Evidence Review for Prescribing Clinical Network

Treatment: Lurasidone (Latuda)

Prepared by: Kath Mageean

Topic Submitted by: Simon Whitfield

Date: 9.10.14

Summary page

- How strong is the evidence for claimed efficacy?
  (Grade A = > 1 RCT or meta-analysis; Grade B = 1 RCT or descriptive study; Grade C = expert committee report/opinion)

  Grade A
  Efficacy against placebo is shown in 5 RCTs
  Evidence of efficacy shown in 3 short-term double-blind, randomised, placebo-controlled trials were considered by the European Medicines Agency (EMA) to be the main trials for licensing (D1050229, D1050231, D1050233)\(^4,5,11\)
  Results from 3 long-term studies are reported in an evidence summary from NICE\(^20\)
  One 12-month, double-blind, active comparator, non-inferiority study, using a previously randomised population from a 6-week double-blind RCT, one 12-month, double-blind, active comparator RCT and a double-blind, placebo-controlled randomised withdrawal study.

- Potential advantages in terms of: efficacy, compliance, pharmacokinetics, drug interactions and adverse effects?
  A new drug licensed for schizophrenia which has a place in contemporary antipsychotic treatment. It is as effective at treating psychotic symptoms, and at preventing relapse in adults with schizophrenia as its comparators, and has a better metabolic profile than some comparators. 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.

- Treatment pathway
  Following treatment with 2 other antipsychotics which have been discontinued due to lack of effect or intolerance (see Recommendations)
- Monitoring for response to treatment, side effects and the emergence of movement disorders should be carried out, as well as physical health monitoring, as for all newly initiated antipsychotics.

- **Dose titration**
  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.

- **Traffic light status – Amber**
- Treatment with Lurasidone must be initiated by a consultant
- GP to prescribe post-initiation if Amber* status is agreed
- Financial implications

In the SABP area, the number of people who will need a change in medication is predicted to be 183. Assuming an uptake of 5.5% of market share by Lurasidone, approximately 9 patients will start taking Lurasidone each year.
The financial impact of the introduction of lurasidone over 3 years is provided in the following table:

<table>
<thead>
<tr>
<th></th>
<th>Year 1</th>
<th>Year 2</th>
<th>Year 3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Population size</strong></td>
<td>183</td>
<td>188</td>
<td>194</td>
</tr>
<tr>
<td><strong>Current prescribing</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment cost</td>
<td>£25,461</td>
<td>£26,156</td>
<td>£26,991</td>
</tr>
<tr>
<td>Total annual cost</td>
<td>£25,461</td>
<td>£26,156</td>
<td>£26,991</td>
</tr>
<tr>
<td><strong>Alternative prescribing</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment cost</td>
<td>£35,571</td>
<td>£36,543</td>
<td>£37,775</td>
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<tr>
<td>Total annual cost</td>
<td>£35,571</td>
<td>£36,543</td>
<td>£37,775</td>
</tr>
<tr>
<td><strong>Difference</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Annual cost difference</td>
<td>£10,111</td>
<td>£10,387</td>
<td>£10,783</td>
</tr>
<tr>
<td>Cumulative cost difference</td>
<td>£10,111</td>
<td>£20,498</td>
<td>£31,281</td>
</tr>
</tbody>
</table>

*Please note that numbers in the table may not sum due to rounding.

Over 3 years, the total financial impact of uptake of lurasidone is a budget impact of £31,281, based on an average annual acquisition cost of lurasidone per patient of £1,183. This does not include costs associated with diabetes. This does not include hospitalisation costs.

The cost to SABP, ignoring any offset costs, over 3 years would be £31,281.

Considering the area covered by the Surrey Prescribing Network, and taking into account offset costs, an uptake of 5.5% of market share by Lurasidone would result in a saving of £15,910 over 3 years (see section 4.5.1. Costs)

- Other issues.
  Aripiprazole will become available as a generic preparation in a few months time when its patent expires. This will result in cost savings where continues to be prescribed.

