Clozaril® connect

DIAGNOSE
TREAT
MANAGE

Bring your Treatment Resistant Schizophrenia patients out of themselves

Clozaril®
(clozapine)

Prescribing Information can be found on pages 10 and 11.

Mylan
Better Health for a Better World

Welcome to Clozaril® Connect, a support programme to help clinicians diagnose, treat, and manage patients with treatment resistant schizophrenia (TRS) who may benefit from clozapine – the only treatment recommended by NICE for TRS.

Clozaril® (clozapine): First-line therapy for Treatment Resistant Schizophrenia

NICE defines 'treatment resistance' in schizophrenia patients as the lack of satisfactory clinical improvement following sequential treatment with at least two different antipsychotic drugs, including at least one second-generation (atypical) antipsychotic.

Clozapine is under-prescribed in the UK

More than 1 in 4 (28%) patients with schizophrenia who fail on at least two antipsychotics, and whose condition may benefit from clozapine treatment are not prescribed it[1].

This is a finding from national audit of schizophrenia (NAS), which was carried out in 2014 by the Royal College of Psychiatrists and involved all 64 Mental Health Trusts in England and Health Boards in Wales[1]. This audit identified three main causes for the under-prescription of clozapine:

1. **More than two antipsychotics are being tried before prescribing clozapine**
   More than half (57%) of schizophrenia patients taking clozapine in 2014 had been prescribed three or more different antipsychotic drugs before initiating treatment with clozapine[1].
2. **Polypharmacy is employed to improve response, rather than moving to clozapine**
   More than 1 in 10 (11%) people with schizophrenia (who were not taking clozapine) were being prescribed more than one type of antipsychotic at the same time. In some areas, this practice occurred in as many as 24% of schizophrenia patients[1].
3. **Patients are treated with higher than recommended doses of antipsychotics**
   One in 10 people are being prescribed antipsychotic drugs – other than clozapine – at a higher dose than that recommended by the British National Formulary[1].

Current trends in prescribing indicate that 28% of patients with TRS are not receiving timely intervention with clozapine, the use of which may improve their symptoms and prognosis.

National Audit of Schizophrenia, 2014[1]

NICE recommends clozapine as first-line treatment for TRS

NICE guidelines recommend that such treatment resistant patients should be offered clozapine as first-line treatment[2].

This is supported by recommendations from other national and international psychiatric organisations. The American Psychiatric Association and the Schizophrenia Algorithm of the International Psychopharmacology Algorithm Project (IPAP: www.ipap.org) have similar recommendations to those of NICE: they recommend that patients who have failed on two or three typical or atypical antipsychotics should be considered as treatment resistant and are eligible for treatment with clozapine[3].

NICE guidelines recommend that clozapine should be offered first-line to schizophrenia patients who have not shown satisfactory clinical improvement following sequential treatment with at least two different antipsychotic drugs, including at least one second-generation (atypical) antipsychotic.

NICE clinical guideline CG178, 2014[2]

Identifying treatment resistant schizophrenia patients

The first step to improving the treatment of TRS is to identify those patients who are failing on their second successive antipsychotic. Employing and adhering to a consistent criterion for treatment response is essential to achieve this.

Although organisations such as NICE do not make recommendations on defining treatment response with antipsychotics, the following criteria have been widely cited in clinical trials:

- At least 20% improvement in global symptoms score such as that of the Brief Psychiatric Rating Scale (BPRS)[4-6]
- At least 30% reduction in Positive and Negative Syndrome Scale (PANSS) total score by week 8 of treatment[7]

Cut short the treatment period for patients failing on antipsychotics

Non-response to antipsychotic medications as early as 2 weeks into treatment has been found to be a good predictor of subsequent lack of response after 8 weeks or 3 months of the same treatment[8,9]. This predictor has 72% specificity and 70% negative predictive value (NPV) for response at 8 weeks[8], with 80% specificity and 84% NPV for response at 3 months[9].

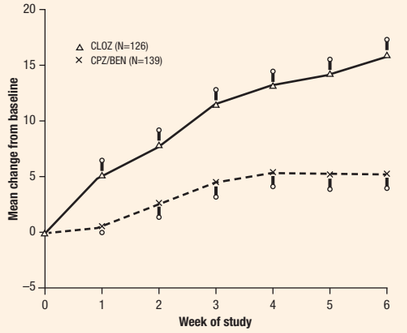
Such an approach can help identify non-responders who may benefit from an alternative antipsychotic treatment[9], and allow timely intervention for patients with TRS.

