

Data Sheet

CLOPINE

Clozapine 25 mg, 50 mg, 100 mg and 200 mg Tablets

Clozapine 50 mg/ml Oral suspension

Name of the Medicine

CLOPINE

Clozapine (Ph Eur) 25 mg, 50 mg, 100 mg and 200 mg tablets and 50 mg/ml oral suspension.

WARNING:

Clozapine can cause potentially fatal agranulocytosis. Consequently the use of clozapine should be limited to the following schizophrenic patients:

- Those who have been demonstrated to be non-responsive to traditional antipsychotic therapy (see Indications).
- Those who have been demonstrated to be intolerant to classical antipsychotic drug treatment, particularly to the extrapyramidal effects of antipsychotics.
- Those who have initially normal leucocyte findings (white blood cell count (WBC) $\geq 3500/\text{mm}^3$ ($3.5 \times 10^9/\text{L}$), and absolute neutrophil counts (ANC) $\geq 2000/\text{mm}^3$ ($2.0 \times 10^9/\text{L}$)),
- and in whom regular leucocyte counts (weekly during the first 18 weeks, at least monthly thereafter, for as long as treatment continues) can be performed.

Prescribing physicians should comply fully with the required safety measures. At each consultation, a patient receiving clozapine should be reminded to contact the treating physician immediately if any kind of infection begins to develop. Particular attention should be paid to flu-like complaints such as fever or sore throat and to other evidence of infection, which may be indicative of neutropenia.

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

CLOPINE may only be prescribed by:

- Registered medical practitioners as defined in the Health Practitioners Competence Assurance Act 2003 who are certified by the Medical Council of New Zealand as competent in the scope of practice of psychiatry, and

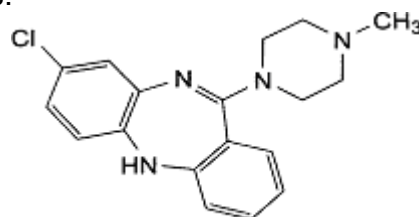
- Medical practitioners employed as registrars in the branch of psychiatry who are under the supervision of persons of the kind referred to above.
- Medical Officers of special scale who:
 - work solely in the field of psychiatry
 - are in the employment of a district health board; and
 - are under the supervision of persons who are registered medical practitioners as defined in the Health Practitioners Competence Assurance Act 2003 who are certified by the Medical Council of New Zealand as competent in the scope of practice psychiatry.
- Registered medical practitioners as defined in the Health Practitioners Competence Assurance Act 2003 who are registered with the Medical Council of New Zealand within the vocational scope of General Practice. The General Practitioner must be continuing the prescribing of clozapine for a specific patient who is considered stable in collaboration, or following consultation, with a Community Health Team.
- Persons prescribing clozapine (CLOPINE) must comply with appropriate local treatment guidelines.
- Clopine tablets and Suspension must be dispensed in accordance with appropriate local dispensing guidelines.
- Prescribers and dispensers should verify that the patient has not previously developed an adverse reaction to clozapine that contraindicates further use of any clozapine containing product.

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

Description

CLOPINE (clozapine) is an atypical antipsychotic agent. Clozapine is chemically identified as 8-chloro-11-(4-methylpiperazin-1-yl)-5H-dibenzo[b,e][1,4]diazepine. Clozapine is a yellow crystalline powder. The Ph Eur monograph for clozapine solubility states that clozapine is freely soluble in methylene chloride, soluble in ethanol and it dissolves in dilute acetic acid. Clozapine does not exhibit any form of isomerism or polymorphism. The CAS number is 5786-21-0; molecular formula is $C_{18}H_{19}ClN_4$ and the molecular weight is 326.8.

The structural formula is:



CLOPINE is available as 25 mg, 50 mg, 100 mg or 200 mg tablets or 50 mg/ml suspension.

The tablets contain as excipients: lactose, microcrystalline cellulose, povidone, sodium starch glycolate and magnesium stearate.

