

NEW ZEALAND DATA SHEET

CLOZARIL[®] **(clozapine)** **25mg and 100mg Tablets**

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CLOZARIL[®]
(clozapine)
25mg and 100mg Tablets

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

- with schizophrenia who are non-responsive to or intolerant of classical antipsychotic agents, or with schizophrenia or schizoaffective disorder who are at risk of recurrent suicidal behaviour (see Therapeutic indications),
- who have initially normal leukocyte findings (white blood cell count (WBC) $\geq 3500/\text{mm}^3$ ($3.5 \times 10^9/\text{L}$), and absolute neutrophil counts (ANC) $\geq 2000/\text{mm}^3$ ($2.0 \times 10^9/\text{L}$)),
- and in whom regular white blood cell counts and absolute neutrophil counts can be performed as follows: weekly during the first 18 weeks of therapy, and at least every 4 weeks thereafter throughout treatment. Monitoring must continue throughout treatment and for 4 weeks after complete discontinuation of Clozaril.

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.

Clozaril must be dispensed in accordance with appropriate local dispensing guidelines.

The following conditions apply to the sale, supply and use of Clozaril in New Zealand under the consent notice from Medsafe. Novartis draws prescribers, nurses and patients attention to the following criteria:

Clozapine may only be prescribed by:

- Registered medical practitioners as defined in the Health Practitioners Competence Assurance Act 2003 who are certified by the Medical Council of New Zealand as competent in the scope of practice of psychological medicine or psychiatry;
- Medical practitioners employed as registrars in the branch of psychological medicine or psychiatry who are under the supervision of the persons referred to above;
- Medical officers of special scale who:
 - work solely in the field of psychiatry;
 - are in the employment of a District Health Board;
 - are under the supervision of persons who are registered medical practitioners as defined in the Health Practitioners Competence Assurance Act 2003 who are certified by the Medical Council of New Zealand as competent in the scope of practice of psychiatry.
- Registered medical practitioners as defined in the Health Practitioners Competence Assurance Act 2003 who are registered with the Medical Council of New Zealand within the vocational scope of practice of general practice. The general practitioner must be continuing the prescribing of clozapine for a specific patient who is considered stable in collaboration, or following consultation, with a Community Mental Health Team.

Persons prescribing clozapine must comply with appropriate local treatment guidelines.

The medicine must be dispensed in accordance with appropriate local dispensing guidelines

Brand swapping between clozapine products is discouraged and should occur on the advice of a clinician.

Prescribers and dispensers should verify that the patient has not previously developed an adverse reaction to clozapine that contraindicates further use of any clozapine containing product.

Qualitative and quantitative composition

25 mg Tablet: each tablet contains 25 mg clozapine

100 mg Tablet: each tablet contains 100 mg clozapine

Clozaril 25mg tablets are light yellowish round, flat with bevelled edges, scored with markings LO on one side, SANDOZ on the other and 6.3mm diameter.

Clozaril 100mg tablets are light yellowish round, flat with bevelled edges scored with markings ZA on one side, SANDOZ on the other and 10mm diameter.

For a full list of excipients, see List of excipients.

Pharmaceutical form

Tablets.

Clinical particulars

Therapeutic indications

Treatment-resistant schizophrenia

Clozaril is indicated in patients with treatment-resistant schizophrenia, i.e. patients with schizophrenia who are non-responsive to or intolerant of classic antipsychotics.

Non-responsiveness is defined as a lack of satisfactory clinical improvement despite the use of adequate doses of at least two marketed antipsychotics prescribed for adequate durations.

Intolerance is defined as the impossibility of achieving adequate clinical benefit with classic antipsychotics because of severe and untreatable neurological adverse reactions (extrapyramidal side effects or tardive dyskinesia).

Dosage and method of administration

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 minimize the risks of hypertension, seizure, and sedation.

Initiation of Clozaril treatment must be restricted to those patients with a white blood cell (WBC) count $\geq 3500/\text{mm}^3$ ($3.5 \times 10^9/\text{L}$) and an absolute neutrophil count (ANC) $\geq 2000/\text{mm}^3$ ($2.0 \times 10^9/\text{L}$), and within standardised normal limits.

