journey to change

NHS
Tees, Esk and Wear Valleys
NHS Foundation Trust

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Guidelines for Prescribing and Administration of Olanzapine Long-acting Injection

Ref: PHARM-0038-v5

Status: Approved
Document type: Procedure
Overarching policy: Medicines Overarching Framework

Contents

1 Introduction

This procedure is needed to ensure that the Trust prescribes and administers olanzapine long-acting injection (Zypadhera®) safely and in line with the manufacturer's requirements.

- **This product has been approved for initiation in Secure In-patient Services (SIS). Each request must be supported by signed approval from the Psychiatry Lead or Associate Medical Director**
- **There may be exceptional cases where applications for initiation in other services will be made. These will be assessed by a panel of Lead Psychiatrist, General Manager and Chief/Deputy Chief Pharmacist before a decision is made.**

This procedure supports Our Journey to Change as set out in the Medicines Overarching Policy

2 Purpose

Following this procedure will help the Trust to ensure safe prescribing and administration of olanzapine long-acting injection (Zypadhera®).

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

3 Who this procedure applies to

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.

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 treatment with olanzapine long-acting injection has been established.

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

4 Related documents

This procedure describes what you need to do to implement sections 4.1.1.2 and 4.6.4 of the Medicines Overarching Framework

The Medicines Overarching Framework defines how to prescribe, administer and monitor pharmacological treatment which you must read, understand and be trained in before carrying out the procedures described in this document.

This procedure also refers to:

- Antipsychotic Depot LAIs - prescribing administration medicines management guidelines

5 Olanzapine long-acting injection as a treatment option

5.1 Indication / scope of approved use

- 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.
- Olanzapine long-acting injection is not indicated for treatment-resistant schizophrenia, unlicensed indications, or for patients intolerant to oral olanzapine.
- Olanzapine long-acting injection may **only** be newly prescribed by consultants. Other prescribers may not adjust doses without direct instruction from their consultant.
- 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.
- Administration may only take place in healthcare premises where post-injection observation for three hours can be assured. Within Secure In-patient Services (SIS), the observation must be undertaken by specifically trained nurses. In other services the observation can be undertaken by other appropriately trained personnel (see appendix 1).
- Olanzapine long-acting injection will not be supplied to wards, units, or teams as stock with the exception of SIS. 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.
- Olanzapine long-acting injection is extremely expensive when compared to conventional antipsychotic depots, oral olanzapine and even to paliperidone and aripiprazole long-acting injections. At highest dose (300 mg every 2 weeks – equivalent to oral 20 mg daily), it costs £5,800 per patient per year.

5.2 Prescribing treatment

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

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

- The maximum licensed dose of olanzapine long-acting injection is 300 mg every 2 weeks or 405 mg every 4 weeks.
- 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. Similarly, olanzapine long-acting injection must be discontinued if a patient is non-compliant or indicates that they will not comply with required monitoring at any time during treatment.
- Even if the patient indicates their understanding and consent to the requirements set out above 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 by the receiving team 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.
- 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.
- 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)

5.3 Other dosing recommendations / considerations

- **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.

- **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).
- **Smokers**: Dose adjustment may be necessary if smoking is started or stopped during treatment.
- **Children & Adolescents**: Olanzapine long-acting injection is not licensed for use in those less than 18 years of age.
- **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.

6 Post injection syndrome

- The exact mechanism remains unknown, but the clinical manifestations are consistent with those of olanzapine toxicity. 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 toxicity.
- In clinical trials the syndrome occurred in less than 0.1% of injections and in approximately 2% of patients.

7 Request Process

- Requests for approval to initiate Olanzapine long-acting injection must be made completing the single application form
- 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 trained 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 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.

8 Discharge Arrangements

- There must be robust discharge planning in-order-to ensure continued administration of olanzapine long-acting injection and compliance with the strict post-injection observation requirements.
- In secure inpatient services, discharge planning should involve the receiving Forensic Community 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 as described in section 10.1. The inpatient team should not discharge the patient until it is assured that these arrangements are in place.
- 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.
- 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.
- The community team remains responsible for ensuring that administration and post-injection observation follows manufacturer's requirements.
- 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 Storage and reconstitution

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.

