## Paliperidone palmitate injection for the management of schizophrenia in adults

### February 2015

### Summary

#### Background and licensed indication

Paliperidone is an atypical antipsychotic; it is the active metabolite of risperidone and an antagonist of serotonin 5-HT2 and dopamine D2 receptors. It is licensed for the maintenance treatment of schizophrenia in adults stabilised with paliperidone or risperidone. In selected adult patients with schizophrenia and previous responsiveness to oral paliperidone or risperidone, paliperidone palmitate injection 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 palmitate injection is available in a pre-filled syringe, ready for administration.

#### 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 to 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. When making dose adjustments, the prolonged release characteristics of paliperidone should be considered, as the full effect of maintenance doses may not be evident for several months.

When switching patients from risperidone long-acting injection, paliperidone injection can be given in place of the next scheduled risperidone injection, and continued at monthly intervals. The initiation dosing schedule is not required and the monthly dosage is twice the two-weekly dosage of risperidone e.g. if a patient is receiving risperidone injection 25mg every 2 weeks, this equates to paliperidone 50mg given monthly.

#### Alternatives

Paliperidone is a second-generation antipsychotic. Risperidone, olanzapine and aripiprazole are the only other second-generation injectable antipsychotics available for use in schizophrenia, although these require reconstitution before administration.

#### NICE

The National Institute for Health and Care Excellence (NICE), in their clinical guideline on the management of psychosis and schizophrenia in adults, suggest considering a depot /long-acting injectable antipsychotic in people 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. Additionally, the guideline specifies that when initiating depot/long-acting injectable antipsychotic medication, the patients’ preference and attitude towards the mode of administration and organisational procedures i.e. home visits or locations of clinics should be accounted for.

#### Clinical studies

A Cochrane review on paliperidone palmitate published in 2012 is based on seven studies (5 compared with placebo, and two with risperidone). Two studies which evaluated paliperidone palmitate vs. an active comparator that were published subsequent to the Cochrane review have been included in the evidence review below.

The ACLAIMS study (A Comparison of Long-acting Injectable Medications for Schizophrenia) compared the effects of long-acting injectable paliperidone palmitate and long-acting haloperidol decanoate (a first-generation antipsychotic). The RCT showed comparable efficacy for both drugs. Additionally, rates of discontinuation of study drug due to any cause or due to adverse effects were similar for both drugs, although patients on
haloperidol decanoate experienced greater increases in BAS scores for akathisia compared to those on paliperidone palmitate. Additionally, although there were no statistically significant differences in changes for ratings of parkinsonism, fewer patients on paliperidone palmitate required the initiation of a medication to treat parkinsonism compared to those on haloperidol decanoate. Paliperidone palmitate did however cause weight gain whereas haloperidol decanoate was associated with weight loss.

A second study evaluated paliperidone palmitate vs. risperidone long-acting injection over a period of 13 weeks, and concluded that paliperidone palmitate injection was non-inferior in efficacy to risperidone long-acting injection, whilst the incidence of treatment-emergent adverse effects were similar in both groups.

| Safety | Data from the Cochrane meta-analysis which pooled data from two studies comparing paliperidone palmitate vs. risperidone showed no difference in the occurrence of extrapyramidal disorder, tardive dyskinesia, tremor, hypertonia, and akathisia. Data from the study comparing paliperidone palmitate vs. haloperidol decanoate showed that on average, participants taking paliperidone palmitate gained weight progressively over time, while those taking haloperidol decanoate lost weight (p<0.001 for all time points up to 24 months). However, the worst change from baseline in blood glucose, HbA1c, total cholesterol, HDL-cholesterol and triglycerides were not statistically significantly different between the two groups. Additionally, there were no statistically significant differences in changes in ratings of abnormal movements as indicated by the change from baseline score of the AIMS global score, and there were no statistically significant differences in the incidence of probable tardive dyskinesia between the 2 groups. Of note though, patients on haloperidol decanoate experienced greater increases in the BARS score (for akathisia) compared to those on paliperidone palmitate (p=0.006), whilst there was no statistically significant difference in ratings of parkinsonism as measured by the mean SAS score (p=0.34). However, fewer patients on paliperidone palmitate than haloperidol decanoate respectively started on medication for the management of parkinsonian symptoms and akathisia. |
| Convenience | Intramuscular paliperidone palmitate is formulated as an aqueous-based nanosuspension that is available in pre-filled syringes and do not require reconstitution or refrigeration. Paliperidone palmitate is administered as a monthly injection, and does not require post-administration observation of the patient. |
| Risk assessment | Other than monitoring for adverse events no additional risks were noted by the EMA Risk Management |
| Budget impact | 20 patients per 100,000 population may be eligible for treatment. Based on an estimated uptake of 3.6% in year 1 (0.72 patients i.e. 1 patient), the annual cost would be £2200 to £4700 per 100,000, and based on an estimated uptake of 5.5% in year 5 (1.1 patient i.e. 1 patient) the annual cost per 100,000 population would be the same. |
| Funding | Proposed for shared-care/transfer of care |
| Suggested place in therapy | An orally administered antipsychotic regimen should be the preferred option as recommended by NICE. The choice of oral antipsychotic drug (first- or second-generation) should take into account the different risk profiles associated with individual drugs and potential impact on the patient. For patients that are felt to be at high risk of non-adherence to an oral regimen and for whom a first-generation depot agent is inappropriate, paliperidone palmitate appears to offer some practical advantages over the other second-generation injectable antipsychotics. Paliperidone does not require dose supplementation during treatment initiation, there is some flexibility around dose administration schedules, an individualised approach to dosing is feasible, no post-injection monitoring is required and it is presented as a ready-to-use prefilled injection which does not require special storage conditions prior to administration. It therefore appears that the choice of long-acting injectable antipsychotic should account the different risk profiles associated with individual drugs and potential impact on the patient. |
1. **Background and introduction**

