Optimising Treatment Management with Clozaril®

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.

This factsheet will cover:

- Initiating treatment with Clozaril®
- Use of Clozaril® in over 60-year-olds
- Treatment compliance with Clozaril®
- Therapeutic drug monitoring with Clozaril®
- Overdose management with Clozaril®
- Discontinuing treatment with Clozaril®

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Initiating treatment with Clozaril®

Background

As per the Summary of Product Characteristics (SmPC) for Clozaril® (Clozapine):[1,2]

The UK/IRL 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 CPMS. Prescribing physicians and lead pharmacists must also be registered with CPMS. Supply of Clozaril® is restricted to hospital and retail pharmacies registered with CPMS.

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.

It is mandatory to monitor the WBC and neutrophils at least weekly for the first 18 weeks, at least fortnightly from weeks 19-52 and at least four-weekly thereafter. Monitoring must continue for 4 weeks following discontinuation of Clozaril® or until haematological recovery has occurred. 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.

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

Colour Alert*	WBC (x10^9/L)	Neutrophils (x10^9/L)
Green	≥3.5	≥2.0
Amber	3.0 to 3.49	1.5 to 1.99
Red	<3.0	<1.5

**For normal (non-special) monitored patients*

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. If a patient has a Red Alert blood result, it is best to contact CPMS immediately for advice. Please refer to the Clozaril® and Red Alert management factsheet for further information. 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.

The SmPC for Clozaril®[1,2] also includes the following information regarding initiation of treatment with Clozaril®:

Treatment-resistant schizophrenic patients

Starting therapy 12.5mg once or twice on the first day, followed by 25mg once or twice on the second day. If well tolerated, the daily dose may then be increased slowly in increments of 25 to 50mg in order to achieve a dose level of up to 300mg/day within 2 to 3 weeks. Thereafter, if required, the daily dose may be further increased in increments of 50 to 100mg at half-weekly or, preferably, weekly intervals.

Switching from a previous antipsychotic therapy to clozapine

It is generally recommended that Clozaril® should not be used in combination with other antipsychotics. When Clozaril® therapy is to be initiated in a patient undergoing oral antipsychotic therapy, it is recommended that the other antipsychotic should first be discontinued by tapering the dosage downwards.

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

The starting dose must not exceed 12.5mg/day, taken in the evening. Subsequent dose increases must be by 12.5mg increments, with a maximum of two increments a week up to a maximum of 50mg, a dose that cannot be reached until the end of the second week. The total daily amount should preferably be given as a single dose in the evening.

Patients aged 60 years and older

Initiation of treatment is recommended at a particularly low dose (12.5mg given once on the first day), with subsequent dose increments restricted to 25mg/day.

Before initiating clozapine

Prior to starting clozapine, all patients must be registered with the CPMS and all patients must have a normal pre-treatment white blood cell (WBC) count and absolute neutrophil count (ANC) (WBC ≥3.5 x10^9/L, neutrophil count ≥2.0 x10^9/L) performed within 10 days prior to initiating Clozaril® treatment. Physicians must ensure, to the best of their knowledge, that the patient has never had a WBC blood count <3.0x10^9/L and/or a neutrophil count <1.5x10^9/L and not previously experienced an adverse haematological reaction to clozapine that necessitated its discontinuation.[1,2]

The following conditions are listed haematological contraindications to Clozaril®:[1,2]

- 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®. Patients who have low WBC counts because of benign ethnic neutropenia (BEN) should be given special consideration and should only be started on clozapine with the agreement of a haematologist. These patients can be registered with the CPMS and monitored under modified parameters. For further information, please see factsheet number 7 - Clozaril® and benign ethnic neutropenia.

Before initiating Clozaril® therapy patients should have a blood test, a medical history check and a physical examination. Patients with history of cardiac illness or abnormal cardiac findings on physical examination should be referred to a specialist for other examinations that might include an ECG, and the patient treated only if the expected benefits clearly outweigh the risks. The treating physician should consider performing a pre-treatment ECG.

For full information on listed contraindications and special warnings and precautions, please refer to the SmPC for Clozaril®.[1,2]

Use of Clozaril® in over 60-year-olds

Background

The SmPC for Clozaril®[1,2] states that Clozaril® is licensed for psychotic disorders occurring during the course of Parkinson's disease in cases where standard treatment has failed.

Clozapine has been shown to be effective in treating elderly patients with schizophrenia.[3,4] However, patients aged 60 years and older may generally be at more risk of adverse effects from medications due to the normal effects of ageing and the fact that they may be more likely to have medical problems. One study reported, 80% of elderly patients have at least one chronic disease[5] and drug interactions are also more likely due to concomitant use of other medications.[5]

The ageing process can affect absorption, distribution, metabolism and clearance of drugs.[5] Drug absorption may be modified by reductions in both gastric acidity and splanchnic blood flow. Lean body mass and total body size decrease with ageing which means that there is a wider distribution of antipsychotics, and other fat-soluble drugs, which may take longer to clear.[5] A decline in liver and kidney function due to ageing may slow the elimination of drugs.[5]

Patients aged 60 years and older are particularly susceptible to extrapyramidal symptoms and tardive dyskinesia secondary to antipsychotics.[5] One small study evaluating clozapine usage in the elderly by Frankenburg *et al* (1994) demonstrated that pre-existing extrapyramidal symptoms and tardive dyskinesia improved after starting clozapine.[6] Another study evaluating patients with Parkinson's disease demonstrated improvements in parkinsonian tremor.[7]

Key side effects of clozapine to note in patients aged 60 years and older

Orthostatic hypotension: Patients aged 60 years and older may be more susceptible to clozapine-induced orthostatic hypotension and particularly if they have compromised cardiovascular function.[1,2] The risk of orthostatic hypotension is higher in patients who are taking other drugs which may cause this and these include antihypertensives and anti-anginal agents.[8] Concomitant use of additional medications, including benzodiazepines which impair balance,[9] may increase the risk of falls.

Anticholinergic effects: Patients aged 60 years and older may be particularly susceptible to the anticholinergic effects of clozapine, such as urinary retention and constipation.[1,2] Clozapine should be used with caution in patients with prostatic enlargement and narrow angle glaucoma due to its anticholinergic effects.[1,2]

Management

In patients aged 60 years and older it is particularly important to consider any concomitant medical conditions prior to starting Clozaril® and review other medications if appropriate.

The recommended dose for clozapine in patients aged 60 years and older is 12.5mg given once on the first day, with subsequent dose increments restricted to 25mg/day. Slow titration of clozapine dose is recommended and, if side effects occur, it may be necessary to reduce the dose and/or speed of titration.[1,2] As the dose of clozapine is increased, consideration should be given to the fact that patients aged 60 years and older, especially female ones, may have higher plasma levels than younger ones.[10]

Chengappa *et al* (1995) reviewed the records of 12 female patients with psychoses all over 60 years of age, who had received clozapine.[8] Their findings confirmed the need for low dose initiation and slow titration. Patients who were titrated slowly tolerated the drug relatively well and remained on it, with clinical improvement over time whereas four of the six patients on standard titration experienced problems with postural hypotension and discontinued the drug. In another review paper, Barak *et al* (1999) noted that elderly patients were managed on much lower maintenance doses than the average, with a mean dose in their review of 134mg/day and that most adverse events occurred in the first 90 days of treatment.[4]

In patients with Parkinson's disease monitoring of standing and supine blood pressure is necessary during the first weeks of treatment.[1,2]

In summary

Treatment with clozapine has been shown to be effective in patients aged 60 years and older in treatment resistant schizophrenia and psychosis occurring in Parkinson's disease. For each patient it is important to undertake a risk-benefit analysis to assess suitability. Careful management of dose and titration rates with monitoring for adverse effects, particularly in the early stages of treatment, may reduce the incidence and severity of side-effects.

