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

No. (624/10)

Eli Lilly and Company Limited

09 July 2010

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

ADVICE: following a full submission

olanzapine long acting injection (ZypAdhera®) is not recommended for use within NHS Scotland.

Indication under review: Maintenance treatment of adult patients with schizophrenia sufficiently stabilised during acute treatment with oral olanzapine.

The pivotal study showed comparable efficacy of olanzapine long-acting injection to oral olanzapine in preventing relapse in stabilised patients over 24 weeks. Supervision requirements in relation to the risk of post injection syndrome may limit the benefit of decreased frequency of administration.

The manufacturer did not present a sufficiently robust economic case to gain acceptance by SMC.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Indication

Maintenance treatment of adult patients with schizophrenia sufficiently stabilised during acute treatment with oral olanzapine.

Dosing information

Prior to administration of olanzapine long acting injection (LAI) patients should be stabilised during acute treatment with oral olanzapine. Olanzapine LAI should only be administered by deep intramuscular gluteal injection.

Recommended dose scheme between oral olanzapine and olanzapine LAI

Target oral olanzapine dose	Recommended starting dose of olanzapine LAI	Maintenance dose after 2 months of olanzapine LAI treatment
10mg/day	210mg/2 weeks or 405mg/4 weeks	150mg/2 weeks or 300mg/4 weeks
15mg/day	300mg/2 weeks	210mg/2 weeks or 405mg/4 weeks
20mg/day	300mg/2 weeks	300mg/2 weeks

Olanzapine LAI should be administered by a healthcare professional trained in the appropriate injection technique and in locations where post-injection observation and access to appropriate medical care in the case of overdose can be assured. After each injection, patients should be observed in a healthcare facility by appropriately qualified personnel for at least 3 hours for signs and symptoms consistent with olanzapine overdose.

Product availability date

March 2010

Summary of evidence on comparative efficacy

Olanzapine is a second generation (atypical), antipsychotic, antimanic and mood stabilising agent that demonstrates a broad pharmacologic profile across several receptor systems. This long action injection (LAI) formulation is administered every two or four weeks.

The submitting company has requested that the Scottish Medicines Consortium considers the use of this product in a sub-population of the licensed population i.e. those patients who have difficulty adhering to their oral medication.

The licence is based on one phase III, double-blind, randomised, active-controlled, maintenance study in 1,065 adult patients with DSM-IV or DSM-IV-TR diagnosis of schizophrenia.

After screening, patients entered a 4- to 8-week period in which they were switched from their previous antipsychotic treatment to open-label oral olanzapine monotherapy (10, 15, or 20mg/day) and had to meet a number of stabilisation criteria for 4 consecutive weeks to be eligible for randomisation.

Patients who met the stabilisation criteria were randomly assigned, in a 1:1:2:1:2 ratio, to 24 weeks treatment with olanzapine LAI: very low=45 mg every 4 weeks; low=150 mg every 2 weeks; medium=405mg every 4 weeks; high=300 mg every 2 weeks; or to remain on their

individually stabilised dose of oral olanzapine (10mg, 15mg or 20mg). All patients received four tablets (drug or placebo) daily and an injection (drug or placebo) every 2 weeks. No oral antipsychotic supplementation was allowed. Exclusion criteria included significant suicidal or homicidal risk; acute, serious, or unstable medical conditions; or substance dependence (except nicotine or caffeine) within the previous month.

The patient population was predominantly male (65%) and Caucasian (72%), with a mean age of 39 years and a mean body mass index of 27. At study entry 60% of patients were receiving olanzapine, 49% were receiving another antipsychotic and 8% were not receiving an antipsychotic. Mean baseline Positive and Negative Symptom Scores (PANSS) total score at randomisation was 54.3 to 57.8.

The primary efficacy outcomes, measured in the intention to treat population, were rates of and time to psychotic exacerbation, defined as 1) an increase of any Brief Psychiatric Rating Scale (BPRS) positive symptom item to a score >4, with an absolute increase ≥2 for the specific item since randomisation; 2) an increase of any BPRS positive symptom item to a score >4, with an absolute increase ≥4 on the positive symptom subscale since randomisation; or 3) hospitalisation as the result of worsening of positive psychotic symptoms. A non-inferiority test compared Kaplan-Meier exacerbation rates for the oral olanzapine group with the olanzapine LAI 2-week combined group (high and low dose) and the 4-week (medium dose) group. Non-inferiority was demonstrated if the upper limit of the 95% confidence interval (CI) for the difference between the groups was <20%.The combined 2-week group was also compared with the 4-week (medium dose) group to assess the effect of dose interval.

The proportion of patients that remained exacerbation-free at 24 weeks was 93%, 95%, 90%, 84% and 69% for the oral olanzapine, high-dose LAI, medium-dose LAI, low-dose LAI and very low reference dose LAI groups, respectively.

