CLOZAPINE

SYCLOP

25 mg /100 mg Tablet
ANTI-PSYCHOTIC

PRODUCT NAME : Syclop

NAME AND STRENGTH: Clozapine Tablets 25 mg/100mg

PHARMACOLOGIC CATEGORY: Antipsychotic agent

PRODUCT DESCRIPTION: Clozapine Tablets 25 mg/100 mg :Light Yellow Coloured, Flat, circular, beveledged uncoated Tablets with a breakline on one surface.

FORMULATION/COMPOSITION:
Each uncoated tablet Contains:
Clozapine USP ……25 mg/100 mg

PHARMACODYNAMICS/PHARMACOKINETICS:
Pharmacodynamics:
Pharmacotherapeutic group: Antipsychotics; Diazepines, oxazepines and thiazepines (ATC code N05A H02)
Mechanism of action: Clozapine has been shown to be an antipsychotic agent that is different from classic antipsychotics.
In pharmacological experiments, the compound does not induce catalepsy or inhibit Apomorphine- or amphetamine-induced stereotyped behaviour. It has only weak dopamine-receptor-blocking activity at D_1, D_2, D_3 and D_5 receptors, but shows high potency for the D_4 receptor.
Pharmacodynamic effects*:* Clozapine has potent anti-alpha-adrenergic, anticholinergic, antihistaminic, and arousal-reaction-inhibiting effects. It has also been shown to possess antiserotonin ergic properties.

Pharmacokinetics:
Absorption: The absorption of orally administered clozapine is 90 to 95%; neither the rate nor the extent of absorption is influenced by food. Clozapine is subject to 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), and the volume of distribution is 1.6 l/kg. Clozapine is approximately 95% bound to plasma proteins.
Biotransformation/metabolism: Clozapine is almost completely metabolised before excretion by CYP1A2 and CYP3A4 and to some extent by CYP2C19 and CYP2D6. Of the main metabolites only the demethyl metabolite was found to be active. Its pharmacological actions resemble those of clozapine, but are considerably weaker and of short duration.
Elimination: Its elimination is biphasic, with a mean terminal half-life of 12 hours (range: 6 to 26 hours). After single doses of 75 mg the mean terminal half-life was 7.9 hours; it increased to 14.2 hours when steady-state conditions were reached by administering daily doses of 75 mg for at least 7 days.
Only trace amounts of unchanged drug are detected in the urine and faeces, approximately 50% of the administered dose being excreted as metabolites in the urine and 30% in the faeces.

INDICATIONS:
Treatment-resistant schizophrenia
Clozapine is indicated in treatment-resistant schizophrenic patients and in schizophrenia patients who have severe, untreatable neurological adverse reactions to other antipsychotic agents, including atypical antipsychotics.
Treatment resistance is defined as a lack of satisfactory clinical improvement despite the use of adequate doses of at least two different antipsychotic agents, including an atypical antipsychotic agent, prescribed for adequate duration.
Psychosis during the course of Parkinson's disease
Clozapine is also indicated in psychotic disorders occurring during the course of Parkinson's disease, in cases where standard treatment has failed.