Clozaril® has clinical efficacy in patients with TRS

Clinical data show that clozapine significantly reduces the overall symptom score, and positive and negative symptoms of schizophrenia in TRS patients[4-6,10-16], with significant improvement seen as soon as 6 weeks from the start of treatment[4,10] (see Figures 1 and 2).

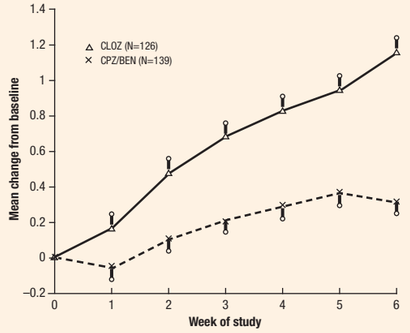
As well as superiority over typical antipsychotics, clozapine has also demonstrated greater clinical efficacy than atypical antipsychotics in TRS patients[6,12]. Trends for greater improvement in positive and negative syndrome scale (PANSS) scores are supported by significant reductions in total PANSS score[12] (see Figure 3).

Figure 1. Clozapine significantly improves the Brief Psychiatric Rating Scale (BPRS) total score compared with the typical antipsychotic chlorpromazine (with benztropine) over 6 weeks



Adapted from Kane *et al.*, 1988[10]

Figure 2. Clozapine significantly improves the Clinical Global Impressions (CGI) severity of illness scale total score compared with chlorpromazine (with benztropine)

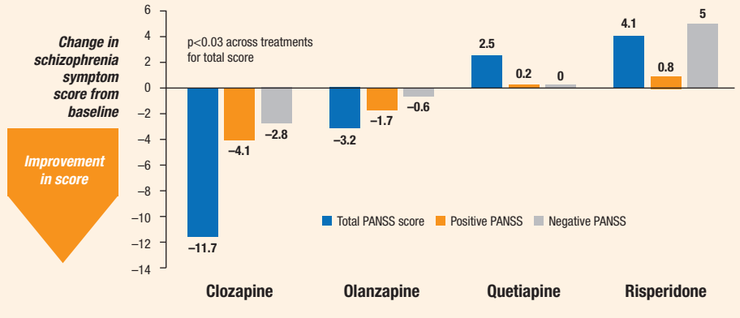


Adapted from Kane *et al.*, 1988[10]

Clozapine has demonstrated superior clinical efficacy over typical and atypical antipsychotics in TRS patients, in total symptom scores and positive and negative syndrome scores.

Kane *et al.*, 1988[10]; Azorin *et al.*, 2001[6]; McEvoy *et al.*, 2006[12]

Figure 3. Clozapine shows greater reduction in symptoms scores than other atypical antipsychotics in total score and positive and negative syndrome scores



Adapted from data in McEvoy *et al.*, 2006[12]

High rates of clinical response to Clozaril®

A large proportion of patients on clozapine show a clinical response to treatment, defined as at least 20% improvement in BPRS score[4-6]. In clinical studies, the proportion of responders ranges from 56.6% (at 29 weeks, mean dose 523 mg/day[5]) to 86% (at 12 weeks, mean dose 600 mg/day[6]), and is higher than that seen in typical antipsychotics (see Table 1). A meta-analysis has shown that clozapine-treated patients are nearly 2.5 times more likely to experience a 20-30% decrease from baseline in total BPRS score compared with those treated with typical antipsychotics (p=0.001)[13].

Table 1. Significantly more patients respond to treatment with clozapine than with typical antipsychotics

	% Responders (≥20% improvement in BPRS score)		
	Clozapine	Typical antipsychotic	
Kane *et al*, 1988 267 patients at 6 weeks	30%	4% (chlorpromazine/ benztropine)	P<0.001
Kane *et al*, 2001 71 patients at 29 weeks	56.6%	24.8% (haloperidol)	P=0.02

Some patients achieve at least 50% improvement in symptoms score[4]. In a 6-week study of 51 patients with TRS, 1 in 10 (10.5%) of the 38 patients who remained on clozapine achieved at least a 50% decrease in BPRS score[4].

