

Olanzapine depot injection (Zyprexa Relprevv) for schizophrenia

(oh-LAN-zah-peen)

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Summary

- Olanzapine as pamoate monohydrate is a long-acting injectable or depot form of olanzapine and provides another option for maintenance treatment of schizophrenia.
- It is administered by deep intramuscular gluteal injection only, every 2 weeks or every 4 weeks.
- There is a risk of post-injection syndrome with every dose of olanzapine depot injection.
- Monitor for signs and symptoms of post-injection syndrome (sedation and/or delirium) for at least 3 hours after each dose.
- As with oral olanzapine, weight gain and metabolic effects (raised serum cholesterol, triglyceride and glucose levels) are common.
- Establish tolerability and response to oral olanzapine before switching to the depot formulation.
- Consider depot antipsychotic therapy in people unable or unwilling to adhere with oral medication, and in those who prefer depot injections to oral therapy.

PBS listing

Authority required (Streamlined)

Schizophrenia.

Caution: Monitor for signs and symptoms of post injection syndrome for at least 3 hours after administering olanzapine depot injection.

Reason for PBS listing

The Pharmaceutical Benefits Advisory Committee recommended olanzapine depot injection for listing consistent with the listings of other long-acting antipsychotic injections for the treatment of schizophrenia.¹

Place in therapy

Olanzapine as pamoate monohydrate is a long-acting injectable or depot form of olanzapine. It is approved for maintenance treatment of schizophrenia in adults sufficiently stabilised during acute treatment with oral olanzapine.² It is given by deep intramuscular (IM) gluteal injection every 2 or every 4 weeks.

The PBS listing of olanzapine depot injection provides an additional long-acting atypical antipsychotic option

to risperidone IM long-acting injection, the only other depot atypical antipsychotic approved (and PBS listed) for maintenance treatment in schizophrenia.

Other antipsychotic depot options include the typical antipsychotics depot flupenthixol, fluphenazine, haloperidol and zuclopenthixol. Without a head-to-head, controlled comparison trial it is unclear how much depot olanzapine's effectiveness, safety, tolerability and patient acceptability differs from that of depot risperidone and other depot antipsychotics.

Establish tolerability and response with oral olanzapine (tablets or wafers) in olanzapine naïve patients before starting treatment with olanzapine depot injection.² There is no published information about switching patients stabilised on other antipsychotics directly to olanzapine depot injection and this is not consistent with the TGA-approved indication.

Do not confuse with rapid-acting IM formulation for use in acute care

There are two IM formulations of olanzapine and these should not be confused:

- olanzapine (Zyprexa IM) 10 mg powder for IM injection (rapid-acting) reconstituted with sterile water for injection

- olanzapine (as pamoate monohydrate) depot injection (Zyprexa Relprevv) 210 mg, 300 mg or 405 mg* powder and sterile diluent for IM injection.

When to consider depot antipsychotic injections

Medication non-adherence is common and associated with poorer outcomes in people with schizophrenia.^{3,4} Depot antipsychotic therapy is an option when medication adherence is inadequate despite appropriate psychosocial interventions aimed at improving adherence, and for people who prefer long-acting antipsychotic injections to oral therapy.^{5–8}

Choose between antipsychotics based on the relative risks and benefits of individual drugs, and patient preference.^{5,9}

Review the need for depot antipsychotic therapy regularly.⁶

Psychological and psychosocial interventions may improve adherence

Consider tailored psychological and psychosocial interventions as an adjunct to drug therapy to improve outcomes for people with schizophrenia.^{5,6,8,9} There is some evidence that family-based interventions, psychoeducational interventions and behavioural therapies may improve medication adherence compared with usual care^{10,11} but no consistent evidence for the effectiveness of compliance therapy.¹²

Efficacy in acutely ill and stabilised patients with schizophrenia

The efficacy of olanzapine depot injection was compared with placebo in acutely ill patients, and with oral olanzapine in patients previously stabilised on oral olanzapine.^{13,14} There are no controlled data directly comparing olanzapine depot injection with any other depot antipsychotics in the treatment of schizophrenia.

