

**This document must be filed prominently in the patient's primary care notes
Clozapine (Clozaril®) for GPs and other health professionals**

A medicine for schizophrenia, and psychosis in Parkinson's disease

Ensure that clozapine is added to the electronic patient's medication list (GP) but not for issuing (appendix 1)

Add patient to the mental health register (GP)

Perform annual primary care review (GP)

Urgent full blood count if signs of infection inc. sore throat & flu symptoms

Clozapine can cause constipation- Act promptly and treat actively when constipation is recognised; if untreated may lead to fatal complications

Do not restart if there has been a break of >48h between doses

Check drug interactions

Stopping smoking can increase clozapine levels; be alert to smoking status

Increased risk of myocarditis or cardiomyopathy may be fatal in rare cases

This document provides important information with respect to the prescribing of clozapine. Clozapine is prescribed, monitored and supplied by the hospital and CMHT, not the GP. **However, familiarity with the contents of this document will serve to protect patients treated with clozapine from adverse events associated with its use.**

Clozapine has been shown to be the drug treatment of choice in treatment resistant schizophrenia. It may also be prescribed for patients with schizophrenia who are intolerant of other antipsychotic drug treatment or for patients with psychosis in Parkinson's disease when other treatment strategies have failed.¹

The Clozaril® brand of clozapine is prescribed in Derbyshire Healthcare Trust. Response rates to Clozaril® in patients with refractory schizophrenia are reported to be 30% at 6 weeks and 60% at one year. The average maintenance dose is around 400mg/day, though it is licensed up to 900mg/day. Some patients will show little or no evidence of adverse effects at 900mg/day, whilst others may complain of adverse effects at much lower doses.²

Dose initiation and breaks in treatment

Since many of the adverse effects of clozapine are dose-dependent and associated with speed of titration, therapy is started at a low dose (12.5mg once a day) and increased slowly. If the patient has not taken clozapine for greater than **48 hours** advise that the usual dose **must not** be resumed. The psychiatrist must be contacted urgently as the dose must be re-titrated from 12.5mg/day. Please report any concerns regarding non-adherence with treatment to the psychiatrist.

Monitoring

All patients receiving clozapine in Derbyshire must be monitored physically by the community team as per the Trust's monitoring guidelines for antipsychotics. In addition, white cells and neutrophils are checked each week, fortnight or 4-weeks depending on the specification of the Clozaril Patient Monitoring Service (CPMS). Clozapine increases the incidences of diabetes and cardiac events in a group already at increased risk.

GPs should liaise with the mental health team if there are any identified physical health concerns that may impact on treatment.

Adverse effects Very common ($\geq 1/10$), common ($\geq 1/100$, $< 1/10$), uncommon ($\geq 1/1,000$, $< 1/100$), rare ($\geq 1/10,000$, $< 1/1,000$), very rare ($< 1/10,000$), including isolated reports.

