Surrey (East Surrey CCG, Guildford & Waverley CCG, North West Surrey CCG, Surrey Downs CCG & Surrey Heath), Crawley CCG and Horsham & Mid-Sussex CCG

Evidence Review for Prescribing Clinical Network

Treatment: Lurasidone (Latuda)

Summary page

This is a follow up review for Lurasidone which was originally reviewed at the Surrey PCN in November 14. The outcome of that review was for the drug to allocated a red status as its place in therapy was unclear.

- **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.

- **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.

  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. This is the same and is in place for all other amber * 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.

- **Place in Therapy**

Metabolic Syndrome in Schizophrenia and the role of Lurasidone

- Schizophrenia is a condition where patients are predisposed to metabolic syndrome.
- Metabolic syndrome consists of three or more of the following: fasting plasma glucose ≥110 mg/dl, serum triglycerides ≥150 mg/dl, serum HDL cholesterol <40 mg/dl, BP ≥130/85 mmHg or on BP medication, or waist girth >102 cm. We used the modified definition of the WHO criteria (13), consisting of hyperinsulinemia (the upper fourth of the fasting insulin level among nondiabetic subjects) or hyperglycemia (fasting glucose ≥110 mg/dl) in addition to at least two of the following: waist girth ≥94 cm, dyslipidemia (triglycerides ≥150 mg/dl or HDL cholesterol <40 mg/dl), or BP ≥140/90 mmHg or taking BP medication.
- Surrey and Borders Partnership NHS Foundation Trust covers a population of 1,139,135
- Around 1% of people will develop schizophrenia during their lifetime.[1] Numerically, this equates to approx. 11,391 schizophrenia patients in Surrey and Borders Partnership NHS Foundation Trust
- After an initial episode, only 14-20% will recover fully. It is estimated that approximately 75% will have recurrent relapse and continued disability.[2] This equates to 8543 patients in Surrey and Borders Partnership NHS Foundation Trust
- The prevalence of metabolic syndrome in these patients is estimated to be around 20% pre antipsychotic treatment and rising to around 33% in patients treated with antipsychotics.[3] For Surrey and Borders, this suggests around 1708 patients (based on 20%) will have Metabolic Syndrome (MetS) pre antipsychotic treatment, rising to 2819 (based on 33%) post antipsychotic treatment.
- People with metabolic syndrome are twice as likely to die from cardiovascular events, and three times as likely to have a heart attack or stroke compared with people without the syndrome.[4]
- People with metabolic syndrome have a five-fold greater risk of developing type 2 diabetes.[4]
- People with schizophrenia have a life expectancy that is 15-20 years shorter than those without the condition.[5]
- The Physical health checks in the current CQUIN[6] will probably identify more patients with MetS where a lower metabolic risk may need to be considered dependant on the CV risk for that patient.

Cost to the system of physical comorbidity in schizophrenia

Schizophrenia patients have a direct effect on secondary outpatient admissions to the acute trust due to CV and Morbidity issues.

HES [35] data for the Surrey locality, when specifically looking at Schizophrenic patients, highlighted significant resource implications to CCG's outside of the block contract.

2014/15 Resource utilisation in Surrey

- Number of patients diagnosed with Schizophrenia as an inpatient/outpatient (any position) in 2014/15: 1209
- Where there is £0.00 cost, this reflects the local block contract agreement. All other costs represent additional costs to the CCG outside of that block contract.

Associated diagnosis as primary admission 34

Code	Description	Total Patients	Total Appointments	Patient Cost
R69X	Unknown and unspecified causes of morbidity	915	9598	£602,650.58
F200	Paranoid schizophrenia	164	866	£0.00
F209	Schizophrenia, unspecified	24	106	£0.00
F259	Schizoaffective disorder, unspecified	21	94	£0.00
Z136	Special screening examination for cardiovascular disorders	16	24	£2,674.11
F251	Schizoaffective disorder, depressive type	12	25	£0.00
F252	Schizoaffective disorder, mixed type	11	35	£0.00
F250	Schizoaffective disorder, manic type	10	19	£0.00
F29X	Unspecified nonorganic psychosis	8	48	£0.00
F239	Acute and transient psychotic disorder, unspecified	8	26	£0.00
H579	Disorder of eye and adnexa, unspecified	8	9	£1,407.95
F062	Organic delusional [schizophrenia-like] disorder	6	18	£0.00
F603	Emotionally unstable personality disorder	6	17	£0.00
F203	Undifferentiated schizophrenia	6	14	£0.00
Z461	Fitting and adjustment of hearing aid	6	11	£0.00
Z719	Counselling, unspecified	5*	7	£1,163.48

Of the patients who have had a diagnosis of Schizophrenia in 2014/15, what were the top 50 Specialties?

