

## Coronavirus (COVID-19) and Clozapine Information for Health Care Professionals

**Version 3** includes confirmation of the arrangements for blood testing that are in place in primary care during the outbreak.

General information
<ul style="list-style-type: none"> <li>Clozapine is an antipsychotic medication licensed for use in Treatment-Resistant schizophrenia (TRS). Oxford Health NHS Foundation Trust uses the brand Denzapine™ in the majority of clozapine-treated service-users and the associated Denzapine Monitoring Service (DMS).</li> <li>A small number of patients are prescribed Clozaril™ (Marlborough House, Milton Keynes) which is managed by the Clozaril Patient Monitoring Service (CPMS).</li> <li>Clozapine can cause agranulocytosis in approximately 1 percent of patients, as well as neutropenia, and regular monitoring of leucocytes and neutrophils is essential, particularly early in treatment when risk is highest</li> <li>Supply of clozapine by the designated pharmacy/clinic occurs on receipt of a ‘green’ result via DMS covering the period until the next blood test.</li> </ul>

Blood Test Validity																
<ul style="list-style-type: none"> <li>Regular testing of white cell count (WCC) and neutrophil (NC) is a requirement for treatment with clozapine. Supply of clozapine is dependent on a valid blood test being obtained and entered into the DMS website. The frequency of blood tests changes with duration of treatment, meaning that the quantity of clozapine that can be supplied also changes. Please see the table below.</li> </ul>																
<table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th style="padding: 5px;">Duration of treatment</th> <th style="padding: 5px;">Usual Monitoring frequency</th> <th style="padding: 5px;">Usual quantity supplied</th> <th style="padding: 5px;">Maximum clozapine supply</th> </tr> </thead> <tbody> <tr> <td style="padding: 5px;">1-18 weeks</td> <td style="padding: 5px;">Weekly</td> <td style="padding: 5px;">7 days</td> <td style="padding: 5px;">10 days</td> </tr> <tr> <td style="padding: 5px;">19-52 weeks</td> <td style="padding: 5px;">Fortnightly</td> <td style="padding: 5px;">14 days</td> <td style="padding: 5px;">21 days</td> </tr> <tr> <td style="padding: 5px;">&gt;52 weeks</td> <td style="padding: 5px;">4-weekly</td> <td style="padding: 5px;">28 days</td> <td style="padding: 5px;">42 days</td> </tr> </tbody> </table>	Duration of treatment	Usual Monitoring frequency	Usual quantity supplied	Maximum clozapine supply	1-18 weeks	Weekly	7 days	10 days	19-52 weeks	Fortnightly	14 days	21 days	>52 weeks	4-weekly	28 days	42 days
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<ul style="list-style-type: none"> <li><b>NOTE - any dispensing beyond the designated maximum supply is considered an “off-label” supply</b></li> </ul>																

Traffic light classification of full blood count results and action required		
<b>Patients WITHOUT Benign Ethnic Neutropenia (BEN):</b>		
<p style="text-align: center; margin: 0;"><b>RED</b></p> <p style="margin: 0;">Action: STOP clozapine immediately. Repeat FBC daily until amber or green.</p>	<p style="text-align: center; margin: 0;"><b>AMBER</b></p> <p style="margin: 0;">Action: Increase monitoring frequency to twice weekly until green.</p>	<p style="text-align: center; margin: 0;"><b>GREEN</b></p> <p style="margin: 0;">Action: continue clozapine and usual monitoring frequency.</p>
<p style="margin: 0;">WBC &lt;3.0 x 10<sup>9</sup>/L or Neutrophils &lt;1.5 x 10<sup>9</sup>/L or platelets &lt;50 x 10<sup>9</sup>/L</p>	<p style="margin: 0;">WBC ≥3.0 and &lt;3.5 x 10<sup>9</sup>/L or Neutrophils ≥1.5 and &lt;2.0 x 10<sup>9</sup>/L</p>	<p style="margin: 0;">WBC ≥ 3.5 x 10<sup>9</sup>/L and Neutrophils ≥2.0 x 10<sup>9</sup>/L and no decrease of &gt;10% or repeatedly decreasing values in the previous test(s)</p>

