Clozapine: processes for prescribing, dispensing, monitoring & supply

journey to change

NHS Tees, Esk and Wear Valleys NHS Foundation Trust

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Top tip for finding content in this guide:
Use "**Ctrl F**" and enter a search term to find specific guidance or processes.

Title	Clozapine: processes for prescribing, dispensing, monitoring & supply	
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Clozapine as a treatment option (1)

Potential benefits of clozapine

- The only licensed medicine for treatment resistant schizophrenia
- Superior to other antipsychotics at reducing positive symptoms in treatment resistant schizophrenia
- Significantly reduces suicidal behaviour and risk of mortality from suicide
- Reduces all-cause mortality including cardiovascular and natural causes
- Reduces aggression and violent behaviours
- Reduces the risk of admission to hospital and shortens the length of hospital stay

Risks of delaying clozapine

- Patients are less likely to respond if it is started later than 3 years after first relapse
- Higher episodes of psychotic relapse leads to decline in socio-economic status, loss of independence, lower quality of life, development of chronic residual symptomatology, and higher risk of mortality
- Use of High Dose Antipsychotic Therapy (HDAT) and polypharmacy instead of clozapine increases the risk of adverse effects and prolongs the duration of sub-optimal treatment

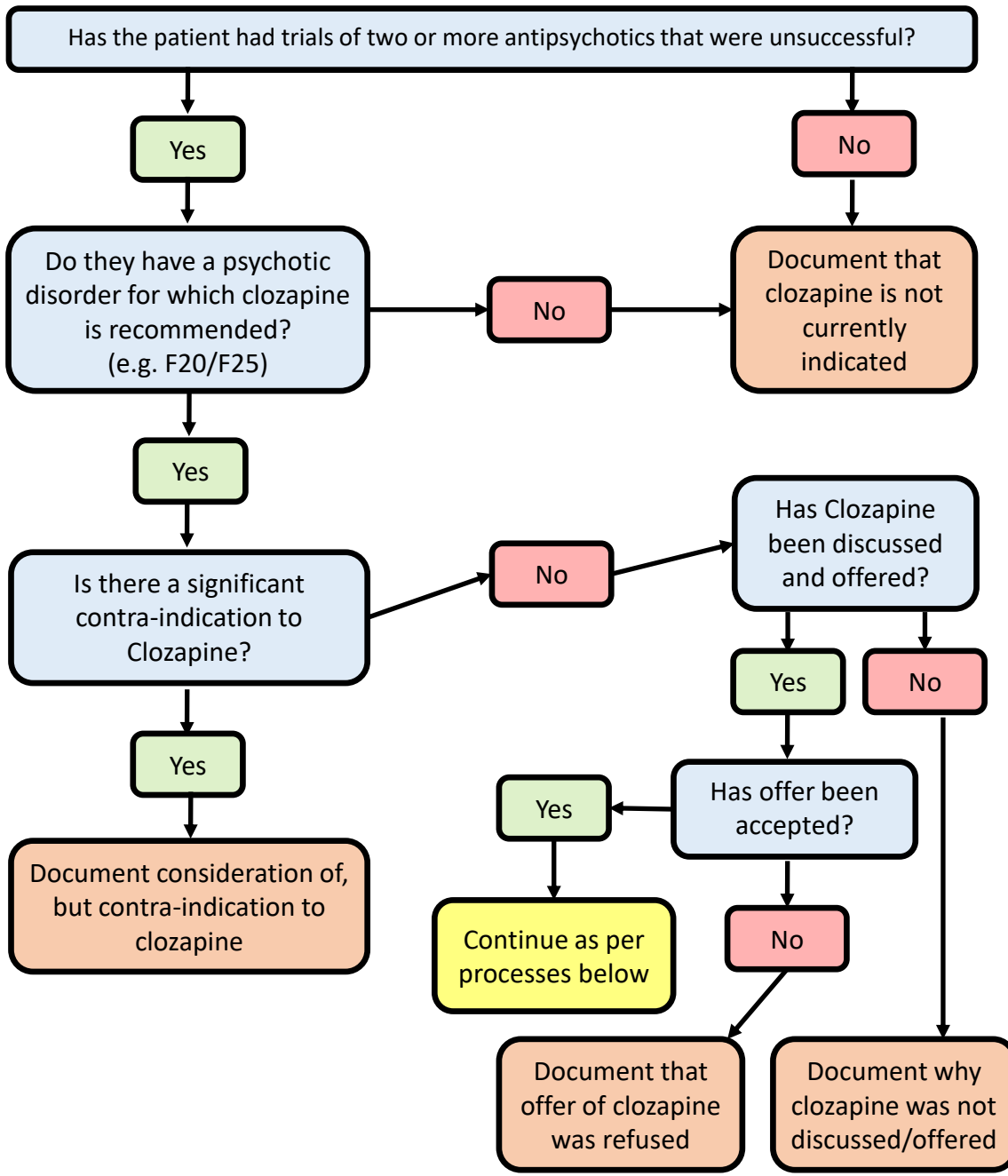
Current Practice

- Clozapine is widely underutilised and possibly as few as 25% of eligible patients are prescribed clozapine across TEWV
- Concern about rare, but potentially life-threatening side effects has generated an overly cautious approach to clozapine

Clozapine as a treatment option (2)

- Licensed indications
  - Schizophrenia in patients unresponsive to, or intolerant of, conventional antipsychotic drugs
  - Psychosis in Parkinson's disease
- NICE guidance (CG178)
  - Offer clozapine to people with schizophrenia whose illness has not responded adequately to treatment despite the sequential use of adequate doses of at least 2 different antipsychotic drugs. At least 1 of the drugs should be a non-clozapine second-generation antipsychotic.
- Contra-indications (Clozaril® / Clozapine Mylan SPC) – *see this slide if clozapine is still being considered*
  - Patients unable to undergo regular blood tests
  - Alcoholic and toxic psychoses; drug intoxication; comatose conditions
  - Bone marrow disorders
  - History of agranulocytosis or neutropenia
  - History of circulatory collapse and/or CNS depression
  - Paralytic ileus
  - Severe renal or cardiac disorders (e.g. myocarditis)
  - Active liver disease associated with nausea, anorexia or jaundice; progressive liver disease, hepatic failure.
  - Uncontrolled epilepsy
- Product options / preferences:
  1. Clozaril®/ Clozapine Mylan tablets – default for all TEWV patients
  2. Zaponex® oro-dispersible tablets – for swallowing / compliance challenges
  3. Denzapine® suspension – by application for exceptional cases only

  Standard tablets of Zaponex or Denzapine should be avoided and patients changed to Clozaril / Clozapine Mylan as soon as appropriate.



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Risks associated with clozapine

- Clozapine is associated with serious and potentially life-threatening adverse effects
- These risks need to be viewed in the context of the risks of untreated schizophrenia, the risks of other antipsychotic use, and the overall reduction in mortality risk associated with clozapine use
- Appropriate monitoring and management can reduce the risk of adverse outcomes

Adverse Effect	Incidence
Mild neutropenia	3.9% (1 in 25)
Severe neutropenia (Agranulocytosis)	0.7% (1 in 143)
Myocarditis	0.3% (1 in 333)
Life-threatening gastric hypomotility	0.3% (1 in 333)
Pneumonia	1.9% (1 in 53)*

*and increases overall mortality risk

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Unlicensed or off-label use of clozapine

Wherever possible, clozapine should be used within the relevant product licence and should not be prescribed for a patient who has a contra-indication. However, it is recognised that there are cases where clozapine is the best or only treatment option and unlicensed or off-label use is necessary.

Unlicensed use:

- Inpatient note - any plan to initiate clozapine outside the product licence for an inpatient must be discussed and agreed with the patient's responsible clinician in the community before proceeding as follows:
- The responsible clinician MUST notify the relevant clozapine monitoring service at the point of registration if treatment with clozapine will be unlicensed, i.e. if any of the following apply:
  - patient has previously stopped treatment due to a confirmed RED result (i.e. this is a re-challenge)
  - standard mandatory blood monitoring is unlikely to be achieved (e.g. frail Parkinson's disease)
  - patient has another contra-indication (see this slide)
- If registration is approved by the monitoring service, this should be documented in the electronic patient record (e.g. copy and paste of email). Trust approval should then be sought via the relevant lead psychiatrist or AMD using the single application form.

Off-label indications:

- Initiation for an off-label indication does not need prior approval of the relevant monitoring service or Trust but must be notified to the monitoring service on the patient registration form.
- All other requirements of off-label prescribing in Trust guidelines apply, e.g. informed patient consent.

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Patient education & information provision

- When clozapine is being considered, the responsible clinician must arrange for an appropriately experienced clinician (e.g. clinical pharmacist) to discuss all aspects of treatment with the patient and/or carer – this is to ensure informed consent. The discussion must include potential benefits, risks, side-effects and monitoring requirements, with provision of appropriate level information leaflet(s) from the relevant manufacturer and/or the Choice & Medication website.
- With patients of child-bearing potential, highlight the need for pre-conception counselling if there are any plans for pregnancy
- Once the patient has provided consent to treatment, the same clinician (ideally) should go through the Choice & Medication patient information with the patient and particularly bring their attention to the following key points:
    - **AVOID MISSING DOSES** – if doses are not taken for >48 hours, treatment will need to be re-started at low dose; tell somebody if you miss any doses
    - **AVOID DRINKING ALCOHOL** - will enhance any drowsiness caused by clozapine; too much alcohol can be dangerous; tell somebody if alcohol consumption increases
    - **AVOID EXCESSIVE CAFFEINE-containing drinks** – may increase the effects of clozapine; tell somebody if caffeine intake changes (increase or decrease)
    - **SMOKING** – tell somebody if you start or stop smoking, this will affect clozapine levels and the dose may need to be adjusted
    - **CONSTIPATION** – tell somebody if you can't poo, have stomach pains or feel sick
    - **FEVER** – tell somebody if you get an unexpected fever, sore throat or other flu-like symptoms

A record of the discussion and provision of information to the patient/carer must be fully documented in the electronic patient record, including any questions asked and the responses given.

Assess patient/carer/family understanding and explain why questions will be regularly asked for monitoring purposes.

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Staff & patient registration

- The default clozapine product used in TEWV is **Clozaril®/Clozapine Mylan**
- The Clozaril Patient Monitoring Service (CPMS) provides the centralised monitoring of leucocyte and neutrophil counts which is a mandatory requirement for all patients in the UK who are treated with clozapine
- The use of Clozaril®/Clozapine Mylan is restricted to patients who are registered with the CPMS. In addition to registering their patients, prescribing physicians must register themselves and a nominated dispensary with the CPMS (if not already registered)
- All Clozaril®/Clozapine Mylan-treated patients must be under the supervision of an appropriate specialist and supply of Clozaril®/Clozapine Mylan is restricted to hospital and retail pharmacies registered with the Clozaril Patient Monitoring Service [each of TEWV's pharmacy dispensaries are registered]
- Patients who need to be prescribed a different brand of clozapine (see this slide) must be registered with the relevant monitoring service – ZTAS (Zaponex) or DMS (Denzapine)

The CPMS **Patient Registration & Transfer Form** is available here:

CPMS Patient Registration & Transfer Form

N.B. this form must be signed by either the supervising specialist (RC) or a "lead pharmacist" registered with CPMS.

The CPMS **Supervising Specialist Registration form** is available here:

CPMS Supervising Specialist Registration form

The **CPMS access form** is available here:

CPMS access form

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Considerations for initiation & titration of clozapine

- Many side effects from clozapine appear early in treatment and the initial months present the highest risk for discontinuation due to side effects; this can be minimised by slow and careful dose titration
- The titration schedule recommended on this slide is recommended for low-risk patients, without co-morbidities
- Variation from these may be necessary according to patient-specific factors, e.g. age, co-morbidity, emergence of early side-effects – see this slide
- Theoretical target doses are broad estimates to reach a minimum therapeutic plasma level (i.e. 0.35 mg/L) but should be personalised based on an individual's metabolism and experience to optimise tolerability
- Prescribers should avoid titrating directly to these doses without assessing an individual's metabolism, using therapeutic drug monitoring
- Some patients may respond with clozapine levels below 0.35 mg/L, however the likelihood of response is doubled once levels are >0.35 mg/L

	Theoretical Target Daily Dose* *Reeves. et al. 2023*		
Gender	**Male**	**Female**	**Ethnicity**
Smoker	375 mg	300 mg	White
	400 mg	325 mg	Afro-Caribbean
	250 mg	225 mg	Asian
Non-Smoker	275 mg	200 mg	White
	300 mg	250 mg	Afro-Caribbean
	250 mg	175 mg	Asian

*Based on assumed weight = 70 kg, age = 40 yrs; do not apply to treatment of Parkinson's disease psychosis – see this slide

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Personalised titration of clozapine for schizophrenia

See here for considerations in under-18s & over-60s
See here for titration in **psychosis associated with Parkinson's disease**

- Measure plasma level at Day 15 and calculate a personalised target dose using the calculation on this slide – maintain the day 14 dose until the plasma level is available and target dose can be calculated (unless there is a clinical indication to increase, or reduce, the dose in the meantime)
- Once the target dose is calculated, continue upward titration in steps of 25mg every 1-2 days
- Once the target dose is reached, and has been taken for at least 4 days, repeat the plasma level measurement and, if required, adjust the clozapine dose to achieve a minimum level of 0.35mg/L
- If a significant response (symptomatically improved) is seen below the target dose (or below 0.35mg/L), maintain the current clozapine dose.

