AUSTRALIAN PRODUCT INFORMATION – CLOZARIL® (CLOZAPINE) TABLETS

WARNING

Cases of myocarditis, some of which have been fatal, and cardiomyopathy have been reported in patients on clozapine (see "4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE" and "4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)").

1 NAME OF THE MEDICINE

Clozapine

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Clozaril tablet contains clozapine 25 mg or 100 mg of the active ingredient, clozapine.

Excipients with known effect: sugars (as lactose monohydrate).

For the full list of excipients, see **Section 6.1 List of excipients**.

3 PHARMACEUTICAL FORM

Tablets, uncoated.

25 mg tablet: yellow, 6.3 mm diameter, scored, marked LO on one side and SANDOZ on the reverse.

100 mg tablet: yellow, 10 mm diameter, scored, marked ZA on one side and SANDOZ on the reverse.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Treatment with Clozaril is indicated in treatment-resistant schizophrenic patients only, i.e. schizophrenic patients who are non-responsive to, or intolerant of, other antipsychotic drugs.

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

Intolerance is defined as the impossibility to achieve adequate benefit with other antipsychotic drugs because of severe and untreatable neurological adverse reactions (extrapyramidal side effects or tardive dyskinesia).

4.2 DOSE AND METHOD OF ADMINISTRATION

(See also Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Dosage

The dosage must be adjusted individually. For each patient the lowest effective dose should be used. Appropriate resuscitative facilities should be available and the patient adequately supervised during initiation of therapy. The following dosages for oral administration are recommended:

Starting therapy:

12.5 mg (half a 25 mg tablet) once or twice daily on the first day, followed by one or two 25mg tablets 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.

Special patient populations

For use in special patient populations, or patients aged 60 years and older, see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE – Other Precautions.

Therapeutic dose range:

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

Because of the significant risk of agranulocytosis and seizure, events which both present a continuing risk over time, the extended treatment of patients failing to show an acceptable level of clinical response should ordinarily be avoided.

Maximum dose:

For most patients the recommended maximum dose is 600 mg/day. However, a few patients may require larger doses to obtain maximum therapeutic benefit, in which case, judicious increments (i.e. not exceeding 100 mg) are permissible up to a maximum of 900 mg/day. The possibility of increased adverse reactions 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 recommended to the level of 150 - 300 mg/day given in divided doses. With daily doses not exceeding 200 mg, a single administration in the evening may be appropriate.

Ending therapy:

In the event of planned termination of Clozaril therapy, a gradual reduction in dose is recommended over a 1 to 2 week period. If abrupt discontinuation is necessary the patient's

mental state should be followed carefully. The patient should also be carefully observed for symptoms related to cholinergic rebound such as profuse sweating, headache, nausea, vomiting and diarrhoea.

Re-starting therapy:

In patients in whom the interval since the last dose of Clozaril exceeds 2 days, treatment should be reinstated with 12.5 mg (half a 25 mg tablet) given once or twice daily on the first day. If this dose is 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 SPECIAL WARNINGS AND PRECAUTIONS FOR USE – Other Precautions) but was then able to be successfully titrated to a therapeutic dose, retitration should be done with extreme caution.

Switching from a previous antipsychotic drug to Clozaril:

It is generally recommended that Clozaril should not be used in combination with other antipsychotic drugs. When Clozaril therapy is to be initiated in a patient undergoing oral antipsychotic therapy, the other antipsychotic drug should first be discontinued by tapering the dosage downward over a period of approximately one week. Once the other antipsychotic drug is completely discontinued for at least 24 hours begin Clozaril as described above.

If, in a particular patient, discontinuation of the antipsychotic drug is not a realistic option prior to institution of Clozaril, combination therapy can be cautiously undertaken in hospital during a transition period. Taper the dose of antipsychotic drug downward over a period of a week, while gradually adding Clozaril in increasing doses.

Administration

Clozaril tablets are administered orally with water or other liquid.

