London Medicines Evaluation Network Review

Lurasidone (Latuda™) tablets for the treatment of schizophrenia in adults

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Summary

Background and licensed indication	Lurasidone (Latuda™) is an oral second-generation antipsychotic drug that inhibits the effects of dopamine and 5-hyroxytryptamine. It is licensed for the treatment of adults with schizophrenia and is available as film-coated tablets (18.5mg, 37mg and 74mg). (In this document lurasidone doses are expressed as lurasidone base. Equivalent doses of lurasidone base and the hydrochloride salt are 18.5mg=20mg, 37mg=40mg, 74mg=80mg, 111mg=120mg and 148mg=160mg).
Dosing	The recommended starting dose is 37 mg once daily with food. No initial dose titration is required and the maximum dose is 148 mg daily. Dose increase is based on physician judgement and observed clinical response and dosage adjustment is required for patients with moderate to severe renal or hepatic impairment. Concomitant use of lurasidone with strong CYP3A4 inducers and inhibitors is contraindicated.
Alternatives	Alternative second-generation antipsychotics include amisulpride, aripiprazole, clozapine, olanzapine, paliperidone, quetiapine, and risperidone.
NICE	Current NICE guidance that was published before the approval of lurasidone for schizophrenia does not address the use of lurasidone. A NICE evidence summary suggests that lurasidone may represent an additional treatment option alongside existing antipsychotics for adults with schizophrenia but does not make clear recommendations on its place in therapy. Lurasidone is accepted for restricted use within NHS Scotland as an alternative treatment option for patients with schizophrenia in whom it is important to avoid weight gain and metabolic adverse effects. Lurasidone was reviewed by AWMSG - the results will be published after ministerial ratification.
Clinical studies	The evidence base consists of three 6-week double-blind RCTs (one with a 12-month blinded extension study), a double-blind withdrawal study and a comparative study with risperidone in clinically stable schizophrenic patients primarily to investigate safety. No pre-specified group of patients who have previously failed treatment with other second generation antipsychotics due to metabolic adverse effects, and who are at risk of metabolic or cardiovascular adverse events were included in the lurasidone clinical trials.
Safety	Lurasidone has a spectrum of adverse events that is similar to that for other second-generation antipsychotics but with a higher rate of akathisia compared with quetiapine or risperidone. However, it is associated with a lower propensity for adverse effects on weight and metabolic outcomes. This favourable metabolic profile is a potential advantage since schizophrenia and its current treatment options are associated with a high degree of metabolic risk.
Convenience	Convenient once-daily oral dosing regimen with no initial dosing titration, no additional monitoring or follow up.
Risk assessment	Not completed.
Budget impact	Base case cost-effectiveness analysis for the primary comparison with aripiprazole, lurasidone was dominant (i.e. more effective and less costly). This was based on a small increase in quality-adjusted life-years (QALYs) of 0.005 and a cost saving of £3,864. For the secondary comparison with quetiapine, lurasidone was also dominant. This was based on a QALY gain of 0.01 and a cost saving of £2,509 compared with quetiapine. The main area driver of the costs savings for both comparisons is reduced relapse with lurasidone, for both inpatient and Crisis Resolution Home Treatment Team (CRHTT) relapse. A range of sensitivity analyses was performed. The results for the primary comparison of lurasidone and aripiprazole showed that the only scenario where the results were sensitive and aripiprazole became dominant was when no difference in relapse rates was assumed. For the comparison of lurasidone and quetiapine, lurasidone remained dominant in all scenarios. Additional sensitivity analysis provided by the company assumed no differences in effect between lurasidone and aripiprazole, and in this analysis, lurasidone is £72 cheaper but no more effective. In a cost-utility analysis comparing lurasidone with aripiprazole, lurasidone was estimated to be £72 cheaper but no more effective.
Funding	CCG funded
Suggested place in therapy	Lurasidone could be considered as a possible treatment option for patients with schizophrenia in whom it is important to avoid weight gain and metabolic adverse effects or who have failed to respond to or not tolerated an alternative second generation antipsychotic. However, it is associated with a higher risk of akathisia, high discontinuation rates and somewhat, modest efficacy. It is not a suitable treatment option in a person with treatment resistant schizophrenia.

