



Schizophrenia: lurasidone

Evidence summary

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www.nice.org.uk/guidance/esnm48

This advice replaces ESNM15.

Key points from the evidence

The content of this evidence summary was up-to-date in September 2014. See [summaries of product characteristics \(SPCs\)](#), [British national formulary \(BNF\)](#) or the [MHRA](#) or [NICE](#) websites for up-to-date information.

Summary

Lurasidone ([Latuda](#), Sunovion Pharmaceuticals Europe Ltd) is licensed for treating schizophrenia in adults aged 18 years and over. It was launched in the UK in August 2014. Evidence from 5 short-term and 3 long-term studies suggests that lurasidone is effective at treating psychotic symptoms, and at preventing relapse in adults with schizophrenia. The [European Public Assessment Report \[EPAR\] for lurasidone](#) states that the adverse event profile of lurasidone is similar to that for other second-generation antipsychotics, the most common adverse events being akathisia and somnolence. NICE published an evidence summary on lurasidone for schizophrenia in April 2013 (ESNM15). However, a further long-term study has been published in full since that summary was prepared, and

another long-term study is described in the EPAR for lurasidone. These have been reviewed in this evidence summary, which now updates and replaces the earlier evidence summary on lurasidone.

Effectiveness	Safety
<ul style="list-style-type: none"> • In 292 adults with schizophrenia, lurasidone was found to be non-inferior to quetiapine prolonged release for preventing relapse of schizophrenia at 12 months. Probability of relapse was 23.7% with lurasidone compared with 33.6% with quetiapine prolonged release, (hazard ratio [HR] 0.728, 95% <u>confidence interval</u> [CI] 0.410 to 1.295, log-rank <u>p</u>=0.280). • In 285 adults with a primary diagnosis of schizophrenia, the probability of relapse up to week 28 was 42.2% with lurasidone and 51.2% with placebo. There was a statistically significant increase in time to relapse with lurasidone compared with placebo (p=0.039). 	<ul style="list-style-type: none"> • The <u>EPAR</u> states that lurasidone has a spectrum of adverse events that is similar to that for other second-generation antipsychotics. • From pooled safety data, there was some evidence of a dose-related effect on the incidence of extrapyramidal symptoms such as dystonia, tremor, Parkinsonism and salivary hypersecretion. These occurred most frequently in the lurasidone 111 mg daily group. • Lurasidone should be used with caution in people at high risk of suicide; people with Parkinson's disease; people with an increased risk of QT-interval prolongation; people with a history of seizures; people who are older and have dementia; people who already have diabetes or who are at high risk of developing it; people at an increased risk of hypotension; and people with renal and hepatic impairment. • Concomitant administration of lurasidone is contraindicated with strong inhibitors (for example clarithromycin) or inducers (for example carbamazepine) of the CYP3A4 enzyme. Dose adjustment of lurasidone is needed if used with moderate CYP3A4 inhibitors or inducers.

User factors	Resource implications
<ul style="list-style-type: none"> In 285 adults with a primary diagnosis of schizophrenia, the rate of discontinuation due to all causes was statistically significantly higher in the lurasidone group compared with the risperidone group (64% compared with 52% respectively, $p=0.004$). The most common adverse events observed with lurasidone are akathisia and somnolence (both occurring with an incidence 1 in 10 or more). People should avoid drinking grapefruit juice whilst taking lurasidone as it may increase the serum concentration of lurasidone. 	<ul style="list-style-type: none"> The cost for 28 days' treatment with lurasidone at a dose of 37–148 mg daily is estimated to be £90.72 to £181.44 (MIMS, September 2014). The cost for 28 days' treatment with alternative second-generation antipsychotics ranges from £0.97 to £194.56 depending on the drug and dose. See the alternative treatments section for more information.

Introduction and current guidance

The NICE clinical guideline on [psychosis and schizophrenia in adults](#) describes schizophrenia as a major psychiatric disorder, or cluster of disorders, characterised by psychotic symptoms that alter a person's perception, thoughts, mood and behaviour.

The NICE clinical guideline recommends that people with a first episode of schizophrenia, or an acute exacerbation or recurrence of schizophrenia, should be offered oral antipsychotic medication in conjunction with psychological interventions. The choice of antipsychotic medication should be made by the service user and healthcare professional together, taking into account the views of the carer if the service user agrees. Information should be provided on, and there should be discussion about, the likely benefits and possible side effects of each drug, including metabolic, extrapyramidal, cardiovascular, hormonal and other side effects (including unpleasant subjective experiences).

[Full text of Introduction and current guidance.](#)

Product overview

Lurasidone (Latuda, Sunovion Pharmaceuticals Europe Ltd) is licensed for treating schizophrenia in adults aged 18 years and over. It was launched in the UK in August 2014.

The recommended starting dose is 37 mg once daily. Dose increases should be based on physician judgement and observed clinical response. Lurasidone is effective at a dose range of 37–148 mg daily, and the maximum dose should not exceed 148 mg daily. It should be taken once daily together with a meal.

For people with moderate or severe renal impairment, end-stage renal disease, moderate or severe hepatic impairment, or people taking moderate CYP3A4 inhibitors, the recommended starting and maximum doses of lurasidone are lower.

The cost for 28 days' treatment with lurasidone at a dose of 37–148 mg daily is estimated to be £90.72 to £181.44 (MIMS, September 2014).