**Patients WITH Benign Ethnic Neutropenia (BEN):**

RED	AMBER	GREEN
<b>Action: STOP clozapine immediately, repeat FBC daily until amber or green.</b>	<b>Action: Increase monitoring frequency to twice weekly until green.</b>	<b>Action: continue clozapine and usual monitoring frequency</b>
WBC <2.5 x 10 <sup>9</sup> /L or Neutrophils <1.0 x 10 <sup>9</sup> /L or platelets <50 x 10 <sup>9</sup> /L	WBC ≥2.5 and <3.0 x 10 <sup>9</sup> /L or Neutrophils ≥1.0 and <1.5 x 10 <sup>9</sup> /L	WBC ≥ 3.0 x 10 <sup>9</sup> /L and Neutrophils ≥1.5 x 10 <sup>9</sup> /L and no decrease of >10% or repeatedly decreasing values in the previous test(s)

**Patients with no symptoms of COVID-19 who are not self-isolating**

- Blood testing should continue as normal.
- Most patients who take clozapine have their blood samples for FBC taken in primary care. Local arrangements for urgent blood testing of patients without COVID-19 symptoms by GP practices should be followed and patients should contact their GP surgery to arrange in the usual way.
- If a blood test cannot be carried out in primary care and needs to be arranged by OHFT, this should be taken at the patient’s home, using personal protective equipment and techniques as recommended by OHFT. See Covid-19 OH ‘[Carrying Out Essential Care](#)’: [Standard Operating Procedure](#).
- There is the potential for treatment breaks in clozapine due to this situation.
- DMS has advised that where patients are unable to have a blood test, there is an option to extend clozapine supply by a further 4 weeks for all patients
- This is a decision that needs to be taken by the Responsible Clinician and we would advise contacting the OHFT Medicines Advice team (see contact details below) or an OHFT Clinical Pharmacist to discuss. It is considered “off-label” use and may not be a suitable option for all patients, depending on past history of RED or AMBER results. An off-label form must be completed by the Responsible Clinician for the patient and sent to DMS by e-mail to [Denzapine@britannia-pharm.com](mailto:Denzapine@britannia-pharm.com).
- The DMS off-label treatment agreement form is available on the homepage of the Trust’s formulary ([www.oxfordhealthformulary.nhs.uk](http://www.oxfordhealthformulary.nhs.uk)) or by clicking [here](#).
- Alternatively, clinicians can contact DMS directly, but please let the Pharmacy team know if extended supply is agreed. The contact details for DMS are at the end of this document.
- Currently, extending the supply to weekly patients by 4 weeks is not recommended by the Trust on the basis that the first 18 weeks of treatment are deemed the highest risk period for the occurrence of agranulocytosis/ neutropenia. However, there may be times when a limited extension is needed to avoid a treatment break and the Pharmacy department should be contacted for advice and an off-label form should be completed in this situation.
- Blood testing for those patients who require weekly or fortnightly blood tests or who have had an AMBER result (WCC ≥3.0 x 10<sup>9</sup>/l to <3.5 x 10<sup>9</sup>/l and/or NC ≥1.5 x 10<sup>9</sup>/l to <2.0 x 10<sup>9</sup>), must be prioritised and it may be necessary for healthcare staff to attend a patient’s home.
- Use the [Domiciliary Visits Care Pathway–COVID-19](#) to ascertain whether personal protective equipment and techniques are required. If so, please refer to [Covid-19 OH ‘Carrying Out Essential Care’](#): [Standard Operating Procedure](#) [both available on the Trust intranet].

**Patients with no symptoms of COVID-19 who are self-isolating**

- Continue clozapine treatment.
- Most patients who take clozapine have their blood samples for FBC taken in primary care. Local arrangements for urgent blood testing of patients by GP practices should be followed and patients should contact their GP practice to arrange in the usual way. GP practices are following local guidance and may use CALM clinics ([Oxfordshire](#)) or hot hubs ([Buckinghamshire](#)) as appropriate.

- If a blood test cannot be carried out in primary care and needs to be arranged by OHFT, this should be taken at the patient's home, using personal protective equipment and techniques as recommended by OHFT. See Covid-19 OH '[Carrying Out Essential Care](#)': Standard Operating Procedure.
- Patients requiring weekly and fortnightly blood tests or those with 'amber' results must be prioritised.

