Paliperidone Palmitate (TREVICTA) Three Monthly Injection for Schizophrenia

September 2016

Summary

Background and licensed indication
TREVICTA is a 3-monthly injection of paliperidone palmitate for the maintenance treatment of adults with schizophrenia who are clinically stable on 1-monthly paliperidone palmitate (Xeplion) 1,2

Dosing
3-monthly paliperidone palmitate may be started after 4 or more 1-monthly paliperidone palmitate injections, on the next scheduled date for a dose of 1-monthly paliperidone palmitate. The dose change from 1-monthly paliperidone palmitate depot (range 50mg, 75mg, 100mg, 150mg) is multiplied by 3.5 to convert to 3-monthly paliperidone palmitate injection (175mg, 263mg, 350mg and 525mg respectively) 3.

Alternatives
In the treatment for schizophrenia, alternative depot formulations include first generation antipsychotic (zuclopenthixol, haloperidol, flupenthixol, and fluphenazine) and second generation antipsychotics (monthly aripiprazole, monthly paliperidone, fortnightly risperidone).

NICE
The National Institute for health and Care Excellence (NICE) schizophrenia guidelines recommend offering long acting depot antipsychotics treatment to people with psychosis or schizophrenia who prefer depots and to those whose treatment plan prioritises clinical treatment as a result of non-adherence. NICE recommends prior initiating an injectable antipsychotic patient’s preferences and attitudes towards the mode of administration and organisational procedures (e.g. home visits, location of clinics) are considered 4.

Clinical studies
Two phase III trials.

Safety
No major safety concerns, 3-monthly paliperidone palmitate has a similar safety profile to 1-monthly paliperidone palmitate injection, although long term studies are not currently available.

Convenience
The 3-monthly paliperidone palmitate depot offers a longer dosing interval, requiring only 4 administrations a year. This potentially offers a wider administration time window that may allow healthcare professionals to intervene if doses have been missed, and may be preferable for patients who dislike injections 5. However, tolerability and therapeutic effect will need to be established prior initiation. Patients may be administered 3-monthly paliperidone palmitate injection 2 weeks before or after next due date 1.

3-monthly paliperidone palmitate injections are available in pre-filled syringes and may be administered via gluteal or deltoid muscles.

At administration it is essential that the syringe if shaken vigorously for at least 15 seconds ensuring a homogenous suspension before use. It must be administered within in 5 minutes of shaking. Failure to shake sufficiently will result in insufficient dosing.

Risk assessment
Low risk, although training would be required to ensure injection is given appropriately.

Budget impact
High cost atypical antipsychotic injection, similar cost price to 1-monthly paliperidone injection. The cost per person per year would be £2,207.04- £4,711.08 excluding VAT.

Funding
Trevicta is currently not in the North West London integrated formulary (application not yet made).

Suggested place in therapy
In patients with chronic schizophrenia who have previously been effectively maintained and stable on monthly paliperidone palmitate injection for at least 6 months.
1. Background and introduction

It is estimated that there are 24 million people with schizophrenia worldwide. Over a lifetime, about 1% of the population will develop psychosis and schizophrenia. Schizophrenia is a chronic disease and is one of the leading causes of disability in adults. People with schizophrenia tend to have additional health risk factors, including substance abuse, alcohol abuse, and smoking. 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. Psychosis and schizophrenia are associated with considerable stigma, fear and limited public understanding. The first few years after onset can be particularly upsetting and chaotic, and there is a higher risk of suicide. Once an acute episode is over, there are often other problems such as social exclusion, with reduced opportunities to get back to work or study, and problems forming new relationships.

Non-adherence to oral antipsychotic treatments is common among patients with schizophrenia and this can result to significant impact to the patient, family and healthcare resources. Long acting antipsychotic depot injections can help to address non-adherence to oral medication, ensure sustained plasma levels and help with reliability with monitoring.

