Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
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NHS SCOTLAND

Re-Submission

paliperidone palmitate 50mg, 75mg, 100mg and 150mg prolonged release suspension for injection (Xeplion) SMC No. (713/11)

Janssen-Cilag Ltd

07 October 2011

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 resubmission

paliperidone palmitate prolonged release suspension for injection (Xeplion) is accepted for use within NHS Scotland.

Indication under review: 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, it may be used without prior stabilisation with oral treatment if psychotic symptoms are mild to moderate and a long-acting injectable treatment is needed.

Paliperidone prolonged release suspension for injection was non-inferior to another atypical antipsychotic depot injection in terms of control of schizophrenia symptoms over a 3-month period and was more effective than placebo in preventing relapse of schizophrenia.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

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Indication

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, it may be used without prior stabilisation with oral treatment if psychotic symptoms are mild to moderate and a long-acting injectable treatment is needed.

Dosing Information

Paliperidone palmitate 150mg intramuscular (im) injection, then after one week 100mg im injection, then continue on a monthly maintenance dose. The recommended monthly maintenance dose is 75mg im; some patients may benefit from lower or higher doses within the recommended range of 25mg to 150mg based on individual patient tolerability and/or efficacy. Patients who are overweight or obese may require doses in the upper range. If switching from oral paliperidone or oral risperidone, these should be discontinued upon initiation of treatment with paliperidone im injection. If switching from long acting risperidone injection, paliperidone im injection should be initiated in place of the next risperidone injection then continued monthly, without the need for the one-week initiation schedule (i.e. 150mg then 100mg one week later) described previously. The dose conversion when switching from risperidone long acting injection is specified in the summary of product characteristics, with the monthly paliperidone dose being double the fortnightly risperidone dose.

Product availability date

18 April 2011

Summary of evidence on comparative efficacy

Paliperidone is an atypical antipsychotic; it is the active metabolite of risperidone and an antagonist of serotonin 5-HT_2 and dopamine D_2 receptors. The Scottish Medicines Consortium has previously not recommended the use of oral paliperidone for the treatment of schizophrenia. This submission relates to paliperidone palmitate formulated as a long acting injection (LAI). paliperidone,

Two similar double-blind non-inferiority studies recruited adults with schizophrenia, as defined in the diagnostic and statistical manual of mental disorders fourth edition (DSM-IV), for at least one year and a positive and negative syndrome scale (PANSS) score of 60 to 120. After a washout of disallowed psychotropic medicines, in the 1-year study patients were randomised equally to paliperidone LAI 50mg intramuscular (im) injection on days 1 and 8 then monthly flexible doses of 25mg to 100mg im from weeks 5 to 51 or oral risperidone 1mg to 6mg daily for 4 weeks plus risperidone LAI 25mg im injection on days 8 and 22 then fortnightly flexible doses of 12.5mg to 50mg from weeks 5 to 51. The initial two doses of paliperidone in this regimen are lower than the licensed dose, which was used in the subsequent 3-month study. In the 3-month study, patients were randomised equally to the previously detailed regimen of risperidone up to 13 weeks or paliperidone LAI 150mg im on day 1 and 100mg im on day 8, then flexible doses every 4 weeks: 50mg or 100mg im on day 36 and 50mg to 150mg im on day 64. The primary endpoint, change in PANSS score from baseline to endpoint, was assessed via analysis of covariance with factors for treatment and country, and baseline PANSS score as covariate in the per protocol population, comprising 570 and 765 patients in the respective studies. The pre-specified non-inferiority margin (lower confidence interval) was 5 points. At baseline, the mean

PANSS total score was 82 in the 1-year study and 84 in the 3-month study. In the 1-year study, the mean change in PANSS score from baseline to endpoint was -11.6 and -14.4 in the paliperidone LAI and risperidone LAI groups, respectively. The difference between paliperidone LAI and risperidone LAI and in the least-square mean for change in PANSS score was -2.6 (95% confidence interval (CI): -5.84 to 0.61) and therefore non-inferiority of paliperidone LAI to risperidone LAI was not demonstrated. In the 3-month study, the mean change from baseline to endpoint in PANSS score was -18.6 in the paliperidone LAI group and -17.9 in the risperidone LAI group. The difference between paliperidone LAI and risperidone LAI in the least-square mean for change in PANSS score was 0.4 (95% CI: -1.62 to 2.38) and therefore non-inferiority of paliperidone LAI to risperidone LAI was demonstrated.

There were no significant differences between the treatment groups for the secondary outcomes, mean change from baseline to endpoint in Clinical Global Impression of Severity (CGI-S) and Personal and Social Performance (PSP), except for CGI-S in the 1-year study. The reduction in severity of symptoms assessed via CGI-S in the 1-year study appears greater with risperidone LAI than paliperidone LAI, with a difference in least square means for change in CGI-S of -0.2 (95% CI: -0.41 to -0.06).

