July 2016

New Medicine Recommendation

Lurasidone 18.5mg, 37mg and 74mg Film-Coated Tablets (Latuda®▼)

Treatment of schizophrenia in adults aged 18 and over

Recommendation:

Red

Lurasidone will be supplied by the specialist service for the duration of the treatment course.

Primary care initiation or continuation of treatment is not recommended unless exceptional circumstances such as specialist GP.

Lurasidone may only be prescribed in the following circumstances:

1. The patient has previously had a trial of and has not responded to aripiprazole
2. The patient does not fulfil the treatment resistance criteria as outlined in NICE Clinical Guideline 178 for the initiation of prescribing of clozapine
3. The patient has
    a. a metabolic disorder, diabetes or obesity **or**
    b. pre-existing risk factors for metabolic disease, diabetes or obesity

All requests for lurasidone will be screened by the pharmacy department of the specialist service provider. Based on current prescribing patterns, the number patients eligible for treatment with lurasidone is expected to be very low (fewer than around five patients per year).

Summary of supporting evidence:

- Two short-term studies were reviewed by AWMSG (**D1050231 and D1050233**), in both studies lurasidone and active comparators demonstrated significant superiority over placebo (mean change in PANSS score (Standard Error) -25.7(2.0) and -22.2(1.8) respectively; $p < 0.001$). [1] An explanation for the disease scores used in the trials is in Appendix 1.
- Longer term study, **D1050234** was a follow on study of **D1050233**, which was designed to compare the efficacy of flexible dose treatment with lurasidone (40 – 160mg once a day) versus quetiapine MR (200 – 800mg once a day). Kaplan-Meier (KM) estimates of the probability of relapse at 12 months were 23.7% for the lurasidone group (n = 151) and 33.6% for the quetiapine MR group (n = 56). Post-hoc analysis results showed the hazard ratio (HR) of lurasidone versus quetiapine MR was 1.08 (95% confidence interval [CI]: 0.79 – 1.49) and it was concluded that non-inferiority versus quetiapine MR was demonstrated. [1]
- A second longer term study, **D1050237** was designed to primarily evaluate long-term safety and tolerability comparing lurasidone with risperidone. The overall relapse rate for all patients was 19% (114/608) equating to 20% (84/410) in the lurasidone group and 16% (32/198) in the risperidone group. The relapse HR comparing lurasidone versus risperidone was 1.31 (95% CI: 0.87 – 1.97; p = 0.194). The non-inferiority of lurasidone compared to risperidone could not be demonstrated as the upper boundary of the 95% CI was greater than the non-inferiority margin of 1.6. [1]
- **Tandon et al, 2016**, conducted a double-blind, placebo-controlled, randomised withdrawal study. [2] It found that lurasidone significantly delayed the time to relapse compared with placebo (log-rank test, p = 0.039) reflecting a 33.7% reduction in risk of relapse (Cox model hazard ratio [95% CI], 0.663 [0.447 – 0.983]; p = 0.041). At week 28 , the Kaplan–Meier (KM) estimate for probability of relapse was 42.2% for patients receiving lurasidone compared with 51.2% for the placebo group (NNT = 12). 29.9% of patients in the lurasidone group and 41.1% in the placebo group discontinued from the study due to an observed relapse event. [2]
- Adverse drug events include: weight gain, prolactin increase, QTc prolongation and incidence of

extra-pyramidal symptoms (EPS) which were reported between lurasidone and the primary comparator, aripiprazole. Weight gain with lurasidone was not significantly different to aripiprazole whilst prolactin increase was significantly less with aripiprazole compared to lurasidone. The incidence of EPS was significantly higher with lurasidone compared to aripiprazole. [1]

- The European Public Assessment Report (EPAR) stated that safety results from the short- and long-term trials showed that effects of lurasidone on blood lipids, glucose and HbA1c were limited and effects on weight gain were moderate, indicating a favourable metabolic profile. [1]
- In study **D1050234**, clinically significant weight gain was reported to be similar between lurasidone and quetiapine (12% versus 15%). Weight gain measured in study **D1050237** was reported in fewer patients in the lurasidone than risperidone group (9.3% versus 20%). The short-term studies showed similar trends. [1]
- Treatment with lurasidone has been shown to produce a higher prevalence of akathisia and/or nausea than quetiapine, risperidone and olanzapine. [1]
- There is a potential annual cost pressure of £3,585 across the Lancashire NHS footprint (based on local prescribing data). As lurasidone is not a high cost drug and will be supplied by the specialist provider, this cost pressure will be covered by tariff.