NICE Schizophrenia guidelines recommend offering long acting depot antipsychotics treatment to people with psychosis or schizophrenia who prefer depots and to those whose treatment plan prioritises clinical treatment as a result of non-adherence. NICE recommends prior initiating an injectable antipsychotic patient’s preferences and attitudes towards the mode of administration and organisational procedures (e.g. home visits, location of clinics) are considered.

Paliperidone 3-monthly injection (Trevicta®) contains the same active ingredient as the paliperidone 1-monthly injection (Xeplion®). The 3-monthly paliperidone depot is licensed for maintenance treatment in adults diagnosed with schizophrenia who have been stabilised on 1-monthly paliperidone depot for at least 4 months. Paliperidone works as an antagonist at serotonin 5-HT2A and dopamine D2 receptors. Paliperidone also bocks alpha 1-adrenergic receptors and slightly less histaminergic and alpha 2-adrenergic receptors.

Paliperidone 3-monthly depot has extremely low water solubility, it dissolves slowly after an intramuscular injection before being hydrolysed to paliperidone and absorbed into the systemic circulation. The active substance is released from day 1 and can last as long as 18 months.

2. Proposed place in therapy

The trusts formulary recommends that when choosing a depot antipsychotic prescribers should first consider using a first generation antipsychotic depot due to the significant financial implications of the second generation antipsychotic depots. Paliperidone palmitate 1-monthly depot can cost up to £5000/year compared to the cost of a first generation antipsychotic depot of £100 -200/year. First generation depots include flupentixol decanoate, fluphenazine decanoate, haloperidol decanoate and zuclopenthixol decanoate. Paliperidone 1-monthly depot has not been demonstrated to show greater efficacy over other first generation antipsychotics.

To initially prescribe 1-monthly paliperidone palmitate injection in the trust, tolerance and response to oral paliperidone should be established, then a consultant must complete an initiation form to acknowledge the cost.

The license for paliperidone palmitate 3-monthly states that it can be used after 4 or more injections of 1-monthly paliperidone palmitate injections. However it is recommended that CNWL patients should not be started on 3-monthly paliperidone palmitate injections unless they have been maintained and stable on 1-monthly paliperidone palmitate injections for 6 months. This is to allow clinicians to assess response and tolerability. The response should be assessed before switching as dose adjustments can only be made every 3 months, and the patient’s response may not be apparent for several months. As it has a slow release profile, it is not proposed for acutely unwell patients or those transitioning from oral or other long acting antipsychotics.

The tolerability should be assessed as once steady state is achieved, the paliperidone plasma levels can last for an average of 395 days from the last 3 monthly paliperidone palmitate injection. It is therefore essential to assess tolerability to reduce risk of adverse effects before switching to the 3-monthly paliperidone palmitate injections. There is no specific antidote to paliperidone supportive measures are recommended if adverse effects are noted theaerafter.
3. Evidence selected for inclusion

i. European commission approved the use of 3-monthly paliperidone palmitate in 2014 available in the European Union for the maintenance for schizophrenia in adult patients stabilised on the monthly formulation. It was approved on the basis of two Phase III studies. The first study was a randomised study looking at relapse prevention (Berwaerts A et al.) and the second compared the efficacy of 1-monthly paliperidone to the 3-monthly formulations (Savitz J et al.). A practical guide for dosing and switching from paliperidone 1-monthly formulation to the 3-monthly formulation is also available.

ii. Berwaerts J et al. 2015. This was a multicentre double-blind, placebo-controlled, relapse prevention study designed to evaluate the efficacy and safety of the 3-monthly paliperidone palmitate depot versus placebo in delaying time to relapse of schizophrenia symptoms in patients previously treated with 1-monthly paliperidone palmitate for at least 4 months.

The study enrolled 602 patients aged between 18-70 years, with diagnosis of schizophrenia for at least 1 year, whose condition was stable for at least 3 months prior and those with a Positive and Negative Syndrome Scale (PANSS) total score lower than 120 at screening and baseline. All patients received flexible doses (from day 36: 50mg -150mg) of 1-monthly paliperidone palmitate depot for 120 days, after which they were randomised to receive the equivalent 3-monthly paliperidone palmitate or placebo.