National Guidance available –

**Lurasidone (Latuda®)** is accepted for restricted use within NHS Scotland.

**Indication under review:** For the treatment of schizophrenia in adults aged 18 years and over.

**SMC Restriction:** as an alternative treatment option in patients in whom it is important to avoid weight gain and metabolic adverse effects.

Lurasidone demonstrated benefit over placebo in mean change from baseline in Positive and
Negative Syndrome Scale (PANSS) total score after six weeks of treatment and was non-inferior to another second generation antipsychotic medicine for time to relapse over 12 months.

**Recommendations:**
Lurasidone should be available as a third-line treatment option in the management of schizophrenia in patients in whom it is important to avoid weight gain and metabolic adverse effects, after two first-line antipsychotics, one of which must have been effective but not tolerated.

Lurasidone is not indicated for patients with treatment resistant schizophrenia.

Lurasidone would be suitable for an amber* traffic light classification, following initiation by secondary care consultants.

**VERSION CONTROL SHEET**

<table>
<thead>
<tr>
<th>Version</th>
<th>Date</th>
<th>Author</th>
<th>Status</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>09.10.14</td>
<td>Kath Mageean</td>
<td></td>
<td>For discussion at SABP MMC</td>
</tr>
<tr>
<td>2</td>
<td>27.10.14</td>
<td>Kath Mageean</td>
<td></td>
<td>Amendment made by Simon Whitfield to reflect MMC recommendation.</td>
</tr>
</tbody>
</table>
1. Purpose of the Review

2. Appropriateness

2.1 The patient: Adults between the ages of 18 and 65

2.2 The problem: With a diagnosis of schizophrenia experiencing weight gain, metabolic issues, cognitive or other side effects related to their current medication.

Definition: Schizophrenia patients not deemed as treatment refractory and having been shown to respond to antipsychotic medication

Effects and prognosis:

Etiology: 33% of people with schizophrenia are obese compared to 21% of people without the illness.\(^{16}\) Weight gain can be significant, within 2 months of first starting an antipsychotic, a gain of 5-6kg is not uncommon in a patient.\(^{17}\) The physical health consequences of this can be significant as weight gain can lead to non-adherence and relapse. The prevalence of type 2 diabetes is 2-3 times higher for people with schizophrenia than in the general population.\(^{17}\) Lurasidone has demonstrated no significant increase in mean weight compared to placebo in short and long-term trials in patients with schizophrenia.\(^{1}\) Patients switching from olanzapine to lurasidone have demonstrated a significant weight decrease of 1.9kg at 6 months.\(^{18}\)

In a pooled analysis of short and long-term studies, there was no significant difference vs placebo in plasma glucose or HbA\(_{1c}\) among patients taking lurasidone.\(^{13}\)

Patients treated with current antipsychotics often have impaired cognitive functioning. In a prespecified secondary analysis of cognitive function in the six-week Pearl 3 study and six month double-blind extension phase, lurasidone (37-148mg/day) showed significantly better cognitive performance compared to quetiapine XR (200-800mg) at both 3 and 6 months in the double-blind extension study.\(^{10}\)

Prolactin increases are common with some atypicals (particularly risperidone) which can lead to troubling side effects such as galactorrhea and impotence. In a one-year study, lurasidone treated patients showed little change from baseline in prolactin for both male and female patients, compared to significantly larger increases in prolactin in patients treated with risperidone.\(^{14}\) Lurasidone can elevate prolactin in some patients.

Relapse prevention and delayed rehospitalisation are major goals of treatment. Lurasidone was able to demonstrate significantly reduced risk of relapse (33.7%) vs placebo in a one year double-blind randomised withdrawal study (P=0.041).\(^{6}\) Non inferiority to quetiapine XR (QXR) in a one year study with demonstrated lower rates of relapse (probability of relapse; lurasidone: 23.7% quetiapine XR: 33.6%, P=0.28)
and hospitalisation vs QXR (probability of hospitalisation; lurasidone: 9.8% quetiapine XR: 23.1%, P=0.049).  

