AUSTRALIAN PRODUCT INFORMATION – CLOPINE® (CLOZAPINE)

WARNING

Clozapine Induced Gastrointestinal Hypomotility: **Severe gastrointestinal adverse reactions have occurred with the use of clozapine resulting in potential outcomes of hospitalisation, surgery and death (see Section 4.4 Special warnings and precautions for use, and Section 4.8 Adverse effects (undesirable effects)). Prior to initiating and during treatment of CLOPINE, screen for constipation and if necessary, manage as per current clinical guidelines.**

Myocarditis/pericarditis/cardiomyopathy**: Cases of myocarditis and cardiomyopathy, some of which have been fatal, and pericarditis have been reported in patients on clozapine (see Section 4.4 Special Warnings and Precautions for Use and Section 4.8 Adverse Effects (Undesirable effects)). If myocarditis or cardiomyopathy is suspected, clozapine treatment should be stopped and the patient immediately referred to a cardiologist. Generally, patients with a history of clozapine-associated myocarditis or cardiomyopathy should not be rechallenged with clozapine.**

1. NAME OF THE MEDICINE

Clozapine

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

CLOPINE® 25
Each 25 mg tablet contains 25 mg clozapine.

CLOPINE® 50
Each 50 mg tablet contains 50 mg clozapine.

CLOPINE® 100
Each 100 mg tablet contains 100 mg clozapine.

CLOPINE® 200
Each 200 mg tablet contains 200 mg clozapine.

CLOPINE® Suspension
Each 1 mL of suspension contains 50 mg clozapine.

Excipients with known effect:

Tablets: Contains Sugars (as lactose monohydrate).

Suspension: sorbitol solution (70 per cent) (crystallising), sodium methyl hydroxybenzoate and sodium propyl hydroxybenzoate.

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

3. PHARMACEUTICAL FORM

CLOPINE® 25 – 25 mg tablets: Round, yellow, flat, beveled edge tablets engraved with '25' over a pressure sensitive breakline on one face. The other face plain.

CLOPINE® 50 – 50 mg tablets: Round, yellow, flat, beveled edge tablets engraved with '50' over a pressure sensitive breakline on one face. The other face plain.

CLOPINE® 100 – 100 mg tablets: Round, yellow, flat, beveled edge tablets engraved with '100' over a pressure sensitive breakline on one face. The other face plain.

CLOPINE® 200 – 200 mg tablets: Oval shaped, yellow tablet with '200' on one side and a breakline on the other side.

CLOPINE® Suspension (50 mg/mL): a free-flowing yellow suspension.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment with CLOPINE® is indicated only in people with treatment-resistant schizophrenia, i.e. people with schizophrenia 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 effects (extrapyramidal side effects or tardive dyskinesia).

4.2 Dose and method of administration

(see also Section 4.4 Special Warnings and Precautions for Use.)

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.

CLOPINE® must be administered by Healthcare Professionals who are staff at centres registered with the Clopine® monitoring and support network - ClopineCentral™.

Suspension: Instructions for use

All doses being measured should be given using an appropriate oral dispenser.

24 hours before the first use:

1. Push down and turn the cap to open the bottle. Remove the cap and push the bottle adaptor into the top of the bottle. Leave the bottle adaptor in place on the bottle.

2. Replace the cap over the bottle adaptor and ensure the cap is tightened.

3. To ensure the suspension is dispersed, before dispensing the **first dose only**, shake the bottle for a period of 90 seconds. This is important to ensure any sedimentation that may have occurred during storage has been re-suspended.

4. Note the expiry date on the product label in permanent marker as ninety (90) days from the date of first opening.

5. Leave the bottle of suspension to stand for 24 hours before dispensing the first dose to allow dissipation of air bubbles formed during shaking.

Immediately before dispensing doses:

1. Immediately before each dose, the bottle should be further shaken for 10 seconds to ensure the suspension is homogeneous.