[Full text of Product overview.](#)

Evidence review

- The [EPAR for lurasidone](#) discusses the short- and long-term studies supporting the marketing authorisation for lurasidone for treating schizophrenia in adults. The EPAR states that overall, short-term efficacy of lurasidone has been sufficiently demonstrated for the dose range 37–148 mg lurasidone daily for treating psychotic symptoms in adults with schizophrenia.
- This evidence summary discusses in further detail, the 3 studies that provide the best long-term evidence of efficacy and safety for lurasidone for treating schizophrenia in adults.
- [Loebel et al. \(2013a\)](#) was a 12-month, double-blind, active comparator, non-inferiority study in 292 adults with a diagnosis of schizophrenia, using a previously randomised population from a 6-week double-blind RCT. Lurasidone (at a mean modal dose of 124.2 mg lurasidone hydrochloride daily) was found to be non-inferior to quetiapine prolonged release (XR; at a mean modal dose of 637.6 mg daily) for preventing relapse of schizophrenia at 12 months. The probability of relapse was 23.7% with lurasidone compared with 33.6% with quetiapine prolonged release (HR 0.728, 95% CI 0.410 to

1.295, log-rank $p=0.280$). The upper limit of the 95% CI was less than the pre-specified margin of 1.93; therefore lurasidone was shown to be non-inferior to quetiapine prolonged release in terms of relapse prevention. Compared with people in the quetiapine prolonged release group, people in the lurasidone group had a statistically significantly greater improvement in the secondary efficacy outcomes of change from 6-week study baseline at 12 months in Positive and Negative Syndrome Scale (PANSS) total score, and PANSS positive subscale score. For PANSS negative subscale score and Clinical Global Impressions Severity scale (CGI-S) score there was no significant difference between lurasidone and quetiapine (p value not stated).

- [Citrome et al. \(2012\)](#) was a 12-month, double-blind, active comparator RCT in 629 adults with schizophrenia or schizoaffective disorder. The trial was primarily a safety and tolerability study and efficacy measures were secondary outcomes. The rate of discontinuation due to all causes was statistically significantly higher in the lurasidone group compared with the risperidone group (64% compared with 52% respectively, $p=0.004$).
- Study D1050238 ([NCT01435928](#); reported in the [EPAR for lurasidone](#)) was a double-blind, placebo-controlled randomised withdrawal study of lurasidone (37 mg or 74 mg lurasidone daily, dosed flexibly) in adults with a primary diagnosis of schizophrenia. The first part of the study consisted of a screening phase and an open-label stabilisation phase (up to a maximum of 24 weeks, $n=676$). Participants whose schizophrenia responded to lurasidone treatment and met stabilisation criteria for at least 12 consecutive weeks were eligible to enter a randomised double-blind, withdrawal phase (up to a maximum of 28 weeks, $n=144$ randomised to lurasidone, $n=141$ randomised to placebo). Overall 30% of people in the lurasidone group, and 41% of people in the placebo group experienced relapse at some point during the study. Up to week 28, the probability of relapse was 42.2% in the lurasidone group, and 51.2% in the placebo group, and there was a statistically significant increase in time to relapse with lurasidone compared with placebo ($p=0.039$). PANSS total score and CGI-S increased (worsened) statistically significantly less in people in the lurasidone compared with the placebo group ($p=0.019$ for PANSS total score, and $p=0.002$ for CGI-S).
- The [EPAR for lurasidone](#) concluded that overall, taking the results from all 3 long-term studies into account, the long-term efficacy for lurasidone has been sufficiently demonstrated.
- The [EPAR for lurasidone](#) pooled safety data from studies including a total 5068 participants (3502 treated with lurasidone, 724 with placebo and 842 with other

medications). The EPAR concluded that lurasidone has a spectrum of adverse events that is similar to that for other second-generation antipsychotics. The incidence of some common adverse events including akathisia, somnolence and dizziness was dose related. In addition there was some evidence of a dose-related effect on the incidence of extrapyramidal symptoms such as dystonia, tremor, Parkinsonism and salivary hypersecretion. These adverse events occurred most frequently in the lurasidone 111 mg daily group. Nausea and vomiting occurred with a higher incidence for lurasidone than for the comparators. Effects of lurasidone on blood lipids, glucose and glycated haemoglobin (HbA1c) were limited, and the effect on weight increase was moderate, which is considered to indicate a relatively favourable metabolic profile.

- The [summary of product characteristics for lurasidone \(Latuda\)](#) states that in clinical studies, the most common adverse events occurring in at least 1 in 10 participants were akathisia and somnolence which were dose-related up to 111 mg daily.
- For a full list of cautions and contraindications with lurasidone, see the [summary of product characteristics for lurasidone \(Latuda\)](#).

[Full text of Evidence review.](#)

Context

The NICE clinical guideline on [psychosis and schizophrenia in adults](#) recommends that the choice of antipsychotic medication should be made by the service user and healthcare professional together, taking into account the views of the carer if the service user agrees. Information should be provided on, and there should be discussion about, the likely benefits and possible side effects of each drug, including metabolic, extrapyramidal, cardiovascular, hormonal and other side effects (including unpleasant subjective experiences).

The second-generation antipsychotics currently listed in the [British national formulary](#) (September 2014) are amisulpride, aripiprazole, clozapine, olanzapine, paliperidone, quetiapine, and risperidone.

The [BNF chapter](#) on antipsychotic drugs describes the relative efficacy and adverse effects of different antipsychotics. A National Prescribing Centre [patient decision aid](#) provides a guide to the relative adverse effects of different antipsychotics, based on information available at that time (2009).

[Full text of Context.](#)

Estimated impact for the NHS

It is likely that lurasidone may represent an additional treatment option alongside existing antipsychotics for adults with schizophrenia. Local decision makers will need to consider the available evidence on efficacy and safety, as well as the higher cost of lurasidone compared with some existing antipsychotic medications (see the [alternative treatments section](#) for more information). As with choice of all antipsychotic medicines, individual factors for people with schizophrenia are a key factor when making treatment decisions.

