Clozaril® (clozapine) and COVID-19 Information Update

Dear Clozaril® Customer,

Mylan is monitoring the development of the COVID-19 pandemic very closely. In alignment with UK government, NHS guidelines and updates from the World Health Organization, Mylan is continuing to take steps to safeguard employees, customers and the patients we serve. In the evolving circumstances of the COVID-19 pandemic, Mylan has gathered information to provide you with reassurance as well as updated advice on the on-going and appropriate use of, and management of patients on Clozaril® (clozapine).

The information in this document is not intended as a definitive treatment strategy, but as a suggested approach for clinicians. It is based on previous successful experience. Each case should, of course, be considered individually. This information is provided for health care professionals and should not be used as a patient information leaflet.

Business Continuity

The UK & Ireland Clozaril Patient Monitoring Service (CPMS) is available 24 hours a day for all our customers.

Mylan have worked extensively with the CPMS team to ensure the robustness of contingency plans. In the event of any impact due to COVID-19 (for example reduced staff numbers at CPMS) core tasks and activities will be prioritised to ensure an effective service. Mylan are also co-ordinating with all our Clozaril® vendors to ensure that the products and services that we have in place remain uninterrupted as far as possible.

Clozapine use and COVID-19

Mylan appreciate these are unprecedented times. There are many questions you may have in relation to management of patients on Clozaril® and the associated mandatory blood monitoring.

As per the Clozaril® (clozapine) Summary of Product Characteristics (SmPC) accessed via www.medicines.org.uk/emc/ (or www.medicines.ie for customers from Ireland):

The UK/IRL Clozaril Patient Monitoring Service (CPMS) was developed in order to manage the risk of agranulocytosis associated with clozapine. When a monitoring service is not used, evidence suggests a mortality rate from agranulocytosis of 0.3%. This is compared to a mortality rate when Clozaril is used in conjunction with the Clozaril Patient Monitoring Service, of 0.01%.

You may want to consider following information:

There is currently no data that suggests that clozapine patients should not continue to take their clozapine if they are suspected to have contracted COVID-19. There also is no evidence to suggest that being on clozapine would make you more at risk from Coronavirus.

The SmPC continues and states:

"At each consultation, a patient receiving clozapine should be reminded to contact the treating physician immediately if any kind of infection begins to develop. Particular attention should be paid to flu-like complaints such as fever or sore throat and to other evidence of infection, which may be indicative of neutropenia. Patients and their caregivers must be informed that, in the event of any of these symptoms, they must have a blood cell count performed immediately."

The supervising specialist is best placed to determine if increased blood monitoring is required to rule out any potential neutropenia related to any viral infection. A benefit risk decision should be taken on a case by case basis however if in doubt, we would recommend additional blood monitoring where possible.

The table below shows a symptom comparison of COVID-19 and a low white cell count:

COVID-19	Low White Cell Count
A high temperature of 38C or above	A high temperature of 38C or above
A new, continuous cough (coughing a lot for more than an hour, or 3 or more coughing episodes in 24 hours)	Flu-like symptoms (aches, lethargy, dry cough, headache, nausea, diarrhoea)
Breathing difficulties	Sore throat
	Chills and shivering

Table 1, source: www.nhs.uk/conditions/

As patients may need to self-isolate in line with national recommendations, we wish to bring to your attention the blood monitoring frequency requirements. CPMS do allow for maximum cover periods for all blood samples depending on the patient's current monitoring frequency. Please see the table below for timelines:

Monitoring Frequency	Sample Due Day	Maximum Cover Period
Weekly	Every 7 Days	10 Days
Fortnightly	Every 14 Days	21 Days
Four Weekly	Every 28 Days	42 Days

Table 2, source: eCPMS Database

CPMS do not encourage use of the maximum cover period for blood samples but given the current circumstances you may wish to consider if this may reduce the burden on clinic staff required to obtain samples. However please note that you should align with the pharmacy department as they would need to approve of any additional supply requests with the patient's responsible clinician.

Blood samples can be:

1. Sent in line with your current method of delivery to our centralised laboratories who will analyse and upload samples to the eCPMS database the same day samples are received. Our centralised laboratories have been deemed an essential service and will continue to operate at normal capacity throughout this period.

2. Analysed at one of our many PocHi sites across the UK and Ireland. A result can be immediately obtained allowing for same day dispensing of medication.

3. Analysed at your local laboratory and then manually uploaded to the eCPMS database or by calling/forwarding results by email directly to CPMS.

Clozaril® Point of Care Clinics

Mylan suggests that all Point of Care (PocHi) clinics review the number of staff accredited to operate the PocHi machine. PocHi certified users can train other available clinic staff (as appropriate) to be able to operate the PocHi to analyse blood samples for Clozaril® patients.

Sysmex®, the manufacturers of the PocHi devices has assured Mylan that they will remain available by phone and provide support as needed.

In the short term, with the health of all in mind, it has been decided that it is currently not appropriate to run PocHi training courses at the Sysmex® office and courses scheduled in the immediate months have been cancelled. These will resume as soon as guidance reasonably allows.

