Northern Treatment Advisory Group

Paliperidone depot injection (Xeplion®) for schizophrenia

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September 2014

Summary

- Paliperidone is an atypical antipsychotic drug used in the treatment of schizophrenia. In April 2011, paliperidone plamitate a long-acting injectable (LAI) formulation of paliperidone was launched in the UK. Currently, the most widely used atypical antipsychotic depot drug in the UK is risperidone LAI, and paliperidone LAI is being targeted as a replacement for risperidone LAI within its licensed indication.

- Paliperidone LAI was shown to be non-inferior to risperidone LAI in two short-term studies which incorporated the licensed initiation dosing schedule. A third study conducted using a lower initiation dosing schedule (un-licensed) failed to demonstrate non-inferiority, which may be attributable to the dosing strategy employed. In a 33-week study, paliperidone LAI significantly delayed time to relapse compared with placebo, and efficacy was maintained for up to 52-weeks as assessed by improvements in mean PANSS scores. There are no data on the efficacy in prevention of relapse relative to an active comparator.

- The overall safety profile of paliperidone LAI appears comparable to the established safety profile of its related compounds, paliperidone and risperidone. There were no new safety signals from either short or long term phase III studies. In the pivotal comparative study with risperidone LAI, insomnia, injection site pain, and anxiety occurred at a ≥2% higher incidence in the paliperidone LAI group than in the risperidone LAI group.

- For patients switching from other LAI antipsychotics, where no initiation dosing regimen is required, the difference in acquisition cost between risperidone LAI and paliperidone LAI at the recommended maintenance dose of 75 mg monthly is around 2% (£45) more per year of treatment. It is unlikely that generic versions of risperidone LAI will be available as early as 2014 due to a combination of patents and complexities in the manufacturing process.

- Although overall net drug expenditure would increase in-line with the small increase in drug acquisition costs, overall savings in healthcare costs may result from the practical advantages of paliperidone LAI compared to risperidone LAI, such as a less frequent dosing schedule, no requirement for reconstitution, and no need for refrigeration, and no requirement for oral antipsychotic supplementation. However, some of these savings may be difficult realise in practice and may not translate in direct financial savings to the NHS commissioning organisation.

- The greatest scope for cost savings originates from the potentially reduced hospital in-patent care provided for dose initiation. It is estimated that a patient would have to be discharged one day earlier for paliperidone LAI to be less costly than risperidone LAI, in a hospital in-patent setting.

- Paliperidone LAI has been approved for use in Wales by the AWMSG and in Scotland by the SMC based upon clinical and economic evaluation vs. LAI.

Introduction and background

Schizophrenia is a major psychiatric disorder in which an individual's perception, thoughts, mood and behaviour are significantly altered. The symptoms of schizophrenia are often differentiated between positive symptoms, including hallucinations, delusions, and behavioural disturbances, and negative symptoms such as emotional apathy, social withdrawal and self-neglect. Each individual will have a unique combination of symptoms and experiences which often leads to other problems such as social exclusion, reduced opportunities to get back to work or study, and problems forming new relationships.[1,2]

Schizophrenia is a relatively common illness with an annual incidence of 15.2 per 100,000 people (range 4.4 to 33), and an estimated overall prevalence of 0.35% (range 0.2% to 0.59%).[2]

Antipsychotics are the mainstay of the treatment of schizophrenia. First-generation antipsychotics, whilst considered to be effective in the treatment of positive, psychotic symptoms, show little benefit in alleviating negative symptoms and the associated cognitive impairment. Second generation 'atypical' antipsychotics differ significantly in their pharmacological and clinical profiles and are generally considered to be effective against both the positive and negative symptoms of schizophrenia and with an superior safety profile with respect to extrapyramidal side effects.

NICE guidance recommends that a depot or long-acting injectable (LAI) antipsychotic medication should be offered 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.[1] Depot antipsychotics are administered by deep intramuscular injection, which are then slowly released from the injection site to give relatively stable drug levels over long periods allowing injections to be given every few weeks. Of the seven atypical antipsychotic drugs available in the UK, four are available in depot injection preparations; olanzapine, risperidone, paliperidone and most recently aripiprazole.

