

National Institute for Health and Clinical Excellence

Proposed Single Technology Appraisal (STA)

Loxapine inhalation for the treatment of acute agitation and disturbed behaviours associated with schizophrenia or bipolar 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	Alexza Pharmaceuticals	Yes as this topic is relevant to New Horizons: A Shared Vision for Mental Health (2009) ¹ and to The National Service Framework for Mental Health: Modern Standards and Service Models (1999). ²	Comment noted. No action required.
	Royal College of Pathologists	The appraisal of use of alternative matrices for drug delivery is important. It is particularly important in situation where there may be difficulties in administering traditional drugs via intramuscular or intravenous routes. Therefore this worthy of NICE appraisal.	Comment noted. No action required.
	Royal College of Nursing	It is appropriate to consider novel methods to administer medications for this condition.	Comment noted. No action required.
Wording	Alexza Pharmaceuticals	Revise to: To appraise the clinical and cost effectiveness of Staccato® loxapine within the licensed indication for the <i>rapid control of agitation and disturbed behaviors in patients with schizophrenia or in patients with bipolar disorder</i> . <i>Staccato</i> Loxapine provides a rapid non-invasive treatment option for agitation in patients with schizophrenia or bipolar disorder. Currently available therapies for agitation have substantial limitations—namely, relatively slow onset of effect	Comment noted. Consultees agreed that the draft remit should be amended to also include patients with ' <i>disturbed behaviours</i> ', that is, 'to appraise the clinical and cost

¹ http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_109705

² http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_4009598

Appendix D- NICE's response to consultee and commentator comments on the draft scope and provisional matrix

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		(oral and IM agents), pain from administration (IM agents), and risks to caregivers of needle-stick injuries (IM agents). <i>Staccato</i> Loxapine addresses the unmet need for rapid onset of effect cited in expert consensus guidelines, while affording patients and clinicians the benefits of reliable, noninvasive administration. The addition of a rapidly-acting and noninvasive anti-agitation agent to the clinician's armamentarium is expected to meet the most important treatment requirements cited in expert consensus guidelines. [REDACTED]	effectiveness of loxapine inhalation for the treatment of acute agitation and disturbed behaviours in people with schizophrenia or bipolar disorder'.
	Royal College of Pathologists	Yes	Comment noted. No action required.
	Royal College of Nursing	No comment	No action required.
Timing Issues	Alexza Pharmaceuticals	[REDACTED]	Comment noted. No action required.
	Royal College of Pathologists	I am unable to provide comment on this as it is outside my or the colleges area of expertise.	Comment noted. No action required.
	Royal College of Nursing	The appraisal is not urgent, and the number of clinical trial is quite small. The time scales are appropriate.	Comment noted. No action required.

Comment 2: the draft scope

Section	Consultees	Comments	Action
Background information	Alexza Pharmaceuticals	Yes	Comment noted. No action required.
	Royal College of Pathologists	As is indicated there needs to be a definition of "agitation". It needs to be made explicit as to the administration route of the traditional medications.	Comment noted. Both oral and intramuscular

Appendix D- NICE's response to consultee and commentator comments on the draft scope and provisional matrix

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			<p>preparations of the comparator treatments have been included in the scope.</p> <p>At the scoping workshop consultees considered that agitation can be defined as a state of motor restlessness accompanied by mental tension. They recognised that in clinical studies, agitation is generally assessed using the 5-item positive and negative syndrome scale – excited component, however in clinical practice, diagnosis is often subjective. No action required.</p>
	Royal College of Nursing	<p>In building the rationale for this appraisal the evidence on the experience of anxiety and agitation from the perspectives of people with schizophrenia and bipolar disorder could be added. Acute anxiety and agitation is predictive of violence and early recognition alongside rapid and effective intervention may have many associated benefits. Episodes of anxiety and agitation are also predictive of relapse for those in remission. People with schizophrenia and bipolar also report that poor control of anxiety and agitation lead to thoughts of relapse and resultant increases in worry.</p>	<p>Comment noted. No action required.</p>
The technology/ intervention	Alexza Pharmaceuticals	<p>Revise: Loxapine inhalation (Staccato® loxapine) is a breath-actuated, single-use, hand-held, drug-device combination product that provides rapid systemic delivery of a</p>	<p>Comment noted. This section of the scope is intended to only provide a</p>

Appendix D- NICE's response to consultee and commentator comments on the draft scope and provisional matrix

