

**Procedure for the care of patients taking clozapine in primary care settings during the COVID-19 pandemic (Med42)**

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This procedure forms part of the AWP [Medicines Policy - P060](#)

And for AWP staff, it should be read in conjunction with both:

[Procedure for the prescribing, administration and monitoring of clozapine \(Med20\)](#)

[Procedure for management of clozapine service during COVID-19 pandemic \(Med40\)](#)

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**Alert**

All patients taking clozapine who have symptoms of COVID-19 must have an **immediate** check of **white cell count and neutrophil count**

The patient's presentation with signs of infection should be **urgently reported to their mental health team** for review and follow-up

**A clozapine plasma level should be arranged as soon as possible** (liaise with the patient's mental health team)

Clozapine should be **stopped** if flu-like symptoms are present **with chest pain** (investigate for myocarditis, highest risk in first 6-weeks of clozapine)



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## 1. Summary on a page

### 1.1. Clozapine in primary care including COVID-19 considerations

- Clozapine is an antipsychotic used most commonly in the treatment of schizophrenia resistant to other medicines. It is a red drug and is prescribed and dispensed by secondary mental health services.
- Patients prescribed clozapine are subject to mandatory regular full blood count monitoring because of a relatively high risk of neutropenia or agranulocytosis.
- Clozapine plasma levels are not mandatory but are routinely monitored to avoid toxicity and optimise treatment. Plasma level tests are obtained by posting a blood sample to a designated laboratory (not via local pathology labs).
- Clozapine toxicity can be fatal. Signs of a raised plasma level may include: drowsiness, sedation, lethargy, confusion, agitation, tachycardia, hypotension, respiratory depression and seizures. Reduce dose and arrange plasma level.
- Smokers require higher clozapine doses due to enzyme induction by tobacco smoke (not nicotine). Patients taking clozapine who reduce their smoking habit need urgent clozapine dose adjustment to avoid toxicity.
- As well as blood dyscrasias, other significant adverse effects of clozapine include:
  - Severe constipation sometimes leading to impaction and obstruction
  - Myocarditis and cardiomyopathy
  - Disturbed glucose control and diabetes
  - Seizures
  - An increased risk of developing pneumonia
- Serious clozapine related adverse effects of myocarditis and neutropenic sepsis may be mistaken for COVID-19 symptoms
- Acute infection can significantly raise clozapine plasma levels with risks of toxicity

All patients taking clozapine who have symptoms of COVID-19 must have an **immediate** check of **white cell count and neutrophil count**

The patient's presentation with signs of infection should be **urgently reported to their mental health team** for review and follow-up

A **clozapine plasma level should be arranged as soon as possible** (liaise with the patient's mental health team)

Clozapine should be **stopped** if flu-like symptoms are present **with chest pain** (investigate for myocarditis, highest risk in first 6-weeks of clozapine)

- Sudden discontinuation of clozapine may result in an abrupt and severe relapse of psychotic symptoms which can be challenging to treat with other medication.
- AWP is working to ensure continuity of clozapine supplies. When safe to do so, limited additional supplies of medication are being dispensed. If you have a patient concerned that they are running out, contact us using the details below.



## 1. What is clozapine?

Clozapine is an antipsychotic used most commonly in the treatment of schizophrenia resistant to other medicines. Therefore patients prescribed clozapine often have an illness that is more challenging to treat with other antipsychotics.

Clozapine is a 'red drug' on all Avon and Wiltshire Mental Health Partnership (AWP) clinical commissioning groups' medicines formularies meaning that it cannot be transferred to primary care.

Prescribing and dispensing is usually entirely managed by the mental health trust. Within the AWP area almost all clozapine dispensing is managed by the two AWP dispensaries in Calne (Wiltshire) and Callington Road Hospital (Bristol).

Clozapine requires mandatory regular full blood count (FBC) monitoring ([see below](#)) and without the results of these blood tests the supplying pharmacy are unable to release the medication to the patient.

## 2. Monitoring of clozapine

### 2.1. Full blood count monitoring

Patients prescribed clozapine are subject to mandatory regular full blood count (FBC) monitoring because of a relatively high risk of neutropenia/agranulocytosis during treatment.

