GUIDELINES FOR THE USE OF OLANZAPINE LONG ACTING INJECTION

Summary

Olanzapine long acting injection (LAI) is indicated for the maintenance treatment of adult patients with schizophrenia who:

- Have responded to oral olanzapine but are non-compliant
- Have responded to typical depot antipsychotics, but have experienced unacceptable side effects.

Olanzapine LAI is not indicated for treatment-resistant schizophrenia, unlicensed conditions or for patients intolerant of oral olanzapine.

KMPT has approved the use of Olanzapine LAI for the following unlicensed indications:
• Bipolar prophylaxis where oral olanzapine has proven efficacy for the patient but long-term oral medication is not appropriate

Because of the risk of post injection syndrome, patients receiving olanzapine LAI must be observed in a healthcare facility for 3 hours post dose.

Olanzapine LAI will only be supplied for individual named patients using the Named Patient Request Form appended to this document.

Olanzapine LAI may only be initiated by a Consultant Psychiatrist.

Olanzapine LAI may only be administered by deep intramuscular gluteal injection by nurses or doctors who have received appropriate training available at https://www.zypadhera.co.uk/SignIn.aspx. Administration may only take place in healthcare premises where post-injection observation for 3 hours can be assured.

Olanzapine LAI is extremely expensive compared with typical depots, oral olanzapine or risperidone LAI – the highest dose of 300mg every 2 weeks costs £5800 per year.

1. Prescribing

1.1 Patients must have a history of response and tolerability to oral olanzapine before olanzapine LAI is prescribed

1.2 In KMPT olanzapine LAI is approved for use in the following indications only:

- Maintenance treatment of adult patients with schizophrenia who have responded to oral risperidone but who are non-compliant (licensed use)
- Bipolar prophylaxis where oral risperidone has proven efficacy for the patient but long-term oral medication is not appropriate (unlicensed use)

1.3 The attached Named Patient Request Form must be completed, with all the necessary signatures and sent to kmpt.lai-authorisation@nhs.net for approval.

If it is being prescribed for an unlicensed indication, other than those defined above, the request must be approved by the relevant Head of Psychiatry. The Trust's policy on prescribing unlicensed medication should also be followed.

1.4 Olanzapine LAI cannot be ordered from suppliers until the prescriber has registered and completed the online Zypadhera training

1.5 Recommended dose regimen

Oral olanzapine dose	Starting dose olanzapine LAI	Maintenance dose olanzapine LAI
10mg daily	210mg/2 weekly or 405mg/4 weekly	150mg/2 weeks or 300mg/4 weeks
15mg daily	300mg/2 weeks	210mg/2 weeks or 405mg/4 weeks
20mg daily	300mg/2 weeks	300mg/2 weeks

1.6 The maximum licensed dose of olanzapine LAI is 300mg/ 2 weeks or 405mg/ 4 weeks

1.7 Before initiation, patients must be warned about the potential for post-injection syndrome and the requirement for them to be observed on healthcare premises by nurses or doctors trained to identify post-injection syndrome for three hours after each injection. This requirement will continue for as long as they remain on olanzapine LAI. If it is felt that the patient will not comply with this requirement, olanzapine LAI should not be initiated.

1.7 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.

1.8 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.

1.9 Olanzapine LAI is not recommended over 65 years unless an effective and well-tolerated oral regimen has been established. A starting dose of 150mg/4 weeks should be considered. Olanzapine LAI should not be initiated over 75 years.

1.10 Olanzapine is not licensed for dementia-related psychoses and or behavioural disturbance

1.11 Olanzapine LAI is not licensed under 18 years

1.12 Plasma half-life of olanzapine LAI is 30 days. Clinicians should note that elimination of olanzapine LAI may not be complete until 6 to 8 months following the last injection.

1.13 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).

2. 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.

