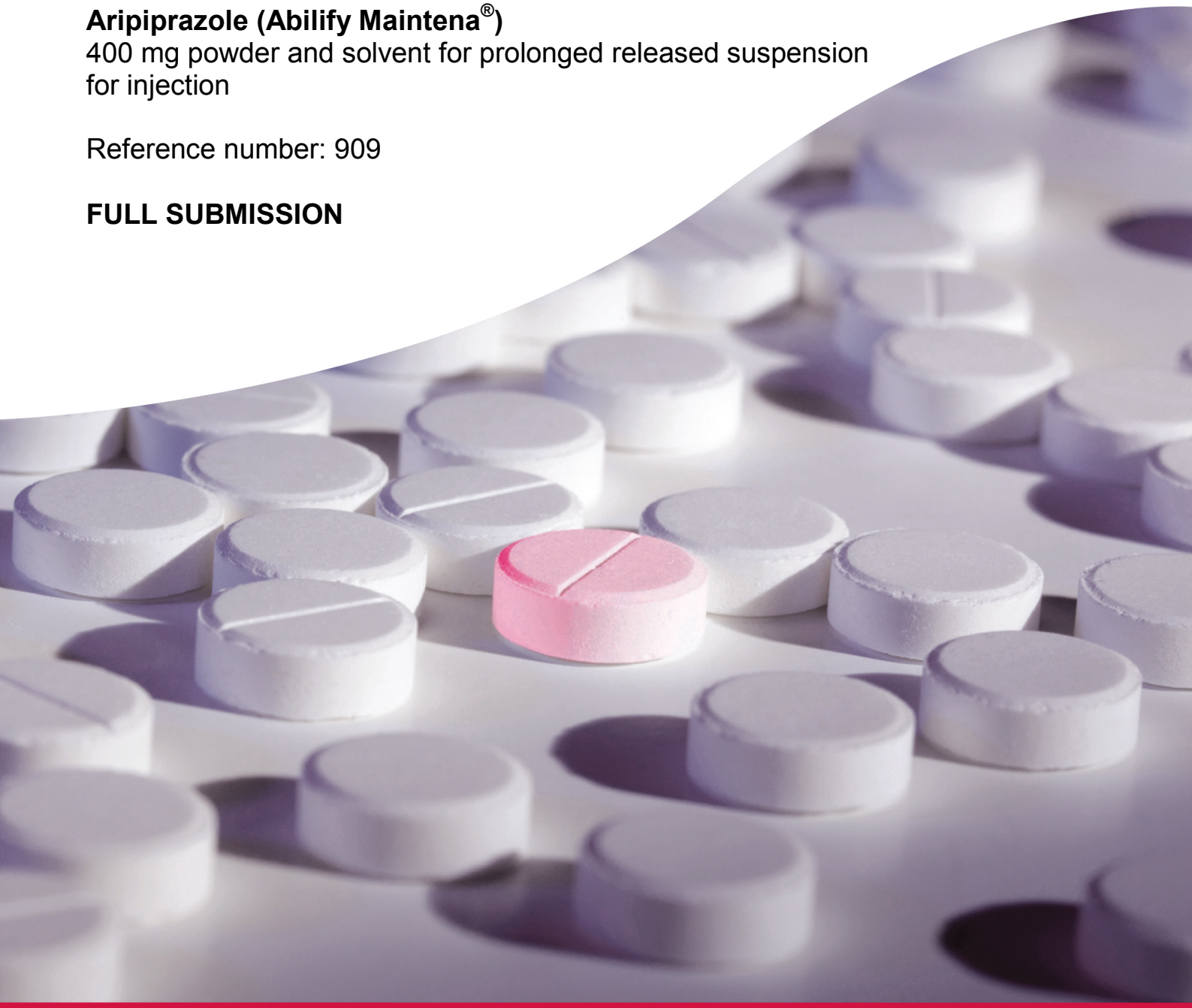
All Wales Therapeutics and Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

AWMSG SECRETARIAT ASSESSMENT REPORT

Aripiprazole (Abilify Maintena®)
400 mg powder and solvent for prolonged released suspension for injection

Reference number: 909

FULL SUBMISSION



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AWMSG Secretariat Assessment Report
Aripiprazole (Abilify Maintena®) 400 mg powder and solvent for prolonged released suspension for injection

This assessment report is based on evidence submitted by Otsuka Pharmaceuticals (UK) Ltd and Lundbeck Ltd on 25 February 2014[1].

1.0 PRODUCT DETAILS

Licensed indication under consideration	Aripiprazole (Abilify Maintena®) is indicated for the maintenance treatment of schizophrenia in adult patients stabilised with oral aripiprazole[2].
Dosing	The recommended starting and maintenance dose of aripiprazole (Abilify Maintena®) is 400 mg once monthly. Titration of the dose of this medicinal product is not required. It should be administered as a single injection (no sooner than 26 days after the previous injection). After the first injection, treatment with 10 mg to 20 mg oral aripiprazole should be continued for 14 consecutive days to maintain therapeutic aripiprazole concentrations during initiation of therapy. If there are adverse reactions with the 400 mg dosage, reduction of the dose to 300 mg once monthly should be considered. Refer to the Summary of Product Characteristics (SPC) for further information[2].
Marketing authorisation date	15 November 2013[2]
UK launch date	07 January 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[3,4]. Estimates vary; however, approximately 1% of the population will develop psychosis and schizophrenia over a lifetime, with an estimated overall prevalence of 0.5% in England[3,5].

