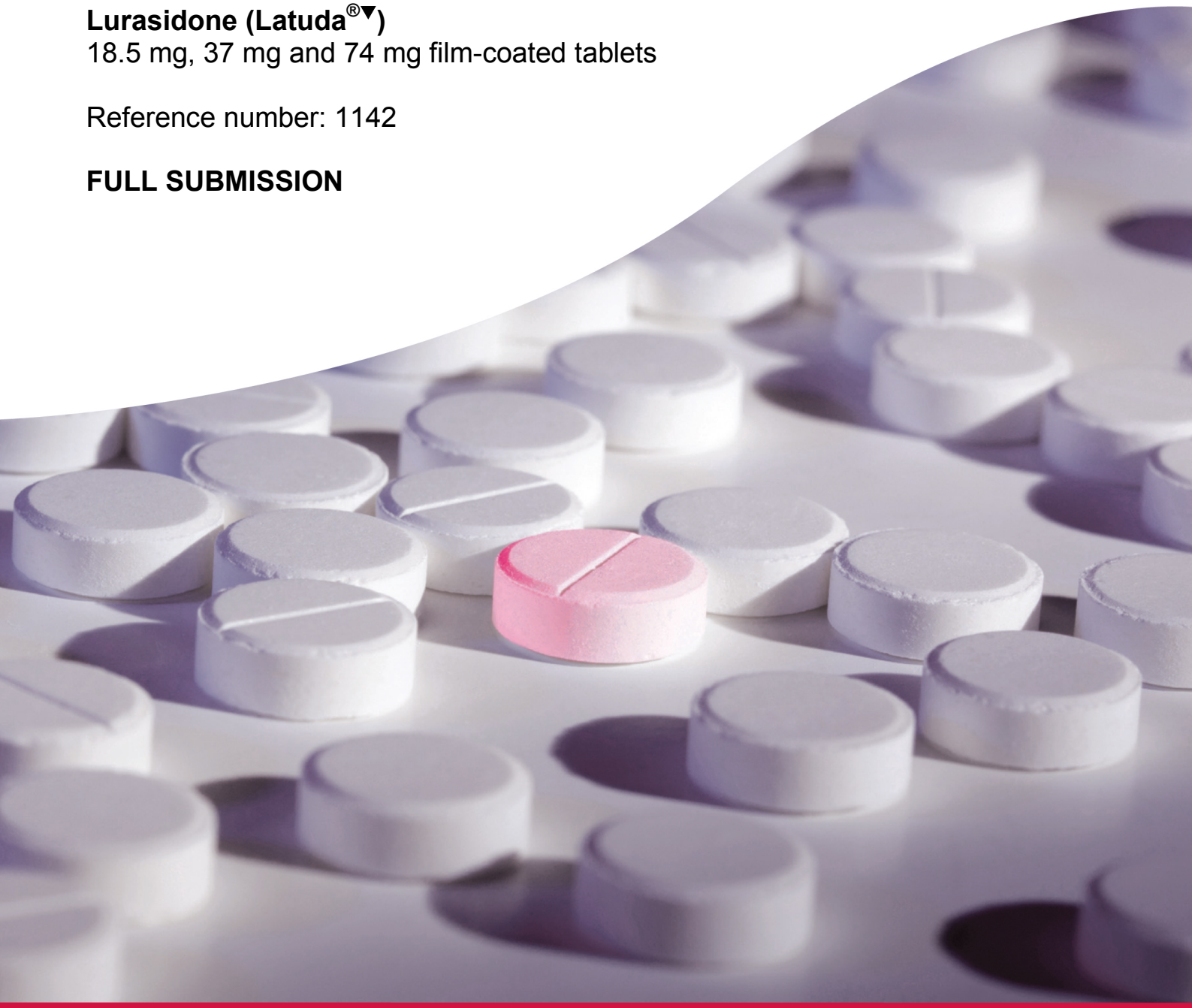
All Wales Therapeutics and Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

AWMSG SECRETARIAT ASSESSMENT REPORT

Lurasidone (Latuda®▼)
18.5 mg, 37 mg and 74 mg film-coated tablets

Reference number: 1142

FULL SUBMISSION



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AWMSG Secretariat Assessment Report
Lurasidone (Latuda®▼) 18.5 mg, 37 mg and 74 mg film-coated tablets

This assessment report is based on evidence submitted by Sunovion Pharmaceuticals Ltd on 10 October 2014[1].

1.0 PRODUCT DETAILS

Licensed indication under consideration	Lurasidone (Latuda®▼) is indicated for the treatment of schizophrenia in adults aged 18 and over[2].
Dosing	The recommended starting dose of lurasidone is 37 mg once daily. It is effective in a dose range of 37–148 mg once daily. Dose increase should be based on physician judgement and observed clinical response. The maximum dose should not exceed 148 mg. Lurasidone doses of 37 mg, 74 mg, 111 mg and 148 mg are equivalent to 40 mg, 80 mg, 120 mg and 160 mg of lurasidone hydrochloride respectively. Refer to the Summary of Product Characteristics (SPC) for further information[2].
Marketing authorisation date	21 March 2014[3]
UK launch date	September 2014[1]

2.0 DECISION CONTEXT

2.1 Background

Schizophrenia is a major psychiatric disorder typically characterised by episodes of psychosis occurring at varying intervals between periods of relative symptomatic stability[4]. Estimates vary; however, approximately 1% of the population will develop psychosis and schizophrenia over a lifetime, with an estimated overall prevalence of 0.46%[5].