Details of Review

Name of medicine (generic & brand name)**:**

Lurasidone (Latuda®▼)

Strength(s) and form(s):

Film-coated tablets: 18.5mg, 37mg and 74mg.

Dose and administration:

ADULT over 18 years, initially 37 mg once daily, increased if necessary to max. 148 mg once daily, equivalent to 40 mg, 80 mg, 120 mg and 160 mg of lurasidone hydrochloride respectively. [3] [4]

BNF therapeutic class / mode of action

4.2.1 Antipsychotic drugs, second-generation antipsychotic drugs.

Licensed indication(s):

Treatment of schizophrenia in adults aged 18years and over. [4]

Proposed use (if different from, or in addition to, licensed indication above):

Licensed indication.

Course and cost:

Dose range = 37mg - 148mg ONCE daily.

28 x 18.5mg, 37mg and 74mg tablets = £90.72

Annual cost of treatment = £1182 – £2365. [3]

Current standard of care/comparator therapies:

Established second-generation antipsychotic drugs.

Relevant NICE guidance:

NICE CG178 - Psychosis and schizophrenia in adults: prevention and management.

Background and context

In England, schizophrenia costs £11.8 billion per year. Around £4 billion of this is spent directly on health and social care. [5]

The prevalence of schizophrenia in the general population is about 1%. The first symptoms tend to start in young adulthood when a person would usually make the transition to independent living. However, symptoms can occur at any age. Risk factors that contribute to the development of schizophrenia are both genetic and environmental (biological and psychosocial). [6] [5]

Schizophrenia represents a major psychiatric disorder in which a person's perception, thoughts, mood and behaviour are significantly altered. The symptoms of schizophrenia are usually divided in to 'positive' and 'negative' symptoms; each person will have a unique combination of symptoms and experiences. [6]

Typically there is a prodromal period or 'at-risk' mental state which precedes the first episode of psychosis and can last from a few days for up to 18months. The prodromal period is frequently characterised by some deterioration in personal functioning and is often followed by an acute episode marked by hallucinations, delusions and behavioural disturbances accompanied by agitation and distress. Following resolution of the acute episode, usually after pharmacological and psychological interventions, symptoms diminish and may disappear, although sometimes a number of negative symptoms remain. This phase, which can last for many years, may be interrupted by recurrent acute episodes that may need additional pharmacological, psychological and other interventions. The course of the disease varies significantly between individuals. [6] [5]

Evidence from pharmacological and brain-imaging studies implicates the dysfunction of dopaminergic neurotransmission as the origin of psychotic symptoms such as delusions and hallucinations. However, other studies have shown that dopaminergic dysfunction is unlikely to explain the full range of clinical features of schizophrenia. Evidence suggests that disturbed glutamatergic function might also contribute to the biological processes underlying some clinical features, particularly cognitive dysfunction. Involvement of additional brain areas and circuits and disturbance of synaptic function have also been linked. [5]

Almost all antipsychotic drugs block dopamine receptor D2 (DRD2). Some antipsychotics also bind to other neurotransmitter receptors, such as clozapine (serotonin; 5HT-2R). Compared to placebo, most antipsychotic drugs are effective in reducing the positive symptoms of schizophrenia, such as auditory hallucinations and delusions. However, antipsychotics drugs lack efficacy for the management of other clinical features such as negative symptoms and cognitive dysfunction. [5]

First-generation antipsychotics are associated with significant side effects such as movement disorders and sedation both of which contribute to poor adherence. However, second-generation antipsychotics, which are also effective in the management psychotic symptoms, have fewer movement disorders associated with their use. However, they carry a higher risk of cardio-metabolic side effects compared to first generation drugs. [5]

