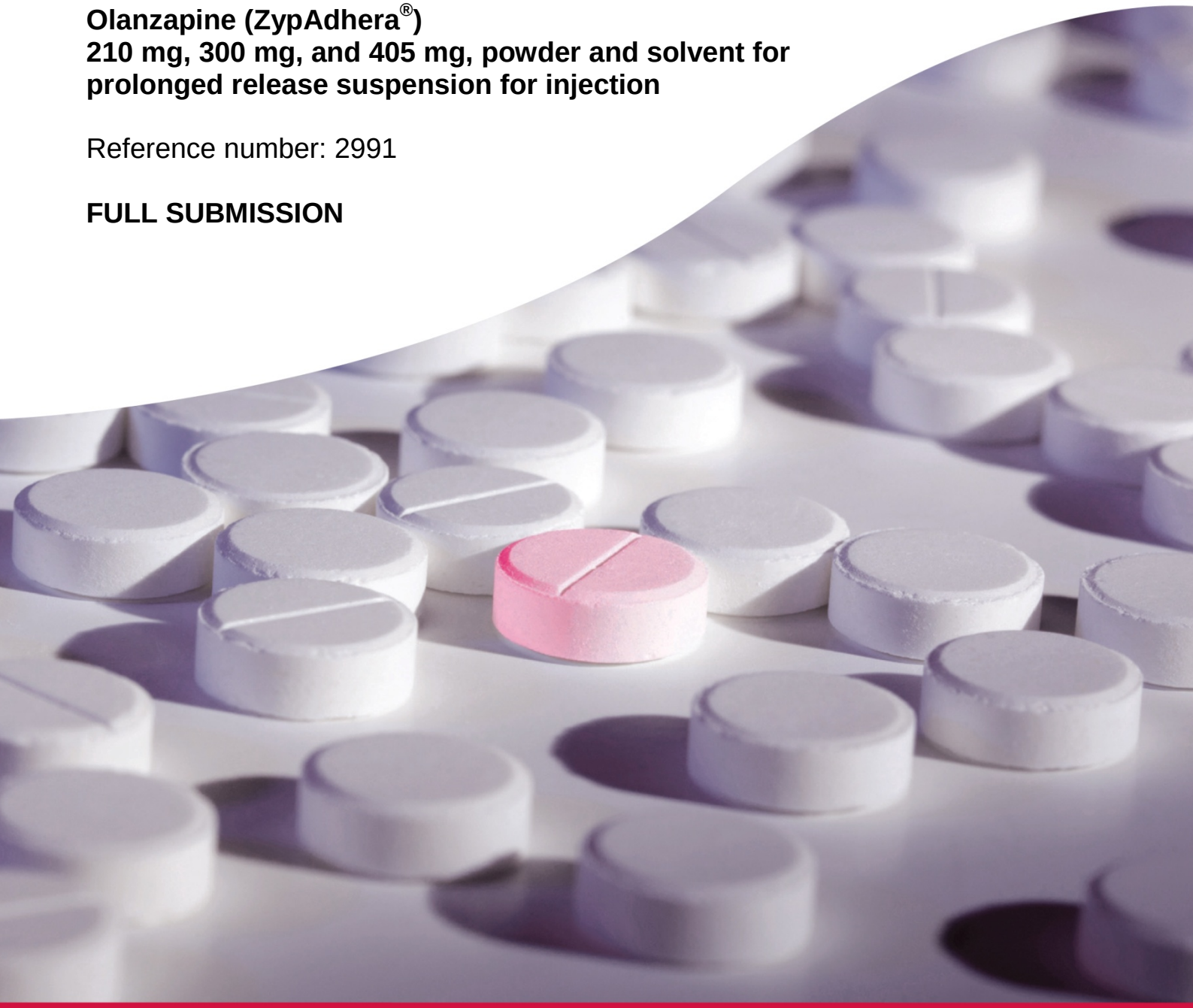
All Wales Therapeutics and Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

AWMSG SECRETARIAT ASSESSMENT REPORT

Olanzapine (ZypAdhera®) 210 mg, 300 mg, and 405 mg, powder and solvent for prolonged release suspension for injection

Reference number: 2991

FULL SUBMISSION



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AWMSG Secretariat Assessment Report
Olanzapine (ZypAdhera®) 210 mg, 300 mg, and 405 mg, powder and solvent for prolonged release suspension for injection

This assessment report is based on evidence submitted by Eli Lilly & Co Ltd[1].