Very few patients discontinue Clozaril® (clozapine) due to poor efficacy

In clinical studies, fewer patients with TRS on clozapine discontinue treatment due to lack of efficacy compared with those on typical[5,11] and atypical antipsychotics[6,12]. Examples include:

- A large study of 423 patients: 6.3% of patients on clozapine discontinued due to lack of efficacy, compared with 36.7% on the typical antipsychotic, haloperidol (p<0.001)[11]
- A study of 273 patients: drop-out rates due to poor efficacy were 0.7% for clozapine compared with 6.7% for the atypical antipsychotic, risperidone (p<0.01)[6]

As an indicator of tolerability, the overall dropout rates from long-term antipsychotic treatment are also lower for clozapine compared with typical antipsychotics. Two meta-analyses of clinical studies show discontinuation rates of 33% and 38% for clozapine, and 56% and 67% for conventional agents[14,15].

For outpatients with TRS, treatment with clozapine results in fewer days in hospital for schizophrenia symptoms compared with typical and atypical antipsychotics (14.4% fewer and 27.3% fewer, respectively)[11,17].

Overcoming barriers to prescribing Clozaril®

Addressing real and perceived barriers to prescribing Clozaril® is the foundation for improving the mental health of TRS patients in the future. Some of the major issues are listed below with suggestions for positive actions that can be employed to allay concerns or overcome them:

Poor adherence to treatment

Poor adherence to clozapine treatment can be a contributing factor to patients' non-response to therapy. If patients are not given information about their medication, their adherence may be suboptimal, resulting in poor outcomes.

Only 4 in 10 schizophrenia patients feel adequately involved in decisions regarding their drug prescriptions (41%), and a similar proportion are given information about their medication in a form they can easily understand (39%)[1].

Building trust between HCP and the patient is important and can improve adherence. This can be simply achieved by giving patients more information about their drug prescriptions in an accessible form that they understand.

Agranulocytosis is uncommon

Agranulocytosis is uncommon in patients on clozapine, and should not be a barrier to prescribing it for patients classed as treatment resistant (patients who have a history of agranulocytosis should not be prescribed Clozaril®). The cumulative incidence of agranulocytosis in the UK Clozaril® Patient Monitoring Service lifetime registry experience is 0.78%[18].

As part of Clozaril® Connect, we offer several support services including the UK Clozaril® Patient Monitoring Service (CPMS). The CPMS is a vital resource for maintaining patient safety while on Clozaril®. Although mortality rates due to agranulocytosis are low (estimated at 0.3%)[19] when a monitoring service is not used, regular blood monitoring by the CPMS can markedly reduce mortality risk due to agranulocytosis to 0.01%[18].

97%
Reduction in agranulocytosis mortality

Regular blood monitoring by the CPMS can reduce mortality risk due to agranulocytosis[18,19].

(Absolute risk reduction of mortality is 0.29%).

Weight gain with Clozaril® (clozapine) is no greater than with other antipsychotics

Weight gain while on clozapine therapy has been shown in clinical studies to be less than, or similar to, that for patients on the atypical antipsychotics olanzapine, risperidone, and quetiapine[12-14,20].

Two systematic reviews – one comparing clozapine with typical antipsychotics and one comparing clozapine with typical and atypical antipsychotics – found that weight gain occurred at a similar frequency in patients on clozapine and on typical/atypical antipsychotics[14,20].

Adverse events with Clozaril® are similar to those experienced on other antipsychotics

Clinical studies and meta-analyses indicate that adverse events (AEs) associated with Clozaril® are generally similar to those of other typical and atypical antipsychotics such as chlorpromazine, haloperidol, risperidone and olanzapine. These include hypotension, seizures, sedation, and weight gain[13-15].

Dizziness, salivation, and nausea have been noted more frequently for clozapine compared with the typical antipsychotics haloperidol and chlorpromazine, whereas dry mouth and extrapyramidal symptoms have been reported more frequently with the latter[5,6,15,16].

For more information on adverse events associated with Clozaril®, please refer to the Summary of Product Characteristics[18].

Agranulocytosis is uncommon with clozapine. The CPMS offers 24/7 support and should aid prescribing of Clozaril® in all potential TRS patients.