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		<p>thermally-generated aerosol of loxapine. Oral inhalation through the product initiates the controlled rapid heating of a thin film of excipient-free loxapine to form a highly pure drug vapor. The rapid absorption of the drug provides peak plasma levels in the systemic circulation within 2 minutes after administration, resulting in a rapid onset of effect compared with currently available treatments. Loxapine is a dopamine-2 and serotonin-2a receptor antagonist which acts as a tranquiliser. The exact mechanism of action of loxapine has not been established.</p> <p>Loxapine inhalation is intended to rapidly treat acute agitation in patients with schizophrenia or bipolar disorder as a substitute for currently available parenteral or oral therapies. <i>Staccato</i> Loxapine is administered as needed at 5mg or 10mg, up to 3 doses in a 24-hour period.</p> <p>In the European Union (EU), oral and IM formulations of loxapine (Loxapac) remain available in France. To Alexza's knowledge, marketing approval of loxapine has never been withdrawn for safety reasons.</p> <p><i>Staccato</i> Loxapine has been studied in Phase II and Phase III clinical trials as an acute treatment in adults with agitation associated with bipolar I disorder or schizophrenia in comparison with placebo. No active comparator trials have been performed to date in this population.</p> <p>Phase II clinical trials of loxapine low-dose inhalation (<i>Staccato</i> Loxapine low dose) for the treatment of migraine have been completed.</p>	<p>brief description of the technology. At the workshop, consultees were reminded that the manufacturer would be able to describe the unique selling points of loxapine relative to other treatments in their submission for the Committee's consideration, should this topic be referred for appraisal. No action required.</p>
	Royal College of Pathologists	Yes	Comment noted. No action required
	Royal College of Nursing	No comment	No action required.
Population	Alexza Pharmaceuticals	<p>Agitation is a severe, disruptive, and morbid complication of many chronic mental illnesses, including schizophrenia and mania. The clinical program reported significant anti-agitation effects in both populations that were studied. Therefore, no evidence from the clinical trials suggests that there are specific sub-groups within this population that should be considered separately.</p>	<p>Comment noted. Consultees agreed that the population should be amended to include patients with either acute</p>

Appendix D- NICE's response to consultee and commentator comments on the draft scope and provisional matrix

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			agitation or disturbed behaviours, in line with the proposed marketing authorisation. The scope has been amended accordingly.
	Royal College of Pathologists	As long as each individual receiving the treatment options has a correct diagnosis made. There should be caution in the diagnosis of agitation in individual with dual diagnosis, such as dementia with cross over symptoms.	Comment noted. No action required.
	Royal College of Nursing	No comment	No action required.
Comparators	Alexza Pharmaceuticals	<p>In order to make relevant comment to this section for comparators reference to current NICE guidelines for violence and rapid tranquilisation³ and bipolar disorder⁴ and schizophrenia⁵ were made.</p> <p>In terms of best alternative care and current practice within the NHS, current NICE guidelines recommend that rapid tranquillisation, physical intervention and/or seclusion should only be considered once other strategies such as verbal de-escalation or intensive nursing techniques have failed to calm down an individual with agitation.</p> <p>In terms of rapid tranquillisation in clinical practice, oral formulations are generally the initial treatment option. If these are refused or unsuitable, parenteral medication is the next option and can be given by intramuscular (IM) injection or, in exceptional circumstances, intravenous injection. A combination of a benzodiazepine and an antipsychotic is commonly used.</p>	<p>Comment noted.</p> <p>Clinical specialists at the scoping workshop confirmed that the following treatments are most commonly prescribed for acute agitation in the UK: lorazepam, haloperidol, olanzapine, aripiprazole and risperidone, and therefore should be the key comparators for an</p>

³ <http://guidance.nice.org.uk/index.jsp?action=download&o=29718>

⁴ <http://guidance.nice.org.uk/CG38/Guidance>

⁵ <http://guidance.nice.org.uk/CG82/Guidance>

Appendix D- NICE's response to consultee and commentator comments on the draft scope and provisional matrix

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		<p>Typical antipsychotics, other than haloperidol, are not recommended due to the risk of cardiac and autonomic side effects. ECG monitoring is required, and there is an association with sudden death. There may also be concern about using a typical antipsychotic in combination with a benzodiazepine because of the risk of over sedation and respiratory depression.</p> <p>NICE guidelines recommend that IM injections of atypical antipsychotics should only be considered for managing an acute schizophrenic episode when discussion with the individual is impossible.</p> <p>Comparators:</p> <p>Oral and IM preparations of:</p> <ul style="list-style-type: none"> • Benzodiazepines (including lorazepam, diazepam, tempazepam) • Haloperidol • Oral atypical antipsychotics (including risperidone, olanzapine, aripiprazole, paliperidone (Schizophrenia only), amisulpiride, quetiapine and zotepine) • A benzodiazepine and haloperidol in combination <p>Also IV preparations</p> <ul style="list-style-type: none"> • Haloperidol 	<p>appraisal. Other benzodiazepines such as diazepam and temazepam are not routinely prescribed in the UK.</p> <p>Additional comparators which were suggested during consultation included paliperidone, amisulpride, quetiapine and zotepine. The clinical specialists at the scoping workshop confirmed that these treatments are not commonly prescribed for acute agitation in the UK. It was noted that zotepine is not available in the UK (treatment has been discontinued).</p> <p>Consultees agreed that the comparators defined in the draft scope are appropriate; however, aripiprazole should be added as another example of a suitable antipsychotic to treat acute agitation. The scope has been amended</p>