Antipsychotic medication is the mainstay of treatment, used for the treatment of acute episodes, relapse prevention, acute behavioural disturbance and symptom reduction. The primary pharmacologic action of all antipsychotic medication is the antagonistic effect at dopamine D2 receptors[4].

Lurasidone is a second-generation atypical antipsychotic medicine, which has a piperidinyl-benzisoxazole derivative with a high affinity for dopamine D2- and serotonergic 5HT2A- and 5-HT7-receptors[6]. The applicant company suggest that lurasidone may provide an additional treatment option for patients with schizophrenia, in particular patients for whom it is clinically beneficial to avoid metabolic adverse events and weight gain[1].

2.2 Comparators

The comparator included in the company submission was aripiprazole (Abilify®).

2.3 Guidance and related advice

- National Institute for Health and Care Excellence (NICE). Clinical Guideline (CG) 178. Psychosis and schizophrenia in adults: treatment and management (2014)[4].
- NICE. Evidence summaries: new medicines (ESNM15). Schizophrenia: lurasidone (2013)[7].

The All Wales Medicines Strategy Group (AWMSG) has previously issued recommendations for the use of quetiapine prolonged-release tablets (Seroquel XL®)[8], olanzapine depot (ZypAdhera®)[9], paliperidone palmitate (Xeplion®)[10] and aripiprazole (Abilify Maintena®)[11].

3.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

Most studies provided by the applicant company in their submission demonstrate the clinical effectiveness of lurasidone compared to placebo in the treatment of schizophrenia in adults. For the purposes of this report, the four phase III, multicentre, randomised, double-blind studies which include an active control are summarised in Sections 3.1 and 3.2. Studies D1050231 and D1050233 were conducted over six weeks to evaluate the efficacy and safety of lurasidone in the treatment of acute schizophrenia compared to olanzapine and quetiapine, respectively[12,13]. D1050234 and D1050237 were longer term studies (up to 12 months) comparing lurasidone to quetiapine and risperidone, respectively[14,15].

As there are no head-to-head comparative data on the efficacy and safety of lurasidone versus aripiprazole, an independent mixed treatment comparison (MTC) was also included[1,16]. A summary of the MTC is provided in Section 3.3.

Note that lurasidone doses of 37 mg, 74 mg, 111 mg and 148 mg are referred to as 40 mg, 80 mg, 120 mg and 160 mg throughout[1].

3.1 Short-term studies

Both studies (D1050231 and D1050233) recruited patients with a diagnosis of schizophrenia (defined by the Diagnostic and Statistical Manual of Mental Health Disorders, fourth edition, Text Revision [DSM-IV-TR] criteria[17]) of more than one year who had been admitted to hospital for two weeks or less with an acute exacerbation of psychotic symptoms[12,13]. Eligible patients had a Positive and Negative Syndrome Scale (PANSS) score of ≥ 80 at screening and baseline and a score of ≥ 4 on the Clinical Global Impression-Severity (CGI-S) score (refer to Glossary) In both studies the primary comparison was between lurasidone and placebo with the active comparators included for assay sensitivity [12,13].

In study D1050231, patients were randomly assigned a once daily dose of lurasidone 40 mg (n = 119) or 120 mg (n = 118), olanzapine 15 mg (n = 122) or placebo (n = 114) for six weeks[13]. In D1050233, patients (n = 482) were randomly (1:1:1:1 ratio) assigned to receive once daily doses of either lurasidone 80 mg, lurasidone 160 mg, quetiapine XR 600 mg or placebo[12]. For both studies, the primary efficacy endpoint was the change from baseline to week six on the PANSS total score. The key secondary efficacy endpoint for both trials was the change in CGI-S score at week six; a further secondary endpoint was the change in Montgomery-Asberg Depression Rating Scale (MADRS) at week six[12,13]. In both studies, all active treatments demonstrated significant superiority over placebo for improvements in PANSS total score and CGI-S scores[12,13]. Results are summarised in Appendix 1.

3.2 Long-term studies

D1050234 was a follow-on study of D1050233 (described in Section 3.1), which was designed to compare the efficacy of flexible dose treatment with lurasidone (40–160 mg once daily) versus quetiapine XR (200–800 mg once daily)[15]. Of the patients who had completed the six-week trial, 151 patients continued on lurasidone and 85 patients continued on quetiapine XR, and 56 patients treated with placebo in the initial trial were started on lurasidone. Results for the latter group were excluded from the efficacy analysis, but were included in the safety analysis. The primary noninferiority comparison was time to relapse of psychotic symptoms (see Glossary)[15].

Kaplan-Meier (KM) estimates of the probability of relapse at 12 months were 23.7% for the lurasidone groups (n = 151) and 33.6% for the quetiapine XR group (n = 56)[15]. Post –hoc analysis results showed the hazard ratio (HR) of lurasidone versus quetiapine XR was 1.08 (95% confidence interval [CI]: 0.79–1.49) and it was concluded that noninferiority versus quetiapine was demonstrated[6]. Secondary endpoints included change in PANSS total score and sub-scores; CGI-S score and MADRS from baseline at 12 months; a post-hoc analysis found that results were supportive of a noninferiority claim for lurasidone[6,15].

Study D1050237 was designed to primarily evaluate the long-term safety and tolerability of lurasidone (safety is discussed in Section 3.4)[14]. Patients were required to have a primary diagnosis of schizophrenia with a duration of illness of more than one year and be clinically stable for a minimum of eight weeks before the baseline. Patients were randomised (2:1) to receive either lurasidone 80 mg per day or risperidone 2 mg per day on days one and two and 4 mg on day three. Doses were adjusted according to response after one week. Secondary objectives included the evaluation of long-term efficacy, measured by relapse rates (see Glossary), powered to test the noninferiority of lurasidone relative to risperisdone. Changes in PANSS total and subscale scores, change in CGI-S and change in MADRS total scores were also analysed[14].