NB. This is regardless of whether schizophrenia was part of the patient's spell/appointment of care or not.

Outpatient Specialty Breakdown 34

Code	Description	Total Patients	Total Appointments	Patient Cost
300	General Medicine	207	2157	£225,656.32
320	Cardiology	129	341	£47,495.03
110	Trauma and Orthopaedics	123	410	£43,856.54
130	Ophthalmology	121	327	£30,525.90
101	Urology	58	160	£23,245.24
304	Clinical Physiology	96	155	£19,485.11
340	Respiratory Medicine	44	126	£16,707.56
330	Dermatology	33	164	£14,689.94
301	Gastroenterology	43	102	£14,601.34
502	Gynaecology	36	100	£13,611.11
100	General surgery	54	103	£13,574.76
361	Nephrology	17	113	£12,690.62
307	Diabetic Medicine	26	87	£11,712.39
144	Maxillo-Facial Surgery	46	106	£11,578.81
430	Geriatric Medicine	24	48	£9,809.64
120	ENT	37	89	£9,125.84
303	Clinical Haemotology	17	55	£9,043.17
410	Rheumatology	18	49	£8,835.28
800	Clinical Oncology	12	133	£8,158.55
160	Plastic Surgery	19	75	£8,086.73
104	Colorectal Surgery	33	66	£8,038.39

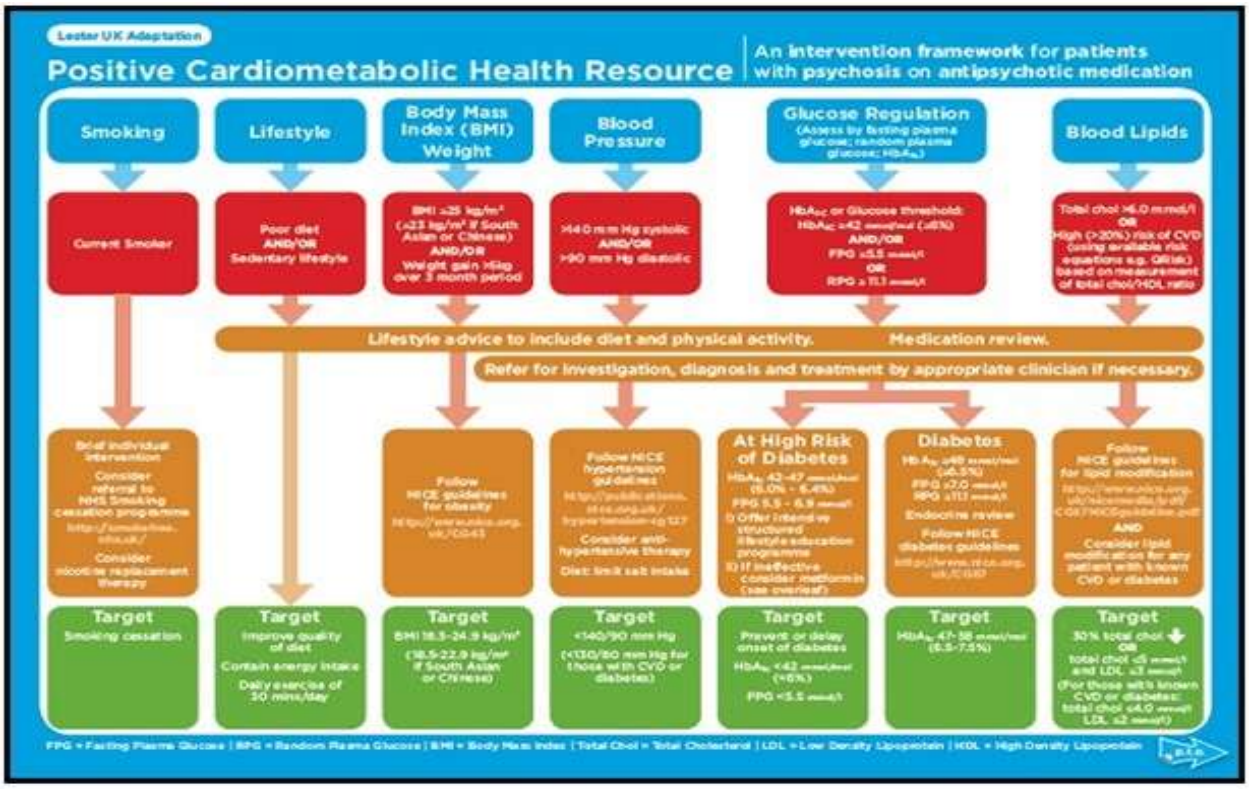
Inpatient Specialty Breakdown [34]