DOSAGE AND MODE/ROUTE OF ADMINISTRATION:
Posology
The dosage must be adjusted individually. For each patient the lowest effective dose should be used. For doses not realisable/practicable with one strength, other strengths of this medicinal product are available. Cautious titration and a divided dosage schedule are necessary to minimise the risks of hypotension, seizure and sedation.
Initiation of clozapine treatment must be restricted to those patients with a WBC count ≥ 3500/mm^3 ($3.5x10^9$/L) and an ANC ≥ 2000/mm^3 ($2.0x10^9$/L) within standardised normal limits.
Dose adjustment is indicated in patients who are also receiving medicinal products that have Pharmacodynamic and pharmacokinetic interactions with clozapine, such as benzodiazepines or selective serotonin re-uptake inhibitors.
Switching from a previous antipsychotic therapy to clozapine
It is generally recommended that clozapine should not be used in combination with other antipsychotics. When clozapine therapy is to be initiated in a patient undergoing oral antipsychotic therapy, it is recommended that the other antipsychotic should first be discontinued by tapering the dosage downwards.
The following dosages are recommended:
Treatment-resistant schizophrenic patients
Starting therapy
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 to 3 weeks. Thereafter, if required, the daily dose may be further increased in increments of 50 to 100 mg at half-weekly or, preferably, weekly intervals.
Therapeutic dose range
In most patients, antipsychotic efficacy can be expected with 200 to 450 mg/day given in divided doses. 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 (not exceeding 100 mg) are permissible up to 900 mg/day. However, the possibility of increased adverse reactions (in particular seizures) 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 therefore recommended. Treatment should be maintained for at least 6 months. If the daily dose does not exceed 200 mg, once daily 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 discontinuation is necessary, the patient should be carefully observed for the occurrence of withdrawal reactions.
Re-starting therapy
In patients in whom the interval since the last dose of clozapine exceeds 2 days, treatment should be re-initiated 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, but was then able to be successfully titrated to a therapeutic dose, re-titration should be carried out with extreme caution.
Psychotic disorders occurring during the course of Parkinson's disease, in cases where standard treatment has failed
Starting therapy
The starting dose must not exceed 12.5 mg/day, taken in the evening. Subsequent dose increases must be by 12.5 mg increments, with a maximum of two increments a week up to a maximum of 50 mg, a dose that cannot be reached until the end of the second week. The total daily amount should preferably be given as a single dose in the evening.
Therapeutic dose range
The mean effective dose is usually between 25 and 37.5 mg/day. In the event that treatment for at least one week with a dose of 50 mg fails to provide a satisfactory therapeutic response, dosage may be cautiously increased by increments of 12.5 mg/week.
Maximum dose
The dose of 50 mg/day should only be exceeded in exceptional cases, and the maximum dose of 100 mg/day must never be exceeded.
Dose increases should be limited or deferred if orthostatic hypotension, excessive sedation or confusion occurs. Blood pressure should be monitored during the first weeks of treatment.
Maintenance dose
When there has been complete remission of psychotic symptoms for at least 2 weeks, an increase in anti-Parkinsonian medication is possible if indicated on the basis of motor status. If this approach results in the recurrence of psychotic symptoms, clozapine dosage may be increased by increments of 12.5 mg/week up to a maximum of 100 mg/day, taken in one or two divided doses (see above).
Ending therapy
A gradual reduction in dose by steps of 12.5 mg over a period of at least one week (preferably two) is recommended.
Treatment must be discontinued immediately in the event of neutropenia or agranulocytosis. In this situation, careful psychiatric monitoring of the patient is essential since symptoms may recur quickly.
Special populations:
Hepatic impairment
Patients with hepatic impairment should receive Clozapine with caution along with regular monitoring of liver function tests.
Paediatric population
No paediatric studies have been performed. The safety and efficacy of Clozapine in children and adolescents under the age of 16 years have not yet been established. It should not be used in this group until further data become available.
Patients 60 years of age and older
Initiation of treatment is recommended at a particularly low dose (12.5 mg given once on the first day) with subsequent dose increments restricted to 25 mg/day.
Method of administration
Clozapine is administered orally.

CONTRAINDICATIONS &PRECAUTION(S), WARNING(S)
Hypersensitivity to the active substance or to any of the excipients
- Patients unable to undergo regular blood tests.
- History of toxic or idiosyncratic granulocytopenia/agranulocytosis (with the exception of granulocytopenia/agranulocytosis from previous chemotherapy).
- History of Clozapine-induced agranulocytosis.
- 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.
- Clozapine treatment must not be started concurrently with substances known to have a substantial potential for causing agranulocytosis; concomitant use of depot antipsychotics is to be discouraged.

PRECAUTIONS & WARNINGS:
Agranulocytosis
Clozapine can cause agranulocytosis. The incidence of agranulocytosis and the fatality rate in those developing agranulocytosis have decreased markedly since the institution of white blood cell (WBC) counts and absolute neutrophil count (ANC) monitoring. The following precautionary measures are therefore mandatory and should be carried out in accordance with official recommendations.
Because of the risks associated with clozapine, its use is limited to patients in whom therapy is indicated as set out in and:
- who have initially normal leukocyte findings (WBC count ≥ 3500/mm^3 ($3.5x10^9$/L) and ANC ≥ 2000/mm^3 ($2.0x10^9$/L), and
- in whom regular WBC counts and ANC can be performed weekly for the first 18 weeks and at least 4-week intervals thereafter.

