Neurological related side effects 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:

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Seizures with Clozaril®

Background

The Summary of Product Characteristics (SmPC) for Clozaril® (clozapine)[1,2] states that: seizures are a common (≥1/100 but <1/10) reaction to Clozaril®. EEG changes are also listed as an adverse reaction which has a frequency of 'not known'. Clozaril® is contraindicated in uncontrolled epilepsy.

Clozapine lowers the seizure threshold in a dose-dependent manner and may induce myoclonic jerks or generalised seizures.[1,2] The overall incidence of seizures during treatment with clozapine has been estimated at 3%.[3,4] Seizures can occur at any time and with any dose.[5] They have been reported in doses as low as 37.5mg.[6] The periods of greatest risk are during the initial titration period and at higher doses or plasma levels. Devinsky (1991) reported a 4.4% risk of seizures at doses above 600mg with a risk of 2.7% in patients on 300-600mg and 1% for patients on less than 300mg.[3]

There is controversy as to how high the clozapine level has to be to put the patient at serious risk of clozapine-induced seizures. A plasma level of between 0.35mg/L and 0.6mg/L has been suggested to optimise response while minimising the risk of side effects such as seizures.[7] Remington (2013) concludes that there is an increased risk of seizures with clozapine doses above 500-600mg but that the relationship between levels and serious side-effects such as seizures is unclear.[8]

The most common clozapine-induced seizures are generalized tonic-clonic although other types have been reported.[5] These include generalized atonic and myoclonic as well as simple and complex partial seizures.[5]

Myoclonus and stuttering

Myoclonus, seen as muscle jerks, orofacial movements or drop attacks, has been reported with clozapine[9] and may precede the development of seizures in some patients.[9] It is also worth noting that myoclonus, or seizures, may be the first indication of an increased clozapine plasma level. Case reports in the literature document patients who developed myoclonus believed to be secondary to increased clozapine levels due to infection or inflammation.[10] In these cases improvement was seen following clozapine dose reduction or a period of withholding the drug.

Stuttering has been reported in patients on clozapine,[11,12] and it has been suggested that this may be an indication of epileptic brain activity.[11] There are cases where stuttering has responded to dose reduction[12] and others where the dose has been increased and seizures have occurred.

EEG changes

Clozaril can cause EEG changes, including the occurrence of spike and wave complexes. It lowers the seizure threshold in a dose-dependent manner and may induce myoclonic jerks or generalised seizures. These symptoms are more likely to occur with rapid dose increases and in patients with pre-existing epilepsy. In such cases the dose should be reduced and, if necessary, anticonvulsant treatment initiated. Carbamazepine should be avoided because of its potential to depress bone marrow function, and with other anticonvulsants the possibility of a pharmacokinetic interaction should be considered.[1,2]

Mechanism and risk factors

The mechanism of drug-induced seizures is not fully understood.[13] Patients are more likely to have drug-induced seizures if they have other risk factors, including epilepsy or other type of neurological illness, alcohol or drug abuse, or a family history of epilepsy.[14]

Factors which increase the risk of seizures with clozapine, may include a history of previous seizures, recent electroconvulsive therapy (ECT), concomitant treatment with other drugs which lower the seizure threshold and head trauma with loss of consciousness.[3] The risk of seizures may also be increased if drugs that raise the seizure threshold (drugs that protect against seizures), such as benzodiazepines, are discontinued during clozapine treatment.[15]