Code	Description	Total Patients	Total Spells	Patient Cost
300	General Medicine	289	392	£798,822.50
110	Trauma and Orthopaedics	74	79	£337,903.24
430	Geriatric Medicine	117	106	£273,319.80
340	Respiratory Medicine	91	98	£224,305.75
180	A&E	283	386	£221,032.42
314	Rehabilitation	25	33	£192,134.48
301	Gastroenterology	91	105	£171,385.97
303	Clinical Haemotology	7	90	£128,327.78
320	Cardiology	43	43	£121,653.24
100	General surgery	50	63	£119,313.57
104	Colorectal Surgery	51	47	£100,071.88
361	Nephrology	12	48	£66,251.85
715	Old Age Psychiatry	54	51	£63,044.28
400	Neurology	12	22	£59,344.58
101	Urology	27	39	£55,586.02
150	Neurosurgery	10	10	£54,682.32
410	Rheumatology	39	28	£51,039.12
106	Upper Gastrointestinal Surgery	26	31	£43,966.43
302	Endocrinology	27	20	£36,658.71
502	Gynaecology	15	18	£24,585.82
130	Ophthalmology	25	29	£23,307.62

- **Management of Metabolic Syndrome in Mental Health**

As part of our drive to improve the physical health of people who use our services we use the Lester tool to help screen and intervene to improve cardiometabolic outcomes.

Lester UK Adaptation – don't just screen – Intervene



For all patients in the red zone, the GP, psychiatrist and patient will work together to ensure appropriate monitoring and interventions are provided and communicated. The GP will usually lead on supervising the provision of physical health interventions. The psychiatrist will usually lead on decisions to significantly change the antipsychotic medication.

Metabolic Syndrome, Risk stratification and prescribing

Using this tool we will identify people with pre-existing metabolic syndrome prior to treatment and those who go onto develop metabolic syndrome as a result of treatment.

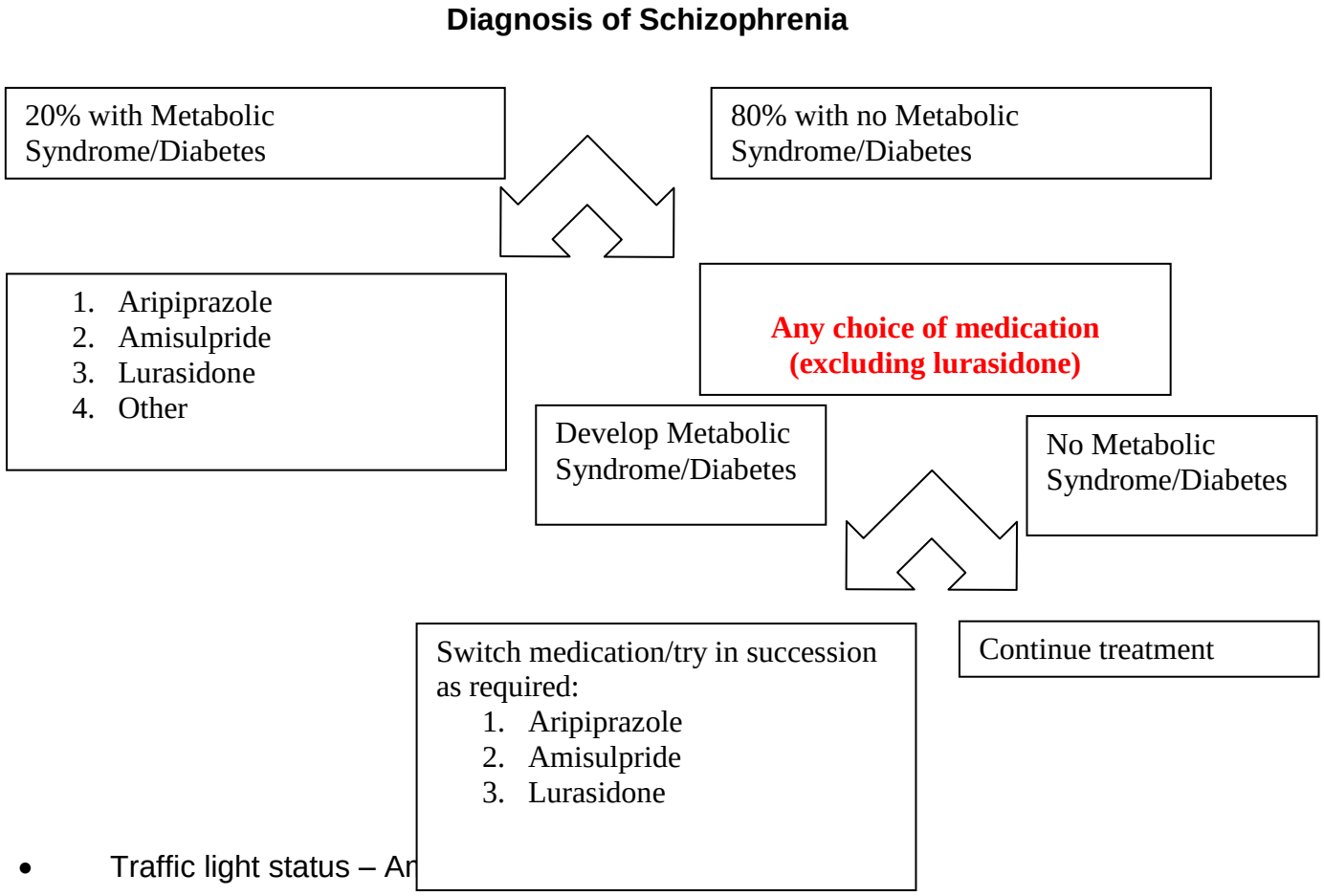
The flow chart below describes the proposed prescribing pathway and place of lurasidone to manage people once metabolic syndrome has been identified. However, access to lurasidone will need to be authorised by the SABP Trust Chief Pharmacist to provide assurance of fidelity to the pathway.