The risks of blood dyscrasia is highest at the start of treatment and consequently FBCs are more frequent when treatment is initiated and become less frequent for those established on treatment without any abnormal blood results.

To manage the risks of clozapine treatment patients must be registered with a clozapine monitoring service which authorises on-going supply of the medicine. There are three in the UK, and each mental health trust will use one for all its patients taking clozapine.

AWP use the Zaponex Treatment Access System (ZTAS).

In order for a patient to be supplied with clozapine, all three of the following must be registered with the appropriate clozapine monitoring services:

- The patient
- Their Consultant Psychiatrist
- The dispensing Pharmacist

Full blood count monitoring for patients taking clozapine is arranged by their community mental health team. Depending on local arrangements, some patients have blood samples taken at their community mental health team base; others have these taken at their GP surgery.

The results of the FBC monitoring are checked by the AWP pharmacy staff before the next supply of clozapine is due. They enter the results on to the ZTAS system to ensure they meet the criteria to allow treatment to continue.

The frequency of blood monitoring for each patient is set by ZTAS and patients receive information with each supply of medication as to when their next blood test is due. The standard frequencies are detailed below:

Duration of treatment	Monitoring frequency	Usual supply quantity
1-18 weeks	Weekly	7 days
19-52 weeks	Fortnightly	14 days
> 52 weeks	4-Weekly	28 days

If there are abnormal blood results or treatment breaks ([see below](#)), more frequent monitoring will be required and ZTAS will advise on the amended schedule.



## 2.2. Clozapine plasma level monitoring

Clozapine plasma levels are also routinely monitored. Although this is not mandatory, it is a useful tool to avoid toxicity and optimise treatment. The plasma level tests are obtained by posting a blood sample to a designated laboratory (not via local pathology service).

## 3. Risks associated with clozapine

Whilst the prescribing and monitoring of clozapine is managed by AWP, there are adverse effects that may first present in primary care. It is important that staff in primary care are aware of these issues so that need for prompt referral is recognised. Some of these are specifically related to the COVID-19 pandemic.

It is not known whether clozapine itself affects the risk of contracting or developing complications of COVID-19, but it does directly increase the risk of certain physical health conditions, including diabetes and cardiomyopathy, and is associated with an increased risk of pneumonia. Patients taking clozapine who contract COVID-19 may therefore be at a greater risk of complications, as a result of physical co-morbidities.

A full list of adverse effects can be reviewed in the Summary of Product characteristics <https://www.medicines.org.uk/emc/product/7715/smhc/> but certain key issues are outlined below.

### 3.1. Smoking and the effect on clozapine levels

During the COVID-19 pandemic, patients may reduce the amount they smoke, or attempt to stop smoking entirely either to reduce their risks of complications due to the illness or because illness and/or isolation are reducing their access to opportunities to smoke.

**If a patient taking clozapine changes their smoking habit, their dose will need rapid adjustment by their mental health team.**

Tobacco smoke (but not nicotine) induces the liver enzymes that metabolise clozapine, so smokers generally require higher clozapine doses. A patient on a stable dose of clozapine who stops smoking might experience a 50% increase in clozapine concentrations within two to four weeks, with some patients experiencing significant increases in plasma levels as soon as three to five days after abruptly stopping smoking.

If a patient reports a significant reduction in smoking habit, (with or without the use of nicotine replacement therapy or vaping) a referral to the team managing the clozapine prescription should be made urgently so the clozapine dose can be reviewed.

Changes in use of nicotine replacement therapy or vaping **do not** require the same considerations because it is specifically components of tobacco smoke that elicit this response.

### 3.2. Acute infection

Neutropenia and agranulocytosis with clozapine can present as a fever in patients taking clozapine but fever is also a key symptom in most presentations of COVID-19.

The possibility of a clozapine induced blood dyscrasia must always be considered in patients taking clozapine, particularly for those early in treatment (initial 18 weeks).

**Acute infections (including COVID-19) can also markedly raise clozapine plasma levels.** This, as well as a possible reduction in smoking habit (see [above](#)) and antibiotic treatment of any secondary bacterial infection, can lead to toxic plasma levels.