2. Push down and turn the cap to open the bottle. Remove the cap from the bottle.

3. Draw air into the oral dispenser (syringe) equivalent to the volume of the dose required.

4. Insert the oral dispenser into the opening of the bottle adaptor. Expel all the air from the oral dispenser into the bottle.

5. Turn the bottle of CLOPINE® suspension upside down and slowly draw the prescribed dose of liquid into the oral dispenser using the graduations displayed in millilitres.

6. Turn the bottle upright and detach the oral dispenser from the bottle adaptor. Invert the oral dispenser to prevent spillage.

7. Administer the CLOPINE® suspension directly from the oral dispenser or add the suspension to a cup with some water. Stir and drink the entire mixture right away.

8. Replace the bottle cap. Do not remove the bottle adaptor before recapping.

9. Oral dispensers may be reused for the same patient only. Wash the oral dispenser in warm soapy water after each use. Rinse well with water.

CLOPINE® Suspension can be used for up to 90 days following the first opening.

CLOPINE® Suspension should be given undiluted, however, if dilution is required, CLOPINE® Suspension may only be mixed with water. Do NOT mix CLOPINE® Suspension with any other beverages as they may change the properties of the active drug.

The recommended dosages which follow are for oral administration.

Starting therapy

Prior to initiating treatment with CLOPINE®, a baseline absolute neutrophil count (ANC) must

be obtained (see also Section 4.4 Special Warnings and Precautions for Use – Agranulocytosis/ Severe Neutropenia).

12.5 mg once or twice daily on the first day, followed by one or two doses of 25 mg 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 two to three 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 populations, or patients aged 60 years and older, see Section 4.4 Special Warnings and Precautions for Use.

Therapeutic dose range

In most patients, antipsychotic efficacy can be expected with 200 to 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 (ie. not exceeding 100 mg) are permissible up to a maximum of 900 mg/day. The possibility of increased adverse effects 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 to 300 mg/day given in divided doses. If the daily dose does not exceed 200 mg, a single administration in the evening may be appropriate.

Ending therapy

In the event of planned termination of clozapine therapy, a gradual reduction in dose is recommended over a one to two-week period. If abrupt discontinuation is necessary, the patient should be carefully monitored for the recurrence of psychotic symptoms and observed for symptoms related to cholinergic rebound such as profuse sweating, headache, nausea, vomiting and diarrhoea. Additional ANC monitoring is required for any patient reporting onset of fever during the two weeks after discontinuation (see Section 4.4 Special Warnings and Precautions for Use).

Restarting therapy

In patients in whom the interval since the last dose of clozapine exceeds two 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.) but was then able to be successfully titrated to a therapeutic dose, re-titration should be done with extreme caution.

Switching from a previous antipsychotic to clozapine

It is generally recommended that clozapine should not be used in combination with other antipsychotic drugs. When clozapine 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 clozapine as described previously.

If, in a particular patient, discontinuation of the antipsychotic drug is not a realistic option prior to institution of clozapine, 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 clozapine in increasing doses.

Dosage adjustment

It may be necessary to reduce the clozapine dose in patients with significant renal or hepatic impairment, or in CYP2D6 poor metabolisers (see Section 4.5 Interactions with Other Medicines and Other Forms of Interactions; Pharmacokinetic – related interactions).

Administration

CLOPINE® tablets are administered orally with water or other liquids. CLOPINE® tablets can be taken with or without food.

4.3 Contraindications

- CLOPINE® is contraindicated in patients with a history of drug-induced granulocytopenia/agranulocytosis; bone marrow disorders.
- Patients unable to undergo regular blood tests.
- Circulatory collapse and/or CNS depression due to any cause.
- Alcoholic and other toxic psychoses; drug intoxication; comatose conditions.
- Severe renal or cardiac disease (e.g. myocarditis).
- Severe hepatic disease including active hepatic disease associated with nausea, anorexia or jaundice; progressive hepatic disease; hepatic failure.
- Uncontrolled epilepsy.
- Paralytic ileus.
- CLOPINE® is contraindicated in patients who have demonstrated hypersensitivity to clozapine or other components of the product.