The current challenge for people who experience metabolic syndrome and who fail to respond to aripiprazole and to amisulpiride is that the options then include typical antipsychotics or remaining on treatment and trying to manage the physical health.
In Surrey we are currently intervening with other interventions like smoking cessation and weight management.

Surrey (East Surrey CCG, Guildford & Waverley CCG, North West Surrey CCG, Surrey Downs CCG & Surrey Heath), Crawley CCG and Horsham & Mid-Sussex CCG

Flowchart showing proposed treatment option:

Prescribing Pathway:



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

Financial implications

Lurasidone	**18.5mg – 148mg**	**No**	***18.5mg,37mg,74mg 111-148mg***	***£90.72 £181.44****

*** 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).*

Predicted cost based on Sussex experience

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. YTD sales within the account is 175 packs since launch which equates to £15K.

This additional system cost can be met directly by benefiting from generic aripiprazole and indirectly by reduced spend on physical health.

National Guidance available –

- **NICE (ESNM-48)[30] 2014,**

  NICE published an evidence summary which stated: *'The studies in this evidence summary demonstrate that Lurasidone is superior to placebo and non-inferior to quetiapine prolonged release for preventing relapse in adults with schizophrenia'*

The NICE evidence summary also stated that: *'Effects of Lurasidone on blood lipids, glucose and glycated haemoglobin (HbA1c) were limited, and the effect on weight increase was moderate, which is considered to indicate a relatively favourable metabolic profile'*

- **Scottish Medicines Consortium (SMC) Advice (994/14)[31]**

In 2014, LATUDA® **q** (Lurasidone) was accepted for restricted use within NHS Scotland for the treatment of schizophrenia in adults aged 18 years and above. Lurasidone accepted by the SMC; *'as an alternative treatment option in patients in whom it is important to avoid weight gain and metabolic adverse effects'*

- **All Wales Medicine Strategy Group (AWMSG) Final Appraisal Recommendation** – 0115[32]

'Lurasidone (LATUDA) is recommended as an option for use within the NHS Wales for the treatment of schizophrenia in adults aged 18 years and over'

- **The Maudsley Guidelines** [33]

  The Maudsley Guidelines recommend switching to Lurasidone is a first option for patients experiencing dyslipidaemia, impaired glucose tolerance, hyperprolactinaemia, postural hypotension, QT prolongation, and weight gain and a second option for patients experiencing acute EPS and sexual dysfunction.

Recommendations:
Lurasidone should be available as per the proposed treatment pathway (captured above) in the management of schizophrenia in patients in whom it is important to avoid weight gain and metabolic adverse effects OR after two first-line antipsychotics, one of which must have been effective but not tolerated.

Lurasidone is not indicated for patients with treatment resistent schizophrenia.

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

1. Purpose of the Review

This is a follow up review for Lurasidone which was originally reviewed at the Surrey PCN in November 14. The outcome of that review was for the drug to allocated a red status as its place in therapy was unclear.

The purpose of this follow up review is to contextualise the place in therapy of lurasidone as a treatment option to manage the risk of metabolic syndrome in the indicated patient population according to the prescribing pathway described above.

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: Schizpohrenia 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.

