

Clozaril[®] therapy: role of therapeutic drug monitoring (TDM)

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.

Although antipsychotic efficacy with Clozaril[®] (clozapine) 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:³

- a patient stops smoking or switches to an e-cigarette¹⁻³
- concomitant medicines may interact to increase blood clozapine levels³
- a patient has pneumonia or other serious infection³
- poor (reduced) clozapine metabolism is suspected¹⁻³
- toxicity is suspected¹⁻³

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.³ Refer to the Summary of Product Characteristics (SmPC) of Clozaril[®] for other important warnings, interactions, and recommendations.³

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.⁴

The best practice to obtain to obtain an accurate level, the patient should have been on a steady dose for at least a week (4-5 plasma half-lives)⁵ and the sample taken either immediately before a normal morning dose or in the morning after an evening dose ('trough' sample)⁵. There should be a minimum of 6 hours since the last dose.⁴ 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 Clozaril[®] Patient Monitoring Service (CPMS) by calling 0845 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.⁵ 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.⁶

Several studies have suggested that efficacy in Treatment Resistant Schizophrenia may be associated with 'trough' clozapine concentrations of 0.35mg/l or above.^{4,7} 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 effect.⁴

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.⁴

Table 1. Plasma clozapine and norclozapine concentrations (median, 10th-90th percentile) and prescribed dose in 85,958 samples in which clozapine and norclozapine were detected⁴

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 partial 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 0.5-2.5.⁵ 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.⁵

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.⁸ 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.⁹ 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.¹⁰

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.¹¹

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.⁷ 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.¹²⁻¹⁴ One of these men also developed stupor and went into a coma.¹²

It is important to consider the need to adjust the clozapine dose quickly in patients who stop smoking during treatment^{7,15} 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 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.^{16,17} Raaska (2002) and Leung (2014) each describe cases where plasma clozapine levels have increased during infection, with patients showing signs of toxicity.^{16,17}

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 state⁵
- 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?

References

1. Clozaril (clozapine) Summary of Product Characteristics (online). Mylan Products Ltd. <http://www.medicines.org.uk/emc/> (Accessed on 08/04/2020).
2. Clozaril (clozapine) Summary of Product Characteristics (online). Mylan IRE Healthcare Limited. <http://www.medicines.ie/> (Accessed on 08/04/2020).
3. Clozapine and other antipsychotics: monitoring blood concentrations for toxicity (online). <https://www.gov.uk/drug-safety-update/clozapine-and-other-antipsychotics-monitoring-blood-concentrations-for-toxicity> (last accessed 08/09/2020).
4. Couchman L, Morgan PE, Spencer EP, Flanagan RJ. Plasma clozapine, norclozapine, and the clozapine:norclozapine ratio in relation to prescribed dose and other factors: Data from a Therapeutic Drug Monitoring service, 1993-2007. *Ther Drug Monit* 2010; **32**: 438-447.
5. Flanagan RJ. Therapeutic Monitoring of Antipsychotics. *CPD Clin Biochem* 2006; **7**: 3-18.
6. Munro J *et al*. Active Monitoring of 12760 Clozapine Recipients in the UK and Ireland. *Br J Psychiatry* 1999; **175**: 576-580.
7. Rostami-Hodjegan A, Amin AM, Spencer EP *et al*. Influence of Dose, Cigarette Smoking, Age, Sex, and Metabolic Activity on Plasma Clozapine Concentrations: a Predictive Model and Nomograms to Aid Clozapine Dose Adjustment and to Assess Compliance in Individual Patients. *J Clin Psychopharmacol* 2004; **24**: 70-78.
8. Schein JR. Cigarette Smoking and Clinically Significant Drug Interactions. *Ann Pharmacother* 1995; **29**: 1139-1148.
9. Meyer JM. Individual Changes in clozapine levels after smoking cessation: results and a predictive model. *J Clin Psychopharmacol* 2001; **21**: 569-574.
10. Seppala NH, Leinonen EVJ, Lehtonen ML *et al*. Clozapine Serum Concentrations Are Lower In Smoking Than In Non-Smoking Schizophrenic Patients. *Pharmacol Toxicol* 1999; **85**: 244-246.
11. Haslemo T *et al*. The effect of variable consumption on the interaction with clozapine or olanzapine. *Eur J Clin Pharmacol* 2006; **62**: 1049-53.
12. Skogh E, Bengtsson F and Nordin C. Could Discontinuing Smoking Be Hazardous For Patients Administered Clozapine Medication? A Case Report. *Ther Drug Monit* 1999; **21**: 580-582.
13. Oyewumi LK. Smoking Cessation and Clozapine Side Effects. *Can J Psychiatry* 1998; **43**: 748.
14. McCarthy RH: Seizures Following Smoking Cessation In a Clozapine Responder. *Pharmacopsychiatry* 1994; **27**: 210-1.
15. Faber MS and Fuhr U. Time Response of Cytochrome P450 1A2 Activity on Cessation of Heavy Smoking. *Clin Pharmacol Ther* 2004; **76**: 178-184.
16. Raaska K *et al*. Bacterial pneumonia can increase serum concentration of clozapine. *Eur J Clin Pharmacol* 2002; **58**: 321-2.
17. Leung JG *et al*. Infection and inflammation leading to clozapine toxicity and intensive care: a case series. *Ann Pharmacother* 2014; **48**: 801-805.

PRESCRIBING INFORMATION**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 AdministrationTreatment-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 10⁹/l and Absolute Neutrophil Count (ANC) > 2.0x 10⁹/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 3.0x10⁹/l or the ANC is less than 1.5x10⁹/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 2.0x10⁹/l occurs or the ANC falls below 1.0x10⁹/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 3.5x10⁹/l and 3.0x10⁹/l or the ANC falls to between 2.0x10⁹/l and 1.5x10⁹/l, haematological evaluations must be performed at least twice weekly until the patient's WBC count and ANC stabilise within the range 3.0-3.5x10⁹/l and 1.5-2.0x10⁹/l respectively, or higher.

Eosinophilia: Discontinuation of Clozaril is recommended if the eosinophil count rises above $3.0 \times 10^9 / l$; therapy should be restarted only after the eosinophil count has fallen below $1.0 \times 10^9 / l$.
Discontinuation of Thrombocytopenia: Clozaril therapy is recommended if the platelet count falls below $50 \times 10^9 / l$.
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 ileus.
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, 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 ($\geq 1/10$), common ($\geq 1/100$, $< 1/10$), uncommon ($\geq 1/1,000$, $< 1/100$), rare ($\geq 1/10,000$, $< 1/1,000$), 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/SystemOne/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 Viatriis via cpms@viatriis.com

uk-pi-clozaril-May20-v5