

# SHARED CARE ARRANGEMENT AND PRESCRIBING INFORMATION FOR CLOZAPINE TREATMENT IN ABERDEENSHIRE



**Note:** This document should be read in conjunction with the current Summary of Product Characteristics (SmPC).

Patient safety is paramount. The prescriber who prescribes the medicine legally assumes clinical responsibility for the drug and the consequences of its use.

## GENERIC AND BRAND NAME (formulations and strength)

**Name:** Clozapine

**Formulation:** Clozapine is available as tablets (all brands), orodispersible tablets (specific brands only) or oral suspension (specific brands only). There are three brands available, which are not interchangeable as each brand has its own registered patient database. In NHS Scotland, there is a national contract for clozapine.

**Strength:** 12.5mg, 25mg, 50mg, 100mg and 200mg Tablets/Orodispersible or 50mg/1mL oral suspension

## STATUS OF MEDICINE

**Licence status:** Licensed

**Formulary status:** Formulary

**Black triangle medicine:** Yes  No

**Risk minimisation materials (RMM):** Yes  No

## CONDITION(S) TO BE TREATED

**Treatment-resistant schizophrenic patients (aged 16 years and older) and schizophrenic patients (aged 16 years and older) who have severe, untreatable neurological adverse reactions to other antipsychotic agents, including atypical antipsychotics.**

**Psychotic disorders occurring during the course of Parkinson's disease, in cases where standard treatment has failed.**

### Caution

Neutropenia/agranulocytosis is a serious adverse drug reaction that may occur with clozapine therapy. Although only 2 - 3% of patients may be affected, it is not possible to predict who will be affected. As a result, blood monitoring (full blood count with white cell differential) is mandatory and clozapine can only be dispensed against a valid blood result and in accordance with the product licence. In addition, there is a requirement for the consultant psychiatrist, patient, pharmacist and dispensing pharmacy to be registered with the company.

## TYPICAL DOSAGE REGIME

Licensed dose

**Resistant schizophrenic patients (aged 16 years and older) and schizophrenic patients (aged 16 years and older) who have severe, untreatable neurological adverse reactions to other antipsychotic agents, including atypical antipsychotics:**

	<p>Usual therapeutic dose: 200mg - 450mg/day in divided doses. Maximum dose: 900mg/day.</p> <p><b>Psychotic disorders in Parkinson's disease where standard treatment has failed:</b></p> <p>Usual therapeutic dose: 25mg - 37.5mg/day as a single dose in the evening. Maximum dose: 100mg/day.</p>
Route of administration	Oral (Tablets, Orodispersible or Oral Suspension)
Recommended starting dose	<p><b>Treatment resistant schizophrenia:</b> 12.5mg once or twice a day on first day, followed by 25mg once or twice a day on second day. Increase dose slowly by increments of 25 - 50mg to achieve 300mg/day within 2 - 3 weeks. Thereafter if required increase in increments of 50 - 100mg at half-weekly or preferably weekly intervals.</p> <p><b>Psychotic disorders in Parkinson's disease:</b> 12.5mg/day in the evening. Increase dose by increments of 12.5mg half-weekly or preferably weekly to achieve 50mg/day. Thereafter if required increase dose cautiously by 12.5mg/week.</p>
Titration dose/increment	Dependant on individual patient response can be titrated up to the maximum recommended daily dose as stated below.
Maximum dose	<p><b>Treatment resistant schizophrenia:</b> Maximum dose - 900mg/day.</p> <p><b>Psychotic disorders in Parkinson's disease:</b> Maximum dose - 100mg/day.</p>
Situations requiring dose adjustment	<p>A treatment break of more than 48 hours will require dose re-titration.</p> <p>If <b>RED</b> status is found concerning clozapine blood test.</p> <p>Changes in smoking habit may require dose adjustment.</p>
Duration of treatment	Contact original prescribing consultant.

## RESPONSIBILITY OF ACUTE CARE/SPECIALIST SERVICE

**Exclude any co-morbidity or concomitant medication, which would contraindicate the prescribing of clozapine.**

**Ensure patient receives appropriate counselling on clozapine therapy prior to initiation of treatment and record in the case notes.** This should include discussion on:

- Changes in smoking status and its effects on clozapine levels and side effects.
- Pregnancy intentions and contraceptive advice (women of reproductive age).