Paliperidone is an atypical antipsychotic, which acts mainly by blocking serotonergic 5-HT_2 and dopaminergic D_2 receptors. Paliperidone is the principal active metabolite of risperidone. Oral paliperidone has been licensed for the treatment of schizophrenia since 2007. In April 2011, paliperidone plamitate a long-acting injectable formulation of paliperidone (Xeplion®, Janssen-Cilag) was launched in the UK.[3] It is licensed for the maintenance treatment of adult patients with schizophrenia stabilised with risperidone or paliperidone. In selected adult patients with schizophrenia and previous responsiveness to oral paliperidone or risperidone, paliperidone 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 LAI requires administration only once monthly. Recommended initiation of paliperidone is with a dose of 150 mg on treatment day 1 and 100 mg one week later (day 8). 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.[3]

Currently, the most widely used atypical antipsychotic depot drug in the UK is risperidone. In August 2011, the North East Treatment Advisory Group considered the use of paliperidone LAI as an alternative to risperidone LAI for the treatment of schizophrenia.[4] The group did not recommend paliperidone LAI within its licensed indication as an alternative to risperidone LAI on the grounds of uncertainty regarding clinical efficacy and that cost-effectiveness had not been adequately demonstrated.[5] In March 2012, NETAG considered an appeal of this recommendation and the group did not change their previous recommendation.[5]

Paliperidone LAI has been approved for use in Wales by the AWMSG and in Scotland by the SMC.[6,7]

Clinical evidence

The clinical efficacy of paliperidone LAI in the treatment of schizophrenia has been assessed in several published short and long-term studies. Short-term efficacy was studied in four placebo-controlled, dose-finding studies (not discussed here), and two flexible-dose, non-inferiority studies (vs. risperidone LAI). Maintenance of effect was studied in one placebo-controlled, flexible-dose, relapse prevention study and one flexible-dose, non-inferiority study (vs. risperidone LAI).

The main inclusion criteria were male or female, aged 18 years or older, with an established diagnosis of schizophrenia as defined by DSM-IV for ≥ one year and a PANSS total score at screening of between 60 and 120 inclusive. Exclusion criteria included any primary active DSM-IV diagnosis other than schizophrenia, patients treated with LAI antipsychotics, electroconvulsive therapy (ECT), MAO-inhibitors, any other antidepressants (unless on a stable dose for at least 30 days), oral antipsychotics or mood stabilizers within different specified time limits, and a significant risk of suicidal or violent behaviour.

Non-inferiority vs. risperidone LAI

Three phase III studies have compared the efficacy of paliperidone LAI (PLAI) with risperidone LAI (RLAI). Only two of these studies (PSY-3006 and PSY-3008) incorporated the licensed initiation dosing schedule for PLAI.

PSY-3006 [8]

This 13-week randomised double-blind study (n=1,220) was to designed to assess non-inferiority of PLAI vs. RLAI for the treatment of schizophrenia. Patients in the PLAI group received deltoid injections of 150 mg on day 1 and 100 mg on day 8, and once monthly flexible dosing on day 36 (50 or 100 mg) and day 64 ((50, 100, or 150 mg). The RLAI group received gluteal injections of on days 8 and 22 (25 mg), days

36 and 50 (25 or 37.5 mg) and on days 64 and 78 (25, 37.5 or 50 mg) in addition to oral risperidone (1 – 6 mg on days 1 to 28). The primary outcome was the change in Positive and Negative Syndrome Scale (PANSS) score from baseline to the end of the double-blind treatment phase. The PANSS score is a widely used and validated tool for assessing the efficacy of treatments for schizophrenia composed of five factors to evaluate positive symptoms, negative symptoms, disorganized thoughts, uncontrolled hostility/excitement, and anxiety/depression (appendix a). It has a range of 30 (absent symptoms) to 210 (maximal symptoms in every category).[9]

In the per-protocol population (n=766) mean change in PANSS scores was -18.6 and -17.9 in the PLAI and RLAI groups, respectively. The least-square mean difference in PANSS scores of 0.4 (95% CI: -1.62 to 2.38). The lower limit of the 95% CI was below the pre-specified margin of -5.0 and therefore non-inferiority of PLAI to RLAI was demonstrated. Data from the intention-to-treat (ITT) population (n=913) were consistent with this finding.