Comparison of exacerbation rates using Kaplan-Meier 24-week percentages indicated no significant difference between the pooled 2-week (high and low doses combined) and therapeutic 4-week (medium dose) regimens, hazard ratio (HR) 1.0 [95% CI: 0.6 to 1.8]. There was also no significant difference between the pooled 2-week regimen and the oral formulation, HR 1.5 [95% CI: 0.8 to 2.7] or between the therapeutic 4-week regimen and the oral formulation, HR 1.4 [95% CI: 0.8 to 2.6]. All comparisons met criteria for non-inferiority.

All three standard long-acting doses of LAI were superior to the very low reference dose. Patients treated with the reference dose had a higher risk of psychotic exacerbation relative to patients in the low dose (HR 2.1 [95% CI: 1.2 to 3.7]), medium dose (HR 3.5 [95% CI: 2.2 to 5.8]), and high dose (HR 7.4 [95% CI: 3.1 to 17.5]) groups. Patients treated with the low dose had a higher risk of exacerbation relative to those treated with the high dose (HR 3.5 [95% CI: 1.4 to 8.7]). There were no other significant differences in risk of exacerbation between the long-acting dose groups.

The secondary outcomes of mean baseline-to-endpoint change in the PANSS total score showed superiority of the three standard LAI groups relative to the very low reference dose group. Similar results were observed for scores on the PANSS subscales, the BPRS, and the Clinical Global Improvement (CGI) scores.

Significantly more patients in all olanzapine LAI groups except the high dose group (300mg/2 weeks) discontinued the study compared with the oral olanzapine group. Discontinuation rates were 20%, 24%, 30%, 36% and 47% for the oral olanzapine, high dose LAI, medium dose LAI, low dose LAI and very low dose LAI groups, respectively.

There were no clinically significant differences between treatment groups in quality of life outcomes. However, all treatment groups showed marked improvement with respect to rates of suicide attempts, suicide threats, and emergency room use by the end of the double-blind maintenance phase.

Data were presented from a 22-month interim analysis of an open-label, uncontrolled, extension study of olanzapine LAI which was primarily designed to investigate safety in 880 patients who had completed one of three core studies. Olanzapine LAI (45 to 405mg) was administered at 2-, 3- or 4-week intervals and 20% of patients received oral olanzapine supplementation (up to 20mg daily). At the interim analysis 77% patients remained in the study. Small improvements from baseline in PANSS, CGI and quality of life scores, suggested maintenance of treatment effect achieved in previous studies.

Summary of evidence on comparative safety

There is no evidence on comparative safety with other antipsychotic drugs. In the pivotal study the most common adverse events were insomnia, weight gain, anxiety, and somnolence. Incidence of local reactions at the injection site (e.g., pain, swelling) was low (n=30, 3%). Incidence of weight gain ≥7% from baseline was 21% for oral olanzapine compared with 21%, 15%, 16%, and 8% for the high, medium, low, and very low olanzapine LAI groups, respectively.

Two patients receiving olanzapine LAI experienced post-injection syndrome events, with symptoms of dizziness and malaise within 10 to 20 minutes of injection, followed by gradual worsening of symptoms of excessive sedation and/or delirium consistent with olanzapine overdose. They were hospitalised and recovered fully within 60 hours of the injection.

Conclusions from the interim analysis of the ongoing, open-label extension safety study described in the comparative efficacy section are that the overall safety profile up to 22 months is generally consistent with the known safety profile of olanzapine. There were very few injection-site-related adverse events. Nine patients receiving olanzapine LAI developed signs consistent with olanzapine overdose following an injection.

The main safety concern specific to the LAI formulation of olanzapine is the risk of post-injection syndrome which has occurred in <0.1% of injections and approximately 2% of patients. It presents with signs and symptoms consistent with olanzapine overdose; most affected patients developed symptoms of sedation (ranging from mild in severity up to coma) and/or delirium (including confusion, disorientation, agitation, anxiety and other cognitive impairment). In most cases, initial signs and symptoms appeared within 1 to 5 hours following injection, and in all cases full recovery was reported to have occurred within 24 to 72 hours after injection. The European Medicines Agency (EMA) Committee for Medicinal Products for Human Use considers post-injection syndrome to be a major safety issue. As part of its Risk Management Plan commitment, the submitting company was required to ensure that doctors and nurses were especially trained in the safe use of olanzapine LAI before making this product available in the UK.

Summary of clinical effectiveness issues

For patients with schizophrenia, non-adherence to medication is a major risk factor for relapse and rehospitalisation; this formulation has been developed to address this issue.