1. Background and introduction

Schizophrenia is 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. Over a lifetime, it has been reported that about 1% of the population will develop schizophrenia.[1,2]

NICE 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). [1,2]

Lurasidone (Latuda™) is an oral second-generation (atypical) antipsychotic drug that inhibits the effects of dopamine and 5-hyroxytryptamine. Lurasidone is licensed for the treatment of adults with schizophrenia and is available as film-coated tablets (18.5mg, 37mg and 74mg). [3]

The Committee for Medicinal Products for Human Use (CHMP) noted that short term studies found the effectiveness of lurasidone to be moderate. Regarding safety, the adverse effects of lurasidone were considered similar to other antipsychotics e.g., extrapyramidal symptoms, nausea, sedation/somnolence, a moderate increase for prolactin, and hypersensitivity reactions. However, potential advantages of lurasidone include a relatively low potential for metabolic effects and the absence of profound effects on QTc prolongation. [4]

2. Proposed place in therapy

The metabolic and anticholinergic adverse effects of antipsychotics are well known. Lurasidone has a lower impact on weight gain or metabolic adverse effects and is not associated with QTc prolongation. These differences in adverse effects may be advantageous when considering choice of antipsychotic.

The NICE Evidence Summary for lurasidone states that lurasidone may represent an additional treatment option alongside existing antipsychotics for adults with schizophrenia but its place in therapy compared with existing medicines is not clear from the evidence reviewed.[1]

In the absence of comparative data, the patient population most likely to benefit would be those who have suffered from, are suffering from or wish to avoid dyslipidaemia, impaired glucose tolerance or diabetes and weight gain, or those with a prolonged QTc interval or known cardiac disease.

Stopping criteria: Failure to resolve psychotic symptoms, unacceptable adverse effects, patient choice or non-compliance with medication.

3. Evidence selected for inclusion

Meta-analysis

A recent multiple-treatments meta-analysis reviewed the available evidence (212 RCTs; n= 43, 049) for the safety and efficacy of 15 oral antipsychotic drugs including lurasidone. The analysis found that all antipsychotics were significantly more effective than placebo for the primary efficacy outcome, as measured by mean overall change in symptoms. Clozapine was significantly more effective than all the other drugs, followed by amisulpride, olanzapine, and risperidone; lurasidone was ranked second to last for efficacy. For other secondary endpoints, lurasidone was ranked third worst for all-cause discontinuation rates (amisulpiride best) and least well tolerated due to extrapyramidal effects (similar to chlorpromazine and risperidone). Lurasidone was ranked best for not affecting QT interval and among the best (along with haloperidol and ziprasidone) for least weight gain compared to placebo.[6]

The evidence base included in this review for lurasidone is based on three 6-week double-blind RCTs (one with a 12-month blinded extension study), a double-blind withdrawal study and a comparative study with risperidone in clinically stable schizophrenic patients primarily to investigate safety [reproduced from SMC review[7]].

Short-term RCT's of lurasidone

The three 6-week studies (D1050233, D1050231 and D1050229) had similar designs and inclusion criteria.[8,9,10] Patients were adults who had recently been admitted to hospital for an acute exacerbation of psychotic symptoms starting within the previous two months; with a primary diagnosis of schizophrenia of duration >1 year; Clinical Global Impression, Severity (CGI-S) score ≥4 (moderate or greater) and a Positive and Negative Syndrome Scale (PANSS) total score ≥80, including a score ≥4 (moderate) on two or more of the following PANSS items: delusions, conceptual disorganisation, hallucinations, unusual thought content and suspiciousness.

