

Lifestyle considerations 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:

- Hypersalivation with Clozaril[®]
- Weight gain with Clozaril[®]
- Diabetes and hyperglycaemia with Clozaril[®]
- Urinary retention with Clozaril[®]

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Hypersalivation with Clozaril[®]

Background

The Summary of Product Characteristics (SmPC) of Clozaril[®] (Clozapine) states that hypersalivation is a very common ($\geq 1/10$) side effect.^{1,2}

Hypersalivation may be defined as an abnormally increased secretion of saliva. It may also be referred to as sialorrhoea or ptyalism. An excess of saliva can lead to pooling in the mouth with subsequent drooling. Hypersalivation is more common at night.³ The incidence of clozapine-induced hypersalivation reported in the literature varies enormously from 10% up to as much as 80%,^{4,5} with several sources quoting incidences in the region of 30%.⁶⁻⁸ Clozapine-induced hypersalivation tends to occur early in treatment⁸ and although some patients may develop tolerance to it, many do not and the problem can persist for years.⁸

Implications and complications of hypersalivation

Hypersalivation is an uncomfortable and embarrassing side-effect which may be a significant cause of non-compliance and discontinuation of clozapine.⁹ It may cause social stigma, disturbed sleep, aspiration, parotitis, maceration and infection of the skin, poor hygiene and a reduced quality of life.⁹ Since each swallow allows some air into the gastrointestinal tract, increased swallowing may result in bloating, pain and flatus.¹⁰ Aspiration is the most serious consequence of hypersalivation as it may lead to coughing, hoarseness, difficulty speaking, choking, bronchitis or pneumonia.^{10,11}

Is clozapine-induced hypersalivation dose-related?

Although hypersalivation in some patients may be improved by dose reduction it is not necessarily dose related.^{12,13}

As with many other side-effects of clozapine, using a slow dose titration on initiation of treatment and using the lowest effective dose may minimise clozapine-induced hypersalivation.¹⁴

Management

Consider checking the patient's plasma level to see whether a dose reduction may be appropriate. Cautious dose reduction may be possible for stable patients with an adequate plasma level although the risk of exacerbating psychosis must be taken into account. As patients commonly experience hypersalivation at night, it can be helpful to use towels over the pillows. Using extra pillows to prop up the head can reduce the amount of saliva produced as it may be posture-related.⁶ Nocturnal hypersalivation can lead to a choking sensation which may be helped by patient education regarding swallowing difficulties. Swallowing two or three times without inhaling (by compression of the nostrils) can reduce the sensation of choking.¹⁵ Advising patients to swallow more frequently may be helpful⁴ and during the daytime this can be encouraged by chewing gum¹⁶ which can help to prevent drooling. Sugar free gum should be used to prevent dental decay and reduce sugar intake.

If hypersalivation is a persistent problem (despite dose review, daytime use of chewing gum and/or extra pillows at night), pharmacological intervention may be necessary. Please refer to your local hospital trust guidelines on effective drug management of hypersalivation.

Weight gain with Clozaril®

Background

The SmPC for Clozaril^{®1,2} states that: Weight gain has been observed with atypical antipsychotic use, including Clozaril[®]. Clinical monitoring of weight is recommended. Weight gain is listed as a common ($\geq 1/100$ to $< 1/10$) adverse reaction to Clozaril[®].^{1,2}

Weight gain is a well-documented side effect of some atypical antipsychotics including clozapine. In addition to weight gain, anti-psychotics are also known to impair glucose metabolism, increase cholesterol and triglyceride levels and cause arterial hypertension, leading to metabolic syndrome. Patients with schizophrenia are more likely to be over weight than the general population.¹⁷ Weight gain with clozapine is thought to be due to appetite stimulation with a multifactorial mechanism including effects on serotonergic, adrenergic and histaminergic neurotransmitter systems.¹⁸ It usually occurs during the first year of treatment.¹⁹ Gaining weight from antipsychotic treatment can have an influence on patient compliance²⁰ and also gives added health risks such as an increase in the risk of hypertension, coronary heart disease and diabetes.

Prevention and Management

The issue of weight gain should be discussed with the patient prior to starting clozapine. Careful monitoring and early intervention are the first step in managing anti-psychotic induced weight gain (AIWG). Interventions that minimise AIWG can be broadly classified as pharmacological and non-pharmacological.

