Guidelines for Prescribing and Administration of Olanzapine Long-acting Injection (Zypadhera®)

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Contents

1. Why we need this guideline

1.1. Purpose

The purpose of this guideline is to inform clinical staff:

- Of clinical appropriateness criteria for using olanzapine long-acting injection
- How to access treatment
- Of pre-requisite training for prescribing and administration
- Of required post administration observations
- Of action to take in the event of a patient experiencing post-injection syndrome

- **This product has been approved for initiation in Secure In-patient Services (SIS). Each request must be supported by signed approval from the Clinical Director**
- **There may be exceptional cases where applications for initiation in other services will be made. These will be assessed by a panel of Clinical Director, Head of Service and Chief Pharmacist before a decision is made.**

1.2. Objectives

This document aims to provide clinical guidance to ensure safe prescribing and administration of olanzapine long-acting injection (Zypadhera®).

2. Scope

2.1. Who this protocol applies to

2.1.1 This treatment will only be provided on an approved named patient basis for the maintenance treatment of schizophrenia in adult patients 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

2.1.2 This treatment has been approved for restricted use:

- In Secure In-patient Services.
- For patients discharged from Secure In-patient Services.
- For patients accepted into service from other Mental Health Trusts, where olanzapine long-acting injection has been initiated

2.1.3 This protocol also applies to exceptional case applications from non-secure services to initiate olanzapine long-acting injection

3. Olanzapine long-acting injection (Zypadhera®) as a treatment option

3.1. Indications / scope of approved use

3.1.1. Olanzapine long-acting injection 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.

3.1.2 Olanzapine long-acting injection is not indicated for treatment-resistant schizophrenia, unlicensed indications or patients intolerant to oral olanzapine.

3.1.3 Olanzapine long-acting injection may only be newly prescribed by consultants. Other prescribers may not adjust doses without direct instruction from their consultant.

3.1.4 Olanzapine long-acting injection may only be administered by deep intramuscular gluteal injection by nurses or doctors who have been trained in the appropriate injection technique.

3.1.5 Administration may only take place in healthcare premises where post-injection observation for 3-hours can be assured. (See section 9, Administration and Post-injection syndrome). Within Secure In-patient Services the observation must be undertaken by specifically trained nurses or doctors. In other services the observation can be undertaken by other appropriately qualified personnel

3.1.6 Olanzapine long-acting injection will not be supplied to wards, units or teams as stock. All supplies must be ordered from pharmacy on a named-patient basis. A named-patient request form must be completed prior to supplies being issued.

3.1.7 Olanzapine long-acting injection is extremely expensive when compared to conventional antipsychotic depots, to oral olanzapine and even to paliperidone and aripiprazole long-acting injections. At highest dose, (300mg / every 2 weeks – equivalent to oral 20mg daily), it costs £5,800 per patient year.

3.2. Prescribing treatment

3.2.1 All patients must have a history of response and tolerability to oral olanzapine before olanzapine long-acting injection is prescribed.

3.2.2 Recommended Doses:

Target oral olanzapine dose	Recommended starting dose of olanzapine long-acting injection	Maintenance dose after two months of treatment
10mg / day	210mg / 2 weeks or 405mg / 4 weeks	150mg every 2 weeks or 300mg every 4 weeks
15mg / day	300mg / 2 weeks	210mg every 2 weeks or 405mg every 4 weeks
20mg / day	300mg / 2 weeks	300mg every 2 weeks

3.2.3 The maximum licensed dose of olanzapine long-acting injection is 300mg every 2 weeks or 405mg when given every 4 weeks.

3.2.4 Before prescribing, patients must be advised about the potential risk of post-injection syndrome and the need to remain in healthcare premises for 3 hours after each injection for post-administration observation. It must be made clear to the patient that this requirement will continue for as long as they remain on this treatment. If it is considered that the patient might not comply with these requirements, olanzapine long-acting injection must not be initiated.

3.2.5 Even if the patient indicates their understanding and consent to the requirements set out in 3.2.4, the consultant and his/her team must consider whether these requirements can be met in the

inpatient setting and whether suitable arrangements for them to be met following discharge into the community are likely to be achievable in terms of access to trained staff and suitable/convenient healthcare premises.

- In SIS, identifying arrangements for administration and post-injection observation in the community must be considered at the earliest point of discharge planning;
- In non-secure services, arrangements for post-discharge administration and post-injection observation must be agreed with the relevant community team and must be specified in the consultant's application to initiate treatment. If post-discharge plans to comply with post-injection observation cannot be assured, the application will not be approved.

3.2.6 Patients must be monitored carefully for signs of relapse during the first one to two months of treatment with olanzapine long-acting injection and the dose should be adjusted according to individual clinical status.