## Patients with mild symptoms of COVID-19

- Patients are generally advised to contact the mental health team as soon as possible if any kind of infection begins to develop while on clozapine, with particular attention paid to flu-like symptoms such as fever (temperature >37.5°) or sore throat and other evidence of infection. NOTE: fever is a common symptom of COVID-19 along with cough\*\*.
- Perform an URGENT full blood count, advise patient to withhold the next dose, and communicate result to DMS/CPMS. Evaluate the patient for underlying infection or development of agranulocytosis. If the result is GREEN, continue clozapine, discuss amber/red results with DMS/CPMS (Red result-STOP treatment). See below for parameters that constitute amber and red results.
- Most patients who take clozapine have their blood samples for FBC taken in primary care. Local arrangements for urgent blood testing of patients by GP practices should be followed and patients should contact their GP practice to arrange in the usual way. GP practices are following local guidance and may use CALM clinics ([Oxfordshire](#)) or hot hubs (Buckinghamshire) as appropriate.
- If a blood test cannot be carried out in primary care and needs to be arranged by OHFT, this should be taken at the patient's home, using personal protective equipment and techniques as recommended by OHFT. See Covid-19 OH '[Carrying Out Essential Care](#)': Standard Operating Procedure.
- The presence of fever is not in itself a reason to cease clozapine, providing an FBC has been taken and the result received is GREEN.
- Fever and rises in CRP can cause a rise in clozapine levels so taking a trough plasma level is advisable if a patient is showing increased side effects (see BNF) - a temporary dose reduction may be necessary until infection resolves.
- Please refer to information below on clozapine plasma levels.

## Patients with Severe Respiratory Illness

- In patients with severe respiratory illness- WITHHOLD CLOZAPINE until symptoms are resolved.
- Seek advice from the Mental Health team/OHFT Pharmacy, including on restarting treatment when infection is resolved, as dose-titration is required if clozapine is withheld for >48 hours and there will be a need to contact DMS/CPMS. See below for further guidance about restarting clozapine following a treatment break.
- ACUTE HOSPITAL TRUSTS - contact OHFT Pharmacy for advice

## Patients presenting with flu like symptoms, chest pain and shortness of breath

- WITHHOLD CLOZAPINE. For patients presenting with flu-like symptoms, chest pain and shortness of breath, suspect myocarditis and investigate accordingly (increased risk of myocarditis greatest in the first 2 months of treatment).
- Seek advice from the Mental Health team/OHFT Pharmacy, including on restarting treatment when infection is resolved, as dose-titration is required if clozapine is withheld for >48 hours and there will be a need to contact DMS/CPMS. See below for further guidance about restarting clozapine following a treatment break.

## Re-titrating clozapine following a treatment break of >48 hours and monitoring guidance advice

- Re-titration schedules need to be individualised and will depend on several issues, including the duration of the break, risk of relapse, indication, patient's age etc.
- Faster titrations may be considered in some instances.
- The pharmacy team must be contacted when a break in treatment has occurred, so that the Denzapine Monitoring Service can be informed.

- Pharmacy can also advise on re-titration dosing regimens, if required.
- If the treatment break has been >72 hours, weekly FBCs for 6 weeks will be necessary before monitoring can return to the usual frequency.

#### **Monitoring arrangements for a re-titration during the coronavirus outbreak**

- The usual recommendation for monitoring a patient's physical observations (obs) is to check BP, pulse and temperature hourly for 6 hours after the first dose, and then twice daily until back at the usual treatment dose, unless tolerability issues indicate more frequent monitoring is necessary.
- In the current circumstances, there is a choice of options. The option chosen will depend on availability of staff to attend the patient's home and a risk assessment of the patient's mental and physical health. Option 1 is probably preferred, but understandably may not be practical.

- **First dose - option 1:**

Take baseline obs and give day 1 dose in the morning. Acknowledge that hourly physical monitoring is not likely to be practical but implement as frequent monitoring (with home attendance) as staffing availability allows. If a home visit can't be made for all of the recommended monitoring frequencies, a telephone call to the patient or carer (if available) should take place to ask the non-physical obs questions as per below ("ask about other side effects").

- **First dose - option 2:** *(if attendance multiple times on day 1 is not likely to be possible and particularly if the frequency of attendance at the patient's home is less than every 2 hours for 6 hours):*

Check baseline obs on day 1. Prescribe the first dose as a night-time dose and recommend it is taken just before bed, to reduce the risk of a fall if a postural drop occurs.