Monitoring must continue throughout treatment and for 4 weeks after complete discontinuation of clozapine.
Before initiating clozapine therapy patients should have a blood test (see "agranulocytosis") and a history and physical examination. Patients with history of cardiac illness or abnormal cardiac findings on physical examination should be referred to a specialist for other examinations that might include an ECG, and the patient treated only if the expected benefits clearly outweigh the risks. The treating physician should consider performing a pre-treatment ECG.
White Blood Cell (WBC) counts and Absolute Neutrophil Count (ANC) monitoring
WBC and differential blood counts must be performed within 10 days prior to initiating clozapine treatment to ensure that only patients with normal WBC counts and ANC (WBC count ≥ 3500/mm^3 ($3.5x10^9$/L) and ANC ≥ 2000/mm^3 ($2.0x10^9$/L)) will receive Clozapine. After the start of clozapine treatment regular WBC count and ANC must be assessed and monitored weekly for the first 18 weeks and at least at four-week intervals thereafter.
Monitoring must continue throughout treatment and for 4 weeks after complete discontinuation of clozapine or until haematological recovery has occurred (see "Low WBC count/ANC" below). At each consultation, the patient must be reminded to contact the treating physician immediately if any kind of infection, fever, sore throat or other flu-like symptoms develop. WBC and differential blood counts must be performed immediately if any symptoms or signs of an infection occur.
Low WBC count/ANC
If, during clozapine therapy, either the WBC count falls to between 3500/mm^3 ($3.5x10^9$/L) and 3000/mm^3 ($3.0x10^9$/L) or the ANC falls to between 2000/mm^3 ($2.0x10^9$/L) and 1500/mm^3 ($1.5x10^9$/L), haematological evaluations must be performed at least twice weekly until the patient's WBC count and ANC stabilise within the range 3000-3500/mm^3 (3.0-$3.5x10^9$/L) and 1500-2000/mm^3 (1.5-$2.0x10^9$/L), respectively, or higher.
Immediate discontinuation of clozapine treatment is mandatory if either the WBC count is less than 3000/mm^3 ($3.0x10^9$/L) or the ANC is less than 1500/mm^3 ($1.5x10^9$/L) during clozapine treatment. 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. Confirmation of the haematological values is recommended by performing two blood counts on two consecutive days; however, clozapine should be discontinued after the first blood count.
Following discontinuation of clozapine, haematological evaluation is required until haematological recovery has occurred.
Table 1

Blood cell count		Action required
WBC/mm^3 (/L)	ANC/mm^3 (/L)	
≥ 3500 (≥ $3.5x10^9$)	≥ 2000 (≥ $2.0x10^9$)	Continue clozapine treatment
3000-3500 ($3.0x10^9$-$3.5x10^9$)	1500-2000 ($1.5x10^9$ -$2.0x10^9$)	Continue clozapine treatment, sample blood twice weekly until counts stabilise or increase
< 3000 (< $3.0x10^9$)	< 1500 (< $1.5x10^9$)	Immediately stop clozapine treatment, sample blood daily until haematological abnormality is resolved, monitor for infection. Do not re-expose the patient