Treatment compliance with Clozaril®

Background

Compliance may be defined as the extent to which a person's behaviour coincides with the medical advice he/she has received.[11] Non-compliance is an issue in general medicine and psychiatry and is particularly likely when the aim of treatmentis to prevent symptom recurrence or illness relapse. The rate of non-compliance in schizophrenia has been estimated at 33%[12] although some studies give figures as high as 80% for non-compliance with antipsychotic medication.[13]

Compliance with medication may be total, partial, nil or erratic, and non-compliance in schizophrenia may be refusal of treatment, discontinuation of treatment or erratic taking of medication. The reasons for non-compliance in patients with schizophrenia vary and may include depression/lack of motivation, side-effects, forgetfulness, comorbid substance abuse and lack of insight or denial of illness.[14] Severity of illness may also be significant since studies have found that patients with more severe psychopathology are less likely to comply with treatment.[15]

Non-compliance can be detected by several means but it is difficult to get an accurate picture. Patient self-reporting is often unreliable since patients may deliberately give false information. Pill counting may be used but the patient may have the correct number of pills left when they have not taken the medication, and biological analysis such as plasma monitoring may also be of limited use as the patient may be compliant only in the period shortly before the blood test.[16]

For the patient, the direct consequence of non-compliance is that they may relapse and experience return of symptoms, which may in turn lead to hospital re-admission. Indirect costs of relapse include personal suffering, high morbidity, mortality and an overall reduction in quality of life for the patient and their family members.[16] From a healthcare professional's perspective, the consequences of lack of compliance may include all the costs of a patient deteriorating, for example, re-hospitalisation, additional clinic and staff resources and the cost of additional drugs.

Until all the barriers to compliance are apparent it is difficult to change the patient's behaviour. However, one of the most important positive factors is the existence of a good relationship between the patient and the healthcare professional and establishing rapport and trust is the first step to changing the patient's attitude to their medication.

Clozapine and compliance rates

It has been shown in several studies that patients stabilized on clozapine are largely content with their treatment and as a result adherence to treatment is good.[17,18] In a survey completed by 570 patients, the majority (62.1%) rated clozapine as much better than their previous treatment, with only 2.7% rating it as slightly or much worse.[17] More importantly from a compliance perspective, 87% of patients in the same study felt that the advantages of clozapine outweighed the disadvantages and 88% of patients stated that they preferred to stay on clozapine rather than change to a different drug.

Compliance with clozapine has been shown to be better than with chlorpromazine or with haloperidol. In a comparative study with chlorpromazine, Claghorn et al (1987) showed that psychotic inpatients treated with clozapine had fewer discontinuations due to side-effects.[19] Rosenheck *et al* (2000) also demonstrated greater continuation with clozapine when compared with haloperidol.[20]

Use of clozapine plasma levels to detect non-compliance

Checking plasma clozapine and norclozapine levels and the clozapine:norclozapine ratio may help in detecting recent clozapine non-compliance. The assay should be a trough sample taken either immediately before a normal morning dose or in the morning after an evening dose. The clozapine:norclozapine ratio should normally be in the range of 0.5-2.5. A low clozapine level and a ratio less than 0.5 may be suggestive of non-compliance within the last 24 hours.[21]

Suggestions to improve compliance with clozapine

To improve compliance, effort should be channelled into supporting patients through the early stages of treatment until the efficacy becomes apparent, early side-effects diminish and a blood taking routine is established. Assess the patient's attitude to therapy to establish the barriers to compliance and develop an individual care programme including an action plan to be used if symptoms start to return. Make sure that the patient knows who to contact for further advice or in case of emergency. Discuss any misconceptions that the patient may have. Stress the benefits of treatment and check the patient is aware of the relationship between non-compliance and relapse. Relate being well to staying out of hospital. Discuss the patient's expectations and compare symptoms to those they had six months ago.

Check that the dose has been optimised and educate the patient on the expected time to response. Treat anxiety or depression where appropriate. Ensure that the current treatment regimen is simple and that explicit written instructions are provided. Use monotherapy wherever possible to reduce the complexity of treatment and reduce the likelihood of interactions. Compliance aids such as monitored dosage systems (MDS) may be useful for some patients. Other strategies include keeping the medication in a visually prominent place, or phone calls or visits to remind patients to take their medication.

Assess the clinic routine and arrangements for blood monitoring and dispensing. If distance to the clinic or waiting times are a problem, consider whether blood sampling at a GP surgery is possible. Create a relationship where the patient feels that they can report side-effects and assess the impact on the patient. For dose related side-effects consider reducing or splitting the dose. Check plasma levels where appropriate. Consider the patient's level of cognitive function since cognitive impairment may reduce the ability to remember to take medication. Provide support and education at a correct level for the patient. Check the patient's support network and provide information and education for carers if necessary.

One strategy which has been effective in improving compliance is compliance therapy, where cognitive-behavioural therapy and motivational interviewing are used to demonstrate the risks and benefits of accepting antipsychotic treatment. Kemp *et al* (1996) compared this with non-specific supportive counselling and found that patients who received compliance therapy had significantly improved compliance from baseline.[22] Another study demonstrated that compliance therapy was more cost effective than non-specific counselling.[23]

Specific factors affecting compliance with clozapine

Time to first response- Studies have shown up to 30% of patients will show a response by six weeks and 60% will have shown a response by twelve months.[24] Patients should be reassured that it may take some time for clozapine to be fully effective. Looking back with the patient over the course of treatment will enable them to appreciate improvements in functioning and motivate them to carry on until they experience a full effect. The SmPC for Clozaril® recommends that treatment should be continued for at least six months.[1,2]

Blood monitoring- Patients on clozapine require regular blood monitoring and for the majority of them this will require frequent attendance at an outpatient clinic. Although the primary objective of blood monitoring is to detect neutropenia, it also assures regular contact between the therapy team and the patient, which offers frequent opportunity to assess progress and to allay concerns the patient may have. It also provides an ongoing general health check, helps in the management of side-effects, and enables early detection of patients who may be defaulting from treatment.

Studies have shown that patients generally understand the need for blood monitoring. In a survey of patients taking clozapine, 80% knew why blood tests were needed and 64% felt they were a necessary part of treatment. Less than 2% of patients wanted to stop their therapy due to the blood monitoring.[17] Other studies have found that although patients may object to blood monitoring at the outset, this diminishes over time as they experience the benefits of treatment.[18]

Patients who do not accept the need for blood monitoring easily at the outset may benefit from early referral to the local clozapine clinic, which may help to allay any concerns the patient has and also help the patient to gain confidence from meeting patients established on clozapine.

Side-effects

Clozaril® can cause a range of side-effects, many of which diminish over time. The most common side-effects are drowsiness/sedation, dizziness, tachycardia, constipation and hypersalivation. Please refer to the SmPC for Clozaril® for a full list of potential side effects.[1,2] It is suggested to follow a few basic principles to minimise these effects:

Tailoring therapy – many side-effects, such as hypotension and tachycardia, are dose-related. By starting with a low dose and titrating the dose slowly the effects of these dose-related side-effects can be reduced. In the case of hypotension, giving the largest part of the dose at night can reduce the effect on blood pressure.

Proactive approach – it is necessary to take a proactive approach if side-effects, such as weight gain and constipation, are to be avoided. Constipation can be a potentially serious side-effect if left untreated and must be taken seriously. Patients should be counselled prior to commencement and given advice on diet, fluid intake and the importance of seeking advice from their doctor if they become constipated. Similarly, by counselling patients on the importance of a healthy diet and exercise, weight gain may be reduced.

Monitoring – although the only mandatory requirements are monitoring of the white cell and neutrophil counts, many units conduct baseline and routine monitoring of other parameters such as pulse, BP, ECG, U&Es and LFTs. This can facilitate the early detection of adverse events and provides a baseline should problems arise later in therapy.