PSY-3008 [10]

This 13-week open label, parallel group study (n=1,220) conducted in an exclusively Chinese population was designed to assess non-inferiority of PLAI vs. RLAI for the treatment of schizophrenia. Dosing and the efficacy outcomes were as described for PSY-3306 above.

In the per-protocol population (n=413) mean change in PANSS scores was -23.6 and -26.9 in the PLAI and RLAI groups, respectively. The least-square mean difference in PANSS scores was -2.3 (95% CI: -5.20 to 0.63). The lower limit of the 95% CI was below the pre-specified margin of -5.5 and therefore non-inferiority of PLAI to RLAI was demonstrated. However, when analysis was conducted with the ITT population (n=446) non-inferiority was not demonstrated.

PSY-3002 [11]

This 53-week randomised, double-blind, parallel group study (n=749) was to designed to assess non-inferiority of PLAI vs. RLAI for the maintenance treatment of schizophrenia. This was the first PIII trial to be conducted an used an initiation dosing schedule of 50 mg on days 1 and 8, which was lower than the licensed dosing schedule of 150 mg on day 1 and 100 mg on day 8 used in the later PIII trails, including PSY-3006 and PSY-3008. The primary outcome was the change in PANSS score from baseline to the end of the double-blind treatment phase.

In the per-protocol population (n=570) mean change in PANSS scores was -11.6 and -14.4 in the PLAI and RLAI groups, respectively. The least-square mean difference in PANSS scores was -2.6 (95% CI: -5.84 to 0.61). The lower limit of the 95% CI was above the pre-specified margin of -5.0 and therefore PLAI failed to demonstrate non-inferior to RLAI. Data from the intention-to-treat (ITT) population (n=674) were consistent with this finding.

Maintenance treatment - relapse prevention

PSY-3001 [12,13]

This 33-week randomised, double-blind, placebo-controlled study (n=849) was designed to assess the efficiency of PLAI in preventing recurrence in subjects with schizophrenia.[12] The study consisted of a screening phase, a nine-week open-label transition phase; a 24-week open-label maintenance phase; a variable duration, event driven double-blind phase in which 'stabilised' patients were randomised to continue with paliperidone or placebo, and an optional 52 week open label extension. The inclusion criteria were similar to the other PIII studies, with the exception that this study also included stable patients. This study used a lower range of paliperidone doses (25 mg to 100 mg monthly) compared with the licensed dose range. The primary outcome was the time to first relapse during the double-blind phase.

The study was terminated prematurely when the pre-planned interim analysis found a significant benefit for paliperidone compared to placebo ($p<0.0001$). In the interim analysis ITT population (n=312) relapse event rates were 10% in the paliperidone group vs. 34% in the placebo group. This was confirmed in the final analysis (ITT, n=408) based on all data from start of the study through to completion of the double-blind phase (18% vs. 48%, respectively, $p<0.0001$). Since the study was terminated early, the preliminary analysis was considered the primary analysis.

PSY-3001 extension [13]

In a 52-week open label extension of the double-blind relapse prevention study described above (PSY-3001)[12], all patients (n=388) received a starting dose of 50 mg followed by once-monthly flexible dosing (25, 50, 75, or 100 mg).[13] Due to blinding constraints supplementation with oral paliperidone ER (3-12mg/day) was allowed during the first 8 weeks of this study for all patients. The primary outcome was the change in PANSS score from open label extension baseline to study end.

Of the 388 enrolled, 288 (74%) completed the study. Patients who had previously received placebo during the double blind phase showed the greatest improvements in mean PANSS score (mean -8.4, SD 19.43). Reductions in mean PANSS score were also seen in the group who had previously been on active treatment and this remained at the reduced level. Patients transferred from the transition phase whilst taking open-label paliperidone exhibited a similar stable maintenance of mean PANSS scores as those who had previously been on active treatment.

Effect on hospitalisation

Interim result of an observational study (n=200) assessing the effect of paliperidone LAI treatment on hospitalisation showed that after one year, 65% of patients were still receiving paliperidone LAI treatment.[14] The mean number of admissions reduced from 0.69 per patient year in the three years before initiation to 0.49 per patient in the year following initiation/discharge on paliperidone LAI. The mean number of bed days fell from 38.78 to 23.09 over the corresponding period ($p=0.0001$).

