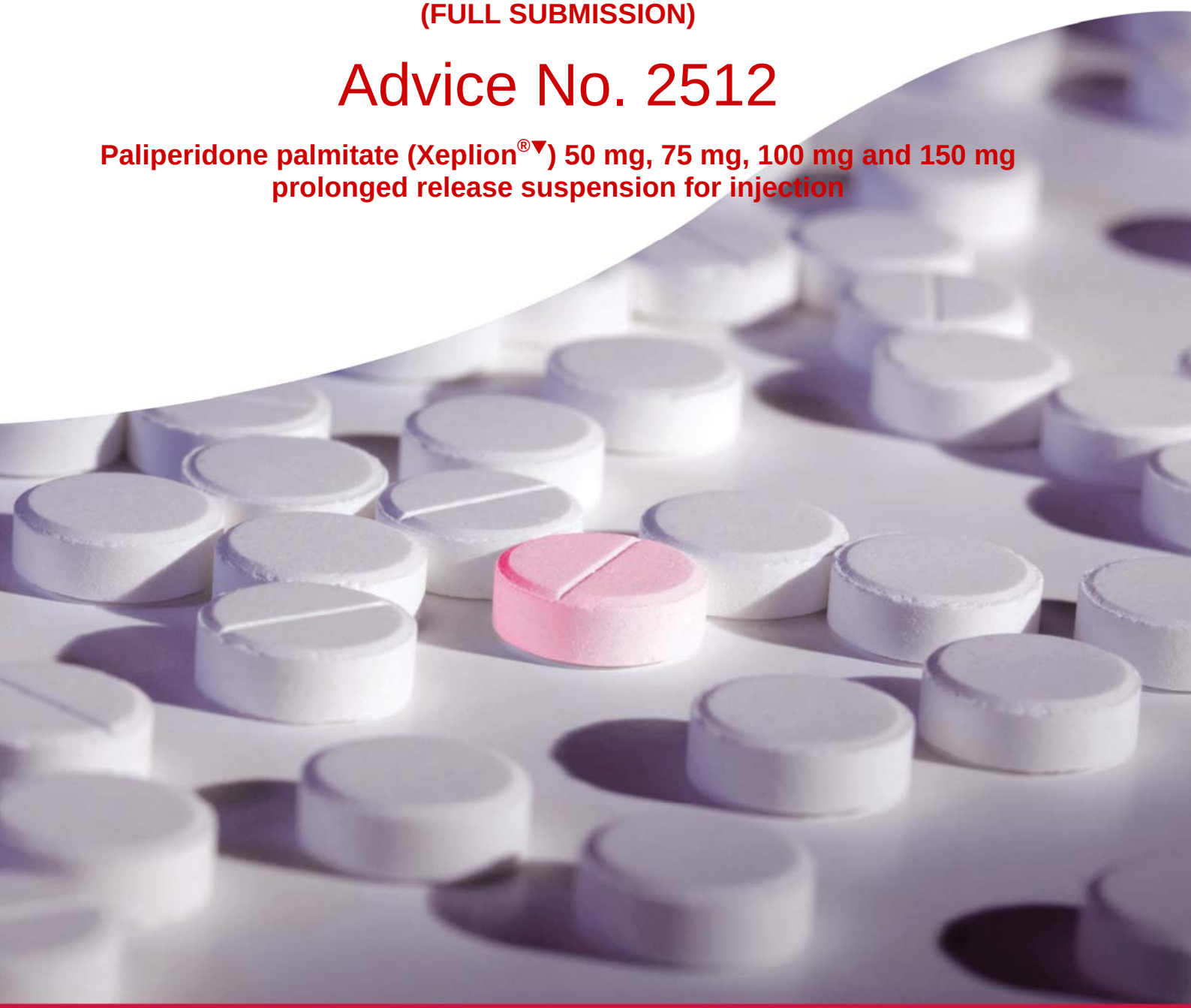
All Wales Therapeutics and Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

AWMSG SECRETARIAT ASSESSMENT REPORT

(FULL SUBMISSION)

Advice No. 2512

Paliperidone palmitate (Xeplion®▼) 50 mg, 75 mg, 100 mg and 150 mg prolonged release suspension for injection



In collaboration with the Centre for Health Economics & Medicines Evaluation, Bangor University

AWMSG Secretariat Assessment Report – Advice No. 2512
Paliperidone palmitate (Xeplion®▼) 50 mg, 75 mg, 100 mg and 150 mg prolonged release suspension for injection

This assessment report is based on evidence submitted by Janssen-Cilag Ltd on 10 April 2012[1].

1.0 PRODUCT DETAILS

Licensed indication under consideration	Paliperidone palmitate (Xeplion®▼) prolonged release suspension for injection is indicated for the maintenance treatment of schizophrenia in adult patients stabilised with paliperidone or risperidone. In selected adult patients with schizophrenia and previous responsiveness to oral paliperidone or risperidone, paliperidone palmitate may be used without prior stabilisation with oral treatment if psychotic symptoms are mild to moderate and a long acting injectable treatment is needed[2].
Dosing	Recommended initiation of paliperidone palmitate is with a dose of 150 mg on treatment day 1 and 100 mg one week later (day 8), both administered in the deltoid muscle in order to attain therapeutic concentrations rapidly. The recommended monthly maintenance dose is 75 mg; some patients may benefit from lower or higher doses within the recommended range of 25–150 mg based on individual patient tolerability and/or efficacy. Patients who are overweight or obese may require doses in the upper range. Following the second dose, monthly maintenance doses can be administered in either the deltoid or gluteal muscle. Adjustment of the maintenance dose may be made monthly. To avoid a missed monthly dose, paliperidone palmitate may be given up to seven days before or after the scheduled date of administration. Refer to the Summary of Product Characteristics (SPC) for further information regarding switching from oral paliperidone or risperidone and for dosing in special populations[2].
Marketing authorisation date	4 March 2011[2].

