Clozapine - ESSENTIAL Information for primary care

Clozapine is an antipsychotic used in the treatment of schizophrenia when other antipsychotics have not worked. It may also be used for psychotic disorders occurring in Parkinson's disease when standard treatment has failed. Clozapine is classed as a **RED** drug which means it must only be prescribed by secondary care mental health services and **prescribing responsibility will not transfer to GPs under any circumstances**.

Please add clozapine to the GP practice medical record as a "Repeat" Hospital Only Medication to prevent inadvertent prescribing of interacting medicines, missed adverse effects and omitted medication on admission to acute services. Annotate with "contact supplying Pharmacy for current dose" or similar rather than specific doses. Link to Surrey PAD guide on how to add secondary care medicines.

While outcomes of clozapine treatment are good, **side effects are common and can have a profound effect on a person's on-going physical health**. Some side effects occur in the first few weeks of treatment and usually wear off. Others persist and can have on-going effects on physical health or indicate serious problems requiring urgent action. Whilst these are routinely monitored by Mental Health (MH) teams, the individual may present at other times or with symptoms that appear unrelated.

People taking clozapine require mandatory blood tests up to every 4 weeks which will normally be organised by the MH team as they retain clinical responsibility for prescribing. The service responsible for organising blood tests must be agreed and clearly documented. On occasions an urgent blood sample may need to be arranged by the MH team, for example through the local acute trust phlebotomy service. The supplying pharmacy will only issue clozapine with an up-to-date blood test result.

See also Specialist Pharmacy Services "Clinical considerations for patients prescribed clozapine"

Adverse effects

	Prevent and look for	Action if suspected
Constipation and Clozapine Induced Gastric Hypomotility (CIGH) See also SPS guidance	▪ Avoid prescribing constipating medicines including anticholinergics and opioids. ▪ Advise person about exercise, fluids and high fibre diet. ▪ Enquire about bowel habit (ask if person has had a bowel movement today or yesterday and which type). ▪ Look for other signs of constipation including overflow diarrhoea, abdominal pain, repeated UTIs, bloating, loss of appetite, nausea, straining, rectal bleeding or pain, bowel incontinence and behavioural changes ▪ Often presents without impaction in rectum but higher obstruction in sigmoid colon. ▪ Constipation can affect 60% of patients. ▪ Many people will not recognise they are constipated or not report. ▪ High incidence of mortality ▪ Check person has access to laxatives either from MH team or GP on repeat medication.	▪ Inform MH team if chronic constipation suspected or constipation persists. ▪ Treat actively with stimulant and softening laxative (e.g. senna and docusate) add PEG osmotic e.g. macrogols if needed. Check compliance, exclude obstruction. ▪ Refer *urgently* to acute care if: Moderate or severe abdominal pain lasting more than 1 hour Abdominal distension Vomiting Overflow diarrhoea or bloody diarrhoea Absent or high-pitched bowel sounds Metabolic acidosis Haemodynamic instability Leukocytosis Signs of sepsis ▪ Have low threshold for referral to acute care, death can occur within hours. ▪ Drug Safety Update 2017