Adverse effect ¹	Incidence ¹	Action
Anticholinergic effects- constipation	Very common	Act promptly and treat actively when constipation is recognised. This side effect must not be ignored. Constipation can lead to clozapine toxicity and deaths have occurred as a result of paralytic ileus and perforation. See appendix 2
dry mouth	Common	Advise symptomatic relief. May be a sign of too high dose, consider informing psychiatrist
blurred vision	Common	May be a sign of too high dose, consider informing psychiatrist. Careful supervision is indicated in the presence of narrow-angle glaucoma.
urinary retention (incontinence can also occur)	Common	Manage in consultation with psychiatrist and urologist. Acute retention may need emergency catheterisation and hospital admission.
Pyrexia (see myocarditis/ cardiomyopathy)	Common	More common at beginning of treatment and can be of no clinical significance, resolving spontaneously after a few days. However, evaluate carefully to rule out possibility of infection, agranulocytosis or myocarditis (see below). Pneumonia is a rare reaction to clozapine. Take urgent full blood count with differential and inform psychiatrist if abnormal. In the presence of high fever the possibility of neuroleptic malignant syndrome (NMS) must be considered. If count is satisfactory and temperature no more than 38.5°C, clozapine may continue. If fever is $> 38.5^\circ\text{C}$ or persistent, the clinician may wish to consider withholding clozapine until the fever subsides. ³
Hypersalivation	Very common	Extra pillows at night/daytime chewing gum may help. Liaise with specialist to consider dose reduction ⁸ . May be treated with hyoscine hydrobromide (Kwells); suck and swallow a 300mcg tablet up to three times a day. Unlicensed.
Nausea and vomiting	Common	More common early in treatment- slowing the titration or reducing the dose may help ⁶ . Avoid prochlorperazine, metoclopramide and domperidone. Antacids and Ranitidine may be of benefit ⁶ . If necessary consider cyclizine with caution for additive drowsiness and antimuscarinic effects (care with constipation) or ondansetron (unlicensed) with caution for additive QTc risks, other medicines which may prolong QTc and cardiac history.
Sedation	Very common	Manipulation of dosage times may alleviate daytime sedation. Dose may be too high. Inform psychiatrist.
Hypertension, postural hypotension, syncope	Common	Dose may have been increased too quickly or dose is too high. Inform psychiatrist.
Tachycardia (see myocarditis/ cardiomyopathy)	Very common	More common at beginning of treatment. Dose may have been increased too quickly or dose is too high. Inform psychiatrist. Where persistent and clinically appropriate consider management with a beta-blocker.
Weight gain	Common	Lifestyle advice. Referral to dietician may be appropriate. Ensure physical monitoring as per the Trust's monitoring guidelines for antipsychotics (e.g. glucose, lipids).
Seizures/convulsions/myoclonic jerks	Common	More common with higher doses of clozapine. May be a sign of toxicity. Inform psychiatrist immediately.
Agranulocytosis/neutropenia (patient may report symptoms of infection e.g, flu-like symptoms, sore throat, high temperature)	Uncommon/ common	Urgent full blood count indicated. Inform psychiatrist immediately. Clozapine to be discontinued if $\text{WCC} < 3.5 \times 10^9/\text{L}$ or $\text{ANC} < 2.0 \times 10^9/\text{L}$.
Myocarditis/Cardiomyopathy	Rare/Very rare	If myocarditis or cardiomyopathy suspected clozapine should be stopped and patient referred to cardiologist. Suspect in patients who have persistent tachycardia at rest, particularly during the first two months, palpitations, arrhythmias, chest pain, and other signs/symptoms of heart failure or symptoms that mimic MI. Flu-like symptoms may also be present. Inform psychiatrist.

Smoking⁵

Smoking tobacco reduces plasma levels of clozapine by up to 50% so smokers may need higher doses. Likewise, patients who stop smoking may experience a 50% increase in plasma level; there have been case reports of adverse effects in patients taking clozapine when they have stopped smoking. This effect is related to inhalation of tobacco smoke and is **independent of any NRT product** used including e-cigarettes (vape).

If your patient wants to quit/cut down smoking inform the psychiatric team. Side effects of clozapine should be reviewed regularly during the period of cutting down.

Interactions

Clozapine is contraindicated with

- other medicines with a substantial potential to depress bone marrow function (e.g. carbamazepine, carbimazole).

Clozapine is cautioned with

- other medicines with anticholinergic effects (additive effect) e.g. some drugs for urinary incontinence - be aware of potential additive constipation burden
- other medicines with hypotensive effects (additive effect)
- erythromycin and ciprofloxacin; may increase clozapine levels and are associated with additive QTc risks⁷
- alcohol, due to potential for sedation
- benzodiazepines, due to increased risk of circulatory collapse.

Try to avoid antibiotics with potential to cause e.g. blood dyscrasias eg cephalosporins, trimethoprim and nitrofurantoin.⁷

This is not an exhaustive list. Please see BNF and summaries of product characteristics for further information.

Contacts

Consultant Psychiatrist	Community Team & Care Coordinator	Pharmacy	Clozaril Patient Monitoring Service
		Ashbourne Centre, Kingsway 01332 623700	0845 7698269 24h emergency- 01276 692504

References

1. Summary of Product Characteristics. Mylan. www.medicines.org.uk/emc Accessed 25th January 2019
2. "Role of Therapeutic Drug Monitoring". <https://www.clozaril.co.uk>. Accessed 4th November 2016 (user id and password required)
3. "Clozaril and Fever". Available [online] <https://www.clozaril.co.uk>. Accessed 4th November 2016 (user id and password required)
4. British National Formulary accessed on-line 4th November 2016
5. Medicines Q&As What are the clinically significant drug interactions with cigarette smoking? www.sps.nhs.uk accessed online 25th January 2019
6. "Clozaril and gastrointestinal side effects" <https://www.hcpinfo.clozaril.co.uk>. Accessed 25th January 2019
7. Stockley's drug interactions www.new.medicinescomplete.com accessed 25th January 2019 (password required)
8. 'Clozapine and hypersalivation' <https://www.hcpinfo.clozaril.co.uk>. Accessed 25th January 2019