For further information regarding side-effect management please contact your local clinical pharmacist or CPMS.

Therapeutic drug monitoring with Clozaril®

Background

Although antipsychotic efficacy with Clozaril® can be expected with doses of 200 to 450mg/day, the maximum licensed dose extends up to 900mg/day.[1,2] Clozapine dose is normally adjusted according to the patient's clinical response and side-effects. Therapeutic Drug Monitoring (TDM) of clozapine is now advised in certain clinical situations such as when:[25]

- A patient stops smoking or switches to an e-cigarette[1,2,25]
- Concomitant medicines may interact to increase blood clozapine levels[25]
- A patient has pneumonia or other serious infection[25]
- Poor (reduced) clozapine metabolism is suspected[1,2,25]
- Toxicity is suspected[1,2,25]

In addition, it may be helpful to measure 'baseline' levels during successful therapy in case problems occur later in treatment. If blood clozapine level monitoring is carried out, this should be in addition to the required blood tests to manage the risk of agranulocytosis.[25] Refer to the SmPC of Clozaril® for other important warnings, interactions and recommendations.[1,2]

Measurement of plasma clozapine and norclozapine, the main metabolite of clozapine, is normally only useful for patients who have been taking clozapine for at least a month although TDM earlier than this may be useful to detect patients who are poor metabolisers of the drug.[26] The best practice to obtain an accurate level, the patient should have been on a steady dose for at least a week (4-5 plasma half-lives)[21] and the sample taken either immediately before a normal morning dose or in the morning after an evening dose ('trough' sample).[21] There should be a minimum of 6 hours since the last dose.[26] The sample should be collected in an EDTA tube and sent to the appropriate toxicology laboratory. It is important to note the time of sampling with respect to the time of the last dose since this may impact interpretation of the result.

Plasma assay kits can be ordered from the CPMS' Non-Drugs Supplies partner – PELI Cool, by calling +44 (0) 845 769 8269 and selecting Option 4.

Establishment of clozapine dose and management of side-effects

There is a wide variation in the clozapine daily dose with some patients managed at 200mg or less while others are on the maximum 900mg. Similarly, some patients will show little or no evidence of adverse effects at 900mg/day, whilst others may experience adverse effects at much lower doses. Adverse effects that may be dose-related include seizures, drowsiness, hypersalivation, tachycardia, postural hypotension and constipation.[21] The risk of clozapine side-effects can be minimised by using a slow titration and, if side-effects occur, a dose reduction may alleviate the problem. Neutropenia/agranulocytosis is not proven to be dose related.[27]

Several studies have suggested that efficacy in Treatment Resistant Schizophrenia may be associated with 'trough' clozapine concentrations of 0.35mg/l or above.[10,26] An upper limit for plasma clozapine has not been established clearly, although it has been suggested that trough concentrations above 0.6mg/l may indicate increased risk of adverse effects.[26]

Use of clozapine plasma levels to detect non-compliance

When checking clozapine and norclozapine plasma levels, the clozapine:norclozapine ratio may help in detecting clozapine non-compliance although it is important to remember that the plasma level reflects adherence in the last few days only.

Couchman et al reviewed the results from a clozapine TDM service between 1993-2007. They found that although clozapine and norclozapine plasma levels were generally related to dose there was a large variation. Their results are shown in Table 1.4. Attempts to define a therapeutic range for plasma clozapine are difficult because of the increased response observed with duration of therapy in some patients and the fact that there is wide (50-fold) variation between patients in the rate at which they metabolise clozapine.[26]

Table 1. Plasma clozapine and norclozapine concentrations (median, 10th-90th percentile) and prescribed dose in 85,958 samples in which clozapine and norclozapine were detected[26]

Clozapine dose (mg/day)	Number of samples	Clozapine (mg/l)	Norclozapine (mg/l)
50-150	2,632	0.20 (0.06-0.55)	0.13 (0.05-0.28)
151-250	8,338	0.30 (0.09-0.72)	0.19 (0.08-0.38)
251-350	18,794	0.34 (0.13-0.79)	0.23 (0.10-0.46)
351-450	20,677	0.40 (0.16-0.90)	0.27 (0.12-0.53)
451-550	14,504	0.45 (0.19-1.00)	0.31 (0.15-0.60)
551-650	10,509	0.50 (0.22-1.08)	0.35 (0.16-0.67)
651-750	5,507	0.54 (0.23-1.16)	0.37 (0.18-0.72)
751-850	3,129	0.57 (0.25-1.25)	0.39 (0.19-0.80)
851	1,868	0.55 (0.25-1.24)	0.41 (0.19-0.84)

The role of norclozapine and the clozapine:norclozapine ratio

Plasma norclozapine does not appear important when assessing clinical effect but can be useful when assessing partial adherence. If both the plasma clozapine and norclozapine are below the bottom tenth percentile (Table 1) this suggests recent poor adherence, although it is possible that the patient may metabolise the drug extremely quickly (typically young male smokers).

The clozapine:norclozapine ratio has been found to average 1.3 and should normally be in the range of 0.5-2.5.[21] A ratio of >2.5 may be due to incomplete absorption of the last clozapine dose prior to collection of the sample or indicate that metabolism of clozapine has become saturated. This may be because the prescribed dose is too high for the patient or due to inhibition of clozapine metabolism as a result of concomitant drug therapy (i.e drug - drug interaction). A clozapine:norclozapine ratio of <0.5 may indicate poor compliance within the last 24 hours, or that the patient may benefit from more frequent dosing.[21]

Cigarette smoking and caffeine intake

Both cigarette smoking and caffeine may affect the plasma level of clozapine.[1,2] It is important to take both smoking habits and caffeine intake into account when starting patients on clozapine and when a patient who has previously done well on clozapine starts to report side-effects.

Cigarette smoking

Tobacco smoke contains polycyclic aromatic hydrocarbons which induce CYP1A2, the enzyme responsible for clozapine metabolism.[28] As a result, smoking increases clozapine metabolism and smokers generally have a lower plasma concentration than non-smokers. Smoking cessation has been reported to increase clozapine levels considerably with figures of up to 70% reported in the literature.[29] In a study of 44 patients (10 non-smokers and 34 smokers) Seppala *et al* (1999) found that both clozapine and norclozapine levels were around 40% lower in the smokers than the non-smokers.[30]

A study by Haslemo *et al* (2006) investigated the dose-dependent effect of cigarette smoking on the plasma level of clozapine and concluded that 7-12 cigarettes per day is likely to be enough for maximum induction of clozapine metabolism.[31]
For patients who smoke and who are not responding to clozapine treatment it may be worth checking the plasma level to ensure that the clozapine dose is high enough to obtain a therapeutic effect. Alternatively, if a patient stops smoking there may be an increase in the clozapine plasma level which can lead to an increase in adverse events, some of which may be serious. This effect can occur very quickly.[10] Case reports have described the occurrence of clozapine-induced seizures in men, who were previously heavy smokers, after they stopped smoking over a short period of time.[32-34] One of these men also developed stupor and went into a coma.[32]

It is important to consider the need to adjust the clozapine dose quickly in patients who stop smoking during treatment[10,35] although possible exacerbation of psychotic symptoms must also be considered. Smoking cessation may be particularly relevant when patients are admitted to hospitals which have a ban on smoking. Plasma level monitoring can be used to establish an appropriate clozapine dose.

Nicotine replacement therapy (NRT) in the form of patches, chewing gum or e-cigarettes do not affect clozapine plasma levels, hence a patient who stops smoking with the aid of NRT is at the same risk of increased levels as one who stops smoking without using NRT.

