

CLOZAPINE: reducing the risk of harm

Key messages

- Common side effects may lead to life-threatening conditions in people who are prescribed clozapine:
 - clozapine-induced constipation
 - clinical or haematological neutropenia or agranulocytosis
 - tachycardia
- Clozapine is designated as a RED drug in Cheshire and Merseyside.
- Clozapine is for specialist use only and any queries regarding treatment should be referred to the specialist.

SAFETY

Everyone involved in the support or care of people receiving clozapine is reminded of the importance of awareness and management of **common side effects that may lead to life-threatening conditions**.

- Constipation must be actively monitored and actively treated. Clozapine carries a serious risk of intestinal obstruction including faecal impaction and paralytic ileus [1].
- Be cautious with signs or symptoms of a low white cell count. Clinical or haematological neutropenia or agranulocytosis can lead to an acute life-threatening condition.
- Monitor closely for tachycardia. Clozapine also carries a serious risk of myocarditis and cardiomyopathy particularly in the first two months of treatment.

Also urgently inform the psychiatrist, CMHT *, care coordinator, or another lead clinician of:

- Episodes of erratic or non-compliance with clozapine therapy.
- A break in treatment of more than 48 hours; do not restart clozapine as this will require re-titration.
- Abrupt discontinuation of clozapine; can lead to an acute rebound psychosis.
- Any change in smoking status.

Share information across the healthcare interface:

- Mental health specialists, communicate all medication changes to the GP.
- GP practices, add clozapine to the electronic health record as repeat medication prescribed elsewhere.

* CMHT (Community Mental Health Team) refers to the relevant, local mental health team providing care for your service user; this may include the Recovery Team, Early Intervention Team, Health and well-being team, etc.

Introduction

Service users supplied with clozapine will have it prescribed, monitored and dispensed by their local mental health trust. Where a service user is under the care of a third party, e.g., during an acute medical admission, this may lead to a breakdown in care. This guidance is aimed at highlighting these risks and providing solutions for the non-specialist.

Administrative action points for general practice

- DO NOT issue clozapine prescriptions.
- Ensure that clozapine is added as a 'medication prescribed elsewhere' on the Primary care clinical system using the 'hospital no print' function to ensure it is listed under the patients medication on their Summary Care Record (SCR) and to allow interactions to be detected. The dose should not be specified.
- Refer to the [Cheshire guidance on repeat prescribing](#) or the [Merseyside guidance on the summary care record](#).

Clinical action points for all prescribers and other non-mental health hospitals

- Clozapine can cause neutropenia (3% of service users) and agranulocytosis (0.5%).
- Consider urgent FBC if there are signs and symptoms of infection, e.g., sore throat, fever, or flu-like symptoms.
- Urgently inform the psychiatrist, CMHT, care coordinator, or another lead clinician if there are:
 - clinical or haematological episodes of neutropenia or agranulocytosis
 - episodes of erratic or non-compliance with clozapine therapy
 - a break in treatment of more than 48 hours; do not restart clozapine as this will require re-titration
 - abrupt discontinuation of clozapine; this can lead to an acute rebound psychosis
 - any change in smoking status
 - potential clozapine-induced constipation; can be life-threatening, consider A&E referral.
- Contact your local CMHT and/or supplying pharmacy for all clozapine admissions and any clozapine-related queries or for advice.
- Contact Psychiatry Liaison during all acute hospital in-patient user stays.
- Carefully consider the potential for drug interactions (see below).
- Always report appropriate clozapine side effects on a Yellow Card, e.g., neutropenia and severe constipation.
- Always consider the potential for clozapine toxicity, i.e., if the patient is experiencing an increasing burden of side effects or changes to smoking habits (see [MHRA guidance 2020 on clozapine blood levels](#)) [2]

Advice for Healthcare professionals

- Monitoring blood clozapine levels for toxicity is now advised in certain clinical situations such as when:
 - a patient stops/reduces smoking or switches to an e-cigarette
 - concomitant medicines may interact to increase blood clozapine levels
 - a patient has pneumonia or other serious infection
 - poor (reduced) clozapine metabolism is suspected
 - toxicity is suspected
- If blood clozapine level monitoring is carried out, this should be in addition to the required blood tests to manage the risk of agranulocytosis. For other antipsychotics, where assays and suggested reference values are available, blood level monitoring for toxicity may be helpful in certain circumstances, for example in the event of symptoms suggestive of toxicity or when concomitant medicines may interact to increase antipsychotic drug levels.
- Refer to the full Summaries of Product Characteristics for other important warnings, interactions, and recommendations for clozapine and other individual antipsychotics.