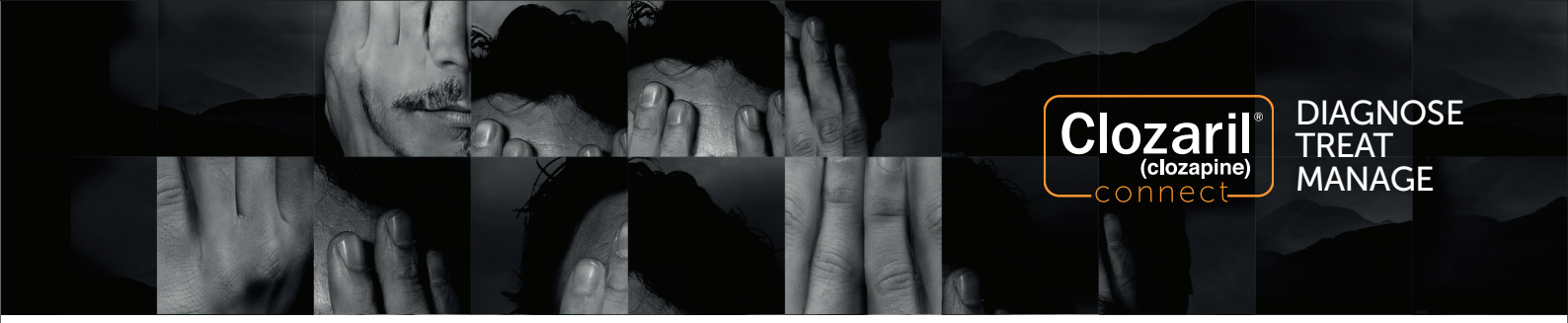
Prevention and management of seizures in patients on clozapine

Using the lowest possible dose and avoiding rapid dose increases may reduce the risk of seizures with clozapine.[16] Patients on clozapine should be observed for any possible signs of seizure activity such as myoclonic jerks or stuttering. In such cases, reduction of the clozapine dose may prevent the patient from developing seizures. Plasma level monitoring may be useful in some patients. Patients with epilepsy may be started on clozapine provided that their seizures are well controlled. These patients should be observed closely during clozapine treatment.[1,2]

Liebermann suggested that if a patient has a seizure whilst on clozapine, the clozapine should be withheld temporarily then restarted, if appropriate, at a lower dose.[17] He also recommended that an EEG and a neurological referral should be considered, particularly if it is the patient's first seizure.[17]

Reducing the dose and re-titrating more gradually may prevent further seizures[18] although the patient may need to be maintained on a lower dose or started on an anticonvulsant.

Consultation with a neurologist is recommended when selecting a drug and the choice is ultimately a clinical decision. Local Trust guidelines should be followed at every step of the management process.



Rare but serious reports of seizures, including onset of seizures in non-epileptic patients, and isolated cases of delirium where Clozaril® was co-administered with valproic acid have been reported.[1,2] These effects are possibly due to a pharmacodynamic interaction, the mechanism of which has not been determined.[1,2] Carbamazepine and phenytoin are not recommended since they may reduce clozapine levels[1,2] and carbamazepine may cause bone marrow depression.[1,2]

Neuroleptic Malignant Syndrome with Clozaril®

Background

The Summary of Product Characteristics (SmPC) for Clozaril® (clozapine) states that Neuroleptic Malignant Syndrome (NMS) is an uncommon (>1/1,000 but <1/100) side effect.[1,2]

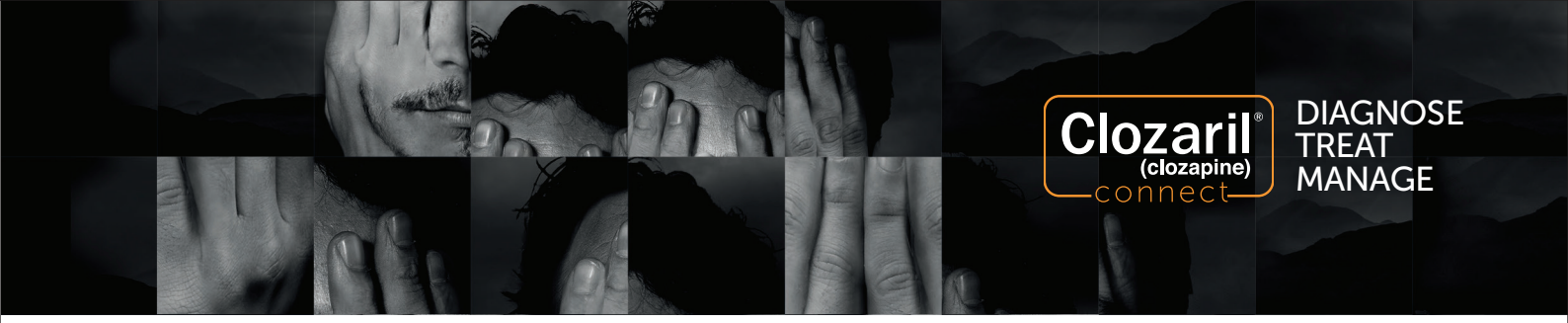
NMS is a serious and potentially fatal symptom complex that has been reported in association with antipsychotic drugs. The incidence of NMS reported with antipsychotics is in the region of 1% and the mortality rate for untreated NMS is in the region of 20%.[19,20] The incidence of NMS reported in patients on clozapine is similar, or possibly slightly less, than that seen with other antipsychotics (due to its lower D2 affinity).[21,22] Cases have been reported in patients using clozapine either as monotherapy or more commonly, in combination with lithium or other central nervous system (CNS) agents, e.g., other neuroleptics.[20,21,23]