Dose adjustment is indicated in patients who are also receiving medicinal products that have pharmacokinetic interactions with clozapine, such as benzodiazepines or selective serotonin re-uptake inhibitors (see Interaction with other medicines).

In patients with a history of seizures or suffering from renal or cardiovascular disorders (note: severe renal or cardiovascular disorders are contraindications) the initial dose should be 12.5mg given once on the first day, and dosage increase should be slow and in small increments.

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 dosage of other antipsychotics be reduced or discontinued by gradually tapering it downwards. Based on the clinical circumstances, the prescribing physician should judge whether or not to discontinue the other antipsychotic therapy before initiating treatment with Clozaril.

Treatment-resistant schizophrenia

Starting therapy

Clozaril should be started with 12.5 mg (half a 25-mg tablet) once or twice on the first day, followed by one or two 25 mg tablets on the second day. If well tolerated, the daily dose may then be increased slowly in increments of 25 mg 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 mg to 100 mg at half-weekly or, preferably, weekly intervals.

Therapeutic dose range

In most patients, antipsychotic efficacy can be expected with 300 to 450 mg/day given in divided doses. Some patients may be treated with lower doses, and some patients may require doses up to 600 mg/day. The total daily dose may be divided unevenly, with the larger portion being taken 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. 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 (e.g. because of leucopenia), the patient should be carefully observed for the recurrence of psychotic symptoms and symptoms related to cholinergic rebound (see Warning and precautions).

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 (half a 25 mg tablet) 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 Special warnings and precautions for use), but was then able to be successfully titrated to a therapeutic dose, re-titration should be done with extreme caution.

Special populations

Cardiovascular disorders

In patients suffering from cardiovascular disorders (note: severe cardiovascular disorders are contraindications) the initial dose should be 12.5 mg given once on the first day, and dosage increase should be slow and in small increments.

Renal impairment

In patients with mild to moderate renal impairment the initial dose should be 12.5 mg given once on the first day, and dosage increase should be slow and in small increments.

Hepatic impairment

Patients with hepatic impairment should receive Clozaril with caution along with regular monitoring of liver function tests (see Warnings and precautions).

Paediatrics

No paediatric studies have been performed.

Children and adolescents

The safety and efficacy of Clozaril in children and adolescents have not been established.

Patients 60 years of age and older

It is recommended that treatment in patients 60 years and older is initiated at a particularly low dose (12.5 mg given once on the first day) with subsequent dose increments restricted to 25 mg/day.

Contraindications

- Known hypersensitivity to *clozapine* or to any of the excipients of Clozaril.
- Patients unable to undergo regular blood tests.
- History of toxic or idiosyncratic granulocytopenia/agranulocytosis (with the exception of granulocytopenia/agranulocytosis from previous chemotherapy).
- 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

Special precautionary measures

Agranulocytosis

Prescribers and dispensers should verify that the patient has not previously developed an adverse reaction to clozapine that contraindicates further use of any clozapine containing product.

Because of the association of Clozaril with agranulocytosis, the following precautionary measures are mandatory:

Drugs known to have a substantial potential to depress bone marrow function should not be used concurrently with Clozaril. In addition, the concomitant use of long-acting depot antipsychotics should be avoided because of the impossibility of removing these medications, which may be potentially myelosuppressive, from the body rapidly in situations where this may be required, e.g. granulocytopenia.

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 who have low white blood cell (WBC) counts because of benign ethnic neutropenia should be given special consideration and may be started on Clozaril after agreement of a haematologist.

White Blood Cell (WBC) counts and Absolute Neutrophil Count (ANC) monitoring

White blood cell (WBC) and differential blood counts must be performed within 10 days prior to starting Clozaril treatment to ensure that only patients with normal leukocyte and absolute neutrophil counts ($WBC \geq 3500/\text{mm}^3$ ($\geq 3.5 \times 10^9/\text{L}$) and $ANC \geq 2000/\text{mm}^3$ ($\geq 2.0 \times 10^9/\text{L}$)) will receive Clozaril. After the start of Clozaril treatment, regular WBC count and ANC must be performed and monitored weekly for 18 weeks, and thereafter at least every four weeks throughout treatment, and for 4 weeks after complete discontinuation of Clozaril.