Action points for community pharmacists

- DO NOT dispense clozapine prescriptions (unless you are registered with the appropriate monitoring service).

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Information for healthcare professionals

Background information

Clozapine is an atypical antipsychotic indicated for treatment-resistant schizophrenia (TRS) or psychotic disorder in Parkinson's disease.

There are 3 brands of clozapine (see below for manufacturer contact details):

- **Clozaril** (Viatris) prescribed by Cheshire and Wirral Partnership NHS FT, Lancashire and South Cumbria NHS FT, Mersey Care NHS FT.
- **Denzapine** (Britannia Pharmaceuticals Ltd) prescribed by Mersey Care NHS FT; only oral suspension prescribed by Cheshire and Wirral Partnership NHS FT.
- **Zaponex** (Leyden Delta) is not prescribed within Cheshire or Merseyside.

Patient registration

Every service user prescribed clozapine must be registered with one of the three manufacturers before they can be prescribed and dispensed clozapine; this is arranged by the secondary care psychiatric team.

The CMHT and/or supplying pharmacy will monitor the efficacy and tolerance of clozapine, manage the ongoing mandatory full blood count testing required and prescribe and supply the clozapine.

Clozapine is usually dispensed only by appropriately registered pharmacies; this is usually the local mental health Trust's dispensary.

Side Effects

Very common side effects include (≥10%)		
Constipation – can be life-threatening (see below) * ‡		Tachycardia †
Drowsiness or sedation ‡		Dizziness
Common side effects include (≥1% and <10%)		
Urinary incontinence	Urinary retention	Weight gain †
ECG changes ‡	Postural hypotension	Syncope
Akathisia ‡	Extrapyramidal symptoms	Seizures, convulsions, or myoclonic jerks
Tremor ‡	Rigidity	Blurred vision
Headache	Fatigue	Anorexia
Hypersalivation ‡	Dry mouth	Nausea
Vomiting	Leucocytosis	Eosinophilia
Leucopenia	Agranulocytosis *	Elevated liver enzymes
Fever or benign hyperthermia (if associated with leucopenia or neutropenia or cardiac symptoms or temperature > 38 °C) *		Disturbances in sweating or temperature regulation (if associated with cardiac symptoms) *
* These side effects can lead to an acute life-threatening condition; consider urgent referral to A&E		
† May persist and indicate the development of myocarditis * or cardiomyopathy *		
‡ Management of these side effects would usually be led by the local mental health team		

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Service users taking clozapine may present at your GP surgery with side effects of clozapine. These can generally be managed symptomatically; however, some will require referral back to the CMHT.

Always inform the CMHT if a service user develops any suspected clozapine-related side-effects.

Clinically significant side effects

Agranulocytosis

Clozapine can cause neutropenia AND agranulocytosis.

- Be cautious if any signs or symptoms of a low white cell count are present; consider taking urgent FBC or refer to A&E.
- Other drugs that cause neutropenia are contraindicated, see **drug interactions** below.
- **Always** report clozapine-associated neutropenia on a [Yellow Card](#).

Constipation

Clozapine can cause constipation (commonly) and exacerbate drug-induced constipation. This can (rarely) lead to intestinal obstruction, faecal impaction, and paralytic ileus. This can be fatal.

