Anzaril Tablets 25 mg & 100 mg

DESCRIPTION :

Anzaril tablets 25 mg : A yellow, scored, flat of diameter 7 mm round tablet with 'MPI' marked.

Anzaril tablets 100 mg : A yellow, flat-bevelled edge tablet with scored at one side, marked 'MPI' on the other, diameter of 10 mm round tablet.

The product shall only be supplied to a patient with a prescription issued by Psychiatrist, Neurologist or Physician.

COMPOSITION :

Each tablet contains:

Anzaril tablets 25 mg : Each tablet contains 25 mg of Clozapine.

Anzaril tablets 100 mg : Each tablet contains 100 mg of Clozapine.

PHARMACODYNAMICS :

Pharmacotherapeutic group: Antipsychotics; ATC code N05AH02

Clozapine has been shown to be an antipsychotic agent that is different from classic neuroleptics.

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, in addition to potent anti-α- adrenergic, anticholinergic, antihistamine, and arousal reaction-inhibiting effects. It has also been shown to possess antiserotoninergic properties.

Clinically, clozapine produces rapid and marked sedation, and exerts antipsychotic effects in patients with schizophrenia resistant to other antipsychotic agents. In such cases, clozapine has proven effective in relieving both positive and negative schizophrenic symptoms. Clinically significant improvement has been observed in about one-third of patients within the first 6 weeks of treatment and in about 60% of patients in whom treatment was continued for up to 12 months.

Clozapine is unique in that it produces virtually no major extrapyramidal reactions such as acute dystonia and tardive dyskinesia; parkinsonian-like side effects and akathisia are rare. In contrast to classical neuroleptics, clozapine produces little or no prolactin elevation, thus avoiding adverse effects such as gynaecomastia, amenorrhoea, galactorrhoea, and impotence.

A potentially serious adverse reaction caused by clozapine therapy are granulocytopenia and agranulocytosis occurring at an estimated incidence of 3% and 0.7% respectively. In view of this risk, the use of clozapine should be limited to patients who are treatment-resistant (see Indications) and in whom regular haematological examinations can be performed (see Precautions/Warnings and Adverse Effects).

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 dimethyl metabolites 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 increases 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.

Linearity/non-linearity

Dosage increases from 37.5 mg to 75 mg 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), and in the peak and minimum plasma concentrations.

INDICATIONS :

Treatment-resistant schizophrenia

Clozapine is indicated in patients with treatment-resistant schizophrenia, i.e. patients with schizophrenia who are non-responsive to or intolerant of classic 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 classic antipsychotics because of severe and untreatable neurological adverse reactions (extrapyramidal side effects or tardive dyskinesia).

Risk of recurrent suicidal behaviour

Clozapine is 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 re-experiencing suicidal behaviour, based on history and recent clinical state. Suicidal behaviour refers to actions by a patient that put him/herself at high risk for death.

DOSAGE /ADMINISTRATION :

The dosage must be adjusted individually. For each patient the lowest effective dose should be used. Careful dose titration and a divided dosage schedule are necessary to minimize the risk of hypotension, seizure, and sedation. The total daily amount may be divided into unequal doses, the largest of which should be taken at bedtime.

The following dosages are recommended:

Starting dose

12.5mg (half a 25mg tablet) once or twice on the first day, followed by one or two 25mg tablets on the second day. If well tolerated, the dose may then be increased in increments of 25-50mg/day in order to achieve a daily dose of 300mg within 2-3 weeks. Thereafter, if required, the daily dose may be further increased in increments of 50-100mg at half-weekly or, preferably, weekly intervals.

Therapeutic dose range

In most patients the onset of antipsychotic effects occurs at a daily dosage of 300-450 mg, given in two to four divided doses. Some patients require lower daily doses, and others up to 600mg.

Maximum dose

To obtain full therapeutic benefit, a few patients may require larger doses; in such cases the maximum permissible dose is 900mg/day, with maximum individual increments of 100mg. Increased adverse effects (in particular seizures) are possible at doses exceeding 450mg/day.

