prevalence of GAD.	Scope amended accordingly
The technology/ intervention	AstraZeneca	AstraZeneca agrees with much of the technology description, however feels that it should be amended slightly to read as below: Quetiapine (Seroquel and Seroquel XL, AstraZeneca) is an oral atypical antipsychotic agent which is available in a standard and prolonged-release formulation. It acts on the norepinephrine, serotonin and dopamine neurotransmitter systems believed to associated with affective disorders. Quetiapine, and the active human plasma metabolite, N-desalkyl quetiapine, exhibit affinity for brain serotonin (5HT2) and dopamine D1- and D2-receptors. Additionally N-desalkyl quetiapine has high affinity for the norepinephrine transporter (NET). Quetiapine does not currently have a marketing authorisation in the UK for the treatment of GAD. The prolonged release formulation has been studied in double blind randomised placebo-controlled clinical trials as a short-term monotherapy for GAD. Two of the studies have incorporated active control arms (escitalopram or paroxetine). Quetiapine prolonged release has also been investigated in a placebo-controlled RCT as a monotherapy for maintenance therapy.	Comment noted. The scope has been updated. The scope is only intended to provide a brief introduction to the technology. Further details will be studied during the course of the appraisal.

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	British Association for Psychopharmacology	clarification that this is quetiapine monotherapy would be helpful	Comment noted. Guidance will only be issued in accordance with the marketing authorisation.
	North Tyneside PCT	OK	Comment noted.
	Royal College of Psychiatrists	Yes	Comment noted.
Population	AstraZeneca	Discussions are currently ongoing with the regulatory authorities regarding the indication and appropriate positioning for Seroquel XL for the treatment of patients with GAD, versus available treatment guidelines. Commercial in confidence information removed.	Comment noted.

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	British Association for Psychopharmacology	It would be worthwhile looking at two groups of adults - those aged 18-65 years and those above 65 years - as a number of studies (including one for quetiapine) have been performed in older adults.Generalised anxiety with comorbid depression needs consideration	At the scoping workshop it was suggested that the trial carried out in people age 65 and over was to satisfy a safety requirement stipulated by regulatory agencies for licensing. Attendees suggested there was no reason to expect that the technology would have a differential effect in people according to age and decided that it was not an appropriate subgroup. Evidence permitting, subgroups will be considered. These may include subgroups by co-morbidities and prior therapies.
	North Tyneside PCT	OK	Comment noted.

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	Royal College of Psychiatrists	It would be worthwhile looking at two groups of adults - those aged 18-65 years and those above 65 years - as a number of studies (including one for quetiapine) have been performed in older adults.	At the Scoping Workshop, it was suggested that the trial carried out in people age 65 and over was to satisfy a safety requirement stipulated by regulatory agencies for licensing. Attendees suggested there was no reason to expect that the technology would have a differential effect in people according to age and decided that it was not an appropriate subgroup.
Comparators	AstraZeneca	Within the draft scope, NICE suggests benzodiazepines, sedative antihistamines and antidepressants as comparators. AstraZeneca would welcome the opportunity to discuss potential comparators further at a confidential meeting with the institute post the scoping workshop in the context of the current proposed indication.	At the scoping workshop, it was suggested that all anti-depressants used in the treatment of GAD should be included as comparators. The decision problem may need to be interpreted in line with the licensed indication once it is known.
	British Association for Psychopharmacology	The comparators should include all drugs that have a current market authorisation for treatment of GAD, so in addition to paroxetine and venlafaxine, pregabalin, escitalopram and duloxetine should be included. The nature of the patient population differs in pharmacological and psychological treatment studies and it would seem sensible to limit the comparison to just pharmacological interventions. Benzodiazepines, however, are not an appropriate comparison as they should be used for only 2-4 weeks, and treatment of patients with GAD should be for a minimum of 6 months, as recommended by current guidance from NICE, the BAP and a number of other organisations.	At the scoping workshop, it was suggested that all anti-depressants used in the treatment of GAD should be included as comparators. The decision problem may need to be interpreted in line with the licensed indication once it is known.

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	North Tyneside PCT	We are pleased to see that a wide range of comparator drugs have been suggested for comparison with quetiapine, however we would welcome the addition of non-drug therapies such as cognitive behavioural therapy.	At the scoping workshop, it was suggested that CBT should be included as a comparator.
	Royal College of Psychiatrists	The comparators should include all drugs that have a current market authorisation for treatment of GAD, so in addition to paroxetine and venlafaxine, pregabalin, escitalopram and duloxetine should be included. The nature of the patient population differs in pharmacological and psychological treatment studies and it would seem sensible to limit the comparison to just pharmacological interventions. Benzodiazepines, however, are not an appropriate comparison as they should be used for only 2-4 weeks, and treatment of patients with GAD should be for a minimum of 6 months, as recommended by current guidance from NICE, the BAP and a number of other organisations.	At the scoping workshop, it was suggested that all anti-depressants used in the treatment of GAD should be included as comparators. The decision problem may need to be interpreted in line with the licensed indication once it is known.
	Department of Health	we feel that the list of comparators appears to be too limited. One of the mainstays of treatment for generalised anxiety disorder is CBT, yet this does not appear in the list of comparators which is restricted to other drugs (all of which have limited use).	At the scoping workshop, it was agreed that CBT should be included as a comparator.