Patients were randomised equally to daily doses of lurasidone 74mg, lurasidone 148mg, quetiapine XR 600mg or placebo in D1050233; lurasidone 37mg; lurasidone 111mg; olanzapine 15mg (initially 10mg daily for one week) or placebo in D1050231 and

lurasidone 37mg, lurasidone 74mg, lurasidone 111mg or placebo in D1050229. The main reason for inclusion of the quetiapine XR and olanzapine groups was to test for assay sensitivity.

The primary outcome in all three studies was least squares (LS) mean change from baseline in PANSS total score at week 6 analysed in the intention to treat (ITT) population. PANSS is a validated 30-item scale (range 30 to 210, higher scores indicate worsening) to assess symptoms of schizophrenia.

Table 1: Primary outcomes in 6-week studies

PANSS total score mean change	Lurasidone 37mg	Lurasidone 74mg	Lurasidone 111mg	Lurasidone 148mg	Quetiapine XR 600mg	Olanzapine	Placebo
D1050233 (n=488)[7]		-22.2**		-26.5**	-27.8**		-10.3
D1050231 (n=478)[8]	-25.7**		-23.6*			-28.7**	-16.0
D1050229 (n=500)[9]	-19.2	-23.4*	-20.5				-17.0

*p<0.05 versus placebo; **p<0.001 versus placebo

There was a statistically significant improvement over placebo for all active treatments in all three 6-week studies in the key secondary outcome of CGI-S, except for the lurasidone 37mg and 111mg groups in D1050229. In D1050233 and D1050231, all active treatments showed significantly greater improvement over placebo at six weeks in the PANSS positive and negative sub-scores. [8,9,10]

Long term studies of lurasidone

Patients who successfully completed the D1050233 6-week study (treatment responders - ≥20% reduction in PANSS total score from acute study baseline and a CGI-S ≤4 at Day 42) could enter a double-blind extension study, D1050234, in which the primary outcome was to demonstrate non-inferiority of lurasidone to quetiapine XR for probability of relapse over 12 months.[11]

Relapse was defined as the earliest occurrence of any of the following 3 criteria:

- worsening of ≥30% in the PANSS total score from Day 42 of the initial acute treatment study and a CGI-S ≥3;
- re-hospitalisation for worsening of psychosis; or
- emergence of suicidal ideation, homicidal ideation and/or risk of harm.

Of the 353 patients who completed the initial 6-week study, 292 (83%) entered the extension study: 151 patients continued to receive lurasidone, 85 patients continued to receive quetiapine XR, and 56 patients treated with placebo in the initial study started treatment with lurasidone. In the extension study, flexible doses of lurasidone (37 to 148mg daily) and quetiapine XR (200 to 800mg daily) were used. Kaplan–Meier estimates of the probability of relapse at 12 months were 24% for the lurasidone group and 34% for the quetiapine XR group (HR, 0.73; 95% CI: 0.41 to 1.30). As the upper limit of the 95% CI of the HR was below the pre-specified margin (1.93), non-inferiority of lurasidone to quetiapine XR was concluded. The secondary outcome of PANSS total score continued to decrease throughout the extension study in the group that had received lurasidone in the acute study; -5.0, (95% CI: -7.8 to -2.1), while it increased in the quetiapine XR group; 1.7 (95% CI: -2.4 to 5.9). The PANSS positive subscale showed a similar pattern. There was no significant difference in CGI-S, PANSS negative subscale or negative symptom assessment (NSA)-16 in the group that received lurasidone throughout both studies compared with the group that received quetiapine XR.[11]

