

Olanzapine Long-Acting Injection (Zypadhera®) - Guidelines for Prescribing and Administration (Version 3 – June 2016)

1. Key Points

- 1.1 Olanzapine long acting injection (LAI) is **indicated** for the maintenance treatment of adult patients with schizophrenia whose condition has been sufficiently stabilised during acute treatment with oral olanzapine, and who have been assessed as having adherence problems with long-term oral medication.
- 1.2 Olanzapine LAI is **not indicated** for treatment-resistant schizophrenia, unlicensed indications or patients intolerant to oral olanzapine.
- 1.3 Olanzapine LAI may only be **newly prescribed** by doctors of associate specialist grade or above. Other grades may not initiate therapy or adjust dose without direct instruction from their consultant.
- 1.4 Olanzapine LAI may only be **administered** by deep intramuscular gluteal injection by nurses or doctors who have been trained in the appropriate injection technique. (See Appendix 1 for training link). **Administration may only take place in healthcare premises where post-injection 3-hours observation (by specifically trained nurses or doctors) can be assured.** (See section 4).
- 1.5 Olanzapine LAI will **not be supplied** to wards, units or teams as stock. All supplies must be ordered from pharmacy on a named-patient basis. **Named-patient application and local monitoring must be undertaken using Trust documentation.** (See appendix 1).
- 1.6 Olanzapine LAI is **extremely expensive** when compared to conventional antipsychotic depots and when compared to oral olanzapine. At highest dose, (300mg / 2 weeks – equivalent to 20mg OD), it costs **£5,800 per patient year.**

2. Prescribing Treatment

- 2.1 All patients must have a history of response and tolerability to oral olanzapine before olanzapine LAI is prescribed.
- 2.2 Recommended Dose Scheme:

Target oral olanzapine dose.	Recommended starting dose of olanzapine LAI.	Maintenance dose after two months of treatment.
10mg / day	210mg / 2 weeks or 405mg / 4 weeks	150mg / 2 weeks or 300mg / 4 weeks
15mg / day	300mg / 2 weeks	210mg / 2 weeks or 405mg / 4 weeks
20mg / day	300mg / 2 weeks	300mg / 2 weeks

If you require this document in an alternative format, ie easy read, large text, audio, Braille or a community language please contact the Pharmacy Team on 01243 623349 (Text Relay calls welcome).

- 2.3 The maximum licensed dose of olanzapine LAI is 300mg 2-weekly or 405mg 4-weekly.
- 2.4 Before prescribing, patients must be advised about the potential risk of post-injection syndrome and the need for them to be observed on healthcare premises, (by nurses or doctors trained to identify post-injection syndrome), for three hours after each injection. If it is felt that the patient might not comply with this continuous requirement, olanzapine LAI must not be initiated.
- 2.5 Before prescribing, and further to 2.4 above, it must be made clear to the patient that the need for 3-hour post-injection monitoring will continue for as long as they remain on the medication. If long-term plans to comply with this requirement cannot be assured, olanzapine LAI must not be initiated.
- 2.6 Patients must be monitored carefully for signs of relapse during the first one to two months of treatment with olanzapine LAI and the dose should be adjusted according to individual clinical status.
- 2.7 Supplementation of olanzapine LAI with oral olanzapine is not contraindicated but the combination has not been studied in clinical trials. The licensed daily maximum dose of olanzapine (by either single or combined routes) is 20mg oral equivalent.

3. Other Dosing Recommendations / Considerations

- 3.1 **The elderly:** Olanzapine LAI is **not recommended** for treatment of those over 65 years unless a well-tolerated and effective oral dose regime has been established. A lower starting dose should be considered, (150mg / 4wks). Olanzapine LAI should not be started in those over 75 years of age. Olanzapine LAI is not licensed for dementia-related psychosis and/or dementia-related behavioural disturbance.
- 3.2 **Children & Adolescents:** Olanzapine LAI is **not licensed** for use in those less than 18 years of age.
- 3.3 **Renal and/or hepatic impairment:** Olanzapine LAI should only be used if a well-tolerated and effective oral dose regime has been established. A lower starting dose should be considered, (150mg / 4wks).
- 3.4 **Plasma half-life:** The plasma half-life of olanzapine after administration of the LAI is **30 days**. (The half-life after oral administration is 30 hours). Clinicians should note that while plasma levels have usually diminished considerably after 8 to 12 weeks, elimination of olanzapine may not be complete until 6 to 8 months after the last injection.