[Full text of Estimated impact for the NHS.](#)

About this evidence summary

'Evidence summaries: new medicines' provide summaries of key evidence for selected new medicines, or for existing medicines with new indications or formulations, that are considered to be of significance to the NHS. The strengths and weaknesses of the relevant evidence are critically reviewed within this summary to provide useful information for those working on the managed entry of new medicines for the NHS, **but this summary is not NICE guidance.**

Full evidence summary

Introduction and current guidance

The NICE clinical guideline on [psychosis and schizophrenia in adults](#) describes schizophrenia as a major psychiatric disorder, or cluster of disorders, characterised by psychotic symptoms that alter a person's perception, thoughts, mood and behaviour. Each person with the disorder will have a unique combination of symptoms and experiences. NICE states that, over a lifetime, about 1% of the population will develop schizophrenia.

The NICE clinical guideline recommends that people with a first episode of schizophrenia, or an acute exacerbation or recurrence of schizophrenia, should be offered oral antipsychotic medication in conjunction with psychological interventions. The choice of antipsychotic medication should be made by the service user and healthcare professional together, taking into account the views of the carer if the service user agrees. Information

should be provided on, and there should be discussion about, the likely benefits and possible side effects of each drug, including metabolic, extrapyramidal, cardiovascular, hormonal and other side effects (including unpleasant subjective experiences).

NICE published an evidence summary on lurasidone for schizophrenia in April 2013 (ESNM15). However, a further long-term study has been published in full since that summary was prepared, and another long-term study is described in the EPAR for lurasidone. These have been reviewed in this evidence summary, which now updates and replaces the earlier evidence summary on lurasidone.

Product overview

Drug action

Lurasidone is a second-generation antipsychotic drug which selectively blocks dopamine and monoamine effects. It binds strongly to certain dopaminergic and serotonergic receptors (primarily D2, 5-HT_{2A} and 5-HT₇), as well as blocking some α -adrenergic receptors. It is a partial agonist of the 5HT_{1A} receptor. Lurasidone does not bind to cholinergic or muscarinic receptors ([lurasidone \[Latuda\] summary of product characteristics](#)).

Licensed therapeutic indication

Lurasidone ([Latuda](#), Sunovion Pharmaceuticals Europe Ltd) is licensed for treating schizophrenia in adults aged 18 years and over. It was launched in the UK in August 2014.

Course and cost

Lurasidone is available as film-coated tablets containing 18.5 mg, 37 mg and 74 mg of lurasidone as lurasidone hydrochloride.

The recommended starting dose for most people is 37 mg once daily. No initial dose titration is required. Dose increases should be based on physician judgement and observed clinical response. Lurasidone is effective at a dose range of 37–148 mg once daily, and the maximum dose should not exceed 148 mg daily. It should be taken once daily together with a meal ([lurasidone \[Latuda\] summary of product characteristics](#)).

For people with moderate or severe renal impairment, end-stage renal disease, moderate hepatic impairment, or people taking moderate CYP3A4 inhibitors, the recommended starting dose of lurasidone is 18.5 mg once daily and the maximum dose should not exceed 74 mg daily. For people with severe hepatic impairment the recommended starting dose of lurasidone is 18.5 mg once daily and the maximum dose should not exceed 37 mg daily ([lurasidone \[Latuda\] summary of product characteristics](#)).

All strengths of lurasidone cost £90.72 per 28 tablets ([MIMS](#), September 2014). Therefore the cost for 28 days' treatment with lurasidone at a dose of 37–148 mg daily is estimated to be £90.72 to £181.44.

Evidence review

The [European Public Assessment Report \(EPAR\) for lurasidone](#) discusses the 5 short-term (6 weeks) and 3 long-term (52 weeks) studies supporting the marketing authorisation for lurasidone for treating schizophrenia in adults. The EPAR states that overall, short-term efficacy of lurasidone has been sufficiently demonstrated for the dose range 40–160 mg lurasidone hydrochloride daily (equivalent to 37–148 mg lurasidone daily) for treating psychotic symptoms in adults with schizophrenia. However, no consistent dose-response relationship was observed.

This evidence summary discusses in further detail, the 3 studies that provide the best long-term evidence of efficacy and safety for lurasidone for treating schizophrenia in adults. Two of the studies ([Loebel et al. 2013a](#) and [Citrome et al. 2012](#)) have been published in full. An additional study (D1050238; [NCT01435928](#)) has only been published in poster form but is reported briefly from the [EPAR for lurasidone](#).

[Loebel et al \(2013a\)](#)

- Design: 12-month, double-blind, non-inferiority study using a previously randomised population from a 6-week, double-blind randomised controlled trial (RCT; [Loebel et al. 2013b](#)).
- Population: 292 adults (83% of participants who completed the original 6-week RCT) aged 18 to 75 years (mean age 37.6 years) with a diagnosis of schizophrenia (defined by Diagnostic and Statistical Manual of Mental Disorders, fourth edition, Text Revision [DSM-IV-TR] criteria), a mean illness duration of 11.2 years, a mean Clinical Global Impressions Severity scale (CGI-S) score of 3.2 (CGI-S has a range of 1 [healthy, not

ill] to 7 [among the most severely ill]), and a mean Positive and Negative Syndrome Scale (PANSS) total score of 68.9 (PANSS is a 30-item 7-point [1–7] scale with higher scores indicating more severe symptoms).