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[3]. Their use for the prevention of relapse in schizophrenia necessitates the long term prescription of these medications either in tablet form or as a long-acting injectable (LAI). The National Institute for Health and Care Excellence (NICE) recommend offering LAI antipsychotic medication preparations as an option for patients who would prefer such treatment or where avoiding covert non-adherence (intentional or otherwise) is of high priority[3]. A satisfactory response to antipsychotic medication should become apparent within four weeks of commencement

of therapy. There is little consensus on the minimum duration of maintenance therapy for prevention of relapse[6].

Aripiprazole is an atypical antipsychotic with partial agonist activity at the dopamine D2 receptors and serotonin 5-HT1A receptors, and antagonism at 5-HT2A receptors[4]. Oral aripiprazole has been licensed for use in the treatment of schizophrenia since 2004[7].

2.2 Comparators

The comparators included in the company submission were:

- Paliperidone palmitate (Xeplion®) prolonged release suspension for injection
- Risperidone (Risperdal consta®) powder and solvent for prolonged-release suspension for intramuscular injection

2.3 Guidance and related advice

- NICE. Evidence summaries: new medicines (ESNM) 39. Schizophrenia: aripiprazole prolonged-release suspension for injection (2014)[8].
- NICE Clinical Guideline (CG) 178. Psychosis and schizophrenia in adults: treatment and management (2014)[3].
- Scottish Intercollegiate Guidelines Network (SIGN). Management of schizophrenia (2013)[9]
- Evidence-based guidelines for the pharmacological treatment of schizophrenia: recommendations from the British Association for Psychopharmacology (2011)[6].

AWMSG has previously issued recommendations for the use of paliperidone and olanzapine in the treatment of schizophrenia:

- Paliperidone palmitate (Xeplion®▼) prolonged release suspension for injection is recommended as an option for use within NHS Wales for the maintenance treatment of schizophrenia in adult patients stabilised with paliperidone or risperidone; and in selected adult patients with schizophrenia and previous responsiveness to oral paliperidone or risperidone, without prior stabilisation with oral treatment when psychotic symptoms are mild to moderate and a long-acting injectable treatment is needed[10].
- Olanzapine depot (ZypAdhera®▼) is not recommended for use within NHS Wales for the maintenance treatment of adult patients with schizophrenia sufficiently stabilised during acute treatment with oral olanzapine. The case for cost-effectiveness has not been proven[11].

3.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENES

In support of the indication under consideration, the applicant company have provided data from two phase III trials[12,13]. The primary pivotal study, 31-07-247, compared aripiprazole LAI with oral aripiprazole and is discussed in further detail in Section 3.1[1,4]. The second study, 31-07-246, was a phase III placebo-controlled study. Efficacy was demonstrated with the time to impending relapse being significantly shorter in the placebo group compared to the aripiprazole LAI group[1,4,13]. The results of this study will not be discussed further as it does not inform a comparison with established antipsychotic medication. Interim results from study 31-08-248[1] and data from study 31-08-283[14] are also included as supporting evidence and are highlighted in sections 3.2 and 3.3 respectively.

As there are no head-to-head comparative data on the efficacy and safety of aripiprazole LAI with other atypical antipsychotic LAIs, the applicant company provided a systematic review and mixed treatment comparison (MTC), summarised in Section 3.4[1].

3.1 Study 31-07-247

This was a multicentre, randomised, double-blind, active-controlled, parallel-group phase III study conducted in adult patients (aged 18–60 years inclusive) with a diagnosis of schizophrenia[1,12] (defined by the Diagnostic and Statistical Manual of Mental Health Disorders, fourth edition, Text Revision [DSM-IV-TR] criteria[15] [see Glossary]) who required chronic treatment with antipsychotic medication (other than clozapine), and had a history of relapse on discontinuation or interruption of medication. The aim was to demonstrate noninferiority and establish efficacy and safety of flexible dose monthly aripiprazole LAI after stabilisation with oral aripiprazole versus daily oral aripiprazole for maintenance treatment of schizophrenia, over a study duration of 38 weeks[1,12]. Noninferiority was considered confirmed if the upper bound of the two-sided 95% confidence interval (CI) was below the predefined margin of 11.5%[1,12].