**Ensure baseline monitoring is performed**

- Full blood count with a white cell differential (mandatory), U&Es, LFTs, fasting blood glucose, fasting lipids, Troponin I, C-Reactive Protein, ECG, blood pressure, pulse, temperature, side-effects (Glasgow Antipsychotic Side-effect Scale for Clozapine – [GASS for Clozapine](#)), weight and BMI.

## **Register with Clozapine Patient Monitoring Service**

- Register with the Clozapine Patient Monitoring Service to prescribe clozapine.
- Register the patient and provide initial full blood count with white cell differential.

## **Complete Clozapine Clinic Referral Form (required at initiation of therapy)**

## **Record baseline monitoring on the Clozapine Physical State Monitoring Form (Weeks 0 - 4)**

### **Prescribe clozapine**

- On confirmation of patient registration and satisfactory blood result initiate treatment as per Summary of Product Characteristics (SmPC).

### **Mandatory Monitoring**

A full blood count with a white cell differential must be monitored:

- Weekly for the first 18 weeks of treatment (assuming satisfactory results).
- Fortnightly between weeks 19 and 52 (assuming satisfactory results).
- Every four weeks after 1 year of treatment (assuming satisfactory results).

### **Physical State Monitoring (during in-patient stay)**

Monitoring for the first 28 days will usually take place during the in-patient stay. Thereafter monitoring may be handed over to the Clozapine Clinic and then the GP on discharge.

- Blood pressure – Baseline, daily during titration, every 3 months for 1 year and then annually. Also following dose changes.
- Pulse – Baseline, daily during titration, at 3 months and then annually.
- Temperature – Baseline and daily during titration.
- Weight and BMI – Baseline, weekly during titration, 3 monthly for 1 year and then annually.
- U&Es – Baseline and then annually, or more frequently if clinically indicated.
- LFTs – Baseline and then annually, or more frequently if clinically indicated.
- Fasting blood glucose – Baseline, at 4 weeks, then 3 monthly from 3 months up to 1 year and then 6 monthly.
- Fasting lipids – Baseline then 3 monthly for 1 year and then 6 monthly.
- Troponin I – Baseline and then weekly for first 4 weeks.
- C-Reactive Protein – Baseline and then weekly for first 4 weeks.
- ECG – Baseline then at 3 weeks, at 3 months and then annually.
- Side-effects – '[GASS for Clozapine](#)' or other recognised side-effect questionnaire for antipsychotic medication, with specific reference to constipation, at baseline, 4 weeks, 3 monthly from 3 months up to 1 year and then annually.
- Smoking status – Baseline, at 4 weeks, 3 monthly from 3 months up to 1 year and then annually.
- Pregnancy/contraceptive status (women of reproductive age) – Baseline, at 4 weeks, 3 monthly from 3 months up to 1 year and then annually.
- Clozapine plasma level – if clinically indicated to determine if the clozapine dose needs adjusted (e.g. following smoking cessation (Note: not required for routine patient management)).

### **Liaison with GP**

Liaise with GP to ensure responsibility for monitoring is agreed and documented in both psychiatric and GP patient records. Send individual pharmaceutical care plan (including this Shared Care Arrangement), prepared by the hospital pharmacist to GP.

## ADMINISTRATIVE RESPONSIBILITIES OF PRIMARY CARE

A Practice agreeing to monitor clozapine should:

- Ensure the practice records clearly indicate that a patient is on clozapine therapy. All therapeutic indications for clozapine treatment would also be reasons for including the patient on the practice Mental Health Register.
- Document that the Practice agrees to monitor the patient in line with this Shared Care Agreement.
- Ensure that the relevant monitoring requirements are undertaken at the correct frequency.
- Ensure that the test results are checked for any abnormality as soon as the results are available.
- Ensure abnormal results from tests performed are acted upon promptly.
- Contact the consultant in the event of a drug reaction, monitoring abnormality, or if you are concerned in any way regarding the current treatment regime.

## CLINICAL CARE WHICH IS THE RESPONSIBILITY OF THE PRIMARY CARE CLINICIAN

On discharge from hospital the following responsibilities are delegated to the GP:

**Ensure no medication is prescribed which is contraindicated with clozapine treatment.**

Ensure that the relevant monitoring requirements have been undertaken at the correct frequency.

Conduct recommended laboratory tests and contact hospital consultant to advise if results are out with range (see below).

### **Ongoing mandatory blood sampling**

Undertake ongoing mandatory blood sampling (FBC with white cell differential) and send for analysis as per patient specific Clozapine Pharmaceutical Care Plan.