Pharmacology and Pharmacokinetics

Lurasidone, a second-generation antipsychotic, selectively blocks DRD2 and serotonergic 5-HT2A and 5-HT7 receptors and also binds to and blocks α2c- and α2a-adrenergic receptors. Lurasidone also exhibits partial agonism at the 5HT-1A receptor. The drug does not bind to cholinergic or muscarinic receptors. [4] [1]

Lurasidone reaches peak serum concentrations approximately 1 – 3 hours after the administration of an oral dose. Higher peak serum concentrations are achieved when lurasidone is administered with food. The mean apparent volume of distribution is 6000L. Lurasidone is highly bound to plasma proteins (~99%). Steady-state plasma concentrations of lurasidone are observed after 7 days of oral continuous administration. [4]

Lurasidone is primarily metabolised by CYP3A4 into two active and two inactive metabolites. The parent drug and one of the active metabolites (ID-14283) are responsible for the pharmacodynamic effect at DRD2, 5-HT2A and 5-HT7 receptors. [4]

The elimination half-life of lurasidone is 20 – 40hours; 67% of an oral dose is recovered in the faeces and 19% in the urine. There is minimal renal excretion of the parent compound. [4]

Summary of evidence

Summary of efficacy data in proposed use:

NICE and the SMC (Scottish Medicines Consortium) have published an evidence review and assessment report respectively for lurasidone (Latuda®). Both were published in autumn 2014. The All Wales Medicines Strategy Group (AWMSG) published a comprehensive assessment report in January 2015. [1] The AWMSG report was chosen as the basis for this review as is it the most recent and was more comprehensively referenced.

Four phase III, multicentre, randomised, double-blind studies which included an active control were considered by AWMSG.

Short-term studies

Two short-term studies were reviewed (**D1050231 and D1050233**), both recruited patients with a diagnosis of schizophrenia of more than one year who had been admitted to hospital for two weeks or less with an acute exacerbation of psychotic symptoms. Eligible patients had a positive and negative syndrome scale (PANSS) score of ≥80 at screening and baseline and a score of ≥4 on the clinical global impression-severity (CGI-S) score. In both studies the primary comparison was between lurasidone and placebo with the active comparators included for assay sensitivity. [1]

During study **D1050231**, patients were randomly assigned a once daily dose of lurasidone 40mg (n = 119) or 120mg (n = 118), olanzapine 15mg (n = 122) or placebo (n = 114) for six weeks.

Study **D1050233** allocated patients (n = 482) randomly (1:1:1:1 ratio) to receive once daily doses of either lurasidone 80mg, lurasidone 160mg, quetiapine MR 600mg or placebo.

For both studies the primary efficacy endpoint was the change from baseline to week six on the PANSS total score. In both studies, all active treatments demonstrated significant superiority over placebo for improvements in PANSS. Results are summarised in the table below:

Table 1: Results of short-term studies. SE = Standard error.

	Study D1050231				Study D1050233			
	Lurasidone 40 mg/day (n =118)	Lurasidone 120 mg/day (n =118)	Olanzapine 15 mg/day (n =121)	Placebo (n=114)	Lurasidone 80 mg/day (n=125)	Lurasidone 160 mg/day (n=121)	Quetiapine XR 600 mg/day (n=116)	Placebo (n =120)
Primary endpoint								
Change in PANSS mean total score, baseline to week six (SE)	−25.7§ (2.0)	−23.6* (2.1)	−28.7§ (1.9)	−16.0 (2.1)	−22.2§ (1.8)	−26.5§ (1.8)	−27.8§ (1.8)	−10.3 (1.8)

*p < 0.05; †p < 0.01; §p < 0.001 (compared with placebo group; p values are unadjusted)

Long-term studies

D1050234 was a follow on study of **D1050233**, which was designed to compare the efficacy of flexible dose treatment with lurasidone (40 – 160mg once a day) versus quetiapine MR (200 – 800mg once a day). Of the patients who had completed the six-week initial trial, 151 patients continued on lurasidone and 85 patients continued on quetiapine MR; 56 patients treated with placebo in the initial trial were started on lurasidone. Results for the placebo-lurasidone conversion group were excluded from the efficacy analysis but were included in the safety analysis. The primary non-inferiority comparison was time to relapse of psychotic symptoms. [1]