Non-pharmacological interventions consist of cognitive-behavioural strategies and lifestyle modifications such as nutritional counselling and exercise.²¹ Cognitive strategies include understanding eating behaviours and physical well-being. Behaviour interventions include training in problem solving, goal setting, social support, monitoring exercise and eating habits. Dietary advice and nutritional counselling includes reducing 500-1000 kcal/daily from the existing diet and reducing dietary fat to 30% of energy intake. Exercise consists of 150 minutes of moderate exercise weekly.²¹ Apart from a significant impact on cardio-metabolic risk factors, non pharmacologic weight prevention or reduction has the potential to improve quality of life, anti-psychotic medication adherence and overall prognosis of the illness.

Pharmacological interventions consist of switching to another anti-psychotic or a drug adjuvant to encourage weight loss via a drug-induced mechanism. Several Random Control Trials (RCTs), meta-analysis and systemic reviews have assessed the effectiveness of pharmacological interventions in managing AIWG. However, the evidence for routine use of pharmacological adjuvants are not strong.²¹ Adjuvant drug treatment for weight gain is mostly indicated when non-pharmacological interventions alone are non-sufficient or impractical.²¹

Combination of interventions may be helpful. Interventions will have to be tailored according to individual needs.

Diabetes and hyperglycaemia with Clozaril®

Background

The SmPC for Clozaril® states that diabetes mellitus and impaired glucose tolerance are rare ($\geq 1/10,000$ but $< 1/1,000$) side effects.^{1,2} Ketoacidosis, hyperosmolar coma and severe hyperglycaemia are listed as very rare ($< 1/10,000$).^{1,2}

Metabolic changes

Atypical antipsychotic drugs, including clozapine, have been associated with metabolic changes that may increase cardiovascular/cerebrovascular risk. These metabolic changes may include hyperglycaemia, dyslipidaemia, and body weight gain. While atypical antipsychotic drugs may produce some metabolic changes, each drug in the class has its own specific profile.^{1,2}

Hyperglycaemia

Impaired glucose tolerance and/or development or exacerbation of diabetes mellitus has been reported rarely during treatment with clozapine. A mechanism for this possible association has not yet been determined. Cases of severe hyperglycaemia with ketoacidosis or hyperosmolar coma have been reported very rarely in patients with no prior history of hyperglycaemia, some of which have been fatal. When follow-up data were available, discontinuation of clozapine resulted mostly in resolution of the impaired glucose tolerance, and reinstitution of clozapine resulted in its reoccurrence. Patients with an established diagnosis of diabetes mellitus who are started on a typical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g., obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Patients who develop symptoms of hyperglycaemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing.^{1,2}

In some cases, hyperglycaemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of antidiabetic treatment despite discontinuation of the suspect drug. The discontinuation of clozapine should be considered in patients where active medical management of their hyperglycaemia has failed.^{1,2}

Dyslipidaemia

Undesirable alterations in lipids have been observed in patients treated with atypical antipsychotics, including clozapine.

Clinical monitoring, including baseline and periodic follow-up lipid evaluations in patients using clozapine, is recommended.^{1,2}

Metabolic and nutritional disorders

Impaired glucose tolerance and/or development or exacerbation of diabetes mellitus has been reported rarely during treatment with clozapine. On very rare occasions, severe hyperglycaemia, sometimes leading to ketoacidosis/hyperosmolar coma, has been reported in patients on Clozaril® treatment with no prior history of hyperglycaemia. Glucose levels normalised in most patients after discontinuation of Clozaril® and in a few cases hyperglycaemia recurred when treatment was reinitiated.

Although most patients had risk factors for non-insulin-dependent diabetes mellitus (NIDDM), hyperglycaemia has also been documented in patients with no known risk factors.^{1,2}

Both diabetes and hyperglycaemia have been reported with a higher overall prevalence in both untreated and (even more so) treated schizophrenia as compared to the general population.²²⁻²⁵

Risk factors

Most, although not all, patients that develop diabetes or impaired glucose tolerance whilst on antipsychotics have risk factors for NIDDM. Important general risk factors include past medical or family history, male gender, obesity and lack of physical activity.²⁶ Physical inactivity may be particularly relevant in Clozaril® patients due to the sedating properties of Clozaril®.