	Prevent and look for	Action if suspected
Neutropenia and agranulocytosis	▪ Signs of infection including sore throat and raised temperature. ▪ Most common in first 18 weeks of therapy.	▪ Check FBC and notify the MH service. ▪ White cells are all normal or raised, treat with an anti-pyretic and antibiotics (see interactions) if indicated. ▪ Severe pneumonia or other serious infection notify the MH team urgently. Plasma levels may be required. ▪ If white cells are **LOWERED** or if there is **ANY** concern, contact the Consultant Psychiatrist or on-call doctor if out of hours. ▪ Drug Safety Update 2020
Nocturnal Enuresis	▪ May occur at any time ▪ Affects 20%	▪ Contact the MH team, clozapine regimen change may be required to avoid deep sedation. ▪ Desmopressin nasal spray may be used if severe.
Smoking tobacco	▪ If a person stops or starts smoking tobacco (including switching to NRT or vaping). ▪ Stopping can increase plasma levels by 70% within 7-10 days	▪ Inform pharmacy Clozapine Service urgently as plasma level needed with dose alteration. ▪ Drug Safety Update 2020 ▪ Specialist Pharmacy Services advice
Increased Heart Rate + Other Cardiac symptoms	▪ Tachycardia is very common in early stages but usually benign. ▪ Sudden deaths associated with myocarditis have occurred most commonly in first 8 weeks, monitor for hypotension, tachycardia, fever, flu like symptoms, fatigue, dyspnoea with increased respiratory rate and chest pain. ▪ Hypotension usually limited to first 4 weeks ▪ Long term weight gain may lead to hypertension.	▪ Seek advice from Psychiatrist/cardiologist if tachycardia occurs in presence of chest pain, heart failure or overt signed of myocarditis. Clozapine should be stopped. ▪ Non-specific cardiac symptoms in a patient on clozapine should be thoroughly investigated. ▪ Benign tachycardia may be treated with bisoprolol or atenolol.
Hypersalivation	▪ Occurs in initial stages and tolerance can develop.	▪ Prop pillows up at night, towel on pillow and chew sugar-free gum. ▪ Encourage adequate fluid intake. For extreme hypersalivation refer back to psychiatrist where hyoscine may be prescribed. ▪ Consider SALT referral
Seizures	▪ **Greater** incidence over total daily dose of 600mg and can occur at any time. ▪ Myoclonus may precede a full tonic clonic seizure and more prevalent in initiation and when plasma level increases.	▪ Clozapine should be withheld and refer urgently to Consultant Psychiatrist. ▪ AVOID prescribing carbamazepine. ▪ In some cases, prophylaxis may be required. If prescribing valproate, note valproate safety measures ; if prescribing topiramate note topiramate safety measures
Weight gain	▪ Usually in first year and can be profound >10Kg.	▪ Dietary counselling and lifestyle advice. ▪ If lifestyle unsuccessful, contact MH team for advice as metformin or aripiprazole may be required.
Sedation	▪ Usually in first few months and wears off.	▪ Contact MH team, regimen may need adjusting.

	Prevent and look for	Action if suspected
Nausea	▪ Usually in first 6 weeks and wears off.	▪ Seek advice from MH. ▪ Cyclizine may be used or ondansetron, however ondansetron worsens constipation. ▪ Avoid metoclopramide, domperidone or prochlorperazine.

Interactions (this table shows common interactions and is for guidance only - list is not exhaustive)

Always check the BNF for up-to-date information on drug interactions

Drug	Interactions	Comments
Bone marrow suppressants (e.g. carbamazepine, chloramphenicol, sulphonamides, pyrazolone analgesics, penicillamine, cytotoxic agents and long-acting depot injections of antipsychotics)	Interact to increase the risk and/or severity of bone marrow suppression.	Clozapine must not be used concomitantly with other agents having a well known potential to suppress bone marrow function.
*Opioids (See also * below)	Concomitant use may increase risk of additive CNS effects and constipation.	Use with caution and enquire about over sedation and bowel activity, prescribe PEG osmotic laxatives and stimulants if needed.
*Benzodiazepines (See also * below)	Concomitant use may increase risk of circulatory collapse, which may lead to cardiac and/or respiratory arrest.	Caution advised if using together. Respiratory depression and collapse more likely to occur at start of this combination or when clozapine is added to an established benzodiazepine regimen.
Anticholinergics	Clozapine potentiates action of these agents through additive anticholinergic activity.	Observe people for anticholinergic side-effects, e.g., constipation, especially when using to help control hypersalivation.
Antihypertensive agents	Clozapine can potentiate hypotensive effects of these agents due to sympathomimetic antagonistic effects.	Caution is advised. People should be advised of the risk of hypotension, especially during the period of initial dose titration.
*Alcohol, MAOIs, CNS depressants, including opioids and benzodiazepines (See also * above)	Enhanced central effects. Additive CNS depression and cognitive and motor performance interference when used in combination with these substances.	Caution is advised if clozapine is used concomitantly with other CNS active agents. Advise people of the possible additive sedative effects and caution them not to drive or operate machinery.
Highly protein bound substances (e.g., warfarin and digoxin)	Clozapine may cause increase in plasma concentration of these substances due to displacement from plasma proteins.	People should be monitored for the occurrence of side effects associated with these substances, and doses of the protein bound substance adjusted, if necessary.
Antibiotics such as erythromycin and ciprofloxacin	Can elevate clozapine levels	Avoid combination if possible. Consider closer monitoring involving FBCs
Phenytoin	Addition of phenytoin to clozapine regimen may cause a decrease in the clozapine plasma concentrations.	If phenytoin must be used, the patient should be monitored closely for a worsening or recurrence of psychotic symptoms. Plasma clozapine levels may be required, notify MH service.
Lithium	Concomitant use can increase the risk of development of neuroleptic malignant syndrome (NMS).	Observe for signs and symptoms of NMS.
CYP1A2 inhibiting substances (e.g. fluvoxamine, caffeine, ciprofloxacin, hormonal contraceptives)	Concomitant use may increase clozapine levels	Potential for increase in adverse effects. Plasma levels may be required. Notify MH service. Care is also required upon cessation of concomitant CYP1A2 inhibiting medications