Kaplan-Meier (KM) estimates of the probability of relapse at 12 months were 23.7% for the lurasidone groups (n = 151) and 33.6% for the quetiapine MR groups (n = 56). Post-hoc analysis results showed the hazard ratio (HR) of lurasidone versus quetiapine MR was 1.08 (95% confidence interval [CI]: 0.79 – 1.49) and it was concluded that non-inferiority versus quetiapine MR was demonstrated. [1]

Study **D1050237** was designed to primarily evaluate the long-term safety and tolerability of lurasidone. Patients were required to have a primary diagnosis of schizophrenia with the duration of illness being more than one year and be clinically stable for a minimum of eight weeks before baseline. Patients were randomised (2:1) to receive either lurasidone 80mg per day or risperidone 2mg per day on days one and two and 4mg on day three. Doses were adjusted according to response after one week. Secondary objectives included the evaluation of long-term efficacy, measure by relapse rates, powered to test the non-inferiority of lurasidone relative to risperidone. [1]

The overall relapse rate for all patients was 19% (114/608) equating to 20% (84/410) in the lurasidone

group and 16% (32/198) in the risperidone group. The relapse HR comparing lurasidone versus risperidone was 1.31 (95% CI: 0.87 – 1.97; p = 0.194). The non-inferiority of lurasidone compared to risperidone could not be demonstrated as the upper boundary of the 95% CI was greater than the non-inferiority margin of 1.6. [1]

Other efficacy data:

Comparator data

The manufacturer included aripiprazole as the comparator in their submission to AWMSG. There was no data directly comparing lurasidone to aripiprazole. There was data available from mixed and indirect treatment comparisons. [1]

The mixed data comparison utilised 212 short-term, blinded, randomised controlled trials to compare the efficacy and tolerability of 15 atypical (second-generation) antipsychotic drugs versus placebo by meta-analysis. The primary efficacy endpoint outcome was mean change in PANSS score. The results showed no significant difference in efficacy after six weeks of treatment with lurasidone or aripiprazole. [1]

Efficacy data since AWMSG:

One additional randomised controlled trial presenting original data has been published since the AWMSG published their review in January 2015.

Tandon et al, 2016, conducted a double-blind, placebo-controlled, randomised withdrawal study. [2] Adult patients diagnosed with schizophrenia and experiencing an acute exacerbation were eligible for enrolment. Antipsychotic medication other than lurasidone was not allowed during the trial. Antidepressant and mood stabilising medication was permitted if the patient had been stabilised for at least 30 days prior to enrolment. Anticholinergic medication was permitted during the trial for the management of acute extrapyramidal side effects. 676 patients were enrolled in the open-label phase of the study, receiving 12–24 weeks of lurasidone (40–80mg/d, flexibly dosed). Patients who maintained clinical stability for ⩾12 weeks were then randomized in double-blind fashion to placebo or lurasidone (40–80 mg/d, flexibly dosed) for an additional 28-week treatment period. 285 participants (42.2% of the initial study population) were randomised to lurasidone (n = 144) or placebo (n = 141) for a 28 week phase of the study. The efficacy and safety population analyses were conducted on all participants that received at least one dose of study drug. The primary efficacy endpoint was time to relapse. [2]

Lurasidone significantly delayed the time to relapse compared with placebo during the double-blind phase (log-rank test, p = 0.039) reflecting a 33.7% reduction in risk of relapse (Cox model hazard ratio [95% CI], 0.663 [0.447 – 0.983]; p = 0.041). At the week 28 endpoint of the double-blind phase, the KM estimate for probability of relapse was 42.2% for patients receiving lurasidone compared with 51.2% for the placebo group (NNT = 12). 29.9% of patients in the lurasidone group and 41.1% in the placebo group discontinued from the study due to an observed relapse event. [2]