Prescribing physicians should comply fully with the required safety measures. At each consultation, the patient 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. A differential blood count must be performed immediately if any symptoms or signs of an infection occur.

Low WBC count and/or ANC

If during the first 18 weeks of Clozaril therapy, the WBC count falls to between $3500/\text{mm}^3$ ($3.5 \times 10^9/\text{L}$) and $3000/\text{mm}^3$ ($3.0 \times 10^9/\text{L}$) and/or the ANC falls to between $2000/\text{mm}^3$ ($2.0 \times 10^9/\text{L}$) and $1500/\text{mm}^3$ ($1.5 \times 10^9/\text{L}$), haematological evaluations must be performed at least twice weekly.

After 18 weeks of Clozaril therapy, haematological evaluations should be performed at least twice weekly if the WBC count falls to between $3000/\text{mm}^3$ ($3.0 \times 10^9/\text{L}$) and $2500/\text{mm}^3$ ($2.5 \times 10^9/\text{L}$) and/or the ANC falls to between $1500/\text{mm}^3$ ($1.5 \times 10^9/\text{L}$) and $1000/\text{mm}^3$ ($1.0 \times 10^9/\text{L}$).

In addition, if, during Clozaril therapy, the WBC count is found to have dropped by a substantial amount from baseline, a repeat WBC count and a differential blood count should be performed. A substantial drop is defined as a single drop of 3000 mm^3 ($3.0 \times 10^9/\text{L}$) or more in the WBC count or a cumulative drop of 3000 mm^3 ($3.0 \times 10^9/\text{L}$) or more within three weeks.

Immediate discontinuation of Clozaril is mandatory if the WBC count is less than $3000/\text{mm}^3$ ($3.0 \times 10^9/\text{L}$) or the ANC is less than $1500/\text{mm}^3$ ($1.5 \times 10^9/\text{L}$) during the first 18 weeks of therapy, or if the WBC count is less than $2500/\text{mm}^3$ ($2.5 \times 10^9/\text{L}$) or the ANC is less than $1000/\text{mm}^3$ ($1.0 \times 10^9/\text{L}$) after the first 18 weeks of therapy. WBC counts and differential blood counts should then be performed daily and patients should be carefully monitored for flu-like symptoms or other symptoms suggestive of infection. Following discontinuation of Clozaril, haematological evaluation is required until haematological recovery has occurred.

If Clozaril has been withdrawn and WBC count falls further to below $2000/\text{mm}^3$ ($2.0 \times 10^9/\text{L}$) and/or the ANC falls below $1000/\text{mm}^3$ ($1.0 \times 10^9/\text{L}$), the management of this condition must be guided by an experienced haematologist. If possible, the patient should be referred to a specialised haematological unit, where protective isolation and the administration of GM-CSF (granulocyte-macrophage colony stimulating factor) or G-CSF (granulocyte colony stimulating factor) may be indicated. It is recommended that the colony stimulating factor therapy be discontinued when the neutrophil count has returned to a level above $1000/\text{mm}^3$ ($1.0 \times 10^9/\text{L}$).

Patients in whom Clozaril has been discontinued as a result of white blood cell deficiencies (see above) must not be re-exposed to Clozaril.

It is recommended that the haematological values be confirmed by performing two blood counts on two consecutive days; however, Clozaril should be discontinued after the first blood count.

Table 1 Blood monitoring during the first 18 weeks of Clozaril therapy

Blood cell count		Action required
WBC/ mm^3 (/L)	ANC/ mm^3 (/L)	
≥ 3500 ($\geq 3.5 \times 10^9$)	≥ 2000 ($\geq 2.0 \times 10^9$)	Continue Clozaril treatment.

Blood cell count		Action required
WBC/mm ³ (/L)	ANC/mm ³ (/L)	
Between 3000 and 3500 (3.0×10^9 - 3.5×10^9)	Between 1500 and 2000 (1.5×10^9 - 2.0×10^9)	Continue Clozaril treatment, sample blood twice weekly until counts stabilise or increase.
≤ 3000 ($\leq 3.0 \times 10^9$)	≤ 1500 ($\leq 1.5 \times 10^9$)	Immediately stop Clozaril treatment, sample blood daily until haematological abnormality is resolved, monitor for infection. Do not re-expose the patient.