### **Additional AD-HOC blood monitoring:**

- If a patient presents with pyrexia, a sore throat, cold or other signs of infection, which could be indicative of neutropenia an additional blood sample (full blood count with white cell differential), should be taken and sent locally for analysis.
- The GP is responsible for ensuring the blood result is checked and taking further action as appropriate (see ongoing mandatory monitoring above for further information).
- The Pharmacy Department, Royal Cornhill Hospital, should be advised so that the result can be entered on to the clozapine patient monitoring database.
- If advice/action is required out of hours the duty doctor, Royal Cornhill Hospital should be contacted.

**Undertake ongoing physical state monitoring - refer to individual patient specific Clozapine Pharmaceutical Care Plan. As treatment is initiated in hospital, GPs will normally pick up monitoring at the 3 month point or later:**

- Weight and BMI - 3 monthly for 1 year and then annually.
- Blood pressure - 3 monthly for 1 year and then annually. Also following dose changes.
- Pulse - At 3 months and then annually.
- U&Es – Annually or more frequently if clinically indicated.
- LFTs - Annually or more frequently if clinically indicated.

- Fasting blood glucose - 3 monthly for 1 year and then 6 monthly.
- Fasting lipids - 3 monthly for 1 year and then 6 monthly.
- ECG - At 3 months and then annually.
- Side-effects - '[GASS for Clozapine](#)' or other recognised side-effect questionnaire for antipsychotic medication, with specific reference to constipation, 3 monthly for 1 year and then annually.
- Smoking status - 3 monthly for 1 year and then annually. Warn patient regarding effect of changes in smoking status on clozapine levels and side-effects.
- Pregnancy/contraceptive status (women of reproductive age) - 3 monthly for 1 year and then annually. Discuss pregnancy intentions. Offer advice/signposting on contraception.
- Clozapine plasma level – if clinically indicated (Note: not required for routine patient management).

**\*\*\*Note: The GP is responsible for acting on any abnormal results and ensuring all relevant information is communicated to the consultant psychiatrist responsible for the patient's care.\*\*\***

### **Supply of clozapine to patient:**

- Clozapine will be dispensed by the Pharmacy Department, Royal Cornhill Hospital only on receipt of a satisfactory blood result from the clozapine monitoring service (i.e. GREEN or AMBER).
- Dispensed clozapine will be sent via hospital transport to the GP practice/Community Hospital for collection by the patient or posted to a nursing home, if appropriate.
- Dispensed supplies will be for 1, 2 or 4 weeks supply, in line with the blood sampling frequency. Occasionally more frequent dispensing is required for patients with concordance difficulties.
- Clozapine supplies are normally due for collection on Thursdays. If the patient fails to attend every effort should be made to contact the patient to prompt them to attend to collect their clozapine.
- If a patient fails to collect their dispensed supply of clozapine on time and turns up at a later date the GP has a responsibility to check that the patient has been concordant with their treatment before supplying medication.

**Note:\*\*\* A treatment break of more than 48 hours requires dose re-titration\*\*\***

**If the GP becomes aware that this has occurred the dispensed supply of clozapine should not be given to the patient and the consultant psychiatrist or a member of their medical team and the Pharmacy Department, Royal Cornhill Hospital should be contacted.**

Ensure no [interacting medications](#) are prescribed in primary care.

Report any adverse events to consultant and the MHRA using the Yellow Card System.

When writing laboratory request forms always include details of the patient's medication.

**Note:** In addition to absolute values for haematological or biochemical indices a rapid change or a consistent upward/downward trend in any value should prompt caution and extra vigilance.

If something unexpected occurs contact consultant. Notify the consultant if the drug is stopped.

## **RESPONSIBILITY OF OTHER HEALTHCARE PROFESSIONALS**

### **RESPONSIBILITY OF REGISTERED HOSPITAL PHARMACY TEAM**

**Provide a clozapine initiation pack to consultant medical team.**

**Ensure compliance with mandatory blood monitoring for clozapine and respond to AMBER/RED alert status as appropriate.** (See below for monitoring and action required).

### **ONGOING MANDATORY BLOOD MONITORING**

- All mandatory blood results (FBC with white cell differential) must be entered onto the clozapine monitoring service database for validation. For samples sent directly to the clozapine monitoring laboratory this is done automatically. When a sample is analysed locally, at the Haematology Laboratory, ARI, it is the responsibility of the pharmacy staff, Royal Cornhill Hospital, to enter the result onto the database. **If action is required out of hours, it is the responsibility of the duty doctor (as per local protocol).**
- Blood results processed by the clozapine monitoring service are colour coded (see table below for on treatment reference ranges).