Summary of safety data:

The mixed treatment comparison provided a comparison of adverse drug events , including weight gain, prolactin increase, QTc prolongation and incidence of extra-pyramidal symptoms (EPS) which were reported between lurasidone and the primary comparator, aripiprazole. Weight gain with lurasidone was not significantly different to aripiprazole whilst prolactin increase was significantly less with aripiprazole compared to lurasidone. The incidence of EPS was significantly higher with lurasidone compared to aripiprazole. [1]

The European Public Assessment Report (EPAR) stated that safety results from the short- and long-term trials showed that effects of lurasidone on blood lipids, glucose and HbA1c were limited and effects on weight gain were moderate, indicating a favourable metabolic profile. [1] In study **D1050234**, clinically significant weight gain was reported to be similar between lurasidone and quetiapine (12% versus 15%). Weight gain measured in study **D1050237** was reported in fewer patients in the lurasidone than risperidone group (9.3% versus 20%). The short-term studies showed similar trends. [1]

Treatment with lurasidone has been shown to produce a higher prevalence of akathisia and/or nausea than quetiapine, risperidone and olanzapine. [1]

No significant difference in discontinuation rates was seen in the mixed treatment comparison groups comparing lurasidone versus aripiprazole and lurasidone versus quetiapine. Similarly, no significant

difference was observed between treatment groups in studies **D1050234** and **D1050237** except for the quetiapine XR group where the discontinuation rate was significantly higher. [1]

Indirect treatment comparison showed lower all-cause discontinuation rate for lurasidone compared to quetiapine and aripiprazole, lower discontinuation rates for lack of efficacy and lower total all-cause annual hospitalisation rates. Pooled data for the short term active-controlled studies **D1050231** and **D1050233** showed that, in general, the discontinuation rate for lurasidone was comparable with olanzapine 15 mg and quetiapine XR 600 mg. [1]

Safety data since AWMSG

The study by **Tandon et al, 2016**, did not describe any significant side effects that are not listed in the summary of product characteristics (SPC). The additional side effects observed, not listed in the SPC, in the lurasidone treatment group were: headache (11.4% and 11.8% in the open-label and double-blind phases respectively) and schizophrenia (3.0% versus 0.7%; potential artefact of treatment failure rather than side effect) and psychotic disorders (1.6% versus 1.4%; treatment failure). [4] [2]

Minimal changes in weight, lipids, glucose and prolactin were observed. In patients treated with lurasidone in both the open-label and double-blind phases, mean weight change was -0.6kg (last observations carried forward [LOCF]); weight gain ≥ 7% and weight loss ≥ 7% were experienced by a similar proportion of patients (17.4% and 16.7% respectively). Median changes in metabolic parameters were: -1.0mg/dL for total cholesterol, -1.0mg/dL for triglycerides and 0.0mg/dL for glucose (LOCF). [2]

Strengths and limitations of the evidence:

Limitations

1. The manufacturer considers aripiprazole to be the only appropriate comparator; none of the studies submitted by the company to AWMSG gave direct comparative data for lurasidone versus aripiprazole. The AWMSG considered the mixed treatment comparison to have a high risk of bias for approximately 50% of the studies. The mixed treatment comparison data should be interpreted with caution. [1]
2. Independent treatment comparison data was provided to inform a comparison of discontinuation rates over a longer period than the mixed treatment comparison. Independent treatment comparison was composed of three studies. The main limitations were: each study had different inclusion criteria and one was of open-label design. Discontinuation rates were adjusted to provide a 12-month discontinuation rate for comparison between studies. This method assumed that discontinuation rates would be constant. No comparative data on metabolic and cardiovascular adverse effects was presented. [1]
3. Lurasidone appears to have a favourable safety profile. However, patient groups such as those with clinically significant cardiovascular disease, Parkinson's disease or active epilepsy were excluded from the trials. [1]

Strengths

1. Discontinuation rates were high in both short- and long-term studies. However, the proportion of patients who completed the studies were considered sufficient large in the EPAR to provide support for the claimed efficacy, including the long-term efficacy has been sufficiently demonstrated. [1]

