

Clozaril® and cardiovascular events

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.

The Summary of Product Characteristics (SmPC) for Clozaril® (clozapine)^{1,2} states the following:

Before initiating clozapine the patient's medical history should be checked and a physical examination performed. If the patient has a history of cardiac illness or has abnormal cardiac findings on examination he/she should be referred to a specialist for other investigations (which might include an ECG). Such patients should be treated only if expected benefits clearly outweigh the risks. With all patients, treating physicians should consider performing a pre-treatment ECG.

Circulatory collapse and severe cardiac disorders (for example, myocarditis) are contraindications to Clozaril®.

Tachycardia

The SmPC for Clozaril® lists tachycardia as a very common ($\geq 1/10$) side-effect.^{1,2}

Tachycardia typically occurs in the first few weeks of treatment and it may persist in some patients. It is usually dose-related.³ To reduce the risk of tachycardia, the lowest possible dose of clozapine should be used. If it occurs, reducing the dose of clozapine is often effective. Decreasing smoking and caffeine intake may also be beneficial,³ although this may affect clozapine plasma levels which should be considered.

Patients who develop tachycardia should have an ECG to exclude other arrhythmias or cardiac abnormalities. Checking the clozapine plasma level may be useful to exclude high levels. Failure to improve following dose reduction should be followed up with a cardiologist consultation. If tachycardia persists when the patient is at rest or if it is associated with other cardiac symptoms, myocarditis and cardiomyopathy should be excluded (see below).

Orthostatic hypotension

The SmPC for Clozaril® states that postural hypotension and syncope are common ($\geq 1/100$ but $< 1/10$) side-effects of Clozaril® and circulatory collapse is listed as rare ($\geq 1/10,000$ but $< 1/1,000$).^{1,2}

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. Such events are more likely to occur with concurrent use of a benzodiazepine or any other psychotropic agent and during initial titration in association with rapid dose escalation; on very rare occasions they may occur even after the first dose. Therefore, patients starting Clozaril treatment require close medical supervision. Monitoring of standing and supine blood pressure is necessary during the first weeks of treatment in patients with Parkinson's disease.^{1,2}

To reduce the risk of orthostatic hypotension the lowest possible dose of clozapine should be used. If it occurs, a reduction in the clozapine dose should be considered and/or the rate of clozapine titration reduced.³ Patients should be advised to stand up slowly and to wear elastic stockings and increased hydration can be considered.³ If orthostatic hypotension persists clozapine plasma level monitoring may be useful to exclude high levels.

Hypertension

Hypertension is listed as a common ($\geq 1/100$ but $< 1/10$) side-effect of Clozaril^{®1,2} and it usually occurs in the first 4 weeks of treatment.⁴

If a patient develops hypertension during clozapine treatment they should be monitored closely and the dose increased slowly. Hypotensive therapy is required in some cases.⁵

ECG changes

ECG changes, like those seen with other antipsychotics, are commonly seen in clozapine-treated patients.^{1,2} They include S-T segment depression and flattening or inversion of T waves.^{1,2} The clinical significance of these changes is unclear and they resolve when clozapine is stopped.^{1,2} Such abnormalities have been seen in some cases of myocarditis and this diagnosis should be considered if ECG changes occur.^{1,2}

ECG changes should be discussed with a cardiologist.

Cardiac arrhythmias

Cardiac arrhythmias occur rarely during clozapine treatment and some have been fatal.^{1,2}

Cardiac arrhythmias should be discussed with a cardiologist and myocarditis and cardiomyopathy should be excluded. Plasma clozapine level monitoring may be useful to exclude high levels.

QT prolongation and Torsades de Pointes

Very rare cases of ventricular tachycardia and QT prolongation, which may be associated with Torsades De Pointes, have been observed with clozapine although there is no conclusive causal relationship to the use of the drug.^{1,2} As with other antipsychotics, caution is advised in patients with known cardiovascular disease or family history of QT prolongation.^{1,2} Caution should be exercised when clozapine is prescribed with medicines known to cause electrolyte imbalance or to increase the QTc interval.^{1,2}

Suspected QT prolongation should be discussed with a cardiologist.

Myocarditis

The SmPC for Clozaril[®] lists myocarditis as a rare ($\geq 1/10,000$ but $< 1/1,000$) side effect of Clozaril[®].

The use of clozapine is associated with an increased risk of myocarditis which has, in rare cases, been fatal.^{1,2} The increased risk of myocarditis is greatest in the first 2 months of treatment.^{1,2}

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 (for example, unexplained fatigue, dyspnoea, tachypnoea), or symptoms that mimic myocardial infarction.^{1,2} Other symptoms which may be present in addition to the above include flu-like symptoms.^{1,2}

There is no classical presentation of clozapine-induced myocarditis and some patients may present with very few symptoms. If present, the clinical symptoms of myocarditis are highly variable and are non-specific in nature.⁶ Also, the features may resemble symptoms of normal clozapine titration.⁷ These factors make myocarditis a difficult condition to monitor and diagnose.