4. Administration

The following conditions apply to every injection of olanzapine LAI. It is essential to ensure that long-term plans for administration and observation are in place before prescribing / administering this product.

- 4.1 Olanzapine LAI may only be administered by a doctor or nurse who has received training in the appropriate injection technique. (See Appendix 1 for training link). The olanzapine LAI will only be supplied from the drug manufacturer to the pharmacy department when both medical and nursing staff complete the required on-line training. The training involves reading through a PowerPoint slide presentation and at the conclusion acknowledging this by pressing the appropriate link. This only needs to be completed once by any individual. Sussex Partnership can be selected in the Institution search during the registration process, although individual wards are not specified.
- 4.2 Olanzapine LAI may only be administered in healthcare premises where 3 hours of observation of the patient by nurses or doctors specifically trained to identify post-injection syndrome can be assured. Rapid access to medical (or paramedical) care, if needed, (to include dialling 999 if a doctor is not on the premises), must be available throughout the observation period.
(See appendices 2 and 3).
- 4.3 During the time following administration and particularly prior to the patient leaving the unit / clinic, it must be confirmed that the patient is alert, orientated and absent of any signs and symptoms of olanzapine overdose. If overdose is suspected, close medical supervision and monitoring must continue until examination indicates that signs and symptoms have resolved. Alternatively, if a doctor is not available, an ambulance must be called.
- 4.4 Patients must be advised to be vigilant for signs and symptoms of olanzapine overdose (secondary to post-injection adverse reactions) for the remainder of the day following administration of olanzapine LAI. Assurance must be sought that they will remain in a position to obtain assistance if needed and that they will not drive or operate machinery.
- 4.5 After administering the injection the nurse / doctor must check that the patient has a Zypadhera[®] patient information card in their possession. As well as providing a record of the injection, this card contains important safety information for the patient on post-injection adverse events. All patients must be issued with a copy of this card before they leave the unit / clinic if they are not already carrying one.
- 4.6 **Olanzapine LAI is for deep intramuscular gluteal injection only.** Extreme care must be taken to avoid intravenous or subcutaneous injection.
- 4.7 Detailed, step-by-step instructions are available for the preparation and administration of olanzapine LAI. These are included in each pack of the injection and must always be available at the time of administration.

5. Post-injection Syndrome

The exact mechanism remains unknown but the clinical manifestations are consistent with those of oral olanzapine overdose. These effects can include sedation (from mild in severity up to coma) and delirium, as well as extrapyramidal symptoms, dysarthria, ataxia, aggression, dizziness, weakness, hypertension and convulsions. In most cases symptoms appear within one hour of injection but rarely may occur later than one hour and very rarely later than three hours after injection. In clinical trials the syndrome occurred in less than 0.1% of injections and in less than 1.5% of patients.

6. Storage

- 6.1 Packs of olanzapine LAI should be stored in a locked medicines cabinet. There is no requirement for fridge storage.
- 6.2 Once reconstituted in the vial, olanzapine LAI should be used immediately. However, if not used right away it will retain efficacy for up to 24 hours at room temperature and will re-suspend if shaken vigorously. Any olanzapine LAI that has been reconstituted for longer than 24 hours must be discarded.
- 6.3 Once drawn into the syringe, olanzapine LAI must be used immediately.

7. Cost Comparison of Antipsychotics

See overleaf.

