Gastroenterology 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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Constipation with Clozaril®

Background

The Summary of Product Characteristics (SmPC) for Clozaril® (clozapine) lists constipation as a very common (>1/10) reaction to Clozaril®. Intestinal obstruction, paralytic ileus and faecal impaction are listed as very rare (<1/10,000).[1,2]

The SmPC continues: Probably on account of its anticholinergic properties, Clozaril® has been associated with varying degrees of impairment of intestinal peristalsis, ranging from constipation to intestinal obstruction, faecal impaction and paralytic ileus. On rare occasions these cases have been fatal. Particular care is necessary in patients who are receiving concomitant medications known to cause constipation (especially those with anticholinergic properties such as some antipsychotics, antidepressants and antiparkinsonian treatments), have a history of colonic disease or a history of lower abdominal surgery as these may exacerbate the situation. It is vital that constipation is recognised and actively treated. Paralytic ileus is a contraindication to Clozaril® use.

Incidence and mechanism

Constipation is a very common side-effect of clozapine with a reported incidence in the literature of up to 60%.[3,4] Shirazi *et al* (2016), in a systematic review and meta-analysis of 32 studies, identified a prevalence of 31.2% with patients on clozapine significantly more likely to be constipated than those on other antipsychotics.[5]

Constipation with clozapine is probably due to its anticholinergic properties[1,2] but antagonism of serotonergic and histamine H1 receptors may contribute to the effect and concomitant medications may exacerbate the problem.[4-7] It often occurs early in treatment, can persist throughout treatment and may be dose-related although it has been reported in doses as low as 50mg.[4]

Clozapine may impair motility of the entire gastrointestinal system from the oesophagus to the rectum.[6] Every-

Palmer *et al* (2016) measured colonic transit times (CTTs) of psychiatric inpatients treated with antipsychotics and found that 80% of clozapine-treated patients had hypomotility with CTTs four times longer than population norms and patients on other antipsychotics.[8]

Risk factors for clozapine-induced gastrointestinal hypomotility

The following factors have been suggested to increase the risk of constipation in patients treated with clozapine.[1,2,5,6]

- Previous history of constipation, gastrointestinal disease or lower abdominal surgery
- Increasing age – patients aged 60 years and older may be particularly susceptible
- Concomitant use of other anticholinergic drugs
- Obesity
- Poor diet
- Low levels of exercise
- Poor bowel habit
- Higher clozapine dose or plasma level
- First 4 months of treatment
- Raised clozapine plasma levels caused by smoking cessation or cytochrome P450 enzyme-inhibiting drugs

It has also been suggested that fever, infection or inflammation may inhibit the metabolism of clozapine leading to increased plasma levels and risk of constipation.[6,9,10]

Consequences of constipation

Clozapine-related constipation may reduce the patient's quality of life and lead to discontinuation of clozapine with subsequent deterioration in mental health. Very rarely patients may develop bowel obstruction, faecal impaction or paralytic ileus and on rare occasions such complications have been fatal.[1,2] The risk of clozapine-induced constipation must not be underestimated. It is important to check that patients are not suffering from constipation and if it occurs it must be treated immediately with follow-up to ensure that the treatment has been effective.

Palmer *et al* (2008) reviewed 102 cases of suspected life-threatening clozapine-induced gastrointestinal hypomotility (CIGH) and found that patients were at risk regardless of age, sex, dose and duration of treatment.[6] The rate of mortality was 27.5% and there was significant morbidity mainly due to bowel resection.[6] Symptoms of serious pathology in the cases reviewed were moderate to severe pain, abdominal distension and vomiting with overflow diarrhoea, reduced appetite, nausea and septic shock cited as justification for urgent medical referral.[6]

Management of clozapine-induced constipation

It is essential that constipation is recognized and managed immediately since if left untreated it can progress to intestinal obstruction, faecal impaction or bowel perforation. Accurate assessment of constipation is essential to determine the extent of the problem, other factors which may be exacerbating the situation and to exclude any complications.

Prior to the initiation of clozapine, patients and their carers should be warned about the risk of constipation and advised to seek medical attention immediately if it occurs.[6] Patients should be asked about their bowel function at each visit to the clinic and information given about preventative measures such as a high fibre diet, maintaining adequate fluids (especially if hypersalivation is a problem also) and increasing activity levels.

Drugs such as tricyclic antidepressants, opioids and anticholinergics should be avoided if possible since they may exacerbate constipation. Consult your local clinical pharmacist for further information about medications which may aggravate or cause constipation.

There are no specific guidelines on the treatment of clozapine-related constipation and insufficient data to support which laxatives are the most effective. A Cochrane Review (2017) concluded that there is inadequate evidence to assess drugs used to treat antipsychotic-related constipation in terms of safety and efficacy.[11]

For information on the management of constipation please refer to a medic, gastroenterologist or your local clinical pharmacist.

Some physicians will decrease the dose of clozapine if a patient develops constipation but, although worth considering, dose reduction may not be successful. In cases of severe constipation, where the patient's condition may be life-threatening, the treating team should consider with holding the clozapine.[6] Patients who have an acute onset of symptoms, have severe symptoms, or who are unresponsive to treatment must be referred to a specialist for further investigation.