Summary of evidence on cost effectiveness:

Cost-utility analysis

Rajagopalan et al, 2016, published a cost-utility analysis (CUA) of lurasidone versus aripiprazole in adults with schizophrenia. [7] The 2016 CUA analysis was published out of the submissions to the Scottish Medicines Consortium (SMC) and AWMSG. [7] [1] [8]

The 2016 analysis is focussed on the population-wide use of lurasidone, which assumes a number of variables that are less relevant when assessing the impact of lurasidone's introduction to be used for a small cohort of patients. The applicant has estimated patient numbers which are substantially lower than those anticipated by whole population estimates. Hence, the discussion that follows is an overview of that conducted by the SMC and is not the basis of the cost estimate for lurasidone use across the Lancashire health economy that has ultimately been presented in this document.

The AWMSG noted that the manufacturer had submitted data that considered only aripiprazole as the comparator for the target population. The target population is composed of patients in whom it is important to avoid weight gain and metabolic adverse events. The AWMSG concluded that the economic evidence is

restricted to a subgroup of its full licensed indication. [1]

The SMC accepted the use of lurasidone within NHS Scotland for the treatment of adult patients with schizophrenia. However, use was restricted as an alternative treatment option in patients in whom it is important to avoid weight gain and metabolic adverse events. [8]

A Markov model was developed and submitted. The model used discontinuation and relapse rates as key measures of efficacy in the short and long term. As no direct comparative data for lurasidone and aripiprazole, the probabilities of discontinuation are derived from mixed treatment comparisons using placebo as the common comparator. Relapse rates were based on relative all-cause hospitalisations as a proxy, this data was used to extrapolate relapse rates over the long term. Cyclical use of antipsychotics in the model, additional to aripiprazole and lurasidone, post-relapse were assumed to have similar release rates to quetiapine. [1]

Adverse effects, EPS and weight gain, were also incorporated in to the model, again using data derived from mixed treatment comparisons. The risk of developing diabetes was assumed to have the same relative as weight gain. [1]

Utility values for stable disease and relapse (0.799 and 0.670 respectively) and decrements to the stable disease utility vale associated with ADRs such as weight gain (-0.959%) and EPS (-0.888%) are based on those adopted by NICE to inform NICE CG 82 (now superseded by NICE CG 178). The ADR of diabetes was assigned a constant utility value of 0.769. [1]

Medicine acquisition costs were based in list prices and mean daily doses. The cost associated with acute relapse were based on the assumption that 30% of cases are managed as hospital inpatients (assuming mean length of stay to be 24.4 days) and 70% are managed in the community by crisis resolution home treatment teams (CRHTT, assuming 21 day treatment contact). [1]

The base-case analyses assume a 10-year time horizon. Cost and outcomes accrued beyond one year are discounted at 3.3% per annum. Results of the base-case analysis can be seen below:

Table 2 - Base-case analysis results for lurasidone versus aripiprazole (10-year time horizon). Data presented relates to the population of Scotland. [7]

	Lurasidone	Aripiprazole	Incremental outcomes[a]
Costs (£)			
Drug acquisition	2195	1779	416
Inpatient relapse	18,933	20,054	−1121
CRHTT relapse	47,844	50,665	−2821
Residential care	56,093	55,962	131
Switching	566	583	−17
AEs	1354	1404	−50
Outpatient/primary/community care	44,344	44,264	80
Total	171,329	174,712	−3383
Outcomes			
QALYs	6.490	6.485	0.005
Relapse-free days	3415	3408	7
Life-years	8.284	8.284	0
Incremental analysis			
ICER (lurasidone vs. aripiprazole)	–	–	Lurasidone-dominant

AEs adverse events, *CRHTT* crisis resolution home treatment team, *ICER* incremental cost-effectiveness ratio, *QALYs* quality-adjusted life-years

[a] Incremental outcome is equal to lurasidone minus aripiprazole

The data shows that lurasidone was associated with an overall cost saving of £3383 per patient and a modest increase of 0.005 QALYs. Similar results were observed when data from Wales were used, there was an overall cost saving of £3072 and an increase of 0.005 QALYs. [7]

A cost-utility analysis based on population data from England was not available in the literature.