7. Cost Comparison of Antipsychotics

<u>Preparation</u>	<u>Dose</u>	<u>Cost per 28 days</u>
Olanzapine LAI (Zypadhera [®])	150mg 2-weekly	£285 (2 x 210mg packs)
	300mg 4-weekly	£223 (1 x 300mg pack)
	210mg 2-weekly	£285 (2 x 210mg packs)
	405mg 4-weekly	£285 (1 x 405mg pack)
	300mg 2-weekly	£446 (2 x 300mg packs)
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Aripiprazole LAI	300mg monthly	£220 – per month
	400mg monthly	£220 – per month
Paliperidone LAI	25mg monthly	£184 – per month
	50mg monthly	£184 – per month
	75mg monthly	£245 – per month
	100mg monthly	£314 – per month
	150mg monthly	£393 – per month
Risperidone LAI	25mg 2-weekly	£160
	37.5mg 2-weekly	£222
	50mg 2-weekly	£285
Flupentixol depot injection	200mg 2-weekly	£36
Fluphenazine depot injection	100mg 2-weekly	£18
Haloperidol depot injection	200mg 4-weekly	£10
Zuclopenthixol depot injection	500mg 2-weekly	£14
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Amisulpride tablets (bd)	300mg – 600mg daily	£7 - £11
Aripiprazole tablets (od)	10mg – 30mg daily	£6 - £103
Olanzapine tablets (od)	10mg – 20mg daily	£1 - £2
Quetiapine tablets (bd)	300mg – 600mg daily	£2 - £4
Risperidone tablets (bd)	2mg – 6mg daily	£1 - £2

Guidelines prepared by:

Jed Hewitt

Chief Pharmacist – Governance & Professional Practice

Originally approved by the Drugs & Therapeutics Group: April 2010.

May 2010 (Web-link added December 2010).

February 2013 - Reviewed and updated.

August 2014 – Reviewed and updated (with DTG approval).

May 2015 – Amended Appendices.

June 2016 – Review and minor update.

Next review – June 2019

Appendix 1

**Olanzapine Long-Acting Injection (Zypadhera®)
Named Patient Request Form.**
(Version 3 – June 2016).

N.B. The annual purchase cost of olanzapine long acting injection is between £3,000 and £6,000 per patient year.

Patient's Initials PIMs No DoB Gender

Consultant Name

**Before this request can be approved the following criteria must be met and confirmed:
(Please initial boxes to confirm)**

1. The patient has successfully responded to oral olanzapine treatment and has been stabilized during acute treatment.
2. The patient has been assessed as having significant adherence problems with oral olanzapine therapy that may compromise on-going therapeutic benefits.
3. Long-term arrangements have been made, (and agreed with the patient), for every injection to be administered in healthcare premises and for a doctor or nurse to be available to observe the patient on site for a minimum of three hours after every injection.
4. All nurses and doctors who will be administering the injection have undergone, or will be undergoing, specific training on product administration. <https://www.zypadhera.co.uk>
5. All nurses and doctors who will be providing the three hour post-injection observation of the patient have undergone, or will be undergoing, specific training on the identification and management of post-injection syndrome. <https://www.zypadhera.co.uk>

Other information to support this request:

e.g. record of admissions over the last 2 years, identified adherence concerns

Supporting signatures must be completed overleaf before this request can be processed.

N.B. The annual purchase cost of olanzapine long acting injection is between £3,000 and £6,000 per patient year.

Confirmatory / Supporting Signatures

I confirm the information provided overleaf, that appropriate training and long-term monitoring arrangements are in place, and that olanzapine long-acting injection will only be used in accordance with Trust guidance and within the terms of the Product Licence.

Initiating Consultant / Associate Specialist.

<i>Signature</i>	<i>Name</i>	<i>Date</i>

This application for use of long-acting olanzapine injection is supported by the undersigned who confirm that training and long-term monitoring requirements have been appropriately addressed.