The primary efficacy outcome was a reduction in relapse, in the 3-monthly paliperidone palmitate group there was reduction in relapse compared to placebo, 23% relapsed in placebo group compared to 7% of 3-monthly placebo group (hazard ratio =3.45; 95% CI,1.73 -6.88; p <0.001). In the final analysis double-blind phase, 29% of patients in placebo group relapsed compared to 9% of treatment group (hazard ratio =3.81; 95% CI, 2.08 -6.99; p <0.001). The median time to relapse was 274 and 395 days in the interim and double-blind phase respectively for placebo group, but the trial was unable to estimate the time for 3-monthly paliperidone palmitate group.

The baseline total PANSS score was similar in the double blind phase for both the placebo and treatment groups, with a significant difference (p<0.005) in mean change from baseline between the group receiving 3-monthly paliperidone palmitate and placebo groups.

This study was conducted over a year, where the 3-monthly paliperidone palmitate steady state levels were found to be consistent during maintenance phase, and similar to the corresponding 1-monthly paliperidone palmitate doses. The tolerability and effectiveness was found to be similar to previous trials with monthly paliperidone palmitate and no new safety concerns were raised.

iii. Savitz A et al. 2016. This was a multicentre, randomised double-blind study comparing the efficacy and safety of 3-monthly to 1-monthly paliperidone palmitate formulations. Overall 1429 patients were enrolled in the study. Patients with a diagnosis of schizophrenia, aged between 18-70 years, with a total PANSS score between 70-120 at screening and baseline, and with worsening symptoms were included.

All patients received 1-monthly paliperidone palmitate for the first 17 weeks, after which a 3.5 fold fixed dose was given in the 3-monthly arm, with placebo injections between doses.

At end point, the percentage of patients who remained relapse free was similar in both treatment groups. The duration of most recent hospital stay was longer in 3-monthly group compared (328.58 days) to 1-monthly group (88.5days), however enrolment criteria included those with worsening of symptoms, 39% of enrolled patients had not been hospitalised in the previous 24months compared to 10% in the non-inferiority study between 1-monthly paliperidone palmitate versus risperidone Consta.
The plasma concentrations for corresponding treatments were similar after the first 4 month treatment phase to end of study. However independent of doses, the pre-dose plasma concentrations following the 3-monthly Paliperidone were 21% lower than the concentrations following 1-monthly Paliperidone whilst the mean peak-trough ratios were higher after administration of Paliperidone 3 monthly (range 1.86 -2.54) compared to 1-monthly paliperidone administration (range 1.30 -1.63).

The safety profile during the double blind phase was similar between the two groups, 5% and 7% experienced treatment emergent adverse events with 3-Monthly Paliperidone Palmitate and 1-monthly paliperidone palmitate respectively. Most commonly associated with worsening of psychiatric illness; others included aggression, somnolence, sedation, prolactin increase, weight gain, QT prolongation. and orthostatic hypotension. Diabetes mellitus and hyperglycaemia reported at a lower frequency in the 3-monthly paliperidone palmitate group (2.6%) than the 1-monthly paliperidone palmitate group (4.9%)

The 3-monthly paliperidone palmitate arm was found to be non-inferior to 1-monthly paliperidone palmitate arm during the double blind phase, with similar relapse rate 8% and 9% respectively and with similar PANSS total score improvement from baseline to endpoint. Over 50% of patients in both groups showed symptomatic remission for last 6 months of study.