Table 2 Blood monitoring after 18 weeks of Clozaril therapy

Blood cell count		Action required
WBC/mm ³ (/L)	ANC/mm ³ (/L)	
≥ 3000 ($> 3.0 \times 10^9$)	≥ 1500 ($> 1.5 \times 10^9$)	Continue Clozaril treatment.
Between 2500 and 3000 (2.5×10^9 - 3.0×10^9)	Between 1000 and 1500 (1.0×10^9 - 1.5×10^9)	Continue Clozaril treatment, sample blood twice weekly until counts stabilise or increase.
< 2500 ($< 2.5 \times 10^9$)	< 1000 ($< 1.0 \times 10^9$)	Immediately stop Clozaril treatment, sample blood daily until haematological abnormality is resolved, monitor for infection. Do not re-expose the patient.

In the event of interruption of therapy for non-haematological reasons

Patients who have been on Clozaril for more than 18 weeks and have had their treatment interrupted for more than 3 days but less than 4 weeks should have their WBC count and 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.

Other precautions

Eosinophilia

In the event of **eosinophilia**, discontinuation of Clozaril is recommended if the eosinophil count rises above $3000/\text{mm}^3$ ($3.0 \times 10^9/\text{L}$). Therapy should be re-started only after the eosinophil count has fallen below $1000/\text{mm}^3$ ($1.0 \times 10^9/\text{L}$).

Thrombocytopenia

In the event of **thrombocytopenia**, discontinuation of Clozaril is recommended if the platelet count falls below $50\,000/\text{mm}^3$ ($50.0 \times 10^9/\text{L}$).

Cardiovascular disorders

In patients suffering from cardiovascular disorders (note: severe cardiovascular disorders are contraindications) the initial dose should be 12.5 mg given once on the first day, and dosage increase should be slow and in small increments (see Dosage and method of administration).

Hypotension

Orthostatic hypotension, with or without syncope, can occur during Clozaril treatment. Rarely (about one case per 3,000 Clozaril-treated patients), collapse can be profound and may be accompanied by cardiac and/or respiratory arrest. Such events are more likely to occur during initial titration in association with rapid dose escalation; on very rare occasions they occurred even after the first dose. Therefore, patients commencing Clozaril treatment require close medical supervision.

Myocarditis/Cardiomyopathy

Tachycardia that persists at rest, accompanied by arrhythmias, shortness of breath or signs and symptoms of heart failure, may rarely occur during the first month of treatment and very

rarely thereafter. The occurrence of these signs and symptoms necessitates an urgent diagnostic evaluation for myocarditis, especially during the titration period. Therefore, the possibility of myocarditis should be considered in patients receiving Clozaril who present with unexplained fatigue, dyspnoea, tachypnoea, fever, chest pain, tachycardia, palpitations, other signs and symptoms of heart failure, ECG changes (such as ST-T wave abnormalities) or arrhythmias. It is not known whether eosinophilia is a reliable predictor of myocarditis. The incidence of myocarditis, reported globally is rare (<0.1%) during the first month of therapy and very rare (<0.01%) thereafter. Some cases of myocarditis have been reported to be fatal (incidence approximately 0.2 cases/100,000 patient years). Most reported cases of myocarditis have occurred in the first month of therapy, therefore there should be a high index of suspicion in the first 6-8 weeks of therapy.

If the diagnosis of myocarditis is confirmed, Clozaril should be discontinued. Later in treatment, the same signs and symptoms may very rarely occur and may be linked to cardiomyopathy. Further investigation should be performed and if the diagnosis is confirmed, the treatment should be stopped unless the benefit clearly outweighs the risk to the patient.

Monitoring of standing and supine blood pressure is necessary during the first weeks of treatment in patients with Parkinson's disease.

Myocardial infarction

In addition, there have been postmarketing reports of myocardial infarction which may be fatal. Causality assessment was difficult in the majority of these cases because of serious pre-existing cardiac disease and plausible alternative causes.

Seizures

Clozaril may lower seizure threshold. In patients with a history of seizures, or suffering from renal or cardiovascular disorders (note: severe renal or cardiovascular disorders are contraindications) the initial dose should be 12.5 mg given once on the first day, and dosage increase should be slow and in small increments (see Dosage and method of administration).