Clinical Pharmacist (Locality Lead)

<i>Signature</i>	<i>Name</i>	<i>Date</i>

Consultant taking long-term responsibility (if not initiating)

<i>Signature</i>	<i>Name</i>	<i>Date</i>

Care co-ordinator

<i>Signature</i>	<i>Name</i>	<i>Date</i>

Clinical Director

<i>Signature</i>	<i>Name</i>	<i>Date</i>

Service Director – (For requests from the Secure & Forensic Service)

<i>Signature</i>	<i>Name</i>	<i>Date</i>

Completed form to be submitted to:

Jed Hewitt

Chief Pharmacist – Governance & Professional Practice

Woodside

jed.hewitt@sussexpartnership.nhs.uk

fax: 01323 445492

Appendix 2

Olanzapine LAI injection - Post Injection Syndrome monitoring

All observations must be recorded in the monitoring sheet (see Appendix 3)

- All patients should be fully informed of the symptoms of post-injection syndrome
- After 3 hours, post-injection syndrome is exceedingly unlikely to occur ¹. Community or out-patients may be allowed home after 3 hours, but they must be advised not drive or operate machinery for the remainder of the day. They should be vigilant for signs of post-injection syndrome (see below) and should be aware of who to contact for assistance if required.
- It should only be administered by deep intramuscular gluteal injection by a healthcare professional trained in the appropriate injection technique and in locations where post-injection observation and access to appropriate medical care in the case of overdose can be assured.
- 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

After the injection, **observations** should be as follows:

<p>Every 10 minutes during first hour</p>	<p>Ensure patient is fully alert and ambulatory Observe for signs of sedation or delirium NB. There is no need to measure any physical parameters</p>
<p>Every 30 minutes from 1-3 hours</p>	<p>As above</p>

If post-injection syndrome occurs:

- Immediately call for medical assistance
- Dial 999
- Give supportive care

Post-injection syndrome:

- Post-injection syndrome is probably caused by unintended partial intravascular injection³. This occurs in a small number of people, even with appropriate injection technique
- The risk of post-injection syndrome is 0.07% (about one in 1400 injections)^{1,4}
- Median time to onset of symptoms is 25 minutes and Post-injection syndrome is seen within one hour of injection in 80% of cases
- If post-injection syndrome is not evident within one hour, the risk of it emerging 1-3 hours after the injection is 0.014% (or about 1 in 7000 injections)⁴

Symptoms of post-injection syndrome typically include⁴:

- Sedation
- Delirium (disorientation and cognitive impairment)
- Confusion
- Dysarthria (slurred speech)
- Ataxia
- Agitation
- Anxiety

References

1. Eli Lilly and Company Limited. Zypadhera SPC.
<http://www.medicines.org.uk/emc/medicine/21361>
2. SMC Drug ID: 624/10; Manufacturer: Eli Lilly and Company Ltd; Indication: Maintenance treatment of adult patients with schizophrenia sufficiently stabilised during acute treatment with oral Olanzapine. Submission Type: Full submission; Status: Not Recommended; Date Advice Published: 09/08/2010. Available at <http://www.scottishmedicinesconsortium.org.uk>
3. McDonnell DP et al. Post injection delirium/sedation syndrome in patients with schizophrenia treated with olanzapine long-acting injection II: investigation of mechanism. BMC Psychiatry 2010; 10:45
4. Dekte HC et al. Post-injection delirium/sedation syndrome in patients with schizophrenia treated with olanzapine long-acting injection, I; analysis of cases BMC Psychiatry 2010; 10:43

Appendix 3:

Monitoring Record for Patients Treated with Olanzapine Embonate LAI

Name of patient _____

Date of Birth _____ NHS Number _____ PIMs number _____

Patient Address _____

Consultant _____ Ward/ Unit _____

Date of Administration _____ Time of administration _____

Administered by _____ Administered by (Designation) _____

0 – 1 hour Post Injection

	0mins	10mins	20mins	30mins	40mins	50mins	60mins
Routine Observations* (tick)							
Completed by							
Date Sign							

1 – 3 hours Post Injection

	90mins	120mins	150mins	180mins
Routine Observations* (tick)				
Completed by				
Date Sign				

* Routine Observations = Ensure patient is fully alert and ambulatory and observe for signs of sedation or delirium