In a short-term trial (8 weeks' duration) patients randomised to olanzapine long-acting injection achieved greater mean decreases from baseline in the positive and negative syndrome scale (PANSS[†]) total score compared with those randomised to placebo.¹³

In an unpublished 24-week maintenance trial, olanzapine depot injection (300mg/2weeks pooled with 150mg/2weeks) was no less effective than oral olanzapine (10–20 mg daily) in terms of exacerbation of symptoms in patients previously stabilised on fixed doses of oral olanzapine (exacerbation rates 10% versus 7% with oral olanzapine, 95% confidence interval –0.02 to 0.08).¹⁴ All 3 doses of olanzapine depot injection used in the trial (405mg/4weeks, 300mg/2weeks and 150mg/2weeks) were more effective than control (45mg/4weeks) in maintaining response.¹⁴

By the end of the study, patients randomised to oral olanzapine had achieved numerically lower symptom scores (mean decrease from baseline PANSS total score) compared with those randomised to olanzapine depot injection. These results might be partially explained by inadequate dosing with depot olanzapine for patients previously stabilised on fixed doses of oral olanzapine. While some patients were randomised to continue on the dose of oral olanzapine at which they demonstrated a response, others may have been randomised to a dose of olanzapine depot injection that was not equivalent to their preceding oral olanzapine dose.¹⁵ Recommended starting doses for olanzapine depot injection are higher than the daily oral doses to minimise the risk of exacerbation (see Dosing issues).

Trial populations may not resemble those for whom depot antipsychotic medication is recommended and likely to be used

Current guidelines recommend the use of depot antipsychotics for people with schizophrenia for whom adherence is a problem.^{5,6,8} Medication adherence was not assessed formally either before or during key studies, but it is conceivable that patients may have been more co-operative than the target population for this drug, as evidenced by their willingness to participate in trials. Discontinuation rates were nevertheless high in a placebo-controlled trial (around 33% for olanzapine depot injection versus 43% for placebo), where patients received a high level of supervision (83% of participants remained inpatients throughout the study)¹³, and may be even higher in real-life settings. Interim results from a long-term (4-year) open-label trial showed that 28% of patients had discontinued from the trial at 1 year and 34% had discontinued at 18 months.¹⁴

* Olanzapine depot injection 405 mg is currently not available in Australia.

† The PANSS is a 30-item, 7-point rating instrument used to measure the prevalence and severity of positive and negative symptoms and general psychopathology in schizophrenia (range 30 = symptom not present to > 200 = symptom extremely severe).^{15,16}

Key trials excluded people with acute, serious or unstable medical conditions or concomitant substance use disorders, and significant suicidal or homicidal risk.^{13,17} In reality the prevalence of physical and psychiatric comorbidity and substance abuse in people with schizophrenia is well documented.^{18,19}

Safety issues

Limited trial data suggest that the adverse effect profile of olanzapine depot injection may be similar to that of oral olanzapine, with the exception of post-injection syndrome (see below) and injection-site pain. Weight gain and lipid parameters were similar between patients treated with oral olanzapine and those treated with olanzapine depot injection.²⁰ Higher-dose regimens (300mg/2 weeks) were associated with statistically higher mean changes in weight, serum prolactin levels and fasting triglyceride levels post baseline compared with lower-dose regimens (405mg/4 weeks and 150mg/2 weeks).^{15,20}

However, olanzapine depot injection is a new formulation with few published safety data from controlled trials; there is therefore some extra uncertainty about its safety profile.

Report suspected adverse reactions to the Therapeutic Goods Administration (TGA) online (www.ebs.tga.gov.au [then click 'Adverse reaction to a medicine' at left]) or by using the 'Blue Card' distributed 3 times a year with *Australian Prescriber*. For information about reporting adverse reactions, see the TGA website (www.tga.gov.au).

The risk of post-injection syndrome remains with every injection

Post-injection syndrome includes a range of signs and symptoms of sedation (ranging from mild sedation to deep sleep and coma) and/or delirium (including confusion/confused state, anxiety and agitation) consistent with olanzapine overdose.¹⁴ Other symptoms include dizziness, weakness, altered speech/dysarthria, hypertension and seizures.^{14,15,20} Post-injection syndrome was reported for 0.07% of injections and in about 1.4% of trial participants.¹⁵

Most events occurred after repeated injection (several months of treatment).¹⁴ In case reports, events typically started with mild symptoms that progressed in severity. In most cases (84%), initial signs and symptoms occurred within the first hour after injection, but onset after 3 hours has been reported.^{14,15}

Accidental contact between olanzapine and blood (inadvertent intravascular injection, or haematoma development) is a possible causal factor.¹⁴ Higher doses and therefore larger final volume for injection, increased age and low body mass index (BMI) may confer a higher risk for post-injection syndrome; however, events have occurred in patients not meeting these criteria.¹⁴

Monitor for alertness every 30 minutes for at least 3 hours after every injection

Check that the patient is alert, orientated and free of any other signs of post-injection syndrome every 30 minutes for at least 3 hours after each injection.¹⁴ Olanzapine depot injection should only be administered by an appropriately trained health professional in a healthcare facility with access to emergency services for the treatment of post-injection syndrome.²

Patients should not be alone after the observation period because events have been reported more than 3 hours post-injection.² Warn patients and carers about possible signs and symptoms of post-injection syndrome and the need for urgent medical attention if they occur.²