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female patients, compared to significantly larger increases in prolactin in patients treated with risperidone.[20] 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).[12] 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).[13]

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:

Lurasidone (active moiety only)	**Lurasidone HCl** (active moiety + HCl)
18.5mg/day	20mg/day
37mg/day	40mg/day
74mg/day	80mg/day
111mg/day	120mg/day
148mg/day	160mg/day

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 D_2 and serotonin $5HT_{2A}$ receptors. However, lurasidone also has high affinity for serotonin $5HT_7$ (higher relative in vitro binding than for dopamine D_2 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.[7] 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.[7]

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.[7]

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.[7]

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.[7]

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'.[21]

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).[8-12]

   - PEARL 2 post-hoc analysis in 478 patients showed no statistically significant difference for change in PANSS total score between lurasidone and olanzapine.[11]

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).[12]

   - 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).[13]

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.[16]

5. Poster; EFFECT OF LONG-TERM TREATMENT WITH LURASIDONE OR RISPERIDONE ON METABOLIC SYNDROME STATUS IN PATIENTS WITH SCHIZOPHRENIA

   J. W. Newcomer, MD1; A. Pikalov, MD, PhD2; K. Watabe, MS2; J. Cucchiaro, PhD2; K. Rajagopalan, PhD2; A. Loebel, MD2

   Of the patients with metabolic syndrome at baseline, 55.9% (19/34) in the Lurasidone group no longer met criteria for metabolic syndrome after 12 months compared with 28.6% (6/21) in the risperidone group (OC, p<0.05).

   Among patients with metabolic syndrome at double-blind baseline, Lurasidone treatment was associated with a significantly greater decrease in prevalence of metabolic syndrome after 12 months compared to risperidone treatment.

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 1

Study Number and author	N Randomised	Lurasidone HCl dose	Active Comparator dose	N Placebo	Outcomes Measures
D1050006 Ogasa *et al.*, 2013[8]	149	37mg and 111mg/day	None	49	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.
D1050196 Nakamura *et al.,* 2009[9]	180	74mg/day	None	90	Lurasidone 74mg/day was superior to placebo on the BPRS, PANSS total score, PANSS positive subscale, negative subscale, general sychopathology 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.
D1050229 "PEARL 1" Nasrallah *et al.,* 2013[410]	496	37, 74, and 111mg/day	None	128	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).
D1050231 "PEARL 2" Meltzer *et al.,* 2011[11]	473	37 and 111mg/day	Olanzapine 15 mg/day	116	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.
D1050233 "PEARL 3" Loebel A *et al.,* 2013[13]	488	74mg and 148mg	Quetiapine XR 600 mg OD	122	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.

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 D_2 and serotonin $5HT_{2A}$ receptors. However, lurasidone also has high affinity for serotonin $5HT_7$ (higher relative in vitro binding than for dopamine D_2 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.[7] 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.[7]

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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.[7] 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).[18] 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.[7]

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.[7]

In short-term studies, treatment with lurasidone was not associated with changes in lipids or measures of glycaemic control.[19]

Long-term data show negligible changes in glucose and BMI, decreased cholesterol and plasma lipids, negligible change in HbA_{1c} and prolactin.[20] There was no QTc prolongation in a one year study.[20]

Interaction with other medicinal products and other forms of interaction

<u>Pharmacodynamic interactions</u>

Given the primary central nervous system effects of lurasidone, lurasidone should be used with caution in combination with other centrally acting medicinal products and alcohol.

Caution is advised when prescribing lurasidone with medicinal products known to prolong the QT interval, e.g. class IA antiarrhythmics (e.g. quinidine, disopyramide) and class III antiarrhythmics (e.g. amiodarone, sotalol), some antihistaminics, some other antipsychotics and some antimalarials (e.g. mefloquine).

Pharmacokinetic interactions

The concomitant administration of lurasidone and grapefruit juice has not been assessed. Grapefruit juice inhibits CYP 3A4 and may increase the serum concentration of lurasidone. Grapefruit juice should be avoided during treatment with lurasidone.

Potential for other medicinal products to affect lurasidone

Lurasidone and its active metabolite ID-14283 both contribute to the pharmacodynamic effect at the dopaminergic and serotonergic receptors. Lurasidone and its active metabolite ID-14283 are primarily metabolised by CYP3A4.

CYP3A4 inhibitors

Lurasidone is contraindicated with strong CYP3A4 inhibitors (e.g. boceprevir, clarithromycin, cobicistat, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole) (see section 4.3).

Coadministration of lurasidone with the strong CYP3A4 inhibitor ketoconazole resulted in a 9- and 6-fold increase in exposure of lurasidone and its active metabolite ID-14283 respectively.