After screening, patients were converted from other antipsychotics to oral aripiprazole monotherapy if required (phase one: 4–6 weeks) and were stabilised on oral aripiprazole (10–30 mg) for a minimum of eight consecutive weeks (phase two). During phase three, stabilised patients (n = 662) were randomised 2:2:1 to three groups: aripiprazole LAI 400 mg (or 300 mg depending on tolerability) once monthly (n = 265); oral aripiprazole 10–30 mg daily (n = 266); or, aripiprazole LAI 50 mg (or 25 mg depending on tolerability) once monthly (n = 131), for 38 weeks. Low dose aripiprazole LAI (50 mg) was included as a pseudo placebo to test assay sensitivity for the noninferiority design. To ensure blinding, all patients received a LAI of aripiprazole or placebo monthly and consumed a specified number of tablets (active or placebo) daily. All patients randomised to receive aripiprazole LAI were given oral aripiprazole for the first 14 days of phase three to maintain therapeutic plasma concentrations of aripirazole[1,4,12].

The primary efficacy endpoint was the proportion of patients in phase three of the trial with impending relapse (see Glossary) by week 26 from the date of randomisation. The estimated impending relapse rate was 7.12% (standard error [SE] 1.62) in the aripiprazole LAI 400 mg group and 7.76% (SE 1.72) in the oral aripiprazole 10–30 mg group, with a treatment difference of −0.6% (95% confidence interval [CI]: −5.26–3.99) demonstrating noninferiority[1,4].

Results of the secondary efficacy endpoints were found to be consistent with the primary efficacy endpoint (refer to Table 1)[1,4].

Table 1. Efficacy results for study 31-07-247[1,4]

		Aripirazole LAI 400 mg		Oral aripiprazole 10–30 mg		Treatment difference (95% CI)
Primary endpoint	**n**		**n**		**n**	
Proportion of patients in phase three of the trial with impending relapse by week 26	265	7.12%	266	7.76%	131	−0.64% (5.26, 3.99) [p = 0.7871]
Secondary endpoints	**n**		**n**		**n**	
Number of patients free of impending relapse at week 38	265	§	266	§	131	N/A
Proportion of responders at study endpoint*	265	89.8% (237/264)	266	89.4% (235/263)	131	0.4% [p = 0.8750]
Proportion of patients achieving remission for six months†	265	48.8% (105/201)	256	53.2% (107/201)	131	4.4%[p = 0.3700]
PANSS total score LS mean (SE) change from baseline at week 38	263	−1.66 (0.718)	266	0.58 (0.714)	131	−2.24% (−4.23, −0.25) [p = 0.0272]
CGI-S LS mean (SE) change from baseline at week	259	−0.13 (0.049)	263	0.05 (0.049)	129	−0.17% (−0.31, −0.04) [p = 0.0123]
CGI-I LS mean (SE)	263	3.27 (1.16)	266	3.66 (1.16)	131	N/A [p = 0.0002]

*Responders: patients who met the stability criteria as described in the Glossary.
†Remission: a score of ≤ 3 on each of the following PANNS items; delusions, unusual thought content, hallucinatory behaviour, conceptual disorganisation, mannerism/posturing, blunted effect, social withdrawal, lack of spontaneity.

§Commercial in confidence figures removed.

CGI-S: Clinical Global Impression-Severity; CGI-I: Clinical Global Impression-Improvement; CI: confidence intervals; LAI: long acting injectable; LS: least squares; PANSS: Positive and Negative Syndrome Scale; SE: standard error

3.2 Study 31-08-248

This was a long-term, multicentre, uncontrolled, open-label study, which included patients from studies 31-07-247 and 31-07-246 as well as *de novo* participants. As for study 31-07-247 (see Section 3.1), patients were screened, converted to oral aripiprazole as required and stabilised on oral aripiprazole before entering the open-label maintenance phase. [Commercial in confidence data removed]. The primary efficacy endpoint was the proportion of patients who remained stable (see Glossary) from baseline to their final visit of the maintenance phase. Although the study is complete, only interim results have been provided by the applicant company. [Commercial in confidence data removed]. These interim results suggest aripiprazole LAI efficacy is maintained in the long-term[1].

3.3 Study 31-08-283

This was a multi-centre, open-label mirror-image study to compare hospitalisation rates in patients with schizophrenia treated with oral antipsychotic medicines (retrospectively) to treatment with aripiprazole LAI for six months (prospectively). The

primary endpoint was the rate of psychiatric hospitalisation for the three month retrospective oral antipsychotic treatment period (months -4 to -1) compared to the prospective aripiprazole LAI period (months 4 to 6). After switching to aripiprazole LAI, the rate of psychiatric hospitalisation was significantly lower compared to the retrospective three month period when the same patients were receiving oral antipsychotic medication (6.6% [n = 8/121] versus 28.1% [n = 34/121] respectively; rate ratio = 0.24)[14].

3.4 Systematic review and MTC

As there are no data directly comparing aripiprazole LAI with other atypical antipsychotic LAIs, the applicant company provided a systematic review and MTC. The MTC was used by the applicant company to inform the pharmacoeconomic evaluation for aripiprazole LAI, summarised in Section 4.0. The systematic review was modified from the review conducted by NICE for CG 82, and was updated in May 2013[1,16]. The company focused on results relevant to this report, i.e. aripiprazole LAI compared with risperidone LAI and paliperidone LAI[1].