**Psychosis and schizophrenia**

Psychosis and the specific diagnosis of schizophrenia represent a major psychiatric disorder (or cluster of disorders) in which a person's perception, thoughts, mood and behaviour are significantly altered. The symptoms of psychosis and schizophrenia are usually divided into 'positive symptoms', including hallucinations (perception in the absence of any stimulus) and delusions (fixed or falsely held beliefs), and 'negative symptoms' (such as emotional apathy, lack of drive, poverty of speech, social withdrawal and self-neglect). Each person will have a unique combination of symptoms and experiences.

Typically there is a prodromal period, which precedes a first episode of psychosis and can last from a few days to around 18 months. The prodromal period is often characterised by some deterioration in personal functioning. Changes include the emergence of transient and/or attenuated psychotic symptoms, memory and concentration problems, unusual behaviour and ideas, disturbed communication and affect, and social withdrawal, apathy and reduced interest in daily activities. The prodromal period is usually followed by an acute episode marked by hallucinations, delusions and behavioural disturbances, usually accompanied by agitation and distress. Following resolution of the acute episode, usually after pharmacological, psychological and other interventions, symptoms diminish and often disappear for many people, although sometimes a number of negative symptoms remain. This phase, which can last for many years, may be interrupted by recurrent acute episodes that may need additional pharmacological, psychological and other interventions, as in previous episodes.

PANSS is used to measure symptom severity of patients with schizophrenia. A trained interviewer applies a 7-point rating to 30 different schizophrenia symptoms. The sum of the scores for each symptom provides the total PANSS score of between 30 and 210. In practice it is reported that stable outpatients usually score 60–80 and inpatients' scores rarely exceed 80–150 even in 'treatment refractory' cases. It is thought that a reduction of at least 25% from baseline might be viewed as a clinically useful effect.

Over a lifetime, about 1% of the population will develop psychosis and schizophrenia. The first symptoms tend to start in young adulthood, at a time when a person would usually make the transition to independent living, but can occur at any age. The symptoms and behaviour associated with psychosis and schizophrenia can have a distressing impact on the individual, family and friends.

Approximately 220,000 people in England and Wales have a diagnosis of schizophrenia.

**Antipsychotic agents**

According to a review in Drugs, second-generation (atypical) antipsychotic agents (oral and long-acting injections) were developed more recently with the hope of overcoming the clinical limitations associated with the first-generation agents. Not only were first-generation antipsychotic agents associated with a high incidence and broad range of adverse effects, including movement disorders, lethargy, sedation, weight gain and sexual dysfunction, but up to 40% of patients continued to be symptomatic despite treatment. Second-generation antipsychotic agents were seen as an advance in treatment and were thought to be of superior clinical efficacy and to have a broader spectrum of activity and an improved tolerability profile. In reality, there is no consistent or robust evidence showing that second-generation antipsychotic agents (long-acting injection or oral) are more effective than the first-generation agents. However, second-generation antipsychotic agents are generally associated with fewer movement disorder-related adverse events than the first-generation agents. In addition, the aqueous-based second-generation long-acting injectable antipsychotic agents are associated with fewer injection-site reactions than the oil-based first-generation long-acting antipsychotic agents. Long-term comparative studies would be helpful in establishing any true differences between first-generation and second-generation long-acting injectable antipsychotic agents.

A meta-analysis comparing oral first- and second-generation antipsychotics concluded that second-generation antipsychotic drugs differ in many properties and are not a homogeneous class, and thus, individualised treatment is required based on efficacy, side-effects and cost.

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Paliperidone palmitate long-acting injection (Xeplion®)

Paliperidone is an atypical antipsychotic; it is the active metabolite of risperidone and an antagonist of serotonin 5-HT2 and dopamine D2 receptors. Paliperidone palmitate injection is licensed for the maintenance treatment of schizophrenia in adults stabilised with paliperidone or risperidone. In selected adult patients with schizophrenia and previous responsiveness to oral paliperidone or risperidone, paliperidone palmitate injection 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 palmitate injection is available in a pre-filled syringe, ready for administration.

National guidance and recommendations

The National Institute for Health and Care Excellence (NICE), in their clinical guideline on the management of psychosis and schizophrenia in adults, suggest considering a depot/long-acting injectable antipsychotic to people 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. Additionally, the guideline specifies that when initiating depot/long-acting injectable antipsychotic medication, the patients’ preference and attitude towards the mode of administration and organisational procedures i.e. home visits or locations of clinics should be accounted for. The guideline therefore makes no recommendation on any particular long-acting injectable antipsychotic.