	Total daily dose (mg)			
Day	**Female NS**	**Male NS**	**Female S**	**Male S**
1	6.25*	6.25*	6.25*	6.25*
2	6.25*	6.25*	12.5	12.5
3	12.5	12.5	25	25
4	18.75	18.75	37.5	37.5
5	25	25	50	50
6	25	25	50	50
7	50	50	75	75
8	50	50	75	75
9	75	75	100	100
10	75	75	100	125
11	100	100	125	150
12	100	100	125	150
13	100	100	125	150
14	100	100	125	150
15	**Measure Plasma level** Onward titration will be based on target dose calculation			

NS = non-smoker; S = smoker
**single daily dose, at bedtime*
Total daily doses of 12.5 mg and above can be prescribed as a single dose at bedtime, or as a divided dose in the morning & at bedtime

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Personalising the target dose in new patients

- Once the titration reaches a stable dose of 100-150 mg/day for a minimum of 4 days, a plasma level should be measured
- This informs calculation of a personalised target dose, accounting for the individual's metaboliser status, using the **Concentration: Dose ratio (C/D Ratio**)
- Higher C/D ratios (e.g. >2) indicate lower metabolism and a need for more cautious titration

Step 1

$$\frac{\text{Plasma Level} \times 1000}{\text{Dose}} = \text{C/D Ratio}$$

Step 2

$$\frac{\text{Target Level} \times 1000}{\text{C/D Ratio}} = \text{Target Dose}$$

Example: dose = 200 mg/day, clozapine level = 0.2 mg/L

Step 1:

$$\frac{0.2 \text{ mg/L} \times 1000}{200 \text{ mg}} = \text{C/D Ratio 1 = Average metabolism}$$

Step2:

$$\frac{0.35 \text{ mg/L} \times 1000}{\text{C/D Ratio 1}} = \text{Target dose } 350 \text{ mg/day}$$

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Considerations for initiation & titration of clozapine	Recommendations
Age under 18 years Akathisia may be more problematic	• Apply the personalised titration schedule but if akathisia or other side-effects occur, reduce dose or slow down titration; continue according to tolerability • Dose must be unchanged for 4-5 days prior to checking plasma levels
Age over 60 years Sedation, orthostasis and tachycardia may contribute to falls risk	• Apply the personalised titration schedule but if side-effects occur, reduce dose or slow down titration; continue according to tolerability • Dose must be unchanged for 4-5 days prior to checking plasma levels
Cardiovascular disease Risk of myocarditis in early treatment	• Seek cardiology advice if any history of cardiac illness or abnormal findings on pre-treatment examination – assess risk : benefit • Consider additional monitoring during initiation, e.g. troponin (check local labs), C-reactive protein (Ronaldson protocol)
Diabetes Blood glucose control may be impaired	• Monitor FBG / HbA1c as per Trust monitoring guidelines • Discontinue clozapine if hyperglycaemia persists despite active medical management
Liver disease Contra-indicated in active liver disease	• Monitor LFTs as per Trust monitoring guidelines
Epilepsy Contra-indicated in uncontrolled epilepsy; clozapine lowers the seizure threshold	• Avoid rapid dose increases and stabilise at lowest effective dose to minimise risk
Gastrointestinal disease Increased risk of constipation – see Trust guidance	• Monitor bowel function - daily during titration / as inpatient; at every clinic visit in community • Avoid / minimise concurrent anticholinergic drugs
Benign Ethnic Neutropenia (BEN) Naturally low WBC counts	• Seek haematology advice before starting treatment • Notify monitoring service of BEN status at registration
Interacting medication May affect metabolism or increase risk of neutropenia	• Check SmPC (section 4.4), this slide and this information – if necessary, seek pharmacy advice before starting treatment • Initiation or discontinuation of hormonal contraceptives may require dose adjustment of clozapine according to individual need
Tobacco smoking Increases clozapine metabolism / reduces levels	• Consider higher target dose • Check levels and/or adjust dose if smoking status changes (temporarily or permanently) as per Trust guidance
Caffeine intake Competes for metabolism / may increase levels	• Check levels and/or adjust dose in response to a significant change in intake (up or down) – see Trust guidance
Infection / inflammation May inhibit clozapine metabolism / increase levels	• Check levels and/or adjust dose in presence of pneumonia or other serious infection (requiring hospital admission), or if there is a history of elevated levels or increase in side-effects associated with less serious infections

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Patients receiving chemotherapy & other immune-modulating medication

- Clozapine is contraindicated if taken with substances known to have a substantial potential for causing agranulocytosis; however, stopping clozapine before or during chemotherapy is likely to have a negative impact on the patient's mental state and may not be clinically appropriate
- Continuation of clozapine in such circumstances is therefore 'off label' and requires completion of a risk acknowledgement form by the RC
- The form also allows authorisation of lower-than-normal thresholds for clozapine FBC RAG alerts and increased frequency of FBC monitoring
- Discussion with the oncology/haematology teams involved is recommended to assess the likelihood of chemotherapy-induced neutropenia and pro-active arrangements for bone-marrow stimulation e.g. granulocyte-colony stimulating factor (GCSF)

Initiation and titration for psychosis associated with Parkinson's disease

- The starting dose must not exceed 12.5 mg/day, administered in the evening
- Dose increments should be of 12.5 mg, at a maximum of twice a week, up to a maximum dose of 50 mg/day, which should not be reached until the end of the second week
- Only use doses >50 mg/day in exceptional cases and never >100 mg/day
- The total daily amount should preferably be given as a single dose in the evening
- Dose increases should be limited or deferred if orthostatic hypotension, excessive sedation or confusion occur
- Blood pressure should be monitored frequently during the first weeks of treatment – DAILY for the first 2 weeks, WEEKLY thereafter
- When there has been complete remission of psychotic symptoms for at least 2 weeks, anti-Parkinsonian medication can be increased if indicated. If there is recurrence of psychotic symptoms, clozapine dosage may be increased by increments of 12.5 mg/week up to a maximum of 100 mg/day taken in one or two divided doses
- Ending therapy: a gradual reduction in dose by steps of 12.5 mg over a period of at least 1 week (preferably 2 weeks) is recommended. Treatment must be ended immediately in the event of neutropenia or agranulocytosis, with careful psychiatric monitoring owing to the risk of recurrence of symptoms

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Inpatient initiation checklist

Document completion of all tasks in the electronic patient record

Pre-initiation:

- ❑ Patient education & information
- ❑ Patient consent (or MHA authorisation)
- ❑ Baseline FBC to local path lab (valid x 10 days)
- ❑ Complete baseline physical examination:
  - *Temperature, BP, pulse, ECG, respiratory rate, joint reflexes, height, weight*, waist circumference*
- ❑ Baseline blood tests:
  - *U&Es, lipids, LFTs, prolactin, HbA1c*
- ❑ Register with CPMS or equivalent
- ❑ Prescribe first dose on EPMA (ideally at bedtime)
- ❑ Order initial supply from Trust dispensary

**calculate weight increase threshold [= baseline weight x 1.05]*

Day 1 – initiation:

- ❑ Complete NEWS immediately prior to first dose* – if no concerns…
- ❑ Administer first dose

If first dose not at bedtime…

- ❑ Complete NEWS-2 hourly x 6 hours
- ❑ Add clozapine to significant medication alert on electronic patient record
- ❑ Arrange date of next FBC (within 10 days of baseline)
- ❑ Prescribe titration doses for next day(s) on EPMA according to initial tolerability

**seek medical advice if any concerns*

Day 2-14 – titration:

- ❑ Prescribe doses for next day(s) on EPMA according to ongoing tolerability
- ❑ Administer doses as prescribed
- ❑ Order further supplies as needed
- ❑ FBC & CRP within 10 days of baseline (repeat +1 week later if needed)
- ❑ Complete NEWS-2 at least **daily** (ideally 2-6 hours post dose)*
- ❑ Check side effects **daily***
  - *Constipation, sedation, hypersalivation, nocturnal enuresis, nausea, infection*
  - *Complete GASS-C **weekly***
- ❑ **Day 7 & 14** – check & record weight*
- ❑ Assess mental state **daily***

**seek medical advice if any concerns*

Day 15+ - stabilisation:

- ❑ **Day 15**: bloods for plasma level
- ❑ Once plasma level known, calculate C/D ratio & target dose; prescribe ongoing titration doses
- ❑ Once target dose reached & taken for 4 days, re-check plasma level; adjust maintenance dose to achieve target level
- ❑ Order further supplies as needed
- ❑ FBC & CRP **weekly**
- ❑ Complete NEWS-2 at least **weekly** (more frequently if any parameters out of range)*
- ❑ Check side effects using GASS-C at least **weekly** (more frequently if indicated)*

• *Constipation, sedation, hypersalivation, nocturnal enuresis, nausea, infection*

- ❑ Check & record weight **weekly****
- ❑ Assess mental state at least **weekly**
- ❑ **Week 4 –** check HbA1c
- ❑ **Week 12** – check ECG, lipids, prolactin

**seek medical advice if any concerns*
***if weight >5% above baseline within 1 month of initiation, consider intervention*

Initiation in community settings

Clozapine initiation in the community offers many advantages over inpatient initiation but there are several important considerations to ensure safety.

Service user criteria for community initiation

- Meets the indications for clozapine; no contra-indications.
- Not in acute crisis requiring weekend monitoring.
- Able to give informed consent to starting clozapine.
- Understands and agrees to blood test and physical health monitoring.
- Engages with health care services, including medical assessment, and will comply with the medication/monitoring schedule.
- Readily contactable in the event of a result that needs follow-up.
- Willingness and consent to access to their home if necessary, and to attend clinic when planned.
- Not on any other medication that may significantly interact with clozapine.
- Able to understand, reliably report and act on side-effects (either to inform the team or seek emergency care if needed) *or* has a reliable carer that can stay with them for the duration of the titration.

Reasons to consider inpatient initiation

- Disorganised or in acute crisis and unable or unwilling to comply with monitoring
- Pregnancy or breast feeding
- Prior hypersensitivity to clozapine or its constituents.
- Myeloproliferative disorders or with a history of toxic or drug-induced neutropenia / agranulocytosis (except for previous chemotherapy or Benign Ethnic Neutropenia (BEN) registration)
- Impaired bone marrow function
- Uncontrolled epilepsy / unexplained seizures
- History of neuroleptic malignant syndrome (NMS)
- Severe cardiac disease (e.g. history of MI, arrhythmia, cardiomyopathy, myocarditis)
- Severe renal impairment
- History of coma / collapse / severe CNS depression
- Paralytic ileus
- Concomitant use of other agents having a well-known potential to cause agranulocytosis or cause bone marrow suppression
- Lives alone / alone overnight

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Initiation in community settings

- Start on MONDAY, if possible, to optimise access to monitoring in early days
- The monitoring frequency during titration can vary based on individual needs. The frequency chosen should be agreed and documented in the patient's EPR

Low Frequency

- Weeks 1 & 2 – three times a week
- Weeks 3 & 4 – two times a week
- Week 5 onwards – once a week or once a fortnight thereafter when there are dose changes (less often if no changes)

Suitable for patients who:

- are able to report side-effects and seek help if needed
- have no indicators that they would be at significant risk from side-effects e.g. history of hypotension, and/or frailty

Higher Frequency

- Weeks 1 & 2 – daily Monday to Friday
- Week 3 – three times
- Week 4 – two time
- Week 5 onwards – once a week

Suitable for patients who:

- need a more rapid titration
- have increased risk of side-effects due to e.g. frailty or history of hypotension

At every monitoring appointment check:

- BP (ideally lying and standing)
- Pulse
- Temperature
- Side-effects (GASS-C weekly)
- Brief mental state

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Community initiation checklist

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Document completion of all tasks in the electronic patient record

Pre-initiation:

- ❑ Patient education & information
- ❑ Patient consent (or MHA authorisation)
- ❑ Baseline FBC to local path lab (valid x 10 days)
- ❑ Complete physical exam:
  - *Temperature, BP, pulse, ECG, respiratory rate, joint reflexes, height, weight*, waist circumference*
- ❑ Baseline blood tests:
  - *U&Es, lipids, LFTs, prolactin, HbA1c*
- ❑ Register with CPMS or equivalent
- ❑ Prescribe first dose on printed titration chart
- ❑ Order initial supply from Trust dispensary
- ❑ Set up arrangements for seeing patient frequently during titration phase

**calculate weight increase threshold [= baseline weight x 1.05]*

Day 1 – initiation:

- ❑ Check & record BP, pulse & temperature immediately prior to first dose* – if no concerns…
- ❑ Administer first dose

If first dose not at bedtime…

- ❑ Check & record BP, pulse & temp hourly x 6 hours
- ❑ Add clozapine to significant medication alert on electronic patient record
- ❑ Arrange date of next FBC (within 10 days of baseline)
- ❑ Prescribe titration doses for next day(s) on chart according to initial tolerability
- ❑ Inform GP that clozapine has been initiated

**seek medical advice if any concerns*

Day 2-14 – titration:

- ❑ Prescribe doses for next day(s) on chart according to ongoing tolerability
- ❑ Arrange further supplies with Trust dispensary
- ❑ FBC & CRP within 10 days of baseline (repeat +1 week later if needed)*