Risk factors

NMS can occur at any stage of clozapine treatment,[23] although the average onset is 4 to 5 days[19] and it has also been reported following abrupt discontinuation of neuroleptics.[24] In one review of NMS, it was reported that 90% of cases of NMS occurred within the first 10 days.[19] There appears to be an association with dose, with an increased risk reported in patients who are started on high doses or who undergo rapid dose titration, or in patients who have had a significant dose alteration.[19,21,25]

Males appear to have twice the risk compared to females.[19,25] The median age reported in the literature is between 20-50, which may correlate with peak neuroleptic use.[19,21,25] Other risk factors/precipitating factors for NMS include:[19,21,25,26]

- History of NMS
- Rechallenge with suspect medication
- History of organic brain disease or alcoholism
- Abrupt cessation of anticholinergics
- History of Parkinson's disease/Huntingdon's Chorea
- Concomitant use of predisposing drugs (e.g., lithium)
- Hyperthyroidism
- Low serum iron concentrations
- Catatonia
- High potency neuroleptics
- Dehydration
- Depots/IM neuroleptic injections
- Agitation
- Extrapyramidal side-effect/tardive dyskinesia
- Elevated temperature



Clozaril® (clozapine) connect

DIAGNOSE
TREAT
MANAGE

Diagnosis

Diagnostic evaluation of patients with NMS is complicated and is based on the history, clinical presentation and laboratory findings. It is important to exclude other drug-induced, systemic or neuropsychiatric illness, but the diagnosis must be considered in any patient presenting with the clinical features of NMS, including those with high fever.

Clinical manifestations may include:[19,20,25,26]

- Hyperthermia/fever
- Muscular rigidity (lead-pipe)
- Altered mental status: confusion, agitation, or altered consciousness
- Evidence of autonomic instability: tachycardia, fluctuating blood pressure with hypertension or hypotension, diaphoresis (sweating, which may be profuse), or tachypnoea
- Laboratory findings can include leucocytosis, metabolic acidosis, increased creatine phosphokinase (CPK) or increased urinary myoglobin

Due to clozapine's different pharmacologic profile NMS may present atypically in clozapine-treated patients.[21,22,26] There maybe fewer motor abnormalities and a milder fever.

As mentioned above, diagnosis of NMS can be difficult, especially as clozapine-induced NMS may not present with all the classical features. Many of the symptoms, signs and laboratory findings seen in NMS are known adverse reactions to clozapine (e.g., fever, rigidity, confusion, agitation, tachycardia, hypertension, hypotension, disturbances in sweating, hypersalivation, incontinence, tremor, leucocytosis and increased CPK) and occur in the absence of NMS. Marked increases of CPK (mostly asymptomatic or less commonly associated with myopathy or rhabdomyolysis) which were not associated with NMS have been reported in patients on clozapine.[27-29]

Differential diagnosis

A number of other differential diagnoses need to be considered, including CNS infections; lethal catatonia; malignant hyperthermia; heat stroke; Serotonin Syndrome; or other drug reactions (e.g., lithium toxicity) or drug withdrawal syndromes.[19,25,29]

It is important to review the complete clinical picture of any patient who presents with features of NMS or in whom a diagnosis of NMS is suspected.