If clozapine has been withdrawn and either a further drop in the WBC count below 2000/mm^3 ($2.0x10^9$/L) occurs or the ANC falls below 1000/mm^3 ($1.0x10^9$/L), the management of this condition must be guided by an experienced haematologist.
Discontinuation of therapy for haematological reasons
Patients in whom clozapine has been discontinued as a result of either WBC or ANC deficiencies (see above) must not be re-exposed to clozapine.
Prescribers are encouraged to keep a record of all patients' blood results and to take any steps necessary to prevent the patient being accidentally rechallenged in the future.
Discontinuation of therapy for other reasons
Patients who have been on clozapine 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 clozapine treatment has been interrupted for 4 weeks or longer, weekly monitoring is required for the next 18 weeks of treatment and the dose should be re-titrated.
Other precautions
This medicinal product contains lactose monohydrate.
Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.
Eosinophilia
In the event of **eosinophilia**, discontinuation of clozapine is recommended if the eosinophil count rises above 3000/mm^3 ($3.0x10^9$/L); therapy should be restarted only after the eosinophil count has fallen below 1000/mm^3 ($1.0x10^9$/L).
Thrombocytopenia
In the event of **thrombocytopenia**, discontinuation of clozapine therapy is recommended if the platelet count falls below 50 000/mm^3 ($50x10^9$/L).
Cardiovascular disorders
Orthostatic hypotension, with or without syncope, can occur during clozapine treatment. Rarely, collapse can be profound and may be accompanied by cardiac and/or respiratory arrest. Such events are more likely to occur with concurrent use of benzodiazepine or any other psychotropic agent and during initial titration in association with rapid dose escalation; on very rare occasions they may occur even after the first dose. Therefore, patients commencing clozapine treatment require close medical supervision. Monitoring of standing and supine blood pressure is necessary during the first weeks of treatment in patients with Parkinson's disease.
Analysis of safety databases suggests that the use of clozapine is associated with an increased risk of **myocarditis** especially during, but not limited to, the first two months of treatment. Some cases of myocarditis have been fatal.
Pericarditis/pericardial effusion and **cardiomyopathy** have also been reported in association with clozapine use; these reports also include fatalities. Myocarditis or cardiomyopathy should be suspected in patients who experience persistent tachycardia at rest, especially in the first two months of treatment, and/or palpitations, arrhythmias, chest pain and other signs and symptoms of heart failure (e.g. unexplained fatigue, dyspnoea, tachypnoea), or symptoms that mimic myocardial infarction. Other symptoms which may be present in addition to the above include flu-like symptoms. If myocarditis or cardiomyopathy is suspected, clozapine treatment should be promptly stopped and the patient immediately referred to a cardiologist.
Patients with clozapine-induced myocarditis or cardiomyopathy should not be re-exposed to clozapine.
Myocardial infarction
In addition, there have been post marketing 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.
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 QTc interval
Cerebrovascular adverse events
An approximately 3-fold increased risk 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.
Risk of thromboembolism
Since clozapine may be associated with **thromboembolism**, immobilisation of patients should be avoided. Cases of venous thromboembolism (VTE) have been reported with antipsychotic drugs. Since patients treated with antipsychotics often present with acquired risk factors for VTE, all possible risk factors for VTE should be identified before and during treatment with clozapine and preventive measures undertaken.
Seizures
Patients with a history of epilepsy should be closely observed during clozapine therapy since dose-related convulsions have been reported. In such cases, the dose should be reduced and, if necessary, an anti-convulsant treatment should be initiated.