As per the protocol set out in NICE CG 82, the review included all blinded randomised control trials (RCTs) that compared LAI antipsychotics versus each other or placebo in adults diagnosed with schizophrenia not resistant to treatment; only studies with ≥ 10 participants and a duration of ≥ 24 weeks were included. Studies must have reported duration of follow up; patients experiencing relapse; patients discontinuing maintenance therapy and patients remaining on maintenance therapy. Information on patients experiencing extrapyramidal symptoms (EPS) and patients experiencing weight gain were also included to compare safety[1,16].

The studies included within the MTC differed with regard to inclusion/exclusion criteria and study methodology, and ultimately data from only four studies were used to inform the specific comparisons[12,13,17,18]. The results of the MTC suggest that aripiprazole LAI is estimated to have a favourable efficacy and safety profile compared to paliperidone LAI and risperidone LAI with no significant clinical differences[1]. MTC efficacy results are summarised in Table 2.

Table 2. Summary of MTC for efficacy outcomes[1]

Efficacy outcome	Placebo	Aripiprazole LAI	Paliperidone LAI	Rispiridone LAI
Relapse: 26-week probability (95% CrI range)	27.6% (18.5–39.3%)	8.4% (3.3–17.1%)	12.2% (3.4–28.7%)	7.7% (1.2–23.8%)
Discontinuation due to AEs: 26-week probability (95% CrI range)	2.5% (1.0–5.0%)	2.1% (0.3–6.8%)	8.5% (0.3–46.9%)	8.4% (0.2–53.0%)
Discontinuation due to reasons other than AEs: 26-week probability (95% CrI range)	11.3% (5.8–18.8%)	8.8% (2.6–21.1%)	14.9% (2.9–42.5%)	16.8% (1.7–58.1%)
Continuing treatment*: 26-week probability (95% CrI range)	58.7% (46.6–68.4%)	80.8% (65.6–89.6%)	64.4% (24.4–83.8%)	67.1% (14.3–89.3%)

*Continuing treatment = 1 - (probability of relapse + discontinuation due to AEs + discontinuation due to reasons other than AEs)

AE: adverse event; CrI: credible interval

3.5 Comparative safety

At the time of licensing, the Committee for Medicinal Products for Human Use (CHMP) concluded that the safety profile of aripiprazole LAI appeared favourable and similar to that of oral aripiprazole. In total, 1,624 adult patients with schizophrenia have been

exposed to aripiprazole LAI. The most frequently observed treatment-emergent adverse events (TEAEs) reported in patients receiving aripiprazole LAI 400 mg were increased weight, akathesia, insomnia, and injection site pain. A higher frequency of EPS was reported in the aripiprazole LAI 400 mg group compared to the oral aripirazole group (18.4% versus 11.7%). In study 31-07-247, a higher incidence of low white blood cell (WBC) count was observed in the aripiprazole LAI 400 mg group compared to oral aripiprazole (2.3% versus 0.8%). Although three of the six patients in the aripiprazole LAI 400 mg group had low WBC at baseline, CHMP considered leukopaenia to be of potential clinical relevance and identified it as a risk related to this formulation. Neutropaenia typically onsets around 16 days after the first injection and lasts a median of 18 days[1,4].

The MTC identified weight gain and EPS as the key AEs to be assessed when comparing aripiprazole LAI with other atypical antipsychotic medicines. Compared with placebo, aripiprazole LAI, paliperidone LAI and risperidone LAI all carried an increased risk of weight gain and EPS. For both of these AEs, the credible intervals were large and overlapping suggesting no important clinical differences between medicines[1]. Results of the MTC for safety outcomes are summarised in Table 3.

Table 3. Summary of MTC for safety outcomes

Safety outcomes	Placebo	Aripiprazole LAI	Paliperidone LAI	Rispiridone LAI
Probability of significant (> 7%) weight gain (95% CrI range)	5.4% (3.6–7.2%)	11.2% (6.5–18.4%)	11.9% (4.2–26.1%)	12.8% (4.2–29.1%)
Probability of development of acute EPS (95% CrI range)	9.1% (6.8–11.5%)	14.3% (9.7–20.4%)	16.3% (8.2–28.4%)	19.1% (9.0–34.5%)
CrI: credible interval; EPS: extrapyramidal symptoms				

3.6 AWTTC critique

- CHMP concluded that the pivotal study, 31-07-247, demonstrated noninferiority of aripiprazole LAI 400 mg compared to oral aripiprazole 10–30 mg. This is within the predefined margin of 11.5% and also falls within the 10% margin suggested in the CHMP scientific advice [4].
- As there are no direct comparative data between aripiprazole LAI and other atypical antipsychotic LAIs, the applicant provided an MTC[1]. Results of the MTC suggested no important clinical differences between aripiprazole LAI, risperidone LAI and paliperidone LAI, as credible intervals were large and overlapping[1]. Due however to the heterogenicity of the trials, the findings of the MTC should be interpreted with caution.
- Patients from the UK were not included in the pivotal study, 31-07-247; however, with participants from Europe and the US, the study population may be considered broadly applicable to Wales[1]. CHMP noted that the mean age (being slightly higher than anticipated) and the long duration of oral stabilisation (at least eight weeks) may have contributed to a lower than anticipated relapse rate[4].
- The safety profile of aripiprazole LAI, from pooled clinical trial data, was found to be favourable and similar to that of oral aripiprazole. Nevertheless, a higher frequency of EPS with aripiprazole LAI 400 mg compared to oral aripiprazole 10–30 mg (18.4% versus 11.7%) was highlighted and CHMP advised a post authorisation safety study to address this concern. They noted that ongoing studies should provide further information on the frequency of EPS. In addition, CHMP commented on the higher incidence of low WBC count in the aripiprazole LAI 400 mg group of study 31-07-247; therefore, the risk of

neutropaenia as an AE is stated in the Summary of Product Characteristics (SPC)[2,4].