2.0 DECISION CONTEXT

2.1 Background

Schizophrenia is one of the terms used to describe a major psychiatric disorder (or cluster of disorders) that alters an individual's perception, thoughts, affect and behaviour[3]. The mean incidence rate of schizophrenia as reported in epidemiological studies is 0.11 per 1,000 (range 0.07 to 0.17 per 1,000), when the diagnosis is limited to core criteria and corrected for age[3]. The lifetime prevalence of schizophrenia as reported in a 1996 study by Cannon and Jones, is 0.4–1.4%[4], while a more recent systematic review (2005) estimates worldwide median point prevalence as 0.46%, although there was substantial variation between sites[5].

Antipsychotic medication is the mainstay of schizophrenia treatment, and its primary pharmacological action is the antagonistic effect on the dopamine D2 receptors[3]. Currently, antipsychotics are used for the treatment of acute episodes, relapse prevention, emergency treatment of acute behavioural disturbance and symptom

reduction. The use of antipsychotics to prevent relapse has led to these medicines being prescribed as long-term maintenance treatments, either as oral preparations or in the form of long-acting injectable (LAI) preparations. National Institute for Health and Clinical Excellence (NICE) guidelines recommend that LAI antipsychotic medication should be used in patients with schizophrenia who would prefer such treatment after an acute episode or where avoiding covert non-adherence (either intentional or unintentional) to antipsychotic medication is a clinical priority[3]. However, it has been noted that amongst all of the available antipsychotic drugs, none has emerged as superior in preventing relapse[6].

Paliperidone palmitate is the palmitate ester prodrug of paliperidone, the major metabolite of risperidone[7]. Paliperidone acts mainly by blocking the serotonergic 5-HT2 and dopaminergic D2 receptors. Oral paliperidone has been licensed for the treatment of schizophrenia since 2007[8] but has not been appraised by the All Wales Medicines Strategy Group (AWMSG) for this indication. On 4 March 2011, paliperidone palmitate prolonged release suspension for injection became the third atypical antipsychotic LAI licensed for the maintenance treatment of schizophrenia in adult patients stabilised with an oral antipsychotic[2], following risperidone LAI (Risperdal Consta®▼)[9] and olanzapine depot (ZypAdhera®▼)[10]. However, unlike olanzapine depot and risperidone LAI, paliperidone palmitate is also licensed for use in selected adult patients with schizophrenia and previous responsiveness to oral paliperidone or risperidone, without prior stabilisation with oral treatment where psychotic symptoms are mild to moderate and a long-acting injectable treatment is needed[2,9,10].

2.2 Comparators

The comparator requested by the All Wales Therapeutics and Toxicology Centre (AWTTC) was risperidone LAI. Olanzapine depot has previously been appraised by AWMSG and received a negative recommendation (see Section 2.3).

2.3 Guidance and related advice

- British Association for Psychopharmacology (BAP). Evidence-based guidelines for the pharmacological treatment of schizophrenia: recommendations from the British Association for Psychopharmacology (2011)[6].
- North East Treatment Advisory Group (NETAG). Paliperidone depot injection (Xeplion®▼) for schizophrenia (2011)[11].
- National Institute for Health and Clinical Excellence (NICE). Clinical Guideline 82. Schizophrenia: Core interventions in the treatment and management of schizophrenia in adults in primary and secondary care (2009)[3].
- Scottish Intercollegiate Guidelines Network (SIGN). SIGN publication number 30: Psychosocial interventions in the management of schizophrenia (1998)[12].

AWMSG has previously issued recommendations for the use of olanzapine depot and oral paliperidone:

- 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[13].
- In the absence of a submission from the holder of the marketing authorisation, paliperidone (Invega®▼) cannot be endorsed for use within NHS Wales for the treatment of psychotic or manic symptoms of schizoaffective disorder[14].

3.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

The company submission includes data from three active comparator-controlled, phase III trials[1]. PSY-3002 was a randomised, double-blind, 53-week, active-controlled, phase III study which failed to show that paliperidone palmitate LAI was non-inferior to risperidone LAI[1,15]. As a result, further clinical and pharmacokinetic investigations were subsequently undertaken to determine the optimal initiation dosing schedule for paliperidone palmitate LAI. The effectiveness of the new initiation dosing schedule was analysed in the phase III, active comparator-controlled study PSY-3006 and the open-label, active comparator-controlled study PSY-3008[1,15], and it is this dosing regimen that was subsequently licensed[2]. The submission also includes several placebo-controlled supportive studies, which are of limited relevance to this comparison of paliperidone palmitate LAI and risperidone LAI, and are therefore not discussed further[1].