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

10 Administration guidance

10.1 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
10 mg / day	210 mg every 2 weeks or 405 mg every 4 weeks	150 mg every 2 weeks or 300 mg every 4 weeks
15 mg / day	300 mg every 2 weeks	210 mg every / 2 weeks or 405 mg every 4 weeks
20 mg / day	300 mg every 2 weeks	300 mg every 2 weeks

- Every effort should be made to administer doses on the exact due date. However, it is recognised this may not always be possible, particularly in community settings, e.g. due to patient non-attendance. There may also be occasions when it is planned to give a dose early or late, e.g. if the patient is going on holiday or unavoidable service/staffing pressures exist. In these circumstances, the acceptable therapeutic tolerance around the due date, within which the dose can be given without clinically significant impact on efficacy or need for supplementary action, is **+/- 2 days for a 2-weekly interval**, and **+/- 4 days for a 4-weekly interval**. Nursing staff may administer doses within these tolerances without prescriber approval but must not repeatedly utilise these tolerances as this may affect long-term efficacy or tolerability.
- If a missed dose cannot be given within these tolerances discuss with the prescriber and seek pharmacy advice on how to restore therapeutic stability, e.g. additional “once only” injection or time-limited oral supplementation. **An incident must be reported if a dose is not given within tolerances due to staff or service error.**

10.2 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
210 mg	1.3 ml
300 mg	1.8 ml
405 mg	2.3 ml

10.3 Volume to inject

This table shows the final olanzapine injection suspension volume to inject

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

10.4 Administration and post-injection observations

- Prescriber and person administering must have had appropriate training - link to Zypadhera training.
- Check patient has eaten and drunk something earlier in the day.
- Advise patient of risk of post-injection syndrome
- Advise patient of requirement of 3-hour post injection observation. (not 'monitoring') in a healthcare facility. Patients should be located where they can be seen.
- Before administering in the community setting, determine that the patient will not be driving to their next destination after they leave the healthcare facility.

10.4.1 Post injection observations

- **0 – 1 hour** At least every 15 minutes, ensuring the patient is fully alert, able to talk coherently and able to walk; observe for signs of sedation or delirium. Physical parameters (BP, pulse, temperature) to be measured only if clinically indicated.
- **1 – 3 hours** At least every 60 minutes; observing for signs as above. Physical parameters (BP, pulse, temperature) to be measured only if clinically indicated.
- **>3 hours** Extend observation period if signs or symptoms of toxicity and clinically appropriate to do so.
- Immediately prior to leaving the healthcare facility, a registered nurse or doctor should be satisfied that the patient is alert, orientated and absent of signs or symptoms of post-injection syndrome.
- Inform all patients about the symptoms of post-injection syndrome and ensure they have been given an appropriate patient information leaflet. Patients should be vigilant for these symptoms for the remainder of the day and advised to not drive or operate machinery.

10.4.2 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	Dysarthria (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 (average time to onset of symptoms is 25 minutes[2])	Patients
<1 hour	~ 80%
1 to 3 hours	~ 20%
>3 hours	~ 5%

- If post-injection syndrome occurs, immediately call for medical assistance, call an emergency ambulance and give supportive care.
- Record details of presentation and intervention required in patient electronic record.

11 Definitions

Term	Definition
Long-acting injection	• A formulation (of an antipsychotic in this context) which does not require daily administration; usually given weekly, 2-weekly or 4-weekly/monthly, or even less frequently; usually referred to as a "depot"

12 How this procedure will be implemented

• This procedure will be published on the Trust's intranet and external website.
• Line managers will disseminate this procedure to all Trust employees through a line management briefing.
• Its publication, and notification of key changes since previous version, will be communicated via the Medicines Optimisation newsletter

12.1 Training needs analysis.

Staff/Professional Group	Type of Training	Duration	Frequency of Training
Medical staff Registered nurses Non-registered healthcare staff who may be required to complete post-injection observations Care home staff who may be required to complete post-injection observations	Product administration and identification & management of post-injection syndrome Self-directed study of manufacturer's slides available zypadhera training link (registration required)	1 hour	Once only

13 How the implementation of this procedure will be monitored

Number	Auditable Standard/Key Performance Indicators	Frequency/Method/Person Responsible	Where results and any Associate Action Plan will be reported to, implemented and monitored; (this will usually be via the relevant Governance Group).
1	Number of approved applications to initiate treatment	Ad-hoc report Deputy Chief Pharmacist	Drug & Therapeutics Committee
2	Incident reports relating to olanzapine LAI (e.g. omitted or incorrect doses, post-injection observations not done)	Monthly incident report Lead Technician Patient Safety	Medicines Management Group

14 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. (Accessed online May 23). http://www.medicines.org.uk/.

4. Original version adapted from Protocol for use of olanzapine pamoate long-acting injection by South London and Maudsley NHS Foundation Trust December 2010

15 Document control (external)

To be recorded on the policy register by Policy Coordinator

Required information type	Information
Date of approval	27 July 2023
Next review date	01 August 2026
This document replaces	V4.1 Guidelines for Prescribing & Administration of Olanzapine Long-acting Injection
This document was approved by	Drug and Therapeutics Committee
This document was approved	27 July 2023
This document was ratified by	n/a
This document was ratified	n/a
An equality analysis was completed on this policy on	Pharmacy Overarching EA applies
Document type	Public
FOI Clause (Private documents only)	n/a

Change record.