The Scottish Medicines Consortium (SMC) has approved the use of paliperidone palmitate but rejected the use of olanzapine embonate. The SMC has not published an evaluation for risperidone long-acting injection although it accepts it as a relevant comparator for both olanzapine embonate and paliperidone palmitate. The SMC accepted the economic case for using paliperidone injection over risperidone injection on the basis that it would cost less to the health service as long as it was associated with a reduction in length of hospital stay of more than 0.6 days. The SMC did not accept that there was a sufficiently robust case to support the preferential use of olanzapine embonate over risperidone long-acting injection primarily because the suggested clinical benefits had not been formally demonstrated. The SMC has also accepted aripiprazole intramuscular injection for the rapid control of agitation and disturbed behaviours in patients with schizophrenia when oral therapy is not appropriate.

The All Wales Medicines Strategy Group (AWMSG) has recommended paliperidone palmitate (Xeplion®) prolonged release suspension for injection for use within NHS Wales for the maintenance treatment of schizophrenia in adults stabilised with paliperidone or risperidone; and in selected adults with schizophrenia and previous responsiveness to oral paliperidone or risperidone, without prior stabilisation with oral treatment when psychotic symptoms are mild to moderate and a long-acting injectable treatment is needed. The AWMSG is of the opinion that paliperidone palmitate (Xeplion®) prolonged release suspension for injection is appropriate for specialist only prescribing within NHS Wales for this indication. The AWMSG has also accepted aripiprazole (Abilify Maintena®) 400 mg powder and solvent for prolonged release suspension as an option for use within NHS Wales for the maintenance treatment of schizophrenia in adult patients stabilised with oral aripiprazole.

The AWMSG however, does not recommend olanzapine depot (ZypAdhera®) for use within NHS Wales for the maintenance treatment of adult patients with schizophrenia sufficiently stabilised during acute treatment with oral olanzapine, as the case for cost effectiveness has not been proven.

2. Proposed place in therapy

It has been proposed that paliperidone may be prescribed for patients:
- Who are non-compliant with oral medication and for whom response and tolerability to risperidone has been assessed.
- Who have experienced extra-pyramidal side effects (EPSEs or tardive dyskinesia) with typical antipsychotics.

Paliperidone does not require dose supplementation during treatment initiation, there is some flexibility around dose administration schedules, an individualised approach to dosing is feasible, no post-injection monitoring is required and it is presented as a ready-to-use prefilled injection which does not require special storage conditions prior to administration.
Olanzapine embonate depot is licensed for monthly administration but requires patients to be observed for at least three hours post-injection due to the risk of post-injection reactions. Risperidone long-acting injection can be given two-weekly or monthly. When initiating the risperidone long-acting injection, sufficient antipsychotic coverage with oral risperidone or the previous antipsychotic should be ensured during the three-week lag period following the first injection. Aripiprazole injection is also licensed for monthly administration in patients already stabilised on the oral formulations respectively. All require reconstitution before administration.

3. Evidence selected for inclusion

A Cochrane review, published in 2012 has described the evidence for paliperidone palmitate, comparing the efficacy, adverse effects and safety of paliperidone palmitate with any other treatment, including placebo, for people with schizophrenia and schizophrenia-like illnesses. The review included all randomised-controlled trials where the primary outcome reported was “global state: relapse” (defined as recurrence of psychotic symptoms) or “global state: no clinically important change in global state” (as defined by individual studies).

Data from a total of seven trials involving 4,184 participants were considered to be appropriate for inclusion: 2,421 patients received paliperidone palmitate, 983 received risperidone long-acting injection, and 695 were randomised to placebo. All participants were over 18 and diagnosed with DSM-IV schizophrenia. Their PANSS score ranged between 60 and 120.

Of the 7 trials included, one was of short duration (9 weeks), one was of long duration (53 weeks), and 5 were of medium duration (4 trials were of 13 weeks duration, while one trial was of variable duration ~ 24 weeks). Two trials compared paliperidone palmitate versus risperidone long-acting injection, whilst 5 studies compared paliperidone palmitate vs. placebo.

The following efficacy results were reported:

- There was no difference between paliperidone palmitate and risperidone long-acting injection for patients leaving the studies early for any reason (n = 1969, 2 RCTs, RR 1.12 CI 1.00 to 1.25).
- Those receiving paliperidone palmitate were statistically no more likely to have a recurrence of psychotic symptoms than those receiving risperidone long-acting injection (n = 1961, 2 RCTs, RR 1.23 CI 0.98 to 1.53).
- While no significant difference in the occurrences of deaths in the pooled trials were reported (n = 1967, 2 RCTs, RR 3.62 CI 0.60 to 21.89), it was noted that a total of six deaths occurred, with five deaths among people who received paliperidone palmitate and one death among people who received risperidone long-acting injection. The authors of the review note that although death is the most serious of adverse events, the small number of these events in these trials makes it unclear if this finding is meaningful.
- Patients randomised to paliperidone palmitate were statistically significantly less likely to use anticholinergic medications compared to those randomised to risperidone (n = 1587, 2 RCTs, RR 0.67 CI 0.55 to 0.82, NNT 13 over 13 to 53 weeks CI 10 to 24).
- Those receiving any dose of paliperidone palmitate were more likely to have an improvement in global state (n = 1696, 4 RCTs, RR 0.79 CI 0.74 to 0.85, number needed to treat 7 CI 5 to 9).
- Participants randomised to paliperidone palmitate were statistically significantly less likely to experience the recurrence of psychotic symptoms than those receiving placebo (n = 1772, 4 RCTs, RR 0.67 CI 0.53 to 0.84, NNT 17 CI 12 to 36).
- Five studies identified a statistically significant improvement in global state as indicated by change in CGI-S by the end of the trial for participants randomised to paliperidone palmitate (n = 2104, 5 RCTs, mean difference (MD) -0.42, CI -0.52 to -0.32).
- Five studies found a statistically significant improvement in mental state as indicated by change in PANSS by the end of the trial for participants randomised to paliperidone palmitate (n = 2104, 5 RCTs, MD -8.07 (-9.75 TO -6.39)).
- Patients randomised to paliperidone palmitate were less likely to experience a recurrence of psychosis (n = 312, 1 RCT, RR 0.28 CI 0.17 to 0.48, NNT 5 over 24 weeks CI 4 to 6) than those allocated to placebo in a single trial specifically designed to study recurrence. In the other studies where recurrence was recorded only as an adverse event, people who received paliperidone palmitate were also less likely to experience a recurrence of psychotic symptoms (n = 1837, 4 RCTs, RR 0.55 CI 0.44 to 0.68, NNT 10 CI 8 to 14).
common with paliperidone palmitate than placebo. While no difference was found in the incidence of reported adverse sexual outcomes, paliperidone palmitate is associated with substantial increases in serum prolactin. When flexibly dosed with a mean dose of approximately 70 to 110 mg every four weeks, paliperidone palmitate appears comparable in efficacy and tolerability to risperidone long-acting injection flexibly dosed with mean doses of approximately 35 mg every two weeks.

The ACLAIMS study (A Comparison of Long-acting Injectable Medications for Schizophrenia) compared the effects of long-acting injectable paliperidone palmitate and long-acting haloperidol decanoate (a first-generation antipsychotic)\(^4\). The double blind, randomised controlled trial was conducted in over 22 sites in the US, and included patients aged between 18 to 65 years with a confirmed diagnosis of schizophrenia or schizoaffective disorder by DSM-IV-TR criteria.

Patients were reviewed at 1, 2, 4, 6, 8, 10, and 12 weeks and then monthly for a period of 2 years. Benztropine was available to both groups if extra-pyramidal side effects occurred.

The primary outcome was efficacy failure, which reflected inadequate control of the psychopathology of schizophrenia or schizoaffective disorder – defined as psychiatric hospitalisation, a need for crisis stabilisation, a clinically meaningful increase in frequency of outpatient visits, a clinicians decision that oral antipsychotic medication could not be discontinued within 8 weeks of starting the long-acting injectable, a clinicians decision to discontinue the drug due to inadequate therapeutic benefit, or for patients already transitioning on long-acting injectable antipsychotic, an ongoing need for adjunctive oral antipsychotic medication.

The secondary outcomes were worst change from baseline in weight at any timepoint, worst change from baseline in blood glucose, HbA1c, LCL cholesterol and triglycerides on blood tests at 3, 6 then every 6 months, highest prolactin concentration, scores of akathisia, parkinsonism, abnormal movements and sexual functioning, and Positive and negative symptoms scale (PANSS).

In the primary analysis, which included all patients who received at least one injection and at least one post-baseline assessment (modified intention to treat population, n=145 in each group), there was no statistically significant difference in the rate of efficacy failure for patients in the paliperidone palmitate group compared to those in the haloperidol decanoate group (49 [33.8%] vs. 47 [32.4%] respectively, p=0.90). The most common reasons for efficacy failure noted by the outcome adjudication committee were psychiatric hospitalisation (44[89.8%] of paliperidone palmitate events and 34 [72.3%] of haloperidol decanoate events) and clinician discontinuation of study medication due to inadequate therapeutic benefit, or for patients already transitioning on long-acting injectable antipsychotic, an ongoing need for adjunctive oral antipsychotic medication.

The following results were reported for secondary outcomes assessed:

- On average, participants taking paliperidone palmitate gained weight progressively over time, while those taking haloperidol decanoate lost weight. At month 24, the least squares mean weight change for participants in the paliperidone palmitate group was increased by 6.04kg (95% CI, 2.88 to 9.20) and for the haloperidol decanoate group was decreased by −3.88 kg (−7.02 to −0.73); p<0.001 for all time points up to 24 months.
- The worst change from baseline in blood glucose, HbA1c, total cholesterol, LDL cholesterol, HDL cholesterol and triglycerides were not statistically significantly different between the two groups.
- There were no statistically significant differences in ratings of abnormal involuntary movements as indicated by change from baseline score in the AIMS global score (0.43 [95% CI, 0.31-0.55] for paliperidone vs 0.50 [95% CI, 0.38-0.62] for haloperidol decanoate; p = 0.39).
- Participants taking haloperidol decanoate experienced greater increases in BAS global scores (for akathisia) (0.45 [95% CI, 0.31-0.59] for those in the paliperidone palmitate group vs 0.73 [95% CI, 0.59-0.87] for the haloperidol decanoate group; p = 0.006).
- There was no statistically significant difference in changes in ratings of parkinsonism, as measured by the mean SAS score (0.21 [95% CI, 0.16-0.27] for the paliperidone palmitate group vs. 0.25 [95% CI, 0.20-0.30] for the haloperidol decanoate group; p = 0.34). Fewer patients taking paliperidone palmitate than haloperidol decanoate started a medication to treat parkinsonism (18 [15.8%] vs. 27 [29.3%]; P = 0.007) and akathisia (5 [3.6%] vs. 16 [11.0%]; p = 0.03).
- Prolactin levels were higher in the paliperidone palmitate group in both men (34.56 mcg vs. 15.41 mcg, p=<0.001) and women (75.19 mcg vs. 26.84 mcg, p=<0.001).
There were no statistically significant differences between the two groups, in sexual dysfunction, gynecomastia, or galactorrhoea.

Decreases in PANSS total scores from baseline were similar for both groups at each time point.

Rates of treatment discontinuation due to any cause, and rates of discontinuation due to adverse effects were similar for both groups.

Another study, conducted in Chinese patients with schizophrenia, evaluated paliperidone palmitate vs. risperidone long-acting injection. The open-label, parallel-group, 13 week study involved 452 patients randomised to receive either paliperidone palmitate (n=229) or risperidone long-acting injection (n=223).

The primary efficacy outcome was the change in PANSS total score from baseline to the last post-randomisation assessment. Non-inferiority of paliperidone palmitate compared to risperidone was to be concluded in the primary population, which included the per-protocol group (n=413) which included randomised patients who received at least 2 injections of the study medication and for whom the time between any 2 injections did not exceed 35 days in the case of paliperidone, and 21 days in the case of risperidone, had a baseline, and at least 1 post-baseline assessment for the primary outcome, had a minimum of 5 weeks exposure to study medications, and did not have any protocol deviations. Non-inferiority of paliperidone to risperidone was concluded if the lower limit of the two-sided 95% CI for the difference in mean change in PANSS total score exceeded -5.5.

Paliperidone palmitate was reported to be non-inferior to risperidone (least-squares mean difference in PANSS -2.3, 95% CI -5.20 to 0.63). Safety findings, which included the intention-to-treat population (n=452), showed that treatment-emergent adverse effects were similar in both groups (73.4% of the paliperidone group, and 74.9% of the risperidone group). Overall, the most commonly reported adverse effects were akathisia (13.1% in the paliperidone group vs. 19.7% in the risperidone group), tremor (10.5% in the paliperidone group vs. 17.9% in the risperidone group) and insomnia, which occurred more frequently in the paliperidone palmitate group compared to the risperidone group.

4. Critical evaluation

4.1 Clinical application

It appears that the studies evaluating paliperidone palmitate have used varying primary and secondary outcomes, and most studies have been of short duration.

There is a lack of comparative head-to-head studies, with a majority of studies evaluating the drug vs. placebo. Additionally, outcomes such as re-hospitalisation rates/number of outpatient visits have not been reported in these studies.

Paliperidone palmitate does not appear to have been evaluated in patients with other clinically significant co-morbidities such as cardiovascular disease or diabetes, and therefore, it is not clear whether the generally “cleaner” side effect profile would confer benefit for these patients (considering paliperidone palmitate is associated with increase in weight)

4.2 Key adverse events

According to the EMA assessment report for intramuscular paliperidone palmitate, the safety database for intramuscular paliperidone palmitate did not appear to reveal any new safety concerns compared with oral paliperidone, except for injection site-related adverse events, which are not an issue with oral formulations.

Overall, the incidence of adverse events was generally similar in intramuscular paliperidone palmitate and placebo recipients in short-term, placebo-controlled trials. Adverse effects occurring in ≥2% of intramuscular paliperidone palmitate recipients in an analysis of pooled results discussed in the EMA assessment report and the manufacturer’s prescribing information included agitation, akathisia, constipation, diarrhoea, dizziness, headache, injection-site reactions, insomnia, nausea, somnolence, tachycardia, tremor, upper respiratory tract infection, vomiting and weight gain. Of these, headache and insomnia were the most frequent, being categorised as ‘very common’ (i.e. occurring in ≥1 in 10 patients); the other adverse events were all categorised as ‘common’ (i.e. occurring in ≥1 in 100 to <1 in 10 patients).
Adverse effect data for the comparison of paliperidone palmitate vs. placebo from the meta-analysis reported\(^3\):