Metabolic issues

The metabolic adverse effects of oral olanzapine can also be expected with olanzapine depot injection. Weight gain is common and can be rapid.^{13,14} Guidelines recommend measuring weight and body mass index every 3 months during treatment with antipsychotic medication.⁶ Consider offering advice on diet and exercise to prevent weight gain or promote weight loss.^{8,9,21} Non-pharmacological interventions (individual and group therapy, cognitive behavioural therapy and nutritional counselling) have been shown to reduce antipsychotic-induced weight gain compared with usual care.²¹

Monitor fasting plasma glycated haemoglobin (HbA_{1c}) and lipid levels at least every 6 months for people taking olanzapine.⁵ Regular screening for metabolic syndrome (3–6 monthly) is recommended for all patients receiving any antipsychotic medication.^{5,6,22}

Dosing issues

Olanzapine depot injection should not be given to olanzapine naïve patients. Establish tolerability and response with oral olanzapine before switching to the recommended starting dose of olanzapine depot injection (see Table 1).

Table 1: Recommended dosing and titration scheme when switching between oral olanzapine and olanzapine depot injection²

Daily oral olanzapine dose	Recommended starting dose of olanzapine depot injection	Maintenance dose after 2 months of treatment
10 mg/day	210mg/2weeks or 405mg*/4weeks	150 mg/ 2 weeks or 300 mg/ 4 weeks [†]
15 mg/day	300mg/2weeks	210 mg/ 2 weeks or 405 mg* / 4 weeks
20 mg/day	300mg/2weeks	300 mg/ 2 weeks

* Olanzapine depot injection 405 mg is currently not available in Australia.

† There are no data from randomised controlled trials on the efficacy of olanzapine depot injection 300 mg / 4 weeks. Pharmacokinetic data indicate that plasma concentrations at this dose are similar to plasma concentrations achieved at the equivalent oral dose.²

Reconstitute with diluent provided to form a suspension. Administer by deep IM gluteal injection only, every 2 weeks or every 4 weeks. Each olanzapine pack includes 3 needles, 1 of which is a 19-gauge 50 mm safety needle for obese patients.²³

If depot injections are required, guidelines recommend using the lowest therapeutic dose at the longest approved dosing interval consistent with desired therapeutic benefit.^{6,9} Dosing with olanzapine depot injection differs from other depots in the following ways:

- patients can be switched abruptly from oral to olanzapine depot injection; supplementation with oral olanzapine is not required at the start of treatment with depot olanzapine
- start with a higher dose than the established oral dose (see Table 1) and titrate downwards after 2 months where possible.

In a placebo-controlled trial, no statistically significant difference in baseline to endpoint PANSS total scores were observed between 2- and 4-week dosing regimens of olanzapine depot injection (210mg/2weeks and 405mg/4weeks) suggesting equivalence, but the study was not powered for this effect.¹³

Monitor carefully for signs and symptoms of exacerbation in the first 2 months of therapy.

In a 6-month maintenance trial, most relapses occurred in the first 2 months of treatment with olanzapine depot injection in patients previously stabilised on oral

olanzapine.¹⁵ However, the doses used during this period may have been lower than the recommended starting doses in Table 1.

Converting to oral olanzapine

If a decision is made to switch from olanzapine depot injection to oral olanzapine, gradually reduce the dose of olanzapine depot injection by the oral equivalent of 5 mg daily or 10 mg daily each month. At the same time gradually increase the dose of oral olanzapine by 5 mg daily or 10 mg daily.²⁴

Information for patients

Advise patients and carers of the following.^{2,25}

- Olanzapine depot injection is given every 2 or every 4 weeks as an injection into the muscle in your buttock.
- Some patients may need to continue oral olanzapine for a limited time after they start treatment with olanzapine depot injection, and at times when their symptoms are worse than usual.
- As with tablets or wafers, common side effects of olanzapine depot injection include weight gain, sleepiness, and increases in the levels of sugar and circulating fats in the blood.
- You will usually be asked to stay at the clinic/GP office for 3 hours after every injection so that you can be checked for symptoms of post-injection syndrome (including drowsiness, dizziness, confusion, disorientation, slurred speech, weakness). If you need to leave before this time you should ensure that you are accompanied by a friend or family member who can continue to observe you for these symptoms.
- Post-injection syndrome occurs in about 1 in 100 patients; it can occur after any dose of olanzapine depot injection.
- Be alert for symptoms of post-injection syndrome later than 3 hours after your injection and contact your GP or clinic immediately if these occur.
- Arrange for someone to accompany you to your destination after your injection. Do not drive or operate heavy machinery for the rest of the day after your injection.

Discuss the Zyprexa Relprevv consumer medicine information (CMI) leaflet with the patient.

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