iv. Srihari et al. 2015

This paper summarises the practical guidance for dosing and switching from 1-monthly paliperidone palmitate to the 3-monthly formulation in patients with schizophrenia. Paliperidone palmitate 3-monthly injection is an insoluble ester prodrug of paliperidone; it has been developed via nanocrystal technology to give a suspension in an aqueous formulation similar to paliperidone 1-monthly injection (Xeplion). There is an additional requirement to vigorously shake paliperidone palmitate for 15 seconds to ensure a homogenous suspension (compared to 10 seconds for paliperidone 1-monthly injection). The apparent half-life of paliperidone 3-monthly injection ranges from 84-95 days following deltoid administration and 118-139 days following gluteal injection. Paliperidone 3-monthly contains the same active substance and excipients as paliperidone 1-monthly, (accept the removal of disodium hydrogen phosphate). The license states that treatment with 1-monthly paliperidone palmitate is required for a minimum of 4 doses prior initiation of 3-monthly paliperidone, this is to allow paliperidone levels to reach near steady state levels, and also allows time for clinicians to assess the tolerance and dose requirements for individual patients.

4. Critical evaluation

- Clinical application

There are currently limited studies looking into long term safety and efficacy of paliperidone 3-monthly, both Phase III studies lasted about year. Paliperidone palmitate 3-monthly injection is a new formulation. The only pharmaceutical difference between the 1-monthly and 3-monthly paliperidone palmitate formulations are the increased particle size, producing an extended duration of action to allow a prolonged dosing interval 11.

The site of injection is an important factor as pharmacokinetics of the 3-monthly paliperidone palmitate depot was 27% higher in the deltoid region than the gluteal route with no difference with AUC between injection sites5,11. It has been suggested once paliperidone plasma concentrations reach steady state, the differences at the site of administration has no clinical significance11. Metabolism and elimination data was given from oral paliperidone studies5

- Safety

4.2.1. Key adverse events

No further adverse effects have been noted paliperidone 3-monthly compared to the paliperidone palmitate 1-monthly injection, refer to SPC for detailed information5.
4.2.2. Risk assessment
A risk management plan has been completed by European Medicines Agency (EMA). There is limited information on the use of 3-monthly paliperidone injections in patients who have severe kidney disease that requires dialysis, in pregnant or breastfeeding women. Safety in the elderly has not been established. The SPC recommends that doses should be adjusted in mild to moderate renal impairment and stabilised with 1-monthly paliperidone palmitate injection.\(^1\)\(^,\)\(^7\)

There is a notable risk of incomplete dose administration if the injection is not prepared appropriately. The syringe must be shaken vigorously for at least 15 seconds within 5 minutes before administration to ensure a homogeneous suspension.\(^1\)

- **Potential advantages and disadvantages over existing technologies**

4.1. **Convenience**

The current licensed depots have maintenance dosing interval ranging from 1-5 weeks. The 3-monthly paliperidone palmitate depot offers a longer dosing interval, requiring administrations only 4 times a year. This could offer a wider window of administration that could be more convenient for healthcare professionals to intervene if doses have been missed and for patients who prefer fewer injections. However, tolerability and therapeutic effect will need to be established prior initiation. This would require patient to have tolerated 1-monthly formulation, meaning patient would need to have tolerated oral risperidone before commencement of paliperidone palmitate 1-monthly injection. This would potentially take several months to establish.

The 3-monthly paliperidone palmitate injections are available in pre-filled syringes and are administered via gluteal or deltoid route only with the thin wall needles provided in package, needle selection is determined by administration site (deltoid or gluteal) and patient weight.\(^1\) There are additional administration requirements for nurses to ensure the Trevicta has been shaken. Patients may be administered 3-monthly paliperidone palmitate injection 2 weeks before or after next due date. If scheduled dose is missed and the time since last injection is greater than 3½ months up to 4 months. The injection should be administered as soon as possible and then resume the 3-monthly injection schedule.

The table below shows the recommended re-initiation regimen after missing 4 months to 9 months of TREVICTA.\(^1\)

<table>
<thead>
<tr>
<th>If the last dose of 3-monthly paliperidone palmitate was</th>
<th>Administer 1-monthly Paliperidone palmitate injectable, two doses one week apart (into deltoid muscle)</th>
<th>Then administer 3-monthly paliperidone palmitate (into deltoid or gluteal muscle)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1</td>
<td>Day 8</td>
<td>1 month after day 8</td>
</tr>
<tr>
<td>175 mg</td>
<td>50mg</td>
<td>50mg</td>
</tr>
<tr>
<td>263 mg</td>
<td>75mg</td>
<td>75mg</td>
</tr>
<tr>
<td>350 mg</td>
<td>100mg</td>
<td>100mg</td>
</tr>
<tr>
<td>525 mg</td>
<td>100mg</td>
<td>100mg</td>
</tr>
</tbody>
</table>

Re-initiation of paliperidone 1-monthly injection is required for patients who miss more than 9 months of 3-monthly paliperidone palmitate.