Appendix D- NICE's response to consultee and commentator comments on the draft scope and provisional matrix

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			accordingly.
	Royal College of Pathologists	I and the College of Pathologist do not treat patients with either disease process, but I am aware that the treatment options appear appropriate.	Comment noted. No action required.
	Royal College of Nursing	In acute care settings anxiolytics and anti-psychotics are commonly used alongside the psychological and psychosocial management of agitation in accordance with NICE Clinical Guideline No. 82. Comparing medication against medication may be confounded by patients' self management skills, and the availability of a carer or support staff with competencies in supporting patients to manage agitation.	Comment noted. Consultees agreed that the comparators defined in the draft scope are appropriate; however, consultees suggested that aripiprazole should be added as another example of a suitable antipsychotic to treat acute agitation. The scope has been amended accordingly.
Outcomes	Alexza Pharmaceuticals	<p>This intervention has the potential to impact both the quality of life of both the patients and any carers.</p> <p>Loxapine inhalation may be faster acting than currently available treatments and more acceptable to patients than intramuscular injections, influencing both patient preference and compliance.</p> <p>For physicians, the onset of effect within 10 minutes in a non-invasive formulation enables the clinician to quickly treat an unpredictable escalation of the agitation symptoms, without antagonizing the patient, thereby avoiding a potentially volatile and dangerous situation for the patient and those nearby.</p> <p>In the clinical trials the following outcomes were assessed:</p> <p>Primary Outcome</p> <ul style="list-style-type: none"> • Positive and Negative Syndrome Scale – Excited Component (P-EC) at 10, 20, 30, 45, 60, 90 minutes, 2, 4, 24 hours <p>Secondary Outcomes</p>	Comment noted. Consultees agreed that the outcomes defined in the draft scope are appropriate. No changes to the scope required.

Appendix D- NICE's response to consultee and commentator comments on the draft scope and provisional matrix

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		<ul style="list-style-type: none"> • Clinical Global Impression – Severity (CGI-I) • Agitation-Calmness Evaluation Scale (ACES) <p>QOL</p> <ul style="list-style-type: none"> • None 	
	Royal College of Pathologists	These are not clearly defined in the scope	<p>Comment noted. Consultees acknowledged that agitation level is a subjective measure; however the primary outcome in the pivotal trials for loxapine (change in PEC score) was well recognised in clinical practice and would serve as a useful outcome measure. Consultees agreed that the outcomes defined in the draft scope are appropriate. No changes to the scope required.</p>
	Royal College of Nursing	<p>Harms associated with agitation are violence, physical threats and verbal aggression. These are important outcomes within acute care settings and have associated costs in respect of increased length of stay, staff sickness, service utilisation, litigation, and harm to other patients. Parallels may be drawn to people at home in respect of family burden and adverse events.</p>	<p>Comment noted. The manufacturer will be encouraged to include all important outcomes in the evidence submission. No changes to the scope required.</p>
Economic analysis	Alexza Pharmaceuticals	A single episode can last for hours to days, and agitation occurs variably within and between patients. The majority of the identified population experience	Comment noted. No action required.

Appendix D- NICE's response to consultee and commentator comments on the draft scope and provisional matrix

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		agitation with a frequency of 10-12 episodes of agitation a year, and will seek medical attention for some fraction of them. Once an agitated patient enters the medical system, they may be treated and discharged from the emergency department; the majority are admitted to a hospital until they are stabilized. The economic analyses performed will be cost utility analyses. The time horizon over which the analysis should be performed is open to discussion. Note that as yet no economic analyses have been performed. No EQ5D or utility data has been defined in this population to date.	
	Royal College of Pathologists	Again there is a lack of this information. I or the College cannot comment on the time frame.	Comment noted. No action required.
	Royal College of Nursing	No comments.	No action required.
Equality and Diversity	Alexza Pharmaceuticals	Although the incidence of schizophrenia is higher in immigrants, urban populations, and possibly also in men and the incidence of bipolar disorder higher in black and other minority ethnic groups ⁶ , having examined recent reporting for mental health ⁷ there are no reasons to suggest that the intended use of this technology within these populations presents any equity issues within the UK NHS setting.	Comment noted. Consultees highlighted that the incidence of schizophrenia and bipolar disorder is higher in specific groups. However, no evidence was received of differential access to therapy or prognosis in these groups. No changes to the draft scope or remit required.
	Royal College of	The main issue here is that the drug will be used in individual who may lack	Comment noted. No