Caffeine

Caffeine, which is an inhibitor of CYP1A2, may increase clozapine levels leading to an increased risk of adverse effects.[1,2] Since the plasma concentration is increased by caffeine intake and decreased by nearly 50% following a five-day caffeine free period, dosage changes of clozapine may be necessary when there is a change in caffeine drinking habit.[1,2] Products which contain caffeine often include coffee, tea, energy drinks, cola and chocolate.

Infection and inflammation

It has been suggested that infection or inflammation may inhibit cytochrome P450 1A2 leading to a reduction in clozapine metabolism and possible toxicity.[36,37] Raaska (2002) and Leung (2014) each describe cases where plasma clozapine levels have increased during infection, with patients showing signs of toxicity.[36,37]

Interpretation of plasma level results

To understand the plasma level result for a patient, consideration should be given to the following points:

- Whether the patient has been on a steady dose for at least a week to allow clozapine to reach a steady state[21]
- Check that the sample was collected at the appropriate time to give a trough level
- Is the patient responding to clozapine and are they suffering with any side-effects?
- Plasma level results may be affected by several factors including age, sex and weight
- Is the patient a smoker and has there been any change in smoking habit recently?
- Is the patient on any other drugs and have there been any changes to medication recently? For further information with respect to drugs which may affect clozapine plasma levels please consult your local clinical pharmacist or contact the CPMS
- Does the patient have any issues with liver function which may be affecting clozapine metabolism?
- Has the patient had clozapine levels checked before? If so, the laboratory may have a record of previous levels for comparison
- Has the patient been unwell with inflammation or infection?

Overdose management with Clozaril®

Background

The SmPC for Clozaril®[1,2] states that: In cases of acute intentional or accidental Clozaril® overdose for which information on the outcome is available, mortality to date is about 12%. Most of the fatalities reported were associated with cardiac failure or pneumonia caused by aspiration and occurred at doses above 2000mg.[1,2]

Patients with treatment-resistant schizophrenia have a higher incidence of suicide compared to the general population.[38] Both intentional and accidental overdoses have been reported with clozapine. Fatalities have also been reported in patients following ingestion of only 1000mg of clozapine[39] or with post overdose plasma levels of approximately 2mg/L.[40] A few adults, especially those not previously exposed to clozapine, have suffered life-threatening comatose conditions with doses as low as 400mg and, in one case, to death.[1,2,38] Seizures have been reported to occur in patients with plasma clozapine levels greater than 1mg/L following overdose.[41]

Conversely, there are reports of patients recovering from overdoses in excess of 10,000mg[1,2,38] or following plasma levels greater than 9mg/L (optimum therapeutic range 0.35-0.6mg/L).[42]

Signs and symptoms of clozapine overdose

All of the side-effects associated with clozapine at therapeutic doses may be seen following overdose except those seen with long-term therapy only, for example: constipation, weight gain and agranulocytosis.[39] In addition, altered respiratory function and aspiration may be observed and these are seldom seen at therapeutic doses. Pulmonary oedema is not a recognised side-effect but has occurred following overdose.[39] The central nervous, cardiovascular and respiratory systems are most commonly affected following acute overdose. Delayed reactions may be seen, including the late occurrence or recurrence of cardiac arrythmias.[39]

Other side effects mentioned in the SmPC of Clozaril® include: drowsiness, lethargy, areflexia, coma, confusion, hallucinations, agitation, delirium, extrapyramidal symptoms, hyperreflexia, convulsions; hypersalivation, mydriasis, blurred vision, thermolability; hypotension, collapse, tachycardia, cardiac arrhythmias; aspiration pneumonia, dyspnoea, respiratory depression or failure.[1,2]

Aspiration of ingested food may occur as a consequence of acute overdosage.[1,2]

Management

Any patient who has taken a clozapine overdose, or is suspected to have done so, should be sent to the nearest Accident and Emergency unit immediately or transferred to a general medical ward with facilities for cardiac monitoring.

There are no specific antidotes for clozapine. Gastric lavage and/or administration of activated charcoal may be appropriate within the first 6 hours after the ingestion of the drug. Activated charcoal may reduce absorption in the gastrointestinal system and is more effective if it is given soon after ingestion of the overdose.[1,2] Peritoneal dialysis and haemodialysis are unlikely to be effective following Clozaril® overdose.[1,2]

Patients should be given symptomatic treatment under continuous cardiac monitoring with surveillance of respiration, monitoring of electrolytes and acid-base balance.[1,2] For hypotension, the use of epinephrine should be avoided due to the possibility of a 'reverse epinephrine' effect[1,2] (patients treated with Clozaril® may paradoxically experience hypotension when administered epinephrine).

Close medical supervision is necessary for at least 5 days following clozapine overdose due to the possibility of delayed reactions.[1,2]

Discontinuing treatment with Clozaril®

Background

The SmPC for Clozaril®[1,2] states: In the event of planned termination of Clozaril® therapy, a gradual reduction in dose over a 1 to 2-week period is recommended. If abrupt discontinuation is necessary, the patient should be carefully observed for the occurrence of withdrawal reactions. In patients with Parkinson's Disease a gradual reduction in dose by steps of 12.5mg over a period of at least one week (preferably two) is recommended.

Treatment must be discontinued immediately in the event of neutropenia or agranulocytosis. In this situation, careful psychiatric monitoring of the patient is essential since symptoms may recur quickly.

Before discontinuing Clozaril® treatment, it may be worth considering whether the following points are relevant:

- Inadequate treatment duration – some patients take up to 12 months to respond[24]
- Inadequate dose – some patients require 900mg/day. Plasma clozapine concentrations provide guidance on required dose. A threshold of 0.35mg/L is generally accepted for good therapeutic response[41]
- Poor compliance – with medication or blood tests
- Side-effects – many side-effects can be managed successfully, please contact your local clinical pharmacist for advice

Suggested steps on how to discontinue Clozaril®

- Clozaril® should be discontinued if the patient has:
  - blood dyscrasias
  - intolerable or serious side-effects (for example, myocarditis)
  - true failure to respond
- Discontinuation of Clozaril® for reasons other than a red alert or other serious side-effect should be done gradually, over at least a 1-2 week period, to minimise the risk of withdrawal effects[1,2]
- In patients with Parkinson's Disease a gradual reduction in dose by steps of 12.5 mg over a period of at least one week (preferably two) is recommended[1,2]
- The CPMS should be notified
- Follow-up samples should be taken for 4 weeks after stopping clozapine at the frequency at which they are currently being monitored, for example, if weekly monitored, sample every week for 4 weeks after stopping clozapine; if 4-weekly monitored, sample once more 4 weeks after stopping.

In patients who stop Clozaril® due to a red alert, blood monitoring will be continued until haematological recovery occurs. CPMS will advise on this.

Breaks in treatment

Patients who have been on Clozaril® for more than 18 weeks and have had their treatment interrupted for more than 3 days but less than 4 weeks should have their white blood cell (WBC) count and absolute neutrophil count (ANC) monitored weekly for an additional 6 weeks. Provided that the blood count remains stable the patient can return to their normal monitoring frequency at the end of this period. If Clozaril® treatment has been interrupted for 4 weeks or longer, weekly monitoring is required for the next 18 weeks of treatment. In patients in whom the interval since the last dose of Clozaril® exceeds 2 days, treatment should be re-initiated with 12.5mg given once or twice on the first day. If this dose is well tolerated, it may be feasible to titrate the dose to the therapeutic level more quickly than is recommended for initial treatment.[1,2]

Please contact CPMS for further information regarding breaks in treatment.

Sudden discontinuation of Clozaril®

When a patient has a red alert or experiences other serious side-effect(s), it is essential to stop clozapine immediately. This sudden cessation of treatment can lead to physical and mental withdrawal effects which may occur within 2-3 days and usually within the first 2 weeks.[43] If abrupt discontinuation is necessary the patient should be observed carefully for return of psychotic symptoms, which may recur quickly. The patient should also be observed for withdrawal symptoms related to cholinergic rebound. In addition, abrupt withdrawal of clozapine has been associated with symptoms such as nausea, vomiting, diarrhoea, headache and agitation[44] and it has been suggested that these are a result of cholinergic rebound since clozapine has strong anticholinergic action.[43] The SmPC for Clozaril® lists cholinergic syndrome (after abrupt withdrawal of Clozaril®) as an adverse reaction which has a frequency of 'not known'.