Every monitoring appointment

- ❑ Check & record BP, pulse & temp (ideally 2-6 hours post dose)**
- ❑ Check side effects**
  - *Constipation, sedation, hypersalivation, nocturnal enuresis, nausea, infection*
  - Complete GASS-C weekly
- ❑ Assess mental state**
- ❑ **Day 7 & 14** – check & record weight**
- ❑ Arrange attendance at clozapine clinic, or alternative if clinic not accessible

**at clozapine clinic or via path lab*
***seek medical advice if any concerns*

Day 15+ - stabilisation:

- ❑ **Day15**: bloods for plasma level
- ❑ Once plasma level known, calculate C/D ratio & target dose; prescribe ongoing titration doses
- ❑ Once target dose reached & taken for 4 days, re-check plasma level; adjust dose to achieve target level; once stable, produce 12-month prescription
- ❑ Arrange further supplies with Trust pharmacy
- ❑ FBC & CRP **weekly**
- ❑ Check & record BP, pulse & temp at least **weekly** (more frequently if any parameters out of range)*
- ❑ Check side effects using GASS-C at least **weekly** (more frequently if indicated)*

• *Constipation, sedation, hypersalivation, nocturnal enuresis, nausea, infection*

- ❑ Check & record weight **weekly****
- ❑ Assess mental state and check smoking status at **every contact**
- ❑ **Week 4 –** check HbA1c
- ❑ **Week 12** – ECG, lipids, prolactin

**seek medical advice if any concerns*
***if weight >5% above baseline within 1 month of initiation, consider intervention*

Management of adverse effects

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Adverse effect	Thresholds	Action(s)
Tachycardia *Typically occurs in first few weeks; may persist* *Usually dose-related*	• Pulse >100 – refer to prescriber • Pulse >120 or +30 from baseline and/or cardiac symptoms– investigate myocarditis [if baseline pulse is raised, prescriber to define threshold increase for referral if treatment is started]	Aim to reduce resting pulse to <100, ideally close to 80 • Reduce dose • Consider checking plasma levels (reduce dose if high) • Reduce tobacco and caffeine intake (but consider effect on plasma levels) • ECG to exclude other arrhythmias or cardiac abnormalities • Refer to cardiologist if tachycardia does not resolve despite these actions
Orthostatic hypotension *Usually diminishes after 4-6 weeks*	Postural drop >20 mmHg systolic or 10mmHg diastolic – refer to prescriber	• Reduce rate of titration if occurs during initiation • Reduce dose and/or increase proportion taken at night • Advise patient to stand up slowly and maintain hydration
Hypertension *Usually occurs in first 4 weeks*	• Systolic >140 or diastolic >90 mmHg – consider ambulatory BP monitoring - link • Systolic >180 or diastolic >120 mmHg – follow NICE referral guidelines	• Reduce rate of titration if occurs during initiation • Reduce caffeine/sodium/nicotine intake • Monitor BP closely
Myocarditis / cardiomyopathy *Highest risk of myocarditis in first 8 weeks; cardiomyopathy occurs later; can be fatal*	• Persistent tachycardia at rest • Unexplained symptoms of heart failure • Abnormal CRP with other abnormal blood tests e.g. Troponin, CK and BNP or ECG changes	• Discontinue clozapine if myocarditis is suspected • Request Troponin, CK, BNP and ECG • Refer to cardiology for ECHO to confirm • DO NOT re-challenge if myocarditis confirmed – see "unlicensed use"
Eosinophilia *Most likely in first 3-6 weeks*	>3.0 x 10^9 / L (smaller rises are usually transient and resolve spontaneously)	• Withhold clozapine until <1.0 x 10^9 / L
Thrombocytopenia	<50 x 10^9 / L	• Discontinue clozapine
Abnormal LFTs *Most likely in first 3 months*	• >3 x UNL • Jaundice	• Withhold clozapine until enzymes return to normal range • Seek advice from liver specialist prior to re-challenge
Glucose / lipid disturbance *Early recognition important*	• Symptoms of hyperglycaemia, e.g. polydipsia • Ketoacidosis or hyperosmolar coma • Triglycerides >5.6 mmol/L (risk of pancreatitis)	• Usual management, with specialist advice as needed • Ketoacidosis / hyperosmolar coma – admit to medical ward and stop clozapine
Raised CRP	>50mg/L	• Maintain current clozapine dose and postpone further titration • Physical assessment for side-effects, infection and myocarditis

Management of adverse effects (continued)

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Adverse effect	Thresholds	Action(s)
Fever / benign hyperthermia	>38°C with associated raised WBC, ESR, CRP, tachycardia or GI/respiratory symptoms (transient temperature rises without other signs or symptoms are common and usually resolve spontaneously)	• Consider possibility of infection – plasma levels and dose adjustment may be necessary • Consider agranulocytosis, myocarditis or NMS – discontinue clozapine if these cannot be excluded
Nausea & vomiting *Usually within first 6 weeks*		• Reduce dose and/or rate of titration if occurs during initiation • Consider antacids or acid suppressants (not cimetidine)
Constipation *Very common; potentially fatal*	Any change in bowel function – early recognition and intervention is essential	• See Trust guidance • Consider prophylactic laxatives – self-care or prescription
Hypersalivation *Very common; more problematic at night*	Risk of aspiration	• Reduce rate of titration if occurs during initiation • Practical advice – extra pillows +/- disposable pillowcases/towels at night; sugar-free gum during day • Dose reduction may help (but balance vs risk of destabilisation of mental state) • Consider anticholinergic medication, e.g. hyoscine hydrobromide, Atropine sublingual drops. Systemic use may worsen constipation
Sedation *Very common, may improve over time*	Significant increase from baseline sleep pattern	• Reduce rate of titration • If divided dose, weight dose towards night. Consider giving as a single dose at night. Up to 500mg can be given as single doses. • Addition of Aripiprazole may be helpful if sedation persists
Weight gain *Common*	>5% gain in first 4-6 weeks (strong indicator of long-term gain)	• Lifestyle advice – diet, exercise • Consider adjuvant pharmacological treatments e.g. aripiprazole or metformin
Seizures / EEG changes *Common; dose/plasma level-related*	Any seizure activity	• Reduce rate of titration if occurs during initiation • Reduce dose • Consider anticonvulsant prophylaxis at dose >600mg/day and/or plasma levels >0.6 mg/L– see Trust guidance
Urinary retention / incontinence *May not be reported; may indicate constipation or glucose impairment*	Any patient/carer-reported concerns	• Advise fluid restriction during evening and urination at bedtime • Avoid / minimise anticholinergic medication • Reduce dose and/or reduce proportion taken at night

Initial 12-month prescription

Following successful titration and dose stabilisation (including adjustment of dose for re-commencement of smoking after discharge):

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Responsible Consultant / Prescriber:

- Notify local pharmacy team – by direct contact with a pharmacy staff member and/or email to the relevant dispensary - that a 12-month prescription for maintenance clozapine (and co meds, if needed pending transfer to GP) is now required
  - RPH dispensary: tewv.pharmacytees@nhs.net
  - WPH dispensary: tewv.pharmacycdd@nhs.net
  - FPH dispensary: tewv.pharmacyyork@nhs.net
- Update EPR medication matrix with Clozapine and any co-meds

Pharmacy Team:

- Electronically produce a prescription for clozapine (plus any required co-meds) using the relevant template in the pharmacy shared drive.
- **For this first prescription only** – "annual review complete" = date clozapine was initiated
- Save the draft prescription in the relevant clinic folder on the pharmacy shared drive
- **Pharmacy technician** complete the following checks, record any actions taken in the EPR and sign "accuracy check complete":
  - Check and reconcile the current clozapine dose using two sources of information, e.g. prescription in dispensary (or EPMA) and electronic patient record including medication matrix.
  - Check and/or update the EPR safety summary for supply risks and dispensing requirements
  - Check GP record (via GNCR, HYCR or SCR) for allergies and any interactions with other prescribed medication – escalate interactions of concern to the prescriber
  - Check if clozapine and any co-meds are on the GP record – if not, email details to GP practice to request addition as a "specialist-prescribed medicine".
  - Check Responsible Consultant on CPMS – request amendment if necessary
  - Check patient demographics and clinic details are accurate
- Add patient to pharmacy-held clinic spreadsheet
- Send prescription to the prescriber for signing via the locally agreed method for that prescriber/clinic, i.e. print & send/deliver hard copy **or** attach to an email with appropriate password protection (share password with prescriber via separate email)

Prescriber (RC or delegated medical prescriber / authorised NMP in team)

- Print (if emailed), check and wet sign/date prescription; return to pharmacy staff member or directly to relevant dispensary using the most appropriate locally agreed method (e.g. scan & email*, via pharmacy driver, via internal or Royal Mail post).

**if urgently needed; original MUST be sent to pharmacy*

Pharmacy Team:

- **Pharmacist -** complete final clinical check which should include:
  - Any dose changes in EPR since prescription was generated?
  - Assessment of any interactions identified by the pharmacy technician and/or check of GP record
  - Calculation of antipsychotic % BNF maximum dose
- Scan and upload prescription onto EPR (See Clozapine and Cito guidance for detailed instructions)
- Add prescription to repeat dispensing template on EMIS

N.B. prescription is valid for 12 months from "annual review complete" date + 1 month extension if required

Dose changes

When a dose change is needed to clozapine or any co-meds:

Prescriber:

- Clearly document the required change in the electronic patient record on the medication matrix, **including the date from when the new dose is to commence**
- Notify local pharmacy team of the dose change via email to the relevant dispensary, using the dose change communication form
  - FPH – tewv.pharmacyyork@nhs.net
  - RPH – tewv.pharmacytees@nhs.net
  - WPH – tewv.pharmacycdd@nhs.net

Is the dose change required immediately / within next 7 days?

YES → Can the current supply be used for the new dose until a new supply can be prescribed, dispensed & delivered to the patient?

- **YES** → **Key worker:** Recover from patient any tablets that are not needed for the new dose and store in team base medicines cupboard for onward return to relevant dispensary; record quantity & strength of tablets recovered on EPR
- **NO** → **Clinical Pharmacist:**
  - Manually "p/c" amend the current prescription to allow dispensing of new supply within validity of bloods; maximum supply against amended prescription = **4 weeks** (regardless of monitoring frequency)
  - upload amended prescription to EPR

  [Inpatients – ward pharmacy team order interim supply at new dose on EMIS]

NO → Is the next scheduled blood test & supply of clozapine within the next 7 days?

- **YES** → **Clinical Pharmacist:** (as above)
- **NO**

Dispensary Team:

- Calculate and dispense quantity of tablets for new dose up to validity of bloods / next clinic appointment
- Liaise with the key worker/pharmacy technician to remove or add extra tablets to correct the dose with the patient.

Clinical Pharmacy team & Prescriber:

- Follow "initial 12-month prescription" process to produce prescription for new dose of clozapine / co-meds
- Amend repeat dispensing template on EMIS
- Update pharmacy-held clinic spreadsheet with new dose

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Clozapine / co-meds dose change request

Email completed form to usual supplying dispensary:
Foss Park (York): tewv.pharmacyyork@nhs.net
Roseberry Park (Middlesbrough): tewv.pharmacytees@nhs.net
West Park (Darlington): tewv.pharmacycdd@nhs.net

Prescriber requesting dose change:	
Patient Name:	
EPR number:	
Date of birth:	
CPMS (or equivalent) number, if known:	
CMHT / Clozapine clinic:	
CURRENT dose clozapine: Co-med: ……:	
NEW dose clozapine: Co-med: ……:	
Urgency of change (tick)	☐ as soon as possible (requires new supply outside clinic) ☐ within the next 7 days (new supply via next clinic) ☐ at patient's next scheduled clinic appointment
Reason for change	
Is dose change recorded in EPR?	YES / NO – *if no, this form must be sent to pharmacy from the requesting prescriber's personal email address*

Please see EPR for current dose / clozapine e-form for date of next clinic appointment

Pharmacy: attach a copy of this form to the new supply to highlight the dose change and ensure appropriate counselling of the patient and/or carer

Annual review & renewal of 12-month prescription

Pharmacy Technician (subject to available local resource and current capacity – note "core" and "enhanced" levels of service)

Up to one month prior to the annual review being due (date on current prescription + 12 months):

- Check and reconcile the current clozapine dose using two sources of information - **core**
- Check and update the EPR safety summary for supply risks and dispensing requirements - **core**
- Check GP record (via GNCR, HYCR or SCR) for current allergy status **(core)** and prescribed medication **(enhanced)**
- Check if clozapine and any co-meds are on the GP record – if not, email details to GP practice to request addition as a "specialist-prescribed medicine" - **core**
- Check Responsible Consultant on CPMS – request amendment if necessary - **core**
- Check patient demographics and clinic details - **core**
- Check ECG, blood tests for physical health monitoring and side-effect screening tool have been done or are planned to be done – **enhanced**
- Check for any clozapine plasma level assay results in the last 12 months - **enhanced**

Communicate the above information, by the locally agreed method (e.g. email, Cito entry, initiation of annual review checklist), to the clinician expected to complete the annual review

↓

Responsible Consultant (or a suitably qualified prescriber in their team):

- Review the patient's primary care record. If not provided by pharmacy technician, check/gather information required for annual review – monitoring results, side-effect screening, plasma levels, and current medication and physical health from GP record
- Complete a full review of the patient and their clozapine treatment according to the annual review checklist.
- Upload the completed checklist to the EPR and send a copy to the patient's GP (to ensure that clozapine + any co-meds prescribed by TEWV are added to the GP / summary care record)