Liver disorder with Clozaril®

Background

The SmPC for Clozaril®[1,2] states that: elevation of liver enzymes is a common (≥1/100 but <1/10) reaction to Clozaril®, hepatitis and cholestatic jaundice are listed as rare (≥1/10,000 but <1/1,000) reactions to Clozaril® and fulminant hepatic necrosis is a very rare (<1/10,000) reaction to Clozaril®.

The following hepatic disorders are also listed as adverse events which have a frequency of 'not known': hepatic steatosis, hepatic necrosis, hepatotoxicity, hepatic fibrosis, hepatic cirrhosis, liver disorders including those hepatic events leading to life-threatening consequences such as liver injury (hepatic, cholestatic and mixed), liver failure which may be fatal and liver transplant.[1,2]

Clozaril® is contraindicated in patients with active liver disease associated with nausea, anorexia or jaundice. It is also contraindicated in patients with progressive liver disease or hepatic failure.[1,2]

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. If the elevation of the values is clinically relevant (more than three times the upper limit of normal) or if symptoms of jaundice occur, treatment with Clozaril® must be discontinued. It may be resumed only when the results of liver function tests are normal. In such cases, liver function should be closely monitored after re-introduction of Clozaril®.[1,2]

Hepatobiliary disorders

Transient, asymptomatic elevations of liver enzymes and, rarely, hepatitis and cholestatic jaundice may occur. Very rarely, fulminant hepatic necrosis has been reported. If jaundice develops, Clozaril® should be discontinued. In rare cases, acute pancreatitis has been reported.[1,2]

Onset of transient or a symptomatic elevation of liver enzymes generally occurs during the first 3 months of treatment,[12] resolving spontaneously within 2-3 months without the need to discontinue clozapine.[13] Raised liver enzymes are reported to affect between 30% and 50% of patients[14] although the incidence reported in the literature varies widely depending on the degree of elevation observed, with incidences of up to 78% reported when any values over the upper limit of normal (ULN) were included, but less than half this when only values of at least twice the upper limit of normal were included.[12-15] The incidence does not appear to be affected by age[12] however, men may have a greater risk.[12,13] There is some evidence that the changes may be dose related.[16]

Less commonly, more serious enzyme elevations may occur,[15] and much more rarely, significant liver toxicity (hepatitis, cholestatic jaundice, fulminant hepatic necrosis) has been observed.[1,2] In addition, there have been isolated case reports of fatal hepatotoxicity in clozapine patients.[14]

Recommencing clozapine

If clozapine has been discontinued, treatment should not be resumed until the liver function has returned to normal. It would be advisable to consult with a hepatologist to discuss the case before recommencing as careful monitoring of the patient's liver function tests (LFTs) may be required.

Recommencing in patients who have had minor elevations of their LFTs is often successful, however recommencing in patients who have previously developed significant LFT elevations may result in rapid re-emergence of abnormalities.[16]

Diabetes and hyperglycaemia with Clozaril®

Background

The SmPC for Clozaril® states that diabetes mellitus and impaired glucose tolerance are rare (≥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 atypical 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.[17-20]

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.[21] 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.

Other gastrointestinal related side effects with Clozaril®

Nausea and vomiting

The SmPC of Clozaril® states that nausea and vomiting are common (≥1/100 but <1/10) side-effects.[1,2] The mechanism is unclear and paradoxical (as antipsychotics can be expected to have antiemetic properties due to D2 blockade). It may be due to the anticholinergic effect of delayed gastric emptying,[22] increased salivation[22] or to a centrally-mediated effect related to clozapine's dopamine or serotonin activity.[23] Onset of symptoms usually occurs within the first 6 weeks of treatment.[24]

Tolerance often develops, however, the symptoms may be helped by decreasing the clozapine dose and titrating more slowly.[25] Other successful treatments include the use of antacids or H2 blockers,[22,23,25] however, cimetidine should not be used as it may lead to increased clozapine plasma concentrations due to its inhibition of the P450 enzyme system.[22,23,26] Antiemetics may also be used but it has been suggested that prochlorperazine and metoclopramide should be avoided due to the risk of extrapyramidal side-effects (EPSE).[25]

The SmPC of Clozaril® recommends that liver function tests (LFTs) are performed on patients on clozapine who experience nausea, vomiting or anorexia as they are also possible signs of liver dysfunction. If the values are elevated to a level which is clinically relevant (more than 3 times the UNL) or if symptoms of jaundice occur, treatment with clozapine must be discontinued.[1,2]

Dysphagia

Dysphagia is listed as a rare (≥1/10,000 but <1/1,000) side effect of Clozaril® in the SmPC.[1,2] Psychiatric patients have been reported to have an increased incidence of dysphagia and choking (which may result in serious sequelae such as aspiration pneumonia or airway obstruction) compared to the normal population. The incidence of fatal asphyxia due to choking among psychiatric patients has been estimated at 0.85 per 1,000 per year,[27] more than 100 times the incidence in the general population.[28]