4.3 CONTRAINDICATIONS

- Patients with a history of drug-induced granulocytopenia/agranulocytosis, or with bone marrow disorders, should not be treated with Clozaril®.
- Patients unable to undergo regular blood tests.
- Circulatory collapse and/or CNS depression due to any cause.
- Previous hypersensitivity to clozapine or to any other components of the formulation.
- Alcoholic and other toxic psychoses, drug intoxication, comatose conditions.
- Severe renal or cardiac disease (e.g. myocarditis).
- Severe hepatic disease including active liver disease associated with nausea, anorexia or jaundice; progressive liver disease; hepatic failure.
- Uncontrolled epilepsy.
- Paralytic ileus.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Special Precautionary Measures

Agranulocytosis

Clozaril can cause agranulocytosis. Its use should be limited to schizophrenic patients who are non-responsive to, or intolerant of other antipsychotic drugs:

- who have initially normal leucocyte findings (white blood cell count > 3.5 x 10^9/L, normal differential blood count) and

- in whom regular white blood cell (WBC) counts and absolute neutrophil counts (ANC) (weekly during the first 18 weeks, at least monthly thereafter throughout treatment, and for 1 month after complete discontinuation of Clozaril) can be performed.

Development of granulocytopenia and agranulocytosis is a risk inherent to Clozaril treatment. Although generally reversible on withdrawal of the drug, agranulocytosis can prove fatal. The majority of cases occur within the first 18 weeks of treatment. Because immediate withdrawal of the drug is required to prevent the development of life-threatening agranulocytosis, monitoring of the WBC count is mandatory.

Prescribing physicians should fully comply with the instituted safety measures. Because of the association of Clozaril with agranulocytosis, the following precautionary measures are mandatory:

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

- 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 inability of these medications, which may have the potential to be myelosuppressive, to be rapidly removed from the body in situations where this may be required, e.g. granulocytopenia.

- Before starting Clozaril treatment, a WBC and differential count (DC) must be performed within 10 days prior to starting Clozaril treatment to ensure that only patients with normal WBC counts and normal absolute neutrophil counts (ANC) will receive the drug. After the start of Clozaril treatment, the WBC and ANC must be performed and monitored weekly for 18 weeks. Thereafter, the WBC and ANC must be performed at least monthly throughout treatment, and for 1 month after complete discontinuation of Clozaril. 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 "4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)"). An immediate differential blood count must be performed if any symptoms or signs of infection occur.

- **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.

- If during Clozaril therapy, infection occurs and/or the WBC count has dropped below 3.5 x 10^9/L or has dropped by a substantial amount from baseline, even if the count is above 3.5 x 10^9/L, a repeat WBC count and a differential count should be done. Should the results confirm a WBC below 3.5 x 10^9/L and/or reveal an absolute neutrophil granulocyte count of between 2.0 x 10^9/L and 1.5 x 10^9/L, the leucocytes and the granulocytes must be checked at least twice weekly. If the WBC falls below 3.0 x 10^9/L and/or the absolute neutrophil granulocyte count drops below 1.5 x 10^9/L, Clozaril must be withdrawn at once and the patients should be closely monitored. 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 must be continued until haematological recovery has occurred.

- If Clozaril has been withdrawn and a further fall of WBC below 2.0 x 10^9/L occurs and/or the neutrophil granulocytes decrease below 1.0 x 10^9/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 may be indicated.

Patients in whom Clozaril has been discontinued as a result of white blood cell deficiencies (WBC count < 3.0 x 10^9/L and/or absolute neutrophil count < 1.5 x 10^9/L), must not be re-exposed to Clozaril.

<u>Other Precautions</u>

Myocardial infarction

There have been postmarketing 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.

Myocarditis / cardiomyopathy

There have been cases of fatal myocarditis with clozapine treatment. Cases of myocarditis (with or without eosinophilia), and cardiomyopathy have been reported in patients on

clozapine. The incidence of myocarditis reported globally is rare (<0.1%) during the first month of treatment and very rare (<0.01%), thereafter. The reported incidence of myocarditis in Australia is slightly higher, being rated as uncommon (≥ 0.1% and < 1%). The reason for this discrepancy is unknown (see "BOXED WARNING").