↓

Pharmacy Team:

- Once there is evidence that the annual review has been completed, electronically produce a new prescription for clozapine (plus any required co-meds) using the relevant template in the pharmacy shared drive, adding the date of the annual review
- Send prescription to the prescriber for wet signing via the locally agreed method for that prescriber/clinic, i.e. print & send/deliver hard copy or attach to an email with appropriate password protection (share password with prescriber via separate email)

↓

RC and pharmacy team to then follow the last two steps of the "initial 12-month prescription process"

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Clozapine: annual review checklist

Tees, Esk and Wear Valleys NHS Foundation Trust

Patient name:	**DOB:**	**NHS number:**
Completed by:	**Date:**	**Contact tel.:**

STEP 1: routine physical health monitoring – see Psychotropic Monitoring Guide		
✓	***Parameter***	***Result / comment***
	Blood pressure	
	Pulse	
	CVD risk assessment (Q-risk score)	
	ECG *(if c/v risk or otherwise clinically indicated)*	
	Prolactin	
	Lipids	
	HbA1c	
	U&Es (inc. creatinine & eGFR)	
	LFTs	
	Weight / BMI / waist circumference	
	General physical examination *(should include, but not restricted to: above parameters + temperature, respiratory rate & joint reflexes)*	
	Pregnancy plans *(offer pre-conception counselling if appropriate)*	

continued…

Clozapine: annual review checklist (continued)

Tees, Esk and Wear Valleys NHS Foundation Trust

STEP 2: monitoring of adherence, side-effects and efficacy			*Date completed / action / comment*
Has an appropriate rating scale been used to assess symptoms & mental state in the last 12 months?		YES / NO	
Is the patient adherent to their regimen? Are any co-meds still required? Does the patient / carer still understand their treatment?		YES / NO	
Is an attempt at dose reduction feasible (to maintain efficacy but minimise risk of side-effects)?		YES / NO	
Has an appropriate rating scale been used to assess side-effects, e.g. GASS for clozapine, in the last 12 months?		YES / NO	
✓	*Check for (including reference to primary care record):*		
	Hypersalivation?	YES / NO	
	Constipation?	YES / NO	
	Sedation?	YES / NO	
	Seizures? *(if no, and taking anticonvulsant for protection – consider checking clozapine levels & stopping if low risk)*	YES / NO	
	Change in smoking status?	YES / NO	
	Change to overall physical health / other medication? *(consider interactions with clozapine)*	YES / NO	
	Any indication for checking clozapine plasma levels? *(see Trust guidance)*	YES / NO	

STEP 3: documentation and follow-up:		*Action / comment*
	Review clozapine plasma levels (if assayed) and make any dose adjustments	
	Ensure any dose changes are clearly communicated to the relevant dispensary as per "dose change" process	
	Ensure all monitoring information is recorded in the EPR (or scan & upload this completed checklist)	
	Ensure as part of routine communication that a copy of this checklist is sent to the patient's GP, or GP is notified that clozapine and/or any co-meds have been discontinued	

STEP 4: current prescription from TEWV *(GP to please ensure these are added to the primary care medication record)*	
1.	CLOZAPINE *(add brand, formulation & current dose)*
2.	

Discontinuation of clozapine

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Discontinuation by patient:

- If a patient is non-compliant with clozapine treatment, assess them with reference to Medication Safety Series 23: Medication Adherence.
- If treatment is re-started, re-titration is necessary if more than 48 hours has elapsed since the last dose was taken; a return to weekly monitoring during re-titration is required if more than 72 hours has elapsed since the last dose was taken.
- If a patient voluntarily stops taking clozapine, with no intention or willingness to re-start, a personalised review should take place to consider immediate risks (including risk of overdose with remaining supplies which should be recovered as soon as possible) and next treatment options. Arrange blood monitoring at usual frequency for 4 weeks post-discontinuation (unless 4 weeks has already elapsed since last dose)

Patient deceased:

- Complete relevant notification, removal, and archiving steps as per "discontinuation by prescriber" process

Discontinuation by prescriber:

Prescriber (ward team if inpatient):

Notify the pharmacy team that clozapine has been discontinued (or there is a plan to discontinue) via email to the relevant dispensary (cc'd to any colleagues and specific pharmacy staff who also need to be aware):

- RPH - tewv.pharmacytees@nhs.net
- WPH – tewv.pharmacycdd@nhs.net
- FPH – tewv.pharmacyyork@nhs.net

Pharmacy team:

- Inform CPMS - CPMS@viatris.com (or equivalent) of date of discontinuation
- Annotate pharmacy-held clinic spreadsheet with "discontinuing clozapine"
- Remove repeat dispensing template on EMIS
- Ensure patient continues to attend clinic (or non-clinic arrangements continue) for blood monitoring at usual frequency for 4 weeks post-discontinuation - i.e. if weekly: 4 x bloods; two-weekly: 2 x bloods; four-weekly: 1 x blood - or as per instructions from CPMS (or equivalent) if discontinuing due to a red result
- Once the required post-discontinuation blood monitoring has been completed, remove the patient from the pharmacy-held clinic spreadsheet
- If clozapine is on the GP medication record, email practice to request removal.
- Ensure any co-meds on clozapine prescription that are to continue are transferred to FP10 and/or consider potential transfer of prescribing to GP.
- Archive current electronic prescription on S drive*
- Add comment to the most recent prescription entry on electronic patient record: "Clozapine discontinued; prescription no longer valid"

** review content of this folder at least annually and permanently delete prescriptions after 12 months*

Dispensary Team:

- Cancel any future issues of medication and upload prescription to EPR
- Archive paper copy of prescription (to be retained for 2 year from date of last dispensing as per Retention of Records procedure)

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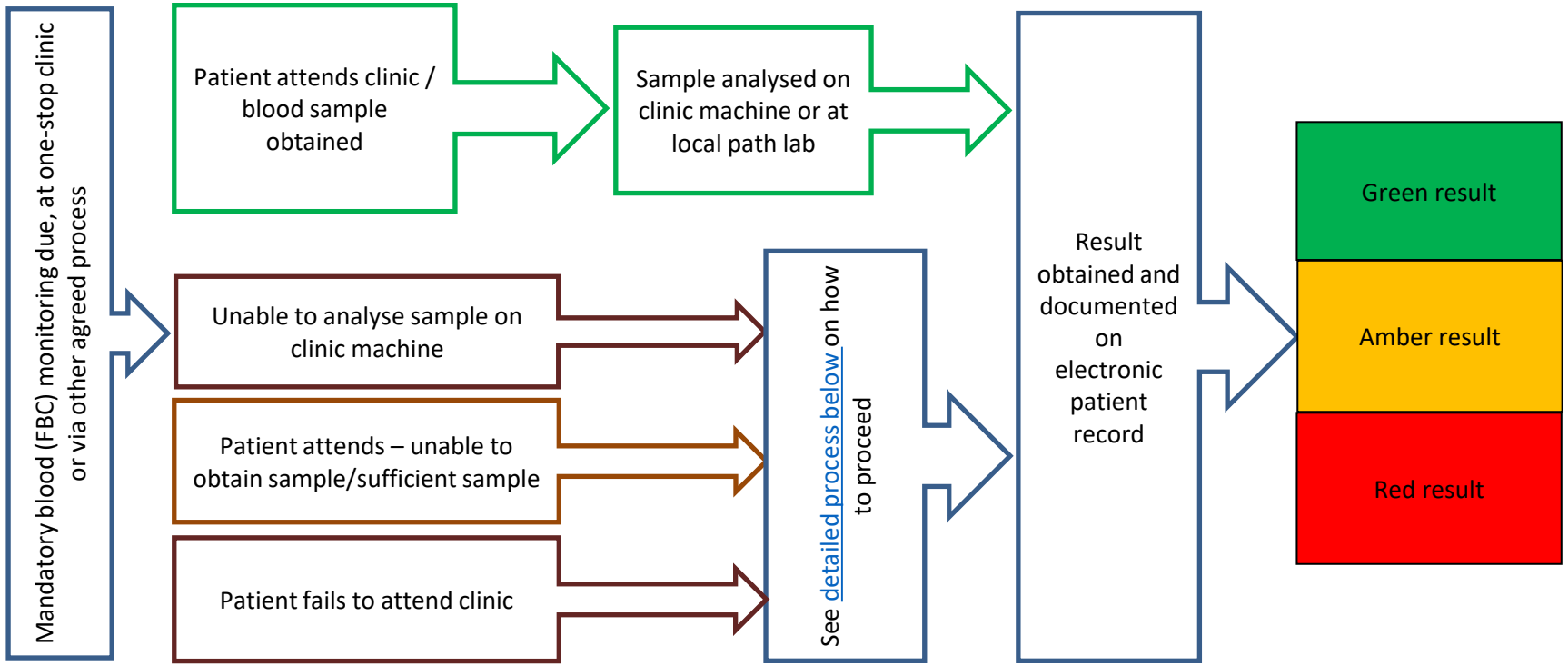
Re-titration

- Re-titration (from 12.5 mg) is required if clozapine doses are missed for >48 hours; if doses are missed for >72 hours weekly FBC monitoring is also required until titration is complete
- Faster titration is possible if antipsychotic efficacy needs to be regained quickly, but must be balanced against safety / tolerability on an individual case basis; more cautious re-titration is recommended for elderly patients and those who poorly tolerated their initial titration
- When a dose in the titration plan is not tolerated, the next dose increase should be delayed; dose reduction with slower titration may be required
- Therefore, doses for re-titration should be prescribed on a daily basis, rather than as a complete schedule which may need to be changed

Standard re-titration		
	Morning	Bedtime
Day 1		12.5 mg
Day 2	25 mg	50 mg
Day 3	50 mg	75 mg
Day 4	75 mg	100 mg
…and continue with 25 mg increases on **alternate doses** until target dose re-established		

Rapid re-titration		
	Morning	Bedtime
Day 1		12.5 mg
Day 2	25 mg	50 mg
Day 3	75 mg	100 mg
Day 4	125 mg	150 mg
…and continue with 25 mg increases at **every dose** until target dose re-established		

Mandatory FBC monitoring - overview



The frequency of mandatory blood (FBC) testing is determined by the duration of treatment:

Weekly for the first 18 weeks of treatment → **Fortnightly between weeks 18 and 52** → **Four weekly after 1 year of treatment**

N.B. the duration of weekly or fortnightly monitoring may be extended if amber results occur during these periods

Blood result validity – the maximum supply of clozapine that can be issued from the date of the most recent **GREEN** result:

Monitoring frequency	Clozaril® / Denzapine®	Zaponex®
Weekly	10 days	14 days
2-weekly	21 days	21 days
4-weekly	42 days	42 days

- Patients are allocated to their nearest clozapine clinic when newly-initiated / discharged or transferred to the Trust
- Pharmacy-held spreadsheets identify which clinic a patient attends and when (weeks 1,2,3,4)
- A supply of clozapine (& co-meds where applicable) for each patient expected to attend each weekly clinic is prepared and sent to each clinic site in advance, and can only be released to the patient with a GREEN or AMBER blood test result
- Changes to a patient's monitoring frequency are notified by CPMS (or equivalent service) to the registered dispensary

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Preparation, delivery, receipt & return of clozapine at one-stop clinics

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Dispensary Team:

- 1-4 weeks before each one-stop clinic*, dispense the medication required for the patient cohort expected at that clinic into a tote box clearly marked with the clinic name & week number, e.g. “Foxrush - week 1” [to minimise errors, only one box per clinic week should be dispensed at a time]
- Once the medication for a particular clinic has been fully checked, seal the box with the current prescriptions for each supply inside; clearly label the box “Quarantined Clozapine” and set it aside for delivery
- 1-4 working days before the clinic, deliver the relevant sealed box to the clinic site

**according to other workload / planning for public holidays*

↓

Clozapine clinic staff:

Receive and sign for delivery and place the sealed box in the agreed secure location (e.g. clinic room)

↓

Pharmacy Technician:

On arrival at the clinic:

- Check boxes are still sealed - if the seals are broken, report to the dispensary team immediately
- Check the bag labels in the box against the pharmacy-held clinic spreadsheet to confirm that medication is available for each patient expected to attend the clinic – if any discrepancy, contact the dispensary immediately.
- Transfer the medication to the quarantine cupboard and record “quarantined medication” on the clinic spreadsheet for each patient.
- Check other relevant cupboards on site for any clozapine supplies not collected / delivered since previous clinic - if present, contact the relevant key worker to ascertain why not collected / delivered and whether a break in treatment has occurred or is likely

During the clinic: follow this process for each patient who attends

At the end of the clinic:

- For patients on 2 or 4-weekly monitoring with a **GREEN** result who collect their medication weekly, transfer the remaining 1- or 3-weeks’ supply to the main clinic medicines cupboard (**NOT** the quarantine cupboard) and record on the medication log for incremental supply
- Secure any other medication not issued (i.e. for non-attenders) in the quarantine cupboard (in the absence of a separate quarantine cupboard this medication should be put into the main medication cupboard with a “quarantined clozapine” sticker attached. This medication can only be issued according to this process.
- Place any medication returned by patients and the prescriptions into a sealed tote box and leave in a secure place for collection by the pharmacy driver and return to the relevant dispensary.
- Check the clinic spreadsheet regularly during the following 6 days and follow up any non-issued clozapine prior to the next clinic

Medication log for incremental supply

Name:

Date put into cupboard	Quantity In (packs)	Date removed from cupboard	Quantity Out (packs)	Remaining quantity (packs)	Signed Out By: (staff print name)	Signed Out By: (staff signature)	Delivered : (✔)	Patient/Proxy if collected

Patient attends clinic as expected:

Clozapine Clinic Team:

- Follow standard venepuncture procedure – take blood sample for mandatory FBC monitoring
- Follow operating instructions for blood analyser; ensure correct patient details selected; confirm blood result (red/amber/green) on CPMS; record details on the clinic spreadsheet and follow relevant process for **RED, AMBER,** or **GREEN** result
- Perform physical observations and other monitoring as appropriate, recording results on electronic patient record

IF A BLOOD RESULT IS NOT IMMEDIATELY OBTAINABLE

Clozapine Clinic Team:

- Send blood sample to local pathology laboratory, requesting "full blood count"
- Check number of days' supply held by patient and ascertain whether a further supply is needed to cover the period until a blood result will be obtained:
  - If no supply needed, follow this process
  - If supply needed, proceed to next step…
- Agree with patient/carer how full or balance of supply will be collected or delivered once **GREEN** result received

Pharmacy technician:

- Determine if a partial supply from the full patient supply is possible - e.g. 1 x 7-day compliance pack
  - If YES - supply within validity, record amount supplied on EPR and quarantine balance of supply until blood result received
  - If NO – arrange **urgent** new supply, up to date of blood validity, with relevant dispensary; arrange delivery or collection of this supply; return "full" supply to dispensary
- Retrieve FBC results from path lab via WebICE and enter onto CPMS – if **GREEN**, arrange delivery or collection of the balance of supply up to next clinic appointment; follow relevant process if **RED** or **AMBER**

Unable to obtain a sufficient blood sample:

- Check if any other phlebotomy-trained staff are available on-site to obtain sufficient sample
- If not, make alternative arrangements to access phlebotomy services elsewhere, e.g. GP practice, local hospital – then follow this process

Unable to analyse sample obtained in clinic:

- **Error on analyser –** allow sample to settle for 2 minutes, then re-mix and re-run, ONCE only; if error persists, follow this process
- **Analyser failure** – contact CPMS / Sysmex; follow this process for each patient
- Patient takes brand other than Clozaril® / Clozapine Mylan – clinic analyser cannot be used, follow this process

Patient fails to attend clinic as scheduled

Pharmacy Technician (in One-stop clinic)**:**

- Do not release medication
- If clinic has a cupboard specifically for quarantined clozapine, secure the patient's medication in this cupboard (with a copy of the prescription) until a FBC result is obtained
- If clinic does not have a separate cupboard for quarantined clozapine, attach a "Quarantined clozapine" sticker (→) to the outer bag and secure the medication (with a copy of the prescription) in the general medicines' cupboard, separate to other medication
- Record details on EPR Clozapine e-form and the "Quarantined clozapine log sheet"

Clozapine Clinic Team / Key worker
Contact patient to arrange attendance at clinic or a home visit to obtain a blood sample, record planned appointment on EPR Clozapine e-form

Clozapine Clinic Team: once sample has been obtained….

- If possible, analyse sample on clinic analyser; if not possible, send sample to local pathology laboratory requesting "full blood count"
- Qualified nurse to contact relevant pharmacy team member or dispensary to request authorisation to release quarantined clozapine

Pharmacy team:

- Check for blood test result on CPMS – if not available and sample was sent to path lab, gather results via WebICE and enter onto CPMS
- If GREEN or AMBER, supply code to release the key for the quarantine cupboard and/or permission to release quarantined medication to the patient; if AMBER, additionally advise clinical team to follow this process
- Update EPR Clozapine e-form with blood result and supply of medication

Under no circumstances should the supply be released in the absence of a valid blood result

QUARANTINED CLOZAPINE

NOT TO BE RELEASED WITHOUT AUTHORISATION FROM PHARMACY

GREEN RESULT

Do not Quarantine

Clozapine Clinic Team / Key worker (qualified nurse):

- Record the name of authorising pharmacy staff on the quarantine cupboard log
- If a "Quarantined clozapine" sticker is attached, attach a "Green result" sticker (↑) covering the "quarantined" sticker.
- Check the following prior to handing medication to patient:
  - Patient name
  - Whether they still have any medication at home in excess of their validity
- Record the issue/collection of the supply on the "quarantine cupboard log sheet"
- Counsel patient as appropriate (See Appendix 8) – refer to another clinician/pharmacist when necessary
- Ensure patient knows the date of their next blood test/clinic appointment

Quarantined Clozapine Log Sheet

Date put into cupboard	Patient ID	Date removed from cupboard / supplied	Nurse Signature	Nurse name	Name of Pharmacy staff authorising release

Green result

GREEN result obtained on clinic analyser or via local pathology lab or CPMS

Clozapine clinic team:

- Record the date and result (GREEN) of the blood test on the dispensing and supply log on the patient's prescription and initial (this should be done BEFORE medication is issued to ensure medication is not given out before blood result is received).
- Go through the counselling checklist with the patient (use this version if outside one-stop clinic setting) - record responses and any actions taken or required on the "clozapine e-form" in the electronic patient record – escalate any concerns to a clinician immediately (by the end of the working day at the latest)
- Complete all other aspects of the clozapine e-form on the electronic patient record
- Release the full or agreed partial supply of medication from quarantine to the patient, checking the patient's name, DOB and CPMS (or equivalent) number against the CPMS (or equivalent) record & the prescription
- Update the clinic spreadsheet
- Inform patient of next blood monitoring appointment and, if applicable, check details of collection / delivery of balance of supply

Counselling checklist for clozapine patients

For use by Pharmacy Technician or nurse at One Stop Clinics – see separate printable form for non-clinic contacts relating to clozapine supply (e.g. in care homes)

Issue	Question (as appear on Cito e-form)	Supplementary questions / further information	Referral / Action criteria
Compliance	• What is your current dose? • Have you missed any doses? • Have you taken any extra doses? • Have you any Clozapine tablets left at home? • How many Clozapine tablets do you have left at home? • Are you managing with how Clozapine is supplied to you? • Reminder – rotate supplies so they don't expire	• If any missed doses, find out when the last dose was taken and how much was taken. • If taking Denzapine liquid, check they are aware of requirements around shaking the bottle before each dose	• Dose not as per script / prepared supply • More than odd doses missed; >48 hours since last dose taken • Any extra doses taken • More than required until end of current week • Request for different method of supply, e.g., compliance aid

Side effects	• Do you have any side effects?
	
	In particular:
	
	• Constipation?
	• Diarrhoea? – may be a sign of overflow from constipation
	• Hypersalivation?
	• Any other physical symptoms that you don't usually have (e.g., sore throat, flu like symptoms, palpitations)
		• Use the Bristol stool chart as a tool to support these discussions
		• Check for any changes in other medication or potential interacting lifestyle choices if new constipation is reported e.g., change to smoking status, caffeine intake
		• Ask when they last had a bowel movement if none in last 2-4 days this requires urgent follow up
		• Check for major infections that may be being treated with antibiotic e.g., pneumonia – this may affect Clozapine plasma level
		• If they report palpitations, are they any other associated symptoms e.g. short of breath, finding it hard to sleep lying on their back, chest pain, sweating, fast heartbeat
		• Check for signs of toxicity:
		  ○ Feeling sleep/tired
		  ○ Feeling dizzy when you stand up
		  ○ Having a fit or seizure
		  ○ Feel more confused
		  ○ Have a racing heart
		  ○ Have problems breathing
			• Constipation if no treatment has commenced or not resolving with treatment
			• Diarrhoea
			• Worsening treated hypersalivation; untreated hypersalivation which has not already been discussed with a prescriber
			• Any other physical health symptoms not normally experienced

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Issue	Question	Supplementary questions / further information	Referral / Action criteria
Smoking status	• Do you smoke cigarettes? • Have you recently stopped smoking cigarettes, or cut down a lot? • Have you recently started smoking cigarettes, or increased the amount you smoke a lot?	• Document current number of cigarettes/days • If status has changed, identify & record when they stopped / started smoking • Check if they smoke other substances e.g., Cannabis, which can also impact clozapine levels if smoked	• Any changes in smoking status, including switch from cigarettes to e-cigarette/vaping or vice versa • Request for support from smoking cessation *Action: notify RC and agree plasma level checks / dose changes as recommended in MSS25*
Alcohol / substance misuse / caffeine / mood	• Do you drink any alcohol at all? • If so, how much do you drink? • Do you use any other substances? • Do you drink excessive amounts of caffeine containing drinks e.g., energy drinks, strong coffee? • How is your mood?	• Check for any changes in alcohol and caffeine consumption (NB. Caffeine also present in chocolate and some OTC painkillers) • If they report that they've stopped drinking alcohol, check they haven't replaced it with something else e.g., energy drinks (high caffeine content) • In relation to other substance use, check particularly for smoking cannabis which has the same impact on Clozapine levels as smoking tobacco	• Regular alcohol use >2 units per day • Increase/change in alcohol or caffeine use • Binge drinking* • Any substance use not already documented
Medication changes	• Do you still need medication supplied in a compliance aid? • Is there something else that would help you take your medication, e.g., app, reminder chart?	• Have you been prescribed any new medication since last clinic? • Have you started taking any new OTC or complimentary medicines since last clinic? • If new medication is e.g., an antibiotic, check what it is being used to treat, serious infections can impact Clozapine levels • Some medication is contra-indicated with Clozapine e.g., Citalopram • Check any OTC medicines are being taken within the recommended dose parameters • Interactions can be checked via BNF or here	• Any change in psychotropic medication • Any new medication which interacts with Clozapine or co meds (check BNF) • Any OTC medication taken regularly but not already recorded

- Binge drinking defined as: In a short space of time (e.g. 1hr) drinking more than 8 units for males or 3 units for female, or drinking to get drunk (Ref http://www.nhs.uk/Livewell/alcohol/Pages/Bingedrinking.aspx)
- Consider issuing patient with Choice and Medication leaflet where appropriate e.g. first presentation of constipation or hypersalivation.
- The routine planned leaflet supply must still be followed.
- Any leaflets supplied at any time must be recorded in the patients EPR, including the version number. Patients and their families/carers should be counselled alongside the leaflet.

Amber result

AMBER result obtained on clinic analyser or via local pathology lab or CPMS

Clozapine Clinic Team:

- Record the date & result (AMBER) of the blood test on the dispensing and supply log on the patient's prescription and initial (this should be done BEFORE medication is issued to ensure medication is not given out before blood result is received) [for inpatients – record result in electronic patient record]
- Go through the counselling checklist, complete "clozapine e-form" in the electronic patient record, release full or partial supply of medication and update clinic spreadsheet as per "GREEN result" process
- Inform RC, key worker, ward staff (inpatients) and relevant dispensary of AMBER result
- Inform patient of need for additional blood monitoring; arrange date, time & place of blood sampling with patient and key worker/community team, according to….

Is the patient physically unwell?

YES → Repeat blood test in 1-2 days, or as advised by CPMS*

NO → Repeat blood test in 2-3 **working** days**, or as advised by CPMS*

Key worker / Community team:
Obtain repeat blood sample and arrange testing on clinic analyser or at local path lab as appropriate

Result of repeat test: GREEN
→ **Return to standard monitoring & testing week**

Result of repeat test: AMBER
→ **Repeat test at above frequency until non-amber result**

Result of repeat test: RED
→ **STOP clozapine & follow RED result process**

Clozapine Clinic Team:

- Inform patient, RC, key worker, ward staff and relevant dispensary of result and subsequent actions taken or required
- Update the clinic spreadsheet; arrange the next sampling appointment & document details in the electronic patient record

*If patient has regular AMBER results, repeat samples may not be required as frequently

**Initial amber result on:

- Monday - next test Wednesday/Thursday;
- Tuesday - next test Thursday/Friday;
- Wednesday - next test Friday
- Thursday/Friday - next test Monday

Return to front page

Red Result

Return to front page

RED result obtained on clinic analyser → Allow sample to stand for at least 2 minutes, re-mix sample then re-run on analyser

- → Second result: **GREEN** or **AMBER**
  Disregard the initial red result & follow the relevant GREEN or AMBER process
- → Second result: **RED** ALERT → Send sample to local path lab for confirmatory test → **RED** result obtained via local pathology lab or CPMS* ALERT

Key tasks:

- Person receiving notification of RED result* - inform RC, key worker, ward staff (inpatients) and relevant dispensary – agree who will contact patient if not present
- Contact patient to explain the significance of the RED result and tell them to **STOP** taking clozapine **IMMEDIATELY;** check if patient has any signs or symptoms of infection, e.g. sore throat, fever; arrange for repeat blood test the next day (see below)
- Inpatients – prescriber to **suspend** clozapine on EPMA

** If result is received out of hours follow advice above & arrange which staff will retrieve further blood results, ensuring arrangements are made for the next blood test. If staff member retrieving result out of hours is unable to access CPMS contact on call pharmacist to have results entered onto CPMS (results must be reported as soon as they are available)*

Re-test next day → GREEN / AMBER / RED - CONFIRMED

GREEN + AMBER → Re-test next day → GREEN / AMBER / RED - CONFIRMED

GREEN + AMBER → Red NOT CONFIRMED
Discuss with CPMS (or equivalent)
Patient can restart treatment, with re-titration if >48 hours since last dose

Sudden cessation of treatment with clozapine can lead to physical & mental withdrawal effects which may occur within 2-3 days, usually within the first two weeks. Patients may experience a rapid deterioration in their mental state with rebound psychosis. Abrupt withdrawal of clozapine has also been associated with symptoms such as nausea, vomiting, diarrhoea, headache, restlessness, agitation & sweating.