3.1 PSY-3006

This double-blind, active comparator-controlled, randomised, phase III trial evaluated the efficacy and tolerability of paliperidone palmitate LAI, and aimed to establish non-inferiority when compared with risperidone LAI for the maintenance treatment of schizophrenia. Inclusion criteria incorporated patients with an established diagnosis of schizophrenia[7], as defined in the Diagnostic and Statistical Manual of Mental Disorders fourth edition (DSM-IV)[16], for ≥ 1 year and a Positive and Negative Syndrome Scale (PANSS) total score at screening between 60 and 120 (inclusive). Eligible patients were randomised 1:1 to receive either paliperidone palmitate LAI (no oral supplementation required) or risperidone LAI with oral risperidone. Patients in the paliperidone palmitate LAI treatment arm received deltoid injections of 150 mg on day 1 and 100 mg on day 8, followed by deltoid or gluteal injections of 50 or 100 mg on day 36, and then 50, 100 or 150 mg on day 64. The risperidone LAI treatment group received gluteal injections of 25 mg on days 8 and 22, 25 or 37.5 mg on days 36 and 50, then 25, 37.5 or 50 mg on days 64 and 78 in addition to 1 to 6 mg of oral risperidone on days 1 to 28. There was the option to continue on 1 to 2 mg of oral risperidone over the following 21 days, with dose increases on days 36 and 64 allowed if the dose of risperidone LAI was increased at these visits. Owing to the difference in the dosing schedules, blinding was achieved through administration of matched placebo injections and oral supplementation[1,7].

The primary efficacy endpoint was the change in the PANSS score from baseline to last post-randomisation assessment in the double-blind period, utilising the per protocol analysis set (n = 765). Main secondary endpoints included changes in scores as assessed using the Personal and Social Performance (PSP) and Clinical Global Impression of Severity (CGI-S) scales, and the responder rate. Refer to the Glossary for definitions of primary and secondary endpoints[7].

At endpoint, the mean change in total PANSS score in the per protocol set was -18.6 and -17.9 in the paliperidone palmitate LAI and risperidone LAI treatment arms, respectively, with a weighted difference in means of 0.4 (95% confidence interval [CI] -1.62 to 2.38). The lower limit of the 95% CI was within the protocol pre-specified non-inferiority margin of -5, demonstrating that paliperidone palmitate LAI was non-inferior to risperidone LAI. Data from the intent-to-treat (ITT) population set were consistent with this conclusion, as were results from secondary endpoint analyses[7].

3.2 PSY-3008

This open-label, rater-blinded, parallel group, phase III trial evaluated the non-inferiority of paliperidone palmitate LAI when compared with risperidone LAI for the treatment of adult Chinese patients with acute schizophrenia. Patients with an established

diagnosis of schizophrenia[17], as defined in DSM-IV[16], and a PANSS total score between 60 and 120 (inclusive) at screening were then randomised to receive either paliperidone palmitate LAI or risperidone LAI with oral risperidone. Dosing of paliperidone palmitate and risperidone and the efficacy endpoints measured were as described for PSY-3006 (see Section 3.1.1)[17].

At endpoint, the mean change in total PANSS score in the per protocol set (n = 413) was -23.6 and -26.9 in the paliperidone palmitate LAI and risperidone LAI treatment arms respectively, with a weighted difference in means of -2.3 (95% CI -5.20 to 0.63). The lower limit of the 95% CI was within the pre-specified non-inferiority margin of -5.5, allowing the conclusion that paliperidone palmitate LAI is non-inferior to risperidone LAI. However, this was not supported by analysis of the ITT data set[17].

3.3 Summary of safety profile

At the time of licensing, the Committee for Medicinal Products for Human Use (CHMP) concluded that the safety profile of paliperidone palmitate LAI appeared favourable and similar to that of oral risperidone, with the exception of local injection site reactions[15]. During the pivotal study, PSY-3006, adverse events (AEs) occurred at similar rates in the paliperidone palmitate LAI and risperidone LAI treatment arms (57.9% versus 52.8%); serious AEs were reported in 6.8% of paliperidone palmitate LAI-treated patients compared with 4.8% of risperidone LAI treated patients[6,14]. As noted by CHMP, the incidence of injection site-related AEs was higher for the paliperidone palmitate LAI group than for the risperidone LAI group: injection site pain (5.1% versus. 0.8 %); injection site induration (1.5% versus. 0.3 %); and injection site swelling (1.0% versus. 0.2%). Other common AEs (occurring in ≥ 5% of patients) were insomnia, headache and somnolence in the paliperidone palmitate LAI treatment arm, and insomnia and headache in patients treated with risperidone LAI[15]. Insomnia, injection site pain and anxiety occurred at a ≥ 2% higher incidence in paliperidone palmitate LAI treated patients than in the risperidone LAI treatment group; only constipation was ≥ 2% more frequent in patients receiving risperidone LAI[7]. Additionally, there was a higher incidence of discontinuation due to psychiatric AEs in the paliperidone palmitate group[15].

3.4 AWTTC critique

- The optimised dosing regimen, which was utilised in study PSY-3006[7] and which subsequently received marketing authorisation[2], was also used in the phase III study PSY-3008, wherein paliperidone palmitate LAI was judged non-inferior to risperidone LAI using predefined CI margins in a per protocol population set[17]. However, these margins were greater than those used for the study PSY-3006[7], and if the stricter margins had been used, non-inferiority would not have been demonstrated. Additionally, the per protocol analysis of the primary endpoint excluded a proportion of the population (n = 413 versus ITT n = 446), and the conclusions drawn from this analysis were not supported by analysis of the ITT population[17]. At the time of licensing, CHMP concluded that the non-inferiority of paliperidone palmitate could not be demonstrated in studies PSY-3002 and PSY-3008[15]. It should be noted that study PSY-3008 was conducted in China which may impact on it's relevance to Welsh patients.
- Paliperidone palmitate is the third atypical antipsychotic to be licensed as a depot formulation and is likely to compete with these agents. The advantages of paliperidone palmitate LAI when compared to risperidone LAI include that it requires less frequent administration, monthly as compared to fortnightly, and that it does not require oral supplementation on initiation of therapy[2,9]. Paliperidone palmitate LAI may be given one week before or one week after the usual date of administration[2]. Additionally, paliperidone palmitate LAI does not require refrigeration during storage or transport and is presented as a pre-filled

syringe, rather than a powder for reconstitution[1]. However, the shelf life of paliperidone palmitate LAI is two years as compared to the three-year shelf life of risperidone LAI[2,9].