In a third double-blind study, 410 adults with schizophrenia as defined in DSM-IV for at least one year were stabilised with a PANSS total score ≤75 and scores ≤4 for PANSS items P1 (delusions), P2 (conceptual disorganisation), P3 (hallucinatory behaviour), P6 (suspiciousness/persecution), P7 (hostility), G8 (uncooperativeness) and G14 (poor impulse control) on monthly im flexible doses of paliperidone LAI 25mg to 100mg and then randomised to continue their maintenance dose of paliperidone LAI or receive placebo. The primary outcome, time-to-first relapse, was assessed via Kaplan-Meier methodology with a two-sided log-rank test to compare treatment differences in the intention-to-treat analysis set, which included all randomised patients who received at least one injection in the double-blind phase and had data available at the analysis cut-off date. Relapse was defined as: hospitalisation for symptoms of schizophrenia; 25% increase in PANSS score for patients with an initial score >40 or a 10-point increase for patients with an initial score ≤40; deliberate self-injury; aggressive behaviour; suicidal or homicidal ideation; or an increase for two consecutive assessments of scores for individual PANSS items P1, P2, P3, P6, P7, P8 to ≥5 for patients with initial scores ≤3 or to ≥6 for patients with initial scores of 4. The study was stopped at a pre-planned interim analysis after 68 relapse events when data from 312 patients indicated that paliperidone LAI, compared to placebo, significantly delayed time-to-first relapse. The median time to relapse in the placebo group was 163 days and could not be estimated in the paliperidone LAI group. Relapse rates were significantly lower in the paliperidone LAI group than in the placebo group: 10% (15/156) versus 34% (53/156).

Summary of evidence on comparative safety

The overall adverse effect profile of paliperidone LAI appears similar to that of risperidone LAI. In the comparisons to risperidone LAI, rates of adverse events were similar, except in the 1-year comparison where paliperidone LAI was associated with a higher incidence of severe psychiatric adverse events (18% versus 14%), mainly psychotic disorder and schizophrenia.

Summary of clinical effectiveness issues

The 3-month study demonstrating non-inferiority of paliperidone LAI to risperidone LAI appears to be contradicted by the 1-year study that failed to show non-inferiority. It has been suggested

that failure to demonstrate non-inferiority in the 1-year study may be due to sub-therapeutic levels of paliperidone at the start of the study resulting from a lower loading dose than the licensed dose which was used in the 3-month study. This may also explain the higher incidence of severe treatment-emergent psychiatric adverse events with paliperidone LAI in the 1-year study.

There are no data on efficacy in prevention of relapse relative to an active comparator. In the clinical studies, the exclusion criteria prevented assessment of paliperidone LAI in treatment-resistant schizophrenia.

Clinical experts consulted by SMC have advised that long acting depot injections are often used when there are compliance issues with oral medication. They note that many patients are stabilised on a first generation (typical) antipsychotic depot injection, but use of second generation (atypical) antipsychotic depot injections is increasing. Paliperidone LAI is the third atypical antipsychotic depot injection licensed for maintenance treatment of schizophrenia.

Clinical experts have identified a number of practical advantages associated with paliperidone LAI. The dosing schedule has potential advantages, as it is given monthly (up to 7 days before or after the date treatment is due) rather than fortnightly, and there is no requirement for initial oral antipsychotic supplementation. In addition, as it is formulated as a pre-filled syringe rather than a vial of powder for reconstitution it can be stored at room temperature rather than in the fridge and may lead to reduced wastage associated with loss of a cold chain.

Summary of comparative health economic evidence

The submitting company conducted a cost-minimisation analysis comparing paliperidone palmitate LAI with risperidone LAI for the treatment of patients requiring an atypical antipsychotic and for whom a long acting formulation is the preferred route of administration. A 1-year time horizon was selected for the base-case.

The clinical evidence demonstrating similar outcomes compared to risperidone LAI, came from a randomised, double-blind, flexible-dose, short-term, non-inferiority study. Resource use was estimated through the use of a Scottish expert group (convened by the submitting company) who were all involved in the routine care of schizophrenia patients. The submitting company stated that they worked with this group to ensure that the modelling framework is representative of practice across Scotland.

The analysis compared the costs associated with initiation and maintenance treatment of schizophrenia and presented the total costs per patient treated over the first year of treatment with paliperidone palmitate LAI and risperidone LAI. The costs included medication costs, cost of wastage, oral antipsychotic drug supplementation cost, hospitalisation cost and the cost of administration in the community.