**Diagnosis:**
There is no single test for schizophrenia. The condition is usually diagnosed after assessment by a specialist in mental health.
To make a diagnosis, most mental healthcare professionals use a 'diagnostic checklist' as outlined in DSM-IV, where the presence of certain symptoms and signs indicate a person has schizophrenia.
Schizophrenia can usually be diagnosed if:

- at least two of the following symptoms are present: delusions, hallucinations, disordered thoughts or behaviour or the presence of negative symptoms, such as a flattening of emotions.
- symptoms have had a significant impact on ability to work, study or perform daily tasks.
- symptoms have been experienced for more than six months.
- all other possible causes, such as recreational drug use or depression, have been ruled out.

**2.3 The Intervention:**
Doses available in the UK are 18.5mg (equivalent to 20mg lurasidone HCl), 37mg (equivalent to 40mg lurasidone HCl) and 74mg (equivalent to 80mg lurasidone HCl). The EMA requires that UK doses are expressed as the active moiety rather than the salt and this differs from outside the EU where doses are expressed as the salt (20mg, 40mg and 80mg lurasidone HCl). In addition all the published studies of lurasidone show doses expressed as the salt.

Below is a table of dose equivalents:

<table>
<thead>
<tr>
<th>Lurasidone (active moiety only)</th>
<th>Lurasidone HCl (active moiety + HCl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>18.5mg/day</td>
<td>20mg/day</td>
</tr>
<tr>
<td>37mg/day</td>
<td>40mg/day</td>
</tr>
<tr>
<td>74mg/day</td>
<td>80mg/day</td>
</tr>
<tr>
<td>111mg/day</td>
<td>120mg/day</td>
</tr>
<tr>
<td>148mg/day</td>
<td>160mg/day</td>
</tr>
</tbody>
</table>

**How does it work:** Lurasidone belongs to the chemical class of benzoisothiazol derivatives.

Similar to most other second-generation antipsychotics, lurasidone is a full antagonist at dopamine D₂ and serotonin 5HT₂A receptors. However, lurasidone also has high affinity for serotonin 5HT₇ (higher relative in vitro binding than for dopamine D₂ and
5HT_{2A}) and is a partial agonist at 5HT_{1A} receptors; it is believed that, in addition to antipsychotic effects, these properties have been shown in preclinical models to be related to effects on cognition and mood amongst others.\textsuperscript{1} Lurasidone has moderate affinity for alpha 2C noradrenergic receptors and minimal affinity for alpha 1 noradrenergic receptors which have been associated with a potential to cause orthostatic hypotension.\textsuperscript{1}

Its lack of affinity for cholinergic M$_1$ receptors may be associated with a low propensity for anticholinergic side effects. In addition it has minimal affinity for 5HT$_{2C}$ receptors and virtually no affinity for histamine H$_1$ which has been associated with a lower liability for weight gain.\textsuperscript{1}

The correlation between receptor-binding affinities and clinical outcomes is uncertain as data is derived from in-vitro studies.

**Care setting:** Lurasidone may be given to patients currently on an antipsychotic, but experiencing side effects including weight gain, metabolic issues, cognition etc whether in the in-patient or out-patient setting

**Frequency:** The recommended starting dose of lurasidone is 37mg once daily, taken with a meal. No initial dose titration is required. The effective dose range is 37 to 148mg once daily. Dose increase should be based on physician judgement and observed clinical response. The maximum daily dose should not exceed 148mg.\textsuperscript{1}

Dose adjustment (starting dose 18.5 mg) is recommended for patients with moderate and severely impaired hepatic and renal function and patients using concomitant moderate CYP3A4 inhibitors. Maximum dose should not exceed 74 mg once daily in End Stage Renal Disease.

Please refer to the full Summary of Product Characteristics (SPC) before prescribing, particularly in relation to side effects, cautions, and contraindications.\textsuperscript{1}

### 2.4 Alternative treatments:

Alternative antipsychotics are available to the Clinician when looking to switch a patient suffering side effects. However ‘Local decision makers will need to consider the available evidence on efficacy and safety, as well as cost and individual factors for people with schizophrenia, when making decisions about using lurasidone’.\textsuperscript{15}
3. Effectiveness

3.1 Expected benefits
The efficacy and safety of lurasidone, 37-148mg (40-160 mg lurasidone HCl), daily for the treatment of schizophrenia in adult patients were evaluated in 16 studies.