The oral suspension contains as excipients: glycerol, monobasic sodium phosphate dihydrate, sorbitol, xanthan gum, povidone, sodium methyl hydroxybenzoate, sodium propyl hydroxybenzoate and purified water.

Pharmacology

Mechanism of Action

CLOPINE tablets and suspension contain clozapine. Clozapine is an atypical antipsychotic, derived from the tricyclic dibenzodiazepine family. Clozapine differs from the traditional 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 antiserotonergic 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 antipsychotics, 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 treatment-resistant and intolerant to the extrapyramidal effects of traditional antipsychotics (**see Indications**), and in whom regular haematological examinations can be performed (**see 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 - 4.2 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 *N*-methylation 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.

Clinical Trials

Preclinical safety data

Preclinical data reveal no special hazards for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenic potential.

Acute toxicity

Acute toxicity studies in mice, rats and guinea pigs revealed oral LD₅₀ values of 190- 681 mg/kg body weight. In dogs, the oral LD₅₀ was approximately 145

mg/kg; signs of overdosage consisted of muscular tremor, aggressive behaviour and vomiting.

Mutagenicity

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

Carcinogenicity

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

Reproductive toxicity

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

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

Indications

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

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

Intolerance is defined as the impossibility of achieving adequate clinical benefit with classical antipsychotic drugs because of severe and untreatable

neurological adverse reactions (extrapyramidal side effects or tardive dyskinesia).

Contraindications

- Previous hypersensitivity to clozapine or other ingredients used in the tablets or suspension.
 - Patients unable to undergo regular blood tests.
 - History of toxic or idiopathic granulocytopenia/agranulocytosis (with the exception of granulocytopenia/agranulocytosis from previous chemotherapy).
 - Impaired bone marrow function
 - Uncontrolled epilepsy
 - Alcoholic and other toxic psychoses, drug intoxication, comatose conditions.
 - Circulatory collapse and/or CNS depression of any cause.
 - Severe renal or cardiac disorders (e.g. myocarditis).
 - Active liver disease associated with nausea, anorexia or jaundice; progressive liver disease, hepatic failure.
 - Paralytic ileus.
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Precautions

General

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

Medicines 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.

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

Patients who have low WBC counts because of benign ethnic neutropenia should be given special consideration and may be started on CLOPINE after agreement of a haematologist.

WBC counts and ANC monitoring

WBC and a differential blood counts must be performed within 10 days prior to starting CLOPINE treatment to ensure that only patients with normal leukocyte and absolute neutrophil counts [WBC \geq 3500/mm³ (3.5×10^9 /L) and ANC \geq 2000/mm³ (2.0×10^9 /L)] will receive CLOPINE. After the start of CLOPINE treatment, the WBC count and ANC must be monitored weekly for 18 weeks, and thereafter at least every four weeks throughout treatment, and for 4 weeks after complete discontinuation of CLOPINE.

At each consultation, the patient should be reminded to contact the treating physician immediately if any kind of infection, fever, sore throat or other flu-like symptoms develop. A differential blood count must be performed immediately if any symptoms or signs of an infection occur.

Low WBC count and/or ANC

If during the first 18 weeks of CLOPINE therapy, the WBC count falls to between 3500/mm³ (3.5×10^9 /L) and 3000/mm³ (3.0×10^9 /L) and/or the ANC falls to between 2000/mm³ (2.0×10^9 /L) and 1500/mm³ (1.5×10^9 /L), haematological evaluations must be performed at least twice weekly.

After 18 weeks of CLOPINE therapy, haematological evaluations should be performed at least twice weekly if the WBC count falls to between 3000/mm³ (3.0×10^9 /L) and 2500/mm³ (2.5×10^9 /L) and/or the ANC falls to between 1500/mm³ (1.5×10^9 /L) and 1000/mm³ (1.0×10^9 /L).

In addition, if, during CLOPINE therapy, the WBC count is found to have dropped by a substantial amount from baseline, a repeat WBC count and a differential blood count should be performed. A substantial drop is defined as a single drop of 3000/mm³ (3.0×10^9 /L) or more in the WBC count or a cumulative drop of 3000/mm³ (3.0×10^9 /L) or more within three weeks.