In patients who develop persistent tachycardia at rest accompanied by other signs and symptoms of heart failure (e.g. tachypnoea, shortness of breath, hypotension, raised jugular venous pressure) or arrhythmias, the possibility of myocarditis or cardiomyopathy must be considered. Other symptoms which may be present in addition to the above include fatigue, flu-like symptoms, chest pain or fever that is otherwise unexplained. The occurrence of these signs and symptoms necessitates an urgent diagnostic evaluation for myocarditis or cardiomyopathy by a cardiologist. If myocarditis is confirmed, Clozaril should be discontinued. If cardiomyopathy is diagnosed, possible discontinuation of Clozaril, based on clinical grounds, should be considered. If patients 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 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)). Most reported cases of myocarditis have occurred in the first month of treatment. Therefore, patients commencing Clozaril treatment require close medical supervision. Patients with a family history of heart failure should have a cardiac evaluation prior to commencing treatment (see "BOXED WARNING" and Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)).

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

Eosinophilia

Unexplained leucocytosis and/or eosinophilia may occur, especially in the initial weeks of treatment. In the event of eosinophilia (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS) - Blood and lymphatic system disorders), it is recommended to discontinue Clozaril if the eosinophil count rises above 3.0×10^9/L, and to re-start therapy only after the eosinophil count has fallen below 1.0×10^9/L.

Thrombocytopenia

In the event of thrombocytopenia (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS) - Blood and lymphatic system disorders), it is recommended to discontinue Clozaril if the platelet count falls below 50×10^9/L.

Orthostatic hypotension

Tachycardia and postural hypotension, with or without syncope, may occur, especially in the initial weeks of treatment and may represent a continuing risk in some patients. Rarely (about

one case per 3,000 patients), collapse can be profound and accompanied by respiratory and/or cardiac arrest. Such events are more likely to occur during initial dose titration in association with rapid dose escalation; on very rare occasions they occurred after the first dose (also see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

Treatment initiation
Patients commencing Clozaril treatment need to be under close medical supervision.

Seizures
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. Caution should be used in administering Clozaril to patients having a history of seizures or other predisposing factors. These symptoms are more likely to occur with rapid dose increase and in patients with pre-existing epilepsy. In this case 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 drugs, the possibility of a pharmacokinetic interaction should be considered. Also see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE - Dosing in special patient populations.

Dosing in special patient populations:
In patients with a history of seizures, or suffering from cardiovascular, renal or hepatic disorders (note: severe hepatic, renal or cardiovascular disorders, including active liver disease associated with nausea, anorexia or jaundice, progressive liver disease and hepatic failure are contraindications), the initial dose should be 12.5 mg given once on the first day, and any dose increase should be slow and in small increments.

Fever
Patients on clozapine can experience fever with temperature elevations above 38°C within the first month of treatment. The overall incidence is 5%; individual studies have reported up to 20%. This should be carefully evaluated to rule out the possibility of the development of agranulocytosis or myocarditis (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE – Agranulocytosis and Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE – Myocarditis). The possibility of an underlying infectious process should also be considered.

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.

Neuroleptic Malignant Syndrome (NMS)

In the presence of high fever, the possibility of neuroleptic malignant syndrome (NMS) must be considered. There have been cases of NMS in patients receiving Clozaril (clozapine), either alone or in combination with lithium or other CNS-active agents (estimated incidence <0.1%). If the diagnosis of NMS is confirmed, Clozaril should be discontinued immediately and appropriate medical measures should be administered.

Anticholinergic effects

Clozaril exerts anticholinergic activity which may produce undesirable effects throughout the body. 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, megacolon and intestinal infarction/ischaemia (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)). On rare occasions these cases have been fatal. Careful monitoring during treatment with Clozaril to early identify the onset of constipation, followed by effective management of constipation are recommended to prevent complications. Careful supervision is indicated in the presence of prostatic enlargement and narrow-angle glaucoma. Clozaril is contraindicated in patients with paralytic ileus.

Metabolic Changes

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

Risk of thromboembolism

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

Increased mortality in elderly patients with dementia-related psychosis:

Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo based on a retrospective analysis conducted by the Food and Drug Administration of seventeen placebo controlled trials with atypical-antipsychotics. This analysis revealed a risk of death in the drug-treated patients of between 1.6 to 1.7 times that seen in placebo-treated patients. Data from Clozaril was not included in this analysis.