1.0 PRODUCT DETAILS

Licensed indication under consideration	Olanzapine (ZypAdhera®) for the maintenance treatment of adult patients with schizophrenia sufficiently stabilised during acute treatment with oral olanzapine[2].
Dosing	Patients should be treated initially with oral olanzapine before administering olanzapine long-acting injection (LAI), to establish tolerability and response. Refer to the Summary of Product Characteristics (SPC) for the recommended dosing scheme for switching from oral olanzapine to olanzapine LAI. Olanzapine LAI should only be administered by deep intramuscular gluteal injection by a healthcare professional trained in the appropriate injection technique. After each injection, patients should be observed in a healthcare facility by appropriately qualified personnel for at least three hours for signs and symptoms consistent with olanzapine overdose. It should be confirmed that the patient is alert, orientated, and absent of any signs and symptoms of overdose. If an overdose is suspected, close medical supervision and monitoring should continue until examination indicates that signs and symptoms have resolved[2].
Marketing authorisation date	19 November 2008[2].

2.0 DECISION CONTEXT

2.1 Background

Overall, approximately 1% of the population will develop psychosis and schizophrenia over a lifetime[3]. The symptoms and behaviour associated with schizophrenia can affect a patient's personal, social or occupational life, and can have a distressing impact on their family and friends[4]. Antipsychotic medication is the mainstay of treatment for schizophrenia, 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. 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)[4]. 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[4].

Olanzapine is an antipsychotic, antimanic and mood stabilising agent that demonstrates a broad pharmacologic profile across a number of receptor systems[2]. The All Wales Medicines Strategy Group (AWMSG) has previously issued a non-recommendation for the use of olanzapine LAI (ZypAdhera®) for the indication under consideration. The submission compared olanzapine LAI to other atypical LAIs.

In this resubmission, the company has highlighted a subpopulation of the indication, where they consider olanzapine LAI may be particularly advantageous[1]. The subset includes service users who should be treated with olanzapine LAI because they meet all the following criteria:

- known to have had a positive response to oral olanzapine during acute treatment;
- more appropriately managed with a LAI formulation because of difficulties adhering to an oral medication regimen, indicated by recurrent relapse or exacerbation of symptoms;
- the clinician/patient treatment choice is for olanzapine LAI (in line with NICE clinical guideline [CG] 178[4] supporting patient-driven treatment choices, and with the Welsh Governments guidelines for implementing the Mental Health [Wales] Measure[5]);
- resource-intensive service users, often resulting in frequent and extended hospitalisation, despite pharmacological treatments, which may include LAIs of other atypical medicines.

With these criteria, the applicant company have defined the target patient as one in whom a sufficient response to another atypical LAI would preclude treatment with olanzapine LAI[1].

2.2 Comparators

The comparator included in the company submission was best supportive care (BSC). The applicant company define BSC as representing the scenario where robust efforts are being made to control and manage the symptoms of schizophrenia using a combination of antipsychotic medication, healthcare and human resources (including, but not restricted to, inpatient days, community-based resources, clinical staff, and pharmacological and psychological therapies)[1].

The applicant company state that the use of other LAI medications (including risperidone, aripiprazole and paliperidone) may be a component of BSC for some patients[1]. However, they have also stated that the target patient is one for whom no atypical LAI, apart from olanzapine LAI, is suitable[1] and therefore, a demonstration of comparative effectiveness versus other atypical LAIs was not provided.

2.3 Guidance and related advice

- NICE. CG178. Psychosis and schizophrenia in adults: prevention and management (2014)[4].
- Hasan A, Falkai P, Wobrock T, et al. World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for biological treatment of schizophrenia, part 2: update 2012 on the long-term treatment of schizophrenia and management of antipsychotic-induced side effects (2013)[6].
- Barnes TRE, and the Schizophrenia Consensus Group of the British Association for Psychopharmacology. Evidence-based guidelines for the pharmacological treatment of schizophrenia: recommendations from the British Association for Psychopharmacology (2011)[7].
- NICE. CG76. Medicines adherence: involving patients in decisions about prescribed medicines and supporting adherence (2009)[8].