- The company submission notes that paliperidone palmitate is not as extensively metabolised in the liver as risperidone, which is suggested to lessen the possibility of interactions with medicines metabolised by the CYP450 pathway[1,2].
- The applicant company propose that the dosing initiation of paliperidone palmitate LAI, whereby no oral supplementation is administered and the second dose can be injected on day 8, could allow for a potentially earlier discharge when compared with patients treated with risperidone LAI, which requires oral risperidone or previous antipsychotic medication during the first three weeks of treatment[1,2,9]. The company also suggests that less frequent paliperidone palmitate injections could result in fewer opportunities for patients to become non-adherent. However, no data has been provided that evaluates the effect of injection frequency on patient adherence[1].
- During study PSY-3006, the frequency of injection-site reactions was higher in paliperidone palmitate-treated patients[7], leading to concerns regarding the risk of reduced compliance associated with these local AEs[15]. CHMP concluded that a reduced compliance with study medication could not be completely ruled out. The SPC was subsequently updated to include a detailed description of the adverse reactions and to recommend alternating injection sites[2,15]. The applicant company note that there were no discontinuations in this study due to injection site reactions and investigator assessment of the site were similar for both groups[18].
- At the time of licensing, CHMP noted that in study PSY-3006, non-inferiority could not be demonstrated for obese patients and concluded that there were uncertainties in the dosing recommendation for this group due to lower exposure and poorer efficacy[15]. This is reflected in the SPC by a suggestion that overweight or obese patients may require doses in the higher dose range[2].
- Following the failure of the long-term phase III study PSY-3002 and subsequent alteration of the initial dosage regimen, there are no data available regarding the long-term use of paliperidone palmitate within the licensed dosage regimen. Furthermore, long-term use of paliperidone palmitate LAI is yet to demonstrate non-inferiority to treatment with risperidone LAI. There are also no data against an active comparator in the prevention of relapse, as the clinical studies excluded patients with a history of treatment resistance[7,17].

4.0 SUMMARY OF THE EVIDENCE ON COST-EFFECTIVENESS

4.1 Cost-effectiveness evidence

4.1.1 Context

The company's submission describes a cost-utility analysis (CUA) of paliperidone palmitate LAI (Xeplion®▼) compared to risperidone LAI (Risperdal Consta®▼) for maintenance treatment of schizophrenia in adult patients stabilised with paliperidone or risperidone[1]. The analysis is based on a Markov model consisting of five health states: 'in remission on LAI therapy', 'in remission on clozapine therapy', 'in remission off-treatment', 'relapse' and 'death'. Patients enter the model treated with either paliperidone palmitate or risperidone LAI and can transit among the health states until they reach the state 'death'. The model allows one relapse episode per model cycle. After relapse it is assumed that two thirds of patients continue on the same LAI maintenance treatment and one third will switch to clozapine. Transition probabilities among health states have been estimated from the PSY-3001 and PSY-3002 clinical studies. Due to a reported lack of direct comparative data for clozapine with

paliperidone palmitate and risperidone LAI, transition probabilities for patients on clozapine were estimated using a series of indirect comparisons. Important assumptions around resource use (e.g. proportions of patients initiating treatment in hospital setting, length of hospital stay with each treatment, number and type of visits from crisis resolution and community mental health teams) are based on Welsh clinical expert opinion. The model assumes a ten-year time horizon and a cycle length of one year. See Appendix 1 for further details.

4.1.2 Results

Results of the base case analysis are summarised in Table 1. Treatment with paliperidone palmitate was estimated to be less costly and more effective than risperidone LAI. The difference in total costs between the two treatments is driven mainly by the modelled additional costs of supervised supplementary oral risperidone and more frequent LAI administration in the community setting for patients receiving risperidone LAI; and the longer duration of inpatient stay for patients initiating risperidone LAI in the hospital setting. The additional quality-adjusted life year (QALY) gains with the use of paliperidone palmitate are driven by the less frequent administration requirements and small differences in AE rates compared with risperidone LAI.

Table 1. Company-reported results of a base case cost-effectiveness analysis of paliperidone palmitate (Xeplion®▼) compared to risperidone LAI (Risperdal Consta®▼) for maintenance treatment of schizophrenia in adult patients.

Base case	Paliperidone palmitate	Risperidone LAI	Difference
LAI drug costs	£7,858	£7,787	£71
Other drug costs	£2,015	£1,987	£28
Non-drug costs	£120,388	£124,259	-£3,872
Total cost	£130,261	£134,033	-£3,773
Total QALYs	4.70	4.57	0.13
Incremental cost per QALY gained	**Paliperidone palmitate strategy dominates risperidone LAI***		
*Applies when drug under appraisal is both less costly and more effective than comparator			

Probabilistic sensitivity analysis conducted for the base case scenario reports almost 100% of simulations falling below cost-effectiveness thresholds of £20,000 and £30,000 per QALY gained. One-way sensitivity analyses presented in the submission include: variation in age, gender, time horizon, time to relapse, AE rates, proportion of hospital initiation of LAI, utilities, treatment-related costs, and other input model parameters. The analyses demonstrate that the model is most sensitive to changes in utilities, probability of treatment discontinuation, cost of maintenance dose and relapse rates; however, all sensitivity analyses suggested that treatment with paliperidone palmitate dominates treatment with risperidone LAI.