D1050238 was a double-blind, randomised, placebo-controlled withdrawal study with a screening/washout and open-label stabilisation phase (up to 24 weeks), a double-blind, randomised withdrawal phase (up to 28 weeks) and a follow-up 12-week open-label extension.[4] Patients were aged between 18 and 75 years and experiencing an acute episode of schizophrenia; had ≥1 prior episode of psychotic exacerbation (investigator evaluated) in the previous two years; had a PANSS total score ≥80 with a score ≥4 on at least one PANSS positive subscale item and a CGI-S score of ≥4; had good physical health and stable living arrangements and agreed not to take prior antipsychotic medication throughout the study. In the open-label stabilisation phase, patients received flexibly-dosed lurasidone 37mg to 74mg daily. Patients who responded and remained clinically stable for at least 12 weeks could enter the double-blind phase and be randomised (1:1 ratio) to receive the same dose of lurasidone as at the end of the open-label period, or matching placebo. Inclusion criteria for the double-blind phase were: PANSS total score ≤70; CGI-S score <4, and a score of ≤4 on all PANSS positive subscale items over ≥12 weeks although two excursions were permitted. Patients also had a PANSS item score of ≤4 on item G8 (uncooperativeness) and were taking a stable dose of lurasidone for the last four weeks of the open-label phase.4 Discontinuation rates were extremely high. Of the 676 patients who entered the open-label stabilisation phase, 42% (285/676) entered the double-blind withdrawal phase and were randomised to receive lurasidone (n=144) or placebo (n=141). Only 19% of patients receiving lurasidone and 14% of patients receiving placebo completed the double-blind phase.[4]

The primary outcome (ITT population) was the time to the first relapse event defined as at least one of the following during the

double-blind phase:
• An increase from double-blind phase baseline in both PANSS total score of ≥25% and a CGI-S worsening of ≥1 point, for two consecutive visits, occurring ≤10 days apart.
• At any single visit, a PANSS item score of ≥5 (moderately severe) on hostility or uncooperativeness, or PANSS item score ≥5 on ≥2 items of unusual thought content, delusions, conceptual disorganisation, or hallucinatory behaviour.
• Protocol-specified treatment interventions

Fewer patients relapsed in the lurasidone group, 30% (43/144), than in the placebo group, 41% (58/141). Kaplan-Meier estimates of the probability of relapse by week 28 were 42% and 51% (HR, 0.663; 95%CI: 0.447 to 0.983) for lurasidone and placebo, respectively, and overall there was a statistically significant increase in the time to relapse for lurasidone compared with placebo (p=0.039). During the double-blind phase, there were smaller increases in PANSS total score and in CGI-S scores for lurasidone versus placebo which were both statistically significant.[4,5]

D1050237 was a 12-month randomised, double-blind safety study comparing lurasidone with risperidone in 629 clinically stable adult outpatients with schizophrenia.[11] Efficacy outcomes were secondary endpoints, however the study was powered to test the non-inferiority of lurasidone relative to risperidone on the basis of the assumption of expected relapse rates of PANSS and CGI-S scores. After a screening/washout period, patients were randomised in a 2:1 ratio to receive lurasidone (74mg daily for 7 days then flexibly dosed 37mg to 111mg daily) or risperidone (2mg daily for 2 days then 4mg daily for five days then flexibly dosed 2mg to 6mg daily). Study medication was taken once daily within 30 minutes of breakfast although patients who experienced sedation could take the study medication with their evening meal.[12]

A numerically, but not statistically significantly, higher proportion of patients receiving lurasidone than risperidone experienced relapse (defined as for D1050238): 20% (82/410) of patients versus 16% (32/198), respectively. As the number of relapses was much lower than anticipated, it was not possible to interpret the non-inferiority test. There was no significant difference between the groups in PANSS total score: lurasidone group – 4.7 (95% CI: – 6.4 to – 3.0) and risperidone group – 6.5 (95% CI: – 8.8 to – 4.3); or in CGI-S score: lurasidone group – 0.4 (95% CI: – 0.5 to – 0.3) and risperidone group – 0.4 (95% CI: – 0.5 to – 0.2); or in Montgomery-Asberg Depression Rating Scale (MADRS) total score: lurasidone group – 0.8 (95% CI – 1.6 to – 0.0) and risperidone group – 2.4 (95% CI: – 3.4 to – 1.4).[12]