1. Proven efficacy in 5 short-term studies
- Demonstrated significantly greater efficacy vs placebo as rated on the PANSS and CGI (37-148mg).²⁻⁶
- PEARL 2 post-hoc analysis in 478 patients showed no statistically significant difference for change in PANSS total score between lurasidone and olanzapine.⁵

2. Proven efficacy in long-term studies
- Significantly reduced risk of relapse (33.7%) vs placebo in a one year double-blind randomised withdrawal study (P=0.041).⁶
- Non inferiority to quetiapine XR (QXR) in a one year study with demonstrated lower rates of relapse (probability of relapse; lurasidone: 23.7% quetiapine XR: 33.6%, P=0.28) and hospitalisation vs QXR (probability of hospitalisation; lurasidone: 9.8% quetiapine XR: 23.1%, P=0.049).⁷

3. Proven maintenance of efficacy after switch from risperidone and olanzapine in two separate 6 month extension studies.⁸⁻⁹

4. In a prespecified secondary analysis of cognitive function in the six-week Pearl 3 study and six month double-blind extension phase, lurasidone (37-148mg/day) showed significantly better cognitive performance compared to quetiapine XR (200-800mg) at both 3 and 6 months in the double-blind extension study.¹⁰
Table 1 presents a summary of the key short term studies – doses are represented as active moiety only as per UK doses 37-148mg (40-160mg lurasidone HCl):

<table>
<thead>
<tr>
<th>Study Number and author</th>
<th>Randomised N</th>
<th>Lurasidone HCl dose</th>
<th>Active Comparator dose</th>
<th>Placebo N</th>
<th>Outcomes Measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>D1050006  Ogasa et al., 2013³</td>
<td>149</td>
<td>37mg and 111mg/day</td>
<td>None</td>
<td>49</td>
<td>Lurasidone 37mg and 111mg/day were each superior to placebo at endpoint in mean changes from baseline for the BPRS total, CGI-S score, CGI-I score and between Lurasidone 111mg and placebo for PANSS total score at Week 6.</td>
</tr>
<tr>
<td>D1050196 Nakamura et al., 2009³</td>
<td>180</td>
<td>74mg/day</td>
<td>None</td>
<td>90</td>
<td>Lurasidone 74mg/day was superior to placebo on the BPRS, PANSS total score, PANSS positive subscale, negative subscale, general psychopathology subscale, and CGI-S. Other evidence of superiority was noted for the PANSS cognitive component, PANSS depression, and MADRS. Effects of Lurasidone versus placebo on the BPRS, PANSS total score and CGI-S were significant starting at 3 days post-randomisation.</td>
</tr>
<tr>
<td>D1050229 “PEARL 1” Nasrallah et al., 2013³</td>
<td>496</td>
<td>37, 74, and 111mg/day</td>
<td>None</td>
<td>128</td>
<td>Lurasidone 74mg/day was superior to placebo on the PANSS total score and CGI-S (37mg or 111mg/day did not demonstrate superiority in this study).</td>
</tr>
<tr>
<td>D1050231 “PEARL 2” Meltzer et al., 2011⁵</td>
<td>473</td>
<td>37 and 111mg/day</td>
<td>Olanzapine 15 mg/day</td>
<td>116</td>
<td>Lurasidone 37 and 111mg/day were each superior to placebo at 6 weeks on the PANSS total score, PANSS positive subscale, PANSS negative subscale, CGI-S. Olanzapine 15mg/day also produced significantly greater improvements than placebo on the PANSS total score, PANSS positive subscale, PANSS negative subscale, and CGI-S.</td>
</tr>
<tr>
<td>D1050233 “PEARL 3” Loebel A et al., 2013¹</td>
<td>488</td>
<td>74mg and 148mg</td>
<td>Quetiapine XR 600 mg OD</td>
<td>122</td>
<td>Lurasidone 74 and 148mg/day were superior to placebo at week six on the PANSS total score, PANSS positive and negative subscale scores, and the CGI-S. QXR 600mg/day was also superior to placebo at week 6 on the PANSS total score, PANSS positive and negative subscale scores and the CGI-S.</td>
</tr>
</tbody>
</table>
3.2 Is there a plausible biological basis for effectiveness?
As previously stated, the mode of action of Lurasidone offers a plausible basis for its effectiveness. Lurasidone is a full antagonist at dopamine D₂ and serotonin 5HT₂A receptors. However, lurasidone also has high affinity for serotonin 5HT₇ (higher relative in vitro binding than for dopamine D₂ and 5HT₂A) and is a partial agonist at 5HT₁A receptors; it is believed that, in addition to antipsychotic effects, these properties have been shown in preclinical models to be related to effects on cognition and mood amongst others.¹ Lurasidone has moderate affinity for alpha 2C noradrenergic receptors and minimal affinity for alpha 1 noradrenergic receptors which have been associated with a potential to cause orthostatic hypotension.¹