AWMSG has previously issued a non-recommendation for the use of olanzapine LAI (ZypAdhera®) stating that the case for cost effectiveness was not proven[9].

3.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

The company submission included four phase III clinical studies and four further studies in support of clinical efficacy. The most relevant studies are described below.

3.1 Study HGKA

This was a 24-week, multicentre, double-blind, randomised controlled study of different doses and formulations of olanzapine in patients with schizophrenia who were stable on oral olanzapine[1,10]. Patients were randomised to a fixed dose of olanzapine LAI (405 mg/four weeks [n = 318], 300 mg/two weeks [n = 141], 150 mg/two weeks [n = 140], or 45 mg/four weeks [n = 144]) or they remained on their stabilisation dose of oral olanzapine (n = 322). The primary objective was to demonstrate that therapeutic doses of olanzapine LAI (300 mg/two weeks and 150 mg/two weeks) were non-inferior to daily oral olanzapine in terms of relapse rates at 24 weeks. At 24 weeks, 93% of oral olanzapine-treated patients, and 90% of olanzapine (medium dose) LAI-treated patients, remained free of relapse or exacerbation of symptoms[1,10]. The difference was not statistically significant and met the predefined criteria for non-inferiority[10]. Secondary objectives included assessment of quality of life using the Quality of Life Scale (QLS) and the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36). There were no clinically relevant significant differences between treatment groups in the change from baseline to midpoint and endpoint of the QLS and SF-36[10].

3.2 Study HGKB

This was a six-year, open-label, non-randomised, multicentre, single-arm extension study in patients with schizophrenia or schizoaffective disorder who had previously completed another olanzapine LAI study (HGJZ, HGKA, or LOBS: a 46 day pharmacokinetic study of olanzapine LAI [n = 134])[1,11]. Patients were permitted to receive up to 20 mg/day supplementary oral olanzapine. All patients (n = 931) received 210 mg olanzapine LAI at the first open-label visit; then were dosed flexibly (45–405 mg) at two week or four week intervals[1,11]. The mean duration of exposure was approximately three years[11]. The primary objective was to assess safety of olanzapine LAI[1,11]; this will be discussed in Section 3.5. Relevant secondary objectives included assessment of the long-term efficacy of olanzapine LAI and its impact on patient quality of life[1,11]. Efficacy was assessed using two measures of schizophrenia severity: the Positive and Negative Syndrome Scale (PANSS) and the Clinical Global Impressions Scale (CGI-S). The mean total PANSS score did not change significantly over the course of the study. There were small mean improvements in the CGI-S score over the duration of the study ($p \leq 0.001$)[1,11]. Further post-hoc analyses (that excluded patients with schizoaffective disorders and any patients who received oral olanzapine supplementation with a total daily dose greater than 20 mg/day oral olanzapine equivalent) showed similar results[12]. Quality of life was assessed using the Patient Satisfaction with Medication Questionnaire (PSMQ): the majority of patients responding to the PSMQ indicated favourable responses for olanzapine LAI compared with previous oral therapy[11].

3.3 Study HGLQ

This was a two-year, multicentre, randomised, open-label study comparing long-term efficacy and safety of monthly olanzapine LAI versus daily oral olanzapine in outpatients with schizophrenia[1,13]. Patients were randomly assigned to olanzapine LAI (405 mg/four weeks; n = 264) or oral olanzapine (10 mg daily; n = 260)[1,13]. Dosing thereafter was flexible (150–405 mg/four weeks of olanzapine LAI versus 5–20 mg daily of oral olanzapine[13]. Supplementation with oral olanzapine was permitted between week two and eight up to 5 mg daily[13]. The primary objective was to assess the time to all-cause discontinuation[1,13]. The median time to all-cause discontinuation was 645 days in the olanzapine LAI group and 678 in the oral olanzapine group; there was no significant difference between the two groups ($p = 0.612$). Secondary objectives included a comparison of time to relapse. Time to relapse was not significantly different between the olanzapine LAI and oral olanzapine groups; the rate of relapse was 20.1% and 18.5%, respectively ($p = 0.659$)[1,13].