- Intervention and comparison: participants remained on the same drug that they were randomised to receive during the initial 6-week double-blind RCT, apart from people that were originally randomised to placebo who were switched to lurasidone. A total of 151 people continued on lurasidone (dosed flexibly from 37–148 mg lurasidone daily, mean modal dose of 124.2 mg lurasidone hydrochloride daily), 56 people changed from placebo to lurasidone (dosed flexibly from 37–148 mg lurasidone daily, mean modal dose of 130.0 mg lurasidone hydrochloride daily) and 85 people continued on quetiapine prolonged release (XR; dosed flexibly from 200–800 mg daily, mean modal dose 637.6 mg) double-blind for 12 months. Allocation concealment was not described and so is unclear.
- Outcomes: The primary outcome was time to relapse of psychotic symptoms. Relapse was defined as the earliest occurrence of any of the following 3 criteria: worsening of 30% or more in the PANSS total score from day 42 of the initial acute treatment study and a CGI-S score of 3 or more, rehospitalisation for worsening of psychosis, or emergence of suicidal ideation, homicidal ideation or risk of harm. Non-inferiority of lurasidone to quetiapine prolonged release was shown if the upper limit of the 95% confidence interval [CI] around the hazard ratio [HR] for the probability of relapse at 12 months between the groups was less than the pre-specified non-inferiority margin of 1.93. Secondary efficacy outcomes included changes in PANSS total and subscale scores, CGI-S score, Negative Symptom Assessment scale, and Montgomery–Åsberg Depression Rating Scale (MADRS; a 10-item, 6 point [0–6] scale with higher scores indicating for severe symptoms). More information on rating scales and their clinical usefulness is available in a review article by [Mortimer \(2007\)](#) and an article by [Montgomery and Asberg \(1979\)](#). Safety evaluations included vital signs, laboratory tests, 12-lead electrocardiogram, adverse events, and extrapyramidal symptoms. The primary relapse analysis population only included subjects who were randomised to lurasidone or quetiapine in the original 6-week study, and who met clinical response criteria on day 42 (defined as a 20% or greater reduction in PANSS total score from acute study baseline and a CGI-S score of 4 or less). The secondary efficacy analysis population and the safety analysis population in addition contained people who were randomised to placebo in the original 6-week study and had been switched to lurasidone in the current study.

Table 1 Summary of [Loebel et al. \(2013a\)](#)

	Lurasidone 37–148 mg daily (who received lurasidone in the original 6-week study)	Quetiapine prolonged release 200–800 mg daily (who received quetiapine prolonged release in the original 6-week study)	Lurasidone 37–148 mg daily (who received placebo in the original 6-week study)	Analysis
Randomised	n=151	n=85	n=56	
Efficacy	n=139	n=79	Not included in the primary relapse analysis	
Primary outcome: probability of relapse at 12 months	23.7%	33.6%		HR for lurasidone compared with quetiapine prolonged release 0.728, 95% CI 0.410 to 1.295, log-rank p=0.280. The upper limit of the 95% CI was less than the pre-specified margin of 1.93, therefore lurasidone was shown to be non-inferior to quetiapine prolonged release in terms of relapse prevention
Selected secondary outcomes:				
Efficacy	n=132	n=72	n=52	

LS mean change in PANSS total score at 12 months from original 6-week study baseline (SE) ^a	-34.6 (1.8) points	-25.7 (2.6) points	-34.0 (2.8) points	At 12 months, lurasidone was statistically significantly more effective than quetiapine ($p < 0.01$) ^b
LS mean change in CGI-S score at 12 months from original 6-week study baseline (SE) ^a	-1.9 (0.1) points	-1.6 (0.1) points	-2.0 (0.1) points	No significant difference between lurasidone and quetiapine (p value not stated) ^b
LS mean change in MADRS score at 12 months from original 6-week study baseline (SE) ^a	-6.0 (0.6) points	-3.8 (0.9) points	-5.3 (1.0) points	At 12 months, lurasidone was statistically significantly more effective than quetiapine ($p < 0.05$) ^b
Safety	n=151	n=85	n=56	
Participants reporting at least 1 adverse event	64.2% (97/151)	71.8% (61/85)	62.5% (35/56)	No statistical analyses reported
Participants reporting akathisia	12.6% (19/151)	2.4% (2/85)	10.7% (6/56)	No statistical analyses reported
Participants reporting extrapyramidal-related adverse events	11.9% (18/151)	3.5% (3/85)	21.4% (12/56)	No statistical analyses reported

Discontinuation of drug (all causes)	48% (73/151)	61% (52/85)	48% (27/56)	No statistical analyses reported
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Abbreviations: CGI-S, Clinical Global Impression, Severity; CI, confidence interval; HR, hazard ratio; LS, least squares; MADRS, Montgomery–Åsberg Depression Rating Scale; n, number of patients; NR, not reported; NS, not significant; p, p-value; PANSS, Positive and Negative Syndrome Scale; SE, standard error.

^a More information on rating scales and their clinical usefulness is available in a review article by Mortimer (2007) and an article by Montgomery and Asberg (1979).

^b Note lurasidone group in this comparison only included people originally randomised to lurasidone. No statistical analysis was reported for the difference between the quetiapine group and the group originally randomised to placebo and switched to lurasidone.