Management

If diagnosis of NMS is confirmed, Clozaril® should be discontinued immediately and appropriate medical measures should be administered.[1,2] Specialist care will be needed. The patient should be given general supportive medical care as an in-patient. Particular attention should be paid to cooling the patient (antipyretics, cooling blanket), adequate rehydration with intravenous fluids and correction of electrolyte abnormalities.[25] There is no proven effective treatment for NMS. Most patients recover from NMS in 2-14 days without any cognitive impairment[25] although mortality from untreated NMS has been reported to be as high as 20%.[19]

Clozaril® rechallenge following NMS

Rechallenge of patients with a history of antipsychotic-induced NMS (including clozapine-induced NMS) is not contraindicated with Clozaril®. However, the decision to rechallenge must be made following a careful risk-benefit assessment of each individual case.

CLOZARIL® Clozapine PATIENT MONITORING SERVICE

Veeva Reference: CLZ-2023-0005
Date of Preparation: April 2023

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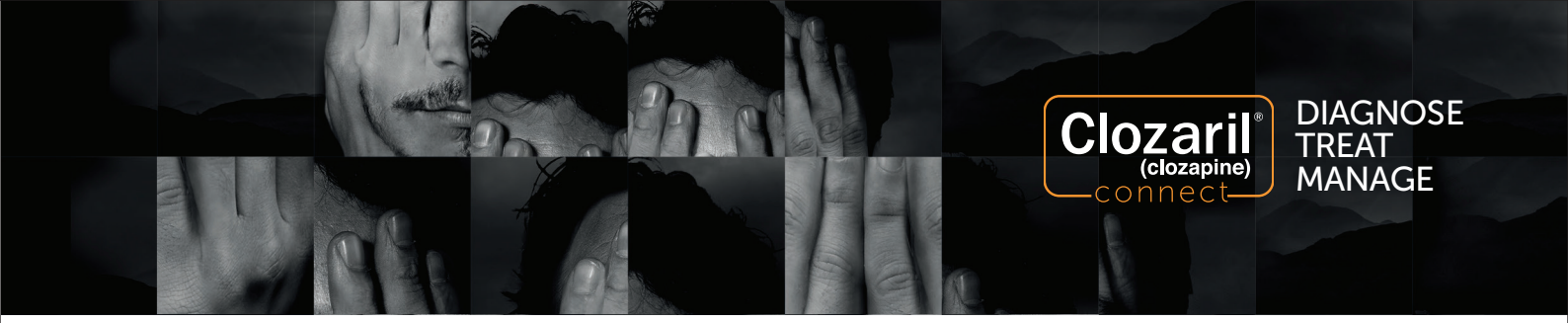


Clozaril® has been used in patients with a history of NMS secondary to typical antipsychotics and, due to its different pharmacological structure, is the recommended choice of some authors.[25] However, there are reports of patients with a history of NMS due to other antipsychotics who developed a further episode of NMS following treatment with clozapine.[20,29,30]

Successful rechallenge after clozapine-induced NMS has also been reported.[20,22,23,29,31] Rechallenge should only be considered after full recovery from the NMS. Low dose restart and slow titration must be used while monitoring the patient carefully for side-effects.

Fever with Clozaril®

Background

The Summary of Product Characteristics of Clozaril® (clozapine) states that fever and benign hyperthermia are a common (≥1/100 but <1/10) side effect.[1,2]

During Clozaril® therapy, patients may experience transient temperature elevations above 38°C, with the peak incidence within the first 3 weeks of treatment. This fever is generally benign. Occasionally, it may be associated with an increase or decrease in the WBC count. Patients with fever should be carefully evaluated to rule out the possibility of an underlying infection or the development of agranulocytosis. In the presence of high fever, the possibility of neuroleptic malignant syndrome (NMS) must be considered. If the diagnosis of NMS is confirmed, Clozaril® should be discontinued immediately and appropriate medical measures should be administered.[1,2]