4.4 Special warnings and precautions for use

Special precautionary measures

Gastrointestinal Hypomotility with Severe Complications

Severe gastrointestinal adverse reactions have occurred with the use of clozapine, primarily due to its potent anti-cholinergic effects and resulting in gastrointestinal hypomotility. In post-marketing experience, reported effects range from nausea, vomiting, overflow diarrhoea, constipation, to paralytic ileus, intestinal impaction and more severe complications. Increased frequency of constipation and delayed diagnosis and treatment increased the risk of severe complications of gastrointestinal hypomotility, resulting in faecal impaction, megacolon, paralytic ileus and intestinal obstruction, ischaemia, infarction, perforation, ulceration or necrosis (see Section 4.8 Adverse effects (Undesirable effects)). These reactions have resulted in hospitalisation, surgery and death. The risk of severe adverse reactions is further increased with anticholinergic medications (and other medications that decrease gastrointestinal peristalsis); therefore, concomitant use should be avoided when possible (see Section 4.4 Special warnings and Precautions for use - Other Precautions, Anticholinergic Toxicity, and 4.5 Interactions with other medicines and other forms of interactions).

Prior to initiating CLOPINE, screen for constipation and treat as necessary. Early diagnosis and treatment of constipation at the start of clozapine therapy is important in preventing serious gastrointestinal-related complications (e.g. appendicitis). Subjective symptoms of constipation may not accurately reflect the degree of gastrointestinal hypomotility in clozapine-treated patients. Therefore, reassess bowel function frequently with careful attention to any changes in the frequency or character of bowel movements, as well as signs and symptoms of complications of hypomotility (eg. nausea, vomiting, abdominal distension, abdominal pain, lack of urge to defecate, constipation, inability to defecate). If constipation or gastrointestinal hypomotility are identified, monitor closely and manage promptly, as per current clinical guidelines to prevent severe complications (please see Boxed Warning at the beginning of the document).

Appendicitis, including perforated appendicitis, have been reported in post-marketing cases in patients treated with clozapine of any duration, regardless of age or gender. Some of these cases have reported fatal outcomes. Appendicitis and perforated appendicitis require intervention with medicine and surgery.

Agranulocytosis /severe neutropenia

Clozapine can cause agranulocytosis and neutropenia (a low absolute neutrophil count (ANC)) which is below the normal pre-treatment levels of blood neutrophils.

The use of clozapine should be limited to patients diagnosed with schizophrenia who are non-responsive to, or intolerant of other antipsychotic drugs and:

- who have initially normal leucocyte findings (white blood cell (WBC) count >$3.5x10^9$/L, normal differential blood count) , and

- in whom regular WBC counts and ANC counts [tested weekly during the first 18 weeks, at least monthly thereafter, throughout treatment, and tested for 1 month after complete discontinuation of clozapine] can be performed.

Development of agranulocytosis/ severe neutropenia is a risk inherent to clozapine treatment. Severe neutropenia, ANC less than $0.5x10^9$/L, occurs in a small percentage of patients taking clozapine and is associated with an increase in the risk of serious and potentially fatal infections. Risk of neutropenia appears greatest during the first 18 weeks of treatment and then declines. Although generally reversible on withdrawal of the drug, agranulocytosis and neutropenia can prove fatal. Because immediate withdrawal of the drug is required to prevent the development of life-threatening agranulocytosis/ severe neutropenia, monitoring of the WBC and ANC counts is mandatory.

Prescribing physicians should fully comply with the instituted safety measures. Because of the association of clozapine with agranulocytosis/ severe neutropenia, the precautionary measures which follow 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 clozapine.

- Drugs known to have a substantial potential to depress bone marrow function should not be used concurrently with clozapine. 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, eg. granulocytopenia.