Citrome et al. (2012)

- Design: 12-month, double-blind RCT in 68 centres.
- Population: 629 adult outpatients aged 18 to 75 years (mean age 42 years) with schizophrenia or schizoaffective disorder. In the safety population (all randomised participants who received at least 1 dose of study medication, n=621), 69% were men. Participants had to have had schizophrenia or schizoaffective disorder for at least a year (mean duration 16.7 years in the safety population); had been clinically stable for at least 8 weeks before randomisation; and had disease scores indicating illness of moderate, or less than moderate, severity. In the safety population at baseline, mean PANSS total score was 65.1; mean CGI-S score was 3.4; and mean MADRS total score was 7.7.
- Intervention and comparison: after a 14-day screening period and a 7-day transition phase during which antipsychotic medication and medication used for movement disorders were discontinued, participants were randomised to receive lurasidone 74 mg once daily or risperidone 2 mg once daily on days 1 and 2, increased to 4 mg once daily on day 3, in a 2:1 ratio. Doses were adjusted at weekly intervals if necessary, 1 dose level at a time, to between 37mg and 111 mg daily for lurasidone and 2 mg and 6 mg daily for risperidone. The mean daily dose of lurasidone hydrochloride was 84.7 mg (\pm 21.8 mg) and the mean daily dose of risperidone was 4.3 mg (\pm 1.0 mg). Allocation to treatment was concealed.

- Outcomes: the main outcomes of this study were safety outcomes, including adverse events, vital signs, electrocardiography and laboratory tests. Secondary outcomes included evaluation of long-term efficacy, such as relapse rates and changes in PANSS total score, CGI-S score and MADRS total score.

Table 2 Summary of [Citrome et al. \(2012\)](#)

	Lurasidone 37–111 mg/ day)^a	Risperidone 2–6 mg/ day)^a	Analyses
Randomised	n=427	n=202	
Safety^{b, c}	n=419	n=202	
Participants reporting at least 1 adverse event	84.5% (354/419)	84.7% (171/202)	No tests of statistical significance reported
Participants reporting at least 1 extrapyramidal adverse event	12.9% (54/419)	15.8% (32/202)	No tests of statistical significance reported
Participants reporting at least 1 metabolic-related adverse event	11.7% (49/419)	20.8% (42/202)	p=0.004
Discontinuation of drug (all causes)	64% (269/419)	52% (105/202)	p=0.004
Efficacy^d	n=410	n=198	

Relapse rate ^e	20% (82/410)	16% (32/198)	Relapse HR for lurasidone compared with risperidone 1.31, 95% CI 0.87 to 1.97, p=0.194. Non-inferiority of lurasidone compared with risperidone was not demonstrated because the upper limit of the 95% CI was greater than the pre-specified margin of 1.6 ^f
Change in PANSS total score, baseline to 12 months ^g	-4.7 points (95% CI -6.4 to -3.0)	-6.5 points (95% CI -8.8 to -4.3)	No significant difference (p value not stated)
Change in CGI-S score, baseline to 12 months ^g	-0.4 points (95% CI -0.5 to -0.3)	-0.4 points (95% CI -0.5 to -0.2)	No significant difference (p value not stated)
Change in MADRS total score, baseline to 12 months ^g	-0.8 points (95% CI -1.6 to -0.0)	-2.4 points (95% CI -3.4 to -1.4)	At 12 months risperidone was statistically significantly more effective than lurasidone (difference 1.6, p=0.007)

Abbreviations: CI, confidence interval; CGI-S, Clinical Global Impressions Severity scale; HR, hazard ratio; MADRS, Montgomery–Åsberg Depression Rating Scale; PANSS, Positive and Negative Syndrome Scale.

^a Dose could be adjusted at weekly intervals.

^b The trial was primarily a safety and tolerability study and efficacy measures were secondary outcomes, therefore safety has been reported first in the table followed by efficacy measures.

^c The safety population included all randomised participants who received at least 1 dose of study medication.

^d Efficacy analyses were undertaken in the intention-to-treat population, defined as all randomised participants who received at least 1 dose of study medication and had baseline and at least 1 post-baseline measure of PANSS or CGI-S scores.

^e Relapse was defined as any of the following: worsening of PANSS total score by more than 30% from baseline and CGI-S score of more than 3; rehospitalisation for worsening of psychosis; emergence of suicidal ideation, homicidal ideation or risk of harm to self or others.

^f The EPAR for lurasidone states that non-inferiority of lurasidone compared with risperidone was not demonstrated. However, the study authors report that interpretation of the pre-planned non-inferiority test was not possible because observed relapse rates in the study were much lower than the relapse rates of 35% that the pre-planned non inferiority margin was based on.

^g More information on rating scales and their clinical usefulness is available in a review article by Mortimer (2007) and an article by Montgomery and Asberg (1979).

Clinical effectiveness

Loebel et al. (2013a) found that lurasidone (at a mean modal dose of 124.2 mg lurasidone hydrochloride daily) was non-inferior to quetiapine prolonged release (at a mean modal dose of 637.6 mg daily) for preventing relapse of schizophrenia at 12 months. The probability of relapse was 23.7% with lurasidone compared with 33.6% with quetiapine prolonged release; HR 0.728, 95% CI 0.410 to 1.295; log rank p=0.280. This was in a population of adults with an acute exacerbation of schizophrenia, whose disease had responded to treatment with lurasidone or quetiapine prolonged release in a 6-week double-blind, placebo-controlled study (the primary relapse analysis population). A sensitivity analysis involving all participants treated with lurasidone or quetiapine in the original 6-week study, irrespective of responder status, found consistent results to the

primary analysis and showed that the probability of relapse was 23.0% with lurasidone compared with 35.8% with quetiapine prolonged release (HR 0.660, 95% CI 0.381 to 1.143, log rank $p < 0.05$).

The probability of hospitalisation at 12 months was statistically significantly lower for people in the lurasidone group compared with the quetiapine prolonged release group in the primary relapse analysis population (9.8% compared with 23.1% respectively, $p < 0.05$).

