Summary of Product Characteristics

IRELAND - Clozaril Official Recommendations

The Clozaril Patient Monitoring Service (CPMS) was developed in order to manage the risk of agranulocytosis associated with clozapine. It is available 24 hours a day. When a monitoring service is not used, evidence suggests a mortality rate from agranulocytosis of 0.3%[1]. This is compared to a mortality rate when Clozaril is used in conjunction with the Clozaril Patient Monitoring Service, of 0.01%[2].

The CPMS provides for the centralised monitoring of leucocyte and neutrophil counts which is a mandatory requirement for all patients in Ireland who are treated with Clozaril. The use of Clozaril is restricted to patients who are registered with the CPMS. In addition to registering their patients, prescribing physicians must register themselves and a nominated pharmacist with the CPMS. All Clozaril-treated patients must be under the supervision of an appropriate specialist and supply of Clozaril is restricted in Ireland to hospital and retail pharmacies registered with the CPMS. Clozaril may only be supplied by way of wholesale dealing by wholesalers which have been specifically qualified by the Marketing Authorisation Holder to supply the product and which have adequate controls in place to assure that only authorised Clozaril customers receive consignments of the product. The Marketing Authorisation Holder has agreed in advance with the HPRA the use of any wholesaler in the supply chain of Clozaril.

The CPMS maintains a database which includes all patients who have developed abnormal neutrophil findings and who should not be re-exposed to Clozaril.

Prescribers and pharmacists should adhere to brand prescribing and dispensing of clozapine in order to prevent the disruption to effective monitoring that may be caused if patients switch brands. Furthermore, in order to protect patient safety, at any one time patients should only be prescribed one brand of clozapine and only registered with the monitoring service connected to that brand.

For further information regarding Clozaril or the Clozaril Patient Monitoring Service please call CPMS by dialling (01)6621141 or email cpms@viatris.com.

[1] De la Chapelle A, et al. *Clozapine-induced agranulocytosis: a genetic and epidemiologic study.* Hum Genet, 1977. 37: p. 183-194.
[2] Clozaril Patient Monitoring Service, data on file.

Clozaril can cause agranulocytosis. Its use should be limited to patients:

- **with schizophrenia who are non-responsive to or intolerant of antipsychotic medication, or with psychosis in Parkinson's disease when other treatment strategies have failed (see section 4.1),**
- **who have initially normal neutrophil findings (Absolute Neutrophil Count; ANC) ≥ 1500/mm^3 (1.5x10^9/L) in general population and ≥ 1000/mm^3 (1.0x10^9/L) in patients with confirmed benign ethnic neutropenia (BEN), and**
- **in whom regular and absolute neutrophil counts (ANC) can be performed as follows: weekly during the first 18 weeks of therapy, then monthly for the following 34 weeks (i.e., until the completion of the first year of treatment). After 12 months, if there has been no history of neutropenia during the first year, ANC monitoring should be reduced to once every 12 weeks. After 24 months, an ANC count should be collected once a year, provided there has been no history of neutropenia during the previous two years. If mild neutropenia has occurred during treatment and has subsequently been stabilised and/or resolved, ANC monitoring should be performed monthly throughout treatment. ANC count must be performed immediately if signs or symptoms of infection occur *(e.g.* fever, sore throat, mouth/throat ulcers). Additional ANC count should be considered in older patients, and after addition of valproic acid to clozapine, especially during the initiation period(see sections 4.4. and 4.5).**

Prescribing physicians should comply fully with the required safety measures. At each consultation, a patient receiving Clozaril should be reminded to contact the treating physician immediately if any kind of infection begins to develop. Particular attention should be paid to flu-like complaints such as fever or sore throat and to other evidence of infection, which may be indicative of neutropenia (see section 4.4).

Clozaril must be dispensed under strict medical supervision in accordance with official recommendations (see section 4.4).

Myocarditis

Clozapine is associated with an increased risk of myocarditis which has, in rare cases, been fatal. The increased risk of myocarditis is greatest in the first 2 months of treatment. Fatal cases of cardiomyopathy have also been reported rarely (see section 4.4).

Myocarditis or cardiomyopathy should be suspected in patients who experience persistent tachycardia at rest, especially in the first 2 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 (see section 4.4).

If myocarditis or cardiomyopathy are suspected, Clozaril treatment should be promptly stopped and the patient immediately referred to a cardiologist (see section 4.4).

Patients who develop clozapine-induced myocarditis or cardiomyopathy should not be re-exposed to clozapine (see section 4.3 and 4.4).

1 NAME OF THE MEDICINAL PRODUCT

Clozaril 200 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 200 mg clozapine.

Excipient(s) with known effect:

Contains 365 mg lactose per tablet.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet

A light yellow, round, biconvex tablet, debossed with press type cross breakline on one side of the tablet and V C 7 cross breakline on the other side.
Diameter: Approximately 13 mm

The tablet can be divided into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Clozaril is indicated in adults for treatment of:

Treatment-resistant schizophrenia

Clozaril is indicated in treatment-resistant schizophrenic patients and in schizophrenia patients who have severe, untreatable neurological adverse reactions to other antipsychotic agents, including atypical antipsychotics.

Treatment resistance is defined as a lack of satisfactory clinical improvement despite the use of adequate doses of at least two different antipsychotic agents, including an atypical antipsychotic agent, prescribed for adequate duration.

Psychosis during the course of Parkinson's disease
Clozaril is also indicated in psychotic disorders occurring during the course of Parkinson's disease, in cases where standard treatment has failed.

4.2 Posology and method of administration

Posology
The dosage must be adjusted individually. For each patient the lowest effective dose should be used.
Cautious titration and a divided dosage schedule are necessary to minimise the risks of hypotension, seizure and sedation.

Initiation of Clozaril treatment must be restricted to those patients with an ANC ≥ 1500/mm^3 ($1.5x10^9$/l) within standardised normal limits.