Sensitivity and scenario analyses

A one-way sensitivity analysis was also conducted. Utility values were explored within the range +/-25% lurasidone remained dominant over aripiprazole. [1]

Scenario analyses were completed which included shorter time horizons, doubling of the assumed cost of lurasidone and equal rates of short-term discontinuation for all second-generation. Lurasidone was dominant in all scenarios excluding when equal relapse rates were assumed. In this scenario aripiprazole was dominant over lurasidone. AWMSG stated that the relapse rates are likely to be dependent on overall efficacy, tolerability and discontinuation rates, and under a scenario of no differences in these, lurasidone would be marginally cost saving compared to aripiprazole. [1]

Limitations

AWMSG found that there are several areas of uncertainty in the evidence available to model the intended use of lurasidone. The clinical trials were not conducted specifically in a population of patients at high risk of weight gain or metabolic adverse events. There are no data specifically examining the impact on related outcomes (i.e. development of diabetes or cardiovascular disease). [1]

The modelled cost-effectiveness of lurasidone is most sensitive to the assumed relative risk of relapse for lurasidone compared with aripiprazole, which are derived from indirect treatment comparison which is subject to considerable uncertainty. [1]

The applicant has estimated that no more than five patients would be treated with lurasidone each year within the Lancashire health economy. The SMC concluded that a cost saving of £3383 per patient could be achieved compared to aripiprazole. However, the model that predicts the costs associated with the management of patient relapses, presented by the SMC, cannot reasonably be applied to such small cohorts of patients. The model that was used by the submitting company was subject to considerable

uncertainty and data was derived from indirect treatment comparisons (as discussed above). For the purposes of this review a simple cost comparison between aripiprazole and lurasidone has been conducted and presented to aid decision making.

Prescribing and risk management issues:

Lurasidone is a prescription only medicine and is subject to the associated supply restrictions. Lurasidone is currently subject to additional monitoring under the 'black triangle' scheme for new medicines. Healthcare professionals should report any suspected adverse reactions associated with lurasidone to the medicines and healthcare products regulatory agency (MHRA). [4]

Lurasidone should be initiated and dose titration conducted by a physician experienced in the treatment of schizophrenia.

Commissioning considerations:

Comparative unit costs:

Drug	Example regimen	Pack cost	Cost per patient per course/ per year (ex VAT)
Lurasidone	37mg - 148mg ONCE a day	28 x 18.5mg, 37mg and 74mg tablets = £90.72 [3]	£1182.60 – £2365.20
Aripiprazole	10 – 30mg ONCE a day	28 x 5mg = £20.63, 28 x 10mg = 20.81, 28 x 15mg = £20.24 and 28 x 30mg = 126.40 [3]	£271.27 - £1647.71
Costs based on BNF list and eDrug Tariff prices May 2016 This table does not imply therapeutic equivalence of drugs or doses.			

Associated additional costs or available discounts:

There are no expected additional costs.

There are no known manufacturer's discounts available.

Productivity, service delivery, implementation:

It is not anticipated that additional secondary care appointment will be required upon initiation of lurasidone. Those commenced on lurasidone are expected to already be under the care of a specialist psychiatric consultant or GPwSI.

Anticipated patient numbers and net budget impact:

Estimation based on SMC data

The adult population of Lancashire is estimated at 1.2million [9].
Point prevalence of schizophrenia = 0.46%. [1]
Estimated number of adults in Lancashire living with schizophrenia = 5520
Assuming an incidence of 0.11 per 1000 population per year, 132 new adult patients per year in Lancashire are estimated. [1]
Assuming: an annual mortality rate of 0.43% (based on standardised mortality rates for 25 year olds), 80% are diagnosed and 95% of those are treated the estimated number of adult patients receiving treatment for schizophrenia in Lancashire in years 1 and 5 would be year 1: 4314 and year 5: 4367. [1]
AMWSG stated that the company estimates that the uptake of lurasidone would be at 66% the rate observed for aripiprazole when it was introduced in 2004. The company estimated that this equated to 0.29% of prescribing for schizophrenia in year one, rising to 2.94% in year five. **Therefore the expected number of patients receiving lurasidone in Lancashire would be 13 in year one, rising to 128 in year five** (1.08 per 100,000 and 10.7 per 100,000 of the population respectively).
This is equivalent to:
£15,373 – £30,747 per annum in year one rising to £151,372 - £302,745 in year five across the Lancashire NHS footprint. [3]