The pivotal study showed comparable efficacy of olanzapine LAI to oral olanzapine in preventing relapse in stabilised patients over 24 weeks. The pooling of results of the high and low dose groups for the primary outcome to produce a combined outcome for the two-weekly dose regimen is a weakness as non-inferiority of the individual low and high dose regimens relative to oral olanzapine was not analysed. Rates of discontinuation from the study were higher in the LAI groups than in the oral group. Although there are inherent difficulties in investigating adherence in randomised controlled studies in this target patient population, no evidence has been provided demonstrating that olanzapine LAI increases adherence compared with oral olanzapine.

The major safety issue of post-injection syndrome necessitates that after each olanzapine injection all patients must be supervised for three hours in a healthcare facility; cannot travel home alone; must be made aware of adverse reactions and be able to obtain help if required. This demands a high level of commitment from the patient and has substantial education and practical implications for the service. It is unclear how much the supervision requirements will militate against the benefit of reduced frequency of administration.

There are no clinical studies comparing olanzapine LAI with any other antipsychotic drugs. A naïve indirect comparison with risperidone LAI, (the only other second generation [atypical] antipsychotic formulated as an LAI), was presented. It excluded the pivotal study and included only uncontrolled studies and no statistical analysis.

SMC clinical experts have suggested that first generation (typical) injectable antipsychotics would also have been an appropriate comparator and should have been considered in the manufacturer's health economic case.

Differences between olanzapine LAI and risperidone LAI include the following: post-injection syndrome has not been reported with risperidone; low and medium doses of olanzapine LAI may be administered monthly (high dose is administered every two weeks) compared with administration every two weeks for risperidone LAI; initial oral supplementation may not be required for olanzapine LAI although it is a requirement for risperidone LAI and olanzapine LAI, unlike risperidone LA, does not require refrigeration.

Summary of comparative health economic evidence

The manufacturer presented a cost-utility discrete event simulation over a five year time horizon. This compared olanzapine LAI with risperidone LAI in the subset of patients with adherence difficulties with oral olanzapine who would otherwise receive risperidone LAI. Within the model patients could relapse and be hospitalised, discontinue their treatment or have their treatment switched by their doctor. When off LAI treatment, patients had an elevated risk of suicide.

Most of the clinical data for olanzapine LAI were drawn from the open-label safety study, though side effect rates were drawn from the pivotal randomised clinical studies. Clinical data for risperidone LAI were taken from a variety of open-label studies published in the literature, with the base case including data from the off-label 75mg dose. This anticipated relative risks of 1.34 for relapse and 1.63 for discontinuation in favour of olanzapine LAI.

The probabilities of treatment switching were estimated from expert opinion. Adverse events including weight gain and extrapyramidal symptoms were included in the model.

The direct drug costs assumed the World Health Organisation defined daily dose which led to price equivalence between olanzapine LAI and risperidone LAI during maintenance. Administration costs were four hours mental health nursing per olanzapine injection (including three hours for observation in relation to post injection syndrome) and one hour mental health nursing per risperidone injection. Dosing frequency was every four weeks for olanzapine LAI and every two weeks for risperidone LAI.

Most other resource use data were drawn from the UK Schizophrenia Care and Assessment Program survey. Resource use for side-effects was limited to the three days care per event assumed for post injection syndrome within the olanzapine LAI arm. Resource use was valued using standard sources. Quality of life values were estimated from EQ-5D data from a large 3 year prospective study of over 10,000 European schizophrenia patients.

This resulted in olanzapine LAI being estimated to yield 0.07 additional quality-adjusted life years (QALYs) over the five years at an additional cost of £889 to give an incremental cost per QALY of £13,162.

Analysis showed that the results were most sensitive to changes in efficacy (particularly discontinuation rates) and administration/observation costs. Excluding discontinuation rates associated with off-label 75mg risperidone LAI worsened the cost effectiveness to between £30,153 per QALY and £44,972 per QALY. Assuming lower costs associated with observation in the post-injection period reduced the incremental costs associated with olanzapine LAI and would improve the cost per QALY.

Additional analyses suggested that applying the drug doses as seen within the trials resulted in an estimated cost effectiveness of £14,574 per QALY. Further to this, applying the olanzapine dosing frequencies as seen within the trials (average of one injection every 19 days) worsened the cost effectiveness to £137,657 per QALY. However, if some nursing supervision time could be used for other care or administration such that the equivalent of only one additional nursing hour of supervision was required for each olanzapine LAI injection, applying the dosing frequency seen in the trial would result in a cost effectiveness estimate of £54,395 per QALY.

Weaknesses of the analysis included:

- the clinical benefits of olanzapine LAI over risperidone LAI not having been formally demonstrated within the submission.
- the open-label olanzapine LAI trial not being directly comparable with the open-label risperidone LAI trials in terms of patient intake and duration, to the possible advantage of olanzapine LAI.
- failure to consider first generation (typical) antipsychotics as potential comparators.