Coadministration of lurasidone with medicinal products that moderately inhibit CYP3A4 (e.g. diltiazem, erythromycin, fluconazole verapamil) may increase exposure to lurasidone. Moderate CYP3A4 inhibitors are estimated to result in a 2-5 fold increase in exposure of CYP3A4 substrates.

Coadministration of lurasidone with diltiazem (slow-release formulation), a moderate CYP3A4 inhibitor, resulted in a 2.2 and 2.4-fold increase in exposure of lurasidone and ID-14283 respectively (see section 4.2). The use of an immediate release formulation of diltiazem could result in a larger increase in lurasidone exposure

CYP3A4 inducers

Lurasidone is contraindicated with strong CYP3A4 inducers (e.g. carbamazepine, phenobarbital, phenytoin, rifampicin, St John's wort (*Hypericum perforatum*)) (see section 4.3).

Coadministration of lurasidone with the strong CYP3A4 inducer rifampicin resulted in a 6-fold decrease in exposure of lurasidone.

Coadministration of lurasidone with mild (e.g. armodafinil, amprenavir, aprepitant, prednisone, rufinamide) or moderate (e.g. bosentan, efavirenz, etravirine, modafinil, nafcillin) inducers of CYP3A4 would be expected to give a <2-fold reduction in lurasidone exposure during co-administration and for up to 2 weeks after discontinuation of mild or moderate CYP3A4 inducers.

When lurasidone is coadministered with mild or moderate CYP3A4 inducers, the efficacy of lurasidone needs to be carefully monitored and a dose adjustment may be needed.

Transporters

Lurasidone is a substrate of P-gp and BCRP *in vitro* and the *in vivo* relevance of this is unclear. Coadministration of lurasidone with P-gp and BCRP inhibitors may increase exposure to lurasidone

Potential for lurasidone to affect other medicinal products

Coadministration of lurasidone with midazolam, a sensitive CYP3A4 substrate, resulted in a < 1.5-fold increase in midazolam exposure. Monitoring is recommended when lurasidone and CYP3A4 substrates known to have a narrow therapeutic index (e.g. astemizole, terfenadine, cisapride, pimozide, quinidine, bepridil or ergot alkaloids [ergotamine, dihydroergotamine]) are coadministered.

Coadministration of lurasidone with digoxin (a P-gp substrate) did not increase the exposure to digoxin and only slightly increased C_{max} (1.3 –fold) and therefore, it is considered that lurasidone can be coadministered with digoxin. Lurasidone is an *in vitro* inhibitor of the efflux transporter P-gp and the clinical relevance of intestinal P-gp inhibition cannot be excluded. Concomitant administration of the P-gp substrate dabigatran etexilate may result in increased dabigatran plasma concentrations.

Lurasidone is an *in vitro* inhibitor of the efflux transporter BCRP and the clinical relevance of intestinal BCRP inhibition cannot be excluded. Concomitant administration of BCRP substrates may result in increases in the plasma concentrations of these substrates.

Coadministration of lurasidone with lithium indicated that lithium had clinically negligible effects on the pharmacokinetics of lurasidone, therefore no dose adjustment of lurasidone is required when coadministered with lithium. Lurasidone does not impact concentrations of lithium.

A clinical drug interaction study investigating the effect of coadministration of lurasidone on patients taking oral combination contraceptives including norgestimate and ethinyl estradiol, indicated that lurasidone had no clinically or statistically meaningful effects on the pharmacokinetics of the contraceptive or sex hormone binding globulin (SHBG) levels. Therefore, lurasidone can be coadministered with oral contraceptives.

Exposure to high dose/overdose

There is minimal data in the literature regarding overdose with lurasidone. Two case reports have been identified. One report is for a patient who ingested an estimated 560mg of lurasidone and recovered without sequelae.

The second report details a 31 year old male who ingested 17 times 80mg tablets as a suicide attempt and recovered with minimal medical difficulties.[36]

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 response to this analysis, a response was requested from Sunovion Medical Information department – letter available within application. Response was as follows :

Data sourced from Medical Information Response from Sunovion (Citrome et al)

- *One of the exclusion criteria was history of poor or inadequate response or intolerability to risperidone; thus, the study population was enriched in terms of potential risperidone responders or at least patients likely to tolerate risperidone. None of the patients in the study had any previous exposure to Lurasidone.*
- *Although a higher proportion of patients discontinued from the study because of a treatment emergent AE in the Lurasidone group compared with the risperidone group, there were no treatment emergent AEs leading to discontinuation with a difference of at least 1% in frequency when comparing the Lurasidone group with the risperidone groups.*

- 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.[26]