The overall relapse rate for all patients was 19% (114/608) equating to 20% (82/410) in the lurasidone group and 16% (32/198) in the risperidone group. The relapse HR comparing lurasidone versus risperidone was 1.31 (95% CI: 0.87–1.97; p = 0.194); the noninferiority of lurasidone relative to risperidone could not be demonstrated as the upper bound of the 95% CI margin was greater than the noninferiority margin of 1.6[6]. Ancillary analysis of the other secondary efficacy endpoints showed no significant treatment differences between lurasidone versus risperidone at any time point on PANSS sub-scores, mean CGI-S or MADRS total score[6,14].

3.3 Mixed treatment comparison and indirect treatment comparison

As there are no data directly comparing lurasidone with the comparator aripiprazole, the applicant company refer to a published MTC[16] and an indirect treatment comparison[18].

The MTC utilised 212 short-term, blinded, randomised controlled trials to compare the efficacy and tolerability of 15 atypical antipsychotic medications versus placebo by meta-analysis. The primary efficacy outcome was mean change in PANSS score. Safety and tolerability measures were secondary outcomes and are summarised in Section 3.4. Results of the MTC demonstrated no significant difference after six weeks of treatment, between lurasidone and the comparator, aripiprazole for efficacy[16].

The indirect treatment comparison investigated discontinuation rates; the results are described in Section 3.4.

3.4 Summary of comparative clinical safety and discontinuations

The MTC provided a comparison of adverse events (AEs) including weight gain, prolactin increase, QTc prolongation and incidence of extra-pyramidal symptoms

(EPS), which were reported between lurasidone and the primary comparator, aripiprazole. Weight gain with lurasidone was not significantly different to aripiprazole whilst prolactin increase was significantly less with aripiprazole when compared with lurasidone [1,16]The incidence of EPS was significantly higher with lurasidone than with aripiprazole[1,16].

CHMP concluded that pooled safety results from the short- and long-term trials showed that the effects of lurasidone on blood lipids, glucose and HbA1c were limited and effects on weight gain were moderate, indicating a favourable metabolic profile[6]. In study D1050234, clinically significant weight gain (≥ 7%) was reported to be similar between lurasidone and quetiapine (12% versus 15%)[15]. Weight gain measured in study D1050237 was reported in fewer patients in the lurasidone than risperidone group (9.3% versus 20%)[14]. This was also reflected in the short term study D1050231 which showed lower rates of weight gain for lurasidone versus olanzapine[12]. Treatment with lurasidone however has been shown to produce higher rates of akathisia and /or nausea than quetiapine, risperidone and also olanzapine[6].

The MTC showed no significant difference in discontinuation rates between lurasidone versus aripiprazole, and lurasidone versus quetiapine[16].

The indirect treatment comparison showed lower all-cause discontinuation rates for lurasidone versus quetiapine and aripiprazole, lower discontinuation rates for lack of efficacy and lower total all-cause annual hospitalisation rates[18]. Pooled data for the short term active-controlled studies (D1050231, D1050233), showed that, in general, the discontinuation rate for lurasidone was comparable with olanzapine 15 mg and quetiapine XR 600 mg. The most common reasons given for discontinuation were withdrawal of consent and lack of efficacy[6].

In the two pivotal long term studies (D1050234, D1050237), discontinuations were similar across the patient groups apart from in the quetiapine XR group where the discontinuation rate was significantly higher. Overall discontinuation in the lurasidone and quetiapine groups were 48% and 61%; of these, 9% in the lurasidone group and 21% in the quetiapine group discontinued due to lack of response[6].

3.5 AWTTC critique

- Initially the applicant company sought a recommendation for lurasidone in the treatment of adults with schizophrenia who have previously failed treatment with other atypical antipsychotics due to metabolic side effects, and who are at risk of metabolic adverse events. Since no evidence of efficacy was available for this specific population, the company have proposed re-positioning lurasidone to be assessed as an alternative treatment when it is important to avoid weight gain and metabolic adverse events among adults with schizophrenia.
- The company consider aripiprazole the only appropriate comparator for the population relevant to the re-positioning of lurasidone[1].
- None of the studies provided by the company give direct comparative data for lurasidone versus aripirazole. So in the absence of any head-to-head comparison data the applicant company submitted an independent peer reviewed MTC.[16] A limitation of the MTC is results were all assessed over a six week acute treatment phase and long term results were excluded.[1,16] The risk of bias was assessed for each study and incomplete outcome data and selective reporting were considered to contribute to a high risk of bias for approximately 50% of studies[19]. It should be noted that due to the heterogeneity of the trials, the findings of the MTC should be interpreted with caution.
- The independent treatment comparison was provided to inform a comparison of discontinuation rates among atypical antipsychotics for schizophrenia over a longer term than the MTC. Three studies were included; a limitation of the comparison was the differing inclusion criteria between these studies.

In addition, one of the studies included was of open-label design and could therefore be a potential source of bias[20]. In order to compare studies, the annual rates for discontinuation and hospitalisation were adjusted from the observed 18 month rates for the study by Lieberman et al (2005) to a 12 month rate[21]. This assumed that discontinuation rates were constant[1]. The independent treatment comparison did not provide any comparative data on the effect on weight change, cardiovascular and metabolic effects.