Additional Preventative measures

The following preventative information is taken from the COVID-19, Guidance for infection prevention and control in healthcare settings. We recommend that you follow the guidance in the following link: https://www.gov.uk/government/publications/wuhan-novel-coronavirus-infection-prevention-and-control *(last accessed 20th March 2020)*

- ✓ **Patient placement/assessment for infection risk**
  - Patients must be promptly assessed for infection risk on arrival at the care area and, if possible, prior to accepting a patient from another care area. Patients should be continuously reviewed throughout their inpatient stay. In all healthcare settings, patients with symptoms of COVID-19 should be segregated from non-symptomatic patients as promptly as possible.
- ✓ **Hand hygiene**
  - Hand hygiene is essential to reduce the transmission of infection in health and other care settings and is a critical element of standard infection control precautions (SICPs). All staff, patients and visitors should decontaminate their hands with alcohol-based hand rub (ABHR) when entering and leaving areas where care for suspected and confirmed COVID-19 patients is being delivered.
  - Hand hygiene must be performed immediately before every episode of direct patient care and after any activity or contact that potentially results in hands becoming contaminated, including the removal of personal protective equipment (PPE), equipment decontamination and waste handling: www.who.int/gpsc/5may/Your_5_Moments_For_Hand_Hygiene_Poster.pdf
- ✓ **Respiratory and cough hygiene**
  - Disposable, single-use tissues should be used to cover the nose and mouth when sneezing, coughing or wiping and blowing the nose. Used tissues should be disposed of promptly in the nearest waste bin.
  - Hands should be cleaned (using soap and water if possible, otherwise using ABHR) after coughing, sneezing, using tissues or after any contact with respiratory secretions and contaminated objects.
  - Encourage patients to keep hands away from the eyes, mouth and nose.
- ✓ **Personal protective equipment (PPE)**
  - Before undertaking any procedures, staff should assess any likely exposure and ensure PPE is worn that provides adequate protection against the risks associated with the procedure or task being undertaken. All staff should be trained in the proper use of all PPE that they may be required to wear.

The CPMS was developed in order to manage the risk of agranulocytosis associated with use of clozapine. Blood monitoring should be carried out in accordance with national-specific official recommendations. The decision to deviate from the national regulatory recommendations would be at the treating physician's discretion based on a benefit, risk assessment. However, as this is an unlicensed use of our product, please advise CPMS as our Pharmacovigilance Department need to collect information on off-license use of Clozaril®.

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.
Healthcare professionals are asked to report any suspected adverse reactions via:
For the UK, reporting forms and information can be found at www.mhra.gov.uk/yellowcard
For Ireland, report adverse events via HPRA Pharmacovigilance at medsafety@hpra.ie
Adverse events should also be reported to Mylan via cpms@mylan.co.uk

Frequently Asked Questions

Q. If a patient contracts COVID-19 (or shows the symptoms) and they have to self-isolate for 7-14 days: would they be able to continue to be prescribed Clozaril if we cannot obtain a recent blood result?

A. Flu-like complaints such as fever, sore throat and any other evidence of infection, may be indicative of neutropenia. Increased blood monitoring may therefore be warranted. The supervising specialist is best placed to determine if increased blood monitoring is required to rule out any potential neutropenia related to any viral infection. The decision to deviate from the national regulatory recommendations would be at the treating physician's discretion based on a benefit, risk assessment. Any deviation would be considered unlicensed and should be reported to the CPMS.

Q. Has there been any changes regarding Clozaril® monitoring requirements and dispensing?

A. At this time the regulatory authorities have not made any announcements to change the current national regulatory recommendations. Please contact CPMS if you are unsure what any of the mandatory monitoring requirements are or if you need guidance on safe dispensing of Clozaril®.

Q. Would the patient be able to have a break in sampling requirements given that they were providing consistent green results prior to the pandemic?

A. There is no data to support sampling breaks, we would always recommend adhering to the national regulatory recommendations. The decision to deviate from the national regulatory recommendations would be at the treating physician's discretion based on a benefit, risk assessment. Any deviation would be considered unlicensed and should be reported to the CPMS.

Q. Is it safe to continue clozapine if they develop fever or any other respiratory problems associated with Covid-19?

A. There is no contraindication to prescribing Clozaril® should the patient develop respiratory symptoms, but signs or symptoms of fever should be investigated for any potential neutropenia. Please see table 1 above for details of symptoms comparison.

As per the SmPC for Clozaril® (Clozapine):

"Patients with fever should be carefully evaluated to rule out the possibility of an underlying infection or the development of agranulocytosis. In the presence of high fever, the possibility of neuroleptic malignant syndrome (NMS) must be considered. If the diagnosis of NMS is confirmed, Clozaril should be discontinued immediately and appropriate medical measures should be administered."

Q. How long is it safe to defer a blood test if one cannot be obtaining by a patient's due date?

A. Please refer to the maximum cover periods as outlined in the table 2 above.

Q. If a patient has been diagnosed with COVID-19: is it safe to analyse the patient's blood sample via a PocHi?

A. All samples analysed via a PocHi should be considered as high risk and therefore all clinic staff analysing samples should continue follow normal procedure and wear correct PPE as instructed. Should there be a spillage of blood please follow your normal infection control procedures. No additional special considerations are necessary for patient's diagnosed with COVID-19.

We appreciate that these are unprecedented time and would encourage you to reach out to us should you have any further queries. Please contact CPMS for support by calling general enquires on 0845 769 8269 (If calling from UK) or (01) 662 1141 (If calling from Ireland) or email queries to cpms@mylan.co.uk