3.2.7 Supplementation of olanzapine long-acting injection with oral olanzapine is not contraindicated but the combination has not been studied in clinical trials. The licensed maximum dose of olanzapine (by either single or combined routes) is 20 mg per day (oral equivalent)

3.3. Other dosing recommendations/considerations

3.3.1 **The elderly**: Olanzapine long-acting injection 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, (150 mg every 4 weeks). Olanzapine long-acting injection should not be started in those over 75 years of age. Olanzapine long-acting injection is not licensed for dementia-related psychosis and/or dementia-related behavioural disturbance.

3.3.2 **Renal and/or hepatic impairment:** Olanzapine long-acting injection should only be used if a well-tolerated and effective oral dose regime has been established. A lower starting dose should be considered (150 mg every 4 weeks).

3.3.3 **Smokers:** Dose adjustment may be necessary if smoking is started or stopped during treatment.

3.3.4 **Children & Adolescents:** Olanzapine long-acting injection is not licensed for use in those less than 18 years of age.

3.3.5 **Plasma half-life:** The plasma half-life of olanzapine after administration of the long-acting injection 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. Post injection syndrome

4.1 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 (confusion, disorientation, agitation, anxiety and other cognitive impairment), as well as extrapyramidal symptoms, dysarthria, ataxia, aggression, dizziness, weakness, hypertension and convulsions. In most cases symptoms appear within one hour of injection but may rarely occur later than one hour and very rarely later than three hours after injection. The 3-hour observation period should be extended if clinically appropriate for a patient exhibiting any signs or symptoms consistent with olanzapine overdose.

In clinical trials the syndrome occurred in less than 0.1% of injections and in approximately 2% of patients.

5. Storage and reconstitution

5.1 Packs of olanzapine long-acting injection should be stored in a locked medicines cabinet. **DO NOT STORE IN THE FRIDGE** as this will render the product unusable.

5.2 Once reconstituted in the vial, olanzapine long-acting injection 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 long-acting injection that has been reconstituted for longer than 24 hours must be discarded.

5.3 Once drawn into the syringe, olanzapine long-acting injection must be used immediately.

6. Request Process

6.1 Requests for approval to initiate Olanzapine long-acting injection must be made completing the single application form **link here** .

6.2 Before the request can be approved, the following criteria must be met and confirmed:

- The patient has successfully responded to oral olanzapine treatment and has been stabilised during acute treatment.
- The patient has schizophrenia and been assessed as having significant adherence problems with antipsychotic therapy that may compromise on-going therapeutic benefits.
- Arrangements have been made, (and agreed with the patient), for every injection to be administered in healthcare premises and for appropriately qualified personnel to be available to observe the patient on site for a minimum of three hours after every injection.
- All nurses and doctors who will be administering the injection have undergone, or will be undergoing, specific training on product administration.
- All appropriate qualified personnel 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.
- Consideration has been given to discharge arrangements including access to suitable community premises for administration and post-injection observation.

7. Training Requirements

7.1 Specific training on product administration and identification & management of post-injection syndrome will involve self-directed study of manufacturer training slides.

- Access to Zypadhera training slides link here – registration will be required.
- Also refer to Administration Guidance found in section 9

8. Discharge Arrangements

8.1 There must be robust discharge planning in order to ensure continued administration of olanzapine long-acting and compliance with the strict post-injection observation requirements

8.2 In secure inpatient services, discharge planning should involve the receiving Forensic Outreach Service and/or Community Mental Health Team at the earliest opportunity after discharge is first considered and no later than 6 months before the Estimated Discharge Date. The receiving team must co-operate with the TEWV inpatient team to ensure that appropriate and robust arrangements are in place for administration and post-injection observation. The inpatient team should not discharge the patient until it is assured that these arrangements are in place.

8.3 In non-secure services, post-discharge arrangements must be agreed with the receiving Community Mental Health Team and must be specified in the application to the panel for approval to initiate treatment. If post-discharge plans to comply with post-injection observation cannot be assured by the panel, the application will not be approved.

8.3 The community team accepting the service user must identify suitable premises for administration and post-injection observation, and ensure staff are trained to do this. This will usually be Trust premises although alternative arrangements may be made in exceptional circumstances. This must be agreed locally with the team and locality managers and the service user must be made aware of arrangements prior to discharge. See appendix 1 for guidance on suitable premises and staff for administration and post-injection observation in community settings.

8.4 The community team remains responsible for ensuring that administration and post-injection observation follows manufacturer's requirements.