In cases where clozapine has been stopped for a confirmed red alert, the patient must not be re-exposed to clozapine. Prescribers are encouraged to keep a record of all patients' blood results and to take any steps necessary to prevent the patient being accidentally rechallenged in the future.[1,2]

PRESCRIBING INFORMATION - UK
CLOZARIL 25 mg Tablets
CLOZARIL 100 mg Tablets

Please see Summary of Product Characteristics (SmPC) for full information before prescribing Clozaril.
The use of Clozaril is restricted to patients, physicians and nominated pharmacists registered with the Clozaril Patient Monitoring Service (CPMS).
In the UK a white cell count with differential count must be monitored:

- At least weekly for the first 18 weeks of treatment
- At least at 2-week intervals between weeks 18 and 52
- After 1 year of treatment with stable neutrophil counts, patients may be monitored at least at 4 week intervals

Monitoring must continue throughout treatment and for at least 4 weeks after discontinuation.
Blood clozapine level monitoring is advised in situations such as a patient ceases smoking or switches to e-cigarettes, when concomitant medicines may interact to increase clozapine blood levels, where poor clozapine metabolism is suspected, when a patient has pneumonia or other serious infection and in the event of onset of symptoms suggestive of toxicity.
Clozaril is associated with an increased risk of myocarditis and cardiomyopathy. If suspected Clozaril must be stopped immediately and the patient referred to a cardiologist and not re-exposed to Clozaril.

Presentations
Clozaril 25 mg Tablets containing 25 mg clozapine. Clozaril 100 mg Tablets containing 100 mg clozapine.

Indications
Treatment-resistant schizophrenic patients and in schizophrenia patients with severe, untreatable neurological adverse reactions to other antipsychotic agents, including an atypical antipsychotic agent prescribed for adequate duration. Psychotic disorders occurring during the course of Parkinson's disease, where standard treatment has failed.

Dosage and Administration
Treatment-resistant schizophrenic patients
12.5 mg once or twice on the first day, followed by 25 mg tablets once or twice on the second day. Increase dose slowly, by increments (see SmPC). In most patients, antipsychotic efficacy can be expected with 200 to 450 mg/day given in divided doses. If dose does not exceed 200 mg/day, it can be given as a single administration in the evening. Once control is achieved, a lower maintenance dose may be effective. Treatment should be maintained for at least 6 months. Doses up to 900 mg/day can be used but the possibility of increased adverse reactions (especially seizures) occurring at doses over 450 mg/day must be considered.
See SmPC for details on re-starting therapy, ending treatment or switching from another antipsychotic.
Psychotic disorders occurring during the course of Parkinson's disease in cases where standard treatment has failed
The starting dose must not exceed 12.5 mg/day taken in the evening. Increase dose by 12.5 mg increments, with a maximum of two increments a week up to a maximum of 50 mg, preferably given as a single dose in the evening. The mean effective dose is usually between 25 and 37.5 mg/day.
The maximum dose of 100 mg/day must never be exceeded. Dose increases should be limited or deferred if orthostatic hypotension, excessive sedation or confusion occurs. Blood pressure should be monitored during the first weeks of treatment. When there has been complete remission of psychotic symptoms for at least two weeks, an increase in anti-parkinsonian medication is possible on the basis of motor status. Cautious titration and a divided dosage schedule are necessary to minimise the risks of hypotension, seizure and sedation.

Method of administration
Clozaril is administered orally.
Switching from a previous antipsychotic therapy to Clozaril
It is generally recommended that Clozaril should not be used in combination with other antipsychotics. When Clozaril therapy is to be initiated in a patient undergoing oral antipsychotic therapy, it is recommended that the other antipsychotic should first be discontinued by tapering the dosage downwards.
Special populations: Hepatic impairment Patients with hepatic impairment should receive Clozaril with caution along with regular monitoring of liver function tests (see section 4.4 of SmPC).
Paediatric population No paediatric studies have been performed. The safety and efficacy of Clozaril in children and adolescents under the age of 16 years have not yet been established. Clozaril should not be used in this group until further data becomes available.

Patients 60 years of age and older Initiation of treatment is recommended at a particularly low dose (12.5 mg given once on the first day), with subsequent dose increments restricted to 25 mg/day.
See SmPC for information on ending therapy.

Contraindications
Hypersensitivity to the active substance or to any of the excipients. 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. Concurrent treatment with substances known to have a substantial potential for causing agranulocytosis; concomitant use of depot antipsychotics is discouraged.
Impaired bone marrow function. Uncontrolled epilepsy. Alcoholic and other toxic psychoses, 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.

Warnings and Precautions
Agranulocytosis: Before initiating clozapine therapy, patients should have a blood test and a history and physical examination. Clozaril can cause agranulocytosis, so is restricted to patients who have initially normal leukocyte findings (White Blood Cell (WBC) count > 3.5x 10^9/l and Absolute Neutrophil Count (ANC) > 2.0x 10^9l), and in whom regular WBC counts and ANC can be performed within 10 days prior to starting Clozaril, weekly for first 18 weeks, thereafter at 4 week intervals throughout treatment and for 4 weeks after complete discontinuation.
Patients with history of cardiac illness or abnormal cardiac findings on physical examination prior to treatment should be referred to a specialist for other examinations that might include an ECG, and the patient treated only if the expected benefits clearly outweigh the risks. The treating physician should consider performing a pre-treatment ECG.
QT interval prolongation: As with other antipsychotics, caution is advised in patients with known cardiovascular disease or family history of QT prolongation. As with other antipsychotics, caution should be exercised when clozapine is prescribed with medicines known to increase QTc interval.
Cerebrovascular adverse events: Clozapine should be used with caution in patients with risk factors for stroke. Risk of thromboembolism: Cases of venous thromboembolism (VTE) have been reported with antipsychotic drugs. If the diagnosis of NMS is confirmed, Clozaril should be discontinued immediately and appropriate medical measures should be administered. Metabolic changes: Atypical antipsychotic drugs, including Clozaril, have been associated with metabolic changes that may increase cardiovascular/cerebrovascular risk. Hyperglycaemia: Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Hepatic impairment: Patients with stable pre-existing liver disorders may receive Clozaril, but need regular liver function tests. Liver function tests should be performed in patients in whom symptoms of possible liver dysfunction, such as nausea, vomiting and/or anorexia, develop during Clozaril therapy.

Prior to treatment initiation, physicians must ensure that the patient has not experienced an adverse haematological reaction to clozapine that necessitated discontinuation.
Immediate discontinuation of Clozaril is mandatory if either the WBC count is less than 3.0x10^9 /l or the ANC is less than 1.5x10^9 /l at any time during Clozaril treatment. Patients in whom Clozaril has been discontinued as a result of either WBC or ANC deficiencies must not be re-exposed to Clozaril. Following discontinuation of Clozaril, haematological evaluation is required until haematological recovery has occurred. **If Clozaril has been withdrawn and either a further drop in the WBC count below 2.0x10^9 /l occurs or the ANC falls below 1.0x10^9 /l the management of this condition must be guided by an experienced haematologist.** The patient should be educated to contact the treating physician immediately if any kind of infection, fever, sore throat or other flu-like symptoms develop. WBC and differential blood counts must be performed immediately if any symptoms or signs of an infection occur.
Low WBC count/ANC: If, during Clozaril therapy, either the WBC count falls to between 3.5x10^9/l and 3.0x10^9/l or the ANC falls to between 2.0x10^9/l and 1.5x10^9/l, haematological evaluations must be performed at least twice weekly until the patient's WBC count and ANC stabilise within the range 3.0-3.5x10^9/l and 1.5-2.0x10^9/l respectively, or higher.