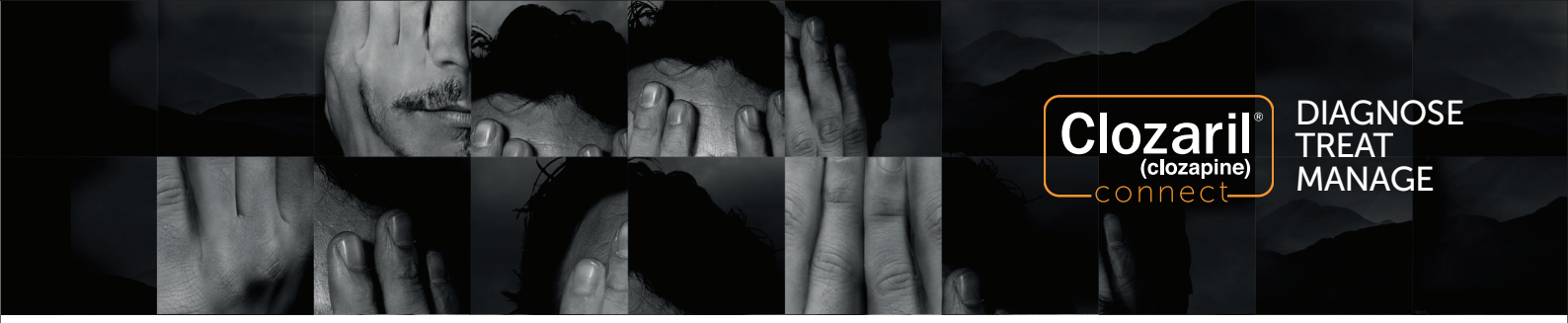
Fever or benign transient hyperthermia (temporary elevation of temperature without serious effects) generally involves an increase in temperature of 0.5-1.5°C,[4] is often spiking in nature[32] and is of no clinical significance, resolving spontaneously over a few days. Although fever in clozapine-treated patients is not usually significant it is important to consider the possibility of more serious conditions such as agranulocytosis, myocarditis, neuroleptic malignant syndrome or an underlying infection. If necessary the clozapine should be withheld until these are excluded. Please see the neutropenia and agranulocytosis, cardiovascular events or neuroleptic malignant syndrome factsheets respectively for more information about management of these conditions.

The incidence of fever in clozapine-treated patients reported in the literature varies considerably from 1.2% up to as much as 55%[32-38] although this wide variation may be due to the different thresholds used to define fever.
The fever may be associated with tachycardia or gastrointestinal or respiratory symptoms,[39] or an elevated white blood cell count (WBC).[32,40] Increases in erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) have also been reported.[37] With respect to risk factors, the incidence does not appear to be affected by gender, although older patients may be at more risk.[32]

Management

It is a clinical decision for the treatment team to stop clozapine if a patient develops a fever. It is important to investigate for all possible causes of fever and treat the underlying cause if necessary.

Most cases of clozapine-induced fever resolve spontaneously, however, whenever a patient on clozapine presents with a raised temperature a full blood count with differential must be undertaken to ensure that the patient does not have an underlying neutropenia. If the patient is neutropenic, Clozaril® must be stopped immediately.



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.

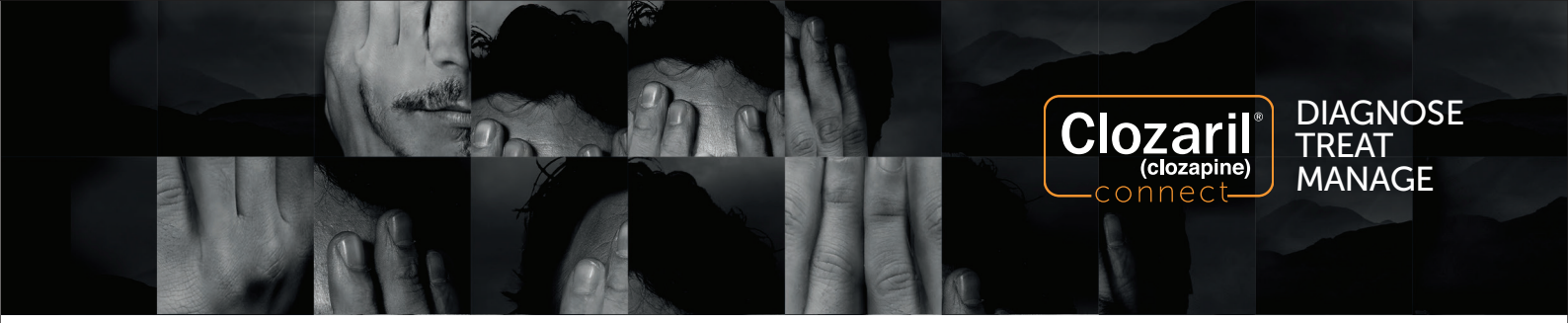
Method of administration Clozaril is administered orally.
Switching from a previous antipsychotic therapy to Clozaril
It is generally recommended that Clozaril should not be used in combination with other antipsychotics. When Clozaril therapy is to be initiated in a patient undergoing oral antipsychotic 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-2023-0005
Date of Preparation: April 2023