RED - CONFIRMED:

- Inpatients: prescriber - **stop** clozapine on EPMA; pharmacy staff - remove supplies from ward
- Community: arrange retrieval of all clozapine held by patient and return to relevant Trust dispensary via clinic tote box
- Contact CPMS (or equivalent) for advice regarding further blood testing; share this information with the RC, key worker and relevant dispensary and document on electronic patient record
- Ensure further blood monitoring is completed as per CPMS (or equivalent) instruction until advised that it can cease
- Remove patient from clinic spreadsheet (future treatment is contra-indicated)

Monitoring & supply to a patient outside a one-stop clinic

- All patients should be supported to attend a one-stop clinic, if one is available locally and it is practical for them to do so. Where this isn't the case, such patients should receive the same level and standard of monitoring and counselling as a patient who does attend a one-stop clinic
- The member of staff handing the clozapine to the patient should go through the same counselling checklist as used in one-stop clinics, and record outcomes and any actions taken on the EPR e-form – escalate any concerns to a clinician immediately (by the end of the working day at the latest)
- A printable version of the counselling checklist is available. This can be supplied to the patient, carer or care home staff to be completed in advance of a scheduled home visit by TEWV staff. The paper form captures the rationale and a review of non-clinic attendance. The paper version is to be uploaded to the EPR and the usual clinic pharmacy technician informed to record any actions or outcomes before releasing the medication

Supplies via GP surgeries

- If the supply of medication is not collected within 3 days the relevant TEWV dispensary must be notified.

Patient name:		Reason for non-attendance at clinic?	
DOB:		When was non-attendance last reviewed?	
NHS number:		Form completed by:	
Clozapine clinic name:		Date completed:	

Issue	Question	Response
Compliance	• What is your current dose? • Have you missed any doses? • Have you taken extra doses? • Have you any Clozapine tablets left at home? • How many Clozapine tablets do you have left at home? • Are you managing with how Clozapine is supplied to you? Reminder - rotate supplies so they don't expire • Do you still need medication supplied in a compliance aid? Is there something else that would help you take your medication, e.g., app, reminder chart?	
Side effects	• Do you have any side effects? In particular: ➢ Constipation? ➢ Diarrhoea? – may be a sign of overflow from constipation ➢ Hypersalivation? ➢ Any other physical symptoms that you don't usually have (e.g., sore throat, flu-like symptoms. Palpitations)	
Smoking status	• Do you smoke cigarettes? • Have you recently stopped smoking cigarettes, or cut down a lot? • Have you recently started smoking cigarettes, or increase the amount you smoke a lot?	
Alcohol/substance misuse/caffeine/mood	• Do you drink any alcohol at all? • If so, how much do you drink? • Do you use any other substances? • Do you drink excessive amounts of caffeine containing drinks? E.g., energy drinks, strong coffee? • How is your mood?	
Medication changes	• Any changes in medication prescribed for you by GP or secondary care? • Do you take any medication you buy over the counter, and have you changed the doses of any of these?	

Return form to:

Tewv.pharmacycdd@nhs.net for patients in County Durham & Darlington (clinics include Goodall Centre, Derwent Clinic, West Park Clinic, Chester Le Street Health Centre, Merrick House & North Moor House)

Tewv.pharmacytees@nhs.net for patients in Teesside (clinics include Brook House, Foxrush House, Parkside, Stewart House)

Tewv.pharmacyyork@nhs.net for patients in North Yorkshire & York (clinics include Huntington House, Worsley Court, The Anchorage, Princess Road Clinic, Ellis Centre, Acomb, Windsor House)

Form to be forwarded to clinic pharmacy technician to review and upload to Cito to allow for release of Clozapine

Pharmacy Technician action/comments:

Plasma level monitoring

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- Monitoring plasma levels of clozapine is recommended during titration to calculate a personalised target dose, but subsequent monitoring is not mandatory; see Trust guidance on therapeutic drug monitoring for when it should be considered – examples include to assess compliance, during serious infection, to help assess poor response or dose-related side-effects, and to monitor the effect of changes in smoking habit
- A plasma clozapine level assay can be performed on a MyCare Insight Analyser (Point of Care Test – POCT), where available (N.B. only the clozapine level can be assayed on these machines)
- If a POCT isn't available, or the plasma norclozapine level is also required (e.g. to assess metaboliser status), the blood sample taken for the FBC should be sent to Synnovis for full analysis – customerservices@synnovis.co.uk

N.B. The result of a plasma level assay is reported in **mg per litre** (mg/L), not as RED/AMBER/GREEN (this terminology is only used in relation to routine, mandatory FBC monitoring)

Clozapine Clinic Team:

- Contact patient and advise them to omit their morning dose of clozapine (if applicable) on the day of their next clinic visit; confirm this has been done prior to proceeding.
- At the clinic visit, if a POCT machine is available:
  - draw an additional finger-prick blood sample into an analyser bottle as per analyser procedures
  - run the sample through the analyser and record the assay result (clozapine plasma level) in the electronic patient record with the current dose, time of last dose taken, and the time of blood sampling (sampling should ideally be within 12 hours of the last dose)
- Notify the RC / appropriate clinician of the result via the most appropriate route (dependent on urgency)
- Advise the patient to take the omitted morning dose (if applicable) as soon as possible

Responsible Clinician / appropriate clinician (inc. pharmacy team):

- Review plasma clozapine level result in the context of other information recorded, with reference to Trust guidance on therapeutic drug monitoring and with consideration to the patient's presentation (control of symptoms vs side-effects) – TREAT THE PATIENT AS A WHOLE, NOT THE LEVELS IN ISOLATION
- If necessary, request a dose change on the current prescription and arrange for a new prescription to be generated
- Re-check plasma levels one week after patient started taking the amended dose and repeat until the clinical indication for checking levels has resolved (e.g. resolution of side-effects, compliance confirmed) and/or levels are as desired
- Record all results, considerations, decisions and follow-up actions in the electronic patient record

Changes in monitoring frequency / weeks

Dispensary Team:
- Receive email from CPMS (or equivalent) authorising change in monitoring frequency
- Identify which clinic the patient attends (or is otherwise monitored / supplied via)
- Notify relevant pharmacy technician

→

Pharmacy technician:
- Update pharmacy-held clinic spreadsheet
- Manually amend "frequency of bloods" and clinic week number(s) on current prescription in dispensary prior to next scheduled dispensing

→

Clozapine Clinic Team:
Notify patient & key worker of any change to next clinic appointment

Communication of other changes

The RC or a member of the clinical team must notify the relevant dispensary, and any specific pharmacy staff who support the team with their clozapine caseload, when:

- A co-medicine is to be started, stopped or the dose changed
- A patient prescribed clozapine is transferred between teams or into TEWV from another Trust
- A change in circumstances requires a change in monitoring arrangements (e.g. no longer able to attend the one stop clinic)
- Patient is admitted to an acute hospital

Any changes must also be recorded in the electronic patient record

Title the email "Clozapine notification" – do not use patient details within the title; include the patient's EPR ID number and date of the relevant EPR record in the email

- RPH – tewv.pharmacytees@nhs.net
- WPH – tewv.pharmacycdd@nhs.net
- FPH – tewv.pharmacyyork@nhs.net

Cito – clozapine e-form (1)

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A Clozapine e-form must be opened for every patient due to attend the Clozapine clinic.

The e-form can be opened by either the pharmacy technician or other healthcare professional working in the Clozapine clinic

The e-form has 10 pages which include:

1. Header
2. Medication
3. Step 1 monitoring
4. Tests
5. ECG
6. Step 2 side effects/efficacy
7. Smoking/alcohol
8. FBC result & supply
9. Actions
10. Sign off

1. Header

The header must be completed by the individual opening the e-form and required fields include:

- Referral team
- Date started
- Time started
- Carried out by

2. Medication

This page includes persistent information and therefore should be a list of medication supplied and monitored by TEWV including Clozapine

The pharmacy technician must check and confirm the dose on the medication grid matches the current prescription

Any discrepancies must be referred to the prescriber for review

3. Step 1 monitoring

This page includes persistent data for physical health monitoring

The physical health results from the last time they were completed will be visible.

Physical health monitoring completed during appointment to be documented on this page

Refer to psychotropic medication monitoring guide

4. Tests

Blood test results from the path lab can be accessed via this page for any patients where it has not been possible to analyse via the clinic machine. (See unable to obtain FBC section)

Additional blood results can be pulled into this page when preparing for the annual review

5. ECG

ECG results can be pulled into this page when preparing for the annual review

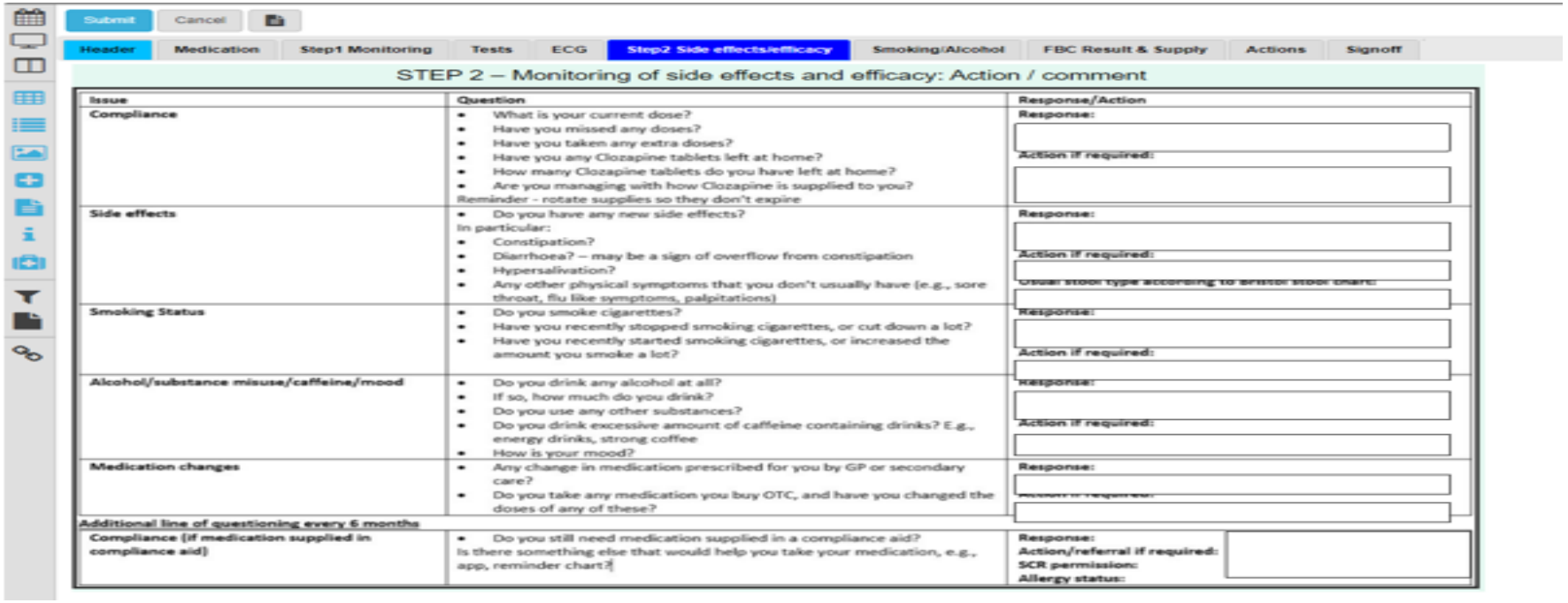
Cito – Clozapine e-form (2)

6. Step 2 side effects/efficacy

This page includes the counselling checklist to be completed by the pharmacy technician

Appendix 9 gives further guidance on supplementary questions, referral and action.

The pharmacy technician will document a summarised response to the counselling questions and record any action if required



7. Smoking and alcohol

The pages provides links to smoking and alcohol forms including Fagerstrom and Audit C

Current forms can be opened or new forms launched when responses to counselling questions on smoking and alcohol indicate a change

8. FBC results and supply

This page includes the documentation of FBC results and supplies of Clozapine and is completed by the pharmacy technician and includes

- Confirmation blood sample obtained – If no blood sample as patient did not attend, fields to be completed with contact and plan
- How the sample was analysed – clinic machine or path lab
- The status of the sample Red, Amber, Green
- How many weeks of Clozapine have been supplied to the patient
- Green result – e-form can be signed off (see step 9)
- Amber result – document date of next blood test, frequency now twice weekly, e-form remains open until Green result received
- Red – document date of next blood test and any advice from CPMS.

One e-form is completed for the whole episode of care regardless of how many blood samples are required until the result is confirmed green and full supply of medication handed to patient.

Return to front page

Cito – Clozapine e-form (3)

8. Actions

Actions as a function have not worked as expected in Cito and have therefore not been recommended for use as part of this e-form

8. Sign off

This page includes safety and risk, activity recording and sign off and is completed by the pharmacy technician

Any additional information not captured elsewhere in the e-form can be added to the notes section of the sign off page this will then pull through into a progress note with the e-form attached.