Document update	Date
Added Appendix 2 clozapine and constipation - advice for GP	August 2019

Appendix 1

Recording medicines prescribed and issued by other Healthcare Providers on GP clinical systems

Background

The Joint Area Prescribing Committee (JAPC) designates medicines as:

- **Red** – prescribing responsibility lies with a hospital consultant or a specialist
- **Amber** – suitable for prescribing in primary care under a shared care agreement
- **Green** – suitable for primary care prescribing
- **Grey** – not recommended for prescribing except in exceptional circumstances
- **Do Not Prescribe (DNP)** – not routinely recommended or commissioned

There are many medications which are prescribed and/or supplied directly to patients by healthcare providers outside of the GP practice. Typically these include specialist drugs which have been designated as 'red' by the JAPC. Practices are actively encouraged to ensure that the prescribing of 'red' drugs remains with the specialist to ensure patient safety is maintained. This may also apply to amber drugs prior to prescribing being transferred to primary care.

This poses a challenge for primary care to ensure that all clinical staff are aware of medication prescribed elsewhere when:

- Making clinical decisions
- Avoiding interacting medication being prescribed or other risks when new medicines are prescribed
- Providing a drug history to hospitals/units on admission

It is important that GP practices have a record of these medicines on their clinical systems for patient safety purposes but do **not** inadvertently issue prescriptions for them.

This guidance aims to provide advice on how non-GP medications can be recorded on the patients' clinical record on each of the GP clinical systems.

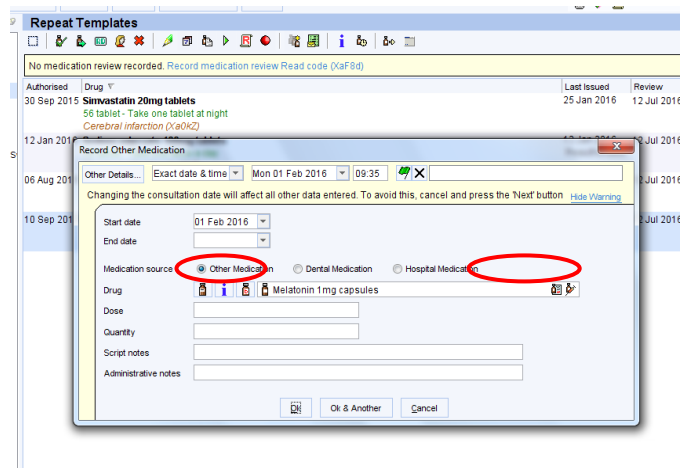
Recording and keeping this information up-to-date also ensures that the patients Summary Care Record (SCR) is accurate. The SCR provides vital information about medicines to other healthcare professionals when patients transfer between different care settings.

Guidance for adding medicines prescribed and issued by other HCPs to GP clinical systems

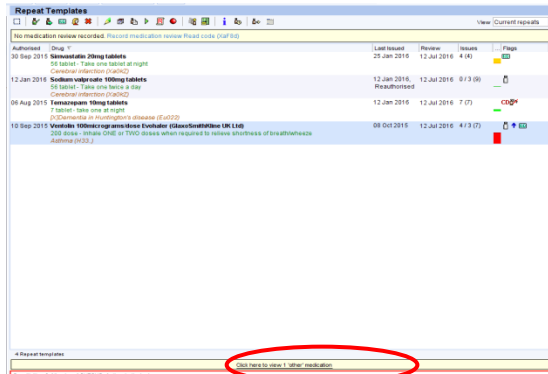
It is essential that practices' clinical systems make users unambiguously aware of patients who are prescribed clozapine. Practices should take appropriate steps to ensure that this information is clearly visible within the patient record. The following guidance suggests methods of achieving this, although the nature of implementation might vary between systems and between practices depending on local policy

SystemOne

1. Use read code **Xalng (hospital prescription)** to document that the patient has a hospital prescription
2. Go to 'medication' on clinical tree, right click and select 'record other medication'
3. A new window titled '**select drug or appliance**' will open
4. Search for the new medication and select the appropriate drug
5. A new window titled '**record other medication**' will appear
6. Under '**medication source**' select '**hospital medication**'