Immediate discontinuation of CLOPINE is mandatory if the WBC count is less than 3000/mm³ (3.0×10^9 /L) or the ANC is less than 1500/mm³ (1.5×10^9 /L) during the first 18 weeks of CLOPINE therapy, or if the WBC count is less than 2500/mm³ or the ANC is less than 1000/mm³ (1.0×10^9 /L) after the first 18 weeks of CLOPINE therapy. WBC counts and differential blood counts should then be performed daily and patients should be carefully monitored for flu-like symptoms or other symptoms suggestive of infection. Following discontinuation of CLOPINE, haematological evaluation is required until haematological recovery has occurred.

If CLOPINE has been withdrawn and WBC count falls below 2000/mm³ (2.0×10^9 /L) and/or the ANC falls below 1000/mm³ (1.0×10^9 /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 and the administration of GM-CSF (granulocyte-macrophage colony stimulating factor) or G-CSF (granulocyte colony stimulating factor) may be indicated. It is recommended that the colony

stimulating factor therapy be discontinued when the neutrophil count has returned to a level above 1000/mm³ (1.0 x 10⁹/L).

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

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

Table 1: Blood monitoring during the first 18 weeks of CLOPINE therapy

Blood cell count		Action required
WBC/mm ³ (/L)	ANC/mm ³ (/L)	
≥3500 (>3.5 x 10 ⁹)	≥2000 (> 2.0 x 10 ⁹)	Continue CLOPINE treatment.
3000-3500 (3.0 - 3.5 x 10 ⁹)	1500-2000 (1.5 - 2.0 x 10 ⁹)	Continue CLOPINE treatment, sample blood twice weekly until counts stabilise or increase.
<3000 (<3.0 x 10 ⁹)	<1500 (<1.5 x 10 ⁹)	Immediately stop CLOPINE treatment, sample blood daily until haematological abnormality is resolved, and monitor for infection. Do not re-expose the patient.

Table 2: Blood monitoring after 18 weeks of CLOPINE therapy

Blood cell count		Action required
WBC/mm ³ (/L)	ANC/mm ³ (/L)	
≥3000 (>3.0 x 10 ⁹)	≥1500 (> 1.5 x 10 ⁹)	Continue CLOPINE treatment.
2500-3000 (2.5 - 3.0 x 10 ⁹)	1000-1500 (1.0 - 1.5 x 10 ⁹)	Continue CLOPINE treatment, sample blood twice weekly until counts stabilise or increase.
<2500 (<2.5 x 10 ⁹)	<1000 (<1.0 x 10 ⁹)	Immediately stop CLOPINE treatment, sample blood daily until haematological abnormality is

Blood cell count		Action required
WBC/mm ³ (/L)	ANC/mm ³ (/L)	
		resolved, and monitor for infection. Do not re-expose the patient.

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

Patients who have been on CLOPINE for more than 18 weeks and have had their treatment interrupted for more than 3 days but less than 4 weeks should have their WBC count and ANC monitored weekly for an additional 6 weeks. If no haematological abnormality occurs, monitoring at intervals not exceeding 4 weeks may be resumed. If CLOPINE treatment has been interrupted for 4 weeks or longer, weekly monitoring is required for the next 18 weeks of treatment.

Use in Pregnancy

Category C. 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.

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 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.

Women of childbearing potential

Some female patients treated with antipsychotics other than clozapine may become amenorrhoeic. A return to normal menstruation may occur as a result of switching from other antipsychotics to CLOPINE. Adequate contraceptive measures must therefore be ensured in women of childbearing potential.

Use in Children

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

Clozapine must be kept out of the reach of children.

Use in the Elderly

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

Clinical studies with clozapine did not include sufficient numbers of subjects aged 65 years and over to determine whether or not they respond differently from younger subjects.

