CLOPINE* 25 MG & 100 MG TABLETS

ACTIVE INGREDIENT

Clopine 25mg- Each tablet contains 25mg of clozapine Clopine 100mg- Each tablet contains
100mg of clozapine

DOSAGE FORM

Tablet

PRODUCT DESCRIPTION

CLOPINE 25 mg tablets are round yellow flat bevel-edged tablets engraved “25” over a pressure sensitive breakline on one face, the other face plain

CLOPINE 100 mg tablets: are round yellow flat bevel-edged tablets engraved “100” over a pressure sensitive breakline on one face, the other face plain.

PHARMACODYNAMICS

CLOPINE tablets contain clozapine. Clozapine is an atypical antipsychotic, derived from the tricyclic dibenzodiazepine family. Clozapine differs from the traditional neuroleptic antipsychotics with respect to its side effect profile.

In pharmacological experiments, clozapine has been shown not to induce catalepsy or inhibit apomorphine – or amphetamine-induced stereotyped behaviour. It possesses weak dopamine receptor-blocking activity at D1, D2, D3 and D5 receptors, but shows high potency for the D4 receptor, in addition to potent anti-alpha-adrenergic, anticholinergic, antihistaminic and sedative properties. Clozapine has also been shown to possess antiserotoninergic properties.

Clinically, the use of clozapine results in rapid and marked sedation, with strong antipsychotic effects. The strong exertion of antipsychotic effects has been observed in schizophrenic patients resistant to other drug treatment. In such cases, clozapine has been demonstrated to be effective in the relief of both the positive and negative symptoms of schizophrenia. Clinically significant improvement has been observed in about one-third of patients within the first 6 weeks of treatment with clozapine and in about 60% of patients in whom treatment is continued for up to 12 months.

Clozapine produces virtually no major extrapyramidal side effects such as acute dystonia. Parkinsonian-like side effects and akathisia are rare. Likewise there have been no reported cases of tardive dyskinesia directly attributable to clozapine treatment alone. In contrast to classical neuroleptics, clozapine produces little to no prolactin elevation, thus reducing the risk of adverse effects such as gynaecomastia, amenorrhoea, and impotence.

Clozapine therapy may result in the potentially serious adverse reactions of granulocytopenia and agranulocytosis. These adverse effects have been reported to occur in approximately 3% and 0.7%, of patients, respectively. In view of these risks the use of clozapine should be limited to patients whom have been demonstrated to be treatmentresistant and intolerant to the extrapyramidal effects of traditional neuroleptics (see Indications), and in whom regular haematological examinations can be performed (see Warnings and Precautions and Adverse Effects).

PHARMACOKINETICS

Clozapine is well absorbed from the gastrointestinal tract (90-95%), neither the rate nor extent of absorption of clozapine is affected by the administration of food. However, clozapine is subject to moderate first pass metabolism resulting in an absolute bioavailability of 50-60%. Peak plasma concentrations occur on average at 2.1 hours (peak concentrations ranging from 0.4-2.4 hours have been reported) after oral administration. Steady state concentrations are attained after 8-10 days of therapy

Clozapine is rapidly and extensively distributed throughout the body and crosses the blood brain barrier freely. The volume of distribution of clozapine is 1.6 L/kg. Clozapine is approximately 95% bound to plasma proteins. Elimination of clozapine is biphasic, with a mean terminal half-life of 12 hours (range: 6-26 hours) at steady state. After single doses of 75 mg the mean terminal half-life was 7.9 hours; this figure increased to 14.2 hours when steady-state conditions were reached by administering daily doses of 75 mg for at least 7 days. Dosage increases from 37.5 to 75 and 150 mg given twice daily were found to result during steady state in linearly dose proportional increases in the area under the plasma concentration/time curve (AUC), as well as in the peak and minimum plasma concentrations.

Clozapine is almost completely metabolised prior to excretion. The main routes of metabolism include
Nmethylation and N-oxidation. Of the main metabolites only the demethyl metabolite was found to be active. The pharmacological actions of the demethyl metabolite resemble those of clozapine, but are considerably weaker and of short duration. Only trace amounts of unchanged drug are detected in the urine and faeces. Approximately 50% of the administered dose is excreted as metabolites in the urine and 30% in the faeces.