- Before starting clozapine treatment, a WBC count and a differential count must be performed within ten days prior to starting clozapine treatment to ensure that only patients with normal leucocyte findings (WBC count $\geq 3.5x10^9$/L, normal differential blood count), and normal ANC will receive the drug. After the start of clozapine treatment, the WBC and ANC must be monitored weekly for 18 weeks. Thereafter the WBC and ANC must be performed at least monthly throughout treatment and for one month after complete discontinuation of clozapine. At each consultation the patient should be reminded to contact the treating doctor immediately if any kind of infection begins to develop. Particular attention should be paid to flu-like complaints such as fever or sore throat and to other evidence of infection, which may be indicative of neutropenia (see Section 4.8 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 clozapine for more than 18 weeks and have had their treatment interrupted for more than three days but less than four weeks should have their WBC count and ANC monitored weekly for an additional six weeks. If no haematological abnormality occurs, monitoring at intervals not exceeding four weeks may be resumed. If clozapine treatment has been interrupted for four weeks or longer, weekly monitoring is required for the next 18 weeks of treatment.

- If, during treatment with clozapine, an infection occurs and/or the WBC count has dropped below 3.5×10^9/L , or has dropped by a substantial amount from baseline (even if the count is above 3.5×10^9/L), a repeat WBC count and a differential count should be done. Should the results confirm a WBC count below 3.5×10^9/L and/or reveal an ANC of between 1.5 and 2.0×10^9/L , the leucocytes and the granulocytes must be checked at least twice weekly. If the WBC count falls below 3.0×10^9/L and/or the absolute ANC drops below

1.5 x 10^9/L, clozapine therapy must be withdrawn at once and the patient 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 clozapine, haematological evaluation must be continued until haematological recovery has occurred.

- If clozapine therapy has been withdrawn and a further fall of WBC count below 2.0 x 10^9/L occurs and/or the ANC 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 clozapine therapy has been discontinued as a result of white blood cell deficiencies (WBC count <3.0 x 10^9/L and/or ANC <1.5 x 10^9/L) must not be re-exposed to clozapine.

Other Precautions

Using Clozapine with Other Drugs Associated with Neutropenia

It is unclear if concurrent use of other drugs known to cause neutropenia increases the risk or severity of clozapine-induced neutropenia. There is no strong scientific rationale to avoid clozapine treatment in patients concurrently treated with these drugs. Patients should be closely monitored if clozapine is used concurrently with an agent known to cause neutropenia (e.g. some chemotherapeutic agents). Consult with the treating oncologist in patients receiving concomitant chemotherapy.

Myocardial Infarction

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

Myocarditis, Pericarditis and Cardiomyopathy

Myocarditis, pericarditis and cardiomyopathy have occurred with the use of clozapine. These reactions can be fatal. 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 (eg. tachypnoea, shortness of breath, hypotension, raised jugular venous pressure) or arrhythmias, the possibility of myocarditis, pericarditis 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, pericarditis or cardiomyopathy by a cardiologist. If myocarditis or cardiomyopathy is suspected, clozapine treatment should be promptly stopped, and the patient immediately referred to a cardiologist. If myocarditis is confirmed, clozapine should be discontinued. If cardiomyopathy is diagnosed, clozapine should be discontinued unless the benefit clearly outweighs the risk to the patient. If patients are diagnosed with cardiomyopathy while on clozapine treatment, there is potential to develop mitral valve incompetence. Mitral valve

incompetence has been reported in cases of cardiomyopathy related to clozapine 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 clozapine 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)).

Generally, patients with a history of clozapine-associated myocarditis or cardiomyopathy should not be rechallenged with clozapine. However, if the benefit of clozapine treatment is judged to outweigh the potential risks of recurrence, the clinician may consider rechallenge with clozapine in consultation with a cardiologist, after a complete cardiac evaluation and under close monitoring.

QT interval prolongation

As with other antipsychotics, caution is advised in patients with known cardiovascular disease or family history of QT prolongation.

As with other antipsychotics, caution should be exercised when clozapine is prescribed with medicines known to increase 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)), it is recommended to discontinue clozapine if the eosinophil count rises above 3.0×10^9/L and to restart 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)), it is recommended to discontinue clozapine if the platelet count falls below 5.0×10^9/L.