3.4 Supporting evidence

Three studies provide data on outcomes before and after initiation of olanzapine LAI, with some patients in the pre-olanzapine LAI period being treated with oral olanzapine. A single arm mirror-image study showed that 77% of the patients had a psychiatric-related hospitalisation in the pre-olanzapine LAI period compared with 67% in the post period[14]. The study also showed that for patients who had at least one psychiatric-related hospitalisation, there were significant reductions in the mean length of stay per hospitalisation (19.6 days versus 3.9 days; $p < 0.001$) and in the mean total number of days spent in hospital per patient after olanzapine LAI treatment (52.3 days versus 16.2 days; $p < 0.001$)[14]. A second mirror-image study reported follow-up costs and outcomes of participants in the HGKA and HGKB studies; hospitalisation durations decreased significantly from a mean of 163 days before olanzapine LAI to 119 days during olanzapine LAI treatment[15]. A third prospective study showed that the rate of psychiatric hospitalisation was lower in the post-olanzapine LAI period (8.3%) than in the pre-olanzapine LAI period (32.6%; $p < 0.001$) and demonstrated a reduction in the mean number of days hospitalised pre-olanzapine LAI (11.5 days) compared with post-olanzapine LAI (2.3 days; $p < 0.001$)[16].

3.5 Safety

The company submitted pooled analyses of clinical study data (n = 1,778) from five open-label studies (LOBE, LOBO, LOBS, HGJW, HGKB [interim data]) and two double-blind studies (HGJZ, HGKA)[1]. The Committee for Medicinal Products for Human Use (CHMP) concluded that overall, the safety profile of olanzapine LAI is consistent with that of the oral form of olanzapine[2,17]. All frequently reported adverse events (AEs) were known effects of oral olanzapine or the underlying disease, with the exception of AEs related to the injection site; the incidence of which was 8%[2]. The incidence and nature of injection site-related AEs with olanzapine LAI are generally similar to those occurring during treatment with other injectable antipsychotics[18]. Post injection syndrome (which presents as symptoms of olanzapine overdose) was observed in approximately 0.07% of injections, or 1.4% of patients[17]. All patients recovered fully within 24–72 hours after injection[17]. Safety measures to monitor for post injection syndrome are detailed in the SPC[2] and risk management plan[17], and include observation for at least three hours post injection.

More recent clinical studies (HGKB [final analysis], HGLQ) provide supporting safety data and demonstrate the long-term safety profile of olanzapine LAI is generally consistent with the known safety profile of oral olanzapine, with the exception of the AEs associated with the method of administration[11,13].

3.6 AWTTC critique

- In their submission, the company have highlighted a subpopulation of the indication under consideration where they consider olanzapine LAI may be particularly advantageous[1].
- This submission focuses on patients who have been treated with atypical oral medications and for whom the treatment decision to move to an LAI formulation has been made[1]. The applicant company highlight evidence that suggests that the choice of LAI should be consistent with the oral medication on which the person is stabilised[2,19,20]. The choice of BSC care which includes other LAIs as the comparator therefore, seems questionable.
- Clinical effectiveness evidence showed olanzapine LAI to be superior to placebo and non-inferior to a therapeutic dose of oral olanzapine. However, in study HGKB (safety study) only 28% of patients had prior exposure to olanzapine.
- In study HGKA, sub-therapeutic dose of oral olanzapine was used by the company as a proxy to reflect the effectiveness of an antipsychotic in someone with adherence difficulties; however, there is no real-life study data included regarding adherence. Patients in this study appeared to be highly adherent to

their oral treatment regimen; therefore, there may be a selection bias in the participants included. The open-label study HGKB however included patients more likely to reflect the non-adherent patients that will be likely to receive olanzapine LAI.

- Real-world studies, highlighted in the submission, demonstrate the advantage of a number of LAI formulations compared with equivalent oral formulations in outcomes such as rehospitalisation rates and number of bed days[1]. The submission also included information on meta-analyses comparing oral versus depot formulations of antipsychotics; however, they were not specifically designed to demonstrate the efficacy of olanzapine LAI.
- Unlike other atypical antipsychotic LAI formulations, the licence for olanzapine LAI includes a requirement for three hours' observation following the injection, in case of post injection syndrome[2,17].