- No difference in the use of anticholinergic medications between participants randomised to paliperidone palmitate and those randomised to placebo (n = 2154, 5 RCTs, RR 1.12 CI 0.90 to 1.39) was noted.
- No difference in the occurrence of hypotension (n = 2160, 5 RCTs, RR 2.33 CI 0.75 to 7.26), hypertension (n = 2160, 5 RCTs, RR 1.33 CI 0.52 to 3.38), prolonged QTc interval (n = 655, 2 RCTs, RR 1.03 CI 0.09 to 11.20), and myocardial infarction (n = 1933, 4 RCTs, RR 0.33 CI 0.01 to 8.06) in participants randomised to paliperidone palmitate compared to placebo.
- The pooled data appear to show a higher incidence of tachycardia in participants receiving paliperidone palmitate, although the difference failed to reach statistical significance (n = 2172, 5 RCTs, RR 2.10 CI 1.00 to 4.42).
- Participants randomised to paliperidone palmitate were less likely to experience agitation or aggression (n = 2180, 5 RCTs, RR 0.65 CI 0.46 to 0.91, NNTB 39 CI 25 to 150) and to use anxiolytic medications (n = 2170, 5 RCTs, RR 0.89 CI 0.83 to 0.96, NNTB 16 CI 11 to 44).
- A consistent and statistically significant elevation in serum prolactin levels for both men and women receiving paliperidone palmitate was noted, although this finding was heterogenous. No significant association between paliperidone palmitate and the incidence of a potentially prolactin-related event (n = 2504, 5 RCTs, RR 1.37 CI 0.62 to 3.04) was found.
- No consistent effect of paliperidone palmitate was observed in serum levels of glucose (n = 2119, 5 RCTs, mean difference MD 0.08 CI -0.04 to 0.20) or insulin (n = 1931, 4 RCTs, MD -5.84 CI -22.25 to 10.57).
- Patients receiving paliperidone palmitate had a significantly greater increase in weight than those allocated to placebo (n = 2052, 5 RCTs, MD 1.34 CI 0.97 to 1.70).
- All five studies presented data for change in serum triglycerides and total cholesterol - No effect was found for either of these outcomes in these short-term trials.
- Patients receiving paliperidone palmitate appeared more likely to experience extrapyramidal disorders (n = 2178, 5RCTs, RR 1.84 CI 0.95 to 3.54).
- No consistent effect of paliperidone palmitate on the incidence of tardive dyskinesia (n = 2178, 5 RCTs, RR 1.40 CI 0.08 to 44.79), tremor (n = 2180, 5 RCTs, RR 0.92 CI 0.49 to 1.74), oculogyric crisis (n = 408, 1 RCT, RR 2.97 CI 0.12 to 72.50), hypertonia (n = 1120, 3 RCTs, RR 2.59 CI 0.68 to 9.85), and akathisia (n = 1767, 4 RCTs, RR 0.89 CI 0.49 to 1.61) were noted.
- All of the studies reported average change in Barnes Akathisia Rating Scale (BARS score), and participants randomised to paliperidone palmitate were significantly more likely to experience a change (decline) in BARS score (n = 2146, 5 RCTs, MD -0.09 CI -0.17 to -0.01) – however, this change appears modest.
- All of the studies reported average change in Abnormal Involuntary Movement Scale (AIMS score), and no difference was identified (n = 2148, 5RCTs,MD-0.04CI -0.15 to 0.07) between participants randomised to paliperidone palmitate and those randomised to placebo.

The following adverse effect data were reported for the comparison between paliperidone palmitate and risperidone\(^3\):

- Patients on paliperidone palmitate were significantly less likely to use anticholinergic medications compared to those on risperidone long-acting injection (n = 1587, 2 RCTs, RR 0.67 CI 0.55 to 0.82, NNTB 13 CI 10 to 24).
- No significant difference in the occurrence of hypotension (n = 1961, 2 RCTs, RR 2.91 CI 0.12 to 71.28), hypertension (RR 0.98 CI 0.39 to 2.47), tachycardia (RR 1.70 CI 0.81 to 3.57), and myocardial infarction (RR 2.91 CI 0.12 to 71.28) was noted.
- Both studies found that the average change in QTc interval was less profound with participants randomised to paliperidone palmitate, but the difference was not statistically significant.
- Both studies reported average change in BARS score (for akathisia), and participants who received paliperidone palmitate experienced greater reductions in the BARS score (MD -0.10 CI -0.18 to -0.02) than those randomised to risperidone, but the effect was modest.
- Both studies reported average change in AIMS score, and no difference was identified (MD 0.00 CI -0.10 to 0.10) between participants randomised to paliperidone palmitate and those randomised to risperidone.
In the ACLAIMS study comparing paliperidone palmitate injection and haloperidol decanoate injection, on average, participants taking paliperidone palmitate gained weight progressively over time, while those taking haloperidol decanoate lost weight (p<0.001 for all time points up to 24 months). However, the worst change from baseline in blood glucose, HbA1c, total cholesterol, HDL-cholesterol and triglycerides were not statistically significantly different between the two groups. Additionally, there were no statistically significant differences in changes in ratings of abnormal movements as indicated by the change from baseline score of the AIMS global score, and there were no statistically significant differences in the incidence of probable tardive dyskinesia between the 2 groups.