⁶ NHS clinical Knowledge Summaries - www.cks.nhs.uk

⁷ <http://www.dh.gov.uk/en/Healthcare/Mentalhealth/Equalities/index.htm>

Appendix D- NICE's response to consultee and commentator comments on the draft scope and provisional matrix

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	Pathologists	capacity due to their underlying schizophrenia. Advice should be taken as to how the investigation will deal with the lack of capacity.	evidence was received of differential access to therapy or prognosis in these groups. No changes to the draft scope or remit required.
	Royal College of Nursing	No comments.	No changes to the draft scope required.
Innovation	Alexza Pharmaceuticals	<p>This technology is innovative in that it provides a genuinely less stressful treatment option to IM injection for healthcare professionals administering treatment and in patients suffering acute agitation associated with schizophrenia and bipolar I disorder.</p> <p>The intervention can be considered a step-wise change in the management of the most challenging and distressed patients as it offers a less aggressive intervention and one that takes effect more rapidly than IM injections and oral treatment options that are currently available.</p>	Comment noted. The Committee will consider the innovative nature of loxapine inhalation, specifically if the innovation adds demonstrable and distinctive benefits of a substantial nature which may not have been adequately captured in the QALY measure. No action required.
Other considerations	Alexza Pharmaceuticals	<p>Patient preference is likely to be an important factor in deciding on suitable treatment options within this patient group.</p> <p>Patients who experience agitation would like to be treated with respect and dignity during an agitation episode. They prefer non-invasive treatments, and prefer to participate in their own treatment decisions.</p> <p>To date no patient preference data is available.</p>	Comment noted. No changes to the draft scope required.
	Royal College of Pathologists	None.	No action required.
	Royal College of	The incidence of respiratory and cardiac disease is higher in this population. The	Comment noted. No

Appendix D- NICE's response to consultee and commentator comments on the draft scope and provisional matrix

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	Nursing	effects of these conditions on concordance and effectiveness may need to be evaluated.	changes to the scope required.
Questions for consultation	Alexza Pharmaceuticals	<p>This technology does not require any service reorganisation or the need for additional staffing requirements for administration.</p> <p>When some affected individuals become agitated there is often the need for many professionals to be involved in the management of the situation. If the individual becomes very difficult or violent there can be the need to draw on the services and support of:</p> <ul style="list-style-type: none"> • Medical staff in primary and secondary care • Ambulance service • Social services • Police <p>The QALY will not identify the reduced burden that this technology has the potential to bestow on key professional that support this population. At the current time no evaluation or assessment has been performed to assess the impact of <i>Staccato</i> loxapine on these services and professionals.</p> <p>In terms of how should acute agitation be defined, which is critical to the development of the STA should this go ahead, and agreement on this definition would be a valuable outcome from the forthcoming scoping meeting.</p> <p>Our current approach to the definition of acutely-treated agitation is as follows: Agitation is a severe, disruptive, and morbid complication of many chronic mental illnesses, including schizophrenia, mania, and dementia. Agitation can be defined as a state of motor restlessness accompanied by mental tension. Signs of mounting tension can include pacing, hand wringing, intense staring, clenching fists, pressured speech, mutism, yelling, banging objects, or threatening others. Acute agitation associated with psychiatric diseases is one of the most important contributors to the continued stigmatization of mental illness. It results in severe distress in patients themselves, and in disruption of the lives of those who care for or live with them. In the clinical studies, agitation was assessed using the 5-item Positive and Negative Syndrome Scale – Excited</p>	<p>Comment noted.</p> <p>Consultees acknowledged that the QALY may not identify any reduced burden that loxapine inhalation could have on services. The Committee will consider the innovative nature of loxapine inhalation, specifically if the innovation adds demonstrable and distinctive benefits of a substantial nature which may not have been adequately captured in the QALY measure. No changes to the draft scope required.</p>