Key scenario analyses included all patients initiating LAI treatment in the hospital or community setting, and removal of the assumed shorter inpatient stay for paliperidone palmitate recipients initiating treatment in the hospital setting. All presented scenarios suggest that paliperidone palmitate would remain the dominant strategy compared to risperidone LAI.

4.1.3 AWTTC critique

Strengths of the economic evidence include:

- The modelled clinical pathway is reported to have been verified by Welsh clinical experts.

- A wide range of sensitivity and scenario analyses have been conducted to address several areas of uncertainty in key assumptions and parameter values.

Limitations of the economic evidence include:

- The modelled population includes patients with schizophrenia who are sufficiently well enough to receive LAIs with either paliperidone or risperidone. It is unclear whether the model adequately reflects use in those selected patients with previous responsiveness to oral paliperidone or risperidone who develop mild to moderate psychotic symptoms, in whom paliperidone LAI may be initiated without prior stabilisation with oral paliperidone or risperidone.
- There are no long-term comparative data relating to relapse rates for paliperidone palmitate and risperidone LAI.
- The frequency and types of visits by crisis resolution and mental health teams in the community setting and the duration of inpatient stay for patients initiating treatment in hospital are key drivers of the modelled differences in total costs of treatment, and are based on expert opinion; however, a wide range of sensitivity and scenario analyses have explored the impact of varying costs over wide ranges, and paliperidone palmitate LAI remained dominant.

4.2 Review of published evidence on cost-effectiveness

Standard literature searches identified one study, published by the company, on the cost-effectiveness of paliperidone palmitate versus risperidone LAI and olanzapine LAI in the treatment of patients with schizophrenia in Sweden[19]. Therapeutic strategies considered in the model included risperidone LAI (mean dose 37.5 mg every two weeks), paliperidone palmitate (mean dose 75 mg every month) and olanzapine (150mg every two weeks or 300 mg every four weeks). The cost-effectiveness analysis is based on a Markov model assuming three health states: a stable state, a relapse state, and a death state. The model considered different levels of patient adherence to treatment (adherent, partially adherent and non-adherent), AEs and treatment discontinuation. The model assumed a monthly cycle and a five-year time horizon. The model estimates paliperidone palmitate to be less costly and more effective compared to both risperidone LAI and olanzapine LAI.

5.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

5.1 Budget impact evidence

5.1.1 Context and methods

Using a prevalence of 1% for schizophrenia in the UK[3] and Welsh population statistics, the company estimates that there are currently 24,931 adults with schizophrenia in Wales[1]. Based on an incidence rate for schizophrenia of 0.11/1000 person-years[3], the company estimates the number of newly diagnosed cases of schizophrenia as 264 in 2012, rising to 268 cases in 2016. A standardized mortality rate of 2.89 is applied to determine the number of deaths each year in people with schizophrenia. Based on internal company estimates (no further details provided), it is assumed that around 75% of patients with schizophrenia are thought to receive treatment in the UK and 18% of these patients are treated with LAI formulations. Assuming an increase in uptake of paliperidone palmitate from 2% (in 2011) to 30% by 2015, the company estimates that the number of patients who may be treated with paliperidone palmitate will increase from 57 in year one to 968 in year five. The company has based its budget impact estimates on maintenance treatment over 12 month periods, assuming paliperidone palmitate to be administered at a dose of 75 mg in each month, and risperidone LAI to be administered at a dose of 37.5 mg every two weeks. As in the economic model, cost savings associated with less frequent administration of paliperidone palmitate,

earlier discharge of patients from hospital, no requirement for cold transportation, and reduced wastage of paliperidone palmitate are assumed.

5.1.2 Results

The company estimates the acquisition costs of paliperidone palmitate to be £2,939 per patient per year, compared to £2,904 for risperidone LAI. The estimated numbers of patients eligible for treatment with paliperidone palmitate and the associated costs over the five-year period are summarised in Table 2.

Table 2. Company-reported costs associated with use of paliperidone palmitate LAI (Xeplion®▼) for maintenance treatment of schizophrenia in adult patients.

	Year 1	Year 2	Year 3	Year 4	Year 5
Number of eligible patients	3,181	3,192	3,204	3,215	3,227
Uptake	2%	18%	20%	25%	28%
Number of treated patients	57	638	801	900	968
Drug costs (difference)	£1,977	£22,051	£27,663	£31,095	£33,437
Nurse administration costs (difference)	-£26,913	-£300,112	-£376,398	-£423,205	-£455,075
Hospital stay costs (difference)	-£11,011	-£122,793	-£154,046	-£173,157	-£186,197
Cold chain/waste costs (difference)	-£2,319	-£25,856	-£32,437	-£36,461	-£39,206
Overall net costs	**-£38,265**	**-£426,710**	**-£535,318**	**-£601,727**	**-£647,042**

Two scenario analyses of resource implications are presented in the company's submission:

- Assuming the same length of hospital stay for paliperidone palmitate and risperidone LAI, the cost savings are estimated to reduce to £27,254 in year one, and £460,845 in year five.
- Assuming 30% lower costs for nurse administration of LAI, the cost savings are estimated to reduce to £30,192 in year one, and £510,519 in year five.

