PRESCRIBING INFORMATION

CLOZARIL® | CLOZAPINE MYLAN 25 MG AND 100 MG TABLETS (clozapine)

Please refer to the Summary of Product Characteristics (SmPC) before prescribing

The use of Clozaril/Clozapine Mylan 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/Clozapine Mylan is associated with an increased risk of myocarditis and cardiomyopathy. If suspected Clozaril/Clozapine Mylan must be stopped immediately and the patient referred to a cardiologist and not re-exposed to Clozaril/Clozapine Mylan.

Indications:

Treatment-resistant schizophrenic patients and in schizophrenia patients who have severe, untreatable neurological adverse reactions to other antipsychotic agents, including atypical antipsychotics. Psychotic disorders occurring during the course of Parkinson's disease, in cases where standard treatment has failed.

Presentation:

Clozaril/Clozapine Mylan 25 mg Tablets containing 25 mg clozapine. Clozaril/Clozapine Mylan 100 mg Tablets containing 100 mg clozapine.

Dosage and administration: Oral administration

<u>Treatment-resistant schizophrenic patients</u>

12.5 mg once or twice on the first day, followed by 25 mg tablets once or twice on the second day. If well tolerated, the daily dose may be increased slowly in increments of 25 to 50 mg in order to achieve a dose level of up to 300 mg/day within 2 to 3 weeks. If required, the daily dose may be further increased in increments of 50 to 100 mg at half-weekly or, preferably, weekly intervals. In most patients, antipsychotic efficacy can be expected with 200 to 450 mg/day given in divided doses. If the daily dose does not exceed 200 mg, it can be taken as a single dose in the evening. Doses up to 900 mg/day can be used but the possibility of increased adverse reactions (in particular seizures) occurring at doses over 450 mg/day must be considered. Once control is achieved, a lower maintenance dose may be effective. Treatment should be maintained for at least 6 months. See SmPC for details on re-starting therapy, ending therapy 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. If satisfactory therapeutic response is not achieved for at least one week with a dose of 50 mg, dosage may be cautiously increased by increments of 12.5 mg/week. 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. A gradual reduction in dose by steps of 12.5 mg over a period of at least one week (preferably two) is recommended in the event of termination.

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 clozapine-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.

Warning and precautions: Contains lactose monohydrate

Agranulocytosis: Clozapine can cause agranulocytosis, so is restricted to patients who have initially normal leukocyte findings (White Blood Cell (WBC) count > 3.5x 109/l and Absolute Neutrophil Count (ANC) > 2.0x 109l), and in whom regular WBC counts and ANC can be performed within 10 days prior to starting clozapine, weekly for first 18 weeks, and at least at 4-week intervals thereafter throughout treatment and for 4 weeks after complete discontinuation. Before initiating clozapine therapy, patients should have a blood test and a history and physical examination. 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. Prescribing physicians must comply fully with the required safety measures. Physicians must ensure that the patient has not previously experienced an adverse haematological reaction to clozapine that necessitated its discontinuation. Prescriptions should not be issued for periods longer than the interval between two blood counts. Immediate discontinuation of clozapine treatment is mandatory if either the WBC count is less than 3000/mm3 (3.0x109/l) or the ANC is less than 1500/mm3 (1.5x109/l) during clozapine treatment. If clozapine has been withdrawn and either a further drop in the WBC count below 2000/mm3 (2.0x109/l) occurs or the ANC falls below 1000/mm3 (1.0x109/l), the management of this condition must be guided by an experienced haematologist. Patients in whom clozapine has been discontinued as a result of either WBC or ANC deficiencies must not be re-exposed to clozapine.

Low WBC count/ANC: If, during clozapine therapy, either the WBC count falls to between 3500/mm^3 (3.5x10^9/l) and 3000/mm^3 (3.0x10^9/l) or the ANC falls to between 2000/mm^3 (2.0x10^9/l) and 1500/mm^3 (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 3000-3500/mm^3 (3.0-3.5x10^9/l) and 1500-2000/mm^3 (1.5-2.0x10^9/l), respectively, or higher.

Eosinophilia: Discontinue clozapine if the eosinophil count rises above 3000/mm^3 (3.0x10^9/l); therapy should be restarted only after the eosinophil count has fallen below 1000/mm^3 (1.0x10^9/l).

Thrombocytopenia: Discontinue clozapine if the platelet count falls below 50 000/mm^3 (50x10^9/l).

Cardiovascular disorders: Orthostatic hypotension, with or without syncope, can occur during clozapine treatment. Rarely, collapse can be profound and may be accompanied by cardiac and/or respiratory arrest. Such events are more likely to occur with concurrent use of a benzodiazepine or any other psychotropic agent (see Section 4.5) and during initial titration in association with rapid dose escalation; on very rare occasions they may occur even after the first dose. Therefore, patients starting clozapine treatment require close medical supervision. Monitoring of standing and supine blood pressure is necessary during the first weeks of treatment in patients with Parkinson's disease. Clozapine is associated with an increased risk of myocarditis, pericarditis/pericardial effusion and cardiomyopathy. 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 (e.g. unexplained fatigue, dyspnoea, tachypnoea), or symptoms that mimic myocardial infarction. Other symptoms which may be present in addition to the above include flu-like symptoms. If myocarditis or cardiomyopathy is suspected, clozapine treatment should be promptly stopped and the patient immediately referred to a cardiologist. In patients who are diagnosed with cardiomyopathy while on clozapine treatment, there is potential to develop either mild or moderate mitral regurgitation. Patients with clozapine-induced myocarditis or cardiomyopathy should not be re-exposed to clozapine.

Myocardial infarction: There have been post-marketing reports of myocardial infarction including fatal cases.