- **Always** ask about constipation in anyone taking clozapine.
- **Always** consider lifestyle factors in managing clozapine-associated constipation, e.g., improving fluid and fibre intake, and exercise.
- **Always** actively treat constipation in anyone taking clozapine to prevent it from deteriorating.
- **Avoid** bulk-forming laxatives.
- **Always** assess anyone taking clozapine for constipation if they are also taking antimuscarinics, e.g., hyoscine or pirenzepine (an unlicensed anti-muscarinic for hypersalivation), etc. Review the prescribed laxatives. Ask the CMHT to review causative medication.
- If you are concerned about the risk of impaction or bowel infarction, immediately refer to A&E for (a surgical) assessment.
- **Always** inform the CMHT of acute constipation and primary care actions.
- **Always** report clozapine-associated severe constipation on a [Yellow Card](#).

Tachycardia

Tachycardia may persist and indicate the development of myocarditis or cardiomyopathy. Clozapine carries a serious risk of myocarditis and cardiomyopathy particularly in the first two months of treatment.

- **Always** ask about signs and symptoms of tachycardia in anyone taking clozapine.
- **Always** inform the CMHT of tachycardia.

Hypersalivation

- Clozapine can cause profound hypersalivation, severely impacting the quality of life.
- Specialists often initiate an off label antimuscarinic like hyoscine (Kwells®) or atropine 1% eye drops (sub-lingual) to help manage hypersalivation.
- Unlicensed pirenzepine is sometimes prescribed by the mental health trust with the clozapine.
- **Always** consider the impact these additional antimuscarinics will have on constipation.
- Refer to local guidance for advice on managing hypersalivation.
 - Glycopyrronium is rarely used for clozapine-induced hypersalivation as it does not feature in mental health treatment algorithms.

Seizure

- Clozapine can rarely cause seizures, typically at doses above 500 mg daily.
- Antiepileptic drugs used for prophylaxis or treatment include valproate, topiramate or lamotrigine.

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- **Always** report clozapine-associated seizures on a [Yellow Card](#).

Drug interactions

Commonly used antibiotics which are safer to co-prescribe, and antibiotics to avoid, are listed below.

This is **not** an exhaustive list.

CARE: It is essential to ensure that an antibiotic is not prescribed for an indication caused by an underlying neutropenia; consider a routine FBC when prescribing antibiotics.		
Antibiotics SAFE to prescribe include	Antibiotics to AVOID because they can cause neutropenia include	Antibiotics to AVOID because they increase serum clozapine concentrations include
Azithromycin Clarithromycin (Caution: QT prolongation) Fusidic acid eye drops Penicillins Tetracyclines	Dapsone Isoniazid Metronidazole Nitrofurantoin Quinolones Rifampicin Sulphonamides Trimethoprim	Erythromycin Quinolones Rifampicin

Other drugs to use with CAUTION include	Other drugs to AVOID include
Mirtazapine due to neutropenia risk and weight gain Topical and ocular chloramphenicol due to neutropenia risk SSRIs including fluoxetine, paroxetine, and fluvoxamine due to increased and toxic serum clozapine concentrations	Carbamazepine Chemotherapy and cytotoxic agents Carbimazole Chloramphenicol (non-eye-drop formulations) Depot antipsychotics

- If the use of an interacting drug is unavoidable, **please inform the CMHT urgently**.
- Contact the CMHT urgently if your service user receives a diagnosis of cancer that will require chemotherapy; **the oncologist must** liaise urgently with the consultant psychiatrist and mental health pharmacist.

Non-Drug Interactions

Smoking: clinically significant

- Inhaled tobacco smoke (not nicotine replacement therapy or e-cigarettes) can significantly reduce clozapine plasma concentrations and can lead to loss of efficacy.
- Stopping smoking can significantly increase clozapine plasma concentrations and can quickly lead to toxicity.
- Therefore, refer to the CMHT before the service user quits or cuts down smoking (including switching to e-cigarettes). The CMHT can then modify the clozapine dose and arrange for the appropriate monitoring.
 - This is especially important during acute in-patient stays where smoking is (temporarily) reduced or stopped.

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Caffeine

- Caffeine may interact with clozapine and can increase plasma clozapine concentrations; a corresponding decrease in clozapine serum concentrations can occur after even a short caffeine-free period
- Advise service users to maintain a stable caffeine intake. Inform the CMHT of any changes
- Caffeine is found in coffee, tea, cola drinks, chocolate, and energy drinks such as Red Bull®, Monster Energy®, etc.