Dose adjustment is indicated in patients who are also receiving medicinal products that have pharmacodynamic and pharmacokinetic interactions with Clozaril, such as benzodiazepines or selective serotonin re-uptake inhibitors (see section 4.5).

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.

The following dosages are recommended. For doses not realisable/practicable with this strength, other strengths of this medicinal product are available.:

Treatment-resistant schizophrenic patients

Starting therapy
12.5 mg once or twice on the first day, followed by 25 mg once or twice on the second day. If well tolerated, the daily dose may then 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. Thereafter, if required, the daily dose may be further increased in increments of 50 to 100 mg at half-weekly or, preferably, weekly intervals.

Therapeutic dose range
In most patients, antipsychotic efficacy can be expected with 200 to 450 mg/day given in divided doses. The total daily dose may be divided unevenly, with the larger portion at bedtime.

Maximum dose
To obtain full therapeutic benefit, a few patients may require larger doses, in which case judicious increments (not exceeding 100 mg) are permissible up to 900 mg/day. However, the possibility of increased adverse reactions (in particular seizures) occurring at doses over 450 mg/day must be borne in mind.

Maintenance dose
After achieving maximum therapeutic benefit, many patients can be maintained effectively on lower doses. Careful downward titration is therefore recommended. Treatment should be maintained for at least 6 months. If the daily dose does not exceed 200 mg, once daily administration in the evening may be appropriate.

Ending therapy
In the event of planned termination of Clozaril therapy, a gradual reduction in dose over a 1 to 2-week period is recommended. If abrupt discontinuation is necessary, the patient should be carefully observed for the occurrence of withdrawal reactions (see section 4.4).

Re-starting therapy
In patients in whom the interval since the last dose of Clozaril exceeds 2 days, treatment should be re-initiated with 12.5 mg given once or twice on the first day. If this dose is well tolerated, it may be feasible to titrate the dose to the therapeutic level more quickly than is recommended for initial treatment. However, in any patient who has previously experienced respiratory or cardiac arrest with initial dosing (see section 4.4), but was then able to be successfully titrated to a therapeutic dose, re-titration should be carried out with extreme caution.

Psychotic disorders occurring during the course of Parkinson's disease, in cases where standard treatment has failed

Starting therapy
The starting dose must not exceed 12.5 mg/day, taken in the evening. Subsequent dose increases must be by 12.5 mg increments, with a maximum of two increments a week up to a maximum of 50 mg, a dose that cannot be reached until the end of the second week. The total daily amount should preferably be given as a single dose in the evening.

Therapeutic dose range
The mean effective dose is usually between 25 and 37.5 mg/day. In the event that treatment for at least one week with a dose of 50 mg fails to provide a satisfactory therapeutic response, dosage may be cautiously increased by increments of 12.5 mg/week.

Maximum dose

The dose of 50 mg/day should only be exceeded exceptionally, and 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.

Maintenance dose
When there has been complete remission of psychotic symptoms for at least 2 weeks, an increase in anti-parkinsonian medication is possible if indicated on the basis of motor status. If this approach results in the recurrence of psychotic symptoms, Clozaril dosage may be increased by increments of 12.5 mg/week up to a maximum of 100 mg/day, taken in one or two divided doses (see above).

Ending therapy
A gradual reduction in dose by steps of 12.5 mg over a period of at least one week (preferably two) is recommended.

Treatment must be discontinued immediately in the event of neutropenia or agranulocytosis (see section 4.4). In this situation, careful psychiatric monitoring of the patient is essential since symptoms may recur quickly.

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).

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. It should not be used in this group until further data become 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.

Method of administration
Clozaril is for oral use.
For doses not realisable/practicable with this strength, other strengths of this medicinal product are available.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- 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.
- Clozaril treatment must not be started concurrently with substances known to have a substantial potential for causing agranulocytosis; concomitant use of depot antipsychotics is to be 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.

4.4 Special warnings and precautions for use

Severe cutaneous adverse reactions (SCARs)
Drug reaction with eosinophilia and systemic syndrome (DRESS), which can be life-threatening or fatal, have been reported in association with clozapine (see section 4.8).
Patients should be advised of the signs and symptoms of DRESS and monitored closely.
If signs and symptoms suggestive of this reaction appear, clozapine should be withdrawn immediately and an alternative treatment considered (as appropriate).
If the patient has developed DRESS with the use of clozapine, treatment with clozapine must not be restarted in this patient at any time.

Agranulocytosis
Clozaril can cause agranulocytosis. The incidence of agranulocytosis and the fatality rate in those developing agranulocytosis have decreased markedly since the institution of absolute neutrophil count (ANC) monitoring. The following precautionary measures are therefore mandatory and should be carried out in accordance with official recommendations.

Because of the risks associated with Clozaril, its use is limited to patients in whom therapy is indicated as set out in section 4.1 and:

- who have initially normal neutrophil findings (Absolute Neutrophil Count; ANC) ≥ 1500/mm^3 ($1.5x10^9$/L) in general population and ≥ 1000/mm^3 ($1.0x10^9$/L) in patients with confirmed benign ethnic neutropenia (BEN), and
- in whom regular ANC can be performed weekly for the first 18 weeks, and then monthly for the next 34 weeks. After 12 months, if there has been no history of neutropenia during the first year, ANC should be monitored every 12 weeks. After 24 months, if there has been no history of neutropenia during the preceding two years, ANC must only be collected once a year. If mild neutropenia has occurred during treatment and has subsequently been stabilised and/or resolved, ANC monitoring should be performed monthly throughout treatment.

Before initiating clozapine therapy patients should have a blood test (see "agranulocytosis") and a history and physical examination. Patients with history of cardiac illness or abnormal cardiac findings on physical examination 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 (see section 4.3). The treating physician should consider performing a pre-treatment ECG.

Prescribing physicians must comply fully with the required safety measures.

Prior to treatment initiation, physicians must ensure, to the best of their knowledge, 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 Clozaril is mandatory if the ANC is less than 1000/mm^3 ($1.0x10^9$/l) at any time during Clozaril treatment. Patients in whom Clozaril has been discontinued as a result or ANC deficiencies must not be re-exposed to Clozaril.