- Safety and risk

There are three options

- Yes – Safety and risk information updated – This option should be selected if the pharmacy technician has updated the safety summary following the clinic consultation
- No – Safety and risk information reviewed. No update required – This would be the field selected when all monitoring and counselling has been completed but no new risks are identified
- No – Safety and risk not reviewed – This would only be selected if the patient refused to engage in monitoring and counselling

- Activity recording

The activity recording section must be completed by all individuals who have contributed to the e-form

- Sign off

Must only be completed when the patient has a green result, and all medication supplied.

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Lost supplies

Reported by patient/carer

- If a patient/carer reports that a supply of clozapine has been lost the priority must be to consider how missed doses can be avoided such that re-titration is unnecessary (doses missed >48 hours). This will usually require an interim/emergency supply while the loss is investigated.
- In working hours - contact the usual supplying Trust dispensary and agree a quantity to be ordered/supplied, taking into consideration:
  - The risk of overdose or diversion (if the reported loss is potentially false)
  - The validity of the most recent blood result and date of next clinic visit
  - The capability of the patient to collect or team to deliver further interim supplies until next full supply
- Out of hours – contact on-call pharmacist and refer to "Accessing clozapine out-of-hours"
- Once an emergency supply has been arranged and missed doses avoided, the clinical team should investigate the validity and circumstances of the loss and report it as a medication incident on InPhase and in the EPR, including the following details:
  - How many days' supply (approx.) were there?
  - Where the supply was lost / last in the patient's possession?
  - What has the patient/carer done to try and find it?
  - Was any other medication lost with it?
  - Has this happened before with this patient?
- Consider any risk to:
  - Patient – loss of symptom control from missed doses; any safeguarding concerns?
  - Family – any risk of accidental ingestion by children if lost at home?
  - Public (e.g. if left on a bus) - has it been reported to bus company?
- If repeat incident, review capability of patient to manage current supply arrangements – are weekly supplies required (within 2-weekly / 4-weekly monitoring)?

Reported by inpatient ward

- If a ward reports that a supply of clozapine for a particular patient has been lost the priority must be to consider how missed doses can be avoided such that re-titration is unnecessary (doses missed >48 hours). This will usually require an interim/emergency supply while the loss is investigated.
- In working hours - contact the usual supplying Trust dispensary and agree a quantity to be ordered/supplied, taking into consideration the validity of the most recent blood result / date of next clinic visit
- Out of hours – refer to "Accessing clozapine out-of-hours"
- Once an emergency supply has been arranged and missed doses avoided, the ward team should investigate the loss and report it as a medication incident on InPhase
- If repeat incident on this ward, review arrangements for safe medicines storage and management of patient-specific supplies

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Transfer between care settings

Admission to TEWV wards – see this checklist for key tasks

Discharge from TEWV wards – see this checklist for key tasks

Transfer between clinics / wards / from another Trust:

Departing Clozapine Clinic / Ward Team:
- Notify relevant Trust dispensary / pharmacy team staff of patient transfer, including all relevant patient details, any comments from clinic spreadsheet and any outstanding monitoring or supply issues (e.g. waiting for plasma level assay result)
- Transfer to another ward – ensure current clozapine supplies are transferred with the patient

Departing Pharmacy Team:
Remove patient from clinic spreadsheet / ward control board and document details of transfer in the electronic patient record

Receiving Pharmacy Team:

Internal clinic-clinic transfer:
- Inform CPMS (or equivalent) of changes to responsible consultant, blood sampling venue or dispensing pharmacy
- Manually amend the current prescription with changes to responsible consultant, blood sampling venue or dispensing pharmacy
- Add patient to receiving clinic spreadsheet
- Document details of transfer in the electronic patient record

Internal ward-ward transfer – see admission checklist

Transfer from another Trust:
- Generate new prescription with details provided by departing Trust – then follow "initial 12-month prescription" process

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Inpatient admission checklist

Patient name: ……

EPR no.: ……

STEP 1: medicines reconciliation

- ❑ Confirm brand of clozapine:

  ……

- ❑ Confirm current dose:

  ……

- ❑ Confirm date: …… and time: …… of last dose *(if >48 hours, re-titration is necessary)*
- ❑ Confirm date: …… & status: RED / AMBER / GREEN of last FBC
- ❑ Confirm frequency of FBC monitoring:

  WEEKLY / 2-WEEKLY / 4-WEEKLY

- ❑ Date next FBC due:

  ……

STEP 2: prescribing

- ❑ Prescribe clozapine on EPMA according to details in step 1

(only if dose confirmed, it is <48 hours since last dose and patient has a valid blood result)

STEP 3: supply

- ❑ Is the patient's own supply available and suitable for use?

  YES / NO – if no…..

- ❑ Order new supply from relevant dispensary

STEP 4: communication & monitoring

- ❑ Notify relevant dispensary of admission (if not already aware via step 3)
- ❑ Suspend 12-month prescription for community supplies
- ❑ Inform CMHT and/or clinic pharmacy technician of admission, and request return of any supplies in team base/clinic to relevant dispensary
- ❑ Inform CPMS (or equivalent) of any permanent changes to RC / dispensing pharmacy / monitoring clinic
- ❑ Update pharmacy-held clinic spreadsheet
- ❑ Record date of next FBC on ward and/or pharmacy control board
- ❑ Implement regular monitoring of physical health side-effects, e.g. Bristol stool chart

Document completion of all tasks in the electronic patient record

Inpatient discharge checklist

Patient name: ……

EPR no.: ……

STEP 1: planning

- ❑ Dose: STABLE / TITRATING
- ❑ If titrating, arrange ongoing physical health monitoring & dose adjustment by community RC
- ❑ Assess need for community supplies in compliance aid
- ❑ Any co-meds to be transferred to community clozapine prescription?
- ❑ Any patient/carer information needs, e.g. PIL, reminder chart, MAR chart?
- ❑ Any further FBC tests before discharge / transfer?
- ❑ Inform patient/carer of date & location of community clinic appointment or alternative arrangements for next blood test
- ❑ Prepare discharge prescription with sufficient supplies until community clinic / blood test, within blood validity

Document completion of all tasks in the electronic patient record

STEP 2: communication

- ❑ Inform clinical pharmacy team and relevant dispensary of intended discharge date
- ❑ Inform relevant community team of intended discharge date
- ❑ Inform clozapine clinic of intended discharge date and date of first visit to clinic (or alternative arrangements)
- ❑ Arrange new or amended 12-month prescription for clozapine (+ co-meds) with community RC - **only** if dose is stable (consider likely dose adjustment for return to smoking)
- ❑ Inform CPMS (or equivalent) of any permanent changes to RC / dispensing pharmacy / monitoring clinic
- ❑ Update pharmacy-held clinic spreadsheet
- ❑ Inform GP, as part of discharge communication, that clozapine has been initiated, with a request to add it to the patient's prescription record (as "specialist" prescribed)

Accessing clozapine out-of-hours

A supply of 84 x Clozaril® / Clozapine Mylan 100mg tablets, 84 x Clozaril® / Clozapine Mylan 25mg tablets is stocked in the EDC at the following locations:

- *Cross Lane Hospital (Danby Ward)*
- *Foss Park Hospital*
- *Lanchester Road Hospital*
- *Roseberry Park Hospital*
- *West Park Hospital*

Ward staff:

- Identifies a shortage of clozapine when trying to administer a dose out-of-hours
- Call on-call pharmacist for advice

On-call pharmacist:

- Check validity of patient's bloods via relevant monitoring service* / EPR
- If necessary, provide details to access the supply of Clozaril® / Clozapine Mylan in the nearest EDC; advise staff to take complete box of each tablet strength(s) required
- Email the relevant dispensary to inform that the EDC supply of clozapine has been released, with details of ward and patient name
- Record activity in relevant EPR

Ward staff:

- Directly accesses EDC supply of clozapine, in a sealed envelope and labelled: "contact on-call pharmacist before removing this medicine"

Dispensary / Clinical pharmacy team:

On the next working day:

- Order and dispense a named-patient supply of the patient's usual brand / formulation of clozapine to the ward in line with blood validity
- Recover the remaining stock of Clozaril® / Clozapine Mylan taken from the EDC – for each strength:
  - if >28 tablets remaining, return to the EDC in a sealed envelope, labelled: "contact on-call pharmacist before removing this medicine";
  - If <28 tablets remaining, return stock to dispensary and re-issue an original pack to the EDC in a sealed envelope labelled: "contact on-call pharmacist before removing this medicine"
- Book out the number of tablets used from the EDC stock to the relevant ward / patient

*CPMS and the other clozapine monitoring services have a "Memorandum of Understanding" such that, in these circumstance, up to 7 days' supply of any brand may be made to ensure continuity of treatment / avoid a treatment break of >48 hours.

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Emergency supply for non-TEWV patient

- It may be necessary to arrange an emergency supply of clozapine to a patient registered with another Trust (e.g. a tourist in the TEWV area who has forgotten to bring their own supply, or has been admitted to a TEWV inpatient unit)
- CPMS and the other clozapine monitoring services have a “Memorandum of Understanding” such that, in these circumstance, up to 7 days’ supply may be made to ensure continuity of treatment / avoid a treatment break of >48 hours. If more than 7 days’ supply is required, the patient must be registered with the relevant monitoring service before further supplies can be made

Prescriber (e.g. Crisis Team):

- Contact patient’s “home” Trust/team to confirm patient details (name, DOB, NHS number & monitoring service number), and current clozapine prescription details (brand, dosage)
- Check the current “blood status” with the relevant blood monitoring service:
  - Clozaril® / Clozapine Mylan — CPMS: 0845 7698269 or CPMS@viatris.com
  - Zaponex® — ZTAS: 0207 3655842 (Mon-Fri 9am-5pm only)
  - Denzapine® — DMS: 0333 2004141
- If current blood status is GREEN (or AMBER) and monitoring is not overdue, contact the local Trust dispensary (in working hours) or on-call pharmacist (out of hours) to arrange a maximum of 7 days’ supply of clozapine at the earliest opportunity (within 48 hours of last dose taken)

Dispensary Team:

- Arrange prescription for 7-day supply with prescriber; arrange collection / delivery of supply with local team
- Confirm patient details and blood status on relevant monitoring service spreadsheet
- Ensure prescriber is aware of arrangements required to enable further supplies if needed, i.e. registration with CPMS

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Patient admitted to acute hospital

Elective admission – remind patient to take their own supply of clozapine into hospital with them.

Emergency admission:

Whichever TEWV team is informed of admission e.g. Liaison Team:
Notify the relevant clozapine clinic team / dispensary that the patient has been admitted and their current location

↓

Clozapine Clinic Team / Key worker:
Arrange for standard monitoring of FBC / pick up admission blood results as appropriate and ensure result is entered onto CPMS

↓

Dispensary Team:
- Issue 7-day supply of clozapine from current prescription – ensure supplementary label (→) is attached to the box
- Transfer medication to acute hospital using whichever method of supply is most appropriate at the time, using scheduled delivery runs if possible & maintaining an audit trail
- Establish communication with acute Trust pharmacy team to arrange further supplies as needed

See: Safety guidance - Clozapine on admission to an acute hospital ward contained in 'mental health medicines: safety guidance for acute hospital teams'

N.B. a small supply of clozapine 25 mg and 100 mg tablets is held in the emergency cupboard at York District Hospital, but not at any other acute hospital within the TEWV footprint

Out of hours, it may be possible to access supplies of clozapine via this process if all other options have been exhausted

This container must NOT be supplied for discharge
Contact TEWV pharmacy for a new supply
Tel: ……..

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Clozapine clinics – pharmacy-held spreadsheet

The Trust pharmacy team maintains a password-protected spreadsheet (or similar) for each one-stop clinic. The format varies according to which dispensary the clinic is linked to. It is used to record:

- demographic details of patients currently attending the clinic
- dispensing & distribution of supplies for weekly clinics
- quarantine status of supplies held at the clinic site
- attendance of patients at the clinic
- current blood status of each patient (R/A/G)
- date of next clinic visit

An example is shown here

Template clinic spreadsheet

Week 1	Next Due Date		Clozapine Clinic						Pharmacy		Clinic		Released	Delayed		Care Co-Ordinator				
Clinic Date	Appointment Time	Patient	Specialty	Consultant	CPMS No:	Paris ID	Frequency	Dose	Dispensed	Clozapine Quarantined	Attended	Blood Status	Clozapine Released	Released (Pharmacist's Initials)	Date	Name	Team	Telephone No:	Contacted by (Initials)	Date and Time

Managing Clozapine Overdose

The information below is not intended to be a definitive treatment strategy, but a suggested approach for clinicians. It is based on previous successful experience. Each case should, of course, be considered individually. This information is provided for healthcare professionals and should not be used as a patient information leaflet. If notified of a potential overdose in the community, the importance of attending A&E should be reiterated and followed up to ensure the patient has been reviewed.