Use of Clozaril has not been studied in patients with dementia-related psychosis and is therefore not recommended in this patient population.

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.

Extrapyramidal effects

Extrapyramidal symptoms may occur but are milder and less frequent than those seen during treatment with "typical" antipsychotic drugs. Rigidity, tremor and akathisia have been reported but acute dystonia is not an established side effect of Clozaril treatment. There have been no reports of tardive dyskinesia directly attributable to Clozaril alone. However, the syndrome has been reported in a few patients who, prior to or concomitantly with Clozaril therapy, have been treated with other antipsychotic agents, so that a causal relationship to Clozaril can neither be established nor excluded.

The presentation of akathisia may be variable and comprises subjective complaints of restlessness and an overwhelming urge to move and either distress or motor phenomena such as pacing, swinging of the legs while seated, rocking from foot to foot or both. Particular attention should be paid to the monitoring for such symptoms and signs, as left untreated, akathisia is associated with poor compliance and an increased risk of relapse.

Suicide

The possibility of a suicide attempt is inherent in schizophrenia, and close supervision of high-risk patients should accompany therapy.

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 increased 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. Precise risk estimates for hyperglycaemia-related adverse events in patients treated with atypical antipsychotics are not available.

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. 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.

Dyslipidaemia

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.

Use in hepatic impairment

Patients with stable pre-existing liver disorders may receive Clozaril but need regular liver function test monitoring. Patients who develop symptoms of possible liver dysfunction such as nausea, vomiting and/or anorexia during treatment with Clozaril should have liver function tests performed immediately. If there is a clinically relevant elevation in liver function values or if symptoms of jaundice occur, treatment with Clozaril must be discontinued. Treatment may be resumed only when liver function tests have returned to normal values. In such cases, liver function should be closely monitored after the re-introduction of the drug.

Acute 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 leukopenia), 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 (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION – Ending therapy).

Use in the elderly

It is recommended to initiate treatment at a particularly low dose (12.5 mg given once on the first day) and to restrict subsequent dose increments to 25 mg/day. Orthostatic hypotension can occur with Clozaril treatment and there have been reports of tachycardia, which may be sustained, in patients taking Clozaril. Elderly patients, particularly those with compromised cardiovascular function, may be more susceptible to these effects. Elderly patients may also be particularly susceptible to the anticholinergic effects of Clozaril, such as urinary retention and constipation.

Use in the elderly with Dementia-related Psychosis

In patients aged 60 years and older with dementia-related psychosis, the efficacy and safety of clozapine have not been studied. Observational studies suggest that patients aged 60 years and older 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 older with dementia.

Paediatric use
No paediatric studies have been performed. The safety and effectiveness in children and adolescents below 16 years of age have not been established. Clozaril must be kept out of reach of children.

Effects on laboratory tests
No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Pharmacodynamic-related interactions:

Drugs known to have a substantial potential to depress bone marrow should not be used concurrently with Clozaril (see also Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE - Special Precautionary Measures).

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

Particular caution is advised when Clozaril therapy is initiated in patients who are receiving (or have recently received) a benzodiazepine or any other antipsychotic drug, as these patients may have an increased risk of circulatory collapse, which on rare occasions may 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.

Clozaril 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 in the concomitant administration of drugs with anticholinergic, hypotensive or respiratory depressant effects is essential.

In Clozaril-treated patients, the blood pressure increasing effect of adrenaline and its derivatives may be reversed.

Pharmacokinetic-related interactions:

Clozapine is a substrate for many cytochrome P (CYP) 450 isoenzymes, in particular 1A2 and 3A4. Caution is called for in patients receiving concomitant treatment with other drugs which are either inhibitors or inducers of these enzymes.

With other drugs known to bind to the CYP450 2D6 isoenzyme, such as antidepressants, phenothiazine and type I_C anti-arrhythmics, no clinically relevant interactions with Clozaril have been observed so far. On theoretical grounds, however, it is possible that the plasma levels of such drugs are increased by Clozaril, so it may be appropriate to use them at doses lower than usually prescribed.