At each consultation, a patient receiving Clozaril must be reminded to contact the treating physician immediately if any kind of infection begins to develop. Particular attention should be paid to flu-like complaints such as fever or sore throat and to other evidence of infection, which may be indicative of neutropenia. Patients and their caregivers must be informed that, in the event of any of these symptoms, they must have a blood cell count performed immediately. Prescribers are encouraged to keep a record of all patients' blood results and to take any steps necessary to prevent these patients from accidentally being rechallenged in the future.

Patients with a history of primary bone marrow disorders may be treated only if the benefit outweighs the risk. They should be carefully reviewed by a haematologist prior to starting Clozaril.

Patients with benign ethnic neutropenia (BEN) should be given special consideration and may be started on Clozaril with the agreement of a haematologist (see section "Patients with Benign Ethnic Neutropenia (BEN)").

Absolute Neutrophil Count (ANC) monitoring

Differential blood counts must be performed within 10 days prior to initiating Clozaril treatment to ensure that only patients with ANC ≥ 1500/mm^3 ($1.5x10^9$/l) will receive Clozaril. After the start of Clozaril treatment ANC must be monitored weekly for the first 18 weeks, and then monthly for the next 34 weeks. After 12 months, if there has been no history of neutropenia during the first year, ANC should be monitored every 12 weeks. After 24 months, if there has been no history of neutropenia during the preceding two years, ANC must only be collected once a year. If mild neutropenia has occurred during treatment and has subsequently been stabilised and/or resolved, ANC monitoring should be performed monthly throughout treatment.

Monitoring must continue throughout treatment as reported before, and for 4 weeks after complete discontinuation of Clozaril or until haematological recovery has occurred (see "Low ANC" below). At each consultation, the patient must be reminded to contact the treating physician immediately if any kind of infection, fever, sore throat or other flu-like symptoms develop. Differential blood counts must be performed immediately if any symptoms or signs of an infection occur.

Low ANC

If, during Clozaril therapy, the ANC falls to between 1500/mm^3 ($1.5x10^9$/l) and 1000/mm^3 ($1.0x10^9$/l), haematological evaluations must be performed at least twice weekly until the patient's ANC stabilises within the 1000-1500/mm^3 ($1.5\text{-}2.0x10^9$/l), respectively, or higher. After stabilisation and/or resolution, ANC monitoring must be performed monthly throughout treatment.

Immediate discontinuation of Clozaril treatment is mandatory if ANC is less than 1000/mm^3 ($1.0x10^9$/l) during Clozaril treatment. Differential blood counts should then be performed daily and patients should be carefully monitored for flu-like symptoms or other symptoms suggestive of infection. Confirmation of the haematological values is recommended by performing two blood counts on two consecutive days; however, Clozaril should be discontinued after the first blood count.

Following discontinuation of Clozaril, haematological evaluation is required until haematological recovery has occurred.

Table 1. Actions to be taken with Clozaril depending on ANC values for general population

Blood cell count ANC/mm^3 (/l)	**Action required**
≥ 1500 (≥ $1.5x10^9$)	Continue Clozaril treatment
1000 - 1500 ($1.0x10^9$ - $1.5x10^9$)	Continue Clozaril treatment, sample blood twice weekly until counts stabilise or increase and then monthly after stabilisation and/or resolution.
< 1000 (< $1.0x10^9$)	Immediately stop Clozaril treatment, sample blood daily until haematological abnormality is resolved, monitor for infection. Do not re-expose the patient.

If Clozaril has been withdrawn and ANC falls below 1000/mm^3 ($1.0x10^9$/l), the management of this condition must be guided by an experienced haematologist.

Patients with Benign Ethnic Neutropenia (BEN)

In patients with confirmed BEN, the adjusted ANC threshold for starting or continuing clozapine is ANC ≥ 1000/mm^3 ($1.0x10^9$/L). If the ANC is between 500 and 999/mm^3 ($0.5\text{-}0.9x10^9$/L), monitoring must be done twice weekly. Clozapine should be discontinued if the ANC falls below 500/mm^3 ($0.5x10^9$/L).

Table 2. Actions to be taken with Clozaril depending on ANC values for BEN patients

ANC/mm^3 (/L)	Action required
≥ 1000 (≥ 1.0x10^9)	Continue Clozaril treatment
500-999 (0.5x10^9-0.9x10^9)	Continue Clozaril treatment, sample blood twice weekly until counts stabilise or increase and then monthly after stabilisation and/or resolution.
<500 (<0.5x10^9)	Immediately stop Clozaril treatment, sample blood daily until haematological abnormality is resolved, monitor for infection. Do not re-expose the patient.

Discontinuation of therapy for haematological reasons
Patients in whom Clozaril has been discontinued as a result of ANC deficiencies (see above) must not be re-exposed to Clozaril.

Prescribers are encouraged to keep a record of all patients' blood results and to take any steps necessary to prevent the patient being accidentally rechallenged. Patients should be monitored weekly for 4 weeks in case of complete discontinuation.

Discontinuation of therapy for other reasons
Patients who have been on Clozaril for more than two years with no history of neutropenia and have had their treatment interrupted for causes different from neutropenia, do not need to resume the weekly monitoring schedule but the one used before the interruption, irrespective of the duration of interruption (i.e yearly controls). In case of complete discontinuation, those patients should not be monitored weekly for 4 weeks.
Patients who have been on Clozaril between 18 weeks and 2 years or for more than 2 years with history of mild neutropenia that did not lead to treatment interruption, or patients who have had their treatment interrupted for more than 3 days but less than 4 weeks should have their ANC monitored weekly for an additional 6 weeks. If no haematological abnormality occurs, monitoring at intervals not exceeding 4 weeks may be resumed. If Clozaril treatment has been interrupted for 4 weeks or longer, weekly monitoring is required for the next 18 weeks of treatment and the dose should be re-titrated (see section 4.2). In case of complete discontinuation those patients should be monitored weekly for 4 weeks.