Treatment

- There are no specific antidotes
- Gastric lavage / activated charcoal within 6 hours of ingestion
- Avoid adrenaline

Monitoring

- Continuous cardiac monitoring
- Surveillance of respiration
- Monitor electrolytes

Serious risks

- Aspiration Pneumonia
- Convulsions
- Arrythmia
- Dyspnoea
- Neuroleptic Malignant Syndrome (NMS)

Discharge

- Can only occur after registered psychiatrist and key worker have been contacted due to risk of delayed reactions, e,g, arrhythmias, for up to 5 days post overdose

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Clozapine overdose: information for TEWV Clinicians

Background	Signs and symptoms of clozapine overdose	Reporting of side effects	Follow up
• Patients with treatment-resistant schizophrenia have a higher incidence of suicide compared to the general population[2]. Both intentional and accidental overdoses have been reported with clozapine. • As noted in the SmPC, mortality associated with clozapine overdose is about 12%[1]. Most of the fatalities reported were associated with cardiac failure or pneumonia caused by aspiration and occurred at doses > 2000mg[1]. In a few adult individuals, primarily those not previously exposed to clozapine, the ingestion of doses as low as 400mg led to life-threatening comatose conditions and, in one case, to death[1,2]. • Seizures have been reported to occur in patients with plasma clozapine levels above 1 mg/L following overdose.[4]	• All of the side-effects associated with clozapine at therapeutic dose may be seen following overdose except those seen with long-term therapy only, e.g. constipation, weight gain and agranulocytosis[3]. In addition, altered respiratory function and aspiration may be observed, and these are seldom seen at therapeutic doses. Pulmonary oedema is not a recognised side-effect but has occurred following overdose[3]. • The central nervous, cardiovascular and respiratory systems are most commonly affected following acute overdose. The signs and symptoms listed in the SmPC are stated above. There is a risk of neuroleptic malignant syndrome • **Delayed reactions may be seen, including the late occurrence or recurrence of cardiac arrythmias[3].**	Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the product. Healthcare professionals are asked to report any suspected adverse reactions via the yellow card system: www.mhra.gov.uk/yellowcard	• Clozapine remains the antipsychotic of choice for schizophrenia patients with a history of suicidality. Overdose is not a reason to discontinue clozapine treatment, but to institute measures (e.g. restricted supplies) to minimise recurrence. • The patient needs to be reviewed with a view to ongoing treatment, overdose risk and quantities to prescribe / supply. • Consideration needs to be made as to any supplies at home and whether these need to be returned to pharmacy for disposal. • A plan for ongoing treatment doses and blood monitoring needs to be carefully made, discussed with the patient and clearly documented in the patient's electronic record. Refer to the information elsewhere in this document for guidance on action to take following a break in treatment, e.g. notifying and re-registration with CPMS, re-titration

Additional information for acute hospital clinicians can be found on the Trust intranet and website

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Clozapine: roles & responsibilities **(inpatients)** – *see processes & checklists for detail of tasks*

Initiation

Consultant (RC)
- Clinical decision to initiate clozapine
- Inform local pharmacy team of intention to initiate clozapine
- Arrange patient education re. monitoring requirements, side-effects, etc
- Obtain patient consent and record in EPR (or MHA basis for treatment
- Ensure baseline FBC and other tests are completed
- Register patient with CPMS (or equivalent)
- Enter significant medication alert [CLOZAPINE] on EPR

Postgraduate Doctor
- Complete baseline FBC and other tests, and record in EPR as a Physical Health case note

Clinical Pharmacist
- Deliver education to patient re. monitoring requirements, side-effects, etc and record in EPR
- Provide inpatient initiation checklist to ward
- Ensure arrangements in place to attend OSC after discharge

Prescribing

Consultant (RC)
- Prescribe clozapine on EPMA
- Sign 12-month prescriptions and return to relevant dispensary (SIS patients)
- Record any changes to dose on EPR and notify relevant clinical pharmacy team and dispensary

NMP
- Sign 6-month prescriptions (if within scope of practice) and return to relevant dispensary
- Record any changes to dose on EPR and notify relevant clinical pharmacy team and dispensary

Pharmacy Technician
- Set up 12-month prescription once stable dose is reached (SIS patients)
- Add patient to relevant prescription tracker and update as necessary
- Produce new prescription when due (including reconciliation), or after changes to dose
- Archive old or discontinued prescriptions

Clinical Pharmacist
- Professionally check new signed 12 month prescriptions on receipt from prescriber

Ordering

Pharmacy Technician
- Acute wards - order supplies of clozapine from dispensary according to dose and blood validity
- Recover supplies from ward after dose changes or cessation of treatment

HCA (SIS) – for weekly clinic
- Venepuncture - obtaining blood sample for clinic machine
- Operation of clinic machine

Dispensing

Pharmacy Assistant (dispensary)
- SIS patients - prepare clozapine supplies in advance of weekly clinic according to each patient's monitoring frequency
- Acute wards – prepare supplies according to technician orders

Accredited Accuracy Checker
- Check prepared and clinically-checked clozapine supplies

Dispensary Pharmacist
- Check prepared clozapine supplies
- Archive old or discontinued prescriptions

Administration

Ward staff nurse
- Administer clozapine according to prescription / titration chart in line with good practice standards

Monitoring

Consultant (RC)
- Oversight of all patients under their RC
- Regular assessment of mental state
- Arrange clozapine level assays if clinically indicated; review and act upon assay results
- SIS - annual review of clozapine treatment according to checklist
- Notify pharmacy if clozapine is discontinued (if not due to red result)

Postgraduate Doctor
- Ensure repeat FBC within 10 days of baseline, and weekly thereafter
- Assess for side-effects during titration (weekly)
- Check random blood glucose at 4 weeks
- Ensure repeat ECG, HbA1c & lipids at 12 weeks
- SIS - complete GASS for clozapine (or other appropriate side-effect rating scale) every 12 months

Ward staff nurse
- Oversight of all aspects of patient care
- Arrange and/or deliver all monitoring requirements: FBC – when due / prompted by pharmacy; physical obs – daily; weight – weekly (new initiations); bowel function - at least weekly*; other side effects – at least weekly*

**depending on environment/individual patient factors*

Pharmacy Technician
- Retrieve blood results from ICE and input to CPMS (or equivalent) if blood not analysed on clinic machine

HCA (inpatients)
- Physical health observations (NEWS) – daily during titration, then as instructed
- Measure weight - weekly during titration, then as instructed

Clinical Pharmacist
- Inform CPMS (or equivalent) if discontinued
- Obtain plasma level assay results and communicate them to RC / enter on EPR

Clozapine: roles & responsibilities in **community** settings – *see processes & checklists for detail of tasks*

Initiation

Consultant (RC)
- Clinical decision to initiate clozapine
- Inform local pharmacy team of intention to initiate clozapine
- Arrange patient education re. monitoring requirements, side-effects, etc
- Obtain patient consent and record in EPR (or MHA basis for treatment
- Ensure baseline FBC and other tests are completed
- Register patient with CPMS (or equivalent)
- Enter significant medication alert [CLOZAPINE] on EPR

Postgraduate Doctor (or CPN)
- Complete baseline FBC and other tests, and record in EPR as a Physical Health monitoring e-form

Pharmacy team (where available) **/ Key worker**
- Deliver education to patient re. monitoring requirements, side-effects, etc and record in EPR
- Check primary care record for potential drug interactions
- Provide community initiation checklist to team
- Ensure arrangements in place to attend OSC

Prescribing

Consultant (RC)
- Prescribe clozapine on Trust community clozapine prescription
- Sign 12-month prescriptions and return to relevant dispensary
- Record any changes to dose or "co-meds" on EPR and notify relevant clinical pharmacy team and dispensary

Non-Medical Prescriber
- Sign 12-month prescriptions (if within scope of practice) and return to relevant dispensary
- Record any changes to dose or "co-meds" on EPR and notify relevant clinical pharmacy team and dispensary

Pharmacy Technician
- Set up 12-month prescription once stable dose is reached
- Add patient to relevant pharmacy-held spreadsheet and update as necessary
- Produce new prescription when due (including reconciliation), or after changes to dose or co-meds
- Archive old or discontinued prescriptions

Clinical Pharmacist
- Professionally check new signed 12 month prescriptions on receipt from prescriber

Dispensing

Pharmacy Assistant (dispensary)
- Prepare clozapine supplies in advance of OSCs according to each patient's monitoring frequency

Accredited Accuracy Checker
- Check prepared and clinically-checked clozapine supplies for OSCs

Pharmacist / Pharmacy technician
- Check prepared clozapine supplies for OSCs
- Archive old or discontinued prescriptions
- Authorise release of quarantined medication outside OSC

Supply

Pharmacy Technician
- In OSC:
  - ➢ Check quarantine cupboard for uncollected medication, and any action required
  - ➢ Check delivered medication vs eVCB
  - ➢ Release medication to patient from quarantine (green/amber result)
  - ➢ Secure any unissued medication in quarantine cupboard
- Notify key worker if patient fails to attend clinic as scheduled

Qualified nurse
- Release of medication to patient from quarantine (green/amber result)

Key worker / CPN
- Arrange blood sampling and testing if patient fails to attend clinic
- Release of medication to patient from quarantine (with pharmacy approval)
- Recover supplies from patient after dose changes or cessation of treatment
- Inform patient to stop taking clozapine if notified of RED result

HCA
- Venepuncture - obtaining blood sample for clinic machine
- Operation of clinic machine

Monitoring

Consultant (RC)
- Oversight of all patients under their RC
- Regular assessment of mental state
- Arrange clozapine level assays if clinically indicated; review and act upon assay results
- Annual review of clozapine treatment according to checklist (may be delegated to a suitably qualified prescriber in team)
- Notify pharmacy if clozapine is discontinued (if not due to red result)

Postgraduate Doctor (or CPN)
- Ensure repeat FBC within 10 days of baseline, and weekly thereafter
- Assess for side-effects during titration (weekly)
- Check random blood glucose at 4 weeks
- Ensure repeat ECG, HbA1c & lipids at 12 weeks

Pharmacy Technician
- Complete counselling checklist in OSC – notify RC if change of smoking status or alcohol intake, or new / worsening side-effects
- Complete or prompt completion of GASS for clozapine (or other appropriate side-effect rating scale) every 12 months
- Retrieve blood results from ICE and input to CPMS (or equiv) if blood not analysed in clinic

Key worker
- Oversee patient care – arrange and/or deliver all monitoring requirements
- Inform pharmacy if break in treatment

HCA (with support of crisis team)
- Complete daily physical health obs – BP, ECG, weight – during titration and record in EPR as Physical Health case note
- Venepuncture – obtain blood sample for any necessary tests or plasma level assays

Pharmacy team
- Inform CPMS (or equiv) if discontinued or break in treatment
- Enter POC plasma level assay results on EPR

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Standards for community caseloads

1. **Annual review:** Clozapine Annual Review Checklist completed (or the content of the checklist evident in annual review)
    - Process standard: every 12 months for all patients
    - Audit standard: within the last 15 months for all patients
2. **Clozapine on Summary Care Record:** Clozapine listed on National Care Record for all patients
3. **Side Effect Monitoring:** GASS for clozapine or other rating scale completed at least once in the last 12 months
4. **Bowel monitoring:** Bristol Stool Chart used and recorded (during constipation counselling) at least once in the last 3 months.
5. **Education & Training:** Evidence of completion of appropriate clozapine training / CPD for all clinic staff & clozapine prescribers within last 3 years
    - TEWV ESR training search “clozapine” – course title: 346 Online Clozapine Theory

These standards will be assessed as part of the Pharmacy audit programme every 12-18 months

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Standards for inpatients (short stay)

1. **Smoking status:** current smoking status and consideration of any change in status at admission / initiation of clozapine is documented in the electronic patient record
2. **Side-effect monitoring:** GASS for clozapine or other adverse effects assessment completed within 2 weeks of admission / initiation
3. **Bowel monitoring:** bowel monitoring chart in place and status recorded daily since admission or during the last 4 weeks, whichever period is shorter
4. **Patient information:** documented evidence that information on clozapine has been provided to patient or carer *(N.B. applicable to all patients, irrespective of whether newly initiated or admitted on clozapine)*
5. **Dose administration:** all doses since admission or within the last 4 weeks (whichever period is shorter) administered or a reason for planned omission is recorded on EPMA/EPR

These standards will be assessed as part of the Pharmacy audit programme every 12-18 months

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Standards for inpatients (long stay - >6 months)

1. **Smoking status:** current smoking status and consideration of any change in status is documented in the electronic patient record
2. **Side-effect monitoring:** GASS for clozapine or other adverse effects assessment completed within the last 6 months (?)
3. **Bowel monitoring:** bowel monitoring chart in place and status recorded daily over the last 4 weeks
4. **Patient information:** documented evidence that information on clozapine has been provided to patient or carer within the last 6 months *(N.B. applicable to all patients, irrespective of whether newly initiated or admitted on clozapine)*
5. **Dose administration:** all doses within the last 4 weeks administered, or a reason for planned omission is recorded on EPMA/EPR

These standards will be assessed as part of the Pharmacy audit programme every 12-18 months

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Glossary

- AMD = Associate Medical Director
- CPMS = Clozaril Patient Monitoring Service
- DMS = Denzapine Monitoring Service
- ZTAS = Zaponex Treatment Access Service
- EDC = emergency drug cupboard
- EPR = electronic patient record
- FBC = full blood count
- RC = responsible consultant
- EMIS = pharmacy dispensing system

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- de Leon et al (2022). An International Adult Guideline for Making Clozapine Titration Safer by Using Six Ancestry-Based Personalized Dosing Titrations, CRP, and Clozapine Levels. Pharmacopsychiatry, 55(2), 73–86

Document Changes

Version	Date of change	Details of change
2.0	22/5/25	Full review of v1.5; re-formatted into interactive slide set • Enhanced guidance on clozapine as a treatment option & patient factors to consider • Personalised approach to initiation and titration to target dose • Change from 6-month to 12-month prescriptions for stable patients with link to strengthened annual review process • More robust process for supply & monitoring outside one-stop clinics

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