4. Summary of Key Points for Consideration

4.1 National guidance: SMC and AWMSG and Maudsley guidance in place

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.[27,7,19,20] (see section 3.3)

Real World Data on the use of Lurasidone in the USA, where it has been licensed for 2 years, supports its long-term efficacy[29]

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:

Medicine	Daily dose range	Generic availability	Cost per 28 days (for orals) Cost per month for depots	
Aripiprazole (Abilify) Abilify Maintena	10mg – 30mg 400mg per month	April 2015	5mg, 10mg, 15mg 30mg	£20.81
Olanzapine*	5mg – 20mg	Yes	5mg – 20mg	£0.96 – £2.09
Paliperidone depot (Xeplion)	75 – 150mg per month	No	50mg -150mg	£183.92- £392.59
Quetiapine	150mg -750mg	Yes	150mg – 750mg	£1.44 – £5.17
Quetiapine modified release	150mg – 750mg	Yes but Drug Tariff price is equivalent to Seroquel XL	150mg – 750mg	£67.66 – £226.20
Risperidone	2mg – 16mg	Yes	1mg – 16mg	£1.00 – £8.32
Risperdal Consta	25 – 50mg per month	No	25mg 37.5mg 50mg	£79.69 £111.32 £142.76
Lurasidone	**18.5mg – 148mg**	**No**	***18.5mg,37mg,74mg 111-148mg***	***£90.72 £181.44****

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).*

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. YTD sales within the account is 175 packs since launch.

Other areas where Lurasidone is set up as shared care :

NHS Greater Glasgow & Clyde
Cheshire & Wirral Partnership Trust
NHS Together Partnership NHS Trust
Mersey Care NHS Trust
NHS Lothian
NHS Leicestershire Partnership NHS Trust
Southern Health & SC Trust
Coventry & Warkwickshire Partnership Trust
5 Boroughs Partnership NHS FT
NHS Lanarkshire Partnership Trust
Aneurin Bevan University HB
NHS Tayside
Northern Health & SC Trust
NHS Ayrshire & Arran
South Eastern Health & SC Trust
Western Health & SC Trust
NHS Forth Valley
NHS Dumfries & Galloway
NHS Borders
Carstairs State hospital
Powys Teaching Health Board
Belfast Health & SC Trust
Hywel Dda University HB
Cwm Taf University Health Board
Abertawe Bro Morgannwg Univ HB
Norfolk & Suffolk NHS FT
Betsi Cadwaladr University HB
NHS Grampian
NHS Highland

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

5. Conclusions and Recommendations

The SABP Medicines Management Committee support access to lurasidone in line with the pathway described above.

Our limited experience demonstrates that lurasidone has a useful role to play for people with metabolic syndrome when other weight sparing antipsychotic treatments have not been efficacious or well tolerated.

Alternative strategies to the use of weight sparing antipsychotics would include the prescribing of combination antipsychotic therapy and / or the use of weight sparing adjuncts such as metformin and topirimate.

Lurasidone should therefore be available as per the proposed treatment pathway (captured above) in the management of schizophrenia in patients in whom it is important to avoid weight gain and metabolic adverse effects OR after two first-line antipsychotics, one of which must have been effective but not tolerated.

Lurasidone is not indicated for patients with treatment resistent schizophrenia.

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

References

1. NICE Clinical Guideline 178. Psychosis and schizophrenia in adults: Treatment and management, NICE, February 2014. http://www.nice.org.uk/nicemedia/live/14382/66534/66534.pdf
2. NICE Clinical Guideline 82. Schizophrenia The NICE Guideline on Core Interventions in the Treatment and Management of Schizophrenia in Adults in Primary and Secondary Care. 2010 http://www.rcpsych.ac.uk/files/samplechapter/niceschizupedsc.pdf
3. Mitchell AJ, et al. Schizophr Bull. 2013;39(2):306-318.
4. The IDF consensus worldwide denition of the METABOLIC SYNDROME. https://www.idf.org/webdata/docs/IDF_Meta_def_final.pdf
5. The Schizophrenia Commission. The Abandoned Illness, November 2012. http://www.rethink.org/media/514093/TSC_main_report_14_nov.pdf
6. Department of Health. Commissioning for quality and innovation (CQUIN). Guidance for 2015/16. London: DH, 2015. http://www.england.nhs.uk/wp-content/uploads/2015/03/9-cquin-guid-2015-16.pdf
7. Latuda (lurasidone) Summary of Product Characteristics 2014.
8. Ogasa *et al.* Lurasidone in the treatment of schizophrenia: a 6-week, placebo-controlled study. *Psychopharmacology* 2013; 225(3): 519–530
9. Nakamura M., *et al.* Lurasidone in the treatment of acute schizophrenia: a double-blind, placebo-controlled trial. *J Clin Psychiatry* 2009;70(6):829-836
10. Nasrallah H.A., *et al.* Lurasidone for the treatment of acutely psychotic patients with schizophrenia: a 6-week, randomised, placebo-controlled study. *J Psych Res* 2013; 47:670-677