4.2. **Healthcare resource utilisation**

Patients attend outpatient appointments for long acting antipsychotic injections to be administered by nursing staff; 3-monthly paliperidone palmitate depot will only require 4 clinic visits to see a nurse per patient per year for administration vs 12 visits for 1-monthly paliperidone palmitate.
4.3. Suitability for shared care
There is potential for shared care, as there is an existing shared care agreement in place for 1-monthly paliperidone palmitate injection in the North West London integrated formulary.

4.4. Drug cost and likely budgetary impact
First generation antipsychotic depots (zuclopenthixol decanoate, flupenthixol decanoate, haloperidol decanoate, and fluphenazine decanoate) costs approximately less than £200 per year per patient compared to £2,000 - £4,700 for second generation antipsychotic depots.
There should be no additional cost for 3-monthly paliperidone palmitate compared with patients who are already established on 1-monthly paliperidone injection provided that they are transferred on the equivalent dose.

The following table shows the cost comparisons for second generation antipsychotic depots/year

<table>
<thead>
<tr>
<th>Depot</th>
<th>Strength</th>
<th>Frequency</th>
<th>Cost per year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paliperidone Palmitate (Trevicta®)</td>
<td>175mg – 525mg</td>
<td>Every 3 months</td>
<td>£2,207.04 - £4,711.08</td>
</tr>
<tr>
<td>Paliperidone Palmitate (Xeplion®)</td>
<td>50mg -150mg</td>
<td>Every month</td>
<td>£2,207.04 - £4,711.08</td>
</tr>
<tr>
<td>Risperdal Consta</td>
<td>25mg -50mg</td>
<td>Every 2 weeks</td>
<td>£2,071.94 - £3711.76</td>
</tr>
<tr>
<td>Aripiprazole (Abily maintena®)</td>
<td>400mg</td>
<td>Every month</td>
<td>£2644.92</td>
</tr>
</tbody>
</table>

*Risperdal additional storage costs not calculated in above price, price based on BNF updated August 2016 excludes 20% VAT

5. Health Economics
No health economic data were identified.

6. Likely commissioning and funding pathway
The majority of usage in CNWL would be within community mental health teams. If prescribing is transferred to primary care CCGs will need to fund the prescribing via a shared care arrangement.

7. Suggested place in therapy
- Maintenance of chronic schizophrenia, in patients who have been clinically stable with proven response and tolerance to 1-monthly paliperidone palmitate injection for at least 6 months
- Monitoring should be continued once patients are established on treatment
- Consideration should be given to establishing criteria for patients suitable to be transferred to the 3-monthly depot

8. Injectable medicines – Risk assessment
Paliperidone palmitate 3-monthly injection is low risk injection (like the 1-monthly injection). The main risk is that if product is not shaken vigorously for 15 seconds prior to administration as required, the dose administered will be incomplete.
This risk should be mitigated by training all nursing staff involved in the administration of 3-monthly paliperidone palmitate injections. The SPC also describes the risks and provides information and recommendations about minimising them.
References

2. Trevicta (paliperidone) Summary of opinion1 (post authorisation). European Medicines Agency, Committee Medicinal Products for Human Use. 1 April 2016
4. Srihari G et al. Practical guidance for dosing and switching from paliperidone palmitate 1 monthly to 3 monthly formulations in schizophrenia. Current Medical Research and Opinion Nov 2015, vol. 31, no. 11, p. 2043-2054
7. European Medicines Agency, Summary of the risk management plan (RMP) for Paliperidone Janssen (paliperidone)