All patients taking clozapine who have symptoms of COVID-19 must have an **immediate** check of **white cell count and neutrophil count**

The patient's presentation with signs of infection should be **urgently reported to their mental health team** for review and follow-up

A **clozapine plasma level should be arranged as soon as possible** (liaise with the patient's mental health team)

Clozapine should be **stopped** if flu-like symptoms are present **with chest pain** (investigate for myocarditis, highest risk in first 6-weeks of clozapine)

Signs of a raised plasma level may include: drowsiness, sedation, lethargy, confusion, agitation, tachycardia, hypotension, respiratory depression or seizures.

Patients should be closely monitored for signs of toxicity, (for example drowsiness, sedation, lethargy, confusion, agitation, tachycardia, hypotension, respiratory depression or seizures), and an **urgent referral** made to the mental health team so they can review if a dose reduction is indicated and arrange a plasma level check. They may decide on a dose reduction in advance of receiving the plasma level.

### 3.3. Myocarditis

Patients presenting with flu-like symptoms **and** chest pain and/or shortness of breath should have clozapine withheld and be referred urgently for investigation of possible myocarditis.

### 3.4. Compromised respiratory function

Patients with compromised respiratory function due to COVID-19 or any other respiratory infection will need regular and ongoing review of all sedating medications (including clozapine) to determine if they are contributing to respiratory distress. If a primary care clinician considers that a clozapine dose reduction is required, this should be discussed urgently with a Psychiatrist.

### 3.5. Pneumonia

Antipsychotics including clozapine can put patients at an increased risk of developing severe respiratory tract infections including pneumonia.

There are currently no data exploring any relationship between antipsychotics or schizophrenia and the risk of contracting COVID-19, or developing severe symptoms to the infection. In the absence of data, it should be assumed that patients taking antipsychotics, especially clozapine, and especially where co-morbidities exist, may be at particular risk from COVID-19 and associated pneumonia.

### 3.6. Diabetes

Clozapine is linked to increased risks of hyperglycaemia, impaired glucose tolerance and diabetic ketoacidosis.

The risk of impaired glucose tolerance due to clozapine may be increased if a patient is also suffering from COVID-19. Monitor for signs and symptoms of hyperglycaemia as usual, but be particularly alert in patients with infection.

### 3.7. Constipation

Whilst not specifically related to the COVID-19 pandemic, constipation due to clozapine is a significant risk and is likely to present first in primary care. It may be severe and fatalities due to bowel obstruction or ischaemia have been reported. Regular long-term laxatives may be needed.



Symptoms that warrant urgent medical attention include: abdominal distension, abdominal pain, vomiting, overflow diarrhoea, or absent bowel sounds. Co-prescription of other medication which increase the risk of constipation such as anticholinergics or opioid analgesics should be avoided if possible.

### 1. Clozapine treatment breaks and need for re-titration

Sudden discontinuation of clozapine may result in an **abrupt and severe relapse of psychotic symptoms** which can be challenging to treat with other medication.

**Omission of clozapine for more than 48hrs necessitates re-titration** of the dose starting at 12.5mg or 25mg daily during which frequent monitoring of physical parameters is mandatory. For this reason, any re-titration is usually undertaken as a hospital inpatient. Alternatively, it may be possible for it to be done in the community with intensive support from a home treatment team. Please contact the patient's mental health team to discuss this.

The consequences of treatment breaks are significant and so such breaks should be avoided if at all possible. Certain scenarios however, do require the sudden cessation of clozapine treatment and should be **urgently** discussed with a psychiatrist, including:

- A red FBC result
- Suspected myocarditis
- Neuroleptic malignant syndrome (NMS)
- Suspected or confirmed COVID-19 infection with shortness of breath and/or chest pain

If a re-titration is required, this must be managed by the mental health team and requires urgent referral.

When reviewing a patient on clozapine treatment, ask specifically about adherence with treatment, notably over the previous 48 hours. If there are any concerns that the patient has been non-adherent for greater than 48 hours, then re-titration may be required.

### 2. Supply of clozapine

Clozapine for community patients in the AWP catchment area is almost always supplied by the AWP Calne Pharmacy Hub (contact number [below](#)). It cannot be supplied by community pharmacies.

The AWP dispensary delivers clozapine to a variety of locations for collection by the patient directly or collection by a member of staff from the mental health team. Most commonly, the delivery location is one of our community mental health teams, but other sites such as GP surgeries are occasionally used. A number of patients have clozapine delivered to their home by an AWP driver. Procedures for delivery may need review during the COVID-19 pandemic, to take account of social distancing requirements and staff availability. These reviews will take place at a local level.