Orthostatic hypotension

Tachycardia, bradycardia 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. These reactions can be fatal. The syndrome is consistent with neurally mediated reflex bradycardia (NMRB). 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 (see Section 4.5 Interactions with Other Medicines and Other Forms of Interactions). When restarting therapy in patients who have had even a brief interruption with clozapine treatment, the dosage must be reduced (see also Section 4.2 Dosage and Administration – Restarting Therapy).

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 leucopenia), the patient should be carefully observed for the recurrence of psychotic symptoms and symptoms related to cholinergic rebound (see Section 4.2 Dose and Method of Administration – Ending therapy).

Treatment initiation

Patients commencing clozapine treatment need to be under close medical supervision.

Seizures

Clozapine can cause EEG changes, including the occurrence of spike and wave complexes. Clozapine lowers the seizure threshold in a dose-dependent manner and may induce myoclonic jerks or generalized seizures. Caution should be used in administering clozapine 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 populations).

Sleep apnoea

Sleep apnoea and related disorders have been reported in patients treated with clozapine, with or without prior history of sleep apnoea, and with or without concomitant weight gain. In patients who have a history of or are at risk for sleep apnoea, or who are concomitantly using central nervous system depressants, clozapine should be used with caution.

Dosing in special populations

In patients with a history of seizures, or suffering from cardiovascular, renal or hepatic disorders (note that severe hepatic, renal or cardiovascular disorders including active hepatic disease associated with nausea, anorexia or jaundice, progressive hepatic 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, neutropenia or myocarditis (see BOXED WARNING, Section 4.4 Special Warnings and Precautions for Use – Myocarditis/cardiomyopathy and Section 4.4 Special Warnings and Precautions for Use – Agranulocytosis/ Severe Neutropenia). The possibility of an underlying infectious process should also be considered.

Falls

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

antipsychotic therapy.

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 clozapine, either alone or in combination with lithium or other CNS-active agents (estimated incidence <0.1%). If the diagnosis of NMS is confirmed, clozapine should be discontinued immediately and appropriate medical measures should be administered.

Anticholinergic Effects

Clozapine has potent anticholinergic effects. Treatment with CLOPINE can result in CNS and peripheral anticholinergic toxicity, especially at higher dosages, or in overdose situations (see Section 4.9 Overdose). Use with caution and careful supervision is required in patients with a current diagnosis or prior history of constipation, urinary retention, prostatic enlargement, narrow angle glaucoma or other conditions in which anticholinergic effects can lead to significant adverse reactions. Where possible, avoid concomitant use, with other anticholinergic medications because the risk for anticholinergic toxicity or severe gastrointestinal adverse reactions is increased (see Section 4.4 Special warnings and Precautions for use and Section 4.5 Interactions with other medicines and other forms of interactions).

Metabolic Changes

Atypical antipsychotic drugs, including clozapine, 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.

Risk of thromboembolism

Venous thromboembolism (VTE), including fatal pulmonary embolism, has been reported with antipsychotic drugs including clozapine in case reports and/or observational studies. When prescribing clozapine, all possible risk factors for VTE should be identified before and during treatment. As clozapine 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 clozapine was not included in this analysis.

Use of clozapine 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. Clozapine 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 clozapine treatment. There have been no reports of tardive dyskinesia directly attributable to clozapine alone. However, the syndrome has been reported in a few patients who, prior to or concomitantly with clozapine therapy, have been treated with other antipsychotic agents, so that a causal relationship to clozapine 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 treated with atypical antipsychotics including clozapine. 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 people 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 clozapine 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 clozapine. 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 clozapine. Clinical monitoring of weight is recommended.

Use in hepatic impairment

Patients with stable pre-existing hepatic disorders may receive clozapine but need regular liver function test monitoring. Patients who develop symptoms of possible hepatic dysfunction such as nausea, vomiting and/or anorexia during treatment with clozapine 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 clozapine 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 reintroduction of the drug. (Also see Section 4.4 Special Warnings and Precautions for Use – Dosing in special populations).