		as there will be a decrease in clozapine levels.
CYP1A2 inducing substances (e.g. omeprazole and smoking tobacco)	Concomitant use may decrease clozapine levels	Potential for reduced efficacy of clozapine should be considered. Consider risk of increased levels when **stopping** smoking

Always check the BNF for up-to-date information on drug interactions

How to contact the relevant service

Contact Details for Surrey and Borders Partnership NHS Foundation Trust

<table>
<tr><th>Supply / blood test queries</th><th colspan="2">Community Mental Health Recovery Services/ Psychiatry</th></tr>
<tr><td>Pharmacy Clozapine team

Clozapine@sabp.nhs.uk
Tel: 01483 443729
Monday- Friday 9am-5pm</td><td colspan="2">For urgent referrals or enquiries:
Single Point of Access service

spa@sabp.nhs.uk
Tel: 0300 456 8342
24hr / 7 days a week</td></tr>
<tr><td rowspan="6">Pharmacy Dispensary

pharmacy@sabp.nhs.uk
Tel: 01483 443697
Monday- Friday 9am-5pm</td><td>Elmbridge
Tel: 0208 7833950
Monday-Friday 9am – 5pm</td><td>Runnymede and Spelthorne
Tel: 01932 587060
Monday-Friday 9am – 5pm</td></tr>
<tr><td>Epsom
Tel: 01372 216460
Monday-Friday 9am – 5pm</td><td>Surrey Heath
Tel: 01276 454200
Monday-Friday 9am – 5pm</td></tr>
<tr><td>Guildford
Tel: 01483 443551
Monday-Friday 9am – 5pm</td><td>Tandridge
Tel: 01883 331889
Monday-Friday 9am – 5pm</td></tr>
<tr><td>Mole Valley
Tel: 01372 216400
Monday-Friday 9am – 5pm</td><td>Waverley
Tel: 01483 528100
Monday-Friday 9am – 5pm</td></tr>
<tr><td>NE Hants/ Aldershot
Tel: 01252 335566
Monday-Friday 9am – 5pm</td><td>Woking
Tel: 01483 756318
Monday-Friday 9am – 5pm</td></tr>
<tr><td colspan="2">Reigate
Tel: 01737 288960
Monday-Friday 9am – 5pm</td></tr>
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Out of hours

The on call pharmacist at SABP may be contacted out of working hours (5pm-9am and at weekends) for urgent queries regarding clozapine.
Contact via SABP switchboard – 0300 5555 222

Missing doses can have a significant impact if dose re-titration is needed. The on call pharmacist should be contacted if medication cannot be sourced from the person's home, in order to avoid any treatment breaks.

References - Prescribing Guidelines in Psychiatry 14th Edition. The Maudsley. 2021

Adapted from BHFT document for Surrey Heartlands by Ozma Tahir, Deputy Chief Pharmacist, May 2022.