5.1.3 AWTTC critique

- There is uncertainty about the number of patients with schizophrenia who are currently treated with LAI formulations in Wales, as supporting information is not provided. This would potentially impact on the number of patients estimated to be treated with paliperidone palmitate.
- The company has adopted a pragmatic approach by focussing its estimates on maintenance costs once patients have already been established on LAI formulations. This excludes differences in some elements of initiation costs that, in the company's CUA, are modelled to be greater for risperidone LAI compared with paliperidone palmitate.
- Apart from the exclusion of initiation costs, the budget impact analysis employs the same assumptions on health resources and associated costs as used in the economic model. The limitations of the economic evidence discussed above therefore apply to the budget impact analysis.
- Collectively, there is uncertainty in the company's net budget impact estimates.

5.2 Table of comparative unit costs

Table 3 includes example acquisition costs of atypical antipsychotic LAIs for maintenance treatment of schizophrenia in adult patients. Note that initiation doses may differ from maintenance doses and that maintenance doses may be adjusted on a monthly basis. See relevant SPCs for full dosing details.

Table 3. Examples of acquisition costs of LAI antipsychotics for maintenance treatment of schizophrenia in adult patients.

Antipsychotics	Example maintenance doses[2,9,10]	Annual cost per patient
Paliperidone palmitate (Xeplion®▼) 50 mg, 75 mg,100 mg and 150 mg suspension for injection in pre-filled syringe	50 mg – 75 mg monthly	£2,207 - £2,938
Risperidone (Risperdal Consta®▼) 25 mg, 37.5 mg 50 mg powder and pre-filled syringe of solvent for suspension	25 mg – 37.5 mg every two weeks	£2,072 - £2,894
Olanzapine (Zypadhera®▼) 210 mg, 300 mg and 405 mg powder and solvent for prolonged-release suspension for injection.	300 mg every four weeks	£2,894
Costs are based on MIMS list prices for 10 August 2012[20]. *See relevant SPC for full dosing details[2,9,10].* *This table does not imply therapeutic equivalence of drugs or the stated doses.*		

6.0 ADDITIONAL INFORMATION

6.1 Appropriate place for prescribing

AWTTC is of the opinion that, if recommended, paliperidone palmitate (Xeplion®▼) prolonged release suspension for injection is appropriate for specialist only prescribing within NHS Wales for the indication under consideration.

6.2 Ongoing studies

The company submission highlighted an ongoing study that is likely to be available within 6–12 months. Study PALMFlexS (PSY-3010) will assess the tolerability, safety and treatment response of a transition to flexible doses of paliperidone palmitate LAI in patients with schizophrenia that were previously treated unsuccessfully (due to intolerance or lack of efficacy) with an oral or LAI antipsychotic. Final data will be available early 2013[1,21].

6.3 AWMSG review

This assessment report will be considered for review three years from the date of Ministerial ratification (as disclosed in the Final Appraisal Recommendation).

6.4 Evidence search

Date of evidence search: 23 March 2012

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

GLOSSARY

Clinical Global Improvement Severity (CGI-S)
A seven-point scale used to rate the overall severity of a subject's psychotic condition[1].

Established diagnosis of schizophrenia
As defined in the Diagnostic and Statistical Manual of Mental Disorders fourth edition (DSM-IV)[16], for ≥ 1 year. This manual is published by the American Psychiatric Association and provides standard criteria for the classification of mental disorders[16].

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[22].

Personal and Social Performance (PSP) scale
A 100-point single-item rating scale, based mainly on the assessment of a patient's functioning in four main areas: socially useful activities, personal and social relationships, self-care, and disturbing and aggressive behaviours[23].

Responder rate
The percentage of patients with a 30% or more reduction in PANSS total score[7].

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Appendix 1. Additional health economic information

Table 1A. Health economic model details

	Base case model	Appropriate?
Comparator(s)	Comparators included treatment strategies with paliperidone palmitate LAI (Xeplion®▼) and risperidone LAI (Risperdal Consta®▼) initiated from oral paliperidone or risperidone, or another LAI. The comparator regimens included: • Paliperidone palmitate initiated from oral therapy: initiation doses of 150 mg on day one and 100 mg on day eight followed by monthly doses of 75 mg. Paliperidone palmitate initiated from LAI therapy: 75 mg injections monthly. • Risperidone LAI initiated from oral therapy: 37.5 mg risperidone LAI injections every two weeks supplemented with 4 mg/day oral risperidone for the first three weeks. Risperidone LAI initiated from LAI therapy: 37.5 mg risperidone LAI injections every two weeks.	Yes, as agreed with AWTTC.
Population	The modelled population includes adult patients with schizophrenia stabilised with paliperidone or risperidone. The base case analysis considers the average age of patients at model entry to be 40 years, 57.9% male. Sensitivity and scenario analyses address variation in age (30 and 50 years) and gender split (100% and 0% male).	Yes, however, the licensed indication under appraisal also includes selected patients with previous responsiveness to oral paliperidone or risperidone who develop mild to moderate psychotic symptoms in whom paliperidone palmitate may be initiated without prior stabilisation with oral paliperidone and risperidone. It is unclear whether the model adequately reflects use in these patients.
Model type and description	The cost-utility analysis (CUA) is based on a Markov model consisting of five health states: 'in remission on LAI therapy'; 'in remission on clozapine therapy', 'in remission off-treatment', 'relapse' and 'death'. Patients enter the model in remission on LAI therapy, from which they can: • experience a relapse; • discontinue LAI therapy due to an AE or other reasons and switch to clozapine or stay off-treatment; • remain on therapy and in remission; • die. Two-thirds of patients who experience relapse on their LAI are assumed to remain on their LAI, and one third are assumed to switch to clozapine. Clozapine is considered as a 'last line' of therapy. Patients experiencing a relapse on clozapine are assumed to remain on clozapine. A one-year cycle length is assumed.	Yes, CUA is the preferred type of analysis. In the model patients can experience only one relapse per year, as assumed in a previous NICE submission.