4. Critical evaluation

4.1. Clinical application

It is not known whether statistically significant effects on the ratings scales used to assess treatment response are also clinically significant. European Medicines Agency guidance states that a reduction of ≥30% on the PANSS total score compared to baseline is generally considered to be clinically relevant. Mean baseline PANSS total scores were 96 to 97 for the three 6-week studies, therefore the treatment effect over placebo was slightly less than 30% in all the studies.

No evidence of efficacy was provided specifically in the relevant population ie. as a treatment alternative when it is important to avoid weight gain and metabolic adverse events among adults with schizophrenia.

The main comparator to lurasidone is aripiprazole but no head to head studies were identified. An indirect comparison of lurasidone with aripiprazole from the multiple-treatments meta-analysis found no significant difference in overall change in symptoms, or all-cause discontinuation, after six weeks of treatment, and both were better than placebo. Weight gain with lurasidone was not significantly different to placebo or aripiprazole; however, due to the short treatment duration, this result should be viewed cautiously. Treatment with lurasidone resulted in significantly more extrapyramidal symptoms and significantly larger increases in prolactin than aripiprazole.[6]

Data are limited on lurasidone's effectiveness in the maintenance treatment of schizophrenia. The only data on the drug's long-term efficacy come from the extension phase of some short-term studies and the placebo-controlled, randomised withdrawal study - D1050238.

In short and long term studies, lurasidone appears to have a low potential for causing weight gain and adverse metabolic effects, but longer-term trials are needed to assess the risk of new-onset diabetes, which is of particular concern with second-generation antipsychotics.

The lack of direct superiority comparative studies and lack of well-designed long-term studies make it difficult to establish the place in therapy of lurasidone.

Lurasidone has not been evaluated in patients with heart disease or recent heart attacks, and it is likely that these patients would have been excluded from the studies. Although lurasidone is not associated with treatment-emergent ECG abnormalities, it should be used with caution in patients with heart disease or recent heart attacks, or in patients at known risk of stroke or low blood pressure.

4.2.Safety

General adverse events

In the 6-week D1050233 study and its 12-month open-label extension, D1050234, comparable proportions of patients receiving lurasidone and quetiapine reported adverse events. During the extension study higher rates of adverse events in the lurasidone versus quetiapine groups included akathisia (13% versus 2.4%) and parkinsonism (6.0% versus 0), however, discontinuation rates were significantly lower in the lurasidone (48%) vs quetiapine (61%) groups.[7]

After 12-months treatment in the D1050237 study, similar proportions of patients in the lurasidone and risperidone groups reported adverse events and serious adverse events. Discontinuations due to adverse events were higher in patients receiving lurasidone than risperidone; 17% versus 11%, respectively. Higher rates of adverse events in the lurasidone versus risperidone groups included nausea (17% versus 11%); akathisia (14% versus 7.9%); vomiting (10% versus 3.5%).[7]

In the 6-week D1050231 study, similar proportions of patients in the lurasidone and olanzapine groups reported adverse events. Higher rates of adverse events reported in the lurasidone 37mg and 111mg groups compared with the olanzapine 15mg group included akathisia (12% and 23% versus 7.4%) and parkinsonism (9.2% and 11% versus 4.9%). Rates of discontinuations due to adverse events were relatively low in the lurasidone 40 mg group (6.7%), the lurasidone 120 mg group (11.8%), and the olanzapine group (6.5%) and were comparable to those in the placebo group (8.6%).[7]

Weight gain

In the 6-week D1050233 study**,** clinically significant weight gain (≥7%) was reported in similar proportions of patients receiving lurasidone and placebo; (80mg, 4.3%; 160mg, 4.4% and placebo 2.6%). In the quetiapine-600mg group, 15% of patients had clinically significant weight change.[8]

