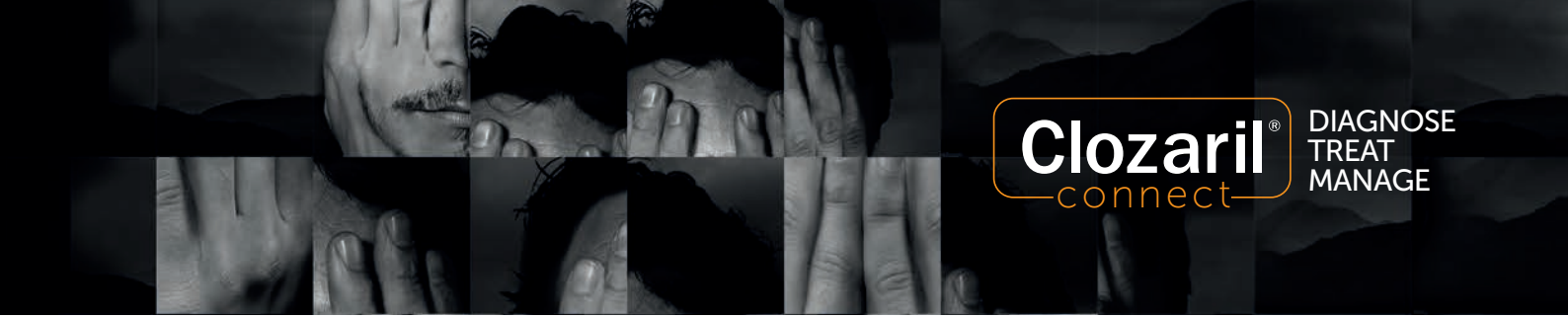


Clozapine, neutropenia and agranulocytosis, red alert management

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 healthcare professionals and should not be used as a patient information leaflet.

Background

The most well recognised side-effects of clozapine are neutropenia, defined as a neutrophil count of less than 1.5 x 10^9/L and agranulocytosis which is a neutrophil count of less than 0.5 x 10^9/L.

Leucopenia (a reduction in the number of white blood cells (WBC)) without neutropenia may also occur.

The Summary of Product Characteristics (SmPC) for Clozaril® (clozapine)[1,2] states that:

Leukopenia, decreased white blood cells (WBC) and neutropenia are common (≥1/100 but <1/10) reactions to Clozaril®. Agranulocytosis is an uncommon (≥1/1,000 but <1/100) reaction.

A study by Munro *et al* (1999) of 12760 Clozaril® Patient Monitoring Service (CPMS) patients found an overall incidence of 0.73% for agranulocytosis and 2.7% for neutropenia.[3]

After the first year on clozapine treatment the incidence of neutropenia and agranulocytosis is comparable to some phenothiazines.[4] A study by Atkin *et al* (1996) on a smaller cohort of the same CPMS population (6316 patients) showed that neutropenia occurred in 2.3% of clozapine patients in the first year and 0.5-0.7% in the 2nd to 4th years.[4] Comparable figures for agranulocytosis were 0.7% for the first year and 0.07% in the second year.[4]

Neutropenia and agranulocytosis are usually reversible on cessation of clozapine but agranulocytosis may result in sepsis and can be fatal.[1,2] When a monitoring service is not used, evidence suggests a mortality rate from agranulocytosis of 0.3%.[5] This is compared to a mortality rate of 0.01% if used in conjunction with the CPMS.[1,2]