The results showed that when treatment was initiated in the inpatient setting the total costs in year 1 were £11,063 per patient treated with paliperidone palmitate LAI, and £14,554 per patient treated with risperidone LAI. As such, the submitting company claimed that paliperidone palmitate LAI was associated with a cost saving of -£3,491 per patient in year 1. A key driver of the result was the assumption that paliperidone palmitate LAI would shorten the length of stay in hospital by one third, resulting in discharge after 18.7 days, compared with 28 days for risperidone LAI. This estimate was obtained from the company's Scottish expert group. When treatment was initiated in the community, the total costs in year 1 were estimated to be £3,791

per patient treated with paliperidone palmitate LAI, and £3,914, per patient treated with risperidone LAI. As such, the submitting company claimed that paliperidone palmitate LAI was associated with a small cost saving of -£122 per patient in year 1. A key driver of the result was the assumption that 71% of patients were switched to paliperidone LAI from oral treatments and 29% from another LAI.

The key finding from the sensitivity analysis was that the estimated base case results were most sensitive to assumptions relating to length of stay in hospital when treatment was initiated in the inpatient setting and previous therapy when treatment was initiated in the community setting. However, a threshold analysis provided by the company showed that providing the reduction in hospital length of stay was greater than 0.6 days paliperidone palmitate LAI would be preferred on cost-minimisation grounds. As such, the economic case was considered demonstrated.

Summary of patient and public involvement

A Patient Interest Group Submission was received from SANE.

Additional information: guidelines and protocols

In 2010 the National Institute for Health and Clinical Excellence (NICE) published clinical guideline number 82 on schizophrenia: core interventions in the treatment and management of schizophrenia in adults in primary and secondary care (updated edition). This recommends considering offering depot or long-acting injectable antipsychotic medication to people 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 within the treatment plan. When initiating depot/long-acting injectable antipsychotic medication take into account the service user's preferences and attitudes towards mode of administration (regular intramuscular injections) and organisational procedures (for example, home visits and location of clinics); take into account the same criteria recommended for the use of oral antipsychotic medication within these guidelines, particularly in relation to the risks and benefits of the drug regimen and initially use a small test dose as set out in the British National Formulary (BNF) or Summary of Product Characteristics (SPC).

The guideline does not include specific guidance on choice of depot or long-acting injectable antipsychotic medication and predates the availability of paliperidone palmitate.

Additional information: comparators

Risperidone LAI and olanzapine LAI, the other atypical antipsychotic LAI, are indicated for the maintenance treatment of schizophrenia. In practice, paliperidone LAI is likely to compete mainly with risperidone LAI. Olanzapine LAI has been not recommended by SMC for use within NHS Scotland.

Cost of relevant comparators

Drug	Dose Regimen	Cost per year (£)
Paliperidone palmitate	**25mg to 150mg every four weeks**	**2,391 to 5,104**
Olanzapine pamoate	150mg to 300mg every two weeks or 300mg to 405mg every four weeks	2,894 to 5,789
Risperidone LAI	25mg to 50mg every two weeks	2,072 to 3,712

Doses are for general comparison and do not imply therapeutic equivalence. In the above table all drugs are long acting injections and all doses are administered as deep intramuscular injections. Costs are from eVadis on 3 August 2011.

Additional information: budget impact

The submitting company estimated the population eligible for treatment to be 1,062 patients. Based on an estimated uptake of 3.6% in year 1 (38 patients) and 5.5% in year 5 (58 patients), the impact on the medicines budget impact was estimated at £125k in year 1 and £191k in year 5. The net medicines budget impact was estimated at £14k in year 1 and £22k in year 5.

References

The undernoted references were supplied with the submission. The references shaded in grey are additional to those supplied with the submission.

Johnson & Johnson. Clinical Study Report for PSY-3002, 6 September 2007.

Fleischhacker WW, Gopal S, Samtani MN et al. Optimization of the dosing strategy for the long-acting injectable antipsychotic Paliperidone Palmitate: Results of two randomized double-blind studies and population pharmacokinetic simulations. 2008; Poster presented at ACNP; Scottsdale, AZ, USA; December 7-11, 2008

Johnson & Johnson. Clinical Study Report for PSY-3006, 30 October 2009.

Pandina GJ, Lane R, Gopal S et al. A double-blind study of paliperidone palmitate and risperidone long-acting injectable in adults with schizophrenia. Progress in Neuro-Psychopharmacology & Biological Psychiatry. 2011; 35: 218-226.

Johnson & Johnson. Clinical Study Report for PSY-3001, 15 January 2009.

Hough D, Gopal S, Vijapurkar U et al. Paliperidone Palmitate maintenance treatment in delaying the time-to-relapse in patients with schizophrenia: A randomised, double-blind, placebo-controlled study. Schizophr Res, 2010; 116: 107-117

European Medicines Agency. European Public Assessment Report for Xeplion.

Johnson & Johnson. Synopsis of clinical study NCT00210717 (PSY-3002), 6 September 2007. www.clinicaltrials.gov.

This assessment is based on data submitted by the applicant company up to and including 16 September 2011.

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.

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.