- Discontinuation rates were high in both short- and long-term studies. However, the proportion of patients who completed the studies were considered sufficiently large by CHMP to provide support for the claimed efficacy, including that the long-term efficacy of lurasidone has been sufficiently demonstrated[6].
- Based on the results of the study D1050231 by Meltzer et al (2011)[13] and D1050237 by Citrome et al. (2012)[14], an Evidence Summary from NICE concluded that lurasidone appears to be more effective than placebo and of similar effectiveness to risperidone and olanzapine[7].
- Lurasidone would appear to have a favourable safety profile. However patients groups such as those with clinically significant cardiovascular disease, Parkinson's disease or active epilepsy were excluded from the trials[6].

4.0 SUMMARY OF THE EVIDENCE ON COST-EFFECTIVENESS

4.1 Cost-effectiveness evidence

4.1.1 Context

The company submission[1] describes a cost utility analysis (CUA) of lurasidone compared against oral aripiprazole in patients with schizophrenia. The company has revised its original submission to focus only on use in patients in whom it is important to avoid weight gain and metabolic adverse events. The company considers aripiprazole to be the only comparator for this target group of patients. The economic evidence is therefore, in effect, limited to use of lurasidone in a subgroup of its full licensed indication[6], where the only alternative agent would be oral aripiprazole.

A Markov model has been developed in which patients experiencing an acute relapse receive second-line treatment with lurasidone or the comparator for an initial six-week trial phase. Those who do not discontinue treatment at the end of that six-week period are assumed to enter into a longer-term maintenance phase in which they continue treatment in a stable disease state until they subsequently discontinue treatment, relapse or die. Those who discontinue treatment at the end of the initial six-week trial phase are assumed to switch immediately to an alternative antipsychotic agent for a further six-week trial phase, whereas those who discontinue treatment at a later point in time are assumed to receive no treatment until the onset of relapse. The alternative antipsychotic agents through which patients are assumed to sequence are amisulpiride, clozapine then augmented clozapine[1].

The model uses discontinuation and relapse rates as key measures of efficacy in the short and long term. In the absence of direct comparative data for lurasidone and aripiprazole, the probabilities of discontinuation at the end of the initial six-week trial phase are derived from a published Bayesian MTC, using placebo as the common comparator[16]. The relative risks of discontinuation during the maintenance treatment phase are derived from adjusted indirect treatment comparisons across trials of quetiapine versus olanzapine, and olanzapine versus aripiprazole[18]. The relative risks of relapse are also estimated from these comparisons; however, the relative relapse rates are reported to be based on relative all-cause hospitalisation rates as a proxy for the relative effect of treatment on relapse rates[1]. Parametric curves have been fitted to these data to extrapolate over the long term. Discontinuation and relapse rates for

subsequent alternative antipsychotics are assumed to be the same as observed for quetiapine[1].

AEs incorporated in the initial six-week trial phase include EPS and weight gain (defined as a gain of 5.2 kg or more, or 7% body weight change), with probabilities derived from the 6-week trial data included in the MTC. In the long-term maintenance phase, the cumulative risks of developing diabetes mellitus are included by assuming that the relative risks of developing diabetes mellitus are equal to the relative risks of experiencing weight gain for each of the antipsychotic agents[1].

Utility values for stable disease (0.799) and relapsed (0.670) states, and decrements to the stable disease state utility value associated with AEs of weight gain (−0.959%) and EPS (−0.888%) are based on those adopted in the NICE economic model developed to inform CG 82[22] (replaced by CG178[4]). Disutility for weight gain is applied throughout treatment to those who experience weight gain but do not develop diabetes, and disutility for EPS is assumed to persist for three months following treatment initiation. For the AE of diabetes, a constant utility value of 0.769 has been assumed based on the absolute value reported for diabetes in a published time-trade-off study in patients with schizophrenia[23].

Medicine acquisition costs are based on list prices and mean daily doses of antipsychotics obtained by the company from market research data. The assumed dose of lurasidone is 40–80mg, based on prescribing data from the USA[1]. Assumptions regarding the costs of managing AEs of weight gain and EPS, the costs of outpatient and primary/community care associated with stable and relapsed states, and the costs of residential care for stable patients are based on those assumed in the economic model developed to inform NICE CG82[22]. The costs of diabetes are based on a published survey of annual resource use and costs of type 2 diabetes in European countries[24], converted from Euros to pounds sterling and inflated to current prices. The costs associated with the management of acute relapse are based on the assumption that 30% of cases are managed as hospital inpatients (assuming a mean length of stay of 24.4 days) and 70% are managed in the community by crisis resolution home treatment teams (CRHTT, assuming 21 day treatment contact), referenced to information in a report for the area served by Abertawe Bro Morgannwg University Health Board, 2013[25].

The base case analyses assume a 10-year time horizon. Costs and outcomes accrued beyond one year are discounted at 3.5% per annum. One-way, threshold and probabilistic sensitivity analyses have been conducted around the base case model, and scenario analyses have been conducted to test structural assumptions[1].

4.1.2 Results

Results of the company's base case analysis is presented in Table 3. Lurasidone is estimated to be [commercial in confidence removed] aripiprazole. The differences in total costs are driven primarily by reduced costs of relapse managed by CRHTT with lurasidone treatment, with the small differences in quality-adjusted life- years (QALYs) driven by relative relapse rates.