Mechanism of Clozaril®-induced neutropenia/agranulocytosis

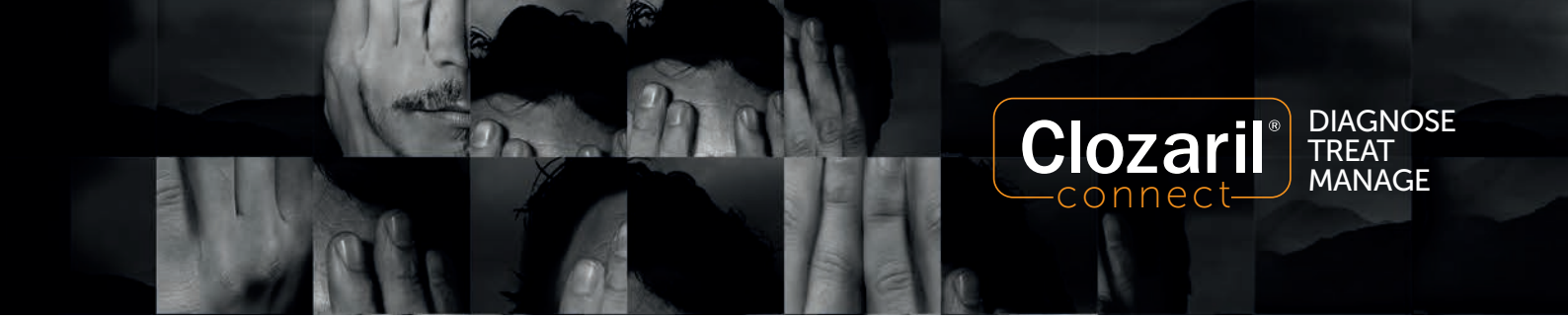
The mechanism of clozapine-induced neutropenia and agranulocytosis has not been established[6,7] although several mechanisms have been proposed. It is likely that different mechanisms are involved for mild-to-moderate neutropenia (absolute neutrophil count 0.5-1.5 x 10^9/L) and agranulocytosis (absolute neutrophil count less than 0.5 x 10^9/L).[8]

Risk factors

The peak risk period for neutropenia and agranulocytosis is between weeks 6-18 and the risk decreases after the first year of treatment. Approximately 70% of agranulocytosis cases occur within the first 18 weeks of treatment.[1,2]

Both neutropenia and agranulocytosis are idiosyncratic reactions and are not dose-related.[4,6]

Since the mechanism of clozapine-induced agranulocytosis is not fully understood, it is difficult to predict whether factors such as other medications could increase the risk. However, there are case reports of patients receiving carbamazepine and clozapine concurrently who developed agranulocytosis.[9,10]



Also, many patients who develop clozapine-induced agranulocytosis are receiving concomitant medication, often with drugs that are known to cause agranulocytosis themselves.[11] Hence, clozapine should not be used with other drugs that are known to depress bone marrow function as these could increase the risk of a patient on clozapine developing neutropenia or agranulocytosis.[1,2]

Long-acting depot antipsychotics should not be used with clozapine as they have the potential to depress bone marrow function and cannot be removed from the body in the event of neutropenia or agranulocytosis.[1,2]

Before starting Clozaril®...

Prior to treatment initiation, physicians must ensure, to the best of their knowledge, that the patient has not previously experienced an adverse haematological reaction to clozapine that necessitated its discontinuation.[1,2]

The following conditions are listed haematological contraindications to Clozaril®:

- Patients unable to undergo regular blood tests
- History of toxic or idiosyncratic granulocytopenia/agranulocytosis (with the exception of granulocytopenia/agranulocytosis from previous chemotherapy)
- History of Clozaril®-induced agranulocytosis
- Impaired bone marrow function
- Clozaril® treatment must not be started concurrently with drugs known to have a substantial potential for causing agranulocytosis; concomitant use of depot antipsychotics is to be discouraged

Patients with a history of primary bone marrow disorders may be treated only if the benefit outweighs the risk. They should be carefully reviewed by a haematologist prior to starting Clozaril®.

Monitoring

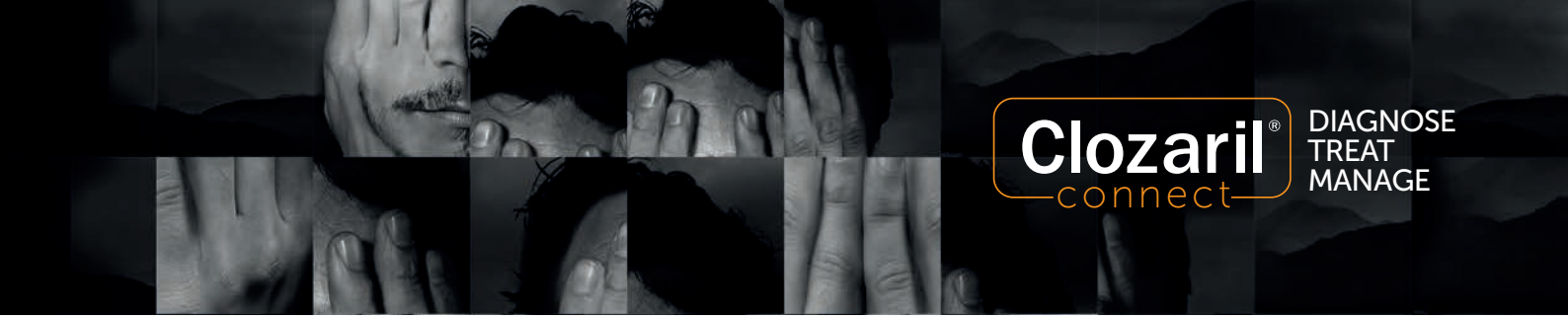
The UK Clozaril® Patient Monitoring Service (CPMS) was developed to manage the risk of agranulocytosis associated with clozapine.