Table 3 below summarises the ANC monitoring after Clozaril interruption.

Table 3. ANC monitoring upon resuming clozapine after treatment interruption for other reasons (not haematological)

Treatment duration before interruption	Neutropenia episodes before interruption	Interruption duration	Recommended ANC monitoring
≥ Two years	No	Irrelevant	Schedule used before the interruption (i.e yearly controls).
≥ Two years	Yes	3 days to <4 weeks	Weekly for 6 weeks. After that period, if no haematological abnormality occurs, monitor at intervals not exceeding 4 weeks.
> 18 weeks – Two years	Yes/No	3 days to <4 weeks	
≥ Two years	Yes	≥ 4 weeks	Weekly for the next 18 weeks of treatment, then monthly and dose should be re-titrated.
> 18 weeks – Two years	Yes/No	≥ 4 weeks	

Other precautions
Eosinophilia
In the event of **eosinophilia**, discontinuation of Clozaril is recommended 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
In the event of **thrombocytopenia**, discontinuation of Clozaril therapy is recommended if the platelet count falls below 50 000/mm^3 (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. 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 Clozaril 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.

Analysis of safety databases suggests that the use of Clozaril is associated with an increased risk of **myocarditis** especially during, but not limited to, the first two months of treatment. Some cases of myocarditis have been fatal.
Pericarditis/pericardial effusion and **cardiomyopathy** have also been reported in association with Clozaril use; these reports also include fatalities. 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, 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. Mitral valve incompetence has been reported in cases of cardiomyopathy related to Clozaril treatment. These cases of mitral valve incompetence reported either mild or moderate mitral regurgitation on two-dimensional echocardiography (2DEcho) (see section 4.8).

Patients with clozapine-induced myocarditis or cardiomyopathy should not be re-exposed to Clozaril.

Myocardial infarction
There have been post marketing reports of **myocardial infarction** including fatal cases. Causality assessment was difficult in the majority of these cases because of serious pre-existing cardiac disease and plausible alternative causes.

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
An approximately 3-fold increased risk of **cerebrovascular adverse events** has been seen in randomised placebo controlled clinical trials in the dementia population with some atypical antipsychotics. The mechanism for this increased risk is not known. An increased risk cannot be excluded for other antipsychotics or other patient populations. Clozapine should be used with caution in patients with risk factors for stroke.

Risk of thromboembolism
Since Clozaril may be associated with **thromboembolism**, immobilisation of patients should be avoided.
Cases of venous thromboembolism (VTE) have been reported with antipsychotic medicinal products. 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 Clozaril and preventive measures undertaken.

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

Anticholinergic effects
Clozaril exerts anticholinergic activity, which may produce undesirable effects throughout the body. Careful supervision is indicated in the presence of **prostatic enlargement** and **narrow-angle glaucoma**. 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**, **paralytic ileus, appendicitis, megacolon and intestinal infarction/ischaemia** (see section 4.8). 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.

Fever

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

Falls
Clozaril 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 medicinal products, including Clozaril, have been associated with metabolic changes that may increase cardiovascular/cerebrovascular risk. These metabolic changes may include hyperglycaemia, dyslipidemia, and body weight gain. While atypical antipsychotic medicinal products may produce some metabolic changes, each medicinal product in the class has its own specific profile.

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. 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 medicinal products. The discontinuation of clozapine should be considered in patients where active medical management of their hyperglycaemia has failed.

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.

Weight gain
Weight gain has been observed with atypical antipsychotic use, including Clozaril. 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.

Special populations
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. If the elevation of the values is clinically relevant (more than 3 times the UNL) or if symptoms of jaundice occur, treatment with Clozaril must be discontinued. It may be resumed (see "Re-starting therapy" under section 4.2) only when the results of liver function tests are normal. In such cases, liver function should be closely monitored after re-introduction of Clozaril.

Patients aged 60 years and older

Initiation of treatment in patients aged 60 years and older is recommended at a lower dose (see section 4.2).

Orthostatic hypotension can occur with Clozaril treatment and there have been reports of tachycardia, which may be sustained. Patients aged 60 years and older, particularly those with compromised cardiovascular function, may be more susceptible to these effects.

Patients aged 60 years and older may also be particularly susceptible to the anticholinergic effects of Clozaril, such as urinary retention and constipation.

Increased mortality in elderly people with dementia:
Data from two large observational studies showed that elderly people with dementia who are treated with antipsychotics are at a small increased risk of death compared with those who are not treated. There are insufficient data to give a firm estimate of the precise magnitude of the risk and the cause of the increased risk is not known.
Clozaril is not approved for the treatment of dementia-related behavioural disturbances.

This medicinal product contains lactose.
Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

Contraindication of concomitant use
Substances known to have a substantial potential to depress bone marrow function must not be used concurrently with Clozaril (see section 4.3).

Long-acting depot antipsychotics (which have myelosuppressive potential) must not be used concurrently with Clozaril because these cannot be rapidly removed from the body in situations where this may be required, e.g. neutropenia (see section 4.3).

Alcohol should not be used concomitantly with Clozaril due to possible potentiation of sedation.

Precautions including dose adjustment
Clozaril may enhance the central effects of CNS depressants such as narcotics, antihistamines and benzodiazepines. Particular caution is advised when Clozaril therapy is initiated in patients who are receiving a benzodiazepine or any other psychotropic agent. These patients may have an increased risk of circulatory collapse, which, on rare occasions, can be profound and may lead to cardiac and/or respiratory arrest. It is not clear whether cardiac or respiratory collapse can be prevented by dose adjustment.

Because of the possibility of additive effects, caution is essential in the concomitant administration of substances possessing anticholinergic, hypotensive, or respiratory depressant effects.

Owing to its anti-alpha-adrenergic properties, Clozaril may reduce the blood-pressure-increasing effect of norepinephrine or other predominantly alpha-adrenergic agents and reverse the pressor effect of epinephrine.