Anticholinergic effects

Clozapine exerts anticholinergic activity, which may produce adverse 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** and **paralytic ileus** (see Adverse effects). On rare occasions these cases have proved fatal. Since complications have been associated with delayed diagnosis, patients should be questioned about their bowel habits.

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 WBC 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.

Neuroleptic Malignant Syndrome (NMS)

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. These metabolic changes may include hyperglycemia, dyslipidemia, and body weight gain. While atypical antipsychotic drugs may produce some metabolic changes, each drug in the class has its own specific risk profile.

Hyperglycaemia and Diabetes Mellitus

Hyperglycaemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients with atypical antipsychotics including Clozaril. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increase background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycaemia-related adverse events is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent hyperglycaemia-related adverse events in patients treated with the atypical antipsychotics studied. Precise risk estimates for hyperglycaemia-related adverse events in patients treated with atypical antipsychotics are not available. The available data are insufficient to provide reliable estimates of differences in hyperglycaemia related adverse event risk among the marketed atypical antipsychotics.

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 baseline and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycaemia including polydipsia, polyuria, polyphagia, and weakness. 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 anti-diabetic treatment despite discontinuation of the suspect drug. In patients with significant treatment-emergent hyperglycaemia, discontinuation of Clozaril should be considered.

There is a risk of altering the metabolic balance resulting in slight impairment of glucose homeostasis and a possibility of unmasking a pre-diabetic condition or aggravating pre-existing diabetes.

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.

Risk of Thromboembolism

Since Clozaril may cause sedation and weight gain, thereby increasing the risk of thromboembolism, immobilisation of patients should be avoided.

Cerebrovascular adverse events

An increased risk of cerebrovascular adverse events has been seen 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. Clozaril should be used with caution in patients with risk factors for stroke.

Prolongation of QT Interval

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 Clozaril is prescribed with medicines known to increase the QTc interval.

Special populations

Liver disease

Patients with stable pre-existing liver disorders may receive Clozaril, but must undergo regular liver function tests. Such tests should be performed immediately in patients who develop symptoms of possible liver dysfunction such as nausea, vomiting and/or anorexia during Clozaril treatment. If the elevation of the values is clinically relevant or if symptoms of jaundice occur, treatment with Clozaril must be discontinued. It may be resumed (see Dosage and method of administration - Re-starting therapy) only when the results of liver function tests are normal. In such cases, liver function should be closely monitored after re-introduction of Clozaril.

Renal impairment

In patients suffering from mild to moderate renal impairment, an initial dose of 12.5 mg/day (half a 25 mg tablet) is recommended (see Dosage and administration).

Patients aged 60 years and older

It is recommended that treatment be initiated at a particularly low dose (12.5 mg given once on the first day) and subsequent dose increments be restricted to 25 mg/day.

Clinical studies with Clozaril did not include sufficient numbers of subjects aged 60 years and over to determine whether or not they respond differently from younger subjects.

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

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

Patients aged 60 years and older with Dementia-related Psychosis

In patients aged 60 years and over with dementia-related psychosis, the efficacy and safety of clozapine has not been studied. Observational studies suggest that patients aged 60 years and over with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. In the published literature, risk factors that may predispose this patient population to increased risk of death when treated with antipsychotics include sedation, the presence of cardiac conditions (e.g. cardiac arrhythmias) or pulmonary conditions (e.g. pneumonia, with or without aspiration). Clozaril should be used with caution in patients aged 60 years and over with dementia.

Rebound, withdrawal effects

If abrupt discontinuation of Clozaril 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.

Interactions with other medicines**Pharmacodynamic-related interactions****Anticipated pharmacodynamic interactions resulting in concomitant use not being recommended**

Medicinal products known to have a substantial potential to depress bone marrow function should not be used concurrently with Clozaril (see Warnings and precautions).

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

Observed pharmacodynamic interactions to be considered

Particular caution is recommended when Clozaril therapy is initiated in patients who are receiving (or have recently received) a benzodiazepine or any other psychotropic agent, as 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.

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.

Anticipated pharmacodynamic interactions to be considered

Clozapine may enhance the central effects of alcohol, MAO inhibitors and CNS depressants such as narcotics, antihistamines, and benzodiazepines.