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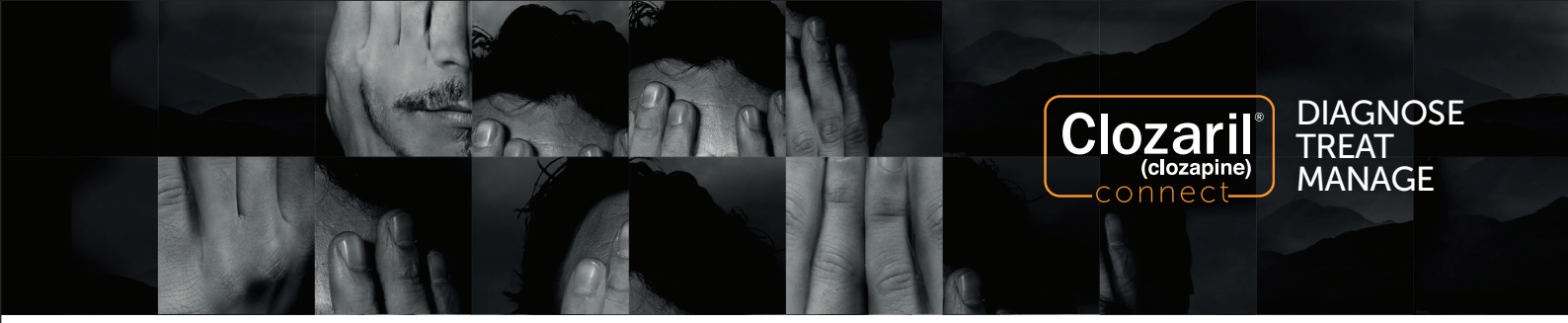

PRESCRIBING INFORMATION - Ireland
CLOZARIL (clozapine) 25 mg Tablets
CLOZARIL (clozapine) 100 mg Tablets

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.

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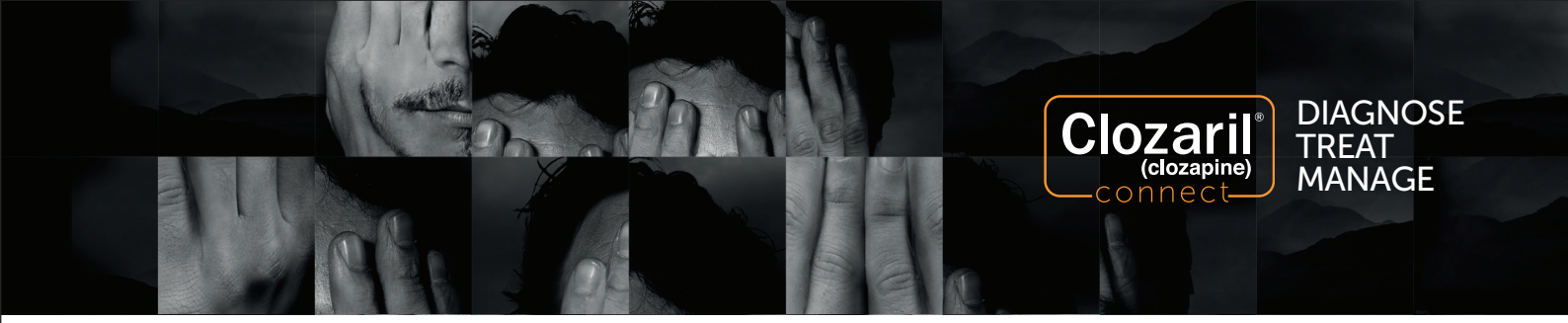

Pyrexia: High temperatures should be evaluated carefully to rule out underlying infection, agranulocytosis or Neuroleptic Malignant Syndrome (NMS). If NMS is confirmed, discontinue Clozaril immediately and administer appropriate medical measures.
Patients with rare hereditary problems of galactose intolerance 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.