Table 3. Results base case CUAs using 10 year time horizon

	Lurasidone	Aripiprazole	Key plausibility considerations
Medicine acquisition costs	¶¶	¶¶	Lack of evidence specifically in the target population of patients Use of indirect comparative data Uncertainty in relative relapse rates, which are a key driver of model outputs
Relapse costs: inpatient	¶¶	¶¶	
Relapse costs: CRHTT	¶¶	¶¶	
Residential care costs	¶¶	¶¶	
Switching	¶¶	¶¶	
Adverse event costs	¶¶	¶¶	
Outpatient/primary/community care	¶¶	¶¶	
Total costs	¶¶	¶¶	
QALYs	¶¶	¶¶	
ICER (Lurasidone versus comparator)	-	¶¶	

CRHTT: Crisis resolution home treatment team; ICER: incremental cost-effectiveness ratio (cost/QALY gained); QALY: quality-adjusted life year

[commercial in confidence data removed]
¶¶ commercial in confidence data removed

In probabilistic sensitivity analysis, lurasidone had a probability of being the most cost-effective treatment strategy of around 68% at willingness to pay thresholds of £20,000–30,000 per QALY gained.

One-way sensitivity analyses indicate that the modelled cost-effectiveness of lurasidone is most sensitive to the assumed relative risk of relapse compared with aripiprazole; within plausible ranges of the 95% CI for the HR for relapse for lurasidone and aripiprazole relative to quetiapine, the model outputs ranged from lurasidone being dominant over the comparator, to aripiprazole being the dominant treatment. When utility values were explored within the range ±25% lurasidone remained dominant over aripiprazole.

Lurasidone remained dominant over aripiprazole in a wide range of scenario analyses, including shorter time horizons of analysis, a doubling of the assumed costs of lurasidone, the same proportions of relapses treated as hospital inpatient cases as assumed in the NICE model for CG82, protracted length of hospital stays, and equal rates of short-term discontinuation for all atypical antipsychotics. However, aripiprazole is reported to be dominant (i.e. less costly and more effective) over lurasidone when equal relapse rates were assumed. It should be noted that the actual reported difference in QALY gains in this scenario is small [commercial in confidence data removed]. The company notes that relapse rates are likely to be dependent on overall efficacy, tolerability and discontinuation rates, and under a scenario of no differences in these, lurasidone would be marginally cost saving compared with aripiprazole.

4.1.3 AWTTC critique

The company's economic model aims to compare lurasidone as an alternative atypical antipsychotic to aripiprazole in patients for whom it is important to avoid weight gain and metabolic adverse events. The company does not consider comparisons against other atypical antipsychotics.

There are several areas of uncertainty in the evidence available to model the intended use of lurasidone. The clinical trials were not conducted specifically in a population of patients at high risk of these adverse events (e.g. patients with diabetes, existing CV

disease), although a beneficial effect on weight and metabolic profile of lurasidone has been consistently demonstrated in clinical trials across different patient profiles. There are no data presented specifically examining the impact on related outcomes (e.g. development of diabetes or CV disease/events). The modelled cost-effectiveness of lurasidone is most sensitive to the assumed relative risks of relapse for lurasidone compared with aripiprazole, which are derived from an indirect treatment comparison which is subject to considerable uncertainty. Within a plausible range of relative relapse rate estimates, lurasidone ranges from [commercial in confidence removed] The model estimates relatively small differences in QALY gains between lurasidone and aripiprazole, which would contribute to the sensitivity of the estimates of incremental cost-effectiveness to changes in relative relapse rates.

Key strengths of the economic evidence include:

- In the absence of direct comparative trial data for lurasidone and aripiprazole, the company has employed published indirect comparisons of trial data to inform its modelling.
- A wide range of sensitivity/scenario analyses have been conducted to explore structural and parameter uncertainty.

Key limitations and uncertainties of the economic evidence include:

- The clinical trials were not conducted specifically in a population of patients at high risk of weight gain and metabolic adverse events The extent to which the trial-based and modelled outcomes would be realised in practice is unclear.
- The modelled cost-effectiveness of lurasidone is most sensitive to the assumed relative risks of relapse for lurasidone and aripiprazole. These relative risks of relapse are derived from indirect treatment comparisons, which are subject to considerable uncertainty:
    - A multistep indirect treatment comparison across three individual trials has been conducted, which may introduce additional uncertainty beyond that which may exist in simple indirect treatment comparisons. Only single trials of aripiprazole and lurasidone were included, linked by a single trial of olanzapine versus quetiapine and other atypical antipsychotics. The basis of selection of those three trials is not clear, and the analysis may neglect useful information from other available trials.
    - The authors of this indirect treatment comparison note potential sources of heterogeneity among the three trials related to the inclusion and exclusion of patients with schizoaffective disorder and treatment-resistant schizophrenia[18]. In addition, Study D1050234, which provides relapse prevention data for lurasidone in the ITC, enrolled lurasidone recipients taking 80mg or 160mg per day and initially dosed them at 120mg per day, which is greater than the 40-80mg dose assumed in the model.
    - As the three trials included in the indirect treatment comparison did not all provide relapse rates, relative risks of all-cause hospitalisation are used as a proxy for relative relapse rates. Study D1050234, the direct comparative trial of lurasidone and quetiapine that was included in the ITC, reports a HR for all-cause hospitalisation of 0.433; however, this study also reports an actual HR for relapse for lurasidone compared with quetiapine of 0.728[15]. The face validity of the relative risks of relapse assumed from this proxy data is therefore uncertain.

- The trial of aripiprazole versus olanzapine included in this indirect treatment comparison did not provide hospitalisation data; instead, the risk of hospitalisation has been estimated based on the relative risk of lack of efficacy for aripiprazole in this study and on the hospitalisation rate for olanzapine from the third trial (CATIE) included in the indirect treatment comparison[4].