Written by Esther Njane, Specialist Pharmacist. [esther.njane@nhs.net].
# Proforma 2: Risk assessment of individual injectable medicine products prepared in clinical areas

<table>
<thead>
<tr>
<th>Clinical area:</th>
<th>Directorate:</th>
<th>Hospital site:</th>
<th>Date:</th>
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<tbody>
<tr>
<td>Mental Health and Allied Services</td>
<td>Mental Health and Allied Services</td>
<td>Trustwide</td>
<td>25/08/2016</td>
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</table>

<table>
<thead>
<tr>
<th>Name and strength of prepared injectable product</th>
<th>Diluent</th>
<th>Final volume</th>
<th>Bag or syringe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paliperidone Palmitate 3-monthly injection (TREVICTA)</td>
<td>Nil</td>
<td>Nil</td>
<td>Pre-filled syringe</td>
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## Risk factors

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Therapeutic risk</td>
</tr>
<tr>
<td>2</td>
<td>Use of a concentrate</td>
</tr>
<tr>
<td>3</td>
<td>Complex calculation</td>
</tr>
<tr>
<td>4</td>
<td>Complex method</td>
</tr>
<tr>
<td>5</td>
<td>Reconstitution of powder in a vial</td>
</tr>
<tr>
<td>6</td>
<td>Use of a part vial or ampoule, or use of more than one vial or ampoule</td>
</tr>
<tr>
<td>7</td>
<td>Use of a pump or syringe driver</td>
</tr>
<tr>
<td>8</td>
<td>Use of non-standard giving set/device required</td>
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<table>
<thead>
<tr>
<th>Total number of product risk factors</th>
<th>Risk assessment undertaken by:</th>
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</thead>
<tbody>
<tr>
<td>Six or more risk factors = high-risk product (Red). Risk reduction strategies are required to minimise these risks. Three to five risk factors = moderate-risk product (Amber). Risk reduction strategies are recommended. One or two risk factors = lower-risk product (Green). Risk reduction strategies should be considered.</td>
<td>Name of pharmacist: Esther Njane</td>
</tr>
</tbody>
</table>

### Risk assessment undertaken by:

Name of pharmacist: Esther Njane

Name of clinical practitioner:
Proforma 3: Risk assessment summary for high and moderate-risk injectable medicines

<table>
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<tr>
<th>Name of clinical area</th>
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<th>Date:</th>
</tr>
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<tbody>
<tr>
<td>Mental Health and Allied Services</td>
<td>Trustwide</td>
<td>25/08/2016</td>
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<table>
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<tr>
<th>Risk factors</th>
<th>Risk reduction method(s)</th>
<th>Revised score</th>
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<tr>
<td>Prepared injectable medicine</td>
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<tr>
<td>Strength</td>
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<tr>
<td>Diluent</td>
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</tr>
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<td>Final volume</td>
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<td>Bag/syringe</td>
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<td>Therapeutic risk</td>
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<td>Use of concentrate</td>
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<td>Complex preparation</td>
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<td>Reconstitute vial</td>
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<td>Part/multiple container</td>
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<td>Infusions pump or driver</td>
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<tr>
<td>Non-standard infusion set</td>
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<td>Risk assessment</td>
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</tbody>
</table>

Paliperidone Palmitate 3-monthly injection (TREVICTA)

| Four different strengths                           | Nil                       | Pre-filled syringe | Pre-filled syringe should be shaken vigorously with a loose wrist for at least 15 seconds with the syringe tip pointing up, for at least 15 seconds to ensure a homogeneous suspension, before administration. If left for 5 minutes, the process should be repeated. | 2 |
| 175 mg - 0.875ml                                   | 263mg - 1.315ml           | 350mg - 1.75ml     | 525mg-2.625ml      |

<table>
<thead>
<tr>
<th>Risk assessment undertaken by:</th>
<th>Name of pharmacist:</th>
<th>Name of clinical practitioner:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Esther Njane</td>
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