Use in renal impairment

See Section 4.4 Special Warnings and Precautions for Use – Dosing in special populations.

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 clozapine treatment and there have been reports of tachycardia, which may be sustained, in patients taking clozapine. 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 clozapine, such as urinary retention and constipation.

Elderly patients with Dementia-related Psychosis

In patients aged 60 years and older with dementia-related psychosis, the efficacy and safety of clozapine has 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). Clozapine should be used with caution in patients aged 60 years and older with dementia.

Paediatric use

No paediatric studies have been performed. Safety and effectiveness in children and adolescents less than 16 years of age have not been established. As with all medicines, clozapine 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 clozapine (see also Section 4.4 Special Warnings and Precautions for Use). Clozapine may enhance the central effects of alcohol, MAOIs and CNS depressants such as narcotics, antihistamines and benzodiazepines.

Particular caution is advised when clozapine 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.

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

Rare but serious reports of seizures, including onset of seizures in non-epileptic patients, and isolated cases of delirium where clozapine 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.

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

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

In clozapine-treated patients, the blood pressure increasing effect of adrenaline (epinephrine) and its derivatives may be reversed.

Pharmacokinetic-related interactions

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

Clozapine is a substrate for many cytochrome P450 isoenzymes, in particular CYP 1A2, CYP 2D6 and CYP 3A4. Caution is called for in patients receiving concomitant treatment with other drugs which are inhibitors or induces of these enzymes.

Concomitant administration of cimetidine, erythromycin and ciprofloxacin, drugs known to inhibit the cytochrome P450 enzyme system, may increase the plasma levels of clozapine, possibly resulting in adverse effects.

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

Potent inhibitors of CYP 3A4, such as azole antimycotics and protease inhibitors, could potentially also increase clozapine plasma concentrations.

Concomitant administration of phenytoin, carbamazepine, rifampicin, St John's wort (*Hypericum perforatum*) [drugs known to induce the activity of CYP 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.

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

With other drugs known to bind to the CYP 2D6 isoenzyme, such as antidepressants, phenothiazines and type 1C antiarrhythmics, no clinically relevant interactions with clozapine have been observed so far. On theoretical grounds, however, it is possible that the plasma levels of such drugs are increased by clozapine, so it may be appropriate to use them at doses lower than are usually prescribed.

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 two-fold), fluvoxamine (up to ten-fold) and oral contraceptives (which inhibits 1A2, 3A4 and 2C19 isozymes). Fluvoxamine is known to inhibit the metabolism of clozapine by the isoenzyme CYP 1A2. Such patients should be monitored closely and dosage adjustments may be indicated.

Tobacco smoke, a known inducer of CYP 1A2, may decrease the plasma levels of clozapine. In such 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 CYP 1A2, could potentially also decrease the plasma levels of clozapine.

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 × 250 mg ciprofloxacin. There have also been reports of interactions with norfloxacin and enoxacin.

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).

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

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 (Category C)

Neonates exposed to antipsychotic drugs (including clozapine) during the third trimester of pregnancy are at risk of experiencing extrapyramidal neurological disturbances and/or withdrawal symptoms following delivery. There are risks to the mother associated with untreated schizophrenia and with exposure to antipsychotics, including CLOPINE, during pregnancy (see Clinical considerations).

Studies in animals are inadequate but available data 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 fetal damage. However, clozapine and/or its metabolites cross the placenta and enter the fetus in rabbits. The adverse pharmacological and toxicological effects of clozapine in adults may also occur in the fetus.

Clinical considerations:

Disease-associated maternal and/or embryo/fetal risk: There is a risk to the mother from untreated schizophrenia, including increased risk of relapse, hospitalisation, and suicide. Schizophrenia is associated with increased adverse perinatal outcomes, including preterm birth. It is not known if this is a direct result of the illness or other comorbid factors.