THEN:

#### **Subsequent monitoring day 2 onwards (following either option above):**

Carry out physical obs the following morning *prior* to the dose of clozapine, and if tolerating well continue with titration schedule. Check physical obs again in the afternoon approx. <6 hours after previous dose. If all normal, advise night-time dose is taken (preferably just before bed). Repeat pre-morning dose obs and afternoon physical obs until back at usual treatment dose, unless additional monitoring is indicated.

**Ask about other side effects** at each contact, including over-sedation, chest pain, shortness of breath, flu-like symptoms, signs of constipation etc. and review as needed. See guidance above if patient presents with flu like symptoms, chest pain or shortness of breath.

#### **Clozapine Plasma Levels**

- A rise in C-reactive protein (CRP) and a fever, which are seen during a systemic inflammatory response, can alter clozapine metabolism via Cytochrome P450 1A2 hepatic enzymes. Metabolism is reduced, leading to a rise in clozapine levels.
- In patients with mild respiratory illness- continue clozapine but check clozapine plasma levels. For a meaningful level, a trough clozapine plasma level should be obtained. Please click on this [ASI](#) link for obtained. Contact Oxford Health Pharmacy to request a clozapine plasma level kit by e-mail ([dispensary@oxfordhealth.nhs.uk](mailto:dispensary@oxfordhealth.nhs.uk)). Please state that the kit is required for a patient who has tested positive for COVID-19 or may have symptoms of COVID-19. further information.
- ASI is the company that processes the majority of OXHFT clozapine plasma levels and the lab has made the following requests in the current situation:
  - **If a patient has tested positive for COVID-19 or is suspected of having COVID-19, ensure that this is clearly documented on the request form.**
  - It is imperative that samples are packaged appropriately using the kits provided, including the rigid tube and absorbent materials that are supplied, since these comply with UN3373 Category B requirements.
- Samples must be posted to ASI as soon as possible.

- Plasma level results may be delayed, so monitor for effects of toxicity- these include sedation, tachycardia, hypotension, constipation, myoclonus and seizures. Temporarily reducing the clozapine dose as a precaution, may be an option while awaiting a plasma level result. Please contact Pharmacy for further advice if needed.
- Smoking induces metabolism of clozapine; the polycyclic aromatic hydrocarbons generated by cigarette smoke induce the hepatic enzyme, cytochrome P450 1A2. Smokers who take clozapine, who are experiencing a mild or severe respiratory illness will likely smoke less or be forced to stop smoking by the illness, which will result in an increase in clozapine plasma levels. Please see the Trust advice on [smoking and psychotropics](#). A trough clozapine plasma level should be taken where possible and dose reduction considered.

## Side effect monitoring

The Glasgow Antipsychotic Side effect Scale (GASS) for clozapine may be a useful tool to aid the monitoring of clozapine side effects and can be completed by the patient. It can be found on the Trust formulary or by clicking [here](#).

## Information for patients

Click for the "[Handy fact sheet: Clozapine, blood testing and the coronavirus / COVID-19 outbreak](#)"  
This is also available at [www.choiceandmedication.org/oxfordhealth](http://www.choiceandmedication.org/oxfordhealth)

Other patient leaflets on clozapine also available include:

[Amber result](#)

[Red result](#)

[Plasma \(blood\) levels](#)

[Constipation](#)

[Smoking](#)

[Hypersalivation](#)

## LOCAL ACUTE HOSPITAL TRUSTS

### **Oxford University Hospitals NHS Trust AND Buckinghamshire Healthcare NHS Trust.**

Please notify Oxford Health NHS Foundation Trust Pharmacy of any clozapine patients who are admitted with suspected Coronavirus so we can notify the Denzapine Monitoring Service and provide advice if needed.

### **Milton Keynes University Hospitals NHS Trust**

Please liaise with the CPMS regarding clozapine treated patients who are admitted with suspected coronavirus.

### **Royal Berkshire NHS Foundation Trust AND Great Western Hospitals NHS Foundation Trust**

Please liaise with Oxford Health NHS Foundation Trust Pharmacy if any OXHFT clozapine patients are admitted with suspected Coronavirus so we can notify the Denzapine Monitoring Service and provide advice if needed.



### **Need more information/advice?**

Please contact the OHFT Medicines Advice Service:

01865 904365 or [medicines.advice@oxfordhealth.nhs.uk](mailto:medicines.advice@oxfordhealth.nhs.uk)