2.1 Olanzapine LAI may only be administered by a doctor or nurse who has carried out online Zypadhera training available at https://www.zypadhera.co.uk/SignIn.aspx

A certificate of completion of training must be sent to kmpt.lai-authorisation@nhs.net

It must be given by deep intramuscular gluteal injection only. Extreme care must be taken to avoid intravenous or subcutaneous injection.

2.2 Olanzapine may only be administered in healthcare premises where the patient can be observed for 3 hours by a doctor or nurse specifically trained to identify post-injection syndrome. A non-registered professional can support with the monitoring as long as they have done the Zypadhera training and are being supervised by a nurse. Rapid access to medical care if needed must be available during the observation period (to include dialling 999 if a doctor is not on the premises).

2.3 During the time following administration and prior to the patient leaving the unit or clinic, it must be confirmed that the patient is alert, oriented and is showing no signs or symptoms of olanzapine overdose. If overdose is suspected, close medical supervision and monitoring must continue until signs and symptoms have resolved. If a doctor is not available, an ambulance must be called.

2.5 Patients must be advised to be vigilant for signs and symptoms of olanzapine overdose for the remainder of the day following the administration of olanzapine LAI, and assurance sought that they will be in a position to obtain assistance if needed, and that they will not drive or operate machinery.

2.6 Following administration of olanzapine LAI the nurse or doctor must ensure that the patient has Zypadhera® patient information card in their possession. This provides a record of the injection and in addition important safety information for the patient on post-injection adverse events

2.7 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.

3. Post-injection Syndrome

It is important to note that proper injection technique does not guarantee that a blood vessel injury has not occurred during the injection.

The clinical presentation is consistent with olanzapine overdose, although the mechanism is unknown. The effects can include sedation – varying from mild in severity to coma – and delirium, extrapyramidal symptoms, dysarthria, ataxia, aggression, dizziness, weakness, hypertension and convulsions. In most cases, symptoms appear within one hour following injection, but rarely may occur later than one hour and very rarely later than three hours following injection. In clinical trials the syndrome occurred in less than 0.1% of injections and in less than 1.5% of patients.

There is no data to suggest that the risk of post-injection syndrome is increased following one episode.

If it is to be continued the next injection should be given at the next scheduled date. If there is a relapse in schizophrenia symptoms then the dose can be given earlier or oral olanzapine initiated until the time of the next injection.

4. Storage

4.1 Olanzapine LAI must be stored in a locked medicines cupboard – there is no requirement for refrigeration

4.2 Once reconstituted in the vial, olanzapine should be used immediately, although 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 should be discarded.

4.3 Olanzapine drawn into the syringe should be used immediately.

5. Cost comparison for antipsychotic long-acting injections

Drug	Dose	Cost for 28 days (£)
Olanzapine LAI	150mg/2 weeks 300mg/4 weeks 210mg/2 weeks 405mg/4 weeks 300mg/ 2 weeks	285 (2 x 210mg packs) 223 (1 x 300mg pack) 285 (2 x 210mg pack) 285 (1 x 405mg pack) 446 (2 x 300mg packs)
Aripiprazole LAI (monthly)	300mg 400mg	£220 – per month £220 – per month
Paliperidone LAI (monthly)	25mg 50mg 75mg 100mg 150mg	£184 – per month £184 – per month £245 – per month £314 – per month £393 – per month
Risperidone LAI	25mg/2 weeks 37.5mg/2 weeks 50mg/2 weeks	160 222 285
Flupentixol Decanoate	200mg/2 weeks	27
Fluphenazine Decanoate	100mg/ 2 weeks	18
Haloperidol Decanoate	200mg/4 weekly	10
Pipotiazine Palmitate	200mg/4 weekly	53
Zuclopenthixol Decanoate	500mg/2 weekly	10

OLANZAPINE LONG-ACTING INJECTION NAMED PATIENT REQUEST FORM

Patient name…… Date of Birth……

Indication for use
(Delete to leave the actual indication only)

- Maintenance treatment of adult patients with schizophrenia who have responded to oral olanzapine but who are non-compliant or have responded to typical depot antipsychotics, but have experienced unacceptable side effects. (licensed use)
- Bipolar prophylaxis where oral olanzapine has proven efficacy for the patient but long-term oral medication is not appropriate (unlicensed route)
- Other (Use must be approved by the Head of Psychiatry)

Specify indication

Initiating Consultant Name……..