7. Complete details of the drug. In the '**quantity**' field enter **ZERO**, or if this is not possible the lowest quantity possible should be entered e.g. 1 tablet, 1mL.
8. In the '**dose**' field enter '**HOSPITAL PRESCRIBED & SUPPLIED – NOT TO BE PRESCRIBED BY THE GP**'.
This information is essential to warn the patient/dispensing pharmacist in the event a prescription is issued by mistake
9. In the '**script notes**' enter details of who is responsible for prescribing i.e. hospital and consultant
10. In the '**administrative notes**' section add dose instructions as per clinic letter including the date of the clinic letter
11. The record will appear in the repeat template screen under '**other**' medication
12. Click on '**OK**' and '**Save Patient Record**'



EMIS Web

1. Use read code **8B2D (hospital prescription)** to document that the patient has a hospital prescription
2. Open **'medication'** tab
3. Select **'add drug'** icon and enter drug details
4. Complete the other required details of the non-practice drug:
 - a. 'Dose': **HOSPITAL PRESCRIBED & SUPPLIED – NOT TO BE ISSUED BY GP**
 - b. 'Quantity': Enter **ZERO** or if this is not possible the lowest possible quantity should be entered e.g. 1 tablet, 1mL
 - c. 'Rx types': Select **'Repeat'**
5. Select **'Issue'**. This will open another window. Go to the **'Change All'** tab and select **'Hospital (No Print)'** from drop down menu
6. Then click on **'Approve and complete'**. The non-practice drug will now be displayed in a different section of the medication screen to the other GP prescribed medicines.

Drug / Dosage / Quantity	Usage Current / Average	Last Issue Date / Authoriser	Last Issue Number / Method
I Ranitidine 150mg tablets two at night, 112 tablet	186% / 104%	16-May-2016 MURRAY, Robert (Dr.)	<i>Print</i>
J Warfarin 1mg tablets Take As Prescribed In Anticoagulant Treatment Book, 168 tablet Altered	>1000% / 105%	13-Jun-2016 BISHOP, Nicholas (Dr)	<i>Print</i>
Hospital			
K Advagraf 0.5mg modified-release capsules (Astellas Pharma Ltd) One To Be Taken Each Day, 1 capsule		12-Nov-2015 MURRAY, Robert (Dr.)	<i>Record Hospital</i>
L Myfenax 500mg tablets (Teva UK Ltd) One To Be Taken Twice A Day, 1 tablet	0% / 0%	12-Nov-2015 MURRAY, Robert (Dr.)	<i>Record Hospital</i>
M Tacrolimus 1mg modified-release capsules Two To Be Taken Daily, 1 capsule		12-Nov-2015 MURRAY, Robert (Dr.)	<i>Record Hospital</i>

On-going updates

Practices should ensure that information about medicines prescribed elsewhere on a repeat basis are kept up-to-date as per the most recent clinic letter to maintain patient safety **and** keep the information on the patients SCR up-to-date.

It is essential practices ensure information about medicines prescribed elsewhere are reviewed on the GP clinical system **at least annually, even if there are no changes to the medication**. Where a hospital consultant/specialist has stopped a patient's medication this should be discontinued on the GP-held record.

Appendix 2 - Clozapine and constipation- advice for GP

Clozapine is associated with gastrointestinal hypomotility. In studies about 50-80% of patients showed objective evidence of slowed colonic transit. In some cases this can lead to paralytic ileus, bowel obstruction, bowel ischaemia and necrosis and can be life-threatening.

Although clozapine is managed by secondary care, patients treated with clozapine may present in Primary care with constipation. It is vital that these patients are promptly and effectively treated.

Clozapine patients and carers are reminded of the symptoms that suggest urgent help is needed and given a copy of the Choice and Medication handy fact sheet 'clozapine and constipation'.

Management of constipation

In patients taking clozapine (or who will be prescribed clozapine) the recommendations are as follows:

First line: docusate plus senna

Second line: add macrogol (e.g. laxido)

If no response, refer for gastroenterologist review.

(Notes: Lactulose is not recommended due to requirement to maintain high fluid intake and delay in time to effect. Avoid ispaghula/fybogel – unsuitable where there is slow transit time/risk of obstruction).

See Derbyshire formulary chapter 1 ([Link](#)) for further detail on assessment and management of constipation in adults