Its lack of affinity for cholinergic M₁ receptors may be associated with a low propensity for anticholinergic side effects. In addition it has minimal affinity for 5HT₂C receptors and virtually no affinity for histamine H₁ which has been associated with a lower liability for weight gain.¹

The correlation between receptor-binding affinities and clinical outcomes is uncertain as data is derived from in-vitro studies.

3.3 Side-effects/complications
The safety of lurasidone has been evaluated at doses of 18.5-148mg (20-160mg lurasidone HCl) in clinical studies in adults with schizophrenia treated for up to 52 weeks and in the post-marketing setting.¹ The most common adverse drug reactions (≥ 10%) were akathisia and somnolence, which were dose related up to 111mg daily. In lurasidone treated patients in the overall safety population, akathisia led to study discontinuation in 1.3% (39/2905).¹² The most common side effects seen in short and long-term studies of lurasidone include insomnia, somnolence; restlessness or akathisia; difficulty moving, slow movements, muscle stiffness or tremor; weight gain and nausea.¹

The Full Summary of Product Characteristics (SPC) is attached.

Lurasidone has demonstrated no significant increase in mean weight compared to placebo in short and long-term trials in patients with schizophrenia.¹

In short-term studies, treatment with lurasidone was not associated with changes in lipids or measures of glycaemic control.¹³

Long-term data show negligible changes in glucose and BMI, decreased cholesterol and plasma lipids, negligible change in HbA₁c and prolactin.¹⁴ There was no QTc prolongation in a one year study.¹⁴
3.4 Review of evidence (See Appendix 1. for Search Strategy and Summary of Results)
(Please see appendix 2 for hierarchy of evidence quality)

In September 2014, NICE published an evidence summary which stated:

‘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.

It reviews a further long-term study that has been published in full since a previous summary was prepared, and another long-term study which is described in the EPAR for lurasidone.

- 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.

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.20
4. Summary of Key Points for Consideration

4.1 National guidance: None presently

4.2 Efficacy
Proven efficacy in treating psychotic symptoms shown in 5 short-term studies and in 3 long-term studies

4.3 Potential Benefits over existing therapy
The European Medicines Association stated in the European Public Assessment Report for ‘Latuda’ that the side effects of Latuda were considered similar to those of other second generation antipsychotics, but it seemed to have fewer effects on body metabolism (such as effects on blood levels of sugar and fat, and body weight) and might have less effect on the activity of the heart than some other available treatments.21,13,14 (see section 3.3)

4.4 Potential disadvantages
Increased cost of treatment if Lurasidone is prescribed in preference to existing generic second generation antipsychotics