Safety

The overall safety profile of paliperidone LAI appears comparable to the established safety profile of its related compounds, paliperidone and risperidone. There were no new safety signals from either short or long term phase III studies. The most common adverse drug reactions listed in the Summary of Product Characteristics are insomnia, headache, anxiety, upper respiratory tract infection, injection site reactions, Parkinsonism, weight gain, akathisia (dose related), agitation, sedation/somnolence (dose related), nausea, constipation, dizziness, musculoskeletal pain, tachycardia, tremor, abdominal pain, vomiting, diarrhoea, fatigue and dystinia.[3]

In the pivotal comparative study with risperidone LAI (PSY-3006) adverse events (AEs) occurred in 57.9% of patients in the paliperidone palmitate LAI group vs. 52.8% with risperidone LAI.[8] The frequency of AEs leading to discontinuation was low in both treatment groups (3% vs. 1.6%). Insomnia (9.4% to 6.7%), injection site pain (5.1% vs. 0.8%), and anxiety (4.3% vs. 2.1%) occurred at a ≥2% higher incidence in the paliperidone LAI group than in the risperidone LAI group. Only constipation (0.8% vs. 3.1%) occurred at ≥2% higher incidence in the risperidone LAI group than the paliperidone LAI group. None of the injection site-related AEs was serious or led to study discontinuation, and the majority were mild to moderate in severity. The incidence of extrapyramidal related AEs was similar for both treatment groups, and none were serious. Over the 13 week study period the mean increase on body weight at endpoint were similar between treatment groups (1.1 kg vs. 1.0 kg). Serious AEs were reported in 6.8% vs. 4.8%, respectively. The most common SAEs were worsening schizophrenia (2.5% vs. 2.1%) and psychiatric disorders (2.1% vs. 1.2%).

In study PSY-3008, the incidence and nature of AEs in the open-label were generally comparable to that in study PSY-3006 and was similar between paliperidone LAI and risperidone LAI (73% vs. 75%).[10]

In the 33-week study PSY-3001, subjects who continued to receive paliperidone LAI following a period of stabilization appeared to have a lower incidence of newly occurring AEs after stabilization compared to subjects for who treatment is newly initiated.[12] Overall, AEs were reported at similar rates for paliperidone LAI and placebo (44% versus. 45%) during the double-blind phase. The majority of patients reported an absence of injection site pain (81% vs. 82%, respectively). Weight increase (7% vs. 1%), and blood glucose increase (3% vs. 1%) occurred more frequently (≥2% difference) in the paliperidone LAI group than the placebo group, respectively. SAEs were mostly related to psychiatric disorder events which occurred in 11% of patients in the transition and maintenance phase, and 4% and 12%, for paliperidone LAI and placebo, respectively in the double-blind phase.

In the long term open-label extension phase (52 weeks), the pattern of newly occurring AEs and SAEs was consistent with that in the double-blind phase.[13] During this phase, AEs were reported for 56% of subjects; the nature and incidence of which were generally consistent with those reported during the earlier phases of the study.

Cost analysis

LAI antipsychotics are typically used for maintenance therapy especially when compliance with oral treatment is unreliable. Paliperidone palmitate (Xeplion®) is available in four different strengths with each supplied as a pre-filled syringe.[3] The time-independent equivalent dose of paliperidone to risperidone injection as recommended in the paliperidone SPC is in the ratio of 2:1. However, risperidone injection is available only at the licensed maximum dose of 50 mg therefore a greater licensed dose range is available with paliperidone than with risperidone injection (table 1). Anecdotally, risperidone injection is used at higher off-license doses of up to 75 mg (e.g. 2 x 37.5 mg).

When a patient is commenced on treatment with risperidone LAI it is recommended that they receive supplemental oral antipsychotic medication, most logically risperidone, for three weeks to maintain adequate plasma levels. The cost of three weeks treatment with risperidone will depend on the dose, but a typical dose of 4 mg daily would cost about £1 and therefore this cost impact is considered negligible and is not further included in analyses. There is no requirement for oral antipsychotic supplementation when commencing treatment with paliperidone LAI; however, a one-week initiation dosing regimen (150 mg on day 1 and 100 mg on day 8) is required to attain rapid therapeutic concentrations. When switching patients from risperidone LAI the one-week initiation dosing regimen is not required. As these are essentially one-off costs associated with initiation of therapy they are not included in this cost analysis which focuses on maintenance treatment where it is expected the majority of treatment costs will arise. Table 1 demonstrates the comparative annual drug acquisition cost per patient for paliperidone LAI versus risperidone LAI, using the dose equivalents as stipulated.