The use of Clozaril® is restricted to patients who are registered with the Clozaril® Patient Monitoring Service. Prescribing physicians and lead pharmacists must also be registered.

Supply of Clozaril® is restricted to hospital and retail pharmacies registered with CPMS and Clozaril® is not sold to, or distributed through, wholesalers.

Prescribing and dispensing of clozapine should be by brand to prevent the disruption to effective monitoring that may be caused if patients switch brands.

To protect patient safety, patients should, at any one time, only be prescribed one brand of clozapine and only registered with the monitoring service connected to that brand.



All patients on Clozaril® must be monitored by the CPMS. Patients must have a normal pre-treatment WBC and differential (WBC ≥3.5 x 10^9/L, neutrophil count ≥2.0 x 10^9/L) and require regular haematological monitoring by the CPMS once they start Clozaril® treatment.[1,2]

It is mandatory to monitor the WBC and neutrophils at least weekly for the first 18 weeks, at least fortnightly from 19-52 weeks and at least four-weekly thereafter. Monitoring must continue for 4 weeks following discontinuation of Clozaril® or until haematological recovery has occurred.[1,2] Patients/carers should be warned to contact the doctor if infection develops, especially fever, sore throat or flu-like symptoms, and an urgent WBC and differential should be arranged.[1,2]

The CPMS categorise blood results according to the following colour-coded system:

Colour alert	WBC x 10^9/L	Neutrophils x 10^9/L
Green	>3.5	>2.0
Amber	3.0 – 3.5	1.5 – 2.0
Red	<3.0	<1.5

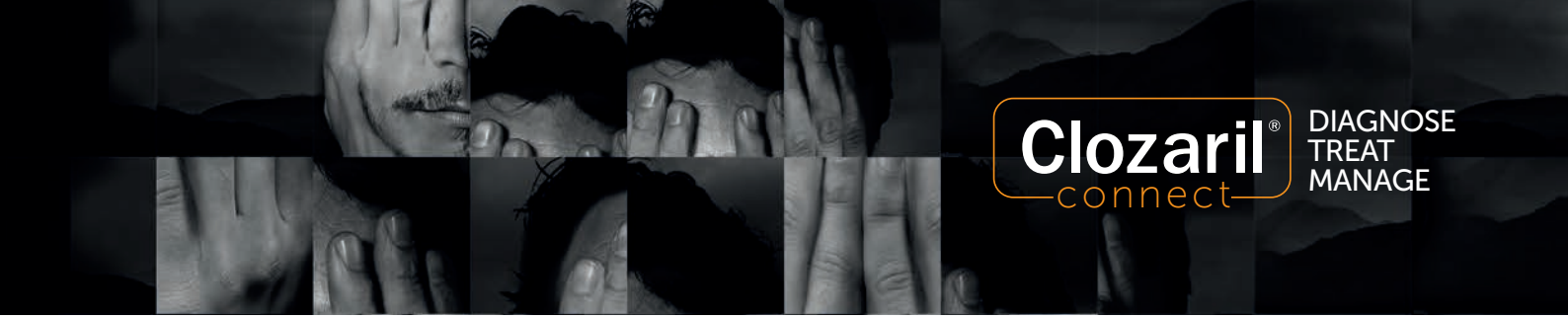
If a patient has an amber blood result a full blood count must be performed twice weekly until the count stabilises in this range or increases.

Weekly patients who have a blood result which is the lowest seen to date will be assessed by CPMS and an extra sample requested if necessary.