Concomitant administration of substances known to inhibit the activity of some cytochrome P450 isozymes may increase the levels of clozapine, and the dose of clozapine may need to be reduced to prevent undesirable effects. This is more important for CYP 1A2 inhibitors such as caffeine (see below), perazine and the selective serotonin reuptake inhibitor fluvoxamine. Some of the other serotonin reuptake inhibitors such as fluoxetine, paroxetine, and, to a lesser degree, sertraline, are CYP 2D6 inhibitors and, as a consequence, major pharmacokinetic interactions with clozapine are less likely. Similarly, pharmacokinetic interactions with CYP 3A4 inhibitors such as azole antimycotics, cimetidine, erythromycin and protease inhibitors are unlikely, although some have been reported. 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. Because the plasma concentration of clozapine is increased by caffeine intake and decreased by nearly 50% following a 5-day caffeine-free period, dosage changes of clozapine may be necessary when there is a change in caffeine-drinking habit. In cases of sudden cessation of smoking, the plasma clozapine concentration may be increased, thus leading to an increase in adverse reactions.

Cases have been reported of an interaction between citalopram and clozapine, which may increase the risk of adverse reactions associated with clozapine. The nature of this interaction has not been fully elucidated.

Concomitant administration of substances known to induce cytochrome P450 enzymes may decrease the plasma levels of clozapine, leading to reduced efficacy. Substances known to induce the activity of cytochrome P450 enzymes and with reported interactions with clozapine include, for instance, carbamazepine (not to be used concomitantly with clozapine, due to its myelosuppresive potential), phenytoin and rifampicin. Known inducers of CYP1A2, such as omeprazole, may lead to decreased clozapine levels. The potential for reduced efficacy of clozapine should be considered when it is used in combination with these substances.

Other
Concomitant use of lithium or other CNS-active agents may increase the risk of development of neuroleptic malignant syndrome (NMS).

Rare but serious reports of seizures, including onset of seizures in non-epileptic patients, and isolated cases of delirium where Clozaril was co-administered with valproic acid have been reported. These effects are possibly due to a pharmacodynamic interaction, the mechanism of which has not been determined.

Concomitant treatment of clozapine and valproic acid may increase the risk of neutropenia and clozapine-induced myocarditis. If concomitant use of clozapine with valproic acid is necessary, careful monitoring is required.

Caution is called for in patients receiving concomitant treatment with other substances which are either inhibitors or inducers of the cytochrome P450 isozymes. With tricyclic antidepressants, phenothiazines and type 1_C anti-arrhythmics, which are known to bind to cytochrome P450 2D6, no clinically relevant interactions have been observed thus far.

As with other antipsychotics, caution should be exercised when clozapine is prescribed with medicines known to increase QTc interval, or causing electrolyte imbalance.

An outline of medicinal product interactions believed to be most important with Clozaril is given in Table 4 below. The list is not exhaustive.

Table 4: Reference to the most common medicinal product interactions with Clozaril

Medicinal product	**Interactions**	**Comments**
Bone marrow suppressants (e.g. carbamazapine, chloramphenicol), sulphonamides (e.g. co-trimoxazole), pyrazolone analgesics (e.g. phenylbutazone), penicillamine, cytotoxic agents and long-acting depot injections of antipsychotics	Interact to increase the risk and/or severity of bone marrow suppression.	Clozaril **must not be used** concomitantly with other agents having a well known potential to suppress bone marrow function (see section 4.3).
Benzodiazepines	Concomitant use may increase risk of circulatory collapse, which may lead to cardiac and/or respiratory arrest.	Whilst the occurrence is rare, caution is advised when using these agents together. Reports suggest that respiratory depression and collapse are more likely to occur at the start of this combination or

		when Clozaril is added to an established benzodiazepine regimen.
Anticholinergics	Clozaril potentiates the action of these agents through additive anticholinergic activity.	Observe patients for anticholinergic side-effects, e.g. constipation, especially when using to help control hypersalivation.
Antihypertensives	Clozaril can potentiate the hypotensive effects of these agents due to its sympathomimetic antagonistic effects.	Caution is advised if Clozaril is used concomitantly with antihypertensive agents. Patients should be advised of the risk of hypotension, especially during the period of initial dose titration.
Alcohol, MAOIs, CNS depressants, including narcotics and benzodiazepines	Enhanced central effects. Additive CNS depression and cognitive and motor performance interference when used in combination with these substances.	Caution is advised if Clozaril is used concomitantly with other CNS active agents. Advise patients of the possible additive sedative effects and caution them not to drive or operate machinery.
Highly protein bound substances (e.g. warfarin and digoxin)	Clozaril may cause an increase in plasma concentration of these substances due to displacement from plasma proteins.	Patients should be monitored for the occurrence of side effects associated with these substances, and doses of the protein bound substance adjusted, if necessary.
Phenytoin	Addition of phenytoin to Clozaril regimen may cause a decrease in the clozapine plasma concentrations.	If phenytoin must be used, the patient

		should be monitored closely for a worsening or recurrence of psychotic symptoms.
Lithium	Concomitant use can increase the risk of development of neuroleptic malignant syndrome (NMS).	Observe for signs and symptoms of NMS.
CYP1A2 inducing substances (e.g. omeprazole)	Concomitant use may decrease clozapine levels	Potential for reduced efficacy of clozapine should be considered.
CYP1A2 inhibiting substances e.g. fluvoxamine, caffeine, ciprofloxacin, perazine or hormonal contraceptives (CYP1A2, CYP3A4, CYP2C19)	Concomitant use may increase clozapine levels	Potential for increase in adverse reactions. Care is also required upon cessation of concomitant CYP1A2 or CYP3A4 inhibiting medications as there may be a decrease in clozapine levels. The effect of CYP2C19 inhibition may be minimal.