4.5 Budgetary Impact

4.5.1 Cost:

<table>
<thead>
<tr>
<th>Medicine</th>
<th>Daily dose range</th>
<th>Generic availability</th>
<th>Cost per 28 days (for orals)</th>
<th>Cost per month for depots</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aripiprazole (Abilify)</td>
<td>10mg – 30mg</td>
<td>April 2015</td>
<td>5mg, 10mg, 15mg 30mg</td>
<td>£96.04 £192.08 £220.41 per month</td>
</tr>
<tr>
<td>Abilify Maintena</td>
<td>400mg per month</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Olanzapine*</td>
<td>5mg – 20mg</td>
<td>Yes</td>
<td>5mg – 20mg</td>
<td>£0.96 – £2.09</td>
</tr>
<tr>
<td>Paliperidone depot (Xeplion)</td>
<td>75 – 150mg per month</td>
<td>No</td>
<td>50mg -150mg</td>
<td>£183.92- £392.59</td>
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<tr>
<td>Quetiapine</td>
<td>150mg -750mg</td>
<td>Yes</td>
<td>150mg – 750mg</td>
<td>£1.44 – £5.17</td>
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<tr>
<td>Quetiapine modified release</td>
<td>150mg – 750mg</td>
<td>Yes but Drug Tariff price is equivalent to Seroquel XL</td>
<td>150mg – 750mg</td>
<td>£67.66 – £226.20</td>
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<tr>
<td>Risperidone</td>
<td>2mg – 16mg</td>
<td>Yes</td>
<td>1mg – 16mg</td>
<td>£1.00 – £8.32</td>
</tr>
<tr>
<td>Risperdal Consta</td>
<td>25 – 50mg per month</td>
<td>No</td>
<td>25mg 37.5mg 50mg</td>
<td>£79.69 £111.32 £142.76</td>
</tr>
<tr>
<td>Lurasidone</td>
<td>18.5mg – 148mg</td>
<td>No</td>
<td>18.5mg,37mg,74mg 111-148mg</td>
<td>£90.72 £181.44**</td>
</tr>
</tbody>
</table>

Prices from BNF
*Generic price only.

** Based on the experience in the US where a higher dose strength of 120mg (111mg) of lurasidone is available, the majority of patients (approx. 90%) are likely to utilise a dose of 74mg or lower in the UK (there is a 9% utilisation of the 120mg (111mg) dose strength in the US).
The Surrey Prescribing Network BIM with offset costs predicts the potential saving that could be made if Lurasidone was used instead of current treatments in 5.5% of cases per year. Savings would be made by reducing the incidence of weight-gain and diabetes, and consequent hospitalisation events, and the costs these incur. The report compares the average probability of weight gain and incidence of diabetes by therapy, and the related costs per patient, by therapy. It also looks at the reduced probability of weight related diabetes and annual probability of hospitalisation if a proportion of current prescribing is replaced by Lurasidone over 3 years. The table below shows the financial impact of introducing Lurasidone over the next 3 years, considering patient numbers, drug costs and the clinical impact of this use of Lurasidone with the associated reduction in weight gain, diabetes and hospitalisation.

<table>
<thead>
<tr>
<th>Population size</th>
<th>Year 1</th>
<th>Year 2</th>
<th>Year 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current prescribing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment cost</td>
<td>£32,139</td>
<td>£33,113</td>
<td>£34,087</td>
</tr>
<tr>
<td>Weight gain cost</td>
<td>£12,266</td>
<td>£372</td>
<td>£372</td>
</tr>
<tr>
<td>Diabetes cost</td>
<td>£2,674</td>
<td>£5,409</td>
<td>£8,202</td>
</tr>
<tr>
<td>Hospitalisation cost</td>
<td>£410,613</td>
<td>£423,056</td>
<td>£435,499</td>
</tr>
<tr>
<td>Total annual cost</td>
<td>£457,692</td>
<td>£461,949</td>
<td>£478,159</td>
</tr>
<tr>
<td>Alternative prescribing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment cost</td>
<td>£44,902</td>
<td>£46,262</td>
<td>£47,623</td>
</tr>
<tr>
<td>Weight gain cost</td>
<td>£11,555</td>
<td>£350</td>
<td>£350</td>
</tr>
<tr>
<td>Diabetes cost</td>
<td>£2,507</td>
<td>£5,071</td>
<td>£7,690</td>
</tr>
<tr>
<td>Hospitalisation cost</td>
<td>£393,276</td>
<td>£405,193</td>
<td>£417,111</td>
</tr>
<tr>
<td>Total annual cost</td>
<td>£452,239</td>
<td>£456,877</td>
<td>£472,774</td>
</tr>
<tr>
<td>Difference</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Annual cost difference</td>
<td>-£5,452</td>
<td>-£5,072</td>
<td>-£5,385</td>
</tr>
<tr>
<td>Cumulative cost difference</td>
<td>-£5,452</td>
<td>-£10,525</td>
<td>-£15,910</td>
</tr>
</tbody>
</table>

*Please note that numbers in the table may not sum due to rounding.