Version	Date	Amendment details	Status
4	26 September 2019	Full review of v3. Minor amendments and updates throughout. Enhanced discharge arrangements added.	Superseded
4.1	21 November 2019	Appendix 2 - administration & post-injection observation guidance + form added. Section 9 amended in line with this.	Superseded
5	27 July 2023	Full review of v4.1. Increased clarity on post-injection observations in community settings – use of “trained” instead of “qualified” in relation to staff who can perform observations. Simplification of observation chart	Published

16 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 they can be seen**.
- Ideally, post-injection observations should be undertaken by a registered nurse. If this is not possible, observation can be undertaken by other appropriately trained personnel – see table below.

Activity	Staff	Location
Administration	TEWV Doctor or any Registered Mental Health Nurse who has been trained in the injection technique.	Access to emergency services is essential. Ideal – Trust healthcare premises Acceptable – Primary healthcare premises; care homes Not acceptable – patient's home
Post-injection observation *N.B. all staff must have read the Zypadhera training slides on post-injection syndrome*	Ideal – any Registered Nurse* Acceptable – other appropriately trained healthcare & care home staff* Not acceptable – untrained staff	Access to emergency services is essential. Ideal – Trust healthcare premises Acceptable – Primary healthcare premises; care homes Not acceptable – patient's home

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

**appropriately trained in post-injection syndrome observations following completion of Zypadhera training slides and understands the signs & symptoms to look for. Team manager is responsible for ensuring that this training has been completed and understood by staff who will be involved in the observations.*

17 Appendix 2 – Process for administration & post-injection observation in the community setting

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.		
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.		
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 trained staff for at least 3 hours for signs and symptoms consistent with olanzapine toxicity		
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 toxicity 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 they must review the safety of continuing this treatment before the next dose is due.		
5. Immediately prior to leaving the healthcare facility, a registered nurse or doctor should be satisfied that the patient is alert, orientated and absent of signs or symptoms of post-injection syndrome.		
6. A summary of the patient's presentation after injection should be made in the clinical notes.		

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

Time injection given:		**Time after injection:**					
Physical health monitoring *(post-injection: only if clinically indicated)*	Baseline (pre-injection):	15 mins Time:	30 mins Time:	45 mins Time:	1 hour Time:	2 hours Time:	3 hours Time:
Blood pressure *							
Pulse **							
Temperature ***							
Observations:							
Patient is alert		Yes / No	Yes / No	Yes / No	Yes / No	Yes / No	Yes / No
Patient is orientated		Yes / No	Yes / No	Yes / No	Yes / No	Yes / No	Yes / No
Patient is free from signs & symptoms of toxicity: • Sedation • Dizziness • Irritable or aggressive • Anxious • Difficulty talking or walking. • Weakness • Muscle stiffness or shaking • Convulsions		Yes / No	Yes / No	Yes / No	Yes / No	Yes / No	Yes / No
Observations completed by (initials):							

Seek medical advice if 'No' is answered to any observation questions and/or 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 > 38.5ºC)
Or any other symptoms that you are concerned about.

Appendix 3 – Approval checklist

To be completed by lead and attached to any document which guides practice when submitted to the appropriate committee/group for consideration and approval.

	Title of document being reviewed:	Yes/No/ Not applicable	Comments
1.	**Title**		
	Is the title clear and unambiguous?	Yes	
	Is it clear whether the document is a guideline, policy, protocol or standard?	Yes	Guideline in procedure format
2.	**Rationale**		
	Are reasons for development of the document stated?	Yes	Not a new document but purpose is stated
3.	**Development Process**		
	Are people involved in the development identified?	Yes	
	Has relevant expertise has been sought/used?	Yes	
	Is there evidence of consultation with stakeholders and users?	Yes	
	Have any related documents or documents that are impacted by this change been identified and updated?	Yes	
4.	**Content**		
	Is the objective of the document clear?	Yes	
	Is the target population clear and unambiguous?	Yes	
	Are the intended outcomes described?	Yes	
	Are the statements clear and unambiguous?	Yes	
5.	**Evidence Base**		
	Is the type of evidence to support the document identified explicitly?	Yes	
	Are key references cited?	Yes	
	Are supporting documents referenced?	Yes	
6.	**Training**		
	Have training needs been considered?	Yes	
	Are training needs included in the document?	Yes	
7.	**Implementation and monitoring**		

	Title of document being reviewed:	Yes/No/ Not applicable	Comments
	Does the document identify how it will be implemented and monitored?	Yes	
8.	**Equality analysis**		
	Has an equality analysis been completed for the document?	No	Overarching EA for pharmacy document applies
	Have Equality and Diversity reviewed and approved the equality analysis?	Yes	Approved above document
9.	**Approval**		
	Does the document identify which committee/group will approve it?	Yes	D&T committee
10.	**Publication**		
	Has the document been reviewed for harm?	Yes	Edit made
	Does the document identify whether it is private or public?	Yes	Public
	If private, does the document identify which clause of the Freedom of Information Act 2000 applies?	N/A	