Eosinophilia: Discontinuation of Clozaril is recommended if the eosinophil count rises above $3.0x10^9$ /l; therapy should be restarted only after the eosinophil count has fallen below $1.0x10^9$ /l. Discontinuation of Thrombocytopenia: Clozaril therapy is recommended if the platelet count falls below $50x10^9$ /l. Cardiovascular disorders: Orthostatic hypotension, with or without syncope, can occur during Clozaril treatment. Rarely, collapse can be profound and may be accompanied by cardiac and/or respiratory arrest which is more likely to occur with concurrent use of certain medications (See SPC for more details) and during initial titration with rapid dose escalation. Patients starting Clozaril treatment require close medical supervision. Clozaril is associated with an increased risk of myocarditis, pericarditis/pericardial effusion and cardiomyopathy; and if suspected, Clozaril treatment should be promptly stopped and the patient immediately referred to a cardiologist. Patients with clozapine-induced myocarditis or cardiomyopathy should not be re-exposed to Clozaril. In patients who are diagnosed with cardiomyopathy while on Clozaril treatment, there is potential to develop mitral valve incompetence, including mild or moderate mitral regurgitation. Myocarditis or cardiomyopathy should be suspected in patients who experience persistent tachycardia at rest, especially in the first two months of treatment, and/or palpitations, arrhythmias, chest pain and other signs and symptoms of heart failure or symptoms mimicking myocardial infarction. Flu-like symptoms may also be present. Myocardial infarction (MI): There have been post marketing reports of MI which include fatal cases. Epilepsy: Patients with a history of epilepsy should be closely observed during Clozaril therapy since dose related convulsions have been reported. Hepatic impairment: Patients with stable pre-existing liver disorders or liver dysfunction need regular liver function tests. If the LFTs are elevated, discontinue Clozaril and resume only if LFTs return to normal. Dyslipidemia: Undesirable alterations in lipids have been observed in patients treated with atypical antipsychotics, including Clozaril. Clinical monitoring, including baseline and periodic follow-up lipid evaluations in patients using clozapine, is recommended.
Anticholinergic effects: Use with care in patients with a history of colonic disease, a history of lower abdominal surgery, glaucoma, narrow angle glaucoma, prostatic enlargement and in patients receiving concomitant medications known to cause constipation, megacolon and intestinal infarction/ischaemia, paralytic ilius. Pyrexia: High temperatures should be evaluated carefully to rule out underlying infection, agranulocytosis or Neuroleptic Malignant Syndrome (NMS). If NMS is confirmed, discontinue Clozaril immediately and administer appropriate medical measures. Patients with rare hereditary problems of galactose intolerance should not take Clozaril. Impaired glucose tolerance and/or development or exacerbation of diabetes mellitus has been reported rarely during treatment with clozapine. Falls: Clozaril may cause seizures, somnolence and other conditions that could lead to falls. Fall risk assessments should be performed on patients with exacerbating conditions. Risk of thromboembolism: Immobilisation of patients should be avoided due to reports of thromboembolism. Increased mortality in elderly patients with dementia. Caution when prescribing to pregnant women. Mothers receiving Clozaril should not breast-feed. Adequate contraceptive measures must be ensured in women of childbearing potential. Neonates exposed to antipsychotic drugs (including Clozaril), during the third trimester of pregnancy are at risk of adverse reactions including extrapyramidal and/or withdrawal symptoms that may vary in severity and duration following delivery. There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress or feeding disorder. Consequently, newborns should be monitored carefully. Activities such as driving or operating machinery should be avoided, especially during the initial weeks of treatment.

Interaction with other medicinal products and other forms of interaction

Clozaril must not be used concomitantly with substances having a well-known potential to suppress bone marrow function. (See Section 4.3 of the SmPC, Contraindications).
Long-acting depot antipsychotics (with myelosuppressive potential) must not be used with Clozaril because these cannot be removed from the body in situations where they may be required e.g. neutropenia. Alcohol should not be used with Clozaril due to possible potentiation of sedation.

Caution is advised if Clozaril is used concomitantly with other CNS active agents such as, MAOIs, perazine, SSRIs especially fluvoxamine, caffeine, CNS depressants including narcotics, antihistamines and benzodiazepines, Caution is advised if Clozaril is used concomitantly with antihypertensive agents, highly protein bound drugs (e.g. warfarin and digoxin), phenytoin, lithium, rifampicin, valproic acid, noradrenaline [norepinephrine], adrenaline [epinephrine] or omeprazole. Cases have been reported of an interaction between citalopram and clozapine, which may increase the risk of adverse events associated with clozapine. The nature of this interaction has not been fully elucidated. Hormonal contraceptives (including combinations of estrogen and progesterone or progesterone only) are CYP 1A2, CYP 3A4 and CYP 2C19 inhibitors. Therefore initiation or discontinuation of hormonal contraceptives, may require dose adjustment of clozapine according to the individual medical need. In cases of sudden cessation of smoking, the plasma clozapine concentration may be increased, thus leading to an increase in adverse effects. See SPC for more details.

Fertility, Pregnancy and Lactation

Pregnancy: Caution should be exercised when prescribing to pregnant women. Neonates exposed to antipsychotics (including Clozaril) during the third trimester are at risk of adverse reactions including extrapyramidal and/or withdrawal symptoms that may vary in severity and duration following delivery. There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, or feeding disorder. Consequently, newborns should be monitored carefully.
Lactation: Animal studies suggest that clozapine is excreted in breast milk and has an effect in the nursing infant; therefore, mothers receiving Clozaril should not breast-feed.
Fertility: Limited data available on the effects of clozapine on human fertility are inconclusive.
Women of child-bearing potential: A return to normal menstruation may occur as a result of switching from other antipsychotics to Clozaril. Adequate contraceptive measures must therefore be ensured in women of childbearing potential.

Ability to Drive and Operate Machinery

Owing to the ability of Clozaril to cause sedation and lower the seizure threshold, activities such as driving or operating machinery should be avoided, especially during the initial weeks of treatment.

Undesirable effects

Adverse reactions are ranked under headings of frequency. Very common (≥1/10), common (≥1/100, <1/10), uncommon (≥1/1,000, <1/100), rare (≥1/10,000, <1/1,000), very rare (<1/10,000), including isolated reports.
The most serious adverse reactions experienced with clozapine are agranulocytosis, seizure, cardiovascular effects and fever.
Very common: Drowsiness/sedation, dizziness, tachycardia, constipation, hypersalivation.
Common: Leukopenia/decreased WBC/neutropenia, eosinophilia, leukocytosis, weight gain, blurred vision, headache, tremor, rigidity, akathisia, extrapyramidal symptoms, seizures, convulsions, myoclonic jerks, ECG changes, hypertension, postural hypotension, syncope, nausea, vomiting, anorexia, dry mouth, elevated liver enzymes, urinary incontinence, urinary retention, fatigue, fever, benign hyperthermia, disturbances in sweating/temperature regulation, dysarthria.
Uncommon: Agranulocytosis, neuroleptic malignant syndrome, dysphemia, falls.
For details of rare, very rare and not known undesirable effects please refer to SmPC.