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, clozapine has been associated with varying degrees of **impairment of intestinal peristalsis**, ranging from **constipation** to **intestinal obstruction**, **faecal impaction** and **paralytic ileus**. On rare occasions these cases have been fatal. Particular care is necessary in patients who are receiving concomitant medications known to cause constipation (especially those with anticholinergic properties such as some antipsychotics, antidepressants and anti-Parkinsonian treatments), have a history of colonic disease or a history of lower abdominal surgery as these may exacerbate the situation. It is vital that constipation is recognised and actively treated.
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. If the diagnosis of NMS is confirmed, clozapine should be discontinued immediately and appropriate medical measures should be administered.
Metabolic changes
Atypical antipsychotic drugs, including clozapine, have been associated with metabolic changes that may increase cardiovascular/cerebrovascular risk. These metabolic changes may include hyperglycaemia, dyslipidaemia, and body weight gain. While atypical antipsychotic drugs may produce some metabolic changes, each drug in the class has its own specific profile.
Hyperglycaemia
Impaired glucose tolerance and/or development or exacerbation of diabetes mellitus has been reported rarely during treatment with clozapine. A mechanism for this possible association has not yet been determined. Cases of severe hyperglycaemia with ketoacidosis or hyperosmolar coma have been reported very rarely in patients with no prior history of hyperglycaemia, some of which have been fatal.
When follow-up data were available, discontinuation of clozapine resulted mostly in resolution of the impaired glucose tolerance, and reinstitution of clozapine resulted in its reoccurrence. 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. 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 antidiabetic treatment despite discontinuation of the suspect drug. The discontinuation of clozapine should be considered in patients where active medical management of their hyperglycaemia has failed.
Dyslipidaemia
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.
Rebound withdrawal effects
Acute withdrawal reactions have been reported following abrupt cessation of clozapine therefore gradual withdrawal is recommended. If abrupt discontinuation is necessary (e.g. because of leukopenia), the patient should be carefully observed for the recurrence of psychotic symptoms and symptoms related to cholinergic rebound, such as profuse sweating, headache, nausea, vomiting and diarrhoea.
Special populations
Hepatic impairment
Patients with stable pre-existing liver disorders may receive clozapine, but need regular liver function tests. Liver function tests should be performed in patients in whom symptoms of possible **liver dysfunction**, such as nausea, vomiting and/or anorexia, develop during clozapine therapy. If the elevation of the values is clinically relevant (more than 3 times the UNL) or if symptoms of jaundice occur, treatment with clozapine must be discontinued. It may be resumed (see "Re-starting therapy" under section 4.2) only when the results of liver function tests are normal. In such cases, liver function should be closely monitored after re-introduction of the drug.
Patients aged 60 years and older
Initiation of treatment in patients aged 60 years and older is recommended at a lower dose.
Orthostatic hypotension can occur with clozapine treatment and there have been reports of tachycardia, which may be sustained. Patients aged 60 years and older, particularly those with compromised cardiovascular function, may be more susceptible to these effects.
Patients aged 60 years and older may also be particularly susceptible to the anticholinergic effects of clozapine, such as urinary retention and constipation.
Increased mortality in elderly people with dementia
Data from two large observational studies showed that elderly people with dementia who are treated with antipsychotics are at a small increased risk of death compared with those who are not treated. There are insufficient data to give a firm estimate of the precise magnitude of the risk and the cause of the increased risk is not known.
Clozapine is not approved for the treatment of dementia-related behavioural disturbances.