There are wide interindividual variations in the plasma concentrations of clozapine and no simple correlation has been found between the plasma concentration and therapeutic effect.

INDICATION

The use of clozapine is indicated in the treatment of resistant schizophrenic patients only, ie. schizophrenic patients who are non-responsive to or intolerant of classical neuroleptics.

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

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

Clozapine is also indicated for reducing the risk of recurrent suicidal behaviour in patients with schizophrenia or schizoaffective disorder who are judged to be at chronic risk for reexperiencing suicidal behaviour, based on history and recent clinical state.

RECOMMENDED DOSAGE

The dosage of clozapine must be individualised by cautious titration. For each patient the lowest effective dose should be used. The following dosages for oral administration are recommended starting therapy:

Starting Dose:
12.5 mg (one-half of a 25 mg tablet) once or twice on the first day, followed by one or two 25 mg tablets on the second day. If well tolerated, the daily dose may then

be increased slowly in increments of 25 to 50 mg in order to achieve a dose level of up to 300 mg/day within 2-3 weeks. Thereafter, if required, the daily dose may be further increased in increments of 50 to 100 mg at half-weekly, or, preferably, weekly intervals. For Use in the Elderly, see Other Precautions.

Therapeutic dose range:
In most patients, antipsychotic efficacy can be expected with 300 to 450 mg/day given in divided doses. Some patients may require doses up to 600 mg/day. The total daily dose may be divided unevenly, with the larger portion at bedtime.

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

Maintenance dose:
After achieving maximum therapeutic benefit, many patients can be maintained effectively on lower doses. Careful downward titration is therefore recommended. Treatment should be maintained for at least 6 months. If the daily dose does not exceed 200 mg, 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 over a 1-to 2-week period is recommended. If abrupt termination of therapy is necessary, (eg. because of leucopenia), the patient should be carefully observed for the recurrence of psychotic symptoms, as rapid decompensation has been reported after sudden withdrawal of therapy.

Re-starting therapy:
In patients in whom the interval since the last dose of clozapine exceeds 2 days, treatment should be reinitiated with 12.5 (one-half of a 25 mg tablet) given once or twice on the first day. If this dose is well tolerated, it may be feasible to titrate the dose to the therapeutic level more quickly than is recommended for initial treatment. However, in any patient who has previously experienced respiratory or cardiac arrest with initial dosing (see Other Precautions), but was then able to be successfully titrated to a therapeutic dose, re-titration should be done with extreme caution.

There may be an increased risk of the occurrence and severity of agranulocytosis. Patients whose WBC counts fall below 1000/mL should not be restarted on clozapine.

Switching from a classical neuroleptic to clozapine:
It is generally recommended that clozapine should not be used in combination with classical neuroleptics. When clozapine therapy is to be initiated in a patient undergoing oral neuroleptic therapy, it is recommended that the classical neuroleptic should first be discontinued by tapering the dosage downwards over a period of approximately one week. Once the neuroleptic is completely discontinued for at least 24 hours, clozapine treatment can be started as described above.

Reducing the risk of recurrent suicidal behaviour in patients with Schizophrenia or Schizoaffective Disorder:
The dosage and administration recommendations outlined above regarding the use of Clopine in patients with treatment-resistant schizophrenia should also be followed when treating patients with schizophrenia or schizoaffective disorder at risk for recurrent suicidal behaviour.

MODE OF ADMINISTRATION

Oral

CONTRAINDICATION

- Previous hypersensitivity to clozapine or other ingredients used in the tablets.
- History of drug-induced granulocytopenia/agranulocytosis, or use with drugs associated with the development of bone marrow suppression (eg. co-trimoxazole, chloramphenicol, sulphonamides, penicillamine, carbamazepine, or antineoplastics associated with bone marrow suppression, refer to Interactions).
- Impaired bone marrow function
- Uncontrolled epilepsy
- Alcoholic and other toxic psychoses, drug intoxication, comatose conditions.
- Circulatory collapse and/or CNS depression of any cause.
- Sever hepatic, renal or cardiac failure.
- Paralytic ileus.