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		<p>Component (PEC) scale. Clinicians rated the severity of each of the 5 items (hostility, uncooperativeness, excitement, poor impulse control and tension) before and after treatment. In the pivotal trials, all items of the PEC showed improvement starting at 10 minutes in both patient populations.</p> <p>The forthcoming related guidelines as listed in appendix B include Clinical Guideline No. 82, Mar 2009 (Core interventions in the treatment and management of schizophrenia in primary and secondary care (update)); Clinical Guideline No. 38, Jul 2006 (The management of bipolar disorder in adults, children and adolescents in primary and secondary care); and Clinical Guideline No. 25, Feb 2005 (Violence: The short-term management of disturbed/violent behaviour in in-patient psychiatric settings and emergency departments).</p> <p>How will the potential STA for Staccato® loxapine be scheduled in relation to the development of these guidelines?</p>	
	Royal College of Pathologists	<p>The use of nasal treatment would likely be of benefit to both the patient, as it will reduce the need for injections, as well as staff as the reduction of the risks of needle stick injuries especially where an agitated individual is concerned will be of significant benefit.</p> <p>In my opinion from the information provided it is unlikely that this treatment will affect life years. Definition of the quality of nasal administration (unpleasant) to intramuscular or intravenous use (again unpleasant) is going to be difficult to quantify.</p>	<p>Comment noted. The Committee will consider the innovative nature of loxapine inhalation, specifically if the innovation adds demonstrable and distinctive benefits of a substantial nature which may not have been adequately captured in the QALY measure. No changes to the draft scope required.</p>
	Royal College of Nursing	<p>In acute settings, an additional safe and effective pharmacological intervention for the rapid treatment of agitation that can be controlled by patients or supervised would be of value. We would not envisage a significant change in clinical outcomes, however patient satisfaction may be improved if greater</p>	<p>The Committee will consider the innovative nature of loxapine inhalation, specifically if</p>

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		<p>control over the management of their health was achieved. For people in community settings and in remission they may have a preference for inhalation over oral administration. Again one would not anticipate any significant impact on health outcomes.</p> <p>We understand that Alexza Pharmaceuticals were advised last year they were concerns about data from phase I studies suggesting impaired lung function associated with the product's proprietary inhaler. The agency also raised questions about the ease with which the inhaler can be used correctly and the drug's stability in this formulation. We consider it pertinent to ensure these questions have been answered.</p> <p>We also note that there were some safety concerns with regards patients with lung function issues i.e. asthma or COPD.</p>	<p>the innovation adds demonstrable and distinctive benefits of a substantial nature which may not have been adequately captured in the QALY measure. No changes to the draft scope required.</p>
Additional comments	Department of Health	<p>In our view this is an appropriate topic for a technology appraisal, and the scope seems to be fine. We think that the comparators are right, and that the scope is aimed at the right population.</p> <p>The question about equalities is raised. We feel that the main issue here is that the target population is likely to have a relatively high proportion of people from the black community. This is because they have higher rates of schizophrenia diagnosed, and higher rates of detention under the Mental Health Act.</p>	<p>Comment noted. Consultees highlighted that the incidence of schizophrenia and bipolar disorder is higher in specific groups. However, no evidence was received of differential access to therapy or prognosis in these groups. No changes to the draft scope or remit required.</p>

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

Medicines and Healthcare products Regulatory Agency
 NHS Quality Improvement Scotland
 Public Health Wales NHS Trust
 Royal College of Physicians

National Institute for Health and Clinical Excellence
 Consultation comments on the draft remit and draft scope for the technology appraisal of loxapine inhalation for the treatment of acute agitation and disturbed behaviours associated with schizophrenia or bipolar disorder

Welsh Assembly Government

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Single Technology Appraisal (STA)

Loxapine inhalation for the treatment of acute agitation and disturbed behaviours associated with schizophrenia or bipolar disorder

Response to consultee and commentator comments on the provisional matrix of consultees and commentators (pre-referral)

Version of matrix of consultees and commentators reviewed:				
Provisional matrix of consultees and commentators sent for consultation				
Summary of comments, action taken, and justification of action:				
	<i>Proposal:</i>	<i>Proposal made by:</i>	<i>Action taken:</i> Removed/Added/Not included/Noted	<i>Justification:</i>
1.	Please invite EUFAMI – European Federation of Families of People with Mental Illness http://www.eufami.org/index.php?option=com_content&task=view&id=51&Itemid=75	Alexza	Not included	EUFAMI seems to be a federation. It has three UK members, two are on the matrix already and the third is Scottish (STAs are not implemented in Scotland).

Appendix D- NICE's response to consultee and commentator comments on the draft scope and provisional matrix

2.	If appropriate, please invite Shine Supporting People Affected by Mental Ill Health http://www.shineonline.ie/	Alexza		Not included	Shine is an Irish organisation.
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