PREGNANCY AND LACTATION:
Pregnancy: For clozapine, there are only limited clinical data on exposed pregnancies. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development. Caution should be exercised when prescribing to pregnant women.
Neonates exposed to antipsychotics (including clozapine) during the third trimester of pregnancy are at risk of adverse reactions including extrapyramidal and/or withdrawal symptoms that may vary in severity and duration following delivery. There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, or feeding disorder. Consequently, new-borns should be monitored carefully.
Lactation: Animal studies suggest that clozapine is excreted in breast milk and has an effect in the nursing infant; therefore, mothers receiving clozapine should not breast-feed.
Fertility: Limited data available on the effects of clozapine on human fertility are inconclusive. In male and female rats, clozapine did not affect fertility when administered up to 40 mg/kg, corresponding to a human equivalence dose of 6.4 mg/kg or approximately a third of the maximum permissible adult human dose.
Women of child-bearing potential A return to normal menstruation may occur as a result of switching from other antipsychotics to clozapine. Adequate contraceptive measures must therefore be ensured in women of childbearing potential.

INTERACTIONS:
Contraindication of concomitant use
Substances known to have a substantial potential to depress bone marrow function must not be used concurrently with clozapine.
Long-acting depot antipsychotics (which have myelosuppressive potential) must not be used concurrently with clozapine because these cannot be rapidly removed from the body in situations where this may be required, e.g. neutropenia.
Alcohol should not be used concomitantly with clozapine due to possible potentiation of sedation.
Precautions including dose adjustment
Clozapine may enhance the central effects of CNS depressants such as narcotics, antihistamines, and benzodiazepines. Particular caution is advised when clozapine therapy is initiated in patients who are receiving a benzodiazepine or any other psychotropic substance. 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. It is not clear whether cardiac or respiratory collapse can be prevented by dose adjustment.
Because of the possibility of additive effects, caution is essential in the concomitant administration of substances possessing anticholinergic, hypotensive, or respiratory depressant effects.
Owing to its anti-alpha-adrenergic properties, clozapine may reduce the blood-pressure-increasing effect of norepinephrine or other predominantly alpha-adrenergic agents and reverse the pressor effect of epinephrine.
Concomitant administration of substances known to inhibit the activity of some cytochrome P450 isozymes may increase the levels of clozapine, and the dose of clozapine may need to be reduced to prevent undesirable effects. This is more important for CYP 1A2 inhibitors such as caffeine (see below), and the selective serotonin reuptake inhibitor fluvoxamine. Some of the other serotonin reuptake inhibitors such as fluoxetine, paroxetine, and, to a lesser degree, sertraline, are CYP 2D6 inhibitors and, as a consequence, major pharmacokinetic interactions with clozapine are less likely. Similarly, pharmacokinetic interactions with CYP 3A4 inhibitors such as azole antimycotics, cimetidine, erythromycin and protease inhibitors are unlikely, although some have been reported. Hormonal contraceptives (including combinations of estrogens and progesterone or progesterone only) are CYP 1A2, CYP 3A4 and CYP 2C19 inhibitors. Therefore, initiation or discontinuation of hormonal contraceptives may require dose adjustment of clozapine according to the individual medical need. Because the plasma concentration of clozapine is increased by caffeine intake and decreased by nearly 50% following a 5-day caffeine-free period, dosage changes of clozapine may be necessary when there is a change in caffeine-drinking habit. In cases of sudden cessation of smoking, the plasma clozapine concentration may be increased, thus leading to an increase in adverse effects.
Cases have been reported of an interaction between citalopram and clozapine, which may increase the risk of adverse events associated with clozapine. The nature of this interaction has not been fully elucidated.
Concomitant administration of substances known to induce cytochrome P450 enzymes may decrease the plasma levels of clozapine, leading to reduced efficacy. Substances known to induce the activity of cytochrome P450 enzymes and with reported interactions with clozapine include, for instance, carbamazepine (not to be used concomitantly with clozapine, due to its myelosuppressive potential), phenytoin and rifampicin. Known inducers of CYP1A2, such as omeprazole, may lead to decreased clozapine levels. The potential for reduced efficacy of clozapine should be considered when it is used in combination with these substances.
Other
Concomitant use of lithium or other CNS-active agents may increase the risk of development of neuroleptic malignant syndrome (NMS).
Rare but serious reports of seizures, including onset of seizures in non-epileptic patients, and isolated cases of delirium where 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.
Caution is called for in patients receiving concomitant treatment with other substances which are either inhibitors or inducers of the cytochrome P450 isozymes. With tricyclic antidepressants, phenothiazines and type 1_c anti-arrhythmics, which are known to bind to cytochrome P450 2D6, no clinically relevant interactions have been observed thus far.
As with other antipsychotics, caution should be exercised when clozapine is prescribed with medicines known to increase QTc interval, or causing electrolyte imbalance
An outline of drug interactions believed to be most important with clozapine is given in Table 2 below. The list is not exhaustive.
Table 2: Reference to the most common drug interactions with clozapine