Of note though, patients on haloperidol decanoate experienced greater increases in the BARS score (for akathisia) compared to those on paliperidone palmitate (p=0.006), whilst there was no statistically significant difference in ratings of parkinsonism as measured by the mean SAS score (p=0.34). However, fewer patients on paliperidone palmitate than haloperidol decanoate respectively started on medication for the management of parkinsonian symptoms (18 [15.8%] vs. 27 [29.3%]; P = 0.007) and akathisia (5 [3.6%] vs. 16 [11.0%]; p = 0.03).

4.3. Potential advantages and disadvantages over existing technologies

4.3.1. Convenience

- Once stabilised, patients receive paliperidone palmitate as a once-monthly intramuscular injection.
  Olanzapine embonate and aripiprazole injections are administered every four weeks, whereas risperidone long-acting injection requires administration every 2 to 4 weeks.
- Paliperidone palmitate is available as a ready formulated pre-filled syringe, and therefore does not require reconstitution before administration. However, olanzapine embonate, aripiprazole and risperidone injections require reconstitution before administration.
- There are no special storage requirements for paliperidone palmitate injection or olanzapine embonate and aripiprazole injections, whilst risperidone injection requires refrigeration. Once reconstituted, it must be used immediately.

4.3.2. Healthcare resource utilisation

Administration of any of these antipsychotic injections is by intramuscular injection, and therefore require outpatient appointments.

For olanzapine injections, 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. Immediately prior to leaving the healthcare facility, it should be confirmed that the patient is alert, oriented, and absent of any signs and symptoms of overdose. The 3-hour observation period should be extended as clinically appropriate for patients who exhibit any signs or symptoms consistent with olanzapine overdose.

In addition to monitoring requirements for specific adverse effects outlined above, these long-acting injectable formulations are also associated with the same adverse effects as their oral equivalents. Therefore, following dose stabilisation, patients treated with these agents may also require regular monitoring of blood lipids, weight, plasma glucose and serum prolactin concentrations. In the Maudsley Prescribing Guidelines in Psychiatry it is recommended that for lipids and weight following baseline assessment, they are undertaken 3 monthly for the first year of treatment and then annually; a plasma glucose level is recommended after 4–6 months and then annually; and, a prolactin concentration measurement after 6 months and then annually. Patients taking antipsychotics associated with a high risk of causing hyperprolactinaemia (e.g. risperidone) should be asked about symptoms at every clinic visit during the first 3 months of treatment or until the dose is stable. Expert consensus from the British Association of Psychopharmacology recommends measuring baseline serum prolactin concentration, with further measurements at 3 months after the dose has become stable and also 3 months after any change in antipsychotic dose. Additionally, it is recommended that urea and electrolytes, full blood count and liver function tests are undertaken annually.
### 4.3.3. Suitability for shared care

Because of the additional monitoring and the method of administration, shared care may not be appropriate.

### 4.3.4. Drug cost and likely budgetary impact

The table below lists the cost of the second-generation antipsychotics, as well as haloperidol decanoate.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose range</th>
<th>NHS cost price for 1 year(^{18})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injectable second-generation antipsychotics (These prices consider the basic cost of the injection. They do not include other related costs such as hospital visit costs)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paliperidone once per month (XEPLION®)</td>
<td>25mg(^*) to 150mg</td>
<td>£2207 to £4711</td>
</tr>
<tr>
<td>Risperidone long-acting injection (Risperdal Consta®) every 2 weeks</td>
<td>25mg to 50mg</td>
<td>£1912 to £3426</td>
</tr>
<tr>
<td>Olanzapine embonate (ZypAdhera®) every 4 weeks</td>
<td>300mg to 405 mg</td>
<td>£2671 to £3426</td>
</tr>
<tr>
<td>Aripiprazole once per month (Abilify Maintena®)</td>
<td>400mg</td>
<td>£2645</td>
</tr>
</tbody>
</table>

**Oral second-generation antipsychotics**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose range</th>
<th>NHS cost price</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amisulpride</td>
<td>400–800 mg daily in 2 divided doses (Lower doses may be used in people with predominantly negative symptoms)</td>
<td>£119 to £488</td>
</tr>
<tr>
<td>Aripiprazole ‡</td>
<td>15 mg daily</td>
<td>£1152</td>
</tr>
<tr>
<td>Lurasidone(^*)</td>
<td>37 to 148 mg once daily</td>
<td>£1080 to £2177(^#)</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>5–20 mg daily</td>
<td>Standard release: £15 to £25 Odorispensible: £33 to £68</td>
</tr>
<tr>
<td>Paliperidone</td>
<td>3–12 mg daily</td>
<td>£1167 to £2335</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>Standard release: 300–450 mg in 2 divided doses. Prolonged release: 600 mg daily</td>
<td>Standard release: £33 to £56 Prolonged release: £2036</td>
</tr>
<tr>
<td>Risperidone</td>
<td>4–6 mg daily</td>
<td>Standard release: £13 to £64 Odorispensible: £449 to £888</td>
</tr>
</tbody>
</table>

**First-generation intramuscular antipsychotic compared with paliperidone palmitate injection**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose range</th>
<th>NHS cost price</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haloperidol decanoate (Haldol Decanoate®) every 4 weeks</td>
<td>30mg to 300mg</td>
<td>£46 to £182</td>
</tr>
</tbody>
</table>

\(^*\)The smallest available strength of prefilled syringe is the 50mg strength, and therefore, will require use of half the dose.