WARNING AND PRECAUTIONS

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

Drugs known to have a substantial potential to depress bone marrow function (such as co-trimoxazole, chloramphenicol, sulphonamides, penicillamine, carbamazepine, or antineoplastics associated with bone marrow suppression) 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 therapy, a white blood cell count (WBC) and a differential blood count (DC) must be performed to ensure that only patients with normal leucocyte findings will receive the medicine. After the start of clozapine treatment, the WBC and DC must be monitored weekly for 18 weeks. Thereafter, the WBC and DC must be performed at least monthly as long as the patient is on this medicine. At each consultation the patient should be reminded to contact the treating physician immediately if any kind of infection begins or fever develops.

If during clozapine therapy, infection occurs and/or the WBC count has dropped below 3.5 x 109/L or has dropped by a substantial amount from the baseline, even if the count is above 3.5 x 109/L, a repeat WBC count and a differential blood count should be done. A substantial drop is defined as a single drop of 3.0 x 109/L or more in the WBC count or a cumulative drop of 3.0 x 109/L or more within three weeks. Should the results confirm a WBC below 3.5 x 109/L and/or reveal an absolute neutrophil granulocyte count of between 2.0 and 1.5 x 109/L, the leucocytes and the granulocytes must be checked at least twice weekly. If the WBC falls below 3.0 x 109/L and/or the absolute neutrophil granulocyte count drops below 1.5 x 109/L, clozapine 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.

If clozapine has been withdrawn and a further drop of WBC below 2.0 x 109/L occurs and/or the neutrophil granulocytes fall below 1.0 x 109/L, the management of this condition must be guided by an experienced haematologist. If possible, the patient should be referred to a specialised haematological unit, where protective isolation and the administration of GM-CSF (granulocytemacrophage colony stimulating factor) or G-CSF (granulocyte colony stimulating factor) may be indicated. It is recommended that the colony stimulating factor therapy be

discontinued when the neutrophil count has returned to a level above 1.0 x 109/L.

Patients in whom clozapine has been discontinued as a result of white blood cell deficiencies (WBC <1.5 x 109/L must not be re-exposed to clozapine.

Other Precautions
Orthostatic hypotension, with or without syncope, can occur with clozapine treatment. Rarely (about one case per 3000 clozapine treated patients), collapse can be profound and may be accompanied by cardiac and/or respiratory arrest. Such events are more likely to occur during initial titration in association with rapid dose escalation; on very rare occasions they occurred even after the first dose. Therefore, patients commencing clozapine treatment require close medical supervision.

Owing to the ability of clozapine to cause sedation and lower the seizure threshold, activities such as driving or operating machinery should be avoided, especially during the initial weeks of treatment.

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

Clozapine exerts anticholinergic activity, which may produce undesirable effect throughout the body. Probably on account of its anticholinergic properties, Clopine has been associated with varying degrees of impairment of intestinal peristalsis, ranging from constipation to intestinal obstruction, fecal impaction, paralytic ileus, megacolon and intestinal infarction/ ischaemia. On rare occasions these cases have proved fatal. Careful monitoring during treatment with Clopine to identify early, the onset of constipation, followed by effective management of constipation are recommended to prevent complications.

In the presence of hepatic dysfunction, liver function must be monitored regularly.

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

Hyperglycemia and Diabetes Mellitus
Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with the atypical antipsychotics. Precise risk estimates for hyperglycemia-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 patients treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotics was discontinued; however, some patients required continuation of antidiabetic treatment despite discontinuation of the suspect drug.

Use in Children: Safety and effectiveness of the use of clozapine in children under the age of 16 years have not been established.

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. The elderly may be at greater risk of orthostatic hypotension and anticholinergic side effects such as confusion and excitement. The risk of age related prostatic hypertrophy in elderly males must be considered prior to the initiation of therapy.
Clozapine must be kept out of the reach of children.

INTERACTION WITH OTHER MEDICAMENTS

Drugs known to have a substantial potential to depress bone marrow function such as co-trimoxazole, chloramphenicol, sulphonamides, penicillamine, carbamazepine and antineoplastics known to depress bone marrow function, should not be used concurrently with clozapine (see also Warnings and Precautions).

Clozapine may enhance the central effects of alcohol, MAO inhibitors, 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) benzodiazepine or any other psychotropic drug, as these patients may have an increased risk of circulatory collapse, which, on rare occasions, can be profound and may lead to cardiac or/or respiratory arrest. Because of the possibility of additive effects, caution is essential in the concomitant administration of drugs possessing anticholinergic, hypotensive, or respiratory depressant effects.