Orthostatic hypotension can occur with CLOPINE treatment and there have been rare reports of tachycardia which may be sustained, in patients taking CLOPINE. 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 elderly patients with dementia-related psychosis, the efficacy of clozapine has not been established. Observational studies suggest that elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Risk factors that may predispose this patient population to increased risk of death when treated with antipsychotics include age >80 years, sedation, concomitant use of benzodiazepines, or presence of pulmonary conditions (e.g. pneumonia, with or without aspiration).

Other Precautions

Lipid Abnormalities

Post-marketing reports have been made concerning lipid abnormalities in patients taking clozapine.

Eosinophilia

In the event of eosinophilia, discontinuation of CLOPINE is recommended if the eosinophil count rises above 3000/mm³ (3.0 x 10⁹/L). Therapy should be re-started only after the eosinophil count has fallen below 1000/mm³ (1.0 x 10⁹/L).

Thrombocytopenia

In the event of thrombocytopenia, discontinuation of CLOPINE is recommended if the platelet count falls below 50,000/mm³ (50 x 10⁹/L).

Hypotension

Orthostatic hypotension, with or without syncope, can occur with CLOPINE 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 CLOPINE treatment require close medical supervision.

Myocarditis/Cardiomyopathy

Tachycardia persisting at rest, accompanied by arrhythmias, shortness of breath or signs and symptoms of heart failure, may rarely occur during the first months of treatment and very rarely thereafter. The occurrence of these signs and symptoms necessitates an urgent diagnostic evaluation for myocarditis, especially during the titration period. Therefore, the possibility of myocarditis should be considered in patients receiving CLOPINE who present with unexplained fatigue, dyspnoea, tachypnoea, fever, chest pain, tachycardia, palpitations, other signs and symptoms of heart failure, ECG changes (such as ST-T wave abnormalities) or arrhythmias. It is not known whether eosinophilia is a reliable predictor of myocarditis. The prompt discontinuation of CLOPINE therapy is warranted upon suspicion of myocarditis. The incidence of myocarditis reported globally is rare (<0.1 %) during the first month of therapy and very rare (<0.01 %) thereafter. Some cases of myocarditis have been reported to be fatal (incidence approximately 0.2 cases/100,000 patient years). Most reported cases of myocarditis have occurred in the first month of therapy, therefore, there should be a high index of suspicion in the first 6-8 weeks of therapy. If the diagnosis of myocarditis is confirmed, CLOPINE should be discontinued. Later in treatment, the same signs and symptoms may very rarely occur and may be linked to cardiomyopathy. Further investigation should be performed and if the diagnosis is confirmed, the treatment should be stopped unless the benefit clearly outweighs the risk to the patient.

Cerebrovascular Adverse Events (CVAE), including Stroke, in Elderly Patients with Dementia

An approximately 3-fold increase of cerebrovascular adverse events has been seen in randomised placebo-controlled clinical trials 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.

Prolongation of QT Interval

- Caution is required in patients with cardiovascular disease or family history of QT prolongation.
- Avoid concomitant QT prolonging medicines

Liver Disease

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

Anticholinergic Effects

Clozapine exerts anticholinergic activity, which may produce undesirable effects throughout the body. Careful supervision is indicated in the presence of prostatic enlargement and narrow-angle glaucoma. Probably on account of its anticholinergic properties, CLOPINE has been associated with varying degrees of impairment of intestinal peristalsis, ranging from constipation to intestinal obstruction, faecal impaction and paralytic ileus (**See Adverse Effects**). On rare occasions these cases have been fatal. Since complications have been associated with delayed diagnosis, patients should be questioned about their bowel habits.

Fever

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.

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 CLOPINE. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycaemia-related adverse events is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent hyperglycaemia-related adverse events in patients treated with the atypical antipsychotics studied. Precise risk estimates for hyperglycaemia-related adverse events in patients treated with atypical antipsychotics are not available. The available data are insufficient to provide reliable estimates of differences in hyperglycaemia-related adverse-event risk among the marketed atypical antipsychotics.

Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g., obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at baseline and periodically during treatment. Any patients 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 were discontinued; however, some patients required continuation of antidiabetic treatment despite discontinuation of the suspect drug.

Thromboembolism

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

Effects on ability to drive and operate machinery

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.

Interactions

Pharmacodynamic interactions

Medicinal products known to have a substantial potential to depress bone marrow function such as co-trimoxazole, chloramphenicol, sulphonamides,

penicillamine, carbamazepine and antineoplastics, should not be used concurrently with CLOPINE (**see Precautions**).

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

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

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

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 Clozaril is prescribed with medicines known to increase the QTc interval, or causing electrolyte imbalance.

Pharmacokinetic interactions

Clozapine is a substrate for many CYP450 isoenzymes, in particular 1A2 and 3A4. The risk of metabolic interactions caused by an effect on an individual isoform is therefore minimized. Nevertheless, caution is called for in patients receiving concomitant treatment with other substances that are either inhibitors or inducers of these enzymes.

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

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

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

- Known inducers of 1A4 include, for instance, omeprazole and nicotine. In cases of sudden cessation of nicotine abuse, the plasma clozapine concentration may be increased, thus leading to an increase in adverse effects.

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

- Substances known to inhibit the activity of the major isoenzymes involved in the metabolism of clozapine and with reported interactions include, for instance, cimetidine, erythromycin (3A4) and fluvoxamine (1A2).
- Potent inhibitors of CYP3A, such as azole antimycotics and protease inhibitors, could potentially also increase clozapine concentrations; no interactions have been reported to date, however.
- The plasma concentration of clozapine is increased by caffeine (1A2) intake and decreased by nearly 50 % following a 5-day caffeine free period.
- Elevated clozapine plasma concentrations also have been reported in patients receiving the substances in combination with selective serotonin re-uptake inhibitors (SSRIs) such as paroxetine (1A2), sertraline, fluoxetine or citalopram.

Adverse effects

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

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

Adverse reactions are ranked under headings of frequency, using the following convention: Very common ($\geq 1/10$), common ($\geq 1/100$, $< 1/10$), uncommon ($\geq 1/1000$, $< 1/100$), rare ($\geq 1/10,000$, $< 1/1000$), very rare ($< 1/10,000$), including isolated cases.

Blood and lymphatic system disorders	
Common	Leukopenia/decreased WBC/neutropenia, eosinophilia, leukocytosis
Uncommon	Agranulocytosis, ESR increased
Rare	Anaemia
Very rare	Thrombocytopenia, thrombocythaemia
Metabolism and nutrition disorders	

Common	Weight gain, weight loss
Rare	Impaired glucose tolerance, diabetes aggravated
Very rare	Ketoacidosis, hyperosmolar coma, severe hyperglycaemia*, hypercholesterolaemia, hypertriglyceridaemia
Psychiatric disorders	
Rare	Restlessness, agitation
Nervous system disorders	
Very common	Drowsiness/sedation, dizziness
Common	Blurred vision, headache, tremor, rigidity, akathisia, extrapyramidal symptoms, seizures/convulsions/myoclonic jerks
Rare	Confusion, delirium
Very rare	Tardive dyskinesia
Cardiac disorders	
Very common	Tachycardia
Common	ECG changes
Rare	Circulatory collapse, arrhythmias, myocarditis**, pericarditis
Very rare	Cardiomyopathy
Vascular system disorders	
Common	Hypertension, postural hypotension, syncope
Rare	Thromboembolism
Respiratory disorders	
Rare	Aspiration of ingested food, Dyspnoea, pneumonia
Very rare	Respiratory depression/arrest
Gastrointestinal disorders	
Very common	Constipation, hypersalivation
Common	Nausea, vomiting, dry mouth, abdominal discomfort, heartburn
Rare	Dysphagia
Very rare	Parotid gland enlargement, intestinal obstruction/ileus/faecal impaction
Hepatobiliary disorders	
Common	Elevated liver enzymes
Rare	Hepatitis, cholestatic jaundice, pancreatitis
Very rare	Fulminant hepatic necrosis
Skin and subcutaneous tissue disorders	
Very rare	Skin reactions
Renal and urinary disorders	