RED	AMBER	GREEN
WBC <3.0 x 10 <sup>9</sup> /L	WBC ≥3.0 < 3.5 x 10 <sup>9</sup> /L	WBC ≥3.5 x 10 <sup>9</sup> /L
Or Neutrophils <1.5 x 10 <sup>9</sup> /L	Or Neutrophils ≥1.5 < 2.0 x 10 <sup>9</sup> /L	And Neutrophils ≥2 x 10 <sup>9</sup> /L
Or Platelets <50 x 10 <sup>9</sup> /L		

- **GREEN** status – Clozapine dispensed.
- **AMBER** status - Pharmacy Department, Royal Cornhill Hospital will contact the Clozapine Clinic to arrange additional blood test to be done and patient must be reviewed for signs of infection, which may be indicative of neutropenia. Clozapine will be dispensed with caution.
- **RED** status - Immediate discontinuation of clozapine is mandatory if a RED status is obtained and clozapine must be removed from the patient. The hospital pharmacy team will contact the consultant psychiatrist to discuss action to be taken, including removal of clozapine from the patient. It is the responsibility of the consultant psychiatrist to liaise with the clozapine monitoring service and coordinate further action to be taken regarding the on-going care of the patient.
- Monitoring must continue throughout treatment and for at least 4 weeks after discontinuation.

**Ensure clozapine ONLY dispensed against a valid blood result.**

**Advise phlebotomist, practice nurse or community nurse of changes in frequency of blood sampling and supply of clozapine.** Make appropriate arrangements for patients going on holiday and for public holidays.

**Arrange transport of clozapine to GP practice or post to nursing home, if appropriate.** Make appropriate arrangements for patients going on holiday and for public holidays.

**Arrange for GP practice to be provided with blood sampling kits, where appropriate and clozapine support material on transfer of care.**

**Provide GP with pharmaceutical care plan (which includes this Shared Care Arrangement and Prescribing Information for Clozapine Treatment in Aberdeenshire) for inclusion in patient's notes.**

**Send letter to practice pharmacist notifying them of patient discharge to primary care.**

**Counsel patient on clozapine treatment and provide support material including a pharmaceutical care plan.**

## RESPONSIBILITY OF THE PATIENT

Take clozapine regularly as directed by the specialist/doctor.

Attend hospital and GP clinic appointments as requested by specialist/GP practice. Failure to attend appointments may result in medication being reviewed/stopped.

Attend for blood tests as requested by phlebotomist/GP practice.

Report any adverse effects/illness to the specialist/GP and present rapidly to specialist/GP should their condition significantly worsen.

Collect dispensed supply of clozapine on time.

Missed dose: If one dose is omitted or forgotten, the next dose should be taken at the normal time.

If a treatment break of more than 48 hours occurs, dose re-titration will be necessary.

## PRESCRIBING INFORMATION

For specific product information consult the current summary of product characteristics (<http://emc.medicines.org.uk/>), the BNF/BNF for Children (<https://www.medicinescomplete.com/mc/index.htm>)

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## CONTRAINDICATIONS

### Contraindications

- Hypersensitivity to active substance or any excipients.
- Patients unable to undergo regular blood tests.
- History of toxic or idiosyncratic granulocytopenia/agranulocytosis (with exception of granulocytopenia/agranulocytosis from previous chemotherapy).
- History of clozapine-induced agranulocytosis.
- Impaired bone marrow function.
- Uncontrolled epilepsy.
- Alcoholic and other toxic psychosis, drug intoxication, comatose conditions.
- Circulatory collapse and/or CNS depression of any cause.
- Severe renal or cardiac disorders (e.g. myocarditis).
- Active liver disease associated with nausea, anorexia or jaundice; progressive liver disease, hepatic failure.
- Paralytic ileus.
- Concurrent treatment with drugs known to have substantial potential for causing agranulocytosis.
- Concomitant use of depot antipsychotics.
- Patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

### Co-prescribing antibiotics

Caution is required when co-prescribing antibiotics as some have a potential to depress neutrophil count and are best avoided (e.g. co-trimoxazole). Check individual drugs before prescribing.