Net budget impact:

Annual cost of aripiprazole per patient at 10mg once a day and 30mg once a day: £271 and £1648 respectively. [3]
Total cost of treating equivalent numbers of patients with aripiprazole that are expected to receive lurasidone: £3523 - £21,424 in year one rising to £34,688 - £210,944 in year five across the Lancashire NHS footprint.
Net budget impact:

Cost pressure:

£11,850 – £9,323 in year one rising to £116,684 – £91,801in year five.

Therefore, using SMC data there is a potential cost pressure of between £9,323 and £116,684 in years one to five respectively across the Lancashire NHS footprint.

Estimation based on applicant data

However, the applicant has stated that lurasidone will only be prescribed in the following circumstances:

1. The patient has previously had a trial of and has not responded to aripiprazole
2. The patient does not fulfil the treatment resistance criteria as outlined in NICE Clinical Guideline 178 for the initiation of prescribing of clozapine
3. The patient has
   a. a metabolic disorder, diabetes or obesity or
   b. pre-existing risk factors for metabolic disease, diabetes or obesity

All requests for lurasidone will be screened by the pharmacy department of the specialist service provider. Based on current prescribing patterns, the number patients eligible for treatment with lurasidone is expected to be very low (fewer than around five patients per year).

Potential net budget impact based on applicant data:

Annual cost of aripiprazole per patient at 10mg once a day and 30mg once a day: £271 and £1648 respectively. [3]

Annual cost of lurasidone per patient at 37mg once a day and148mg once a day: £1182 – £2365. [3]

Cost of treating five patients with aripiprazole at maximum dose – cost of treating five patients with lurasidone at maximum dose = £8,240 – £11,825 = £3,585.

There is a potential cost pressure of £3,585 across the Lancashire NHS footprint (based on the applicant's local prescribing data). As lurasidone is not a high cost drug and will be supplied by the specialist provider, this cost pressure will be covered by tariff.

Innovation, need, equity:

Lurasidone is not an innovative new treatment. QALY gains compared to the existing, comparator treatment, aripiprazole, are minimal. [1] However, inter-individual variability in response generally to antipsychotic drugs as a class could mean that specific individuals may respond well to lurasidone.

There is some evidence that metabolic effects of lurasidone are less when compared to other second generation antipsychotics. [1] [2]

Lurasidone is a more cost-effective choice compared to aripiprazole.

Appendix 1: Disease Severity Scores

The Clinical Global Impression Severity (CGI-S) scale

A clinician-rated instrument that measures the patient's current illness state on a 1- to 7-point scale. Response choices for CGI-S include: 0 = not assessed; 1 = normal, not ill at all; 2 = borderline mentally ill; 3 = mildly ill; 4 = moderately ill; 5 = markedly ill; 6 = severely ill; and 7 = among the most extremely ill patients.

Positive and Negative Syndrome Scale (PANSS)

A system used for measuring symptom severity of patients with schizophrenia, where a trained interviewer applies a seven-point rating to 30 different schizophrenia symptoms. The sum of the scores for each provides the total PANSS score.

Montgomery-Asberg Depression Rating Scale (MADRS)

A 10-item questionnaire that measures severity of depressive episodes. Higher score indicates more severe depression, and each item yields a score of 0 to 6. The overall score ranges from 0 to 60.

Relapse

For studies D1050234 and D1050237, relapse is defined as the earliest occurrence of any one of the following:

- a worsening of ≥ 30% PANSS total score from baseline
- re-hospitalisation for worsening psychosis
- emergence of suicidal ideation, homicidal ideation, and/or risk of harm to self or others.

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