Fetal/Neonatal adverse reactions: There have been post-market reports of extrapyramidal and/or withdrawal symptoms such as agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, and feeding disorder in neonates who have been exposed to antipsychotic drugs, including clozapine, during the third trimester of pregnancy. 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. Monitor neonates for extrapyramidal and/or withdrawal symptoms and manage symptoms appropriately.

Clozapine should be used during pregnancy or in women likely to become pregnant 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. In women of child-bearing potential, adequate contraceptive measures must be ensured (see Section 4.5 Interactions with Other Medicines and Other Forms of Interactions - Pharmacokinetic-related interactions).

Use in Lactation

Animal studies suggest that clozapine 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.

Clozapine is present in human milk. There is one case report of sedation and a report of agranulocytosis in an infant exposed to clozapine through human milk. There is no information on the effects of clozapine on milk production.

Mothers receiving clozapine should not breast feed.

4.7 Effects on ability to drive and use machines

Owing to the ability of clozapine 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/ severe neutropenia (see Section 4.4 Special Warnings and Precautions for Use).

The most serious adverse reactions experienced with clozapine are agranulocytosis, seizure, cardiovascular effects, severe gastrointestinal effects (intestinal obstruction, severe constipation, gastrointestinal hypomotility) 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 ranked under the 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 Section 4.4 Special Warnings and Precautions for Use 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:

Common:	leukopenia/decreased WBC/neutropenia, eosinophilia, leukocytosis
Uncommon:	agranulocytosis
Rare:	anaemia

Very rare:	thrombocytopenia, thrombocythemia

Nervous system disorders:

Very common:	fatigue/drowsiness/sedation (overall incidence 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

Eye disorders:

Common:	blurred vision

Cardiac disorders:

Very common:	tachycardia
Common:	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

Hepatobiliary disorders:

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

Investigations:

Rare:	increased CPK

General disorders:

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

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, obesity

Very rare:	hypertriglyceridaemia, hypercholesterolaemia

Psychiatric disorders:

Common:	dysarthria
Uncommon:	dysphemia
Rare:	restlessness, agitation
Very rare:	obsessive compulsive symptoms

Renal and urinary disorders:

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

Reproductive system disorders:

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

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, sleep apnoea syndrome
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)

Injury, poisoning and procedural complications:

Uncommon:	Falls (associated with clozapine-induced seizures, somnolence, postural hypotension, motor and sensory instability)

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 clozapine 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, appendicitis*, appendicitis perforated* *May be fatal
Immune system disorders	Drug rash with eosinophilia and systemic symptoms (DRESS), angioedema, leukocytoclastic vasculitis
Endocrine disorders	Pseudophaeochromocytoma
Nervous system disorders	Cholinergic syndrome, EEG changes, pleurothotonus, restless legs syndrome
Cardiac disorders	Myocardial infarction*, myocarditis*, pericarditis*, 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, nasal congestion
Gastrointestinal disorders	Megacolon*, faecal incontinence, intestinal infarction/ischaemia*, intestinal necrosis*, intestinal ulceration*, 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

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 http://www.tga.gov.au/reporting-problems.

4.9 Overdose

Symptoms

Human experience. The most commonly reported signs and symptoms associated with clozapine overdose are altered states 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 clozapine, generally at doses above 2,500 mg. There have also been reports of patients recovering from overdoses well in excess of 4g. 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 (epinephrine) and derivatives when treating hypotension, and quinidine and procainamide when treating cardiac arrhythmia, because all of these drugs may exacerbate hypotension.

There are no specific antidotes for 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

Clozapine 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 D2- and D1-receptor blocking activity, but potent noradrenolytic, anticholinergic, antihistaminic and arousal reaction inhibiting effects. It has also been shown to possess antiserotonergic properties.