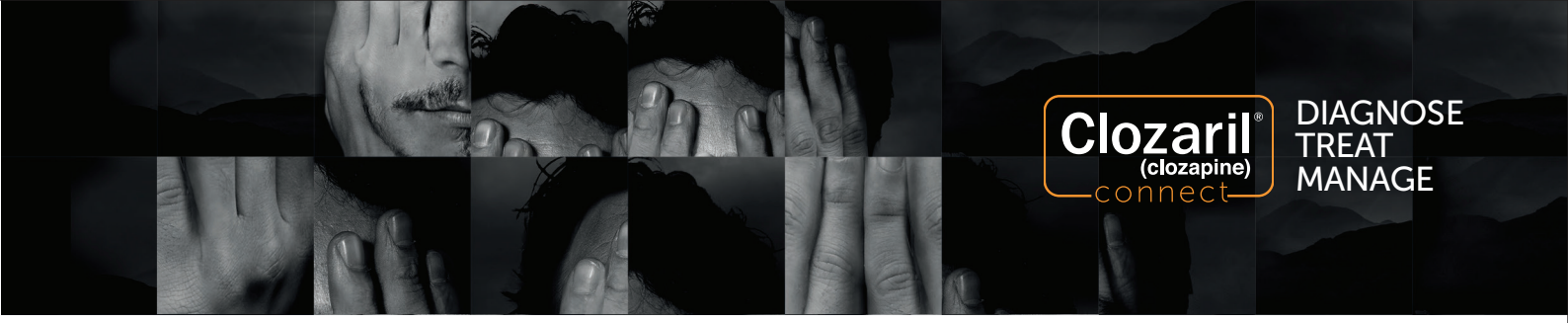
Possible causes include tardive dyskinesia, parkinsonism, anticholinergic effects of medications leading to impairment of the gag reflex, antidopaminergic effects of medications leading to direct impairment of the swallowing process, fast eating or gorging as a part of the psychiatric disorder or an unrelated medical illness.[27-34]

Dysphagia may result in the aspiration of ingested food.[1,2] Clozapine has both dopamine-blocking and anticholinergic properties and such effects may be responsible for some cases of dysphagia seen during clozapine treatment. Additionally, hypersalivation is a very common side-effect of clozapine and some cases of swallowing difficulties are attributed to sialorrhea.[34]

Patient education regarding swallowing may help in cases of dysphagia. This may include teaching the patient to swallow using the correct posture and to eat more slowly with several swallows per bite.[33] In addition, dose reduction has been reported to ameliorate symptomatic dysphagia.[34]

Dry mouth

The SmPC of Clozaril® states that dry mouth is a common (≥1/100 but <1/10) side-effect.[1,2] Although hypersalivation is more commonly seen in patients on clozapine, dry mouth may occur as a result of the anticholinergic effect.



Parotid gland enlargement

Parotid gland enlargement is listed as a very rare (<1/10,000) side effect of Clozaril® in the SmPC.[1,2] Onset has generally been reported to occur within a few weeks of initiating treatment,[35-37] although in one case it presented after approximately 10 months of treatment.[36] In one publication the onset of swelling occurred during periods of dose increases.[35] The mechanism is uncertain, but it has been suggested that it may be due to stasis of saliva or sustained hypersalivation, resulting in inflammation of the gland and/or formation of calculi which block the ducts.[35,36] Both unilateral and bilateral enlargement has been reported in the literature and some cases were associated with a history of hypersalivation whilst others were not.[35,36]

Other gastrointestinal side-effects mentioned in the SmPC for Clozaril®

Megacolon*, intestinal infarction/ischaemia*, intestinal necrosis*, intestinal ulceration*, intestinal perforation*, diarrhoea, abdominal discomfort/heartburn/dyspepsia and colitis are also listed as adverse reactions which have a frequency of 'not known'[1,2]

**These adverse drug reactions were sometimes fatal*[1,2]

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

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

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

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

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

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

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

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

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

Contraindications
Hypersensitivity to the active substance or to any of the excipients. Patients unable to undergo regular blood tests. History of toxic or idiosyncratic granulocytopenia /agranulocytosis (with the exception of granulocytopenia /agranulocytosis from previous chemotherapy). History of Clozaril induced agranulocytosis. Concurrent treatment with substances known to have a substantial potential for causing agranulocytosis; concomitant use of depot antipsychotics is discouraged.
Impaired bone marrow function. Uncontrolled epilepsy. Alcoholic and other toxic psychoses, drug intoxication, comatose conditions. Circulatory collapse and/or CNS depression of any cause. Severe renal or cardiac disorders (e.g. myocarditis). Active liver disease associated with nausea, anorexia or jaundice; progressive liver disease, hepatic failure. Paralytic ileus.

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

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

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

Interaction with other medicinal products and other forms of interaction

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

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

Fertility, Pregnancy and Lactation

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

Ability to Drive and Operate Machinery

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

Undesirable effects

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

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

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

uk-pi-clozaril-May20-v5

CLOZARIL® Clozapine PATIENT MONITORING SERVICE

Veeva Reference: CLZ-2023-0004
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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