4.6 Fertility, pregnancy and lactation

Pregnancy

For clozapine, there are only limited clinical data on exposed pregnancies. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development (see section 5.3). Caution should be exercised when prescribing to pregnant women.

Neonates exposed to antipsychotics (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.

Breastfeeding

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. In male and female rats, clozapine did not affect fertility when administered up to 40 mg/kg, corresponding to a human equivalence dose of 6.4 mg/kg or approximately a third of the maximum permissible adult human dose.

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.

4.7 Effects on ability to drive and use machines

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.

4.8 Undesirable effects

Summary of the safety profile

For the most part, the adverse reaction event profile of clozapine is predictable from its pharmacological properties. An important exception is its propensity to cause agranulocytosis (see section 4.4). Because of this risk, its use is restricted to treatment-resistant schizophrenia and psychosis occurring during the course of Parkinson's disease in cases where standard treatment has failed. While blood monitoring is an essential part of the care of patients receiving clozapine, the physician should be aware of other rare but serious adverse reactions, which may be diagnosed in the early stages only by careful observation and questioning of the patient in order to prevent morbidity and mortality.

The most serious adverse reactions experienced with clozapine are agranulocytosis, seizure, cardiovascular effects and fever (see section 4.4). The most common side effects are drowsiness/sedation, dizziness, tachycardia, constipation, and hypersalivation.

Data from the clinical trials experience showed that a varying proportion of clozapine-treated patients (from 7.1 to 15.6%) were discontinued due to an adverse event, including only those that could be reasonably attributed to clozapine. The more common events considered to be causes of discontinuation were leukopenia, somnolence, dizziness (excluding vertigo) and psychotic disorder.

Blood and lymphatic system

Development of granulocytopenia and agranulocytosis is a risk inherent to Clozaril treatment. Although generally reversible on withdrawal of treatment, agranulocytosis may result in sepsis and can prove fatal. Because immediate withdrawal of treatment is required to prevent the development of life-threatening agranulocytosis, monitoring of the ANC count is mandatory (see section 4.4). Table 5 below summarises the estimated incidence of agranulocytosis for each Clozaril treatment period.

Table 5: Estimated incidence of agranulocytosis[1]

Treatment period	Incidence of agranulocytosis per 100,000 person-weeks[2] of observation
Weeks 0-18	32.0
Weeks 19-52	2.3
Weeks 53 and higher	1.8

[1] From the UK Clozaril Patient Monitoring Service lifetime registry experience between 1989 and 2001.

[2] Person-time is the sum of individual units of time that the patients in the registry were exposed to Clozaril before experiencing agranulocytosis. For example, 100,000 person-weeks could be observed in 1,000 patients who were in the registry for 100 weeks (100*1000=100,000), or in 200 patients who were in the registry for 500 weeks (200*500=100,000) before experiencing agranulocytosis.

The cumulative incidence of agranulocytosis in the UK Clozaril Patient Monitoring Service lifetime registry experience (0-11.6 years between 1989 and 2001) is 0.78%. The majority of cases (approximately 70%) occur within the first 18 weeks of treatment.

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, hyperglycaemia has also been documented in patients with no known risk factors(see section 4.4).

Nervous system disorders

The very common adverse reactions observed include drowsiness/sedation, and dizziness.

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

Very rarely, tardive dyskinesia has been reported in patients on Clozaril who had been treated with other antipsychotic agents. Patients in whom tardive dyskinesia developed with other antipsychotics have improved on Clozaril.

Cardiac disorders
Tachycardia and postural hypotension with or without syncope may occur, especially in the initial weeks of treatment. The prevalence and severity of hypotension is influenced by the rate and magnitude of dose titration. Circulatory collapse as a result of profound hypotension, in particular related to aggressive titration, with the possible serious consequences of cardiac or pulmonary arrest, has been reported with Clozaril.

A minority of Clozaril -treated patients experience ECG changes similar to those seen with other antipsychotics, including S-T segment depression and flattening or inversion of T waves, which normalise after discontinuation of Clozaril. The clinical significance of these changes is unclear. However, such abnormalities have been observed in patients with myocarditis, which should therefore be considered.

Isolated cases of cardiac arrhythmias, pericarditis/pericardial effusion and myocarditis have been reported, some of which have been fatal. The majority of the cases of myocarditis occurred within the first 2 months of initiation of therapy with Clozaril. Cardiomyopathy generally occurred later in the treatment.

Eosinophilia has been co-reported with some cases of myocarditis (approximately 14%) and pericarditis/pericardial effusion; it is not known, however, whether eosinophilia is a reliable predictor of carditis.

Signs and symptoms of myocarditis or cardiomyopathy include persistent tachycardia at rest, 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.

Sudden, unexplained deaths are known to occur among psychiatric patients who receive conventional antipsychotic medication but also among untreated psychiatric patients. Such deaths have been reported very rarely in patients receiving Clozaril.

Vascular disorders
Rare cases of thromboembolism have been reported.

Respiratory system
Respiratory depression or arrest has occurred very rarely, with or without circulatory collapse (see sections 4.4 and 4.5).

Gastrointestinal system
Constipation and hypersalivation have been observed very frequently, and nausea and vomiting frequently. Very rarely ileus may occur (see section 4.4). Rarely Clozaril treatment may be associated with dysphagia. Aspiration of ingested food may occur in patients presenting with dysphagia or as a consequence of acute overdosage.

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 (see section 4.4). In rare cases, acute pancreatitis has been reported.

Renal disorders
Isolated cases of acute interstitial nephritis have been reported in association with Clozaril therapy.

Reproductive and breast Disorders
Very rare reports of priapism have been received.

General disorders
Cases of neuroleptic malignant syndrome (NMS) have been reported in patients receiving Clozaril either alone or in combination with lithium or other CNS-active agents.

Acute withdrawal reactions have been reported (see section 4.4).

Tabulated list of adverse reactions:
The table below (Table 6) summarises the adverse reactions accumulated from reports made spontaneously and during clinical studies.