Table 1. Comparative annual drug acquisition costs per patient for paliperidone LAI vs. risperidone LAI (dm+d August 2014).

Paliperidone			**Risperidone**			**Difference**
Dose (monthly)	Cost per dose	Cost per year (12 doses)	Dose (fortnightly)	Cost per dose	Cost per year (26 doses)	PLAI minus RLAI
50 mg	£183.92	£2,207	25 mg	£79.69	£2,072	£135 (+5%)
75 mg	£244.90	£2,939	37.5 mg	£111.32	£2,894	£44 (+2%)
100 mg	£314.07	£3,769	50 mg	£142.76	£3,712	£57 (+2%)
150 mg	£392.59	£4,711	2 x 37.5 mg *	£222.64	£5,788	£1,077 (-23%)

* Unlicensed dose

At the recommended maintenance dose of 75 mg monthly, paliperidone LAI costs around 2% (£45) more per year of treatment compared to the equivalent dose of risperidone LAI. Patients prescribed an unlicensed 75 mg dose of risperidone LAI could switch to 150 mg paliperidone LAI which is 23% (£1,077) less costly. However this simple and conservative analysis excludes important differences in the overall treatment costs arising from the practical advantages of paliperidone LAI compared

to risperidone LAI, such as a less frequent dosing schedule, no requirement for reconstitution, and no need for refrigeration (table 2).

A key benefit of paliperidone LAI vs. risperidone LAI is a substantially reduced administration frequency. Not only is this likely to be more convenient for patients but will be associated with reduced healthcare utilisation. However, where administration is performed by a practice or district nurse (i.e. non mental health nurse) there will be no direct financial saving to the NHS commissioning organisation. The majority of patients on a depot antipsychotic injections are likely to be administered the drug by a trained mental health nurse either in an outpatient or in community setting. In addition, each appointment may require less time as paliperidone LAI is supplied in pre-filled syringes so there is no need for reconstitution of dilution, whereas risperidone LAI requires diligent and time-consuming preparation. Unlike paliperidone LAI which can be stored at room temperature, risperidone LAI requires specific storage conditions, in particular refrigeration. On occasion where these conditions cannot be maintained the product is no longer suitable for use and must be disposed.

Although overall net drug expenditure is anticipated to increase in-line with the small increase in drug acquisition costs, overall savings in healthcare costs may result from reduced nursing appointments for administration and reduced wastage due to reconstitution problems and cold chain failures. However, these savings my be difficult for NHS commissioning organisations to realise and may be difficult to recognise as direct savings by provider organisations. The largest scope for cost savings originates from the potentially reduced hospital in-patent care provided for dose initiation.

The SMC accepted the use of paliperidone LAI based upon a cost-minimisation analysis vs. LAI.[6] The analysis compared the costs associated with the initiation and maintenance treatment of schizophrenia over the first year of treatment with paliperidone LAI and risperidone LAI. The analysis incorporated drug acquisition costs, cost of wastage, oral antipsychotic drug supplementation cost, administration (in the community) and hospitalisation for treatment initiation. Evidence of comparative efficacy was taken from the short-term non-inferiority study PSY-3006.[8] Resource use was estimated through the use of an expert group involved in the routine care of schizophrenia patients, and included; hospital costs £401; cost of administration in the community £41.42; cost of wastage £26.27, cost of oral supplementation £1.34, and drug acquisition costs as presented in table 1. A one-year time horizon was selected for the base-case, with a split by initiation from previous treatment of 71% for oral antipsychotics and 29% from other LAIs.