As a consequence, the manufacturer did not present a sufficiently robust economic case to gain acceptance by the SMC.

Summary of patient and public involvement

A Patient Interest Group submission was received from the National Schizophrenia Fellowship (Scotland).

Additional information: guidelines and protocols

In 2010 the National Institute for Health and Clinical Excellence published Clinical Guideline 82: Schizophrenia – core interventions in the treatment and management of schizophrenia in adults in primary and secondary care (updated edition). It notes that there are unanswered questions regarding the relative efficacy, tolerability and long term use of second generation (atypical) antipsychotics (SGAs) compared with first generation (typical) antipsychotics (FGAs). For SGAs, the risks of long-term metabolic disturbance and of movement disorders such as tardive dyskinesia are not yet fully quantified compared with FGAs, so any small advantage that may be offered by reduced extrapyramidal symptoms may be offset by these other adverse consequences not shown by the earlier drugs.

Although some SGAs show a modest benefit over haloperidol, there is insufficient evidence to choose between antipsychotics in terms of relapse prevention.

The guideline recommends that prescribers consider offering depot/long-acting injectable antipsychotic medication to people with schizophrenia:
- who would prefer such treatment after an acute episode
- where avoiding covert non-adherence (either intentional or unintentional) to antipsychotic medication is a clinical priority within the treatment plan.

When initiating depot/long-acting injectable antipsychotic medication:
- take into account the service user's preferences and attitudes towards the mode of administration (regular intramuscular injections) and organisational procedures (for example, home visits and location of clinics).

Additional information: comparators

Oral olanzapine, depot injections of risperidone (atypical antipsychotic), flupentixol decanoate, fluphenazine decanoate, haloperidol decanoate, pipotiazine palmitate, zuclopenthixol decanoate.

Cost of relevant comparators

Drug	Dose regimen	Annual cost (£)
Olanzapine long acting injection	**By deep intramuscular injection, 150 to 300mg every two weeks or 300 to 405mg every 4 weeks**	**2,894 to 5,789**
Oral		
Olanzapine tablets	Orally, 5 to 20mg daily	568 to 2,066
Long acting injection		
Risperidone long acting injection	By deep intramuscular injection, 25 (most patients) to 50mg every two weeks	2,072 to 3,712
Pipotiazine palmitate long acting injection	By deep intramuscular injection, 50 to 200mg every 4 weeks	211 to 693
Flupentixol decanoate long acting injection	By deep intramuscular injection 50mg every 4 weeks to 300mg every 2 weeks	25 to 275

Zuclopenthixol decanoate long acting injection	By deep intramuscular injection, 200mg every 4 weeks to 600mg every week	26 to 293
Fluphenazine decanoate long acting injection	By deep intramuscular injection, 12.5mg every 5 weeks to 100mg every 2 weeks	14 to 227
Haloperidol decanoate long acting injection	By deep intramuscular injection, 50 to 300mg every 4 weeks	50 to 197

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 26.04.10

Additional information: budget impact

The manufacturer estimated a gross drug cost of £188k in year 1, rising to £1.8m by year 5. Administration costs would add £83k to the gross drug costs in year 1, rising to £810k by year 5.

Based upon olanzapine LAI displacing risperidone LAI the manufacturer estimated a net drug cost of £2k in year 1, rising to £18k by year 5. Administration costs would add £42k to the net drug costs in year 1, rising to £405k by year 5. This was based upon a patient population eligible for depot medication of 14,000, coupled with a market share of 62 patients (0.4%) in year 1, rising to 603 patients (3.9%) by year 5.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

This assessment is based on data submitted by the applicant company up to and including 18 June 2010.

Drug prices are those available at the time the papers were issued to SMC for consideration. These have been confirmed from the eVadis drug database. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

The undernoted references were supplied with the submission. The reference shaded grey is additional to those supplied with the submission.

Kane JM, Detke HC, Naber D et al. Olanzapine Long-Acting Injection: A 24-week, randomized, double-blind trial of maintenance treatment in patients with schizophrenia. Am. J. Psychiatry AJP in Advance. Published December 15, 2009 (doi: 10.1176/appi.ajp.2009.07081221)

Eli Lilly and Company Limited Abbreviated Clinical Study Report: An open-label study of intramuscular olanzapine depot in patients with schizophrenia or schizoaffective disorder

Eli Lilly and Company Limited Clinical Study Report: A double-blind randomized study comparing intramuscular olanzapine depot to oral olanzapine and low-dose intramuscular olanzapine depot in the maintenance therapy of patients with schizophrenia

European Medicines Agency (EMA) Assessment Report for Zypadhera (olanzapine long acting injection). Document Reference: EMEA/608654/2008. www.ema.europa.eu