Concomitant administration of phenytoin, carbamazepine, rifampicin, St John's wort (Hypericum perforatum) [drugs known to induce the activity of CYP450 3A4] and possibly other drugs known to induce the cytochrome P450 enzyme system, may reduce the plasma levels of clozapine and may be associated with the recurrence of psychotic symptoms.

Competition for protein binding sites may lead to adverse effects as a result of changes in plasma levels of Clozaril or other highly protein-bound drugs such as warfarin and digoxin.

Concomitant administration of drugs known to inhibit the CYP450 enzyme system, may increase the plasma levels of clozapine, possibly resulting in adverse effects. Substances known to inhibit the activity of the major isozymes involved in the metabolism of clozapine and with reported interactions include: cimetidine, erythromycin and ciprofloxacin.

The concomitant administration of enzyme inhibitors such as clarithromycin or azithromycin with high doses of clozapine has been associated with increased plasma clozapine levels and the occurrence of adverse effects.

A significant increase in the levels of clozapine and n-desmethyl-clozapine was reported when concomitant treatment was given with 2 x 250 mg ciprofloxacin. There have also been reports of interactions with norfloxacin and enoxacin.

In one study of 7 patients, the plasma concentration of clozapine was increased by caffeine (an inhibitor of CYP 450 1A2) intake and decreased by 29 to 80% following a 5-day caffeine-free period.

Discontinuation of the concomitant administration of carbamazepine has resulted in an increase of the clozapine plasma levels.

There have been isolated reports of interactions with proton pump inhibitors (elevated concentrations of clozapine when given with omeprazole and pantoprazole, or with combinations of lansoprazole and paroxetine).

Elevated serum levels of clozapine have been reported in patients receiving the drug in combination with selective serotonin re-uptake inhibitors (SSRIs) such as fluoxetine, paroxetine, citalopram, sertraline (up to 2-fold), fluvoxamine (up to 10-fold) and with oral contraceptives (inhibits 1A2, 3A4 and 2C19 isozymes). Such patients should be monitored closely and dosage adjustment may be indicated.

Increased concentrations of clozapine have also been reported in patients who received clozapine in combination with venlafaxine.

Tobacco smoke, a known inducer of CYP450 1A2, may decrease the plasma levels of clozapine. In cases of sudden cessation of tobacco smoking, the plasma clozapine concentration may be increased, thus leading to an increase in adverse effects.

Omeprazole, another known inducer of CYP450 1A2, could potentially also decrease the plasma levels of clozapine.

Potent inhibitors of CYP450 3A, such as azole antimycotics and protease inhibitors, could potentially also increase clozapine plasma concentrations.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

Clozapine did not affect fertility in rats at oral doses less than the maximum human dose (mg/m^2 basis), but in long term dietary studies, dosing at less than the maximum human dose (mg/m^2 basis) inhibited spermatogenesis in mice and produced testicular atrophy in rats.

Use in pregnancy – Pregnancy Category C

Studies in animals are inadequate but available data from studies in rats and rabbits with daily oral administration of clozapine during the period of organogenesis at doses less than the maximum human dose (mg/m^2 basis) show no evidence of an increased occurrence of foetal damage. However, clozapine and/or its metabolites cross the placenta and enter the foetus in rabbits. The adverse pharmacological and toxicological effects of clozapine in adults may also occur in the foetus. Therefore, the drug should be used in pregnancy, or in women likely to become pregnant, only if the expected benefit is considered to outweigh the potential risk. In women of child-bearing potential, adequate contraceptive measures must be ensured.

Non-teratogenic class effect: Neonates exposed to antipsychotic drugs (including Clozaril) during the third trimester of pregnancy are at risk of experiencing extrapyramidal neurological disturbances and/or withdrawal symptoms following delivery. There have been post-market 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 additional medical treatment or monitoring.

Clozaril, should be used during pregnancy only if the anticipated benefit outweighs the risk and the administered dose and duration of treatment should be as low and as short as possible.

Use in lactation.