4.0 SUMMARY OF THE EVIDENCE ON COST-EFFECTIVENESS

4.1 Cost-effectiveness evidence

4.1.1 Context

The company submission[1] includes a within-study threshold analysis, based on a cost-minimisation analysis (CMA) approach, of olanzapine LAI 150 mg/ml compared with BSC for service users who should be treated with atypical depot formulations but for whom no LAI other than olanzapine LAI is appropriate. This represents a subset of the licensed indication, but reflects the stated indication for this submission. BSC is a composite of various measures, including: a combination of antipsychotic medication, healthcare and human resources (including, but not restricted to, inpatient days, community based resources, clinical staff, and pharmacological and psychological therapies). This definition of BSC has been validated by three company-sourced clinical experts, who confirmed it represents current standard care in Wales[1].

The threshold analyses adopt an NHS Wales/Personal Social Services (PSS) perspective and a six month time horizon. The company consider the key cost driver for this patient group to be hospitalisation. The submission therefore seeks to examine the reduction in number of hospital bed-days required with olanzapine LAI, to offset the additional costs of care associated with its administration, monitoring, and management of post injection syndrome events. Hospitalisation data were sourced from a retrospective cohort single-arm study combining records from three nationwide health registers in Sweden. The rationale provided for not performing a more formal cost-effectiveness analysis is the paucity of relevant data for the target population and the BSC comparator. The analyses assumes that olanzapine LAI and BSC are equally effective in terms of improvements in PANSS scores, CGI scores, discontinuation rates, and safety profile (apart from post injection syndrome); and that olanzapine LAI affects only the length of inpatient stay. Ultimately, this approach assumes no difference in health related quality of life for service users receiving olanzapine LAI and BSC.

The base case model is populated with resource use data collected from retrospective real-world single-arm studies conducted in Sweden[1,14], together with estimates based on clinical expert opinion. The resource use inputs sourced from the studies include: antipsychotic drug acquisition and administration costs for both olanzapine LAI and BSC; post-injection observations and management of post injection syndrome for those receiving olanzapine LAI; and number of days hospitalisation. Resource use associated with post injection syndrome has been guided by two post-marketing safety studies and spontaneous AE reports over a five year period[21]. All other resource use has been approximated by clinical experts. Unit costs are taken from the Monthly Index of Medical Specialities[22] (MIMS), the Personal Social Services Research Unit[23] (PSSRU), and Department of Health reference prices[24].

In addition to those mentioned above, the base case is characterised by a number of assumptions, including: all service users complete an uninterrupted six months of treatment (i.e. it does not take into account missed doses, or delayed or reduced administration); all LAIs are administered by a nurse in an outpatient clinic, or in a community based treatment setting; all licensed dosages of comparator treatments are used in equal proportions; the proportion in each oral dose stratum for olanzapine LAI is equally split across each injection schedule; and there is no discontinuation post AE.

Scenario and univariate sensitivity analyses explore alternative management pathways that may exist in NHS Wales. These include: a community setting for administration; varying hospitalisation length of stay assumptions; different dosing and administration assumptions for olanzapine LAI and medicine acquisition costs; and an alternative observation protocol for, and management, of post injection syndrome.

4.1.2 Results

The base case analyses report that the administration of olanzapine LAI compared with BSC results in an incremental cost of £5,426. Taking a threshold analysis approach, these results indicate that in order to be cost neutral the administration of olanzapine LAI requires a saving of greater than nine hospital days to offset these increased costs.

Table 1. Results of the base case analysis.

Costs per service user per six months	Olanzapine LAI	BSC	Incremental cost
Medicine costs			
Medicine acquisition costs	£2,489	£465	**£2,023**
Administration	£168	£45	**£123**
Observation/monitoring	£252	£0	**£252**
Management of post injection events	£5	£0	**£5**
Total cost per service user per six months (excluding hospitalisation costs)	**£2,914**	**£510**	**£2,404**
Threshold analysis			
Number of bed days required to offset additional medicine costs with olanzapine LAI treatment	**9.05 days***		
Estimated hospitalisation costs			
Estimated hospitalisation days	10.9	40.3	**29.4**
Estimated hospitalisation costs	£2,890	£10,720	−£7,830
Total costs	**£5,804**	**£11,230**	**−£5,426**

BSC: best supportive care; LAI: long acting injection.
*Calculated as £2,404/£265.70; where £265.70 represents average hospital cost per day.