Due to the high plasma binding of clozapine the concurrent use of clozapine with high plasma protein binding drugs such as warfarin, phenytoin, digoxin, heparin may result in the increased plasma concentrations of these drugs, potentially resulting in adverse effects. Conversely, adverse effects may result from displacement of protein-bound clozapine by other highly protein-bound drugs. Clozapine binds cytochrome P450 2D6 and part of the metabolism of clozapine is mediated through this isoenzyme. Consequently, the concomitant administration of drugs which possess affinity to the same enzyme may result in either a decrease or an increase in the plasma levels of clozapine and/or the co-administered drug:

Administration of cimetidine concomitantly with high-dose clozapine therapy was associated with increased plasma clozapine levels and the occurrence of adverse effects.

Increased plasma clozapine levels may result from the discontinuation of the concomitant administration of carbamazepine.

The concomitant use of phenytoin has been found to decrease the clozapine plasma concentration, resulting in reduced effectiveness of a previously effective clozapine dose.

With other drugs known to bind to cytochrome P450 2D6, such as antidepressants, phenothiazines and type IC anti-arrhythmics, 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 that it may be appropriate to use them at doses lower than usually prescribed.

In one patient the concomitant administration of fluvoxamine has been reported to cause a 10-fold increase of the clozapine plasma concentration.

Concomitant use of lithium or other CNSactive agents may increase the risk of seizures, confusional states, neuroleptic malignant syndrome and dyskinesias.

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

Tobacco smoking may decrease the serum concentrations of clozapine.

Due to the possibility of additive effects, caution is essential when substances possessing anticholinergic effects are given concomitantly with Clopine

PREGNANCY AND LACTATION

Use in Pregnancy: Category B. Clozapine has been demonstrated to cross the placenta. However, adequate, well controlled studies in humans have not been performed. Reproduction studies in animals have revealed no evidence of impaired fertility or harm to the foetus due to clozapine. However, the safe use of clozapine in pregnant women has not been established. Therefore, the drug should be used in pregnancy only if the expected benefit clearly outweighs any potential risk.

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

CLOPINE tablets should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus

Use in Lactation: Animal studies suggest that clozapine is excreted in breast milk; therefore mothers receiving clozapine should not breastfeed. Potentially clozapine may cause sedation, cardiovascular instability, restlessness or irritability or seizures in the nursing infant

SIDE EFFECTS

Haematological: Clozapine may result in reversible neutropenia, which if the drug is not withdrawn immediately may result in potentially fatal agranulocytosis.

In the majority of reported cases (approximately 85%), granulocytopenia occurred in the first 18 weeks of treatment. Because immediate withdrawal of the drug is required to prevent the development of lifethreatening agranulocytosis, monitoring of the WBC count (as described under Warnings and Precautions) is mandatory.

Eosinophilia and/or unexplained leucocytosis may occur, especially in the initial weeks of treatment. Isolated cases of various types of leukaemia have been reported in patients treated with clozapine. However, there is no evidence to suggest a causal relationship between the drug and any type of leukaemia. The reported occurrence rate is in the range of the background incidence of these diseases in the general population.

Thrombocytopenia may occur very rarely after the use of clozapine.

Central Nervous System: Fatigue, drowsiness and sedation are among the most common adverse effects observed. Dizziness or headache may also occur.

Clozapine can cause EEG changes, including the occurrence of spike and wave complexes. It lowers the seizures threshold in a dose-dependant manner and may induce myoclonic jerks or generalised seizures. 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.

In rare cases clozapine may cause confusion, restlessness, agitation and delirium. Extrapyramidal symptoms may occur but are milder and less frequent than those seen during classical neuroleptic treatment. Rigidity, tremor and akathisia have been reported but acute dystonia is not an established adverse effect of clozapine treatment.

There have been no reports of tardive dyskinesia directly attributed to clozapine alone.

There have been several reported cases of neuroleptic malignant syndrome (NMS) in patients receiving clozapine, either alone or in combination with lithium or other CNS-active agents.

Autonomic Nervous System: Dry mouth, blurred vision and disturbances in sweating and temperature regulation have been reported. Hypersalivation is a pharmacologically unexpected but relatively common adverse effect.

Cardiovascular/Respiratory System: Tachycardia and postural hypotension, with or without syncope, may occur, especially in the initial weeks of treatment. Paradoxically hypertension has been reported to occur rarely. In rare cases profound circulatory collapse has been reported (see Other Precautions and Interactions).