In the 6-week D1050231 study**,** clinically significant weight gain (≥7%) was reported in similar proportions of patients receiving lurasidone and placebo; (40mg, 7.6%; 120mg, 4.2% and placebo 7.0%). In the olanzapine group, 34.4% of patients had clinically significant weight change. [9]

In the 6-week D1050229 study, weight gain ≥7% occurred in 8.2% of patients receiving lurasidone and 3.2% receiving placebo.[10]

In the 12-month open-label extension (D1050234) clinically significant weight gain (≥7%) at month 12 was reported in similar proportions of patients receiving lurasidone and placebo; (11.5% versus 13.8%) compared with quetiapine (15.2%).[11]

After 12-months treatment in the D1050237 study, weight gain was reported in fewer patients in the lurasidone than risperidone groups (9.3% versus 19.8%).[12]

Metabolic adverse events

In the 6-week D1050233 study**,** categorical shifts from normal to high (abnormal) values for lipid and glucose parameters were as follows:

- total cholesterol (lurasidone 80 mg, 7.2%; lurasidone 160 mg, 5.3%; QXR-600 mg, 15.9%; placebo, 6.3%)
- LDL cholesterol (lurasidone 80 mg, 7.2%; lurasidone 160 mg, 6.1%; QXR-600 mg, 15.0%; placebo, 4.5%)
- triglycerides (lurasidone 80 mg, 2.7%; lurasidone 160 mg, 5.3%; QXR-600 mg 10.4%; placebo, 6.3%),
- glucose (lurasidone 80 mg, 15.3%; lurasidone 160 mg, 18.8%, QXR-600 mg, 26.2%; placebo 18.2%).[7]

In the 6-week D1050231 study, endpoint changes in total cholesterol, triglycerides, HDL and LDL cholesterol were similar for both lurasidone groups and the placebo group. Compared to placebo, olanzapine was associated with significant increases in levels of glucose, total cholesterol, LDL and especially triglycerides [9]

In the 12-month open-label extension (D1050234), minimal changes in lipids and glucose were seen with lurasidone and quetiapine at month 12. [11]

In the 12-month D1050237 study, there were decreases from baseline to month 12 in the mean total cholesterol and LDL cholesterol in both groups, while triglycerides decreased only in the lurasidone group. Median and mean decreases were observed for HDL-cholesterol in the risperidone group but with no change in the lurasidone group. [12]

Cardiac adverse events

Lurasidone has not been evaluated in patients with heart disease or recent heart attacks. In the 6-week D1050233 and D1050231 studies, treatment with lurasidone was not associated with any treatment-emergent ECG abnormalities compared with placebo.[8,9]

In the 12-month studies (D1050234 and D1050237), at month 12, no clinically significant treatment-emergent ECG abnormalities were observed with any of the lurasidone, comparator antipsychotic or placebo groups. [11,12]

Overall lurasidone appears to have a favourable safety profile in terms of metabolic parameters such as glucose and lipids. Treatment with lurasidone produced higher rates of akathisia than quetiapine, risperidone and olanzapine and higher rates of parkinsonism than quetiapine and olanzapine. Nausea was more common with lurasidone than with the other three drugs.[7]

4.2.2. Risk assessment.
Other than monitoring for adverse events and interactions with CYP3A4 inhibitors or CYP3A4 inducers, no additional risks were noted by the EMA Risk Management Plan.[13]

4.3. Potential advantages and disadvantages over existing technologies

4.3.1. Convenience

Convenient once-daily oral dosing regimen with no initial dosing titration, no additional monitoring or follow up. However, to optimise bioavailability, lurasidone needs to be administered with food. Furthermore, as it is primarily biotransformed by CYP3A4, co-administration with strong inducers and inhibitors of CYP3A4 is contraindicated.