A patient can only be supplied with clozapine by their registered pharmacy if they have an up-to-date FBC entered on the relevant monitoring system. The required frequency of the FBCs depends on both how long a patient has been taking clozapine and whether the previous results were within an acceptable range. **Without a valid blood result the registered pharmacy cannot supply medication.**

The AWP Pharmacy Hub is working hard to ensure the continuity of clozapine supplies to patients in the face of the challenges caused by the COVID-19 pandemic. When it is safe to do so, limited additional supplies of medication are being dispensed. We are doing our best to liaise with patients about these measures but if you have a patient who is concerned they are running out of medication, please contact us using the details below.



### 3. Recording clozapine in the primary care record

Although GPs are not involved in the prescription of clozapine, it is important that it is documented clearly in the primary care record so interactions and clozapine side effects can be easily recognised. This also helps reduce the risk of clozapine being missed during medicines reconciliation during any transfers of care.

For all patients taking clozapine an entry should be made in their record (following the standard template for hospital-only medicines used in your IT system):

- List clozapine under 'other medication' in the GP medication record
- Ensure it is marked as a 'hospital only medication'

### 4. Assistance with blood tests in primary care

The FBC blood testing for patients taking clozapine is usually undertaken by the mental health team but in some circumstances we have been fortunate to have the assistance of primary care. During the pandemic, when staffing in the community mental health teams may be even more limited than usual, we may ask for additional short-term assistance from primary care to support the vital blood monitoring for our clozapine patients.

If your surgery is able to offer assistance with the full blood count monitoring for a patient taking clozapine please mark the blood request form with CLOZAPINE FBC and (if possible) the patient's ZTAS PIN, which can be provided by the relevant community mental health team.

If you are asked to assist with taking a sample for clozapine plasma level monitoring, a separate pre-addressed kit will be provided for this by the mental health team.

### 5. Patient information about clozapine

More information about clozapine is available on the AWP Choice and Medication website:  
<https://www.choiceandmedication.org/awp/medication/clozapine/>

Information about the COVID-19 pandemic is available here:  
<https://www.choiceandmedication.org/awp/generate/handyfactsheetclozapinecovid19.pdf>

Information about the effects of smoking cessation on clozapine levels is available here:  
<https://www.choiceandmedication.org/awp/generate/handyfactsheetsmokingandclozapine.pdf>

### 6. Urgent assistance out-of-hours

If you need urgent assistance with the management of a patient taking clozapine out-of-hours then the AWP on-call pharmacist or on-call medical staff can be contacted via the switchboard 01225 325680.

The ZTAS monitoring service have an emergency out-of-hours service and can be contacted by calling 0207 365 5842 and listening to the recorded message.

### 7. Local contacts

AWP pharmacy hub clozapine extension: 01225 675473 (9am to 5pm)

AWP on-call pharmacist via the switchboard: 01225 325680 (out-of-hours)

Local primary care liaison team: please use local contact details

Zaponex Treatment Access System (ZTAS): 0207 365 58 42



## 8. References

Summary of Product Characteristics Zaponex 25 mg Tablets Leyden Delta accessed via: <https://www.medicines.org.uk/emc/product/7138/smpc> Last updated: 07 Nov 2019; accessed 31 Mar 2020

The Maudsley Prescribing Guidelines (Thirteenth edition) 2018 Wiley Blackwell

South London and Maudsley NHS Trust (March 2020) *Clozapine and blood dyscrasias in patients with coronavirus (COVID-19)*

South London and Maudsley NHS Trust (March 2020) *Clozapine and COVID-19 Initiation, continuation and special precautions*

[Monitoring and Supply of Clozapine during COVID-19 pandemic](#) (endorsed by RPharmS and CMHP)

Clozapine drug monitoring during COVID-19 for stable adult patients (Specialist Pharmacy Service) last updated 7th April 2020 accessed via <https://www.sps.nhs.uk/articles/clozapine-drug-monitoring-in-primary-care-during-covid-19-for-stable-patients/>

Version History				
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1.1	09.04.2020	Updated to include more information about standard monitoring practice	S. Jones	Draft
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