Maintenance dose

Once the maximum therapeutic effect has been attained, many patients can be effectively maintained on a lower dose. Careful downward titration is therefore recommended. Treatment should be maintained for at least 6 months. If the daily dose does not exceed 200mg, once-daily administration in the evening may be appropriate.

Withdrawal of treatment

In the event of planned withdrawal of clozapine, it is recommended that the dose be reduced gradually over a period of 1-2 weeks. If abrupt discontinuation is necessary (e.g. because of leukopenia), the patient should be closely monitored for recurrence of psychosis and symptoms of cholinergic rebound (e.g. increased sweating, headache, nausea, vomiting and diarrhea).

Resumption of treatment

If more than two days have elapsed since the last dose of clozapine, treatment should be resumed with 12.5mg (half a 25mg tablet) once or twice on the first day. If this dose is well tolerated, titration to the therapeutic level can then proceed more quickly than is recommended for initial treatment. However, re-titration should be carries out with extreme caution in any patient who has previously experiences respiratory or cardiac arrest with initial dosing, but was the able to be successfully titrated to a therapeutic dose.

Switching from another antipsychotic therapy to Clozapine

It is generally recommended that clozapine should not be combined with other antipsychotic agents. When clozapine therapy is to be initiated in a patient undergoing oral antipsychotic therapy, it is recommended that if possible, the other antipsychotics agent should first be discontinued by tapering the dosage downwards over a period of about one week. Once the antipsychotic agent has been completely discontinued for at least 24 hours, clozapine treatment can be started as described above.

A lower starting dose and slower build-up are recommended for patients with a history of seizures or with cardiovascular, renal or hepatic disorders.

Dose adjustment is necessary in patients receiving drugs that interact with clozapine. Such as benzodiazepines, carbamazepine or selective serotonin reuptake inhibitors.

(Long-term) reducing the recurrent suicidal behavior in patients with schizophrenia and schizoaffective disorder

The dosage and administration guidelines described above for the use of clozapine in patients with treatment-resistant schizophrenia are also valid when clozapine is used in patients with schizophrenia or schizoaffective disorder who show evidence of a long-term risk for recurrent suicidal behavior.

Special patient group

Patients with heart disease

The starting dose should be low (1x12.5 mg on the first day) in patients with heart disease. It should be increased slowly and in small increments. It is contraindicated for patients with severe cardiovascular disease.

Patients with renal insufficiency

The starting dose should be low (1x12.5 mg on the first day) in patients with mild to moderate renal insufficiency. It should be increased slowly and in small increments.

Patients with hepatic insufficiency

In patients with hepatic insufficiency, clozapine should only be administered with care and regular monitoring.

Children and adolescents

There are no studies in children and adolescents on the safety and effectiveness of clozapine.

Elderly patients

In older patients (≥ 60 years) initiation of treatment at a particularly low dose is recommended (12.5mg given once on the first day), with subsequent dose increments restricted to 25mg/day.

ROUTE OF ADMINISTRATION :

Oral

CONTRAINDICATIONS :

- Previous hypersensitivity to clozapine or any other components of the formulations.
- History of toxic or idiosyncratic 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.
- Several renal or cardiac disorders (eg. myocarditis).
- Active liver disease associated with nausea, anorexia or jaundice, progressive liver disease, hepatic failure.
- Patients unable to undergo regular blood tests.
- History of clozapine-induced agranulocytosis.
- Paralytic ileus.

PRECAUTIONS/ WARNINGS :

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 should not be used concurrently with clozapine. In addition, the concomitant use of long-acting depot antipsychotics should be avoided because it is impossible to remove these medications, which may be potentially myelosuppressive, from the body rapidly 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 clozapine.