- Aripiprazole LAI is the fourth atypical antipsychotic licensed as a depot formulation. Aripiprazole LAI may provide an additional treatment option for patients with schizophrenia, and may also allow patients already stabilised on oral aripiprazole to switch to a LAI formulation without necessarily changing medication[1]. Unlike paliperidone LAI, no titration of aripiprazole LAI is required; however, oral aripiprazole is required for 14 days after the initial injection to maintain therapeutic plasma levels[2,19].
- Although improved adherence to medication with aripiprazole LAI over oral aripiprazole was not demonstrated explicitly, study 31-07-247 showed longer time to medication discontinuation due to all reasons ($p < 0.05$, no figures supplied)[1]. However, LAI formulations of antipsychotic medicines are known to overcome problems associated with covert non-adherence to medication[20]. A patient's non-attendance to clinic or refusal to receive an injection would be immediately identified so that action may be taken[20].
- No dose adjustment of aripiprazole LAI is required for patients with renal or mild to moderate hepatic impairment. Whereas, dose adjustment of paliperidone is advised in patients with mild renal impairment and is not recommended in moderate to severe renal impairment. There is not sufficient evidence to inform the use of risperidone in such patients[2,19,21].
- Unlike paliperidone LAI, aripirazole LAI requires reconstitution, which may be considered less convenient[1]. Aripirazole LAI and risperidone LAI have a three year shelf-life; however, aripiprazole LAI does not require refrigeration. In comparison, paliperidone LAI has a two year shelf-life[1,2,19,21].

4.0 SUMMARY OF THE EVIDENCE ON COST-EFFECTIVENESS

4.1 Cost-effectiveness evidence

4.1.1 Context

The company submission described a cost-utility analysis (CUA) of aripiprazole LAI compared to paliperidone LAI and risperidone LAI for the maintenance treatment of schizophrenia in adult patients stabilised with oral antipsychotics in Wales.

A decision analytic Markov model is used to estimate the incremental costs and health outcomes over a lifetime horizon. The model includes health states for remission, relapse and death with six-monthly cycles. Two remission health states are included to distinguish between patients who are fully compliant (FC) and those who are non-compliant (NC). Within each cycle, patients may remain in remission, experience a relapse, stop the antipsychotic due to AEs, stop the antipsychotic for other reasons, or die[1].

Three lines of therapy are modelled. First-line therapy comprises aripiprazole LAI or its comparators (paliperidone or risperidone LAIs). Second-line treatment comprises a second LAI, with event probabilities assumed as the average of paliperidone LAI and risperidone LAI, weighted by their respective market share. Third-line treatment is assumed to be oral clozapine. The cost and health disutility associated with EPS and weight gain is modelled to represent treatment-emergent AEs[1].

Patients enter the model at initiation of therapy with an LAI (aripiprazole, paliperidone or risperidone) in the FC remission state. Treatment discontinuation due to intolerable AEs can only occur in the first cycle of treatment. Treatment discontinuation due to other reasons (including lack of efficacy) can occur in any cycle. The model assumes differential rates of relapse for FC and NC patients; NC patients are assumed to relapse at a rate equivalent to placebo LAI. Antipsychotic treatment following

resolution of a relapse also differs between FC and NC patients: all FC patients transit to the next line of therapy, whereas a proportion of previously NC patients are assumed to recommence prior antipsychotic treatment (50% in the base case) with the remainder transitioning to next-line therapy[1].

The main efficacy and safety data used to populate the model are obtained from a MTC that included aripiprazole LAI and its comparators (paliperidone LAI and risperidone LAI [see section 3.4])[1]. Other data used to populate the model were obtained from published sources[16,19,21–34].

4.1.2 Results

Results of the base case analysis suggest that aripiprazole LAI is dominant to both paliperidone LAI and risperidone LAI, i.e. it is associated with lower costs and higher quality-adjusted life-years (QALYs). The key drivers of cost-effectiveness were two efficacy parameters (probability of relapse and probability of treatment discontinuation due to other reasons), the costs associated with relapse and the costs associated with NC patients.