Because of the possibility of additive effects, caution is essential when substances possessing anticholinergic, hypotensive, or respiratory depressant effects are given concomitantly.

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

Pharmacokinetic-related interactions

Clozapine is a substrate for many CYP 450 isoenzymes, in particular 1A2 and 3A4. The risk of metabolic interactions caused by an effect on an individual isoform is therefore minimised. Nevertheless, caution is called for in patients receiving concomitant treatment with other substances that are either inhibitors or inducers of these enzymes.

No clinically relevant interactions have been observed thus far with tricyclic antidepressants, phenothiazines or type 1_C anti-arrhythmics, which are known to bind to cytochrome P450 2D6.

Observed pharmacokinetic interactions to be considered

Concomitant administration of substances known to induce cytochrome P450 enzymes may decrease the plasma levels of clozapine.

- Substances known to induce the activity of 3A4 and with reported interactions with clozapine include, for instance, carbamazepine, phenytoin and rifampicin.

Concomitant administration of substances known to inhibit the activity of cytochrome P450 isozymes may increase the plasma levels of clozapine.

- Substances known to inhibit the activity of the major isozymes involved in the metabolism of clozapine and with reported interactions include, for instance, cimetidine, erythromycin (3A4), fluvoxamine (1A2) and ciprofloxacin (1A2).
- The plasma concentration of clozapine is increased by caffeine (1A2) intake and decreased by nearly 50% following a 5-day caffeine-free period.
- Elevated clozapine plasma concentrations also have been reported in patients receiving the substances in combination with selective serotonin re-uptake inhibitors (SSRIs) such as paroxetine (1A2), sertraline, fluoxetine or citalopram.

Anticipated pharmacokinetic interactions to be considered

Concomitant administration of substances known to induce cytochrome P450 enzymes may decrease the plasma levels of clozapine.

- Known inducers of 1A2 include, for instance, omeprazole and tobacco smoke. In cases of sudden cessation of tobacco smoking, the plasma clozapine concentration may be increased, thus leading to an increase in adverse effects.

Concomitant administration of substances known to inhibit the activity of cytochrome P450 isozymes may increase the plasma levels of clozapine.

- Potent inhibitors of CYP3A, such as azole antimycotics and protease inhibitors, could potentially also increase clozapine plasma concentrations; no interactions have been reported to date, however.

Use during pregnancy and lactation

Pregnancy

Reproduction studies in animals have revealed no evidence of impaired fertility or harm to the foetus due to clozapine. However, the safe use of Clozaril in pregnant women has not been established. Therefore, Clozaril should be used in pregnancy only if the expected benefit clearly outweighs any potential risk.

Non-teratogenic effects

Neonates exposed to antipsychotic drugs, during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms following delivery. There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress and feeding disorder in these neonates. These complications have varied in severity; while in some cases symptoms have been self-limited, in other cases neonates have required intensive care unit support and prolonged hospitalization.

Antipsychotic drugs, including Clozaril, should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

Lactation

Animal studies suggest that clozapine is excreted in breast milk and has an effect in the suckling offspring; therefore, mothers receiving Clozaril should not breast-feed.

Women of childbearing potential and contraceptive measures

Some female patients treated with antipsychotics other than Clozaril may become amenorrhic. 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.

Driving and using 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.

Adverse effects

The adverse effects of clozapine are most often predictable based on its pharmacological properties with the exception of agranulocytosis (see Special warnings and precautions for use).

The most serious adverse reactions experienced with clozapine are agranulocytosis, seizure, cardiovascular effects and fever (see Warnings and precautions). 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.

Table 3 Treatment-Emergent Adverse Experience Frequency estimate from Spontaneous and Clinical Trial Reports

Adverse reactions are ranked by MedDRA system organ class under headings of frequency, using the following convention: 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.