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

WBC counts and ANC monitoring

Before starting clozapine treatment, a WBC count and a differential blood count must be performed within 10 days prior to clozapine treatment to ensure that only patients with normal leukocyte count and normal absolute neutrophil count (WBC count ≥ 3500/mm³ and ANC ≥ 2000/mm³) will receive the drug. After the start of clozapine treatment, the WBC count and if possible, ANC must be monitored weekly for 18 weeks and thereafter at least monthly throughout treatment, and for 1 month after complete discontinuation of clozapine.

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. An immediate differential blood count must be performed if any symptoms or signs of an infection occur.

In case of low WBC count / ANC

During the first 18 weeks of clozapine therapy, if the WBC count falls to between 3500/mm³ and 3000/mm³ and/or the ANC falls to between 2000/mm³ and 1500/mm³, at least twice weekly haematological evaluations are necessary. After 18 weeks of clozapine therapy, at least twice weekly haematological evaluations are necessary if the WBC count falls to between 3000/mm³ and 2500/mm³ and/or the ANC falls to between 1500/mm³ and 1000/mm³.

In addition, if during clozapine therapy, the WBC count has dropped by a substantial amount from baseline, repeat WBC count and a differential blood count should be done. A substantial drop is defined as a single drop of 3000/mm³ or more in the WBC count or a cumulative drop of 3000/mm³ or more within three weeks.

Immediate discontinuation of clozapine treatment is mandatory if the WBC count is less than 3000/mm³ or the ANC is less than 1500/mm³ during the first 18 weeks of clozapine therapy and if the WBC count is less than 2500/mm³ or the ANC is less than 1000/mm³ after the first 18 weeks of clozapine 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 clozapine, haematological evaluation is required until haematological recovery has occurred.

If clozapine has been withdrawn and a further drop in the WBC count below 2000/mm³ occurs and/or the neutrophil granulocytes fall below 1000/mm³, the management of this condition must be guided by an experienced haematologist. If possible, the patient should be referred to a specialized 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.

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

Confirmation of the haematological values is recommended by performing 2 blood counts done on 2 consecutive days. However, clozapine should be discontinued after the first blood count.

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

Patients who have been on clozapine for more than 18 weeks and have had their treatment interrupted for more than 3 days but less than 4 weeks should have their WBC count and if possible 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.

Other precautions

In the event of eosinophilia (see Adverse Effects, Blood and lymphatic system), it is recommended to discontinue clozapine if the eosinophil count rises above 3000/mm³ and to re-start therapy only after the eosinophil count has fallen below 1000/mm³.

In the event of thrombocytopenia (see Adverse Effects, Blood and lymphatic system), it is recommended to discontinue clozapine therapy if the platelet count falls below 50,000/ mm³.

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.

Tachycardia that persists at rest, accompanied by arrhythmias, shortness of breath or signs and symptoms of heart failure, may rarely occur during the first month 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. If the diagnosis of myocarditis is confirmed, clozapine 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.

In patients with a history of seizures, or suffering from renal or cardiovascular disorders (note: severe renal or cardiovascular disorders are contraindications), the initial dose should be 12.5 mg given once on the 1st day, and dosage increase should be slow and in small increments.

Patients with stable pre-existing liver disorders may receive clozapine, but need regular liver function tests. In patients in whom during clozapine treatment, symptoms of possible liver dysfunction such as nausea, vomiting and/or anorexia develop, liver function tests should be performed immediately. If the elevation of the values is clinically relevant or if symptoms of jaundice occur, treatment with clozapine must be discontinued. It may be resumed (see Dosage/Administration, Resumption of treatment) only when the liver function tests have returned to normal values. In such cases, liver function should be closely monitored after the re-introduction of the drug.

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

During clozapine therapy, patients may experience transient temperature elevation 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 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 patient 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 antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug.