Table 4. Company-reported results of the base case analysis

	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER Aripiprazole versus comparator
Aripiprazole LAI	£458,580	15.0461	–	–	–
Paliperidone LAI	£468,811	14.9748	−£10,231	0.0713	Dominant
Risperidone LAI	£462,721	14.9957	−£4,141	0.0504	Dominant
ICER: incremental cost effectiveness ratio; QALY: quality-adjusted life-year					

The company conducted univariate analyses to assess the sensitivity of the net monetary benefit (NMB) statistic ($NMB = Threshold \times \Delta QALYs - \Delta Cost$) to changes in model inputs. Based on a threshold of £20,000 per QALY, the analysis showed that when compared with paliperidone LAI, aripiprazole LAI was dominant or cost-effective (NMB > £0) in all the sensitivity analyses performed. Similarly, aripiprazole was dominant or cost-effective in the majority of sensitivity analyses when compared with risperidone LAI. However, aripiprazole LAI was not cost-effective when compared with risperidone LAI when parameter estimates were changed with respect to treatment efficacy (probability of relapse and probability of discontinuing treatment due to reasons other than AE), cost of acute relapse treatment and the percentage of remission costs attributable to NC patients (compared to FC patients). The parameters subject to the most variation in the univariate sensitivity analyses for each comparison are shown in Table 5.

Table 5. Selected company-reported sensitivity analyses

Parameter	ICER Aripiprazole versus comparator	Comment
Aripiprazole LAI versus paliperidone LAI		
Probability of relapse with aripiprazole LAI (upper 95% CI from MTC)	£35,935*	Represents the highest ICERs within the bounds of the 95% CI for the probability of relapse
Probability of relapse with paliperidone LAI (lower 95% CI from MTC)	Dominant†	
Cost of acute relapse treatment (lower value)	Dominant†	Plausible as base case cost of acute relapse treatment is high
Aripiprazole LAI versus risperidone LAI		
Probability of relapse with aripiprazole LAI (upper 95% CI from MTC)	Dominated§	Represents the highest ICERs within the bounds of the 95% CI for the probability of relapse
Probability of relapse with risperidone LAI (lower 95% CI from MTC)	Dominated§	
Cost of acute relapse treatment (lower value)	£21,290	Plausible as base case cost of acute relapse treatment is high

CI: confidence interval
*cost-effective with lower costs and lower QALYs; †dominant = lower costs and higher QALYs; §dominated = lower costs and higher QALYs associated with comparator.

Scenario analyses were conducted based on time horizon of analysis, adherence rates, utility values, and costs associated with relapse and remission. In all scenarios conducted, aripiprazole LAI was modelled to result in lower costs and higher QALYs than both paliperidone and risperidone LAIs. Adjusting the time horizon from between 10 years and lifetime resulted in a minimal impact on incremental costs and QALYs; neither did the introduction of a state of partial compliance (PC). Using the utility values from NICE CG 82[16], which were the same utility values from the updated NICE CG 178[3], reduced the magnitude of QALY gains associated with aripiprazole LAI though it still maintained dominance over paliperidone and risperidone LAIs. The use of different published costs for relapse and remission reduced the difference in relapse and remission health state costs and hence the incremental cost savings associated with aripiprazole LAI was reduced compared to both paliperidone and risperidone LAI (though aripiprazole LAI maintained dominance)[1].

Probabilistic sensitivity analysis undertaken for the base-case analysis indicates that aripiprazole had the highest probability of being the cost-effective treatment at all thresholds of cost-effectiveness (£0 to £100,000 per QALY).

4.1.3 AWTTC critique

The company's estimate of the cost-effectiveness of aripiprazole LAI compared to palperidone LAI and risperidone LAI is dependent on the results of an MTC which estimated small numerical differences in favour of aripiprazole LAI for the majority of the outcomes analysed, including discontinuation, EPS and weight gain. However, for each of the outcomes investigated in the MTC, the credible intervals were large and overlappping implying no statistical significance in the differences between aripiprazole LAI, paliperidone LAI and risperidone LAI.

Strengths of the company's economic evidence include:

- The model structure is clear and largely in line with the model reported in the NICE CG 82[16].
- The clinical pathway and assumptions used in the model are reported to have been validated by Welsh clinical experts.

Limitations of the economic evidence include:

- The use of key efficacy and safety data from an MTC in which small numerical differences in outcomes were observed; none of these were statistically significant. This is particularly relevant as the probability of relapse and discontinuation rates due to other reasons were key drivers of cost-effectiveness.
- Efficacy and safety were considered to be independent of dose[1]. There are no data to support this assumption, though it was reported to be verified by Welsh clinical experts[1].
- The use of different doses for estimating the costs of maintenance treatment with LAIs. Average doses, weighted according to data on prescriptions dispensed, were used for paliperidone LAI (96.7 mg per month) and risperidone LAI (38.54 mg every two weeks). However, the SPCs for paliperidone and risperidone LAIs refer to recommended maintenance doses of 75 mg per month, and 25 mg per fortnight, respectively[19,21].
- Lack of utility estimates from the LAI clinical trials meant that utility values were obtained from the literature[23], adding uncertainty to the model. In addition, these utility values differed from those used in the NICE CG 82 model[16].
- There is no evidence to support the assumption that the reduction in quality of life resulting from weight gain would be permanent.
- The hospital length of stay of 97 days associated with an acute episode (relapse) appears long. The company does not fully address this in sensitivity analysis.
- Costs for the relapse and remission health states were based on assumptions about mode of treatment, adding further uncertainty to the model.