Table 6: Treatment-emergent adverse experience frequency estimate from spontaneous and clinical trial reports

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).

Infections and infestations		
	Not known:	Sepsis*
Neoplasms Benign, malignant and unspecified (incl cysts and polyps)		
	Not known:	Haematological malignancy
Blood and lymphatic system disorders		
	Common:	Leukopenia/decreased WBC/neutropenia, eosinophilia, leukocytosis
	Uncommon:	Agranulocytosis
	Rare:	Anaemia
	Very rare:	Thrombocytopenia, thrombocythaemia
Immune system disorders		
	Not known:	Angioedema*, leukocytoclastic vasculitis*, Drug rash with eosinophilia and systemic symptoms (DRESS)*
Endocrine disorders		
	Not known:	Pseudophaeochromocytoma*
Metabolism and nutrition disorders		
	Common:	Weight gain
	Rare:	Diabetes mellitus, impaired glucose tolerance, obesity*
	Very rare:	Hyperosmolar coma, ketoacidosis, severe hyperglycaemia, hypercholesterolemia, hypertriglyceridemia
Psychiatric disorders		
	Common:	Dysarthria
	Uncommon:	Dysphemia
	Rare:	Agitation, restlessness
Nervous system disorders		
	Very common:	Drowsiness/sedation, dizziness
	Common:	Seizures/convulsions/myoclonic jerks, extrapyramidal symptoms, akathisia, tremor, rigidity, headache

	Uncommon:	Neuroleptic malignant syndrome
	Rare:	Confusion, delirium
	Very rare:	Tardive dyskinesia, obsessive compulsive symptoms
	Not known:	Cholinergic syndrome (after abrupt withdrawal)*, EEG changes*, pleurothotonus*, restless legs syndrome*
Eye disorders		
	Common:	Blurred vision
Cardiac disorders		
	Very common:	Tachycardia
	Common:	ECG changes
	Rare:	Circulatory collapse, arrhythmias, myocarditis, pericarditis/pericardial effusion
	Very rare:	Cardiomyopathy, cardiac arrest
	Not known:	Myocardial infarction*, **, myocarditis *, **, chest pain/angina pectoris*, atrial fibrillation*, palpitations*, mitral valve incompetence associated with clozapine related cardiomyopathy*
Vascular disorders		
	Common:	Syncope, postural hypotension, hypertension
	Rare:	Thromboembolism
	Not known:	Hypotension*, Venous thromboembolism
Respiratory, thoracic and mediastinal disorders		
	Rare:	Aspiration of ingested food, pneumonia and lower respiratory tract infection which may be fatal, sleep apnoea syndrome*
	Very rare:	Respiratory depression/arrest
	Not known:	Pleural effusion*, nasal congestion*
Gastrointestinal disorders		
	Very common	Constipation, hypersalivation
	Common:	Nausea, vomiting, anorexia, dry mouth
	Rare:	Dysphagia
	Very rare:	Intestinal obstruction/paralytic ileus/faecal impaction, parotid gland enlargement,
	Not known:	Megacolon *,**, intestinal infarction/ischaemia*,**, intestinal necrosis*,**, intestinal ulceration*,** and intestinal perforation*,**, diarrhoea*, abdominal discomfort/heartburn/dyspepsia*, colitis*, appendicitis***
Hepatobiliary disorders		
	Common:	Elevated liver enzymes
	Rare:	Pancreatitis, hepatitis, cholestatic jaundice
	Very rare:	Fulminant hepatic necrosis
	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*.
Skin and subcutaneous tissue disorders		
	Very rare:	Skin reactions
	Not known	Pigmentation disorder*
Musculoskeletal and connective tissue disorders		
	Not known:	Rhabdomyolysis*, muscle weakness*, muscle spasms*, muscle pain*, systemic lupus erythematosus*
Renal and		

urinary disorders		
	Common:	Urinary retention, urinary incontinence
	Very rare:	Tubulointerstitial nephritis
	Not known:	Renal failure*, Nocturnal enuresis*
Pregnancy, puerperium and perinatal conditions		
	Not known	Drug withdrawal syndrome neonatal (see 4.6)
Reproductive system and breast disorders		
	Very rare:	Priapism
	Not known	Retrograde ejaculation*
General disorders and administration site conditions		
	Common:	Benign hyperthermia, disturbances in sweating/temperature regulation, fever, fatigue
	Very rare:	Sudden unexplained death
	Not known:	Polyserositis*
Investigations		
	Rare:	Increased CPK
Injury, poisoning and procedural complications		
	Uncommon:	Falls (associated with clozapine-induced seizures, somnolence, postural hypotension, motor and sensory instability)*

* Adverse drug reactions derived from post-marketing experience via spontaneous case reports and literature cases.
** These adverse drug reactions were sometimes fatal.
*** Including appendicitis perforated.

Description of Selected Adverse Reactions

Haematological malignancy (HM)

Epidemiological studies have shown a cumulative dose- and time-dependent association between clozapine and haematological malignancy. In a large cohort study, the absolute risk of developing a haematological malignancy was 61 cases per 100,000 person-years among clozapine-treated patients, versus 41 cases per 100,000 person-years in those receiving other antipsychotic medicines, corresponding to 0.7% in clozapine users versus 0.5% in the other group, over a mean follow-up of 12.3 years. A high cumulative clozapine exposure was associated with an adjusted odds ratio (aOR) of 3.35 (95% CI: 2.22–5.05), and treatment duration ≥ 5 years with an aOR of 2.94 (95% CI: 2.07–4.17). A cumulative dose–response relationship was also observed for lymphoma, with an aOR of 4.06 (95% CI: 2.60–6.33) at the same cumulative dose threshold. The extent to which haematological monitoring of clozapine-treated patients may contribute to these estimates is not known.

Very rare events of ventricular tachycardia and QT prolongation which may be associated with Torsades De Pointes have been observed although there is no conclusive causal relationship to the use of this medicine.

Reporting of suspected 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.