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. Since patients treated with antipsychotics often present with acquired risk factors for VTE, all possible risk factors for VTE should be identified before and during treatment with clozapine and preventive measures undertaken.

Seizures: Patients with a history of epilepsy should be closely observed during clozapine therapy since dose-related convulsions have been reported. In such cases, the dose should be reduced (see Section 4.2 of SmPC) and, if necessary, an anti-convulsant treatment should be initiated.

Anticholinergic effects: Clozapine exerts anticholinergic activity, which may produce undesirable effects throughout the body such as impairment of intestinal peristalsis, ranging from constipation to intestinal obstruction, faecal impaction, paralytic ileus, megacolon and intestinal infarction ischaemia (see Section 4.8 of SmPC). Careful supervision is indicated in the presence of prostatic enlargement and narrow-angle glaucoma and 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.

Fever: Patients may experience transient temperature elevations above 38°C and should be carefully evaluated to rule out the possibility of an underlying infection or the development of agranulocytosis. In the presence of high fever, the possibility of neuroleptic malignant syndrome (NMS) must be considered. If the diagnosis of NMS is confirmed, clozapine should be discontinued immediately and appropriate medical measures should be administered.

Falls: Clozapine may cause seizures, somnolence, postural hypotension, motor and sensory instability, which may lead to falls and, consequently, fractures or other injuries. For patients with diseases, conditions, or medications that could exacerbate these effects, complete fall risk assessments when initiating antipsychotic treatment and recurrently for patients on long-term antipsychotic therapy.

Metabolic changes: Atypical antipsychotic drugs, including clozapine, have been associated with metabolic changes (hyperglycaemia, dyslipidaemia, and body weight gain) 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. 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.

Dyslipidaemia: Clinical monitoring, including baseline and periodic follow-up lipid evaluations in patients using clozapine, is recommended.

Weight gain: Clinical monitoring of weight is recommended.

Rebound, withdrawal effects: Acute withdrawal reactions have been reported following abrupt cessation of clozapine therefore gradual withdrawal is recommended. If abrupt discontinuation is necessary (e.g. because of leucopenia), the patient should be carefully observed for the recurrence of psychotic symptoms and symptoms related to cholinergic rebound, such as profuse sweating, headache, nausea, vomiting and diarrhoea.

<u>Special populations</u>

Hepatic impairment: Patients with hepatic impairment should receive clozapine 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 clozapine in children and adolescents under the age of 16 years have not yet been established. Clozapine 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.

Interaction with other medicinal products: Clozapine must not be used concomitantly with substances having a well-known potential to suppress bone marrow function (see Section 4.3 of SmPC). Long-acting depot antipsychotics (with myelosuppressive potential) must not be used because these cannot be removed from the body in situations where they may be required e.g. neutropenia. Alcohol should not be used with clozapine due to possible potentiation of sedation. Caution is advised if clozapine is used concomitantly with other CNS active agents such as MAOIs, CNS depressants (such as benzodiazepines, narcotics, antihistamines), substances possessing anticholinergic, hypotensive, or respiratory depressant effects, highly protein bound substances (e.g. warfarin and digoxin), phenytoin, lithium, CYP1A2 inducing substances (e.g. omeprazole), and CYP1A2 inhibiting substances (e.g. fluvoxamine, caffeine, ciprofloxacin, perazine) or hormonal contraceptives as they are CYP1A2, CYP3A4, CYP2C19 inhibitors. See SmPC for more details.

Pregnancy and lactation: Caution should be exercised when prescribing to pregnant women. Neonates exposed to antipsychotics (including clozapine) 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, new-borns should be monitored carefully. Animal studies suggest that clozapine is excreted in breast milk and has an effect in the nursing infant; therefore, mothers receiving clozapine should not breast-feed.

Effects on ability to drive and use machines: Owing to the ability of clozapine 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, using the following convention: Very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), not known (cannot be estimated from the available data).
Very common: Drowsiness/sedation, dizziness, tachycardia, constipation, hypersalivation.
Common: Leukopenia/decreased WBC/neutropenia, eosinophilia, leukocytosis, weight gain, dysarthria, seizures/convulsions/myoclonic jerks, extrapyramidal symptoms, akathisia, tremor, rigidity, headache, blurred vision, ECG changes, syncope, postural hypotension, hypertension, nausea, vomiting, anorexia, dry mouth, elevated liver enzymes, urinary retention, urinary incontinence, benign hyperthermia, disturbances in sweating/temperature regulation, fever, fatigue.
Uncommon: Agranulocytosis, dysphemia, neuroleptic malignant syndrome, falls.
For details of rare, very rare and not known undesirable effects please refer to SmPC.

Legal Category: POM

Marketing Authorisation Numbers: 25 mg tablets: PL 46302/0054; 100 mg tablets: PL 46302/0057

MAH: Mylan Products Limited, 20 Station Close, Potters Bar, Herts, EN6 1TL, UK

NHS Price: 28 x 25 mg tablets: £3.02; 84 x 25 mg tablets: £8.40; 100 x 25 mg tablets: £10.00 28 x 100 mg tablets: £12.07; 84 x 100 mg tablets: £33.60; 100 x 100 mg tablets: £39.00

Date of Revision of Prescribing Information: September 2024

CLZ-2024-0034

The SmPC for this product, including adverse reactions, precautions, contra-indications, and method of use can be found at: http://www.mhra.gov.uk/Safetyinformation/Medicinesinformation/SPCandPILs/index.htm and from Viatris Medical Information, Building 4, Trident Place, Hatfield Business Park, Mosquito Way, Hatfield, Hertfordshire, AL10 9UL, phone no. 01707 853000, Email: info.uk@viatris.com.

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: http://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 MAH at e-mail address: cpms@viatris.com.