- In line with the economic model developed by NICE for CG82, the risk of development of diabetes is assumed to be determined by the risk of weight gain; the development of diabetes was not assessed in the clinical studies providing weight gain data for lurasidone. In contrast to the economic model developed by NICE for CG82, the company's model does not consider the impact of diabetes on cardiovascular risk factors. However, although diabetes contributes to the total QALY gains for each agent, the actual differences in QALYs between lurasidone and the comparators due to differences in the risk of developing diabetes and weight gain appear to be small.

4.2 Review of published evidence on cost-effectiveness

Standard literature searches conducted by AWTTC have identified three fully published economic evaluations of lurasidone compared against aripiprazole[26], quetiapine[27], and various atypical antipsychotics, including olanzapine and risperidone[28]. All were conducted from a USA health care perspective, and provide incremental cost estimates per hospitalisation or other event avoided, rather than incremental costs per QALY gained. The studies comparing lurasidone against aripiprazole[26] and various other atypical antipsychotics[28] employed the same published multistep indirect treatment comparison as used in the company's submission[1], and so would appear subject to many of the potential limitations outlined in Section 4.1.3. However, in contrast to the company's submission, these published analyses also modelled the cardiovascular events based on weight changes and metabolic risk factors. The analysis comparing lurasidone against quetiapine employed direct comparative data from study D1050234[27].

These analyses estimated lurasidone to dominate aripiprazole as a second-line agent[26], and to dominate any use of olanzapine, aripiprazole and quetiapine[28], in terms of costs per hospitalisation avoided. The incremental cost per hospitalisation avoided versus risperidone was approximately $26,000[28]. All were conducted by the company, and as they relate to use in the USA health system, their applicability to NHS Wales is unclear.

5.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

5.1 Budget impact evidence

5.1.1 Context and methods

Based on the adult population of Wales[29] and a published point prevalence of schizophrenia of 0.46%[5], the company estimates there are approximately 11,238 adults with schizophrenia in Wales. Assuming an incidence of 0.11 per 1000 population per year, as in the NICE CG82[22], 269 new adult cases per year are estimated. Assuming an annual mortality rate of 0.43% (reportedly based on standardised mortality rates for 25-year olds of 2.83–2.94), the company estimates there would be a net number of 11,457 adult patients in year 1, rising to 12,329 in year 5[1]. Based on company data on file (not verified), it is assumed that 80% of patients are diagnosed, and that 95% of those are treated, therefore the number of patients estimated to receive any treatment is 8,707 in year 1, rising to 9,370 in year 5[1].

The company anticipates uptake of lurasidone will be at 66% of the rate of uptake observed for aripiprazole when it was introduced in 2004. The company estimates this to equate to 0.29% of prescribing for schizophrenia in year 1, rising to 2.94% in year 5.

Annual drug acquisition costs are based on current list prices assuming daily doses of 40–80 mg for lurasidone ([commercial in confidence data removed]), and 15 mg for aripiprazole (£1,251.95).

5.1.2 Results

The company anticipates that introduction of lurasidone will result in cost savings compared with the use of aripiprazole, due to its lower anticipated list price.

Table 4. Company base case budget impact estimates

	Year 1	Year 2	Year 3	Year 4	Year 5
Number of patients eligible for treatment for schizophrenia	8,707	8,874	9,040	9,205	9,370
Uptake of lurasidone (%)	0.29%	1.16%	1.87%	2.44%	2.94%
Number of lurasidone-treated patients	25	103	169	225	275
Overall net cost	¶¶	¶¶	¶¶	¶¶	¶¶
¶¶ Commercial in confidence data removed					

Two scenario analyses have been provided: i) assuming a dose of lurasidone of 120 mg or greater, accruing the costs of 2 tablets per day; and, ii) assuming an increased cost of aripiprazole based on doses in Maudsley prescribing guidelines (£2,365 per annum). Results are as would be expected from i) increasing the assumed costs of lurasidone relative to aripiprazole, or ii) increasing the assumed cost of aripiprazole relative to lurasidone, while assuming the same efficacy (see Table 5).

Table 5. Company budget impact scenario analyses

Scenario	Year 1	Year 2	Year 3	Year 4	Year 5
i) assuming a dose of lurasidone of 120mg or greater	¶¶	¶¶	¶¶	¶¶	¶¶
ii) assuming an increased annual cost of aripiprazole based on doses in Maudsley prescribing guidelines (£2,365)	¶¶	¶¶	¶¶	¶¶	¶¶
¶¶ Commercial in confidence data removed					

5.1.3 AWTTC critique

- There appears to be a range of prevalence and incidence estimates available in the literature, which introduces uncertainty into the estimation of eligible patient numbers.
- The company estimates lurasidone uptake with reference to the observed uptake of aripiprazole. Anticipated uptake figures are subject to uncertainty, as in all budget impact estimates.
- The base case analysis assumes daily lurasidone doses of 40–80 mg, [commercial in confidence data removed]. As the budget impact analysis relates only to drug acquisition costs, lurasidone at this dose is implicitly assumed to therapeutically equivalent to aripiprazole at a dose of 15mg daily.
- Irrespective of actual uptake, use of lurasidone in place of aripiprazole is anticipated to be cost saving based on these assumed doses and list prices.

5.2 Comparative unit costs

Example comparative annual costs of lurasidone and other oral atypical antipsychotics are presented in Table 6, based on usual dose ranges and list prices in the British National Formulary (BNF)[30], irrespective of anticipated places in therapy..