Drug	Interactions	Comments
Bone marrow suppressants (e.g. carbamazepine, chloramphenicol), sulphonamides (e.g. co-trimoxazole), pyrazolone analgesics (e.g. phenylbutazone), penicillamine, cytotoxic agents and long-acting depot injections of antipsychotics	Interact to increase the risk and/or severity of bone marrow suppression.	Clozapine **must not be used** concomitantly with other agents having a well-known potential to suppress bone marrow function
Benzodiazepines	Concomitant use may increase risk of circulatory collapse, which may lead to cardiac and/or respiratory arrest.	Whilst the occurrence is rare, caution is advised when using these agents together. Reports suggest that respiratory depression and collapse are more likely to occur at the start of this combination or when clozapine is added to an established benzodiazepine regimen.
Anticholinergics	Clozapine potentiates the action of these agents through additive anticholinergic activity.	Observe patients for anticholinergic side-effects, e.g. constipation, especially when using to help control hyper salivation.
Antihypertensive	Clozapine can potentiate the hypotensive effects of these agents due to its sympathomimetic antagonistic effects.	Caution is advised if clozapine is used concomitantly with antihypertensive agents. Patients should be advised of the risk of hypotension, especially during the period of initial dose titration.
Alcohol, MAOIs, CNS depressants, including narcotics and benzodiazepines	Enhanced central effects. Additive CNS depression and cognitive and motor performance interference when used in combination with these substances.	Caution is advised if clozapine is used concomitantly with other CNS active agents. Advise patients of the possible additive sedative effects and caution them not to drive or operate machinery.
Highly protein bound substances (e.g. warfarin and digoxin)	Clozapine may cause an increase in plasma concentration of these substances due to displacement from plasma proteins.	Patients should be monitored for the occurrence of side effects associated with these substances, and doses of the protein bound substance adjusted, if necessary.
Phenytoin	Addition of phenytoin to clozapine regimen may cause a decrease in the clozapine plasma concentrations.	If phenytoin must be used, the patient should be monitored closely for a worsening or recurrence of psychotic symptoms.
Lithium	Concomitant use can increase the risk of development of neuroleptic malignant syndrome (NMS).	Observe for signs and symptoms of NMS.
CYP1A2 inducing substances (e.g. omeprazole)	Concomitant use may decrease clozapine levels	Potential for reduced efficacy of clozapine should be considered.
CYP1A2 inhibiting substances e.g. fluvoxamine, caffeine, ciprofloxacin, or hormonal contraceptives (CYP1A2, CYP3A4, CYP2C19)	Concomitant use may increase clozapine levels	Potential for increase in adverse effects. Care is also required upon cessation of concomitant CYP1A2 or CYP3A4 inhibiting medications as there may be a decrease in clozapine levels. The effect of CYP2C19 inhibition may be minimal.

ADVERSE DRUG REACTIONS:
Adverse reactions are ranked under headings of frequency, using the following convention: Very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), not known (cannot be estimated from the available data).

BLOOD AND LYMPHATIC SYSTEM DISORDERS	
Common:	Leukopenia/decreased WBC/neutropenia, eosinophilia, leucocytosis
Uncommon:	Agranulocytosis
Rare:	Anaemia
Very rare:	Thrombocytopenia, Thrombocythemia
IMMUNE SYSTEM DISORDERS	
Not known:	Angioedema*, leukocytoclastic Vasculitis*
ENDOCRINE DISORDERS	
Not known:	Pseudophaeochromocytoma*
METABOLISM AND NUTRITION DISORDERS	
Common:	Weight gain
Rare:	Impaired glucose tolerance, diabetes mellitus
Very rare:	Ketoacidosis, hyperosmolar coma, severe hyperglycaemia, hypertriglyceridemia, hypercholesterolemia
PSYCHIATRIC DISORDERS	
Common:	Dysarthria
Uncommon:	Dysphemia
Rare:	Restlessness, agitation
NERVOUS SYSTEM DISORDERS	
Very common:	Drowsiness/sedation, dizziness
Common:	Headache, tremor, rigidity, akathisia, extrapyramidal symptoms, seizures/convulsions/myoclonic jerks
Uncommon:	Neuroleptic malignant syndrome
Rare:	Confusion, delirium
Very rare:	Tardive dyskinesia, obsessive compulsive symptoms
Not known:	Cholinergic syndrome (after abrupt withdrawal)*, EEG changes*, pleurothotonus*
EYE DISORDERS	
Common:	Blurred vision
CARDIAC DISORDERS	
Very common:	Tachycardia
Common:	ECG changes
Rare:	Circulatory collapse, arrhythmias, myocarditis, pericarditis/ pericardial effusion
Very rare:	Cardiomyopathy, cardiac arrest
Not known:	Myocardial infarction which may be fatal*, chest pain/angina pectoris*
VASCULAR DISORDERS	
Common:	Hypertension, postural hypotension, syncope
Rare:	Thromboembolism
Not known:	Venous thromboembolism, including cases of pulmonary embolism and cases of deep vein thrombosis
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	
Rare:	Aspiration of ingested food, pneumonia and lower respiratory tract infection which may be fatal
Very rare:	Respiratory depression/arrest
Not known:	Nasal congestion*
GASTROINTESTINAL DISORDERS	
Very common:	Constipation, hyper salivation
Common:	Nausea, vomiting, anorexia, dry mouth
Rare:	Dysphagia
Very rare:	Parotid gland enlargement, intestinal obstruction/paralytic ileus/faecal impaction
Not known:	Diarrhoea*. Abdominal discomfort/heartburn/dyspepsia*, colitis*
HEPATOBILIARY DISORDERS	
Common:	Elevated liver enzymes
Rare:	Hepatitis, cholestatic jaundice, pancreatitis
Very rare:	Fulminant hepatic necrosis
Not known:	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	
Very rare:	Skin reactions
Not known	Pigmentation disorder*
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	
Not known:	Muscle weakness*, muscle spasms*, muscle pain*, systemic lupus erythematosus*
RENAL AND URINARY DISORDERS	
Common:	Urinary incontinence, urinary retention
Very rare:	Interstitial nephritis
Not known:	Renal failure*, Nocturnal enuresis*
PREGNANCY, PUERPERIUM AND PERINATAL CONDITIONS	
Not known	Drug withdrawal syndrome neonatal
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	
Very rare:	Priapism
Not known	Retrograde ejaculation*
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	
Common:	Fatigue, fever, benign hyperthermia, disturbances in sweating/temperature regulation
Very rare:	Sudden unexplained death
INVESTIGATIONS	
Rare:	Increased CPK