Over 3 years, the total financial impact of uptake of lurasidone is a cost saving of £15,910, based on an average annual acquisition cost of lurasidone per patient of £1,183.

4.5.2 Precedent setting:

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).

In the NICE clinical guidelines CG178 ‘Psychosis and Schizophrenia in Adults: treatment and management’, treatment options include second generation antipsychotics which are available as generic preparations e.g. Olanzapine, risperidone, quetiapine, or are soon to become available as a generic preparation, e.g. aripiprazole. Treating people with a branded product rather than generically available preparations will increase costs.
Evidence of NHS provision of this treatment in other NHS Organisations
Sussex Partnership NHS Foundation Trust supports the use of lurasidone as a third line treatment after two first-line antipsychotics, one of which must have been effective but not tolerated, and this has been supported by their local Prescribing Network as an amber* drug.

In patients with identified risks, e.g. diabetes, then it may be considered for second-line use. In such situations, aripiprazole should have been tried before lurasidone unless there are compelling reasons not to.
Not for patients with treatment resistant schizophrenia

The Coventry and Warwickshire Area Prescribing Committee supports the use of lurasidone as a second line treatment i.e. where a patient has failed to respond to, or not tolerated, treatment with an established antipsychotic. Not suitable for a person with treatment resistant schizophrenia. To be initiated by a Consultant Psychiatrist

5. Conclusions and Recommendations
The following SABP consultants are supportive of the introduction of Lurasidone: 9 consultants named in list

Consultant comment
‘Given that the data so far indicate neutral side-effects on weight, sedation and prolactin amongst other things, it might end up being an alternative to aripiprazole where that is ineffective or leads to intolerable agitation or akathisia.
I would therefore be pleased if the trust could consider where it would fit in our prescribing at this early stage, hopefully with the result that we can prescribe it perhaps as 2nd or 3rd line therapy initially’.

Real World Data on the use of Lurasidone in the USA, where it has been licensed for 2 years, supports its long-term efficacy

References
8. Tandon et al. Poster presented at BAP 2014
12. Data on File, Sunovion Pharmaceuticals Europe Ltd UK/ LUR/14/0012
17. LSE Effective Interventions in Schizophrenia, the economic case. November 2012
   http://www.rethink.org/media/514083/LSE_economic_report_16nov.pdf (Accessed 1 April 2014)
22. The Surrey Prescribing Network BIM with offset costs. Lurasidone (Latuda®) for the treatment of schizophrenia in adults.
23. Real World data based on studies on ‘Indirect Comparison of Treatment Discontinuations’, ‘Adherence Among Patients with Schizophrenia in the USA’, ‘Inpatient Admissions among schizophrenia patients before and after initiating Lurasidone’ ‘Comparison of Treatment Adherence in New Start Patients on Lurasidone vs other Atypical Antipsychotics’
24. Report 1 SABP acquisition impact
Appendix 1: Evidence search

Search terms used:

<table>
<thead>
<tr>
<th>Resource</th>
<th>Used in this review?</th>
</tr>
</thead>
<tbody>
<tr>
<td>National Library for Health (NHL)</td>
<td>✓</td>
</tr>
<tr>
<td><a href="http://www.library.nhs.uk/Default.aspx">http://www.library.nhs.uk/Default.aspx</a></td>
<td></td>
</tr>
<tr>
<td>A gateway site with access to other resources such as Reviews (Bandolier, Cochrane, CRD etc), Guidelines (e.g. NICE), Clinical Knowledge Summaries (CKS) and Journals including AMED, British Nursing Index, CINAHL, E-books, EMBASE, HMIC, MEDLINE, My Journals, PsycINFO, PubMed, Databases from Dialog.</td>
<td></td>
</tr>
<tr>
<td>National Institute of Health and Clinical Excellence (NICE)</td>
<td>✓ (through NHL)</td>
</tr>
<tr>
<td><a href="http://www.nice.org.uk/">http://www.nice.org.uk/</a></td>
<td></td>
</tr>
<tr>
<td>NICE produces national guidance in three areas of health:</td>
<td></td>
</tr>
<tr>
<td>1. Public health - guidance on the promotion of good health and the prevention of ill health</td>
<td></td>
</tr>
<tr>
<td>2. Health technologies - guidance on the use of new and existing medicines, treatments and procedures within the NHS</td>
<td></td>
</tr>
<tr>
<td>3. Clinical practice - guidance on the appropriate treatment and care of people with specific diseases and conditions within the NHS.</td>
<td></td>
</tr>
<tr>
<td>Bandolier</td>
<td>✓ (through NHL)</td>
</tr>
<tr>
<td><a href="http://www.medicine.ox.ac.uk/bandolier/index.html">http://www.medicine.ox.ac.uk/bandolier/index.html</a></td>
<td></td>
</tr>
<tr>
<td>Bandolier is a website about the use of evidence in health, healthcare, and medicine. Information comes from systematic reviews, meta-analyses, randomised trials, and from high quality observational studies.</td>
<td></td>
</tr>
<tr>
<td>Centre for Reviews and Dissemination</td>
<td>✓ (through NHL)</td>
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<tr>
<td><a href="http://www.york.ac.uk/inst/crd/">http://www.york.ac.uk/inst/crd/</a></td>
<td></td>
</tr>
<tr>
<td>CRD undertakes high quality systematic reviews that evaluate the effects of health and social care interventions and the delivery and organisation of health care. Databases maintained by CRD include Database of Abstracts of Reviews of Effects (DARE), NHS Economic Evaluation Database (NHS EED), Health Technology Assessment (HTA) Database</td>
<td></td>
</tr>
<tr>
<td>Scottish Intercollegiate Guidelines Network (SIGN)</td>
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<tr>
<td><a href="http://www.sign.ac.uk/">http://www.sign.ac.uk/</a></td>
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<tr>
<td>Scottish equivalent of NICE</td>
<td>✓</td>
</tr>
<tr>
<td>Medical Services Advisory Committee (Australia)</td>
<td>✓</td>
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<tr>
<td><a href="http://www.msac.gov.au/internet/msac/publishing.nsf/Content/home-">http://www.msac.gov.au/internet/msac/publishing.nsf/Content/home-</a></td>
<td></td>
</tr>
</tbody>
</table>
The principal role of the Medical Services Advisory Committee (MSAC) is to advise the Australian Minister for Health and Ageing on evidence relating to the safety, effectiveness and cost-effectiveness of new medical technologies and procedures.

**Canadian Agency for Drugs and Technologies in Health (CADTH)**

The Canadian Agency for Drugs and Technologies in Health (CADTH) is a national body that provides Canada’s federal, provincial and territorial health care decision makers with credible, impartial advice and evidence-based information about the effectiveness and efficiency of drugs and other health technologies.

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**Evidence retrieved**

**Guidelines**
Brief description of any guidelines found

**Reviews:**
Brief description of any reviews found through Bandolier/Cochrane/CRD etc

**Journals**
Brief description of any further published studies found outside those already covered in any reviews described above. E.g. if a review only covered a certain time period, the journals could be searched to find studies published outside these dates. Briefly describe in table below.

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Number of participants</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Title:</td>
<td></td>
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<tr>
<td>Citation:</td>
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<td></td>
</tr>
<tr>
<td>Author(s):</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Appendix 2: Grading of evidence

- Ia: systematic review or meta-analysis of randomised controlled trials
- Ib: at least one randomised controlled trial
- IIa: at least one well-designed controlled study without randomisation
- IIb: at least one well-designed quasi-experimental study, such as a cohort study
- III: well-designed non-experimental descriptive studies, such as comparative studies, correlation studies, case–control studies and case series
- IV: expert committee reports, opinions and/or clinical experience of respected authorities

Appendix 3: References