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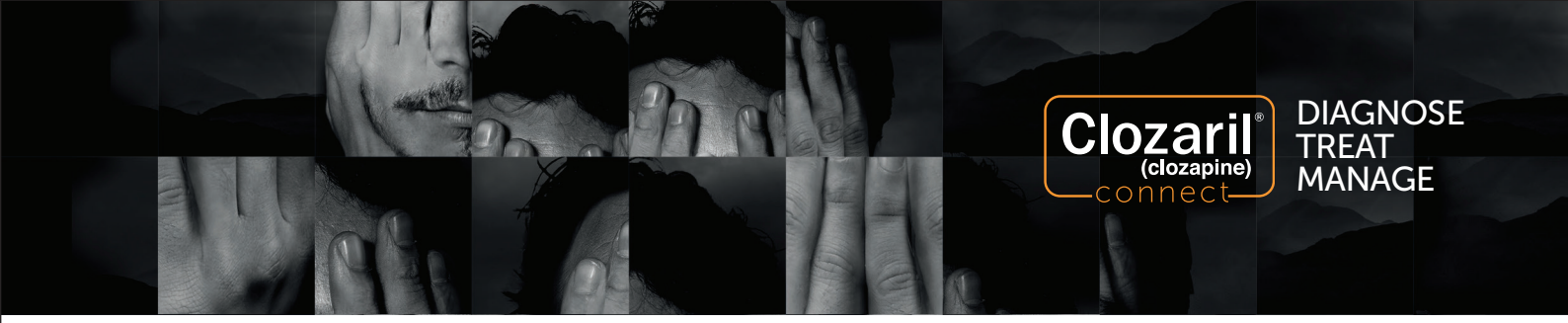