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Outcomes	AstraZeneca	The outcomes measured in the registration studies included: Change from baseline in severity of anxiety as measured by the HAM-A total score and psychic/somatic cluster scores Response rates (≥50% reduction HAM-A total score) Remission rates (HAM-A total score ≤7) Clinical Global Impression Improvement (CGI-I) score of 1 ("very much improved" or 2 ("much improved") Time to recurrence of an anxiety event Change in depressive symptoms as measured by MADRS total score Health related quality of life and functioning as measured by the Q-LES-Q, SDS (Sheehan Disability Scale) Quality of sleep as measured by PSQI Tolerability and safety	Comment noted. Scope amended as per discussion at the Scoping Workshop.
	British Association for Psychopharmacology	In general terms, yes, but symptomatic remission is not included as an outcome measure for judging the efficacy of acute treatment, and the proportion who relapse (as well as the time to relapse) should be considered in longer term treatment. Metabolic changes need to be measured	Scope amended as per discussion at the Scoping Workshop.
	North Tyneside PCT	OK	Comment noted.
	Royal College of Psychiatrists	In general terms, yes, but symptomatic remission is not included as an outcome measure for judging the efficacy of acute treatment, and the proportion who relapse (as well as the time to relapse) should be considered in longer term treatment.	Scope amended as per discussion at the Scoping Workshop.
Economic analysis	AstraZeneca	AstraZeneca suggest using a cost utility analysis based on a Markov model design with a minimum of 1 year time horizon	Comment noted.
	British Association for Psychopharmacology	No comment	Comment noted.
	North Tyneside PCT	OK	Comment noted.

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	Royal College of Pathologists	Costs of monitoring therapy should be included in the economic analysis (see 'other considerations')	All costs incurred by the NHS will be included.
	Royal College of Psychiatrists	This seems appropriate.	Comment noted.
Equality and Diversity	British Association for Psychopharmacology	No comment	Comment noted.
	Royal College of Psychiatrists	No comment.	Comment noted.
Other considerations	British Association for Psychopharmacology	The review should focus on potential adverse effects of treatment particularly weight gain, altered glucose tolerance and metabolic syndrome as weight gain is a troublesome adverse effect seen in routine clinical practice.	Adverse effects are included as an outcome measure.
	Royal College of Pathologists	Scope should include a consideration of routine monitoring of quietapine therapy and the role (if any) of plasma quietapine measurements.	All costs incurred by the NHS will be included.
	Royal College of Psychiatrists	The review should focus on potential adverse effects of treatment particularly weight gain, altered glucose tolerance and metabolic syndrome as weight gain is a troublesome adverse effect seen in routine clincial practice.	Adverse effects are included as an outcome measure.

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Questions for consultation	AstraZeneca	Q. What is the likely place of quetiapine in the clinical treatment pathway? A. This would be based on our anticipated licence following regulatory review. Q. Quetiapine is available in a standard and sustained release preparation. Should both preparations be included as interventions, should the standard preparation be a comparator? A. Data on the use of the standard release formulation of quetiapine in GAD is limited and restricted to investigator sponsored studies in small patient numbers. The sustained release formulation is considered to potentially provide advantages over the standard release formulation in this patient population, and therefore the ongoing regulatory assessment relates to the sustained release formulation only. It is not considered appropriate to include the standard release formulation in the appraisal. As detailed above, AstraZeneca would welcome the opportunity to discuss potential comparators further at a confidential meeting with the institute post the scoping workshop. Q. Have the most appropriate comparators for the treatment of generalised anxiety disorder been included in the scope? Should off license use of anti-psychotics also be included? A. See above section on Comparators. Regarding inclusion of antipsychotics, this would depend on the availability of trial data. Q. Should psychological therapies be a comparator or are they used in combination with pharmaceutical treatments? A. See comments in the comparator section Q. Are there any 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? A. AstraZeneca suggest that sub groups by baseline severity of GAD may also be considered.	Responses noted. Guidance will only be issued in accordance with the marketing authorisation. As per above, the comparators have been changed to reflect the discussions at the workshop. The decision problem may need to be interpreted in line with the licensed indication once it is known.

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	British Association for Psychopharmacology	Please see the comment about including the full range of licensed comparator drugs, mentioned earlier. Psychological treatments should be alluded to but there have been no comparisons of quetiapine with CBT or other psychological treatments so lengthy consideration would not be worthwhile.	Comments noted. Attendees at the Scoping Workshop confirmed that CBT is currently used in clinical practice and it has been included as a comparator. Guidance will only be issued in accordance with the marketing authorisation.
	Royal College of Psychiatrists	Place in the clinical pathway: SSRIs are likely to remain the first line pharmacological treatments. Quetiapine is likely to be most appropriate for non-responders. Standard or sustained release: The marketing authorisation is likely to be for the XL version since this has a longer patent life. Both formulations should be considered. Unfortunately there is next to no data comparing the two formulations. Comparator drugs: Please see the comment about including the full range of licensed comparator drugs, mentioned earlier. Psychological treatments should be alluded to but there have been no comparisons of quetiapine with CBT or other psychological treatments so lengthy consideration would not be worthwhile. It would be pertinant to also compare the drug with off label uses of other antidepressants (e.g. other SSRIs e.g. fluoxetine). Subgroups: It would be advantageous to consider quetiapine in mixed anxiety and depression given the data suggesting effectiveness of quetiapine in depression.	Attendees at the Scoping Workshop confirmed that CBT is currently used in clinical practice and it has been included as a comparator. Guidance will only be issued in accordance with the marketing authorisation. Comments noted. Scope amended accordingly.
Additional comments on the draft	AstraZeneca	AstraZeneca has found it challenging to provide relevant comments given the stage within the regulatory process that quetiapine prolonged release finds itself. At this stage AstraZeneca has no further comments.	Adverse effects are included as an outcome measure.

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scope.	Royal College of Psychiatrists	It would perhaps be most sensible to consider an MTA of quetiapine for both depression and GAD, rather than reviewing these as two separate STAs.	This topic has been referred to NICE as an STA.

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

NHS Quality Improvement Scotland
Royal College of Nursing
Welsh Assembly Government
Public Health Wales NHS Trust
Pfizer