CLOPINE®
PRODUCT INFORMATION

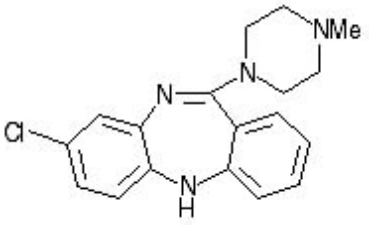
WARNING

***Myocarditis/cardiomyopathy*: Cases of myocarditis, some of which have been fatal, and cardiomyopathy have been reported in patients on clozapine (see "PRECAUTIONS" AND "ADVERSE EFFECTS").**

NAME OF THE MEDICINE

CLOPINE® 25
CLOPINE® 50
CLOPINE® 100
CLOPINE® 200
CLOPINE® Suspension

Active: Clozapine.



Chemical name: 8-chloro-11-(4-methyl-1-piperazinyl)-5H-dibenzo[b,e][1,4] diazepine.
CAS No: 5786-21-0
Molecular formula: $C_{18}H_{19}ClN_4$.
Molecular weight: 326.83

DESCRIPTION

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

CLOPINE® Tablets (25 mg, 50 mg, 100 mg, 200 mg)
Other ingredients: Lactose monohydrate, cellulose microcrystalline, povidone, sodium starch glycollate and magnesium stearate.

CLOPINE® Suspension (50 mg/mL)
Other ingredients: sorbitol solution (70 per cent) (crystallising), povidone, monobasic sodium phosphate dihydrate, sodium methyl hydroxybenzoate, sodium propyl hydroxybenzoate, xanthan gum, glycerol and purified water.

PHARMACOLOGY

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 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, 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 "INDICATIONS") and in whom regular haematological examination can be performed (see "PRECAUTIONS, Special precautionary measures" and "ADVERSE EFFECTS").

Pharmacokinetics

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.

Elimination

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.

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).

CONTRAINDICATIONS

- CLOPINE® is contraindicated in patients with a history of drug induced granulocytopenia/agranulocytosis; bone marrow disorders.
- 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.

PRECAUTIONS

Special precautionary measures

Agranulocytosis
Clozapine can cause agranulocytosis. Its use should be limited to people with schizophrenia who are non-responsive to, or intolerant of other antipsychotic drugs:

- who have initially normal leucocyte findings (white blood cell count > 3500/mm^3, 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 clozapine] can be performed.

Development of granulocytopenia and agranulocytosis is a risk inherent to clozapine 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 white blood cell (WBC) count is mandatory.

Prescribing physicians should fully comply with the instituted safety measures. Because of the association of clozapine with agranulocytosis, 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 white blood cell (WBC) count and a differential count (DC) must be performed within ten days prior to starting clozapine treatment to ensure that only patients with normal leucocyte findings (WBC count >3500/mm^3, normal differential blood count), and normal absolute neutrophil counts (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 "ADVERSE 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 3,500/mm^3, or has dropped by a substantial amount from baseline (even if the count is above 3,500/mm^3), a repeat WBC count and a differential count should be done. Should the results confirm a WBC count below 3,500/mm^3 and/or reveal an absolute neutrophil granulocyte count of between 2,000 and 1,500/mm^3, the leucocytes and the granulocytes must be checked at least twice weekly. If the WBC count falls

below 3,000/mm^3 and/or the absolute neutrophil granulocyte count drops below 1,500/mm^3, 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 2,000/mm^3 occurs and/or the neutrophil granulocytes decrease below 1,000/mm^3, 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 <3,000/mm^3 and/or ANC <1,500/mm^3) must not be re-exposed to clozapine.

Other Precautions

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

Myocarditis / Cardiomyopathy
Cases of myocarditis (with or without eosinophilia), some of which have been fatal, 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 (eg. 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, clozapine should be discontinued. If cardiomyopathy is diagnosed, possible discontinuation of clozapine, based on clinical grounds, should be considered. 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 "ADVERSE 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 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 "ADVERSE EFFECTS, Haematological"), it is recommended to discontinue clozapine if the eosinophil count rises above 3,000/mm^3 and to restart therapy only after the eosinophil count has fallen below 1,000/mm^3

Thrombocytopenia
In the event of thrombocytopenia (see "ADVERSE EFFECTS, Haematological"), it is recommended to discontinue clozapine if the platelet count falls below 50,000 / mm^3.

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 (see "INTERACTIONS WITH OTHER MEDICINES").

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 "DOSAGE AND 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-dependant 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 "PRECAUTIONS – Dosing in special populations").

Driving and using machines
Owing to the ability of clozapine to cause sedation and lower the seizure threshold, activities such as driving or operating machinery and other activities where sudden loss of consciousness could cause serious risk to the patient or others should be avoided, especially during the initial weeks of treatment.