References

1. Clozaril® (clozapine) Summary of Product Characteristics (online). Mylan Products Ltd. http://www.medicines.org.uk/emc/ (Accessed on 17/01/2023).
2. Clozaril® (clozapine) Summary of Product Characteristics (online). Mylan IRE Healthcare Limited. http://www.medicines.ie/ (Accessed on 17/01/2023).
3. Devinsky O, Honigfeld G and Patin J. Clozapine-related seizures. *Neurology* 1991; 41: 369-71.
4. Dev VJ and Krupp P. Adverse Event Profile and Safety of Clozapine. *Rev Contemp Pharmacother* 1995; 6: 197-208.
5. Wong J. Clozapine-Induced Seizures: Recognition and Treatment. *Can J Psychiatry* 2007; 52: 457-463.
6. Landry P. Gabapentin for clozapine-related seizures. *Am J Psychiatry.* 2001; 158(11): 1930-1.
7. 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.
8. Remington G. Clozapine and therapeutic drug monitoring: is there sufficient evidence for an upper threshold? *Psychopharmacology* 2013; 225: 505-518.
9. Berman I, Zalma A, DuRand CJ *et al.* Clozapine-induced myoclonic jerks and drop attacks (letter). *J Clin Psychiatry* 1992; 53: 329-330.
10. Liang CS and Hsieh TH. Myoclonus as an indicator of infection in patients with schizophrenia treated with clozapine. *J Psychiatry Neuroscience* 2011; 36(1): E1- E2.
11. Supprian T *et al.* Clozapine-Induced Stuttering: Epileptic Brain Activity? *Am J Psychiatry* 1999; 156(10): 1663.
12. Hallahan BP *et al.* Clozapine induced stuttering. *Ir J Psych Med* 2007; 24(3): 121.
13. Ruffmann C, Bogliun G, Beghi E. Epileptogenic drugs: a systematic review. *Expert Rev Neurother.* 2006; 6(4): 575-89.
14. Murphy K and Delanty N. Drug-Induced Seizures. *CNS Drugs* 2000; 14: 135-46.
15. Young CR, Bowers MB, Jr. and Mazure CM. Management of the Adverse Effects of Clozapine. *Schizophr Bull* 1998; 24: 381-390.
16. Toth P and Frankenburg FR. Clozapine and Seizures: A Review. *Can J Psychiatry* 1994; 39: 236-238.
17. Lieberman JA, Kane JM and Johns CA. Clozapine: Guidelines for Clinical Management. *J Clin Psychiatry* 1989; 50: 329-338.
18. Pacia SV and Devinsky O. Clozapine-related seizures: Experience with 5,629 patients. *Neurology* 1994; 44: 2247-2249.
19. Heiman-Patterson T. Neuroleptic Malignant Syndrome and Malignant Hyperthermia: Important Issues for the Medical Consultant. *Med Clin N Am* 1993; 77(2): 477-489.
20. Reddig S *et al.* Neuroleptic Malignant Syndrome and Clozapine. *Ann Clin Psych* 1993; 5: 25-27.
21. Amore M *et al.* Atypical Neuroleptic Malignant Syndrome Associated with Clozapine Treatment. *Neuropsychobiology* 1997; 35: 197-199.
22. Cohen S. Successful Clozapine Rechallenge Following Prior Intolerance to Clozapine. *J Clin Psych* 1994; 55: 498-499.
23. D'Silva K and Quinn P. Successful Clozapine Rechallenge in Atypical NMS. *Progress in Neurol and Psych* 2001; 5: 26-27.
24. Amore M and Zazzeri N. Neuroleptic Malignant Syndrome after Neuroleptic Discontinuation. *Prog Neuro-Psychopharmacol and Biol Psychiat* 1995; 19: 1323-1334.
25. Taylor D *et al.* The Maudsley Prescribing Guidelines in Psychiatry 13th Edition. Wiley-Blackwell. 2015.
26. Pelonero A *et al.* Neuroleptic Malignant Syndrome – A Review. *Psychiatr Serv* 1998; 49: 1163-72.
27. Scelsa SN *et al.* Clozapine-Induced Myotoxicity in Patients with Chronic Psychotic Disorders. *Neurology* 1996; 47: 1518-23.
28. Keshavan MS, Stecker J and Kambhampati RK. Creatine Kinase Elevations with Clozapine. *Br J Psychiatry* 1994; 164: 118-20.
29. Hasan S and Buckley P. Novel Antipsychotics and the Neuroleptic Malignant Syndrome: A Review and Critique. *Am J Psychiatry* 1998; 155: 1113-6.
30. Sachdev P *et al.* Clozapine-Induced Neuroleptic Malignant Syndrome: Review and Report of New Cases. *J Clin Psychopharmacology* 1995; 5: 365-371.
31. Manu P *et al.* When can Patients with Potentially Life-threatening Adverse Effects be Rechallenged with Clozapine? A Systematic review of the Published Literature. *Schizophr Res* 2012; 134(2-3): 180-186.
32. Tham JC and Dickson RA. Clozapine-Induced Fevers and 1-Year Clozapine Discontinuation Rate. *J Clin Psychiatry* 2002; 63: 880-4.
33. Safferman A *et al.* Update on the Clinical Efficacy and Side Effects of Clozapine. *Schizophr Bull* 1991; 17: 247-261.
34. Nitenson NC *et al.* Fever Associated with Clozapine Administration (letter). *Am J Psychiatry* 1995; 152: 1102.
35. Pollmächer T *et al.* The Influence of Clozapine Treatment on Plasma Granulocyte Colony-Stimulating (G-CSF) Levels. *Pharmacopsychiatry* 1997; 30: 118-121.
36. Juul Povlsen U *et al.* Tolerability and Therapeutic Effect of Clozapine: a Retrospective Investigation of 216 Patients Treated With Clozapine For Up To 12 Years. *Acta Psychiatr Scand* 1985; 71: 176-185.
37. Müller H *et al.* Influence of Clozapine on Body Temperature and on Acute Phase Proteins. *Pharmacopsychiatry* 1992; 25: 109.
38. Naber D *et al.* Clinical Management of Clozapine Patients in Relation to Efficacy and Side-Effects. *Br J Psychiatry* 1992; 160(17): 54-59.
39. Trémeau F *et al.* Spiking Fevers with Clozapine Treatment. *Clinical Neuropharmacology* 1997; 20: 168-170.
40. Lieberman JA and Safferman AZ. Clinical Profile Of Clozapine: Adverse Reactions and Agranulocytosis. *Psychiatric Quarterly* 1992; 63: 51-70.