Blood and lymphatic system disorders	
Common	Leukopenia/decreased WBC/neutropenia, eosinophilia, leukocytosis
Uncommon	Agranulocytosis
Rare	Anaemia
Very rare	Thrombocytopenia, thrombocythaemia
Metabolism and nutrition disorders	
Common	Weight gain
Rare	Impaired glucose tolerance, new onset diabetes, diabetes aggravated
Very rare	Ketoacidosis, hyperosmolar coma, severe hyperglycaemia, hypercholesterolaemia, hypertriglyceridaemia
Psychiatric disorders	
Common	Dysarthria
Uncommon	Dysphemia
Rare	Restlessness, agitation
Nervous system disorders	
Very common	Drowsiness/sedation, dizziness
Common	Blurred vision, headache, tremor, rigidity, akathisia, extrapyramidal symptoms, seizures/convulsions/myoclonic jerks
Uncommon	Neuroleptic malignant syndrome
Rare	Confusion, delirium
Very rare	Tardive dyskinesia, obsessive compulsive symptoms
Eye disorders	
Common	Blurred vision
Cardiac disorders	
Very common	Tachycardia
Common	ECG changes
Rare	Circulatory collapse, arrhythmias, myocarditis, pericarditis
Very rare	Cardiomyopathy

Vascular system disorders	
Common	Hypertension, postural hypotension, syncope
Rare	Thromboembolism
Respiratory disorders	
Rare	Aspiration of ingested food, pneumonia and lower respiratory tract infection which may be fatal
Very rare	Respiratory depression/arrest
Gastrointestinal disorders	
Very common	Constipation, hypersalivation
Common	Nausea, vomiting, dry mouth
Rare	Dysphagia
Very rare	Parotid gland enlargement, intestinal obstruction/ileus/faecal impaction, abdominal discomfort, heartburn
Hepatobiliary disorders	
Common	Elevated liver enzymes
Rare	Hepatitis, cholestatic jaundice, pancreatitis
Very rare	Fulminant hepatic necrosis
Skin and subcutaneous tissue disorders	
Very rare	Skin reactions
Renal and urinary disorders	
Common	Urinary incontinence, urinary retention
Very rare	Interstitial nephritis, nocturnal enuresis
Reproductive system disorders	
Very rare	Priapism
General disorders	
Common	Fatigue, benign hyperthermia, disturbances in sweating/temperature regulation
Uncommon	Neuroleptic malignant syndrome
Very rare	Sudden unexplained death
Investigations	
Rare	Increased CPK

* Occasionally patients with pre-existing hyperglycaemia have had an exacerbation

** The prompt discontinuation of Clozaril therapy is warranted upon suspicion of myocarditis (see Special warnings and precautions for use).

AEs from spontaneous reports and literature (frequency unknown)

The following post-marketing adverse effects were derived from experience with Clozaril via spontaneous case reports and literature cases and have been categorized according to MedDRA system organ class (Table 4). Because these have been reported voluntarily from a population of uncertain size and are subject to confounding factors, these post-marketing AEs have been categorized with a frequency of “unknown” since it is not possible to reliably estimate their frequency. Adverse effects are listed according to system organ classes (SOC) in MedDRA. Within each system organ class, AEs are presented in order of decreasing seriousness.

Table 4: Adverse effects from spontaneous reports and literature (frequency unknown)

SOC	Adverse effect
Nervous system disorders	Cholinergic syndrome, EEG changes
Cardiac disorders	Myocardial infarction which may be fatal, chest pain/angina pectoris
Respiratory disorders	Nasal congestion
Gastrointestinal disorders	Diarrhoea, abdominal discomfort/heartburn/dyspepsia
Musculoskeletal & connective tissue disorders	Muscle weakness, muscle spasms, muscle pain
Renal and urinary disorders	Renal failure

Very rare events of ventricular tachycardia, cardiac arrest 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.

Overdose

In cases of acute intentional or accidental Clozaril overdosage, for which information on the outcome is available, to date the mortality 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 mg 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, hyper-reflexia, 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 the administration of activated charcoal within the first 6 hours after Clozaril ingestion. (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 adrenaline should be avoided in the treatment of hypotension because of the possibility of a 'reverse adrenaline effect'.

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

Pharmacological properties

Pharmacodynamic properties

Pharmacotherapeutic group: Antipsychotic agent (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 D₁, D₂, D₃ and D₅ receptors, but shows high potency for the D₄ receptor, in addition to potent anti-alpha-adrenergic, anticholinergic, antihistaminic, and arousal reaction-inhibiting effects. It has also been shown to possess antiserotonergic properties.