Contact details for the community mental health teams

Cheshire and Wirral Partnership

Stein centre (where both CMHT's are based in Wirral) 0300 3033157

Upton Lea 01244 397451

Cherrybank 0151 4888434

Vale House 01606 555103

Jocelyn Solly Resource Centre 01625 505600

Delamere Resource Centre 01270 655200

Mersey Care

If you are unsure which team the patient falls under then please contact the CCTT via email for further advice

Community Clozapine Titration Team (CCTT)

clozapinetitrationteam@merseycare.nhs.uk

Key Contacts and Clozapine Clinic / Health & Wellbeing Clinic Details

Clozapine Patient Monitoring Service (CPMS)

0845 769 8269 – have the patient's details & CPMS number ready

Denzapine Monitoring Service (DMS)

0333 200 4141 – have the patient's details & DMS number ready

Community Clozapine Titration Team (CCTT)

clozapinetitrationteam@merseycare.nhs.uk

Medicines Management Department (Maghull)
Dispensary – 0151 250 6061 / 6028
Clozapine Dispensary – 0151 250 6169
Medicines Information – 0151 250 6011
Medicines Management Building, Maghull Health Park,
Maghull, Liverpool

Mersey Care, Hollins Park Pharmacy – 01925 629200
Hollins Park Hospital (1st Floor), Hollins Park, Winwick
Lane, Warrington

For all clozapine queries out of hours

Emergency Duty Pharmacist

(via the Trust switchboard) 0151 473 0303

Emergency Medical Advice

(via the Trust switchboard) 0151 473 0303

Crisis Resolution Home Treatment Team (24hrs)

(via the Trust switchboard) 0151 473 0303

Site	Blood Test Clinic Location	Day of Clinic	Contact Number of Clinic
Knowsley	Yew Trees, Capper Grove, Huyton	Mon	Knowsley Recovery Team 0151 290 4999
St Helens	Harry Blackman House	Tues, Wed & Thurs	St Helens Recovery Team 01744 736708
Warrington	Masefield Suite Hollins Park	Tues, Wed & Thurs	01925 664826
Halton	Runcorn Brooker Centre	Tuesday	01928 753968
	Widnes St John's Unit	Thursday	0151 422 6801
Sefton	Clock View Hospital 2a Oak House Park, L9 1EP	Mon, Tues & Wed	0151 330 7275
North Liverpool	Broadoak Unit Thomas Drive, L14 3PJ	Mon, Tues & Wed	0151 250 5078
Southport	Hartley Hospital 1b Curzon Road, PR8 6PL	Mon and Tuesday	01704383086

Service user information about clozapine

- www.choiceandmedication.org/cheshire-and-wirral
- www.choiceandmedication.org/merseycare
- www.choiceandmedication.org/lancashirecaretrust

Prescribing information for clozapine

- Clozapine: <https://www.medicines.org.uk/emc/search?q=clozapine>
- Clozaril SPC: <https://www.medicines.org.uk/emc/product/4411>
- Denzapine SPC: <https://www.medicines.org.uk/emc/product/6087/smpc>
- Zaponex SPC: <https://www.medicines.org.uk/emc/product/7715/smpc>
- BNF: <https://bnf.nice.org.uk/drug/clozapine.html>

Contact details for clozapine manufacturers

- Clozaril Connect, Viatrix' portal, <https://www.clozaril.co.uk/> has professionals and service user resources
Tel: 0845 - 769 8269
- Denzapine's portal: <https://www.denzapine.co.uk/> Tel: 0333 - 200 4141
- Zaponex portal: <https://www.zaponex.co.uk/> Tel: 0207 - 365 58 42

Bibliography

1. MHRA Drug Safety Update (October 2017). [Clozapine: reminder of potentially fatal risk of intestinal obstruction, faecal impaction, and paralytic ileus](#). [Accessed 3rd November 2020]
2. MHRA Drug Safety Update (August 2020). [Clozapine and other antipsychotics: monitoring blood concentrations for toxicity](#). [Accessed 02 February 2023]