The univariate sensitivity analyses reveal how the threshold estimate of nine days is relatively robust. The results are most sensitive to the dosing regimens used to cost olanzapine long lasting injection. If all patients are assumed to receive the highest dose of olanzapine LAI, then this would necessitate a saving of 10.76 days hospitalisation to offset the additional costs. The incremental cost savings produced by the univariate analyses range from £4970 to £6270 (these incorporate medicine costs and hospitalisation costs).

The scenario analyses revealed a wider distribution of incremental cost effects, ranging from −£15,331 to £2161. Table 2 details some of the most noteworthy results of the analyses.

Table 2. Results of scenario analyses.

Scenarios	Estimated total costs	Plausibility
Scenario 1 – base case Community based service user	**−£2,460**	Resource use for this scenario is guided by a Welsh nurse practitioner. This scenario adopts the assumption that one-to-one psychological intervention can be replaced with group sessions in the olanzapine LAI group, which reduces the costs of therapy. It is uncertain whether this assumption is a realistic reflection of resource use in practice.
Scenario 1, plus removal of the cost of daily domiciliary support for service users treated with BSC	**£1270**	Given that the majority of anti-psychotics included in the BSC arm are also LAIs, this scenario cannot be ruled out as being implausible.
Scenario 1, plus replacing all components of community care for the BSC group with Assertive Outreach Team support for six months	**£2161**	Given that these teams are designed to assist in the management of patients in the community who are not adequately managed on standard care pathways, this scenario is also arguably a plausible alternative to the base case.
Scenario 2 – base case Hospital based service user	**−£15,331**	This scenario assumes that service users in the BSC group spend six months as inpatients, compared with seven weeks for those in the olanzapine LAI group. This assumption is based on advice received from a UK clinical expert, which inherently introduces some uncertainty.
LAI: olanzapine long acting injection; BSC: best supportive care.		

4.1.3 AWTTC critique

The reliability of the CMA is dependent on the extent to which olanzapine LAI is considered to be therapeutically equivalent to BSC. No head-to-head comparison has been conducted to demonstrate this assumption of equivalence. Previous studies have, however, compared the cost-effectiveness of olanzapine LAI with other LAIs, one of the components of BSC[25-30], and these suggest differences in effects between antipsychotic LAIs. The basis for CMA is therefore, unproven.

The strengths and limitations of the economic analysis are as follows:

- The submission gives a detailed and transparent account of the methods, data sources and analyses undertaken. Extensive analyses are undertaken to address parameter uncertainties.
- Given the criteria for this target population, particularly in relation to which LAIs are suited to the service user, it is questionable whether BSC can be considered the best comparator for this group. BSC includes administration of other LAIs. However, the target population are considered to only be suitable for olanzapine LAI. Thus there appears to be a contradiction between the target population criteria and comparator.
- The key driver in the model is length of hospitalisation due to psychotic episodes. Hospitalisation data were collected via a retrospective study conducted in Sweden. It is uncertain whether or not practices for such hospitalisations differ between Sweden and the UK.
- The costs apportioned to the administration of the alternative LAIs in the base case may bias in favour of olanzapine LAI, given that administration in an outpatients department is not generally a requirement for these treatments.
- The observation time is based on clinician estimates of the time required for each observation, combined with observation frequency protocols of two NHS Foundation Trusts in England, rather than study/observational data.