The results showed that when initiated in the hospital setting the total costs in year one were £11,063 per patient treated with paliperidone LAI compared with £14,554 per patient treated with risperidone LAI, which equates to a cost saving of 31.5% (£3,491) per patient year with paliperidone LAI treatment. The duration of inpatient stay for patients initiating treatment in hospital was a key driver in the differences in total costs of treatment, and is based upon expert opinion. It was estimated that paliperidone LAI treatment would shorten the length of stay in hospital by around one third, resulting in discharge after 18.7 days, compared with 28 days for risperidone LAI. However, where an equal length of hospital stay is assumed for patients initiated in a hospital setting the cost for paliperidone LAI is £14,792 per

year compared with £14,554 for risperidone LAI, which equates to a small cost increase associated with paliperidone LAI treatment of 1.6% (£238). A subsequent threshold analysis showed that providing the reduction in hospital length of stay for those patients prescribed paliperidone LAI was greater than 0.6 days then paliperidone LAI would be preferred on cost minimisation grounds.

When treatment was initiated in the community setting, the total costs in year one were £3,791 per patient treated with paliperidone LAI compared with £3,914 per patient treated with risperidone LAI, which equates to a small cost saving of 31.5% (£122) per patient year with paliperidone LAI treatment. A key driver in this result was the assumption that 71% of patients were switched from oral antipsychotics and 29% from other LAIs. However, it should be noted that other potential benefits of treatment such as improved compliance and service implications have not been accounted for in this model. Furthermore, this analysis was undertaken from the perspective of NHS Scotland, and as such may not be fully representative of practices across England.

The potential cost impact of switching patients form risperidone LAI to paliperidone LAI is highly sensitive to the price of risperidone LAI. The intellectual property rights to Risperidone LAI are protected by more than one patent. The first patent is due to expire in 2014, whilst others do not expire until 2017. No Clinical Trial Applications or Marketing Authorisation Applications for a generic version of risperidone appear to be reported on the European Medicines Agency (EMA) website. Therefore, it is very unlikely that generic versions of risperidone LAI will become available as early as 2014. As both paliperidone LAI and risperidone LAI are marketed by Janssen-Cilag, the prices of the proprietary products are unlikely to change in the immediate future. If generic versions of risperidone LAI do become available they are likely to substantially undercut the current price of the proprietary product. Any such reduction in the price of risperidone LAI compared to paliperidone LAI would significantly affect the overall cost impact in favour of risperidone LAI on cost minimisation grounds.

Patient impact

Paliperidone LAI is administered monthly compared to every two weeks for risperidone LAI, which would reduce visits to secondary care, and potentially fewer visits from community psychiatric nurses if required.

An extended dose interval (+/- seven days from usual date of administration) offers the potential to support patient adherence and could therefore assure compliance when treating patients in the community setting. Flexibility allows care closer to home and in the community

The overall safety profile of paliperidone LAI appears comparable to the established safety profile of its related compounds, paliperidone and risperidone, with treatment continuation rates as high as 65% one year after initiation.

Paliperidone LAI requires a smaller needle size compared to risperidone LAI, and can be administered into either the deltoid or gluteal muscle.

Points to consider

Paliperidone palmitate is one four antipsychotics available in depot injection preparations. Currently, the most widely used atypical antipsychotic depot drug in the UK is risperidone LAI, and paliperidone LAI is being targeted as a replacement for risperidone LAI within its licensed indication. In this respect, paliperidone LAI provides several practical advantages over risperidone LAI: substantially reduced administration frequency (monthly vs. every two weeks); easier dose initiation without the need for oral antipsychotic supplementation; no special storage conditions; no requirement for complex dose preparation, and a greater licensed dose range.

Paliperidone LAI was shown to be non-inferior to risperidone LAI in two short-term studies which incorporated the licensed initiation dosing schedule. A third study conducted using a lower initiation dosing schedule (un-licensed) failed to demonstrate non-inferiority, which may be attributable to the dosing strategy employed. Apart from the dose-finding studies this was the only clinical evidence not considered in the either NETAG appraisal. In a 33-week study, paliperidone LAI significantly delayed time to relapse compared with placebo, and efficacy was maintained for up to 52-weeks as assessed by improvements in mean PANSS scores. There are no data on the efficacy in prevention of relapse relative to an active comparator.

The overall safety profile of paliperidone LAI appears comparable to the established safety profile of its related compounds, paliperidone and risperidone. There were no new safety signals from either short or long term phase III studies.