Table 1A. Continued.

	Base case model	Appropriate?
Perspective	NHS Wales and Personal Social Services	Yes.
Time horizon	The base case analysis assumes a ten-year time horizon. Sensitivity analyses have been conducted for 5 and 60 years.	Schizophrenia is a chronic life-long condition. Sensitivity analyses using time horizons of 5 and 60 years estimate paliperidone palmitate therapy to dominate risperidone LAI.
Discount rate	A 3.5% p.a. discount rate is applied to both costs and outcomes. Scenario analyses include discount rates of 0% and 6%.	Yes.
Efficacy	Efficacy parameters used in the model relate to relapse rates. Rates of relapse for patients 'in remission on LAI' and 'in remission off treatment' were estimated from the paliperidone palmitate and placebo arms of the PSY-3001 study. Assuming an exponential distribution, annual probabilities of relapse are estimated to be 33.6% for patients in remission on paliperidone treatment and 77.1% for patients in remission off treatment. Due to a reported lack of comparative data on the relapse rate for risperidone LAI versus paliperidone palmitate, it is assumed that patients treated with risperidone LAI experience the same annual probability of relapse as patients treated with paliperidone palmitate (33.6%). This is based on the findings of non-inferiority in total PANSS scores of paliperidone palmitate to risperidone LAI observed in the PSY-3006 and PSY- 3008 studies. Of patients who experience relapse whilst on treatment, two-thirds are assumed to continue on the same LAI maintenance treatment and one-third to switch to clozapine. Patients who experience relapse whilst on clozapine are assumed to remain on clozapine treatment. The annual probability of relapse on clozapine is estimated as 10.5%, which is derived from a series of sequential indirect comparisons between relapse rates for olanzapine, conventional depot antipsychotics, and placebo using published observational data[24] and company-conducted meta-analyses[1]. Discontinuation of LAI treatment for reasons other than lack of efficacy or AEs (e.g. lack of adherence, treatment choice) is derived from the PSY-3002 study. These patients are assumed to be in remission, off treatment.	Actual effectiveness in terms of control of symptoms and relapse is assumed to be equivalent for paliperidone palmitate and risperidone LAI, although there appears to be a number of limitations to the available effectiveness evidence. The primary endpoint of the PSY-3001 trial, used to provide annual probabilities of relapse for LAI treatment and those not on treatment, was time to first relapse; however, this was assumed to apply throughout for the two-thirds of patients assumed to remain on their current LAI following relapse. In addition, this trial used lower doses of paliperidone palmitate than subsequently licensed, which the company considers may bias the analysis against paliperidone. In the absence of comparative relapse data, the company assumes risperidone LAI and paliperidone palmitate to have the same probabilities of relapse, based on non-inferiority of these in terms of PANSS scores observed in the PSY-3006 and PSY- 3008 studies (the latter of which demonstrated non-inferiority using a wider margin than the former trial). The company has acknowledged the lack of long-term comparative data on relapse prevention as a limitation of the current submission. Probabilities of relapse for patients on clozapine treatment are derived from a series of indirect comparisons based on a range of data sources relating to conventional and atypical antipsychotics, which would also appear subject to limitations. Due to the lack of clinical data, a number of transition probabilities used in the model have been informed by Welsh expert opinion. Duration of relapse (61 days) is based on Welsh expert opinion.

Table 1A. Continued.

	Base case model	Appropriate?
Adverse effects	AEs incorporated in the model included extrapyramidal symptoms, weight gain, tardive dyskinesia and hyperprolactinaemia. AE rates and discontinuations due to AEs for risperidone LAI and paliperidone palmitate were derived from the PSY-3002 study, and for clozapine from an observational study[24].	Discontinuations due to treatment emergent AEs were 7.7% for paliperidone palmitate and 6.3% for risperidone LAI. It should be noted that the PSY-3002 study used a lower paliperidone palmitate initiation dosing schedule (50 mg on day one and 50 mg on day eight) compared with that subsequently licensed, and the paliperidone palmitate group had a lower overall plasma exposure of active drug compared with the risperidone LAI group. AE rates observed in the PSY-3002 study may therefore be lower than would have been observed had the higher, recommended doses been used. However, one way sensitivity analyses exploring the impact of assumed discontinuations due to AEs in the range +/- 15% suggest paliperidone palmitate remains dominant over risperidone LAI.
Utility values	Utility values were derived from an unpublished study that used time trade off approaches in 98 members of the public in Australia. Values were derived for untreated patients (representing relapsed patients), patients treated with once monthly LAI (representing patients in remission on paliperidone palmitate treatment in the model), once fortnightly LAI (representing patients in remission on risperidone LAI treatment in the model) or three monthly LAI (which is used to represent patients in remission and off treatment). The utility weight associated with patients in remission receiving oral clozapine treatment is presumed to be the same as for paliperidone palmitate, as clozapine recipients need monthly blood tests. Disutilities associated with AEs (EPS, weight gain, tardive dyskinesia and hyperprolactinaemia) are derived from a published study that directly elicited utility values for schizophrenia treatment-related AEs from 75 lay members of the public[25]. As the utility values derived in this study for patients with schizophrenia and experiencing AEs of treatment were greater than published population norms, the company has estimated relative utility weights associated with AEs, using stable schizophrenia as a baseline. These are used as multipliers in the company's model to incorporate a reduction in utility associated with AEs.	Utility values used in the model aim to account for differences in preferences for treatment based on injection frequency. These are based on a single, non-UK study. The company rejected the adoption of utility values used in a previous NICE economic model of schizophrenia treatment as Welsh experts felt those utility values lacked face validity (being larger than population norms). It is not clear from the company submission whether attempts were made to identify alternative published utility values for patients with schizophrenia. Utility weights for relapse are applied for six months, with the remaining six months of each cycle being weighted as in remission. The elicitation study used to provide utility decrements for AEs also appears to lack face validity, as the actual utility values were also greater than population norms. The company has estimated relative utility values using these data, which are used as multipliers applied to the utility values of the health state in which the AE occurs. Collectively, there are a number of uncertainties and potential sources of bias in the utility weights and relative decrements that have been assumed. However, sensitivity analyses around remission and relapse-related utilities explored within the range of their 95%CIs, and around AE-related disutilities explored within the range +/-15%, indicate that paliperidone palmitate remains dominant over risperidone LAI.