Compared with people in the quetiapine prolonged release group, people in the group originally randomised to lurasidone had a statistically significantly greater improvement in the secondary efficacy outcomes of change from 6-week study baseline at 12 months in PANSS total score, PANSS positive subscale score and MADRS. For PANSS negative subscale score and CGI-S score there was no significant difference between lurasidone and quetiapine (p value not stated).

Citrome et al. (2012) was primarily a safety and tolerability study, and efficacy measures were secondary outcomes. Relapse rates were 20% with lurasidone (at a mean dose of 84.7 mg lurasidone hydrochloride daily) and 16% with risperidone (at a mean dose of 4.3 mg daily). The relapse HR comparing lurasidone with risperidone was 1.31 (95% CI 0.87 to 1.97; $p = 0.194$). Non-inferiority for lurasidone compared with risperidone was pre-planned as being demonstrated if the upper limit of the 95% CI was lower than the pre-specified non-inferiority margin of 1.6. The EPAR for lurasidone states that non-inferiority of lurasidone relative to risperidone was not demonstrated since the upper limit was greater than 1.6. However, the non-inferiority margin was based on expected relapse rates of 35% for both treatment groups after 1 year. The observed relapse rates were much lower than this and Citrome et al. (2012) report that the pre-planned non-inferiority test of lurasidone compared with risperidone was not interpretable because of the much smaller number of observed relapse events.

No significant differences in improvements in PANSS total scores and CGI-S scores were observed at any point during the 12-month study between the lurasidone and risperidone groups. When MADRS scores were considered, risperidone was found to be statistically significantly more effective than lurasidone at 12 months (difference 1.6, $p = 0.007$) but not at any other time point analysed.

Study D1050238 (NCT01435928; reported in the EPAR for lurasidone).

Study D1050238 was a double-blind, placebo-controlled randomised withdrawal study of

lurasidone in adults with a primary diagnosis of schizophrenia. The first part of the study consisted of a screening phase and an open-label stabilisation phase (up to a maximum of 24 weeks, n=676). Participants whose schizophrenia responded to lurasidone treatment, and met stabilisation criteria for at least 12 consecutive weeks were eligible to enter a double-blind randomised withdrawal phase (up to a maximum of 28 weeks, n=144 randomised to lurasidone, n=141 randomised to placebo). During the open-label stabilisation phase, participants received lurasidone 37 mg or 74 mg daily, flexibly-dosed. People who entered the double-blind withdrawal phase received either the same dose of lurasidone they were on at the end of the open-label stabilisation phase, or matching placebo.

The primary objective was evaluation of efficacy of lurasidone for maintenance treatment of schizophrenia, assessed by the time to first relapse event during the double-blind phase. Secondary objectives included safety and tolerability.

Overall 30% of people in the lurasidone group (43/144), and 41% of people in the placebo group (58/141) experienced relapse at some point during the study. Up to week 28, the probability of relapse was 42.2% in the lurasidone group and 51.2% in the placebo group, and there was a statistically significant increase in time to relapse with lurasidone compared with placebo ($p=0.039$). Sensitivity analysis found a statistically significant difference between the groups in favour of lurasidone (HR for lurasidone compared with placebo 0.66, 95% CI 0.45 to 0.98, $p=0.041$).

Overall, PANSS total score and CGI-S score increased (worsened) statistically significantly less in people in the lurasidone group compared with the placebo group ($p=0.019$ for PANSS total score and $p=0.002$ for CGI-S).

Safety and tolerability

Citrome et al. (2012) found that the proportion of participants reporting 1 or more adverse event was similar in the lurasidone (mean dose of 84.7 mg lurasidone hydrochloride daily) and risperidone (mean dose 4.3 mg daily) groups (84.5% compared with 84.7% respectively). Extrapyramidal symptom-related adverse events were less frequent in the lurasidone group (12.9% in the lurasidone group compared with 15.8% in the risperidone group; no p value given). Metabolic-related adverse events were statistically significantly less frequent in the lurasidone group (11.7% in the lurasidone group compared with 20.8% in the risperidone group, $p=0.004$). However, the rate of discontinuation due to all causes was statistically significantly higher in the lurasidone group compared with the risperidone

group (64% compared with 52% respectively, $p=0.004$).

Statistically significantly more participants in the lurasidone group reported nausea (16.7%), vomiting (10.0%) and akathisia (14.3%) compared with the risperidone group (10.9%, 3.5% and 7.9% respectively). Conversely, statistically significantly more participants in the risperidone group reported constipation (6.9%) and weight gain (19.8%) compared with the lurasidone group (1.9% and 9.3% respectively).

Loebel et al. (2013a) found that the proportion of participants reporting 1 or more adverse event was 62.5% in the group originally randomised to placebo then switched to lurasidone (mean modal daily dose of 130.0 mg lurasidone hydrochloride), 64.2% in the group originally randomised to lurasidone (mean modal daily dose of 124.2 mg lurasidone hydrochloride) and 71.8% in the group originally randomised to quetiapine (mean modal daily dose of 637.6 mg). The majority of adverse events in all treatment groups were reported as being mild to moderate. Extrapyramidal symptom-related adverse events occurred more frequently with lurasidone (21.4% in the group originally randomised to placebo then switched to lurasidone, 11.9% in the group originally randomised to lurasidone, and 3.5% in the group originally randomised to quetiapine prolonged release [no p values given]). Akathisia was also more common with lurasidone (10.7% in the group originally randomised to placebo then switched to lurasidone, 12.6% in the group originally randomised to lurasidone, and 2.4% in the group originally randomised to quetiapine [no p values given]).