- There is evidence to suggest that 45% of patients who experience post injection syndrome discontinue treatment after such an event[21]; however, the base case assumes no discontinuation post-event.
- The six month time horizon avoids the introduction of uncertainty associated with extrapolation. However, given the chronic nature of this illness, it could be considered insufficient for capturing all significant costs and effects.
- Dosing for BSC is based on clinical expert opinion sought by the applicant company. It is uncertain how accurately this reflects current prescribing patterns in Wales for the target population. Exploration of the cost-effectiveness evaluations[3] used to inform NICE guidance[4] reports that flupentixol decanoate was the most commonly prescribed depot anti-psychotic in the UK in 2007[31]; 2014–2015 primary care prescription data for Wales is consistent with this. Flupentixol deconoate is considerably less costly than many of the comparator medicines used in the comparative analysis. If it is still heavily used in the target patient population, then its omission may bias the results in favour of olanzapine LAI.

4.2 Review of published evidence on cost-effectiveness

No economic evaluations have been conducted with a focus on olanzapine LAI compared with BSC. However, as mentioned above, a number of cost-effectiveness analyses have compared olanzapine LAI with other LAIs. The results from these studies are varied; in some instances olanzapine LAI has been found to be dominant, i.e. less costly and more effective[26], but another study found olanzapine LAI to be dominated[27]. Given that previous studies have used a cost utility analysis approach to evaluation; this would seem to endorse the suggestion that CMA may be inappropriate in this instance.

5.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

5.1 Budget impact evidence

5.1.1 Context and methods

Prevalence for schizophrenia in Wales has been estimated using population and population growth rate data sourced from Knowledge and Analytical Services Welsh Government, combined with prevalence data from the National Collaborating Centre for Mental Health[3]. Incidence and mortality rates are informed by a systematic review (which was not solely UK focused)[32]. The model assumes a 0% recovery rate for this population, given the lack of data for the target population. Prevalence, incidence and mortality rates are assumed to be constant and not influenced by new treatments.

In order to quantify how many patients are likely to make up the target population, the company combine NHS Wales GP prescriber data for oral atypical drugs for May–July 2015 with non-adherence data from a clinical study and observational study[33,34]. The company assume that 33.3% of these patients are eligible to receive olanzapine LAI, i.e. no other LAI is appropriate. This assumption is based on treatment data from the NHS Trust in Leicestershire, where olanzapine LAI is available as a treatment option. The uptake of olanzapine LAI is estimated to be 50% in year one, increasing to 100% in year five. Dosing regimens are guided by Swedish real-world data[1]; over 50% of service users are assumed to receive the highest dose. The base case model does not include displaced alternative treatments, or resource use associated with post injection syndrome. The base case assumes administration and monitoring in a hospital setting.

Sensitivity analyses were conducted to gauge the impact of alternative assumptions; including those related to post-injection monitoring and events, dosing regimens and recovery rate.

5.1.2 Results

Tables 3 and 4 detail the base case results for the budget impact analysis and scenario analyses respectively.

Table 3. Company-reported costs associated with use of olanzapine long acting injection.

	Year 1	Year 2	Year 3	Year 4	Year 5
Number of eligible patients (Indication covered in this submission)	43	44	44	44	44
Uptake (%)	50%	60%	70%	85%	100%
Treated patients	22	27	31	38	44
Total costs					
Medication acquisition (per service user)	£4,880	£4,880	£4,880	£4,880	£4,880
Medication Administration (per service user)	£333	£333	£333	£333	£333
Post-injection observation	£499	£499	£499	£499	£499
Total cost per service user	£5,213	£5,213	£5,213	£5,213	£5,213
Total cost	**£125,668**	**£154,229**	**£177,078**	**£217,063**	**£251,336**
Cumulative cost	**£125,668**	**£279,897**	**£456,975**	**£674,038**	**£925,374**

Table 4. Budget impact scenario for olanzapine long acting injection.