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 or myocarditis (see "BOXED WARNING", "PRECAUTIONS – Myocarditis" and "PRECAUTIONS - Agranulocytosis"). 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 exerts anticholinergic activity which may produce undesirable effects throughout the body. Probably on account of its anticholinergic properties, clozapine 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 "ADVERSE EFFECTS"). On rare occasions these cases have been fatal. Since complications have been associated with delayed diagnosis, patients should be questioned about their bowel habits. Careful supervision is indicated in the presence of **prostatic enlargement** and **narrow angle glaucoma**. Clozapine is contraindicated in patients with paralytic ileus.

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.

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.

Risk of thromboembolism
As clozapine may cause sedation and weight gain, thereby increasing the risk of thromboembolism, immobilisation of patients should be avoided.

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.

Liver 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.

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)
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 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. (see "INTERACTIONS WITH OTHER MEDICINES, Pharmacokinetic-related interactions").

Non-teratogenic class effect: 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 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.

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.

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. Mothers receiving clozapine should not breast feed.

Paediatric use
No paediatric studies have been performed. Safety and effectiveness in children less than 16 years of age have not been established. As with all medicines, clozapine must be kept out of reach of children.

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.

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.

INTERACTIONS WITH OTHER MEDICINES

Pharmacodynamic-related interactions
Drugs known to have a substantial potential to depress bone marrow should not be used concurrently with clozapine (see also "PRECAUTIONS, Special precautionary measures"). 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 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. Fluvoxamine is known to inhibit the metabolism of clozapine by the isoenzyme CYP 1A2.

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 fluoxetine, paroxetine, sertraline (up to two fold), fluvoxamine (up to ten fold), citalopram and oral contraceptives. Such patients should be monitored closely and dosage adjustments may be indicated.

Nicotine, a known inducer of CYP 1A2, may decrease the plasma levels of clozapine. In such cases of sudden cessation of nicotine (eg. Cessation of cigarette 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.

ADVERSE EFFECTS

The adverse effects (AEs) of clozapine are most often predictable based on its pharmacological properties with the exception of agranulocytosis (see "PRECAUTIONS").

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

Data from the clinical trials experience showed that a varying proportion of clozapine- treated patients 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 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 the "PRECAUTIONS" 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:

Common:	leucopenia/decreased WBC/neutropenia, eosinophilia, leucocytosis
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, obsessive compulsive symptoms

Eye disorders:

Common:	blurred vision

Cardiac disorders:
Very common: tachycardia
Common: ECG changes
Rare: circulatory collapse, arrhythmias, myocarditis, pericarditis
Very rare: cardiomyopathy, cardiac arrest

Gastrointestinal disorders:
Very common: constipation, hypersalivation
Common: nausea, vomiting, dry mouth
Rare: dysphagia, ileus impactation
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
Very rare: hypertriglyceridaemia, hypercholesterolaemia

Psychiatric disorders:
Common: dysarthria
Uncommon: dysphemia
Rare: restlessness, agitation

Renal and urinary disorders:
Common: urinary incontinence, urinary retention
Very rare: acute interstitial 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
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 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
Immune system disorders	Angioedema, leukocytoclastic vasculitis
Endocrine disorders	Pseudophaeochromocytoma
Metabolism and nutrition Disorders	Obesity
Nervous system disorders	Cholinergic syndrome, EEG changes, pleurothotonus
Cardiac disorders	Myocardial infarction which can be fatal, chest pain/ angina pectoris, palpitations, atrial fibrillation, mitral valve incompetence associated with clozapine related cardiomyopathy
Vascular disorders	Hypotension
Respiratory, thoracic and mediastinal disorders	Pleural effusion, sleep apnoea syndrome, nasal congestion
Gastrointestinal disorders	Megacolon which can be fatal, intestinal infarction/ ischaemia which can be fatal,

	diarrhoea, abdominal discomfort/heartburn/dyspepsia,colitis
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)

DOSAGE AND ADMINISTRATION

(see also "Other Precautions")

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® Suspension must be administered by Healthcare Professionals who are staff at centres registered with Hospira's 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

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 "Other Precautions".

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 150-300 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'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 (see "Other Precautions").

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 "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 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.

Administration
Clozapine tablets are administered orally with water or other liquids.

OVERDOSAGE

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 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.

In case of overdose, immediately contact the Poisons Information Centre for advice on management. (In Australia, call 13 11 26; in New Zealand call 0800 764 766.)

PRESENTATION AND STORAGE CONDITIONS

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® 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): a free flowing yellow suspension, available as 100 mL in 125 mL bottle.

CLOPINE® Tablets
Store below 30°C in a cool dry place. Protect from light.

CLOPINE® Suspension
Store below 25°C. CLOPINE® Suspension may be used for up to 90 days after first opening.
Recap the bottle tightly following each use.

NAME AND ADDRESS OF SPONSOR

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POISONS SCHEDULE OF THE MEDICINE

Prescription Only Medicine (S4)

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (the ARTG)

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

DATE OF MOST RECENT AMENDMENT

9 November 2017