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

INTERACTIONS WITH OTHER MEDICAMENTS :

Pharmacodynamic-related interactions

- Drugs known to have a substantial potential to depress bone marrow function should not be used concurrently with clozapine (see Precautions/Warnings).
- 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) a 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 drug possessing anticholinergic, hypotensive or respiratory depressant effects.
- Concomitant use of lithium or other CNS-active agents may increase the risk of development of neuroleptic malignant syndrome (NMS).
- Owing to its anti-α-adrenergic properties, clozapine may reduce the blood pressure-increasing effect of norepinephrine or other predominantly α-adrenergic agents and reverse the pressor effect of epinephrine.
- Rare but serious reports of seizures, including onset of seizure in non-epileptic patient, and isolated cases of delirium where clozapine was co-administered with valproic acid have been reported. These effects are possible due to pharmacodynamic interaction, the mechanism of which has not yet been determined.

Pharmacokinetic-related interactions

Clozapine is a substrate for many CYP 450 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 drugs, which are either inhibitors or inducers of these enzymes.

No clinically relevant interactions have been observed thus far with tricyclic antidepressants, phenothiazines or type 1C anti-arrhythmics, which are known to bind to cytochrome P450 2D6.Concomitant administration of drugs known to induce cytochrome P450 enzymes may decrease the plasma levels of clozapine.

Observed pharmacokinetic interactions to be considered

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.

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

- Substances known to inhibit the activity of the major isozymes involved in the metabolism of clozapine and with reported interactions include, for instance, cimetidine, erythromycin (3A4), fluvoxamine (1A2), perazine (1A2), ciprofloxacin (1A2) and oral contraceptives (1A2, 3A4, 2C19).
- The plasma concentration of clozapine is increased by caffeine (1A2) intake and decrease 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.

Anticipated pharmacokinetic interactions to be considered

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

- Known inducers of 1A2 include, for instance, omeprazole and tobacco smoke. In cases of sudden cessation of tobacco smoking, 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 isozymes may increase the plasma levels of clozapine.

- Potent inhibitors of CYP3A, such as azole antimycotics and protease inhibitors, could potentially also increase clozapine plasma concentrations; no interactions have been reported to date, however.

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

PREGNANCY AND LACTATION :

Pregnancy

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. Anzaril should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

Lactation

Animal studies suggest that clozapine is excreted in breast milk and has an effect in the nursing infant. Therefore, mother receiving clozapine should not breast-feed.

ADVERSE EFFECTS :

Summary of the safety profile

For the most part, the adverse event profile of clozapine is predictable from its pharmacological properties. An important exception is its propensity to cause agranulocytosis. Because of this risk, its use is restricted to treatment-resistant schizophrenia and psychosis occurring during the course of Parkinson's disease in cases where standard treatment has failed. While blood monitoring is an essential part of the care of patients receiving clozapine, the physician should be aware of other rare but serious adverse reactions, which may be diagnosed in the early stages only by careful observation and questioning of the patient in order to prevent morbidity and mortality.

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

Data from published clinical trials showed that a varying proportion of clozapine-treated patients (from 7.1 to 15.6%) were discontinued due to an adverse event, including only those that could be reasonably attributed to clozapine. The more common events considered to be causes of discontinuation were leukopenia, somnolence, dizziness (excluding vertigo) and psychotic disorder.

Blood and lymphatic system

Development of granulocytopenia and agranulocytosis is a risk inherent to clozapine treatment. Although generally reversible on withdrawal of treatment, agranulocytosis may result in sepsis and can prove fatal. Because immediate withdrawal of treatment is required to prevent the development of life-threatening agranulocytosis, monitoring of the WBC count is mandatory.

Metabolic and nutritional disorders

Impaired glucose tolerance and/or development or exacerbation of diabetes mellitus has been reported rarely during treatment with clozapine. On very rare occasions, severe hyperglycaemia, sometimes leading to ketoacidosis/hyperosmolar coma, has been reported in patients on clozapine treatment with no prior history of hyperglycaemia. Glucose levels normalised in most patients after discontinuation of clozapine and in a few cases hyperglycaemia recurred when treatment was reinitiated. Although most patients had risk factors for non-insulin dependent diabetes mellitus, hyperglycaemia has also been documented in patients with no known risk factors.

Nervous system disorders

The very common adverse reactions observed include drowsiness/sedation, and dizziness.