	Total annual cost range: Year 1 to Year 5	Plausibility
Scenario 1: Inclusion of one post injection syndrome event necessitating A&E admission and monitoring	£125,755 to £251,510	This provides a worst case scenario with regards to costing in post injection syndrome events.
Scenario 2: Observations performed by nurse eight times over a three hour period, three minutes per assessment	£132,258 to £264,516	This reflects the observation protocol of the Surrey and Borders NHS Trust, and is therefore a plausible alternative to the base case.
Scenario 3: Observations performed by occupational therapist, twelve times over a three hour period, three minutes per assessment	£125,148 to £250,297	Given that South London and Maudsley and South Staffordshire NHS Trusts use both nurses and occupational therapists for observations, this is a plausible alternative.
Scenario 4: Service users are treated with oral target doses of 10 mg, 15 mg and 20 mg in equal proportions	£114,065 to £228,130	There is uncertainty surrounding this assumption. However, there is also uncertainty surround the budget impact base case assumption for dosing, which is based on Swedish data that may or may not reflect prescribing patterns in Wales.
Scenario 5: Recovery rate of 13.7	£108,532 to £217,063	Given that this scenario is based on study data[35] (albeit of a different target group, and is therefore, likely to overestimate recovery), this could possibly be considered a best case scenario with regards to recovery rates – and a plausible alternative to simplifying assumptions applied to the budget impact base case.

5.1.3 AWTTC critique

Strengths and limitations of the budget impact analyses are as follows:

- The submission gives a detailed and transparent account of the methods and data sources used in the budget impact analysis.
- The analyses do not include costs associated with displaced medicines, or overheads associated with administration and monitoring of olanzapine LAI.
- The sensitivity analyses explore predominantly plausible alternatives to the base case and the effects of altering some of the assumptions underpinning the base case.

5.2 Comparative unit costs

Annual acquisition costs associated with olanzapine and a number of other antipsychotic drugs are detailed in Table 5. Oral olanzapine has been included to provide an indication of the magnitude of change in acquisition costs associated with a switch from oral to depot injection. Both typical and atypical antipsychotic LAIs are included, given that BSC incorporates both of these groups.

Table 5. Examples of medicine acquisition costs for atypical and typical antipsychotics.

Regimens	Example doses	Approximate costs per patient/per annum (unit cost)
Atypical/second generation antipsychotics		
Olanzapine LAI (ZypAdhera®)	Maintenance in patients tolerant to 10 mg orally once daily: • 150 mg every two weeks, or • 300 mg every four weeks Maintenance in patients tolerant to 15 mg orally once daily: • 210 mg every two weeks, or • 405 mg every four weeks Maintenance in patients tolerant to 20 mg orally once daily: • 300 mg every two weeks	**£3,711.76** **£2,894.32** **£3,711.76** **£5,788.64**
Oral olanzapine	10 mg once daily 15 mg once daily 20 mg once daily	**£18.72** **£23.01** **£23.14**
Risperidone LAI (Risperdal Consta®)	25 mg to 50 mg every two weeks	**£2,071.94 to £3,711.76**
Aripiprazole LAI (Abilify Maintena®)	400 mg monthly	**£2,865.33**
Paliperidone (Xeplion®)	Maintenance dose 75 mg monthly (range 25 mg to 150 mg monthly)	**£2,390.96 to £5,103.67**
Typical/first generation antipsychotics		
Flupentixol decanoate (Depixol®/Depixol Conc®)	Maintenance dose: 50 mg every four weeks to 300 mg every two weeks	**£52.78 to £487.50**
Zuclopenthixol decanoate (Clopixol®)	200 mg to 600 mg weekly	**£163.80 to £491.40**
Fluphenazine decanoate	12.5 mg to 100 mg repeated at intervals of 14 to 35 days (costed for 12.5 mg every two weeks and 100 mg every four weeks)	**£58.76 to £113.75**
Haliperidol decanoate (Haldol Decanoate®)	300 mg every four weeks	**£65.65**
Perphanazine (Fentazin®)	4 mg three times a day, adjusted according to response; maximum 24 mg per day	**£376.75 to £753.50**

LAI: long acting injection.
Not all regimens may be licensed for use in this patient population. See relevant Summaries of Product Characteristics for full licensed indications and dosing details.
Costs are based on British National Formulary (BNF) list prices as of February 2016[36], assuming vial wastage.
Costs of administration are not included.
This table does not imply therapeutic equivalence of drugs or the stated doses.
Costs calculated assuming a 52 week year.

6.0 ADDITIONAL INFORMATION

6.1 Prescribing and supply

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

The company do not anticipate that olanzapine (ZypAdhera®) will be supplied by a home healthcare provider.

6.2 Ongoing studies

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

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: 18 February 2016.
Date range of evidence search: No date limits were applied to database searches.

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