The following criteria must be confirmed before the request can be approved (tick box to confirm)

The patient has responded successfully to oral olanzapine treatment	
The patient has been assessed as having significant adherence problems with oral olanzapine	
Other long-acting antipsychotic injections have been considered	
Long-term arrangements have been made and agreed with 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 3 hours after every injection	
All nurses and doctors who will be administering the injection have undergone specific online training on product administration, provided by Lilly	
All nurses and doctors who will be providing 3 hours post-injection observation of the patient have undergone specific online training on the identification and management of post-injection syndrome, provided by Lilly	

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

OLANZAPINE LONG-ACTING INJECTION NAMED PATIENT REQUEST FORM

Patient Name…… Date of Birth……

I confirm that long-term monitoring arrangements are in place and that appropriate training has taken place, and that olanzapine LAI will only be used in accordance with the terms of the Product Licence

Initiating Consultant

Signature	Name	Date

Consultant taking ongoing responsibility (if different)

Signature	Name	Date

Care Co-ordinator

Signature	Name	Date

Patient

I confirm that I have been given written information about olanzapine long acting injection and I consent to remain in the health care facility for a minimum of 3 hours following every injection.

Signature	Name	Date

Please scan and e mail completed form to: kmpt.lai-authorisation@nhs.net

LAI Approval

Pharmacist 1	Signature	Date
Pharmacist 2	Signature	Date
Head of Psychiatry (other unlicensed use only*)	Signature	Date

Olanzapine LAI injection - Post Injection Syndrome Monitoring

All observations must be recorded using the monitoring sheet

• 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.
It is important to note that proper injection technique does not guarantee that a blood vessel injury has not occurred during the injection.
• After each injection, patients should be observed in a healthcare facility by **appropriately qualified and trained personnel (a nurse or a doctor)** for at least 3 hours for signs and symptoms consistent with olanzapine overdose

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

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

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 injection[3]. 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 include[4]:

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

Continuation of treatment following post-injection syndrome[5]:

- There is no data to suggest that a patient is more likely to suffer a recurrence of post-injection syndrome following an episode
- If treatment is to be continued the next dose should be given at the previously scheduled time
- If symptoms of schizophrenia occur the injection can be given earlier or oral olanzapine can be initiated until the time of the scheduled injection

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. McDonell 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
5. Data on file, Eli Lilly and Company and/or one of its subsidiaries. Received by KMPT 31/7/2108

Monitoring Record for Patients Treated with Olanzapine Embonate Long Acting Injection

Name of patient: _____

Date of Birth: _____ NHS Number: _____

Patient Address: _____

Consultant: _____ Ward/ Unit: _____

Date of Administration: _____ Time of administration: _____

Administered by (name & designation): _____

Time injection given:		**Time after injection:**					
Physical health monitoring *(if clinically indicated)*	Baseline (pre-injection):	15 mins	30 mins	45 mins	1 hour	2 hours	3 hours
Blood pressure *							
Pulse **							
Temperature ***							

Routine Observations to ensure patient is fully alert and ambulatory and observe for signs of sedation or delirium

0 – 1 hour Post Injection

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

1 – 3 hours Post Injection

	90mins	120mins	150mins	180mins
Routine Observations**** (tick)				
Completed by:				
Signature:				

Seek medical advice if the patient experiences:

* A decrease in blood pressure of > 20mmHg (diastolic) OR an increase in blood pressure of > 20mmHg (diastolic)
** A pulse over 100 beats per minute OR a pulse less than 55 beats per minute
*** Pyrexia (temperature > 38.5^{o}C)
**** Sedation – asleep and unarousable
Or any other symptoms that you are concerned about.