Animal studies suggest that Clozaril is excreted in milk. Oral administration of clozapine to rats during late gestation and throughout lactation at a dose less than the maximum human dose (mg/m^2 basis) was associated with reduced offspring survival and offspring hyperactivity, but no lasting effect on pup development after weaning. Mothers receiving Clozaril should not breastfeed.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Owing to the ability of Clozaril to cause sedation and lower the seizure threshold, patients should be advised not to engage in activities such as driving or operating machinery and other activities where sudden loss of consciousness could cause serious risk to the patient or others, especially during the initial weeks of treatment.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

The adverse effects (AEs) of clozapine are most often predictable based on its pharmacological properties with the exception of agranulocytosis (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

The most serious adverse reactions experienced with clozapine are agranulocytosis, seizure, cardiovascular effects and fever (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE). 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 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.

The following section (Table 1) lists treatment-emergent adverse effects from spontaneous and clinical trial reports. Adverse effects are listed by MedDRA system organ class and are ranked under headings of frequency, using the following convention: very common (≥10%), common (≥1% to <10%), uncommon (≥0.1% to <1%), rare (≥0.01% to <0.1%), very rare (<0.01%), including isolated reports.

Note: refer to the Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE section for further information on important adverse reactions.

Table 1: Treatment-Emergent Adverse Experience Frequency estimate from Spontaneous and Clinical Trial Reports

Blood and lymphatic system disorders:

Common:	leukopenia / decreased WBC / neutropenia, eosinophilia, leucocytosis
Uncommon:	Agranulocytosis
Rare:	Anaemia
Very rare:	thrombocytopenia, thrombocythemia

Cardiac disorders:

Very common:	Tachycardia
Common:	Electrocardiogram (ECG) changes
Rare:	circulatory collapse, arrhythmias, myocarditis, pericarditis
Very rare:	cardiomyopathy, cardiac arrest

Gastrointestinal disorders:

Very common:	constipation, hypersalivation
Common:	nausea, vomiting, dry mouth
Rare:	dysphagia, ileus impaction
Very rare:	parotid gland enlargement, intestinal obstruction/faecal impaction

General disorders:

Common:	fatigue, benign hyperthermia, disturbances in sweating/temperature regulation
Very rare:	sudden unexplained death

Hepatobiliary disorders:

Common:	elevated liver enzymes
Rare:	hepatitis, cholestasis, cholestatic jaundice, acute pancreatitis
Very rare:	fulminant hepatic necrosis

Investigations:

Rare:	increased creatine phosphokinase (CPK)

Metabolism and nutrition disorders:

Common:	weight gain
Rare:	impaired glucose tolerance, diabetes aggravated, diabetes mellitus, including in patients with no history of hyperglycaemia or diabetes mellitus, ketoacidosis, hyperosmolar coma, severe hyperglycaemia
Very rare:	hypertriglyceridaemia, hypercholesterolaemia

Nervous system disorders:

Very common:	fatigue / drowsiness / sedation (overall incidence about 40%), dizziness
Common:	headache, tremor, rigidity, akathisia, extrapyramidal symptoms, seizures / convulsions / myoclonic jerks
Uncommon:	neuroleptic malignant syndrome
Rare:	confusion, delirium, intensification of dream activity
Very rare:	tardive dyskinesia

Psychiatric disorders:

Common:	Dysarthria
Uncommon:	Dysphemia
Rare:	restlessness, agitation
Very rare:	obsessive compulsive symptoms

Eye Disorders:

Common:	blurred vision

Renal and urinary disorders:

Common:	urinary incontinence, urinary retention
Very rare:	tubulointerstitial nephritis

Reproductive system disorders:

Very rare:	priapism, impotence, changes in ejaculation, dysmenorrhoea

Respiratory disorders:

Rare:	aspiration of ingested food (in patients with dysphagia or as a consequence of acute overdosage), respiratory depression / arrest with or without circulatory collapse, pneumonia and lower respiratory tract infection which may be fatal

Very rare:	one case of allergic asthma

Skin and subcutaneous tissue disorders:

Very rare:	skin reactions

Vascular system disorders:

Common:	hypertension, postural hypotension, syncope
Rare:	Thromboembolism (including pulmonary embolism)

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.

Post-Marketing Experience

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 2). 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 in MedDRA. Within each system organ class, AEs are presented in order of decreasing seriousness.