8.5 The Trust Pharmacy Team should also be involved in the discharge planning process, including identifying suitable premises and arranging the best method of supplying olanzapine long-acting injection to the community team.

9. Administration guidance

Dose

Check dose and frequency on the prescription and administration record.

Target oral olanzapine dose	Recommended starting dose of olanzapine long-acting injection	Maintenance dose after two months of treatment
10mg / day	210mg every 2 weeks or 405mg every 4 weeks	150mg every 2 weeks or 300mg every 4 weeks
15mg / day	300mg every 2 weeks	210mg every / 2 weeks or 405mg every 4 weeks
20mg / day	300mg every 2 weeks	300mg every 2 weeks

Reconstitution

It is important to note that there is more solvent in the vial than is needed to reconstitute.

Olanzapine long-acting injection vial strength	Volume of solvent to add
210mg	1.3 ml
300mg	1.8 ml
405mg	2.3 ml

Volume to inject

This table shows the final olanzapine injection suspension volume to inject.

Dose	Final volume to inject
150mg	1.0 ml from 210mg vial
210mg	1.4 ml
300mg	2.0 ml
405mg	2.7 ml

Administration

- Prescriber and person administering must have had appropriate training - link here
- Advise patient of risk of post-injection syndrome
- Advise patient of requirement of 3 hour post injection observation (not 'monitoring') in a healthcare facility
- Post injection observations as follows:
  - 0 – 1 hour: At least every 15 minutes, ensuring the patient is fully alert and ambulatory; observe for signs of sedation or delirium. Physical parameters (BP, pulse, temperature) to be measured if clinically indicated
  - 1 – 3 hours: At least every 60 minutes; observing for signs as above. Physical parameters (BP, pulse, temperature) to be measured if clinically indicated
  - >3 hours: Extend observation period if signs or symptoms of overdose and clinically appropriate to do so.
- Tell all patients about the symptoms of post-injection syndrome and give them a Zypadhera® patient information card

Post-injection syndrome

- Post-injection syndrome is probably caused by unintended partial intravascular injection[1]. This occurs in a small number of people, even with appropriate injection technique
- The risk of post-injection syndrome is 0.07%[2] [3] (about one in 1,400 injections).
- Symptoms of post-injection syndrome typically include:

Most commonly reported	**Other Symptoms**
Sedation	Extrapyramidal symptoms
Delirium – including:	Dizziness
Confusion	Dysathria (slurred speech)
Disorientation	Ataxia
Agitation	Aggression
Anxiety	Hypertension
Cognitive impairment	Convulsions

- Typically begins with milder symptoms which progress in severity and/or number and can appear similar to alcohol intoxication.[2]

Time of Onset of Symptoms	Patients
<1 hour	**~ 80%**
1 to 3 hours	**~ 20%**
>3 hours	**~ 5%**

NB: Average time to onset of symptoms in 25 minutes[2]

- If post-injection syndrome occurs immediately call for medical assistance, call an emergency ambulance, give supportive care

References

1. McDonnell DP et al. Post-injection delirium/sedation syndrome in patients with schizophrenia treated with olanzapine long-acting injection, II: investigations of mechanism. BMC Psychiatry 2010; 10:45. 2. Detke 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. 3. Eli Lilly and Company Limited. Zypadhera 210 mg, 300 mg and 405 mg, powder and solvent for prolonged release suspension for injection. Updated 2018. http://www.medicines.org.uk/. Original version adapted from *Protocol for use of olanzapine pamoate long-acting injection* by South London and Maudsley NHS Foundation Trust December 2010

10. Related documents

Medicines Overarching Framework

Depot and Long-Acting Injections - Inpatient Procedure

Depot and Long-Acting Injections - Community Procedure

11. Document control

Date of approval:	26th September 2019	
Next review date:	1st October 2022	
This document replaces:	Version 4	
Lead:	Name	Title
	Richard Morris	Deputy Chief Pharmacist
Members of working party:	Name	Title
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This document has been agreed and accepted by: (Director)	Name	Title
	Ruth Hill	Chief Operating Officer
This document was approved by:	Name of committee/group	Date
	Drug and Therapeutics Committee	21st November 2019)
An equality analysis was completed on this document on::	General pharmacy EA statement applies	

Change record

Version	Date	Amendment details	Status
4	26 Sept 2019	Full review of v3.Minor amendments and updates throughout. Enhanced discharge arrangements added.	Withdrawn
4.1	21 Nov 2019	Appendix 2 - administration & post-injection observation guidance + form added. Section 9 amended in line with this.	Published

Appendix 1 – Arrangements for administration and post-injection observation in community settings

Olanzapine long-acting injection must only be administered by nurses or doctors who have been trained in the appropriate injection technique [Zypadhera training slides link here]

Ideally, administration should take place in healthcare premises – see table below for alternatives if this is not possible.