* Adverse drug reactions derived from post-marketing experience via spontaneous case reports and literature cases.
Very rare events of ventricular tachycardia 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.

OVERDOSAGE AND TREATMENT:
In cases of acute intentional or accidental clozapine overdose for which information on the outcome is available, mortality to date is about 12%. Most of the fatalities were associated with cardiac failure or pneumonia caused by aspiration and occurred at doses above 2000 mg. There have been reports of patients recovering from an overdose in excess of 10 000 mg. 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.
Signs and symptoms
Drowsiness, lethargy, areflexia, coma, confusion, hallucinations, agitation, delirium, extrapyramidal symptoms, hyperreflexia, convulsions; hyper salivation, mydriasis, blurred vision, thermo ability; hypotension, collapse, tachycardia, cardiac arrhythmias; aspiration pneumonia, dyspnoea, respiratory depression or failure.
Treatment
There are no specific antidotes for clozapine.
Gastric lavage and/or 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 epinephrine should be avoided in the treatment of hypotension because of the possibility of a 'reverse epinephrine' effect.
Close medical supervision is necessary for at least 5 days because of the possibility of delayed reactions.

STORAGE CONDITION: Store at a temperatures not exceeding 30°C.

DOSAGE FORMS AND PACKAGING AVAILABLE:
Clozapine Tablets 25 mg: Blister Foil by 10's (Box of 30's)
Clozapine Tablets 100 mg: Blister Pack (Box of 10's, 30's and 100's)

INSTRUCTIONS AND SPECIAL PRECAUTIONS FOR HANDLING AND DISPOSAL (IF APPLICABLE): Not Applicable

NAME AND ADDRESS OF MARKETING AUTHORIZATION HOLDER:
Marketing Authorization Holder
Brown & Burk Philippines Inc
U-501, 5/F., SEDCCO 1 Bldg., 120 Rada cor.
Legaspi Sts., Legaspi Village, Makati City, Philippines

NAME AND ADDRESS OF MANUFACTURER:
MICRO LABS LIMITED
No 92, Sipcot Industrial Complex,
Hosur – 635 126, India

CAUTION STATEMENT: FOODS, DRUGS, DEVICES, AND COSMETICS ACT PROHIBITS DISPENSING WITHOUT PRESCRIPTION.

ADR REPORTING STATEMENT:
"FOR SUSPECTED ADVERSE DRUG REACTION, REPORT TO THE FDA: www.fda.gov.ph
Seek medical attention immediately at the first sigh of Adverse Drug Reaction.

REGISTRATION NUMBER:
Clozapine Tablets 25 mg: DR-XY33116
Clozapine Tablets 100 mg: DR-XY31926

DATE OF FIRST AUTHORIZATION:
Clozapine Tablets 25 mg: 15 Mar.2007
Clozapine Tablets 100 mg: 30 JUN.2007

DATE OF REVISION OF PACKAGE INSERT:
April 2018