Management of a red alert

If a patient's WBC is less than 3.0 x 10^9/L and/or the neutrophil count is less than 1.5 x 10^9/L this is known as a **RED ALERT** and the following action must be taken:

- **STOP CLOZARIL® TREATMENT IMMEDIATELY**
- Check the patient for any signs of infection and contact the CPMS as soon as possible
- Arrange to take follow-up blood samples on the 2 days following the date of the red alert sample. If either of these follow-up blood counts is in the red alert range then the red alert is confirmed and Clozaril® is contraindicated
- If the red alert is confirmed **THE PATIENT MUST NOT RESTART CLOZARIL® TREATMENT**
- Full blood counts with differential should be performed **DAILY** whilst the blood counts remain in the red range, and the patient must be observed closely for signs of infection, such as a sore throat or fever
- Blood results should be reported to the CPMS as soon as they are available
- If antipsychotic medication is considered essential use a drug with a low potential to cause neutropenia and avoid depot preparations
- Review all other medication. Consider stopping any drugs which may reduce the WBC and/or neutrophil counts. If necessary introduce a more appropriate alternative



If the patient's neutrophil count falls to less than 1.0 x 10^9/L or the WBC falls to less than 2.0 x 10^9/L OR if the patient develops a fever it is extremely important to contact a haematologist, or failing this, a general medical physician, for advice regarding appropriate treatment for the patient. This may include transferring the patient to a ward with facilities for the care of neutropenic patients.

Granulocyte colony-stimulating factor (G-CSF) or granulocyte-macrophage colony stimulating factors have been used in the management of clozapine-induced agranulocytosis,[12,13,14] although this is not a licensed indication.

Clozapine rechallenge is contraindicated in any patients who have experienced a red alert. All patients with a confirmed red result will be entered onto the Central Non-Rechallenge Database (CNRD UK or CNRD Ireland) to ensure that they are not inadvertently re-exposed to clozapine from alternative suppliers.

Prescribers are encouraged to keep a record of all patients' blood results and to take any steps necessary to prevent the patient being rechallenged in error in the future.

Effect of sudden discontinuation of Clozaril®

When a patient has a red alert it is essential to stop clozapine immediately. Careful psychiatric monitoring of the patient is essential since symptoms may recur quickly.

Stopping clozapine suddenly can lead to physical and mental withdrawal effects which may occur within 2-3 days and usually within the first 2 weeks.[15] Patients may experience a rapid deterioration in their mental state with rebound psychosis.[16] In addition, abrupt withdrawal of clozapine has been associated with symptoms such as nausea, vomiting, diarrhoea, headache, restlessness, agitation and sweating[15] and it has been suggested that these are a result of cholinergic rebound since clozapine has strong anticholinergic action.[16] Discontinuation of clozapine for reasons other than a red alert, or other serious side-effect, should be done gradually to minimise the risk of withdrawal effects.

Red alert confirmation procedure

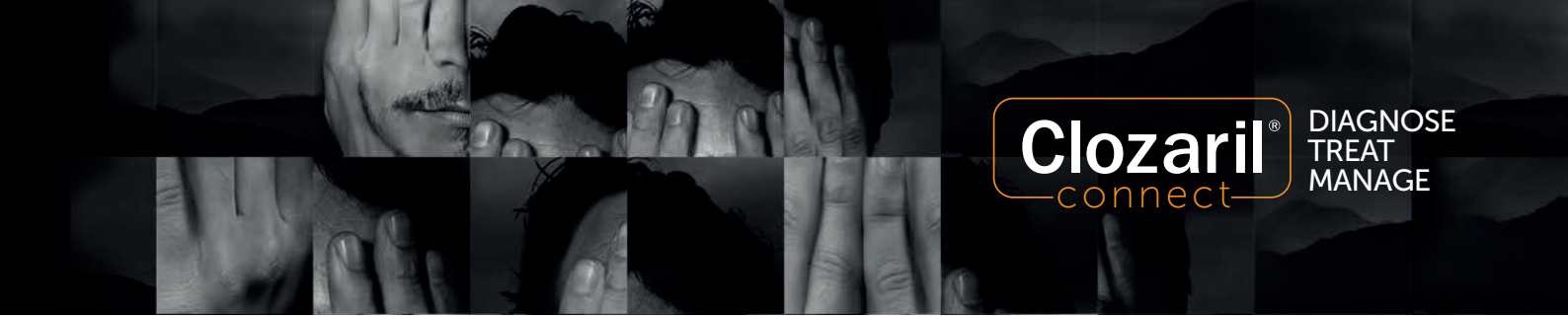
The SmPC for Clozaril® states: Immediate discontinuation of Clozaril® treatment is mandatory if either the WBC count is less than 3.0x10^9/l or the ANC is less than 1.5x10^9/l during Clozaril® treatment. WBC counts and differential blood counts should then be performed daily and patients should be carefully monitored for flu-like symptoms or other symptoms suggestive of infection. Confirmation of the haematological values is recommended by performing two blood counts on two consecutive days; however, Clozaril® should be discontinued after the first blood count.