Eosinophilia has been co-reported with some cases of myocarditis (approximately 14%) and pericarditis/pericardial effusion. However, it is not known whether eosinophilia is a reliable predictor of carditis.^{1,2} Discontinuation of Clozaril® is recommended if the eosinophil count rises above $3.0 \times 10^9/L$ and treatment should be restarted only after the eosinophil count has fallen below $1.0 \times 10^9/L$.^{1,2}

If myocarditis is suspected, clozapine should be discontinued and the patient referred to a cardiologist immediately. Patients who have had myocarditis should not be re-exposed to clozapine.^{1,2}

Cardiomyopathy

Very rarely patients receiving clozapine have developed cardiomyopathy and some cases have been fatal.^{1,2} It generally occurs later in treatment than myocarditis.^{1,2}

Cardiomyopathy should be suspected if a patient develops persistent tachycardia at rest, palpitations, arrhythmias, chest pain, signs and symptoms of heart failure (unexplained fatigue, dyspnoea or tachypnoea), symptoms mimicking myocardial infarction.^{1,2} Flu-like symptoms may be present in association with any of these symptoms.^{1,2}

If cardiomyopathy is suspected, clozapine should be discontinued and the patient referred to a cardiologist immediately.^{1,2} Patients who have had cardiomyopathy should not be re-exposed to clozapine.^{1,2}

Pericarditis/pericardial effusion

Pericarditis and pericardial effusion have been reported rarely in clozapine-treated patients and some cases have been fatal.^{1,2} Eosinophilia has been reported in association with some of these cases, but it is unclear whether eosinophilia is a reliable predictor of carditis.^{1,2}

If pericarditis or pericardial effusion is suspected the patient should be referred to a cardiologist for confirmation of the diagnosis and further management.^{1,2}

Thromboembolism

There have been rare cases of thromboembolism reported in association with clozapine treatment.^{1,2} Since patients treated with antipsychotics often present with acquired risk factors for thromboembolism, all possible risk factors should be identified before and during treatment with clozapine and preventive measures undertaken.^{1,2}

Risk factors for developing thromboembolism include heavy smoking, obesity, poor health, polypharmacy, sedation and low levels of exercise. To reduce this risk, immobilisation should be avoided and this may be especially relevant for sedated patients. Weight gain should be addressed and any other risk factors should be reduced if possible. Appropriate care should be taken with air travel.

If a thromboembolism occurs, it should be treated as per your Trust's guidelines.

Risk of stroke

An approximately 3-fold increased risk of cerebrovascular adverse events has been seen in randomised placebo controlled clinical trials in the dementia population with some atypical antipsychotics.^{1,2} The mechanism for this increased risk is not known.^{1,2} An increased risk cannot be excluded for other antipsychotics or other patient populations.^{1,2} Clozapine should be used with caution in patients with risk factors for stroke.^{1,2}

Myocardial Infarction, chest pain/angina pectoris

Myocardial infarction which may be fatal and chest pain/angina pectoris are listed as adverse effects to Clozaril[®] which have a frequency of 'not known'.^{1,2}

There have been post marketing reports of myocardial infarction, in Clozaril[®]-treated patients, which may be fatal. In most of these cases, assessment of causality was difficult because of serious pre-existing cardiac disease and possible alternative causes.^{1,2}

Metabolic changes

Atypical antipsychotic drugs, including clozapine, have been associated with metabolic changes that may increase cardiovascular/cerebrovascular risk.^{1,2} These metabolic changes may include hyperglycaemia, dyslipidemia, and body weight gain.^{1,2}

The SmPC for Clozaril[®] lists hypertriglyceridaemia and hypercholesterolaemia as a very rare (<1/10,000) side effects of Clozaril[®].^{1,2}

Dyslipidemia

Undesirable alterations in lipids have been observed in patients treated with atypical antipsychotics, including clozapine.^{1,2} Clinical monitoring, including baseline and periodic follow-up lipid evaluations in patients using clozapine, is recommended.^{1,2}

Sudden unexplained death

Sudden unexplained death has been reported very rarely in patients receiving Clozaril[®].^{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 > 3.5x10⁹/l and Absolute Neutrophil Count (ANC) > 2.0x10⁹/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 hematologist.** 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. **Caution when 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 ($\geq 1/10$), 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 Viatris via cpms@viatris.com

uk-pi-clozaril-May20-v5

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 $> 3.5 \times 10^9/l$ and Absolute Neutrophil Count (ANC) $> 2.0 \times 10^9/l$), 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 $3.0 \times 10^9/l$ or the ANC is less than $1.5 \times 10^9/l$ 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 $2.0 \times 10^9/l$ occurs or the ANC falls below $1.0 \times 10^9/l$ 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 $3.5 \times 10^9/l$ and $3.0 \times 10^9/l$ or the ANC falls to between $2.0 \times 10^9/l$ and $1.5 \times 10^9/l$, haematological evaluations must be performed at least twice weekly until the patient's WBC count and ANC stabilise within the range $3.0 - 3.5 \times 10^9/l$ and $1.5 - 2.0 \times 10^9/l$ 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 $1.0 \times 10^9/l$. **Thrombocytopenia:** Discontinuation of 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. 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.

Dyslipidaemia: 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.

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 ($\geq 1/10$), 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.

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.

References

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