Common	Urinary incontinence, urinary retention, nocturnal enuresis
Very rare	Interstitial nephritis
Reproductive system disorders	
Very rare	Priapism
General disorders	
Common	Fatigue, benign hyperthermia, disturbances in sweating/temperature regulation
Uncommon	Neuroleptic malignant syndrome
Very rare	Sudden unexplained death
Investigations	
Rare	Increased CPK

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

** The prompt discontinuation of Clopine therapy is warranted upon suspicion of myocarditis (see **Precautions**).

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.

Dosage and Administration

The dosage of clozapine must be individualised by cautious titration. For each patient the lowest effective dose should be used.

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

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

When first dispensed or when there is visible settling of the suspension, Clozapine Suspension should be vigorously shaken for 90 seconds before being dispensed or used. In all other instances the bottle should be shaken for 10 seconds before a dose is dispensed.

If dilution is required, the suspension may be mixed with water but not fruit juice or any other form of liquid.

The following dosages for oral administration are recommended starting therapy:

Starting Dose

12.5 mg once or twice on the first day, followed by 25 mg once or twice 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.

Use in the elderly

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

Use in children

The safety and efficacy of clozapine in children has not been established.

Therapeutic dose range

In most patients, antipsychotic efficacy can be expected with 300 to 450 mg/day given in divided doses. Some patients may be treated with lower doses, and some patients may require doses up to 600 mg/day. The total daily dose may be divided unevenly, with the larger portion at bedtime. For maintenance dose, see below.

Maximum dose

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

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 and symptoms related to cholinergic rebound such as profuse sweating, headache, nausea, vomiting and diarrhoea.

Re-starting therapy

In patients in whom the interval since the last dose of clozapine exceeds 2 days, treatment should be reinitiated with 12.5 mg 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 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 antipsychotic to clozapine

It is generally recommended that clozapine should not be used in combination with classical antipsychotics. When clozapine therapy is to be initiated in a patient undergoing oral antipsychotic therapy, it is recommended that the classical antipsychotic should first be discontinued by tapering the dosage downwards. Based on the clinical circumstances, the prescribing physician should judge whether or not to discontinue the other antipsychotic therapy before initiating treatment with CLOPINE.

Seizures

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

Overdosage

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 (2 g). There have been reports of patients recovering from an overdose in excess of 10000 mg (10 g). However, 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.

Symptoms

Drowsiness, lethargy, areflexia, coma, confusion, hallucinations, agitation, delirium, extrapyramidal symptoms, hyper-reflexia, convulsions; hypersalivation, mydriasis, blurred vision, thermolability; hypotension, collapse; tachycardia, cardiac arrhythmias, aspiration pneumonia, dyspnoea, respiratory depression or failure.

Management

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.

Presentation and Storage conditions

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 50 mg tablets: are round yellow flat bevel-edged tablets engraved "50" 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.

CLOPINE 200 mg tablets: are oval shaped, yellow tablets engraved "200" on one face, and a pressure sensitive breakline on the other face.

CLOPINE 50 mg/ml suspension: a free flowing yellow suspension.

Storage

CLOPINE tablets: Store below 30°C. Protect from light and moisture. The shelf life of CLOPINE 25 mg, 50 mg and 100 mg tablets is 5 years from date of manufacture. The shelf life of CLOPINE 200 mg tablets is 4 years from date of manufacture.

CLOPINE Suspension: Store below 25°C. Protect from light. The shelf life of CLOPINE suspension is 2 years from date of manufacture. CLOPINE suspension may be used for up to 90 days after first opening.

Pack quantities

CLOPINE tablets: blister packs containing 50 and 100 tablets and bottle packs containing 50 and 100 tablets.

CLOPINE suspension: 100 mL

Further Information

This medicine has been granted provisional consent for distribution under Section 23 of the Medicines Act 1981

Medicine Classification

Prescription Medicine

Name and Address of Sponsor

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