4.3.2. Healthcare resource utilisation

None required as it is an oral treatment with no additional monitoring or follow-up.

4.3.3. Suitability for shared care

No additional monitoring or follow-up necessary compared with existing treatments therefore it is suitable for shared care with transfer of care to GPs after one year of treatment.

4.3.4. Drug cost and likely budgetary impact

Drug	Usual daily dose	28 day cost (£)	Annual cost (£)
Lurasidone	37-148 mg	90.72	1,180 to 2,359
Aripiprazole	10-30 mg	96.04 to 192.08	1,252 to 2,503
Olanzapine	5-20 mg	1.18 to 2.23	15 to 29
Risperidone	4-6mg	1.11 to 1.91	14 to 25
Quetiapine	Standard release: 300–750 mg in 2 divided doses	2.05 to 5.41	27 to 70
	Prolonged release: 600 mg daily	158.66	2,068

Prices calculated from the January 2015 Electronic Drug Tariff. These price comparisons are likely to change once generic aripiprazole becomes available.

4.3.4.1. Budget Impact Model

In its submission to the SMC, the company provided a cost-utility analysis comparing lurasidone with aripiprazole as a primary comparison and quetiapine as a secondary comparison, for its initial positioning for the treatment of adults with schizophrenia who have previously failed treatment with other atypical antipsychotics due to metabolic side effects, and who are risk of metabolic adverse events. The SMC noted the submitting company estimated that in the base-case analysis for the primary comparison with aripiprazole, lurasidone was dominant (i.e. more effective and less costly). This was based on a small increase in quality-adjusted life-years (QALYs) of 0.005 and a cost saving of £3,864. For the secondary comparison with quetiapine, lurasidone was also dominant. This was based on a QALY gain of 0.01 and a cost saving of £2,509 compared with quetiapine. The main area driver of the costs savings for both comparisons is reduced relapse with lurasidone, for both inpatient and Crisis Resolution Home Treatment Team (CRHTT) relapse. A range of sensitivity analyses was performed. The results for the primary comparison of lurasidone and aripiprazole showed that the only scenario where the results were sensitive and aripiprazole became dominant was when no difference in relapse rates was assumed. For the comparison of lurasidone and quetiapine, lurasidone remained dominant in all scenarios. To address uncertainty in the model, the SMC conducted a sensitivity analysis for which they noted that for the primary comparison of lurasidone versus aripiprazole, lurasidone is £72 cheaper but no more effective. For the comparison with quetiapine, the incremental cost-effectiveness ratio (ICER) is £143,950 with an incremental cost of £1,003 and a QALY gain of 0.007, with the QALY gain being driven by a significant difference in weight gain, but the change in positioning by the company suggests that the comparison with aripiprazole is the more relevant analysis. Despite these issues, the economic case has been demonstrated.[7]

NICE estimates the number of people taking antipsychotic drugs in England and Wales to be 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.[1]

5. Health Economics

No health economic data were identified.

6. Likely commissioning and funding pathway

CCG commissioned but funding pathway remains to be determined.

7. Suggested place in therapy

Lurasidone is licensed for the treatment of schizophrenia in adult patients. It is more expensive than existing second generation antipsychotics, especially once aripiprazole becomes available as a generic. It would not be considered suitable as a first-line second generation antipsychotic because the evidence to support its efficacy is moderate compared to placebo. Furthermore, lurasidone is associated with higher rates of akathisia compared with quetiapine or risperidone and higher rates of discontinuation. However, evidence suggests that it has a favourable metabolic adverse event profile therefore could be considered as a possible treatment option for patients with schizophrenia in whom it is important to avoid weight gain and metabolic adverse effects or who have failed to respond to or not tolerated an alternative second generation antipsychotic because of weight gain and/or metabolic adverse effects. Further long term data focusing on rates of new-onset diabetes and cardiovascular events are required to establish its place in therapy for this specific patient population.

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