Table 6. Example annual acquisition costs of lurasidone and other atypical antipsychotics

Medicine	Example regimen	Annual cost*
Lurasidone (Latuda®▼)	40–80mg daily	¶¶
Amisulpride (non-proprietary)	400–800 mg daily in two divided doses	£120 to £241
Aripiprazole (Abilify®)	15 mg daily	£1252
Olanzapine (non-proprietary)	5–20 mg daily	Standard release: £16 to £27 Orodispersible: £36 to £74
Paliperidone (Invega®)	3–12 mg daily	£1268 to £2529
Quetiapine (non-proprietary)	Standard release: 300–450 mg in two divided doses Modified release: 600 mg daily	Standard release: £34 to £57 Modified release: £2068
Risperidone (non-proprietary)	4–6 mg daily	Standard release: £13 to £23 Orodispersible: £488 to £873

*Based on BNF list prices and usual doses 17 July 2014[30] except lurasidone based on company information on expected usual dose and cost[1]
This table does not imply therapeutic equivalence of medicines or doses.
See relevant Summaries of Product Characteristics (SPCs) for full dosing details.
¶¶ Commercial in confidence data removed

6.0 ADDITIONAL INFORMATION

6.1 Prescribing and supply

AWTTC is of the opinion that, if recommended, lurasidone (Latuda®▼) for the indication under consideration may be appropriate for use within NHS Wales prescribed under specialist recommendation.

The company do not anticipate that lurasidone (Latuda®▼) will be supplied by a home healthcare provider.

6.2 Ongoing studies

The company submission states that there are no ongoing studies from which additional evidence is likely to be available within the next 6–12 months[1].

6.3 AWMSG review

This assessment report will be considered for review three years from the date of the Final Appraisal Recommendation.

6.4 Evidence search

Date of evidence search: 30 June 2014
Date range of evidence search: No date limits were applied to database searches.

GLOSSARY

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

Positive and Negative Syndrome Scale (PANSS)[31]
A system used for measuring symptom severity of patients with schizophrenia, where a trained interviewer applies a seven-point rating to 30 different schizophrenia symptoms. The sum of the scores for each provides the total PANSS score.

Montgomery-Asberg Depression Rating Scale (MADRS)[32]
A 10-item questionnaire that measures severity of depressive episodes. Higher score indicates more severe depression, and each item yields a score of 0 to 6. The overall score ranges from 0 to 60.

Relapse – Studies D1050234, D1050237[14,15]
For studies D1050234 and D1050237, relapse is defined as the earliest occurrence of any one of the following:

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

REFERENCES

1 Sunovion Pharmaceuticals Ltd. Form B: Detailed appraisal submission. Lurasidone (Latuda®▼). Sep 2014.

2 Sunovion Pharmaceuticals Ltd. Latuda®▼. Summary of Product Characteristics. 2014.

3 European Medicines Agency. Latuda®▼. Authorisation details. Apr 2014. Available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002713/human_med_001737.jsp&mid=WC0b01ac058001d124. Accessed Jul 2014.

4 National Institute for Health and Care Excellence. Clinical Guideline 178. Psychosis and schizophrenia in adults: treatment and management 7. Feb 2014. Available at: http://guidance.nice.org.uk/CG178. Accessed Jul 2014.

5 Saha S, Chant D, Welham J et al. A systematic review of the prevalence of schizophrenia. *PloS Medicine* 2005; 2 (5): e141.

6 European Medicines Agency. Assessment Report for lurasidone. Procedure No.: EMEA/H/C/002713/0000. Jan 2014. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002713/WC500164684.pdf. Accessed Jul 2014.

7 National Institute for Health and Care Excellence. ESNM15: Schizophrenia: lurasidone. 2013. Available at: http://www.nice.org.uk/Advice/ESNM15. Accessed Jul 2014.

8 All Wales Medicines Strategy Group. Final Appraisal Report. Quetiapine prolonged-release tablets (Seroquel®▼). Aug 2009. Available at: http://www.awmsg.org/awmsgonline/app/appraisalinfo/252. Accessed Jul 2014.

9 All Wales Medicines Strategy Group. Final Appraisal Recommendation - 1510. Olanzapine depot (ZypAdhera®). 5. Oct 2010. Available at: http://www.awmsg.org/awmsgonline/app/appraisalinfo/225. Accessed Jul 2014.

10 All Wales Medicines Strategy Group. Final Appraisal Recommendation - 2512. Paliperidone palmitate (Xeplion®) 50 mg, 75 mg, 100 mg and 150 mg prolonged release suspension for injection. 44. Oct 2012. Available at: http://www.awmsg.org/awmsgonline/app/appraisalinfo/1579. Accessed Jul 2014.

11 All Wales Medicines Strategy Group. Final Appraisal Recommendation - 2214. Aripiprazole (Abilify Maintena®) 400 mg powder and solvent for prolonged-release suspension for injection. Jul 14 A.D. Available at: http://www.awmsg.org/awmsgonline/app/appraisalinfo/909. Accessed Aug 2014.

12 loebel A, Cucchiaro J, Sarma K et al. Efficacy and safety of lurasidone 80 mg/day and 160 mg/day in the treatment of schizophrenia: A randomised, double-blind, placebo- and active-controlled trial. *Schizophrenia Research* 2013; 145: 101-9.

13 Meltzer HY, Cucchiaro J, Silva R et al. Lurasidone in the treatment of schizophrenia: A randomised, double-blind, placebo- and olanzapine-controlled study. *American Journal of Psychiatry* 2011; 168 (9): 957-67.