Safety analyses based on observed cases (those participants with 6-week study baseline and extension study 12-month values available) found that both lurasidone and quetiapine prolonged release had minimal effect on weight, body mass index and waist circumference. At 12-months, minimal effects on metabolic parameters including lipids and measures of glycaemic control were observed in both lurasidone and quetiapine prolonged release groups. Median changes in prolactin levels were similar for lurasidone and quetiapine prolonged release at 12 months and no other clinically relevant differences were observed for any other laboratory values. There were no clinically significant treatment-emergent ECG abnormalities with lurasidone or quetiapine prolonged release.

In study D1050238 (NCT01435928) the overall safety profile of lurasidone was broadly comparable to placebo during the double-blind phase. Metabolic parameters, prolactin, and weight increase were similar in both groups, and no changes in QT interval were observed. No safety signal in terms of suicidality was noted with lurasidone.

The [EPAR for lurasidone](#) pooled safety data from studies including a total 5068 participants with schizophrenia (3502 treated with lurasidone, 724 with placebo and 842 with other medications). The EPAR concluded that lurasidone has a spectrum of adverse events that is similar to that for other second-generation antipsychotics. The incidence of some common adverse events including akathisia, somnolence and dizziness was dose related. In addition, there was some evidence of a dose-related effect on the incidence of extrapyramidal symptoms such as dystonia, tremor, Parkinsonism and salivary hypersecretion. These adverse events occurred most frequently in the lurasidone 111 mg daily group. Nausea and vomiting occurred with a higher incidence for lurasidone than for the comparators. Effects of lurasidone on blood lipids, glucose and glycated haemoglobin (HbA1c) were limited, and the effect on weight increase was moderate, which is considered to indicate a relatively favourable metabolic profile.

The [summary of product characteristics for lurasidone \(Latuda\)](#) states that in clinical studies, the most common adverse events occurring in at least 1 in 10 participants were akathisia and somnolence which were dose-related up to 111 mg daily.

The [summary of product characteristics](#) states that precautions for using lurasidone include people who have a high risk of suicide; people with Parkinson's disease; people with an increased risk of QT-interval prolongation; people with a history of seizures; people who are older and have dementia; people who already have diabetes or who at high risk of developing it; people at an increased risk of hypotension; and people with renal and hepatic impairment. It also states that antipsychotics can increase the risk of a person developing extrapyramidal symptoms, tardive dyskinesia, neuroleptic malignant syndrome, venous thromboembolism, hyperprolactinaemia, and weight gain.

The [summary of product characteristics](#) states that concomitant administration of lurasidone and strong CYP3A4 inhibitors (for example clarithromycin) or strong CYP3A4 inducers (for example carbamazepine) is contraindicated. When lurasidone is used with moderate CYP3A4 inhibitors a lower starting dose of 18.5 mg once daily is recommended and the maximum dose should not exceed 74 mg once daily. When lurasidone is used with mild or moderate CYP3A4 inducers, the efficacy of lurasidone should be carefully monitored and dose adjustment may be needed.

Because grapefruit juice inhibits CYP3A4, it may increase serum concentrations of lurasidone, however concomitant use of grapefruit juice and lurasidone has not been assessed. The [summary of product characteristics](#) states that people should avoid drinking grapefruit juice whilst taking lurasidone.

Some [product-specific information and advice](#) about antipsychotic drugs provided by the Medicines and Healthcare Products Regulatory Agency warned that there is an increased risk of stroke and a small increased risk of death when antipsychotics are used in older people with dementia. The [summary of product characteristics for lurasidone \(Latuda\)](#) states that lurasidone has not been studied in elderly patients with dementia, and that it should be used with caution in elderly patients with dementia who have risk factors for stroke.

Evidence strengths and limitations

The studies included in this evidence summary provide longer-term data on the efficacy, safety and tolerability of lurasidone for treating schizophrenia in adults, however they have some limitations.

The included studies report whether or not treatments had a statistically significant effect on several rating scales used to assess treatment response in schizophrenia. However, whether statistically significant effects on these scales are also [clinically significant](#) is difficult to establish. [Mortimer \(2007\)](#) discusses the usefulness of symptom rating scales in evaluating the outcome of people with schizophrenia.

The dropout rates seen in the studies were high. In [Citrome et al. \(2012\)](#), only 34% of participants were still taking lurasidone at 12 months compared with 44% still taking risperidone. In [Loebel et al. \(2013a\)](#) 52% of people were still taking lurasidone at 12 months, compared with 39% still taking quetiapine prolonged release. The [EPAR for lurasidone](#) states that it is questionable whether any of the various types of statistical analyses performed were conservative enough to address these missing values.

In [Loebel et al. 2013a](#), participants were enrolled from an initial 6-week study, and did not undergo re-randomisation. This could have potentially introduced selection bias into the groups. The EPAR for lurasidone states that the degree of selection bias meant that the results of the study could not be considered as sufficiently robust.

The EPAR for lurasidone states that in [Citrome et al. \(2012\)](#), non-inferiority of lurasidone compared with risperidone was not shown because the upper limit of the 95% CI was greater than the pre-specified non-inferiority margin. [Citrome et al. \(2012\)](#) report that the pre-planned non-inferiority test of lurasidone compared with risperidone was not interpretable because the observed relapse rate was much smaller than the planned relapse rate that the non-inferiority margin was based on.

To further support the maintenance of effect with lurasidone the manufacturer submitted data from the completed, but not yet fully published D1050238 study. This study demonstrated superiority of lurasidone compared with placebo in time to relapse of psychotic symptoms. These results were supported by sensitivity analyses.