Table 1A. Continued.

	Base case model	Appropriate?
Resource use and costs	The base case scenario assumes that 71% of patients would initiate LAI treatment in the community setting, and 29% as hospital inpatients, based on Welsh expert opinion. Also based on expert opinion, patients initiated on risperidone LAI in a hospital setting are assumed to be discharged after 24.5 days on average, while patients initiated on paliperidone palmitate are discharged after 17.5 days (after their second injection). After discharge from hospital, these patients are assumed to require CRHTT visits (three visits on week one, two visits on week two, and one visit on weeks 3–6) at a cost £182.55 per visit. Initiation of risperidone LAI treatment in the community setting would require seven CRHTT visits each week for three weeks (21 visits) to ensure that patients take oral supplementation. In contrast, initiation of paliperidone palmitate in the community setting is assumed to require six visits over the first three weeks. Additional costs attached to risperidone LAI treatment relate to cold chain delivery and wastage costs due to error, refusal and no-show were incorporated. Other resources and costs are assumed for AEs. Relapse costs include olanzapine 15 mg daily, and assumptions that 40% would be managed by acute hospitalization for two months, 10% would be managed by CRHTT alone for two months, and 50% would be managed by acute hospitalization for one month and CRHTT for one month. Costs of relapse for patients on treatment are increased by 50% to reflect the more severe nature of relapses for patients already on treatment, all based on Welsh expert opinion.	Important areas of resource use are reported to be based on company-sought expert opinion, which would appear to be subject to uncertainty. The proportion of patients assumed to initiate treatment in the community and hospital settings is somewhat different to that reported in a nurse audit of risperidone LAI use[26], which was used by the company in its original submission to support the assumption that 34% of LAI prescribing would be initiated in the community and 66% in the hospital setting. Based on the limited information provided by the company regarding their Welsh expert panel, paliperidone palmitate is assumed to result in seven days shorter length of hospital stay based on one expert, who stated a preference for patients to have at least two injections before discharge. AWTTC-sought expert opinion suggests there are difficulties in estimating the proportion of patients who would be initiated on LAI in hospital versus community settings. The decisions to admit and then to discharge a patient from hospital, and the level of support required once discharged are multi-factorial. The company has highlighted potential additional costs associated with cold storage and delivery, although only one out of 25 pharmacist members of a Delphi panel felt risperidone LAI would attract additional cold chain costs. This proportion is assumed in the model. The proportion of patients requiring hospitalisation for treatment of relapse is at odds with that assumed for LAI initiation, although scenario analyses explore 0% and 100% initiation in the hospital setting and suggest paliperidone palmitate dominates risperidone irrespective of setting of initiation. A wide range of sensitivity analyses conducted around the assumed costs all demonstrate paliperidone palmitate dominates risperidone LAI treatment. No analyses appear to be reported around the assumed differences in the number and type of visits received by patients in the community setting by the CRHTT, CMHT and CPNs/CPAs; however, the wide variations in assumed costs explored in sensitivity analyses would potentially incorporate this. A scenario analysis assuming equal length of stay (3.5 weeks) for patients initiating LAI treatment in hospital reports paliperidone palmitate to be dominant over risperidone LAI.
Uncertainty	A wide range of sensitivity analyses were conducted by the company to address variation in age, gender, time horizon, time to relapse, AE rates, proportion of hospital initiation of LAI, utilities, treatment-related costs, and other input model parameters. Model outputs were sensitive to changes in utilities, probability of treatment discontinuation, cost of maintenance dose and relapse rates, but in all analyses paliperidone palmitate was reported to be dominant over risperidone LAI.	A wide range of sensitivity and scenario analyses were reported, all of which estimated paliperidone palmitate to be dominant over risperidone LAI.
Model provided?	Yes.	Yes.

AE: adverse event; AWTTC: All Wales Therapeutics and Toxicology Centre; CMHT: community mental health team; CPN: community psychiatric nurses; CPA: Care Programme Approach; CRHTT; crisis resolution and home treatment team; CUA: cost-utility analysis; EPS: extrapyramidal symptoms; LAI: long-acting injectable; NICE: National Institute for Health and Clinical Excellence; PANSS: Positive and Negative Syndrome Scale.