5.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

5.1 Budget impact evidence

5.1.1 Context and methods

The company estimates the total number of adult patients with schizophrenia in Wales to be 12,216. This is based on a prevalence of schizophrenia and related disorders of 0.5% in England and Welsh population statistics[5]. Based on an increase in the prevalence of schizophrenia by 16% between 2007 and 2026[5], the company assumes an increase in the prevalence of schizophrenia of 0.745% per annum. They thus assume 12,216 patients with schizophrenia in year 1 increasing to 12,584 patients in year 5. Based on estimates from NICE CG 82[16], they assume that 90% of patients with schizophrenia receive pharmacological treatment, with two thirds of these treated with an atypical antipsychotic. Based on regional sales analysis and hospital pharmacy audit, the company assumes that 10% of those treated with an atypical antipsychotic receive an LAI. Assuming aripiprazole achieves an LAI market share of 4% in year 1, increasing to 20% in year 5, the number of patients who will be treated with aripiprazole LAI is estimated to increase from 29 in year 1 to 151 in year 5[1].

The company has based its budget impact analyses on maintenance treatment over 52 weeks plus initiation costs. In addition, it included the costs associated with administration of the different LAIs at the doses used in the economic evaluation. The company estimates the market share of paliperidone LAI and risperidone LAI at 11.2% and 88.8% respectively, and assumes that the use of aripiprazole will reduce their market shares proportionally[1].

5.1.2 Results

The company estimates the acquisition costs of maintenance treatment with aripiprazole LAI to be £2,638 per patient per year, compared to £3,569 for paliperidone LAI and £2,960 for risperidone LAI[1]. The estimated number of patients and the associated costs as described by the company in their budget impact analysis are summarised in Table 6.

Table 6. Company-reported net costs associated with the use of aripiprazole LAI for maintenance treatment of schizophrenia in adult patients

	Year 1	Year 2	Year 3	Year 4	Year 5
Number of LAI treated patients	735	740	746	752	757
Aripiprazole LAI uptake	4%	8%	12%	16%	20%
Treated patients aripiprazole LAI	29	59	90	120	151
Treated patients, paliperidone LAI	627	605	583	561	538
Treated patients, risperidone LAI	79	76	74	71	68
Net costs					
Medicine costs	−£11,685	−£23,347	−£35,182	−£47,193	−£59,380
Staffing	−£9,062	−£18,258	−£27,592	−£37,063	−£46,673
Overall net cost	−£20,747	−£41,605	−£62,774	−£84,255	−£106,053

The company conducted a number of scenario analyses to assess the impact of varying input parameters on the overall budget impact. The scenarios considered were:

i. aripiprazole LAI prescribed every four weeks rather than monthly
ii. differences in initiation costs favouring the comparators
iii. lower doses for paliperidone LAI (63.5 mg) and risperidone LAI (32.4 mg)
iv. less community psychiatric nurse time associated with administration of treatment
v. LAI administration by consultant rather than community psychiatric nurse.

In addition, the company conducted one multi-way analysis comprising i and iv above. In all scenarios, both medicine and staffing costs were expected to be lower with the use of aripiprazole LAI. The main driver of the projected cost savings were lower acquisition costs versus both paliperidone and risperidone LAIs as well as reduced LAI administrations versus risperidone LAI[1].

5.1.3 AWTTC critique

The company estimated the eligible patient numbers based on prevalence and incidence rates and assumptions rather than attempt to estimate the actual number of eligible patients in Wales. In addition:

- There is uncertainty about the number of adult patients with schizophrenia in Wales. The company assumed a prevalence rate of 0.5% based on a Kings Fund report[5]. Whereas NICE refer to a prevalence rate of 1% in their updated clinical guideline on schizophrenia[3].
- There is uncertainty about the number of patients receiving LAIs in Wales. Hence there is also uncertainty in the number of patients eligible for treatment with aripiprazole LAI.
- The company did not factor in any change in the LAI atypical antipsychotic market; they assumed that this was fixed at 10% of the atypical antipsychotic market over the five-year period.
- The company may have overestimated the costs of paliperidone LAI and risperidone LAI in the budget impact analysis. The doses of paliperidone LAI and risperidone LAI as recommended in their respective SPCs are lower than the average dose weighted by prescription data used in the analysis.

- The company may have overestimated the costs in year 1 by assuming that all patients will receive treatment at the beginning of that year. In reality, initiation of treatment will take place over the course of the year.

5.2 Comparative unit costs

Table 7 includes example acquisition costs of atypical antipsychotic LAIs for the maintenance treatment of schizophrenia in adult patients. It should be noted that initiation doses may differ from maintenance doses and that maintenance doses may be adjusted as per the specific product SPC. The example acquisition costs are based on an annual treatment period. The equivalent cost per patient for a patient receiving aripiprazole LAI (Abilify Maintena®) 400 mg every month would be £2,645 per year.