If a patient has a red result, Clozaril® treatment must be stopped immediately and the patient checked for any signs of infection. 2 follow-up blood samples are taken; one on the day following the red result and the other the day after that.

The red alert is **confirmed** if one of the follow-up blood counts is in the red range, after which follow-up samples are taken for until the count recovers.

If neither follow-up sample is red then the red alert is **unconfirmed** and the patient may resume Clozaril® treatment. This may be at the normal dose, if the break in treatment is less than 48 hours, or with retitration from 12.5mg, if over 48 hours. **The patient must remain off Clozaril® until the second follow-up result is obtained**.

Following an **unconfirmed** red additional monitoring is needed as a precaution if the follow-up results are either amber or green, but still low for that patient, whether Clozaril® is restarted or not.



Clozaril® connect

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Patients with benign ethnic neutropenia

Patients with diagnosed benign ethnic neutropenia (BEN) may be considered for treatment with Clozaril®, with the agreement of a haematologist. The CPMS colour-coded ranges are all decreased by 0.5 x 109/L for these patients, hence a red alert for a patient with BEN is WBC <2.5 x 10^9/L and/or neutrophils <1.0 x 10^9/L.

Any patients who develop a red or amber alert within the modified ranges will be treated as per standard CPMS procedures.

References

1. Clozaril Summary of Product Characteristics (online). Mylan Products Limited. <http://www.medicines.org.uk/emc/> (Accessed on 26/04/2018).
2. Clozaril Summary of Product Characteristics (online). BGP Products Ireland Limited. <http://www.medicines.ie/> (Accessed on 26/04/2018).
3. Munro J *et al.* Active Monitoring of 12760 Clozapine Recipients in the UK and Ireland. *Br J Psychiatry* 1999; **175**: 576-580.
4. Atkin K *et al.* Neutropenia and Agranulocytosis in Patients Receiving Clozapine in the UK and Ireland. *Br J Psychiatry* 1996; **169**: 483-488.
5. De la Chapelle A *et al.* Clozapine-Induced Agranulocytosis: A Genetic and Epidemiologic Study. *Hum Genet* 1977; **37**: 183-94.
6. Pirmohamed M and Park K. Mechanism of Clozapine-Induced Agranulocytosis. Current Status of Research and Implications for Drug Development. *CNS Drugs* 1997; **2**: 139-158.
7. Mendelowitz AJ *et al.* Clozapine-Induced Agranulocytosis. Risk Factors, Monitoring and Management. *CNS Drugs* 1995; **4**: 412-21.
8. Gerson SL. Clozapine – Deciphering the Risks. *New England Journal of Medicine* 1993; **329**: 204-205.
9. Gerson SL *et al.* Polypharmacy in Fatal Clozapine-Associated Agranulocytosis. *Lancet* 1991; **338**: 262.
10. Junghan U, Albers M and Woggon B. Increased Risk of Haematological Side-Effects in Psychiatric Patients Treated with Clozapine and Carbamazepine. *Pharmacopsychiatry* 1993; **26**: 262.
11. Krupp P and Barnes P. Clozapine-Associated Agranulocytosis: Risk and Aetiology. *Br J Psychiatry* 1992; **160** (suppl 17): 38-40.
12. Chengappa KNR *et al.* The Treatment of Clozapine-Associated Agranulocytosis With Granulocyte Colony-Stimulating Factor (G-CSF). *Psychopharmacology Bulletin* 1996; **32**: 111-121.
13. Gerson SL *et al.* G-CSF and the Management of Clozapine-Induced Agranulocytosis. *J Clin Psychiatry* 1994; **55** (suppl B): 139-42.
14. Chin-Yee I, Bezchlibnyk-Butler K and Wong L. Use of Cytokines in Clozapine-Induced Agranulocytosis. *Canadian Journal of Psychiatry* 1996; **41**: 280-284.
15. Verghese C *et al.* Clozapine Withdrawal Effects and Receptor Profiles of Typical and Atypical Neuroleptics. *Biological Psychiatry* 1996; **39**: 135-138.
16. Shiovitz TM *et al.* Cholinergic Rebound and Rapid Onset Psychosis Following Abrupt Clozapine Withdrawal. *Schizophr Bull* 1996; **22**: 591-5.

Clozaril® (clozapine)

CLOZARIL® Clozapine PATIENT MONITORING SERVICE

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