Clozapine can cause EEG changes, including the occurrence of spike and wave complexes. It lowers the seizure threshold in a dose-dependent manner and may induce myoclonic jerks or generalised seizures. These symptoms are more likely to occur with rapid dose increases and in patients with pre-existing epilepsy. In such cases 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 the possibility of a pharmacokinetic interaction should be considered. In rare cases, patients treated with clozapine may experience delirium.

Very rarely, tardive dyskinesia has been reported in patients on clozapine who had been treated with other antipsychotic agents. Patients in whom tardive dyskinesia developed with other antipsychotics have improved on clozapine.

Cardiac disorders

Tachycardia and postural hypotension with or without syncope may occur, especially in the initial weeks of treatment. The prevalence and severity of hypotension is influenced by the rate and magnitude of dose titration. Circulatory collapse as a result of profound hypotension, in particular related to aggressive titration, with the possible serious consequences of cardiac or pulmonary arrest, has been reported with clozapine.

A minority of clozapine-treated patients experience ECG changes similar to those seen with other antipsychotics, including S-T segment depression and flattening or inversion of T waves, which normalise after discontinuation of clozapine. The clinical significance of these changes is unclear. However, such abnormalities have been observed in patients with myocarditis, which should therefore be considered.

Isolated cases of cardiac arrhythmias, pericarditis/pericardial effusion and myocarditis have been reported, some of which have been fatal. The majority of the cases of myocarditis occurred within the first 2 months of initiation of therapy with clozapine. Cardiomyopathy generally occurred later in the treatment. Eosinophilia has been co-reported with some cases of myocarditis (approximately 14%) and pericarditis/pericardial effusion; it is not known, however, whether eosinophilia is a reliable predictor of carditis.

Signs and symptoms of myocarditis or cardiomyopathy include persistent tachycardia at rest, 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 flulike symptoms.

Sudden, unexplained deaths are known to occur among psychiatric patients who receive conventional antipsychotic medication but also among untreated psychiatric patients. Such deaths have been reported very rarely in patients receiving clozapine.

Vascular disorders

Rare cases of thromboembolism have been reported.

Respiratory system

Respiratory depression or arrest has occurred very rarely, with or without circulatory collapse.

Gastrointestinal system

Constipation and hypersalivation have been observed very frequently, and nausea and vomiting frequently. Very rare intestinal obstruction, ileus, faecal impaction may occur. Rarely clozapine treatment may be associated with dysphagia. Aspiration of ingested food may occur in patients presenting with dysphagia or as a consequence of acute overdosage.

Hepatobiliary disorders

Transient, asymptomatic elevations of liver enzymes and, rarely, hepatitis and cholestatic jaundice may occur. Very rarely, fulminant hepatic necrosis has been reported. If jaundice develops, clozapine should be discontinued. In rare cases, acute pancreatitis has been reported.

Renal disorders

Isolated cases of acute interstitial nephritis have been reported in association with clozapine therapy.

Reproductive and breast disorders

Very rare reports of priapism have been received.

General disorders

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

Acute withdrawal reactions have been reported.

Tabulated list of adverse 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).