Table 2: Adverse effects from spontaneous reports and literature (frequency unknown)

Infections and infestations	Sepsis
Immune system disorders	Drug rash with eosinophilia and systemic symptoms (DRESS), angioedema, leukocytoclastic vasculitis
Endocrine disorders	Pseudophaeochromocytoma
Metabolism and nutrition disorders	Obesity
Nervous system disorders	Cholinergic syndrome, EEG changes, pleurothotonus, restless legs syndrome
Cardiac disorders	Myocardial infarction*, myocarditis*, chest pain/ angina pectoris, palpitations, atrial fibrillation, mitral valve incompetence associated with clozapine related cardiomyopathy *May be fatal
Vascular disorders	Hypotension

Respiratory, thoracic and mediastinal disorders	Pleural effusion, sleep apnoea syndrome, nasal congestion
Gastrointestinal disorders	Megacolon*, intestinal infarction/ischaemia*, intestinal necrosis*, intestinal ulceration* and intestinal perforation*, diarrhoea, abdominal discomfort/heartburn/dyspepsia, colitis *May be fatal
Hepatobiliary disorders	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	Pigmentation disorder
Musculoskeletal & connective tissue disorders	Rhabdomyolysis, muscle weakness, muscle spasms, muscle pain, systemic lupus erythematosus
Renal and urinary disorders	Renal failure, nocturnal enuresis
Reproductive system and breast disorders	Retrograde ejaculation
General disorders and administration site conditions	Polyserositis
Injury, poisoning and procedural complications	Falls (associated with clozapine-induced seizures, somnolence, postural hypotension, motor and sensory instability)

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Symptoms

The most commonly reported signs and symptoms associated with Clozaril (clozapine) overdose are: altered state of consciousness, including drowsiness, delirium and coma; tachycardia; hypotension; respiratory depression; hypersalivation. Seizures have occurred in a minority of reported cases. Other reported symptoms include lethargy, areflexia, confusion, hallucinations, agitation, extrapyramidal symptoms, hyper-reflexia, mydriasis, blurred vision, thermolability, cardiac arrhythmias, aspiration pneumonia, dyspnoea and respiratory failure.

Fatal overdoses have been reported with Clozaril (clozapine) generally at doses above 2500mg. There have also been reports of patients recovering from overdoses well in excess of 4 g.

However, in a few adults, primarily those not previously exposed to clozapine, the ingestion of doses as low as 400 mg led to life-threatening comatose conditions and, in one case, to death.

Treatment

Establish and maintain an airway; ensure adequate oxygenation and ventilation. Activated charcoal, which may be used with sorbitol, should be considered in treating overdosage. Cardiac and vital signs monitoring is recommended along with general symptomatic and supportive measures. Additional surveillance should be continued for several days because of the risk of delayed effects. Avoid adrenaline and derivatives when treating hypotension, and quinidine and procainamide when treating cardiac arrhythmia because all these drugs may exacerbate hypotension.

There are no specific antidotes for Clozaril (clozapine). Forced diuresis, dialysis, haemoperfusion and exchange transfusion are unlikely to be of benefit.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Clozaril has been shown to be an antipsychotic agent different from "typical" antipsychotic drugs.

In animal experiments, the compound does not induce catalepsy or inhibit apomorphine- or amphetamine-induced stereotyped behaviour. It has weak D_2 and D_1 receptor-blocking activity, but potent noradrenolytic, anticholinergic, antihistaminic and arousal reaction inhibiting effects. It has also been shown to possess antiserotonergic properties.

Clinically, Clozaril produces rapid and marked sedation, and exerts antipsychotic effects. In particular, the latter have been shown in schizophrenic patients resistant to other drug treatment. In such cases, Clozaril has proven effective in relieving both positive and negative schizophrenic symptoms, with about one-third of patients showing clinically relevant improvement. Clozaril is relatively free from extrapyramidal side effects, such as acute dystonia or a fully developed Parkinsonian syndrome, when compared with "typical" antipsychotic agents. There have been no reports of tardive dyskinesia directly attributable to Clozaril alone. However, the syndrome has been reported in a few patients who prior to or concomitantly with Clozaril therapy have been treated with other antipsychotic agents, so that a causal relationship to Clozaril can neither be established nor excluded. In contrast to "typical" antipsychotic drugs, Clozaril therapy produces little or no prolactin elevation, sparing adverse effects such as gynaecomastia, amenorrhoea, galactorrhoea or impotence.