Pharmacodynamics

Clinically Clozaril produces rapid and marked sedation, and exerts antipsychotic effects in patients with schizophrenia resistant to other antipsychotic agents. In such cases, Clozaril has proven effective in relieving both positive and negative schizophrenic symptoms in short- and long-term trials.

Clozaril is unique in that it produces virtually no major extrapyramidal reactions such as acute dystonia and tardive dyskinesia. Furthermore, parkinsonian-like side effects and akathisia are

rare. In contrast to classical antipsychotics, clozapine produces little or no prolactin elevation, thus avoiding adverse effects such as gynaecomastia, amenorrhoea, galactorrhoea, and impotence.

Potentially serious adverse reactions caused by Clozaril therapy are granulocytopenia and agranulocytosis occurring at an estimated incidence of 3% and 0.7% respectively (see Special warnings and precautions for use).

Pharmacokinetics

Absorption

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

Clozapine 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. Clozapine is approximately 95% bound to plasma proteins.

Biotransformation/metabolism

Clozapine is almost completely metabolised before excretion. Of the main metabolites only the desmethyl 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 drug 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.

Clinical studies

Clinical studies in treatment-resistant schizophrenia

Clozapine study 30

In a double-blind clinical trial performed in 319 treatment-resistant patients, clinically relevant improvement was observed within 6 weeks in about 30% of the Clozaril-treated patients. Two open-label trials in which patients were treated for 12 months, showed clinically relevant improvement in 37% of patients within the first 6 weeks of treatment and in an additional 39%-44% of patients by the end of 12 months. The improvement was defined

as a reduction of more than 20% from baseline in Brief Psychiatric Rating Scale Score. In addition, improvement in some aspects of cognitive dysfunction has been described.

Preclinical safety data

Preclinical 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 Use during pregnancy and lactation).

Mutagenicity

Clozapine and/or its metabolites were devoid of genotoxic potential when investigated for induction of gene mutations, chromosome aberrations and primary DNA-damage in a spectrum of *in vitro* mutagenicity tests. No clastogenic activity was observed *in vivo* (bone marrow micronucleus test in mice).

Carcinogenicity

In Sprague-Dawley (CD) rats treated in the diet for 24 months, maximum tolerated doses of 35 mg/kg per day revealed no carcinogenic potential of clozapine. Likewise, no evidence of tumorigenic effects was obtained in two 78-week feeding studies in Charles River (CD) mice. In the first study, oral dose levels of up to 64 mg/kg were administered to males, and of up to 75 mg/kg to females respectively. In the second study, the drug intake achieved for both sexes was 61 mg/kg per day.

Reproductive toxicity

No embryotoxic or teratogenic potential of clozapine was observed in rats or rabbits. In male rats treated for 70 days prior to mating, fertility was unaffected.

In female rats, fertility as well as pre- and postnatal development of the offspring was not adversely affected by oral clozapine treatment prior to mating. When rats were treated during the later part of pregnancy and during lactation, survival rates of the youngs from lactating dams, treated at dose levels up to 40 mg/kg body weight, were lowered and the youngs were hyperactive. However, there was no lasting effect on pup development after weaning.

Pharmaceutical particulars

List of excipients

Clozaril tablets: magnesium stearate; silica, colloidal anhydrous; povidone; talc; maize starch; lactose monohydrate.

Incompatibilities

Not applicable.

Shelf life

Clozaril packed in blisters: 48 months

Clozaril packed in bottles: 60 months

Special precautions for storage

Blisters: No special precautions for storage

Bottles: store below 25°C

Clozaril must be kept out of the reach and sight of children.

Nature and content of container

Clozaril 25mg and 100mg tablets are available in bottles made of type III brown glass with a closure consisting of a stopper made of colourless low-density polyethylene containing 100 tablets, and in PVC or PVC/PVDC blister packs containing 50 tablets.

Instructions to use and handling

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

Further Information

Provisional consent for distribution of Clozaril under Section 23 of the Medicines Act has been granted. This consent is valid for 2 years from 28 May 2010. The consent is given subject to the conditions detailed at the beginning of the data sheet.

Medicine classification

Prescription Medicine

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