The choice of premises must enable post-injection observation at least hourly for 3-hours; the patient should be located where s/he can be seen and/or heard.

Ideally, post-injection observations should be undertaken by registered nurses. If this is not possible, observation can be undertaken by other appropriately qualified personnel – see table below

	Location	Staff
Administration	Ideal – Trust healthcare premises Acceptable – Primary healthcare premises; care homes Not suitable – patient's home	TEWV Doctor or any Registered Mental Health Nurse who has been trained in the injection technique
Post-injection observation *N.B. all staff must have read the Zypadhera training slides on post-injection syndrome – link here*		Ideal – any Registered Nurse Acceptable – other qualified healthcare & care home staff Not suitable – non-qualified staff

Arrangements outside of these guidelines could be considered, if appropriate, through the application process

Appendix 2 - Administration & Post-injection Observation

All patients receiving Olanzapine Long-Acting Injection must be observed for a period of **3 hours** post injection. **It must be administered in a healthcare facility by trained staff, unless approval has been granted for alternative arrangements.**

Prior To Injection

1. Before administering each dose of olanzapine LAI, the nurse must check that the patient is aware of the 3 hour post-injection observation requirements and that they are agreeable to comply with these. **If the patient offers any indication that they will not comply seek medical advice on whether to proceed with administration.**
2. Confirm that the patient has consented to receive olanzapine LAI. If the patient is detained under the Mental Health Act, its use should be clearly stated on the relevant T2/T3 form.
3. Ensure the patient is aware of possible side effects and the reason why they are receiving this medication
4. Confirm that the patient is not sedated and is orientated in time and place.
5. Complete baseline observations of **BP, pulse and temperature** before administration and record on the observation chart. This is essential.

Administering Olanzapine Long-acting Injection

Olanzapine LAI should only be administered via deep intramuscular gluteal injection by a healthcare professional trained in the appropriate injection technique. All nurses involved in administration should read and sign below that they have understood the "ZypAdhera Reconstitution and Administration Training" – link

Print Name	*Signature*	*Date*

Following Injection

1. After each injection, patients should be observed by appropriately qualified staff for at least 3 hours for signs and symptoms consistent with olanzapine overdose
2. Record the observations as detailed in the chart below
3. For the remainder of the day following administration, patients should be vigilant for signs and symptoms of olanzapine overdose secondary to post injection adverse reactions, be able to obtain medical assistance, if needed, and not drive or operate machinery.
4. If the patient refuses to stay for the full 3 hours required for post-injection observations, against clinical advice, their blood pressure should be checked prior to leaving the premises. The responsible clinician must be informed as soon as possible, and s/he must review the safety of continuing this treatment before the next dose is due.
5. A summary of the patient's presentation after injection should be made in the clinical notes.

OLANZAPINE LAI – POST-INJECTION OBSERVATION CHART Patient name: …….. Date: ……

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 ***							
Symptoms of Post-Injection Syndrome		*Tick circle to indicate absence / presence*					
Sedation **** (ranging from mild to coma)		O Absent O Present	O Absent O Present	O Absent O Present	O Absent O Present	O Absent O Present	O Absent O Present
Delirium (confusion, disorientation, agitation, anxiety, other cognitive impairment)		O Absent O Present	O Absent O Present	O Absent O Present	O Absent O Present	O Absent O Present	O Absent O Present
Dizziness		O Absent O Present	O Absent O Present	O Absent O Present	O Absent O Present	O Absent O Present	O Absent O Present
Aggression		O Absent O Present	O Absent O Present	O Absent O Present	O Absent O Present	O Absent O Present	O Absent O Present
Weakness		O Absent O Present	O Absent O Present	O Absent O Present	O Absent O Present	O Absent O Present	O Absent O Present
Acute extrapyramidal symptoms		O Absent O Present	O Absent O Present	O Absent O Present	O Absent O Present	O Absent O Present	O Absent O Present
Dysarthria (slurred speech)		O Absent O Present	O Absent O Present	O Absent O Present	O Absent O Present	O Absent O Present	O Absent O Present
Ataxia		O Absent O Present	O Absent O Present	O Absent O Present	O Absent O Present	O Absent O Present	O Absent O Present
Convulsions		O Absent O Present	O Absent O Present	O Absent O Present	O Absent O Present	O Absent O Present	O Absent O Present
Meiosis – constriction of pupils		O Absent O Present	O Absent O Present	O Absent O Present	O Absent O Present	O Absent O Present	O Absent O Present
Observations completed by (initials):							
Time observations taken:							

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.