Infections and infestations	
Not known	Sepsis*
Blood and lymphatic system disorders	
Common	Leukopenia/decreased WBC/neutropenia, eosinophilia, leukocytosis
Uncommon	Agranulocytosis
Rare	Anaemia
Very rare	Thrombocytopenia, thrombocythaemia
Immune system disorders	
Not known	Angioedema*, leukocytoclastic vasculitis*, Drug rash with eosinophilia and systemic symptoms (DRESS)*
Endocrine disorders	
Not known	Pseudophaeochromocytoma*
Metabolism and nutrition disorders	
Common	Weight gain
Rare	Diabetes mellitus, impaired glucose tolerance, obesity*
Very rare	Hyperosmolar coma, ketoacidosis, severe hyperglycaemia, hypercholesterolemia, hypertriglyceridemia
Psychiatric disorders	
Common	Dysarthria
Uncommon	Dysphemia
Rare	Agitation, restlessness
Nervous system disorders	
Very common	Drowsiness/sedation, dizziness
Common	Seizures/convulsions/myoclonic jerks, extrapyramidal symptoms, akathisia, tremorrigidity, headache
Uncommon	Neuroleptic malignant syndrom
Rare	Confusion, delirium
Very rare	Tardive dyskinesia, obsessive compulsive symptoms
Not known	Cholinergic syndrome (after abrupt withdrawal)*, EEG changes*, pleurothotonus*, restless leg syndrome*
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*,**, myocarditis*,**, chest pain/angina pectoris*, atrial fibrillation*, palpitations*, mitral valve incompetence associated with clozapine related cardiomyopathy*
Vascular disorders	
Common	Syncope, postural hypotension, hypertension
Rare	Thromboembolism
Not known	Hypotension*, Venous thromboembolism
Respiratory, thoracic and mediastinal disorders	
Rare	Aspiration of ingested food, pneumonia and lower respiratory tract infection which may be fatal, Sleep apnoea***
Very rare	Respiratory depression/arrest
Not known	Pleural effusion*, nasal congestion*
Gastrointestinal disorders	
Very common	Constipation, hypersalivation
Common	Nausea, vomiting, anorexia, dry mouth
Rare	Dysphagia
Very rare	Intestinal obstruction, ileus, faecal impaction, parotid gland enlargement
Not known	Megacolon*,**, intestinal infarction/ischaemia*,**, intestinal necrosis*,**, intestinal ulceration*,** and intestinal perforation*,**, diarrhoea*, abdominal discomfort/heartburn/dyspepsia*, colitis*
Hepatobiliary disorders	
Common	Elevated liver enzyme
Rare	Pancreatitis, hepatitis, cholestatic jaundice
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	Rhabdomyolysis*, muscle weakness*, muscle spasms*, muscle pain*, systemic lupus erythematosus*
Renal and urinary disorders	
Common	Urinary retention, urinary incontinence
Very rare	Tubulointerstitial 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	Benign hyperthermia, disturbances in sweating/temperature regulation, fever fatigue
Very rare	Sudden unexplained death
Not known	Polyserositis*
Investigations	
Rare	Increased CPK
Injury, poisoning and procedural complications	
Uncommon	Falls (associated with clozapine-induced seizures, somnolence, postural hypotension, motor and sensory instability)*

*Adverse drug reactions derived from post-marketing experience via spontaneous case reports and literature cases.

** These adverse drug reactions were sometimes fatal.

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

Post-marketing: megacolon**, intestinal infarction/ischaemia**, intestinal necrosis**, intestinal ulceration**, intestinal perforation**, colitis

(**These adverse drug reactions were sometimes fatal).

***Atypical antipsychotic drugs, such as clozapine, have been associated with cases of sleep apnoea, with or without concomitant weight gain. In patients who have a history of or are at risk for sleep apnoea, Anzaril should be prescribed with caution.

SYMPTOMS AND TREATMENT OF OVERDOSE :

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.

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.

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 and 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.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

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.

STORAGE CONDITIONS :

Store below 30°C in well closed container. Protect from light, heat and moisture.

Keep out of the reach and sight of children.

SHELF LIFE :

Three years from the date of manufacture.

PACK SIZE/ PRESENTATION :

10 x 10's (blister pack)

NAME AND ADDRESS OF MANUFACTURERS:

Packed and released by:
GoodScience Sdn. Bhd.
No. 7, Jalan KPK 4/3 Kawasan Perindustrian Kundang, Kundang Jaya,
48020 Rawang, Selangor, Malaysia.

Manufactured by:
Malaysian Pharmaceutical Industries Sdn. Bhd.,
Plot 14, Lebuhraya Kampung Jawa,
11900 Bayan Lepas, Pulau Pinang, Malaysia.

PRODUCT REGISTRATION HOLDER :

GoodScience Sdn. Bhd.
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