The annual acquisition costs are similar for approximately equivalent doses of paliperidone LAI and risperidone LAI. The total cost of paliperidone LAI is more in the first year due to the one-week initiation dosing regimen. However, for patients switching from other LAI antipsychotics, where no initiation dosing regimen is required, the difference in cost between risperidone LAI and paliperidone LAI at the recommended maintenance dose of 75 mg monthly, is only around 2%. It is unlikely that generic versions of risperidone LAI will be available as early as 2014 due to a combination of patents and complexities in the manufacturing process.

Although overall net drug expenditure would increase in-line with the small increase in drug acquisition costs, overall savings in healthcare costs may result from reduced nursing appointments for administration and reduced wastage due to reconstitution problems and cold chain failures. However, these savings my be difficult for NHS commissioning organisations to realise and may be difficult to recognise as direct savings by provider organisations. The largest scope for cost savings originates from the potentially reduced hospital in-patent care provided for dose initiation. In addition, an extended dose interval may support patient adherence and could therefore assure compliance when treating patients in the community setting.

Paliperidone LAI is approved for use by the SMC and AWMSG following economic evaluation.

Author's declaration: The author has no relevant interests to declare.

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Table 2. Key differences between paliperidone LAI and risperidone LAI.

	Paliperidone LAI	Risperidone LAI
Licensed indication	Maintenance treatment of adult patients with schizophrenia stabilised with risperidone or paliperidone. In selected adult patients with schizophrenia and previous responsiveness to oral paliperidone or risperidone, paliperidone may be used without prior stabilisation with oral treatment if psychotic symptoms are mild to moderate and a long-acting injectable treatment is needed	Maintenance treatment of schizophrenia in patients currently stabilised with oral antipsychotics.
Presentation	Pre-filled syringe	Vial and solvent for reconstitution
Storage	No special conditions	Refrigeration
Preparation	Must be removed from fridge ~ 30 minutes before administration. Recommended 18-step procedure.	No special conditions
Dose interval	Monthly (12 injections per annum).	Two weeks (26 injections per annum).
Licensed dose range	Four doses: (50, 75, 100 and 150 mg)	Three doses: (25, 37. 5, and 50 mg)
Initiation of treatment	No requirement for initial oral antipsychotic supplementation. By deep intramuscular, 150 mg on day 1, then 100 mg on day 8, then adjusted at intervals of 4 weeks according to response; Note: Following the second dose, monthly maintenance doses can be administered into either the deltoid or gluteal muscle	For most patients the recommended dose is 25 mg every two weeks by deep intramuscular deltoid or gluteal injection using the appropriate safety needle. Sufficient antipsychotic coverage with oral risperidone or the previous antipsychotic should be ensured during the three-week lag period following the first injection It should not be used in acute exacerbations of schizophrenia without ensuring sufficient antipsychotic coverage with oral risperidone or the previous antipsychotic during the three-week lag period following the first injection
Maintenance dose	Recommended maintenance dose 75 mg (range 25–150 mg) monthly (can be given up to 7 days before or after the treatment due date)	25 to 50 mg every two weeks No specific manufacturer recommendation for missed doses.

Appendix A:

Positive and Negative Syndrome Scale (PANSS)

30-item scale with 3 domains. Each item is scored from 1 (absent) to 7 (extreme), resulting in a minimum score of 30 and a maximum of 210.

- Positive scale (7 items, min. score 7, max. score 49)
  - Delusions
  - Conceptual disorganisation
  - Hallucinatory behaviour
  - Excitement
  - Grandiosity
  - Suspiciousness
  - Hostility

- Negative scale (7 items, min. score 7, max. score 49)
  - Blunted affect
  - Emotional withdrawal
  - Poor rapport
  - Passive-apathetic social withdrawal
  - Difficulty in abstract thinking
  - Lack of spontaneity and flow of conversation
  - Stereotyped thinking

- General psychopathology scale (16 items, min. score 16, max. score 112)
  - Somatic concern
  - Anxiety
  - Guilt feelings
  - Tension
  - Mannerisms and posturing
  - Depression
  - Motor retardation
  - Uncooperativeness
  - Unusual thought content
  - Disorientation
  - Poor attention
  - Lack of judgement and insight
  - Disturbance of volition
  - Poor impulse control
  - Preoccupation
  - Active social avoidance