14 Citrome L, Cucchiaro J, Sarma K et al. Long-term safety and tolerability of lurasidone in schizophrenia: a 12-month, double-blind, active-controlled study. *International Clinical Psychopharmacology* 2012; 27 (3): 165-76.

15 loebel A, Cucchiara J, Xu J et al. Effectiveness of lurasidone vs. quetiapine XR for relapse prevention in schizophrenia: A 12-month, double-blind, noninferiority study. *Schizophrenia Research* 2013; 147: 95-102.

16 Leucht S, Cipriani A, Spineli L et al. Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis. *The Lancet* 2013; 382 (9908): 1874-5.
17 American Psychiatric Association. Diagnostic and Statistical Manual of Mental Health Disorders fourth edition Text Revision. 48. 2000. Available at: http://www.dnalc.org/view/899-DSM-IV-Criteria-for-Schizophrenia.html. Accessed Jul 2014.
18 Rajagopalan K, O'Day K, Meyer K et al. Discontinuation rates among atypical antipsychotics for schizophrenia: an indirect treatment comparison. Presented at Academy of Managed Care Pharmacy Educational Conference. 2012.
19 Leucht S, Cipriani A, Spineli L et al. Supplementary Appendix to Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis. *The Lancet* 2014; 382 (9908).
20 Chrzanowski WK, Marcus RN, NyilasM et al. Effectiveness of long-term aripiprazole therapy in patients with acutely relapsing or chronic, stable schizophrenia: a 52-week, open-label comparison with olanzapine. *Psychopharmacology* 2006; 189 (259): 266.
21 Lieberman JA, Stroup TS, McEvoy JP et al. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. *The new England Journal of Medicine* 2005; 353 (12): 1209-23.
22 National Institute for Health and Care Excellence. Clinical Guideline 82: Core interventions in the treatment and management of schizophrenia in primary and secondary care (replaced by CG178). 51. Mar 2009. Available at: http://guidance.nice.org.uk/CG82. Accessed Mar 2014.
23 Briggs A, Wild D, Lees M et al. Impact of schizophrenia and schizophrenia treatment-related adverse events on quality of life: direct utility elicitation. *Health and Quality of Life Outcomes* 2008; 6: 105.
24 Jönsson B. Revealing the cost of Type II diabetes in Europe. *Diabetologia* 2002; 45: S5-S12.
25 Abertawe Bro Morgannwg University Health Board. Case for change and non financial option appraisal report; November 2013. Nov 2013. Available at: http://www.wales.nhs.uk/sitesplus/863/opendoc/228170. Accessed Jul 2014.
26 Rajagopalan K, Hassan M, O'Day K. Cost-effectiveness of lurasidone vs aripiprazole among patients with schizophrenia who have previously failed on an atypical antipsychotic: an indirect comparison of outcomes from clinical trial data. *Journal of Medical Economics* 2013; 16: 951-61.
27 Rajagopalan K, O'Day K, Meyer K et al. Annual cost of relapses and relapse-related hospitalizations in adults with schizophrenia: results from a 12-month, double-blind, comparative study of lurasidone vs quetiapine extended-release. *Journal of Medical Economics* 2013; 16 (8): 987-96.
28 O'Day K, Rajagopalan K, Meyer K et al. Long-term cost-effectiveness of atypical antipsychotics in the treatment of adults with schizophrenia in the US. *ClinicoEconomics and Outcomes Research* 2013; 4: 459-70.
29 Office for National Statistics. Population estimates for England and Wales, Mid 2012-2013. 2013. Available at: http://www.ons.gov.uk/ons/taxonomy/index.html?nscl=Population#tab-data-tables. Accessed Jul 2014.
30 British Medical Association, Royal Pharmaceutical Society of Great Britain. British National Formulary. Apr 2014. Available at: http://www.bnf.org/bnf/index.htm. Accessed Aug 2014.
31 Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophrenia Bulletin* 1987; 13 (2): 261-76.
32 Muller-Thomsen T, Arlt S, Mann U et al. Detecting depression in Alzheimer's disease: evaluation of four different scales. *Archives of Clinical Neuropsychology* 2005; 20 (2): 271-6.

APPENDIX 1. Results of short term studies[1]

	Study D1050231				Study D1050233			
	Lurasidone 40 mg/day (n =118)	Lurasidone 120 mg/day (n =118)	Olanzapine 15 mg/day (n =121)	Placebo (n=114)	Lurasidone 80 mg/day (n=125)	Lurasidone 160 mg/day (n=121)	Quetiapine XR 600 mg/day (n=116)	Placebo (n =120)
Primary endpoint								
Change in PANSS mean total score, baseline to week six (SE)	−25.7[§] (2.0)	−23.6* (2.1)	−28.7[§] (1.9)	−16.0 (2.1)	−22.2[§] (1.8)	−26.5[§] (1.8)	−27.8[§] (1.8)	−10.3 (1.8)
Secondary endpoints								
Key secondary outcome: CGI severity score change (SE)	−1.5[†] (0.1)	−1.4* (0.1)	−1.5[§] (0.1)	−1.1 (0.1)	−1.5[§] (0.1)	−1.7[§] (0.1)	−1.7[§] (0.1)	−0.9 (0.1)
Selected secondary outcome: MADRS total score change (SE)	−3.5 (0.5)	−3.2 (0.6)	−0.5[†] (0.5)	−2.8 (0.6)	−4.0[§] (0.5)	−4.4[§] (0.5)	−4.3[§] (0.5)	−1.0 (0.5)

SE: Standard error; MADRS: Montgomery-Asberg Depression Rating Scale; PANSS: Positive and negative Syndrome Scale

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