ECG changes may occur and cases of cardiac arrhythmias, pericarditis and myocarditis (with or without eosinophilia) have been reported, some of which have been fatal. For myocarditis specifically the risk is greatest in the first month of therapy where the incidence may be as high as 6 in 10,000. Special care in detecting onset of myocarditis is needed during the first 6 – 8 weeks of therapy. Therefore the possibility of myocarditis should be considered in patients receiving CLOPINE (clozapine) who present with unexplained fatigue, dyspnoea, tachypnea, fever, chest pain, palpitations, other signs or symptoms of heart failure, or electrocardiographic findings such as ST-T wave abnormalities or arrhythmias. It is not known whether eosinophilia is a reliable predictor of myocarditis. Tachycardia, which has been associated with clozapine treatment, has also been noted as a presenting sign in patients with myocarditis. Therefore tachycardia during the first month of therapy warrants close monitoring for other signs of myocarditis. Prompt discontinuation of CLOPINE (clozapine) treatment is warranted upon suspicion of myocarditis. Patients who develop clozapine-related myocarditis should not be rechallenged with any product containing clozapine.

Respiratory System: In isolated cases, with or without circulatory collapse, respiratory depression or arrest has

occurred (see Other Precautions and Interactions). Rarely, aspiration of ingested food may occur in patients presenting with dysphagia or as a consequence of acute overdosage.

Gastrointestinal System: Nausea, vomiting, constipation and, very rarely, intestinal obstruction, ileus, faecal impaction may occur.

Increases in hepatic enzymes and, in rare cases, cholestasis have been reported.

As a rare event, clozapine treatment may be associated with dysphagia, a possible cause of aspiration.
Genito-urinary System: Both urinary incontinence and retention and, in a few cases, priapism have been reported.

Miscellaneous: Benign hyperthermia may occur, especially in the initial weeks of treatment. Isolated reports of skin reactions have been received.

On rare occasions severe hyperglycaemia, sometimes leading to ketoacidosis has occurred in patients with no history of hyperglycaemia. Exacerbation of preexisting diabetes mellitus has also been reported (See Warnings and
Precautions).

Rarely, increases in CPK values have occurred. With prolonged treatment considerable weight gain has been observed in some patients.

Sudden, unexplained deaths are known to occur among psychiatric patients who receive conventional antipsychotic medication but also among untreated psychiatric patients. Isolated cases of such deaths have been reported in patients receiving clozapine.

Hyponatraemia has been reported to occur with a single patient.

There have been isolated reports of pancreatitis after the use of clozapine.

Megacolon*, intestinal infarction/ ischaemia*, intestinal necrosis*, intestinal ulceration*, intestinal perforation*, colitis

(*These adverse drug reactions were sometimes fatal)

SYMPTOMS & TREATMENT OF OVERDOSE

In cases of acute intentional or accidental clozapine overdosage, for which information on the outcome is available, to date the mortality is about 12%. Most of the fatalities have been associated with cardiac failure or pneumonia caused by aspiration and have occurred at doses above 2000 mg. However, there have been reports of patients recovering from an overdose in excess of 10000 mg.

In a few adult individuals, 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. In young children, the intake of 50 to 200 mg resulted in strong sedation or coma without being lethal.

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

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

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

STORAGE CONDITION

Store below 30°C.
Protect from light and moisture
Keep out of the reach of children *Jauhi daripada kanak-kanak*

SHELF LIFE

3 years

THERAPEUTICAL CODE

Pharmacotherapeutic group: Diazepines, Oxazepines & Triazepines Code: N05AH02

PACKING

Pack of 50's and 100's

PRODUCT OWNER

Douglas Pharmaceuticals Ltd
PO Box 45027 AUCKLAND
0651 New Zealand

MANUFACTURER

Douglas Manufacturing Ltd
Central Park Drive
Lincoln, Auckland
New Zealand 0610

PRODUCT REGISTRATION HOLDER

SCHMIDT BIOMEDTECH SDN. BHD
5th Floor Wisma Tecna
18A, Lot 318, Jalan 51A/223
46100 Petaling Jaya Selangor

*Clopine is a registered trademark in New Zealand and Malaysia.

DATE OF REVISION

July 2023