\(^\dagger\) Generic aripiprazole will be available soon

\(^#\) Prices obtained from the NICE evidence summary for lurasidone

According to the evidence submission for paliperidone palmitate use in NHS Scotland, the submitting company estimated the population eligible for treatment to be 1,062 patients (equating to 0.02% of the Scottish population based on 2013 population statistics\(^5\)). 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 was estimated at £125k in year 1 and £191k in year 5.

Extrapolating this to the population in England and Wales, it is estimated that approximately 11,350 patients may be eligible for treatment with paliperidone palmitate. Based on an estimated uptake of 3.6% in year 1 (408 patients), and 5.5% in year 5 (624 patients), the impact on the medicines budget is estimated at £900k to £1.9 million in year 1, and £1.4 million to £3 million in year 5.

In summary, 20 patients per 100,000 population may be eligible for treatment. Based on an estimated uptake of 3.6% in year 1 (0.72 patients i.e. 1 patient), the annual cost would be £2200 to £4700 per 100,000, and based on an estimated uptake of 5.5% in year 5 (1.1 patient i.e. 1 patient) the annual cost per 100,000
population would be the same.

5. Health Economics
The SMC accepted the economic case for using paliperidone injection over risperidone injection on the basis that it would cost less to the health service as long as it was associated with a reduction in length of hospital stay of more than 0.6 days. According to an observational study evaluating the effect on hospitalisations administration of paliperidone palmitate reduced hospital bed days by around 16/patient/year.

6. Likely commissioning and funding pathway
It has been proposed for shared-care/transfer of care.

7. Suggested place in therapy
Paliperidone palmitate injection has been licensed for schizophrenia since April 2011 in the UK.

An orally administered antipsychotic regimen should be the preferred option as recommended by NICE. The choice of oral antipsychotic drug (first- or second-generation) should take into account the different risk profiles associated with individual drugs and potential impact on the patient. For patients that are felt to be at high risk of non-adherence to an oral regimen and for whom a first-generation depot agent is inappropriate, paliperidone palmitate appears to offer some practical advantages over the other three drugs. Paliperidone does not require dose supplementation during treatment initiation, there is some flexibility around dose administration schedules, an individualised approach to dosing is feasible, no post-injection monitoring is required and it is presented as a ready-to-use prefilled injection which does not require special storage conditions or reconstitution prior to administration.

Paliperidone palmitate long-acting injection has been compared with haloperidol decanoate injection in one small RCT which showed comparable efficacy for both drugs. Additionally, rates of discontinuation of study drug due to any cause or due to adverse effects were similar for both drugs, although patients on haloperidol decanoate experienced greater increases in BAS scores for akathisia compared to those on paliperidone palmitate. Additionally, although there were no statistically significant differences in changes for ratings of parkinsonism, fewer patients on paliperidone palmitate required the initiation of a medication to treat parkinsonism compared to those on haloperidol decanoate. Paliperidone palmitate did however cause weight gain whereas haloperidol decanoate was associated with weight loss.

Similar to the choice between oral first- and second-generation antipsychotics, it appears that the choice of long-acting injectable antipsychotics should account the different risk profiles associated with individual drugs and the potential impact on the patient.

Currently, it is unclear how clinicians choose between the various options available, and having a treatment pathway would be helpful given the large cost differential between the drugs.

References
1. NICE clinical guideline on the management of schizophrenia (CG 178) February 2014
   https://www.nice.org.uk/guidance/cg178
4. Paliperidon palmitate (XEPLION) SPC (date of revision = 3 December 2013)
   http://www.medicines.org.uk/emc/medicine/24403
5. Scottish Medicines Consortium summary on paliperidone palmitate (7 October 2011)
7. Scottish Medicines Consortium summary on aripiprazole prolonged release suspension for injection (Abilify Maintena®) (12 May 2014) 
8. All Wales Medicines Strategy Group summary on paliperidone palmitate (Xeplion®) 9 November 2012 http://www.awmsg.org/awmsgonline/app/appraisalinfo/1579
10. All Wales Medicines Strategy Group summary on olanzapine depot (ZypAdhera®) (17 November 2010) http://www.awmsg.org/awmsgonline/app/appraisalinfo/225
11. Olanzapine embonate (ZypAdhera®) SPC (Date of revision = 25 April 2014) http://www.medicines.org.uk/emc/medicine/21361
12. Risperidone long-acting injection SPC (Risperdal Consta®) (Date of revision = November 2013) http://www.medicines.org.uk/emc/medicine/9939
17. Mawdsley Prescribing Guidelines

Medline: paliperidone.ti,ab AND *SCHIZOPHRENIA/
Embase: *PALIPERIDONE/ AND *SCHIZOPHRENIA/ (restricted to intramuscular drug administration)

Written by Hina Radia, London Medicines Information Service, Guy’s Hospital, St. Thomas Street, London, SE1 9RT [hina.radia@gstt.nhs.uk]. Janssen-Cilag Ltd has had the opportunity to carry out a factual check on this review.