The EPAR for lurasidone concludes that overall, taking the results from all 3 long-term studies into account, the long-term efficacy for lurasidone has been sufficiently demonstrated.

Context

Alternative treatments

The NICE clinical guideline on [psychosis and schizophrenia in adults](#) recommends that people with a first episode of schizophrenia, or an acute exacerbation or recurrence of schizophrenia, should be offered oral antipsychotic medication in conjunction with psychological interventions. Regular combined antipsychotic medication should not be initiated, except for short periods (for example, when changing medication).

The NICE clinical guideline recommends that the choice of antipsychotic medication should be made by the service user and healthcare professional together, taking into account the views of the carer if the service user agrees. Information should be provided on, and there should be discussion about, the likely benefits and possible side effects of each drug, including metabolic, extrapyramidal, cardiovascular, hormonal and other side effects (including unpleasant subjective experiences).

NICE advises that clozapine should be offered to people with schizophrenia whose illness has not responded adequately to treatment despite the sequential use of adequate doses of at least 2 different antipsychotic drugs. At least 1 of the drugs should be a non-clozapine second-generation antipsychotic.

The second-generation antipsychotics currently listed in the [British national formulary](#) (September 2014) are amisulpride, aripiprazole, clozapine, olanzapine, paliperidone, quetiapine, and risperidone.

The [BNF chapter](#) on antipsychotic drugs describes the relative efficacy and adverse effects of different antipsychotics. A National Prescribing Centre [patient decision aid](#)

provides a guide to the relative adverse effects of different antipsychotics, based on information available at that time (2009).

Table 3 Costs of alternative treatments

Drug ^a	Usual dosage ^b	28-day costs excluding VAT ^c
Amisulpride	400–800 mg daily in 2 divided doses (Lower doses may be used in people with predominantly negative symptoms)	£9.21 to £35.57
Aripiprazole	15 mg daily	£96.04
Lurasidone	37–148 mg once daily	£90.72 to £181.44 ^d
Olanzapine	5–20 mg daily	Standard release: £1.12 to £2.09 Orodispersible: £2.73 to £5.66
Paliperidone	3–12 mg daily	£97.28 to £194.56 ^d
Quetiapine	Standard release: 300–450 mg in 2 divided doses Prolonged release: 600 mg daily	Standard release: £2.31 to £4.22 Prolonged release: £158.67
Risperidone	4–6 mg daily	Standard release: £0.97 to £5.25 Orodispersible: £37.92 to £67.00

^a Only costs for second-generation oral antipsychotics are listed in the table to keep the table concise. NICE does not differentiate between first and second-generation antipsychotics and the choice of drug should be made by the service user and healthcare professional together, taking into account the views of the carer if the service user agrees. The costs for clozapine are not listed as an alternative in the table because clozapine is indicated for treatment-resistant schizophrenia.

^b Doses are taken from individual [summaries of product characteristics](#). The doses shown do not all represent the full range that can be used and they do not imply therapeutic equivalence.

^c Costs taken from [Drug Tariff](#) September 2014

^d Cost taken from [MIMS](#) September 2014

Estimated impact for the NHS

Likely place in therapy

The studies in this evidence summary demonstrate that lurasidone is superior to placebo and non-inferior to quetiapine prolonged release for preventing relapse in adults with schizophrenia. However, the EPAR states that non-inferiority to risperidone has not been demonstrated. The spectrum of adverse events with lurasidone is stated to be similar to other second-generation antipsychotic drugs in the EPAR for lurasidone.

The NICE clinical guideline on [psychosis and schizophrenia](#) in adults recommends that the choice of antipsychotic medication should be made by the service user and healthcare professional together, taking into account the views of the carer if the service user agrees. Information should be provided on, and there should be discussion about, the likely benefits and possible side effects of each drug, including metabolic, extrapyramidal, cardiovascular, hormonal and other side effects (including unpleasant subjective experiences).

It is likely that lurasidone may represent an additional treatment option alongside existing antipsychotics for adults with schizophrenia. Local decision makers will need to consider the available evidence on efficacy and safety, as well as the higher cost of lurasidone compared with some existing antipsychotic medications (see the [alternative treatments section](#) for more information). As with choice of all antipsychotic medicines, individual factors for people with schizophrenia are a key factor when making treatment decisions.

Estimated usage

The estimated number of people taking antipsychotic drugs in England and Wales is 365,394, 39% of whom (142,504) are taking drugs for schizophrenia. Sunovion Pharmaceuticals Europe Ltd anticipates that the uptake of lurasidone in England and Wales will be 0.39% (556 people) in year 1, with an increase to 2.59% (3,742 people) by year 3 (Sunovion Pharmaceuticals Europe Ltd personal communication, August 2014).

Relevance to NICE guidance programmes

Lurasidone was not considered appropriate for a NICE technology appraisal and is not currently planned into any other NICE work programme.

NICE has issued a clinical guideline on [Psychosis and schizophrenia in adults: treatment and management](#) (NICE clinical guideline 178, February 2014).

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Development of this evidence summary

The [integrated process statement](#) sets out the process NICE uses to select topics for the evidence summaries: new medicines and how the summaries are developed, quality assured and approved for publication.

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Declarations of interest

No relevant interests declared

About this evidence summary

'Evidence summaries: new medicines' provide summaries of key evidence for selected new medicines, or for existing medicines with new indications or formulations, that are considered to be of significance to the NHS. The strengths and weaknesses of the relevant evidence are critically reviewed within this summary to provide useful information for those working on the managed entry of new medicines for the NHS, **but this summary is not NICE guidance.**

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