Package Quantities and basic NHS price
28 x 25 mg tablets : £2.95 ; 84 x 25 mg tablets : £6.30; 100 x 25 mg tablets : £7.50
28 x 100 mg tablets : £11.76 ; 84 x 100 mg tablets : £25.21 ; 100 x 100 mg tablets : £30.01
Supply of Clozaril is restricted to hospital pharmacies registered with the CLOZARIL Patient Monitoring Service.
Marketing Authorisation Holder
Mylan Products Limited, 20 Station Close, Potters Bar, Herts, EN6 1TL, UK.
Product Authorisation Numbers
25 mg tablets: PL 46302/0054
100 mg tablets: PL 46302/0057
Legal Category: POM
Further information is available in the UK from: BGP Products Ltd., Building Q1, Quantum House, 60 Norden Road, Maidenhead, Berkshire, SL6 4AY, UK.
Date of last revision: May 2020
Clozaril is a registered Trademark

Reporting of adverse reactions:
Please continue to report suspected adverse drug reactions with any medicine or vaccine to the MHRA through the Yellow Card Scheme.
It is easiest and quickest to report adverse drug reactions online via the Yellow Card website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store. Alternatively, you can report via some clinical IT systems (EMIS/SystmOne/Vision/MiDatabank) or by calling the Commission on Human Medicines (CHM) free phone line: 0800-731-6789. Adverse reactions/events should also be reported to Viatris via cpms@viatris.com

uk-pi-clozaril-May20-v5

CLOZARIL® Clozapine PATIENT MONITORING SERVICE

Veeva Reference: CLZ-2023-0003
Date of Preparation: April 2023

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PRESCRIBING INFORMATION - Ireland
CLOZARIL (clozapine) 25 mg Tablets
CLOZARIL (clozapine) 100 mg Tablets

Please refer to Summary of Product Characteristics (SmPC) before prescribing.
The use of Clozaril is restricted to patients, physicians and nominated pharmacists registered with the Clozaril Patient Monitoring Service (CPMS).
White cell count with differential count must be monitored according to the Irish Official Recommendations.

Indications, Dosage and Administration:

Treatment-resistant schizophrenia and schizophrenia patients with severe, untreatable neurological adverse reactions to other antipsychotic agents, including an atypical antipsychotic agent prescribed for adequate duration. Psychotic disorders occurring during the course of Parkinson's disease, where standard treatment has failed.

Treatment-resistant schizophrenic patients

12.5 mg once or twice on the first day, followed by 25 mg tablets once or twice on the second day. Increase dose slowly, by increments (see SmPC). In most patients, antipsychotic efficacy can be expected with 200 to 450 mg/day given in divided doses. If dose does not exceed 200 mg/day, it can be given as a single administration in the evening. Once control is achieved, a lower maintenance dose may be effective. Treatment should be maintained for at least 6 months. Doses up to 900 mg/day can be used but the possibility of increased adverse reactions (especially seizures) occurring at doses over 450 mg/day must be considered.

See SmPC for details on re-starting therapy, ending treatment or switching from another antipsychotic.

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

The starting dose must not exceed 12.5 mg/day taken in the evening. Increase dose by 12.5 mg increments, with a maximum of two increments a week up to a maximum of 50 mg, preferably given as a single dose in the evening. The mean effective dose is usually between 25 and 37.5 mg/day.

The maximum dose of 100 mg/day must never be exceeded. Dose increases should be limited or deferred if orthostatic hypotension, excessive sedation or confusion occurs. Blood pressure should be monitored during the first weeks of treatment. When there has been complete remission of psychotic symptoms for at least two weeks, an increase in anti-parkinsonian medication is possible on the basis of motor status. Cautious titration and a divided dosage schedule are necessary to minimise the risks of hypotension, seizure and sedation.

Method of administration: Clozaril is administered orally.

Switching from a previous antipsychotic therapy to Clozaril

It is generally recommended that Clozaril should not be used in combination with other antipsychotics. When Clozaril therapy is to be initiated in a patient undergoing oral antipsychotic therapy, it is recommended that the other antipsychotic should first be discontinued by tapering the dosage downwards.

Special populations: *Hepatic impairment* Patients with hepatic impairment should receive Clozaril with caution along with regular monitoring of liver function tests (see section 4.4 of SmPC).

Paediatric population No paediatric studies have been performed. The safety and efficacy of Clozaril in children and adolescents under the age of 16 years have not yet been established. Clozaril should not be used in this group until further data becomes available.

Patients 60 years of age and older Initiation of treatment is recommended at a particularly low dose (12.5 mg given once on the first day), with subsequent dose increments restricted to 25 mg/day. See SmPC for information on ending therapy.

Presentations

Clozaril 25 mg Tablets containing 25mg clozapine. Clozaril 100 mg Tablets containing 100mg clozapine.

Contraindications:

Hypersensitivity to the active substance or to any of the excipients. 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. Concurrent treatment with substances known to have a substantial potential for causing agranulocytosis; concomitant use of depot antipsychotics is discouraged.

Impaired bone marrow function. Uncontrolled epilepsy. Alcoholic and other toxic psychoses, 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.

Warnings and Precautions:

Agranulocytosis: Before initiating clozapine therapy, patients should have a blood test and a history and physical examination. Clozaril can cause agranulocytosis, so is restricted to patients who have initially normal leukocyte findings (White Blood Cell (WBC) count > 3.5x 10^9/l and Absolute Neutrophil Count (ANC) > 2.0x 10^9/l), and in whom regular WBC counts and ANC can be performed within 10 days prior to starting Clozaril, weekly for first 18 weeks, thereafter at 4 week intervals throughout treatment and for 4 weeks after complete discontinuation.

Patients with history of cardiac illness or abnormal cardiac findings on physical examination prior to treatment should be referred to a specialist for other examinations that might include an ECG, and the patient treated only if the expected benefits clearly outweigh the risks. The treating physician should consider performing a pre-treatment ECG.

QT interval prolongation: As with other antipsychotics, caution is advised in patients with known cardiovascular disease or family history of QT prolongation. As with other antipsychotics, caution should be exercised when clozapine is prescribed with medicines known to increase QTc interval.

Cerebrovascular adverse events: Clozapine should be used with caution in patients with risk factors for stroke. Risk of thromboembolism: Cases of venous thromboembolism (VTE) have been reported with antipsychotic drugs. If the diagnosis of NMS is confirmed, Clozaril should be discontinued immediately and appropriate medical measures should be administered. Metabolic changes: Atypical antipsychotic drugs, including Clozaril, have been associated with metabolic changes that may increase cardiovascular/cerebrovascular risk. Hyperglycaemia: Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Hepatic impairment: Patients with stable pre-existing liver disorders may receive Clozaril, but need regular liver function tests. Liver function tests should be performed in patients in whom symptoms of possible liver dysfunction, such as nausea, vomiting and/or anorexia, develop during Clozaril therapy.

Prior to treatment initiation, physicians must ensure that the patient has not experienced an adverse haematological reaction to clozapine that necessitated discontinuation.

Immediate discontinuation of Clozaril is mandatory if either the WBC count is less than 3.0x10^9/l or the ANC is less than 1.5x10^9/l at any time during Clozaril treatment. Patients in whom Clozaril has been discontinued as a result of either WBC or ANC deficiencies must not be re-exposed to Clozaril. Following discontinuation of Clozaril, haematological evaluation is required until haematological recovery has occurred. **If Clozaril has been withdrawn and either a further drop in the WBC count below 2.0x10^9/l occurs or the ANC falls below 1.0x10^9/l the management of this condition must be guided by an experienced haematologist.** The patient should be educated to contact the treating physician immediately if any kind of infection, fever, sore throat or other flu-like symptoms develop. WBC and differential blood counts must be performed immediately if any symptoms or signs of an infection occur.

Low WBC count/ANC: If, during Clozaril therapy, either the WBC count falls to between 3.5x10^9/l and 3.0x10^9/l or the ANC falls to between 2.0x10^9/l and 1.5x10^9/l, haematological evaluations must be performed at least twice weekly until the patient's WBC count and ANC stabilise within the range 3.0-3.5x10^9/l and 1.5-2.0x10^9/l respectively, or higher.