Prevention and monitoring

Before starting Clozaril® it is advisable that patients should be assessed with respect to risk factors for impaired glucose tolerance and diabetes, though this is not a mandatory requirement. Routine glucose monitoring again is not mandatory. If it is carried out as part of good clinical practice, it is a clinical decision how often the test should be performed.

Management and re-challenge

It is very important to recognise impaired glucose tolerance and diabetes early. The possibility should be considered in any patient receiving clozapine who develops symptoms of hyperglycaemia, such as polydipsia or polyuria, and the patient referred for assessment of their condition. Management advice should be sought from the medical team if necessary. If ketoacidosis or hyperosmolar coma develop clozapine should be stopped immediately and the patient admitted to a medical ward. Re-challenge in these patients should be done cautiously and with careful monitoring of the patient's glucose levels.

Urinary incontinence / Urinary retention with Clozaril®

Background

The SmPC for Clozaril®^{1,2} states that: Urinary incontinence and urinary retention are common ($\geq 1/100$ but $< 1/10$) side-effects of Clozaril®. Nocturnal enuresis is also listed as an adverse effect which has a frequency of 'not known'. There is evidence to suggest that it is often an under-reported side-effect due to the associated social stigma.^{27,28}

Urinary incontinence is known to be associated with severe mental illness and neuroleptic medications, including clozapine.²⁷ While not usually a health risk, it is a major negative influence on a patient's quality of life and can lead to non-compliance. It may occur at any time during clozapine treatment, at any dose and is frequently nocturnal. It has been reported in males and females of all ages,²⁷ although the elderly may be particularly susceptible.

Childhood enuresis has been identified as a risk factor, as has severity of mental illness, constipation, sedation, diabetes and seizures.^{27,28} Urinary retention may be serious enough to require emergency treatment.^{29,30} Patients at most risk of developing retention are those with pre-existing conditions that involve incomplete voiding of the bladder, such as prostatic enlargement.⁸ Patients aged 60 years and older may also be particularly susceptible to the anticholinergic effects of Clozaril®.^{1,2}

Mechanism

There are a number of possible mechanisms that can explain the occurrence of urinary retention and incontinence. The potent anticholinergic activity of clozapine may result in urinary retention with subsequent overflow resulting in incontinence. It has also been proposed that the antiadrenergic activity of clozapine decreases bladder sphincter tone and causes bladder emptying. Urinary disorders may also occur as a secondary consequence of other disorders or side-effects associated with clozapine, for example, incontinence may be secondary to excessive sedation which then prevents the patient from waking during sleep to empty the bladder. Clozapine-induced constipation may aggravate urinary retention resulting in secondary overflow, and incontinence secondary to diabetes and seizures may also occur.^{27,28}

Prevention

It may be necessary to enquire specifically about incontinence since there is evidence to show that patients are reluctant to report what they see as an embarrassing side-effect.

Urinary incontinence often occurs at night (nocturnal enuresis) and it may be helpful to restrict fluids during the evening and make sure that patients urinate before going to bed. Patients should have easy access to a toilet and, in addition, it may be worth waking the patient during the night to use the toilet. Another consideration is to reduce the clozapine dose or alter the dosage schedule,¹⁹ reducing the evening dose to avoid deep sedation.

Due to the severity of urinary retention, it is recommended that elderly patients and those with prostatic enlargement or other pre-existing conditions that involve incomplete voiding of the bladder, are carefully supervised.^{1,2} Constipation in patients on clozapine should be identified and managed due to the risk of developing gastrointestinal obstruction, in addition to the aggravation of retention.

Other drugs with anticholinergic or sedative side-effects should be avoided where possible.

Management

Urinary incontinence, as mentioned above, may be secondary to constipation, seizures or diabetes mellitus and it is important to distinguish and manage the underlying cause prior to initiating any treatment. It is also important to ensure that urinary retention is excluded before treating the patient for urinary incontinence. Some cases of urinary incontinence may resolve spontaneously.²⁷

For pharmacological treatment, please check local hospital trust guidelines on effective drug management of urinary incontinence. Urinary retention should be managed in consultation with a urologist. Acute retention may require emergency catheterisation and hospital admission.

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. 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 ($\geq 1/10$), 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.

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