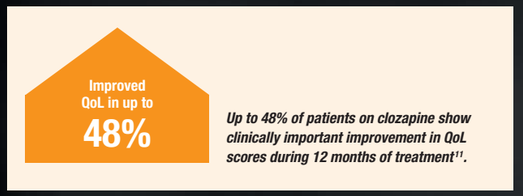
Clozaril® connect

The Clozaril® Connect programme, in addition to our continued CPMS offering, provides exciting new initiatives to give you the best support in diagnosing, treating and managing treatment resistant schizophrenia patients.

1. **Point of Care (POC) testing:** As part of Mylan's endeavour to improve access to clozapine for TRS patients, **provision of a POC device will be no longer be linked to a minimum number of patients**. If your trust can allocate resources, Mylan are very happy to provide a device on loan with training to support its functioning.
2. **Plasma Assay test:** Mylan is partnering with Analytical Services International (ASI) to provide plasma serum testing for Clozaril® patients. From the new ASI Laboratory Portal (available now at www.asilab.co.uk), you can download request forms which can be customised as required for your local clozapine teams. Samples will continue to be collected in purple-topped blood tubes, and **will be analysed within 48 hours of receipt**. Registered users can view and print results via the Laboratory Portal, **including historical results** for monitoring trends. ASI will also offer expert interpretation and advice on results by phone upon request. The cost per test has been negotiated to **£15 for trusts with Clozaril®** (please liaise directly with ASI to use this service).
3. **Patient Support Website:** Mylan is in the process of building a patient/carer information portal that will be launched in April 2018. This website will provide patients and carers with useful insights into treatment resistance in schizophrenia, and provide simple support plans on how to effectively manage the side effects of clozapine treatment.
4. **HCP (Healthcare Practitioner) Website:** Mylan is constructing a best-in-class HCP website to provide in-depth and insightful education on TRS. This is also due to be launched in April 2018.
5. **Partnership in Education:** Mylan is also currently developing an education program to better equip HCPs for managing patients with TRS. This is expected to be launched in June 2018.

Clozaril® improves quality of life in patients with TRS

Clinical data in patients with TRS followed-up for 12 months show that clozapine significantly improves the total score and all 21 item scores of the quality of life scale (QLS)[4]. Significant improvement can occur from as early as 6 weeks into treatment[11], and improvements in social and occupational functioning have been seen during long-term therapy[16].



Up to 48% of patients on clozapine show clinically important improvement in QoL scores during 12 months of treatment[11].

Partnering with Mylan to give your patients the clinical benefits of Clozaril®

Clozapine is under-prescribed in the UK, so many patients with TRS are not being given the opportunity to make a real difference to their schizophrenia symptoms. By partnering with Mylan and engaging with the Clozaril® Connect programme, we can take positive action together to ensure the timely prescribing of Clozaril® as first-line TRS treatment, and improve the positive and negative symptoms of schizophrenia, social functioning, and the quality of life of your patients with TRS.

PRESCRIBING INFORMATION

CLOZARIL 25 mg Tablets

CLOZARIL 100 mg Tablets

Please see Summary of Product Characteristics (SmPC) for full information before prescribing Clozaril.

The use of Clozaril is restricted to patients, physicians and nominated pharmacists registered with the Clozaril Patient Monitoring Service (CPMS).

In the UK a white cell count with differential count must be monitored:

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

Monitoring must continue throughout treatment and for at least 4 weeks after discontinuation.

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 $\geq$3.5 x 10^9/l and Absolute Neutrophil Count (ANC) $\geq$2.0 x 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 x 10^9/l or the ANC is less than 1.5 x 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 x 10^9/l occurs or the ANC falls below 1.0 x 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 x 10^9/l and 3.0 x 10^9/l or the ANC falls to between 2.0 x 10^9/l and 1.5 x 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 x 10^9/l and 1.5-2.0 x 10^9/l respectively, or higher.

Eosinophilia: Discontinuation of Clozaril is recommended if the eosinophil count rises above 3.0 x 10^9/l; therapy should be restarted only after the eosinophil count has fallen below 1.0 x 10^9/l. Discontinuation of Thrombocytopenia: Clozaril therapy is recommended if the platelet count falls below 50 x 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 may be 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.

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.

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.

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: January 2017
Clozaril is a registered Trade Mark

Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store. Adverse events should also be reported to Mylan via CPMS@mylan.co.uk

uk-pi-clozaril-Nov17-v3

Clozaril® connect

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