## Smoking cessation

The polycyclic aromatic hydrocarbons in cigarette smoke are inducers of hepatic enzymes, which metabolise clozapine. Therefore, sudden smoking cessation may result in a significant increase in clozapine plasma level with associated adverse effects, e.g. seizures. Nicotine replacement therapy (NRT) has no effect on this process. Smoking cessation should be conducted in a planned way in discussion with the consultant psychiatrist, as clozapine dose may need to be adjusted. Handy fact sheet for patients available at [www.choiceandmedication.org/nhs24/](http://www.choiceandmedication.org/nhs24/).

## PREGNANCY

Discuss with consultant. There is only limited clinical data on exposed pregnancies.

## BREAST-FEEDING

Clozapine is excreted in breast milk and has an effect in the nursing infant; therefore, mothers receiving clozapine should not breast-feed.

## COMMON SIDE EFFECTS AND THEIR MANAGEMENT

### Nausea

Nausea is a common side effect (>1 in 100 <1 in 10), which usually does not require treatment.

### Constipation

Constipation is very common (>1 in 10). It has been associated with varying degrees of impairment of intestinal peristalsis, ranging from constipation to intestinal obstruction, faecal impaction, paralytic ileus, megacolon and interstitial infarction ischaemia. On rare occasions, these cases have been fatal. When a patient develops constipation, it is important to make a full assessment to ascertain the contribution of clozapine treatment, identify any complications that may be present and to exclude the more serious causes of the constipation. Current drug therapy should be reviewed to identify any other medication, e.g. those with anticholinergic properties such as antipsychotics, antidepressants and antiparkinson treatments, which may be contributing to constipation. Particular caution is required where there is a history of colonic disease or lower abdominal surgery, which may cause constipation. Advice on diet, fluid intake and physical exercise should be given and if necessary consider the use of laxatives (osmotic +/- stimulant). Handy fact sheet for patients available at [www.choiceandmedication.org/nhs24/](http://www.choiceandmedication.org/nhs24/).

### Hypersalivation

Hypersalivation is very common. Although not serious, it can be debilitating. The discomfort can be minimised by propping up pillows at night and using a towel to cover the top pillow. If severe, the use of a low dose anticholinergic drug, e.g. hyoscine hydrobromide 300micrograms may be beneficial but patient should be monitored for signs of constipation. Handy fact sheet for patients available at [www.choiceandmedication.org/nhs24/](http://www.choiceandmedication.org/nhs24/).

### Metabolic Syndrome

Clozapine is associated with a range of metabolic side-effects (weight gain, hyperglycaemia and dyslipidaemia) and there is close overlap with metabolic syndrome, which contributes to a 5 - 6 fold increase in diabetes and a 3 - 6 fold increase in death from coronary heart disease. As up to 50% of clozapine patients develop symptoms associated with metabolic syndrome, it is important to monitor metabolic risk factors regularly.

### Weight Gain

Weight gain is common. Dietary counselling and regular exercise is recommended.



### **Sedation**

Sedation is common and may be minimised by giving clozapine in divided doses with a larger dose at bedtime.

### **Hypotension**

Postural drop in blood pressure may occur with or without subjective dizziness. Patient should be advised to stand up slowly from lying or sitting position.

### **Hypertension**

Hypertension may occur. Monitor closely and treat as appropriate.

### **Tachycardia**

Tachycardia is very common in the early stages of treatment but is usually benign and typically resolves after 4 - 6 weeks. Since it is also a key symptom of myocardial disease it is essential that patients who have persistent tachycardia at rest, especially in the first two months of treatment, are closely observed for other signs of myocarditis and cardiomyopathy. These include palpitations, arrhythmias, symptoms mimicking myocardial infarction, chest pain and other unexplained symptoms of heart failure. Referral to a cardiologist is advised. Clozapine treatment should be stopped if tachycardia occurs in the context of chest pain or heart failure. The GP must liaise with the consultant psychiatrist. Idiopathic sinus tachycardia should not lead to clozapine discontinuation – a dose reduction may be effective. However if it persists a cardioselective beta-blocker (e.g. atenolol) may be tried.

### **Seizures**

Seizures are a common dose related side effect. If a seizure does occur the clozapine dose should be withheld for 24 hours, the consultant psychiatrist contacted as the dose of clozapine should be reduced by 50%, and the dose increased gradually until clinical response achieved. Current drug therapy should be reviewed to identify any other medication, which may lower seizure threshold. Consideration should be given to recent changes in smoking habit as smoking cessation or reduction can increase clozapine plasma level. An EEG and referral to a neurologist should be considered. If a patient experiences a sequential seizure, pharmacological management is advised. The choice of antiepileptic should be based on seizure type and safety profile in combination with clozapine. (Note: Due to valproate's teratogenicity and risk of infertility in males, it must not be used in women of childbearing potential unless there is a pregnancy prevention programme in place or in males under 55 years unless there is no suitable alternative available. Carbamazepine is contraindicated due to its potential to cause neutropenia. Phenytoin is not recommended as it reduces clozapine levels).