11. Meltzer HY, *et al.* Lurasidone in the Treatment of Schizophrenia: A Randomized, Double-Blind, Placebo – and Olanzapine – Controlled Study. *Am J Psychiatry*. 2011;168:957–67.
12. G. W. Mattingly et al. Poster presented at APA 20149.
13. Loebel A, *et al.* Efficacy and safety of lurasidone 80 mg/ day and 160 mg/day in the treatment of schizophrenia: A randomized, double-blind, placebo- and active-controlled trial. *Schizophr Res*. 2013;145:101–9.
14. Tandon et al. Poster presented at BAP 2014
15. Stahl, S.M., *et al. J Clin Psychiatry* 201310.
16. Harvey PD, *et al.* European Neuropsychopharmacol.2013;23:1373–82.
17. Loebel A, *et al*. Schizophr Res. 2013;145:101–9.
18. Data on File, Sunovion Pharmaceuticals Europe Ltd UK/ LUR/14/0012
19. Data on File, Sunovion Pharmaceuticals Europe Ltd. UK/ LUR/14/0039.
20. Citrome L, *et al.* Long term safety and tolerability in schizophrenia: a 12-month, active-controlled study. *International Clinical Psychopharmacology*. 2012; 27:165–176.
21. National Institute for Health and Clinical Excellence. ESNM15: Schizophrenia: lurasidone 2013.
22. National Institute for Health and Clinical Excellence (NICE) clinical guidance 178. Psychosis and schizophrenia in adults: treatment and management; 2014:1–54.
23. 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)
24. The Schizophrenia Commission – The Abandoned Illness. November 2012. http://www.rethink.org/media/514093/TSC_main_report_14_nov.pdf(Accessed 1 April 2014)
25. Stahl SM, *et al. J Clin Psychiatry*. 2013;74:507-15.
26. National Institute for Health and Clinical Excellence. ESNM48: Schizophrenia: lurasidone Sept 2014
27. European Medicines Association stated in the European Public Assessment Report for 'Latuda' 11/8/14
28. The Surrey Prescribing Network BIM with offset costs. Lurasidone (Latuda®) for the treatment of schizophrenia in adults.
29. 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'
30 National Institute of health and clinical excellence ESNM-48 schizophrenia: lurasidone 2014. Available at: http://www.nice.org.uk/advice/esnm48,
31 Scottish Medicines Consortium. Lurasidone, 18.5mg, 37mg, 74mg film-coated tablets (Latuda®). SMC No. (994/14). Glasgow: SMC, 2014.
https://www.scottishmedicines.org.uk/files/advice/lurasidone__Latuda__FINAL_Sept_2014_amended_15.09.14_for_website.pdf
32 AWMSG Website. Available at:
http://www.awmsg.org/awmsgonline/app/appraisalinfo/1142
33 http://maudsley-prescribing-guidelines.co.uk/
34 Copyright © 2015 Re-used with the permission of the Health and Social Care Information Centre. All rights reserved
35 HES data report commissioned by Sunovion from Harvey Walsh (approved HSCIC provider)
36 Journal of Clinical Psychopharmacology Vol 34, Number 6, Dec 14

REFERENCES

Appendix 1: Evidence search

Resource	Used in this review?
National Library for Health (NHL) http://www.library.nhs.uk/Default.aspx 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.	✓
National Institute of Health and Clinical Excellence (NICE) http://www.nice.org.uk/ NICE produces national guidance in three areas of health: 1. Public health - guidance on the promotion of good health and the prevention of ill health 2. Health technologies - guidance on the use of new and existing medicines, treatments and procedures within the NHS 3. Clinical practice - guidance on the appropriate treatment and care of people with specific diseases and conditions within the NHS.	✓ (through NHL)
Bandolier http://www.medicine.ox.ac.uk/bandolier/index.html 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.	✓(through NHL)
Centre for Reviews and Dissemination http://www.york.ac.uk/inst/crd/ 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	✓(through NHL)
Scottish Intercollegiate Guidelines Network (SIGN) http://www.sign.ac.uk/ Scottish equivalent of NICE	✓
Medical Services Advisory Committee (Australia) http://www.msac.gov.au/internet/msac/publishing.nsf/Content/home-1 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) http://www.cadth.ca/index.php/en/home 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.	✓