4.9 Overdose

In cases of acute intentional or accidental Clozaril overdose for which information on the outcome is available, mortality to date is about 12%. Most of the fatalities were associated with cardiac failure or pneumonia caused by aspiration and occurred at doses above 2000 mg. There have been reports of patients recovering from an overdose in excess of 10 000 mg. However, in

a few adult individuals, primarily those not previously exposed to Clozaril, the ingestion of doses as low as 400 mg led to life-threatening comatose conditions and, in one case, to death. In young children, the intake of 50 to 200 mg resulted in strong sedation or coma without being lethal.

Signs and symptoms
Drowsiness, lethargy, areflexia, coma, confusion, hallucinations, agitation, delirium, extrapyramidal symptoms, hyperreflexia, convulsions; hypersalivation, mydriasis, blurred vision, thermolability; hypotension, collapse, tachycardia, cardiac arrhythmias; aspiration pneumonia, dyspnoea, respiratory depression or failure.

Treatment
There are no specific antidotes for Clozaril.

Gastric lavage and/or administration of activated charcoal within the first 6 hours after the ingestion of the medicinal product. Peritoneal dialysis and haemodialysis are unlikely to be effective. Symptomatic treatment under continuous cardiac monitoring, surveillance of respiration, monitoring of electrolytes and acid-base balance. The use of epinephrine should be avoided in the treatment of hypotension because of the possibility of a 'reverse epinephrine' effect.

Close medical supervision is necessary for at least 5 days because of the possibility of delayed reactions.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antipsychotics; Diazepines, oxazepines, thiazepines and oxepines,
ATC code: N05A H02

Mechanism of action
Clozaril has been shown to be an antipsychotic agent that is different from classic antipsychotics. In pharmacological experiments, the compound does not induce catalepsy or inhibit apomorphine- or amphetamine-induced stereotyped behaviour. It has only weak dopamine-receptor-blocking activity at D_1, D_2, D_3 and D_5 receptors, but shows high potency for the D_4 receptor.

Pharmacodynamic effects
Clozaril has potent anti-alpha-adrenergic, anticholinergic, antihistaminic, and arousal-reaction-inhibiting effects. It has also been shown to possess antiserotoninergic properties.

Clinical efficacy and safety
Clinically Clozaril produces rapid and marked sedation and exerts antipsychotic effects in schizophrenic patients resistant to other medicinal product treatment. In such cases, Clozaril has proven effective in relieving both positive and negative schizophrenic symptoms mainly in short-term trials. In an open clinical trial performed in 319 treatment resistant patients treated for 12 months, a clinically relevant improvement was observed in 37% of patients within the first week of treatment and in an additional 44% by the end of 12 months. The improvement was defined as about 20% reduction from baseline in Brief Psychiatric Rating Scale Score. In addition, improvement in some aspects of cognitive dysfunction has been described.

Compared to classic antipsychotics, Clozaril produces fewer major extrapyramidal reactions such as acute dystonia, parkinsonian-like side effects and akathisia. In contrast to classic antipsychotics, Clozaril produces little or no prolactin elevation, thus avoiding adverse events such as gynaecomastia, amenorrhoea, galactorrhoea and impotence.

A potentially serious adverse reaction caused by Clozaril therapy is granulocytopenia and agranulocytosis occurring at an estimated incidence of 3% and 0.7%, respectively. In view of this risk, the use of Clozaril should be limited to patients who are treatment-resistant or patients with psychosis in Parkinson's disease when other treatment strategies have failed (see section 4.1) and in whom regular haematological examinations can be performed (see sections 4.4 and 4.8).

5.2 Pharmacokinetic properties

Absorption
The absorption of orally administered Clozaril is 90 to 95%; neither the rate nor the extent of absorption is influenced by food.

Clozaril is subject to moderate first-pass metabolism, resulting in an absolute bioavailability of 50 to 60%.

Distribution
In steady-state conditions, when given twice daily, peak blood levels occur on an average at 2.1 hours (range: 0.4 to 4.2 hours), and the volume of distribution is 1.6 l/kg. Clozaril is approximately 95% bound to plasma proteins.

Biotransformation/metabolism
Clozaril is almost completely metabolised before excretion by CYP1A2 and CYP3A4, and to some extent by CYP2C19 and CYP2D6. Of the main metabolites only the demethyl metabolite was found to be active. Its pharmacological actions resemble those of clozapine, but are considerably weaker and of short duration.

Elimination
Its elimination is biphasic, with a mean terminal half-life of 12 hours (range: 6 to 26 hours). After single doses of 75 mg the mean terminal half-life was 7.9 hours; it increased to 14.2 hours when steady-state conditions were reached by administering daily doses of 75 mg for at least 7 days.
Only trace amounts of unchanged active substance are detected in the urine and faeces, approximately 50% of the administered dose being excreted as metabolites in the urine and 30% in the faeces.

Linearity/non-linearity
Dosage increases from 37.5 mg to 75 mg and 150 mg given twice daily were found to result during steady state in linearly dose-proportional increases in the area under the plasma concentration/time curve (AUC), and in the peak and minimum plasma concentrations.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenic potential (for reproductive toxicity, see section 4.6).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Magnesium stearate
Silica, colloidal anhydrous
Povidone K30
Talc
Maize starch
Lactose monohydrate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

This medicinal product does not require any special storage precautions

6.5 Nature and contents of container

PVC/PE/PVdC – Aluminium blister
Pack sizes: 20, 30, 40, 50, 100 tablets.

PVC/PE/PVdC – Aluminium perforated unit-dose blister
Pack sizes: 20 x 1, 30 x 1, 40 x 1, 50 x 1, 100 x 1 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements

7 MARKETING AUTHORISATION HOLDER

Viatris Healthcare Limited
Damastown Industrial Park
Mulhuddart
Dublin 15
Dublin
Ireland

8 MARKETING AUTHORISATION NUMBER

PA23355/022/003

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 15th November 2024

10 DATE OF REVISION OF THE TEXT

July 2026