Eosinophilia: Discontinuation of Clozaril is recommended if the eosinophil count rises above 3.0x10^9/l; therapy should be restarted only after the eosinophil count has fallen below 1.0x10^9/l. Thrombocytopenia: Discontinuation of Clozaril therapy is recommended if the platelet count falls below 50x10^9/l.

Cardiovascular disorders: Orthostatic hypotension, with or without syncope, can occur during Clozaril treatment. Rarely, collapse can be profound and may be accompanied by cardiac and/or respiratory arrest which is more likely to occur with concurrent use of certain medications (See SPC for more details) and during initial titration with rapid dose escalation. Patients starting Clozaril treatment require close medical supervision. Clozaril is associated with an increased risk of myocarditis, pericarditis/pericardial effusion and cardiomyopathy; and if suspected, Clozaril treatment should be promptly stopped and the patient immediately referred to a cardiologist. In patients who are diagnosed with cardiomyopathy while on Clozaril treatment, there is potential to develop mitral valve incompetence. Patients with clozapine-induced myocarditis or cardiomyopathy should not be re-exposed to Clozaril.

Myocarditis or cardiomyopathy should be suspected in patients who experience persistent tachycardia at rest, especially in the first two months of treatment, and/or palpitations, arrhythmias, chest pain and other signs and symptoms of heart failure or symptoms mimicking myocardial infarction. Flu-like symptoms may also be present.

Myocardial infarction (MI): There have been post marketing reports of MI including fatal.

Epilepsy: Patients with a history of epilepsy should be closely observed during Clozaril therapy since dose related convulsions have been reported.

Hepatic impairment: Patients with stable pre-existing liver disorders or liver dysfunction need regular liver function tests. If the LFTs are elevated, discontinue Clozaril and resume only if LFTs return to normal.

Dyslipidemia: Undesirable alterations in lipids have been observed in patients treated with atypical antipsychotics, including Clozaril. Clinical monitoring, including baseline and periodic follow-up lipid evaluations in patients using clozapine, is recommended.

Anticholinergic effects: Use with care in patients with a history of colonic disease, a history of lower abdominal surgery, glaucoma, narrow angle glaucoma, prostatic enlargement and in patients receiving concomitant medications known to cause constipation.

CLOZARIL Clozapine PATIENT MONITORING SERVICE

Veeva Reference: CLZ-2023-0003
Date of Preparation: April 2023

VIATRIS

Pyrexia: High temperatures should be evaluated carefully to rule out underlying infection, agranulocytosis or Neuroleptic Malignant Syndrome (NMS). If NMS is confirmed, discontinue Clozaril immediately and administer appropriate medical measures.
Patients with rare hereditary problems of galactose intolerance should not take Clozaril.
Impaired glucose tolerance and/or development or exacerbation of diabetes mellitus has been reported rarely during treatment with clozapine.
Risk of thromboembolism: Immobilisation of patients should be avoided due to reports of thromboembolism.
Increased mortality in elderly patients with dementia.
Caution when prescribing to pregnant women. Mothers receiving Clozaril should not breast-feed. Adequate contraceptive measures must be ensured in women of childbearing potential. Neonates exposed to antipsychotic drugs (including Clozaril), during the third trimester of pregnancy are at risk of adverse reactions including extrapyramidal and/or withdrawal symptoms that may vary in severity and duration following delivery. There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress or feeding disorder. Consequently, newborns should be monitored carefully. Activities such as driving or operating machinery should be avoided, especially during the initial weeks of treatment.

Interaction with other medicinal products and other forms of interaction:

Clozaril must not be used concomitantly with substances having a well-known potential to suppress bone marrow function. (See Section 4.3 of the SmPC, Contraindications).
Long-acting depot antipsychotics (with myelosuppressive potential) must not be used with Clozaril because these cannot be removed from the body in situations where they may be required e.g. neutropenia. Alcohol should not be used with Clozaril due to possible potentiation of sedation.
Caution is advised if Clozaril is used concomitantly with other CNS active agents such as, MAOIs, perazine, SSRIs especially fluvoxamine, caffeine, CNS depressants including narcotics, antihistamines and benzodiazepines, Caution is advised if Clozaril is used concomitantly with antihypertensive agents, highly protein bound drugs (e.g. warfarin and digoxin), phenytoin, lithium, rifampicin, valproic acid, noradrenaline [norepinephrine], adrenaline [epinephrine] or omeprazole. Cases have been reported of an interaction between citalopram and clozapine, which may increase the risk of adverse events associated with clozapine. The nature of this interaction has not been fully elucidated. Hormonal contraceptives (including combinations of estrogen and progesterone or progesterone only) are CYP 1A2, CYP 3A4 and CYP 2C19 inhibitors. Therefore initiation or discontinuation of hormonal contraceptives, may require dose adjustment of clozapine according to the individual medical need.
In cases of sudden cessation of smoking, the plasma clozapine concentration may be increased, thus leading to an increase in adverse effects. See SPC for more details.

Fertility, Pregnancy and Lactation:

Pregnancy: Caution should be exercised when prescribing to pregnant women. Neonates exposed to antipsychotics (including Clozaril) during the third trimester are at risk of adverse reactions including extrapyramidal and/or withdrawal symptoms that may vary in severity and duration following delivery. There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, or feeding disorder. Consequently, newborns should be monitored carefully.
Lactation: Animal studies suggest that clozapine is excreted in breast milk and has an effect in the nursing infant; therefore, mothers receiving Clozaril should not breast-feed.
Fertility: Limited data available on the effects of clozapine on human fertility are inconclusive.
Women of child-bearing potential: A return to normal menstruation may occur as a result of switching from other antipsychotics to Clozaril. Adequate contraceptive measures must therefore be ensured in women of childbearing potential.

Undesirable effects:

Adverse reactions are ranked under headings of frequency. Very common (≥1/10), common (≥1/100, <1/10), uncommon (≥1/1,000, <1/100), rare (≥1/10,000, <1/1,000), very rare (<1/10,000), including isolated reports.
The most serious adverse reactions experienced with clozapine are agranulocytosis, seizure, cardiovascular effects and fever.
Very common: Drowsiness/sedation, dizziness, tachycardia, constipation, hypersalivation.
Common: Leukopenia/decreased WBC/neutropenia, eosinophilia, leukocytosis, weight gain, blurred vision, headache, tremor, rigidity, akathisia, extrapyramidal symptoms, seizures, convulsions, myoclonic jerks, ECG changes, hypertension, postural hypotension, syncope, nausea, vomiting, anorexia, dry mouth, elevated liver enzymes, urinary incontinence, urinary retention, fatigue, fever, benign hyperthermia, disturbances in sweating/temperature regulation, dysarthria.
For details of uncommon, rare and very rarely reported adverse events and those of unknown frequency, see SmPC.

Legal Category: Subject to prescription which may not be renewed.
Marketing Authorisation Holder
Mylan IRE Healthcare Limited, Unit 35/36, Grange Parade, Baldoyle Industrial Estate, Dublin 13, Ireland.
Product Authorisation Numbers
25 mg tablets: PA 2010/20/1
100 mg tablets: PA 2010/20/2
Full prescribing information is available on request from: Viatris, Dublin 17. Phone 01 8322250.
Supply of Clozaril is restricted to hospital and retail pharmacies registered with the CLOZARIL Patient Monitoring Service.
Date of Revision of Abbreviated Prescribing Information: 15th February 2022
Reference Number: IE-AbPI-Clozaril-v006

Reporting of adverse reactions:
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 HPRA Pharmacovigilance, Website: www.hpra.ie.
Adverse reactions/events should also be reported to the marketing authorisation holder at the email address: cpms@viatris.com.

CLOZARIL® Clozapine PATIENT MONITORING SERVICE

Veeva Reference: CLZ-2023-0003
Date of Preparation: April 2023

VIATRIS

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