Clinically, clozapine produces rapid and marked sedation, and exerts antipsychotic effects. In particular, the latter have been shown in people with schizophrenia that are resistant to other drug treatment. In such cases, clozapine has proven effective in relieving both positive and negative symptoms of schizophrenia, with about one-third of patients showing clinically relevant improvement. Clozapine 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 clozapine alone. However, the syndrome has been reported in a few patients who prior to or concomitantly with clozapine therapy have been treated with other antipsychotic agents, so that a causal relationship to clozapine can be neither established nor excluded. In contrast to typical antipsychotic drugs, clozapine 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 clozapine therapy is granulocytopenia/agranulocytosis. In view of this risk the use of clozapine should be limited to people who are treatment-resistant (see Section 4.1 Therapeutic Indications) and in whom regular haematological examination can be performed (see Section 4.4 Special Warnings and Precautions for Use 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 clozapine is 90 to 95%; the rate or extent of absorption is not influenced by food.

Clozapine, the active ingredient, is subject to a 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). Clozapine is 95% bound to plasma proteins.

Metabolism

Clozapine is almost completely metabolised prior to excretion. Of the main metabolites, only one, the desmethyl 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 approximately fourteen hours (range 7.9 – 29.1 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

CLOPINE® Tablets (25 mg, 50 mg, 100 mg, 200 mg)

Lactose monohydrate, microcrystalline cellulose, povidone, sodium starch glycollate and magnesium stearate.

CLOPINE® Suspension (50 mg/mL)

Sorbitol solution (70 per cent) (crystallising), povidone, monobasic sodium phosphate dihydrate, sodium methyl hydroxybenzoate, sodium propyl hydroxybenzoate, xanthan gum, glycerol, hydrochloric acid, sodium hydroxide and purified water.

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

CLOPINE® Tablets

Store below 30ºC in a cool dry place. Protect from light.

CLOPINE® Suspension

Store below 25ºC. CLOPINE® Suspension may be used for up to 90 days after first opening.

Recap the bottle tightly following each use.

6.5 Nature and contents of container

CLOPINE® 25, CLOPINE® 50, CLOPINE® 100 and CLOPINE® 200 are available in blister packs or bottles, in pack sizes of either 50 (not marketed) or 100 tablets.

CLOPINE® Suspension (50 mg/mL) is available as 100 mL in 125 mL bottle (not marketed).

6.6 Special precautions for disposal

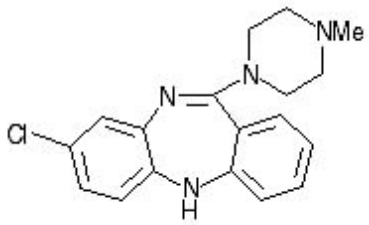
In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 Physicochemical properties

Chemical Structure

CLOPINE® Tablets and suspension contain clozapine which is a tricyclic dibenzodiazepine derivative. This compound is practically insoluble in water.

Active: Clozapine.



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

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

Molecular weight: 326.83

CAS number

5786-21-0

7. MEDICINE SCHEDULE (POISON STANDARD)

Prescription Only Medicine (S4)

8. SPONSOR

Pfizer Australia Pty Ltd
Level 17, 151 Clarence Street
SYDNEY NSW 2000
Toll Free number: 1800 675 229
www.pfizermedicalinformation.com.au

9. DATE OF FIRST APPROVAL

4 October 2000: 25 mg and 100 mg blister packs
14 April 2003: 25 mg and 100 mg bottles
10 October 2003: 50 mg and 200 mg blister packs and bottles
16 May 2008: 50 mg/mL suspension

10. DATE OF REVISION

09 July 2025

CLOPINE® is a registered trademark of Douglas Pharmaceuticals Limited, used under licence.

Summary table of changes

Section changed	Summary of new information
Throughout	Minor editorial changes.
Boxed Warning	Updated 'Myocarditis/Cardiomyopathy' sub-section to include pericarditis.
4.4	Updated 'Myocarditis/Cardiomyopathy' sub-section to include pericarditis. Correction of mathematical units.
4.6	Updated information concerning pregnancy and use in lactation.
4.8	Added pericarditis and faecal incontinence to 'Post Marketing Experience' sub-section.