A serious adverse reaction which may occur with Clozaril therapy is granulocytopenia/ agranulocytosis. In view of this risk the use of Clozaril should be limited to patients who are treatment-resistant (see Section 4.1 THERAPEUTIC INDICATIONS) and in whom regular haematological examinations can be performed (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE - Special Precautionary Measures and Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)).

Clinical trials

See Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS).

5.2 PHARMACOKINETIC PROPERTIES

Absorption

The absorption of orally administered Clozaril is 90-95%; the rate or extent of absorption is not influenced by food.

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

Distribution

In steady state conditions, when given twice daily, peak blood levels occur on an average at 2.1 hours (range: 0.4-4.2 h). Clozapine is 95% bound to plasma proteins.

Metabolism

Clozapine is almost completely metabolised prior to excretion by CYP1A2 and 3A4, and to some extent by CYP2C19 and 2D6. Of the main metabolites, only one, the des-methyl metabolite, was found to be active. Its pharmacological actions resemble those of clozapine, but are considerably weaker and of shorter duration.

Excretion

Its elimination is biphasic with a mean terminal half-life of 12 hours (range: 4-66 hours).

Only trace amounts of unchanged drug are detected in the urine and faeces. Approximately 50% of the administered dose is excreted in the urine and 30% in the faeces.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

No evidence of genotoxicity was observed in assays for gene mutations, chromosomal damage or DNA damage.

Carcinogenicity

No evidence of carcinogenicity was observed following dietary administration of clozapine for at least 78 weeks to mice and for 108 weeks to rats, with the highest dose equivalent to less than the maximum human dose on a mg/m^2 basis.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Excipients: magnesium stearate, colloidal anhydrous silica, povidone, purified talc, maize starch, lactose monohydrate. The tablets contain no colouring agent.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Blister packs: Store below 30°C

Bottle packs: Store below 25°C

This medicinal product does not require any special storage precautions.

6.5 NATURE AND CONTENTS OF CONTAINER

Clozaril® is supplied in PVC blister packs of *28 and 100 tablets and polyethylene bottles of *100 tablets.

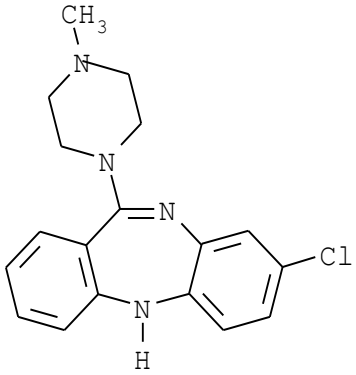
*Products not currently marketed in Australia

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure



Chemical name: 8-Chloro-11-(4-methyl-1-piperazinyl)-5*H*-dibenzo[b,e][1,4] diazepine

Molecular formula: $C_{18}H_{19}ClN_4$

Molecular weight: 326.83

CAS number

5786-21-0

Clozapine, a tricyclic dibenzodiazepine derivative, is a yellow crystalline powder, odourless or with a weak characteristic odour.

7 MEDICINE SCHEDULE (POISONS STANDARD)

Prescription Only Medicine (S4)

8 SPONSOR

Mylan Health Pty Ltd

Level 1, 30 The Bond

30-34 Hickson Road

Millers Point, NSW 2000

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9 DATE OF FIRST APPROVAL

Blister packs: 21 November 1994

Bottle packs: 22 August 2001

10 DATE OF REVISION

05 February 2019

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
4.4	Inclusion of precautionary information under 'Anticholinergic effects'.
4.8	o Moved 'obsessive compulsive symptoms' under system class 'Psychiatric disorders'. o Revised to 'tubulointerstitial nephritis' from 'acute interstitial nephritis'. o Under sub-heading 'Post-Marketing Experience', inclusion of 'Drug rash with eosinophilia and systemic symptoms (DRESS)' and update to adverse effects under system class 'Cardiac disorders' and 'Gastrointestinal disorders'.