Table 7. Examples of acquisition costs per patient of LAI antipsychotics for the maintenance treatment of schizophrenia in adult patients

Regimens	Example maintenance doses	Annual cost per patient*
Aripiprizole (Abilify Maintena®) Injection 400 mg	400 mg every month	£2,645
Paliperidone palmitate (Xeplion®) Injection 50 mg, 75 mg, 100 mg, 150 mg	75 mg every month	£2,939
Risperidone (Risperdal Consta®) Injection 25 mg, 37.5 mg, 50 mg	25 mg every two weeks	£2,072
Olanzapine (ZypAdhera®) Injection 210 mg, 300 mg, 405 mg	300 mg every four weeks	£2,894
Costs based on British National Formulary prices as of April 2014[35] Costs of administration and monitoring are not included. Olanzapine (ZypAdhera®) was not recommended by AWMSG[11].		

6.0 ADDITIONAL INFORMATION

6.1 Prescribing and supply

AWTTC is of the opinion that, if recommended, aripiprazole (Abilify Maintena®) is appropriate for specialist only prescribing within NHS Wales for the indication under consideration.

The company anticipate that aripiprazole (Abilify Maintena®) may be supplied by a home healthcare provider[1].

6.2 Ongoing studies

The company submission highlighted two ongoing studies that are likely to be available within 6–12 months:

- Study 31-08-248 (NCT00731549): An open-label, follow up study investigating the safety, tolerability and effectiveness of aripiprazole LAI[36]. Full results are expected to become available in March 2014. However, interim results have been provided by the applicant company; these are briefly summarised in Section 3.2.
- QUALIFY (NCT01795547): A phase IIIb, open-label study designed to evaluate the efficacy of aripiprazole LAI 400 mg versus paliperidone LAI 50–150 mg over a period of 28 weeks[37]. Preliminary results are expected in October 2014[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: 06 March 2014
Date range of evidence search: No date limits were applied to database searches.

GLOSSARY

Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR)
The DSM-IV-TR criteria for schizophrenia require that an individual must display:

- Two or more criterion A symptoms of schizophrenia (delusions, hallucinations, disorganised speech, disorganised behaviour or negative symptoms). Only one criterion A symptom is required if delusions are bizarre or hallucinations consist of voices keeping up a running commentary on the person's thoughts or behaviour, or two or more voices conversing with each other.
- Social or occupational dysfunction for a significant portion of time since onset.
- Continuous signs of the disturbance persisting for six months, including one month of continuous symptoms.
- Schizoaffective and mood disorder and substance or general medical condition causes should be excluded[15].

Clinical Global Impression Improvement (CGI-I)
This is used to rate the improvement of a patient's condition since a defined (baseline) time. CGI-I is measured on a 0–7 scale where 0 = not assessed, 1 = very much improved through to 7 = very much worse[1].

Clinical Global Impression Severity (CGI-S)
CGI-S consists of one question which rates disease severity on a 7-point scale[1].

Clinical Global Impression Severity of Suicide (CGI-SS)
This is a two part scale: part one assesses severity of suicidality over the week prior to the evaluation with a 5-point rating scale ranging from 1 (not at all suicidal) to 5 (attempted suicide). Part two evaluates change in suicidality from baseline with a 7-point scale ranging from 1 (very much improved) to 7 (very much worse)[1].

Positive and Negative Syndrome Scale (PANSS)
A system used for measuring symptom severity of patients with schizophrenia, where a trained interviewer applies a seven-point rating to 30 different schizophrenia symptoms. The sum of the scores for each provides the total PANSS score[38].

Impending relapse criteria – Study 31-07-247
Impending relapse is defined as ≥ 1 of the following criteria:

1. Clinical worsening as defined by CGI-I score of ≥ 5 **AND**
    - An increase of any of the four individual PANSS items (conceptual disorganisation, hallucinatory behaviours, suspiciousness, or unusual thought content) to a score of > 4 with an absolute increase of ≥ 2 on that specific item since randomisation **OR**
    - An increase > 4 on any of the four PANSS items and an absolute increase of ≥ on the combined score of these items since randomisation **OR**
2. Hospitalisation due to worsening of psychotic symptoms **OR**
3. A risk of suicide as defined by a CGI-SS score of 4 or 5 on Part 1 of 6 or 7 on Part 2 **OR**
4. Violent behaviour resulting in clinically relevant self-injury, injury to another individual or damage to property[1].

Stability criteria – Study 31-07-247 and Study 31-08-248

1. Outpatient status **AND**
2. PANSS total score ≤ 80 **AND**
3. Lack of specific psychotic symptoms on the PANSS as measured by a score of ≤ 4 on each of the following items (possible scores of 1 to 7 for each item):
    - Conceptual disorganisation

- Suspiciousness
- Hallucinatory behaviour
- Unusual thought content, **AND**

4. CGI-S ≤ 4 (moderately ill) **AND**
5. CGI-SS ≤ 2 (mildly suicidal) on Part 1 and ≤ 5 (minimally worsened) on Part 2[1].

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