### **Fever**

Fever or benign transient hyperthermia is a common side-effect typically occurring in the first 3 weeks. If signs of fever develop, a full blood count with a white cell differential should always be performed to rule out the possibility of neutropenia. In addition, it is critical to differentiate benign fever from dangerous conditions such as agranulocytosis, neuroleptic malignant syndrome or myocarditis. Infection should also be ruled out.

### **Neutropenia/Agranulocytosis**

May occur at any time but more commonly during the first 18 weeks of treatment. Stop clozapine; inform consultant and admit to hospital.

## COMMON DRUG INTERACTIONS (for a full list see SmPC)

Drug	Interactions	Comments
Bone marrow suppressants (e.g. carbamazepine, chloramphenicol, sulphonamides (e.g. co-trimoxazole), pyrazolone analgesics (e.g. phenylbutazone), penicillamine, cytotoxic agents and long-acting depot injections of antipsychotics)	Increased risk and/or severity of bone marrow suppression.	Clozapine <b>must not be used</b> concomitantly with other agents having a well-known potential to suppress bone marrow functions.
Benzodiazepines	Concomitant use may increase risk of circulatory collapse, which may lead to cardiac and/or respiratory arrest.	Whilst the occurrence is rare, caution is advised when using these drugs together. Reports suggest that respiratory depression and collapse are more likely to occur at the start of this combination or when clozapine is added to an established benzodiazepine regimen.
Anticholinergics	Clozapine potentiates the action of these drugs through additive anticholinergic activity.	Observe for anticholinergic side-effects, e.g. constipation, especially when using to help control hypersalivation.
Antihypertensives	Clozapine can potentiate the hypotensive effects of these agents due to its sympathomimetic antagonistic effects.	Caution is advised if clozapine is used concomitantly with antihypertensive agents. Patients should be advised of the risk of hypotension, especially during the period of initial dose titration.
Alcohol, MAOIs, CNS depressants, including narcotics and benzodiazepines	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 patients 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 an increase in plasma concentration of these substances due to displacement from plasma proteins.	Patients should be monitored for the occurrence of side-effects associated with these substances, and doses of the protein bound substance adjusted, if necessary.
Phenytoin	Addition of phenytoin to clozapine regimen may cause a decrease in the clozapine plasma concentration.	If phenytoin must be used, the patient should be monitored closely for a worsening or recurrence of psychotic symptoms.

Drug	Interactions	Comments
Lithium	Concomitant use can increase the risk of development of neuroleptic malignant syndrome (NMS).	Observe for signs and symptoms of NMS.
CYP1A2 inducing substances (e.g. omeprazole)	Concomitant use may decrease clozapine level.	Potential for reduced efficacy of clozapine should be considered.
CYP1A2 inhibiting substances e.g. fluvoxamine, caffeine, ciprofloxacin, perazine or hormonal contraceptives (CYP1A2, CYP3A4, CYP2C19)	Concomitant use may increase clozapine level.	Potential for increase in adverse effects. Care is also required upon cessation of concomitant CYP1A2 or CYP3A4 inhibiting medications as there may be a decrease in clozapine level. The effect of CYP2C19 inhibition may be minimal.

## ADVERSE DRUG REPORTING

If an adverse reaction should occur inform relevant medical practitioner as soon as possible.

Report to the MHRA using the Yellow Card System <https://yellowcard.mhra.gov.uk/>

## REFERENCES

<https://www.medicines.org.uk/emc/product/10290/smpc>

<https://www.clozaril.co.uk/>

[https://www.sehd.scot.nhs.uk/cmo/CMO\(2017\)04.pdf](https://www.sehd.scot.nhs.uk/cmo/CMO(2017)04.pdf)

## ACUTE CARE/SPECIALIST SERVICE CONTACT INFORMATION

In the event of a concern being raised, the primary care practitioner should contact the referring consultant via the hospital switchboard, via their secretary, by e-mail or letter, whichever is more appropriate. If the concern is urgent, and out of hours advice is required, the on call doctor or pharmacist may be contacted via switchboard.

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