PRESCRIBING INFORMATION

CLOZARIL®
(Clozapine Tablets)

Antipsychotic Agent

Novartis Pharmaceuticals Canada Inc.
Dorval, Quebec
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DATE OF PREPARATION:
March 20, 1991

DATE OF REVISION:
June 16, 2000
PRESCRIBING INFORMATION

NAME OF DRUG

CLOZARIL®
(Clozapine)

THERAPEUTIC CLASSIFICATION

Antipsychotic Agent

CLINICAL PHARMACOLOGY

CLOZARIL® (clozapine), a dibenzodiazepine derivative, is an atypical antipsychotic drug because its profile of binding to dopamine receptors and its effects on various dopamine-mediated behaviours differ from those exhibited by conventional antipsychotics. In contrast to conventional antipsychotics, CLOZARIL produces little or no prolactin elevation. CLOZARIL exerts potent anticholinergic, adrenolytic, antihistaminic and antiserotonergic activity.

Controlled clinical trials indicate that CLOZARIL improves both positive and negative symptoms.

Patients on rare occasions may report an intensification of dream activity during CLOZARIL therapy. Rapid eye movement (REM) sleep was found to be increased to 85% of the total sleep time. In these patients, the onset of REM sleep occurred almost immediately after falling asleep.

As is true of more typical antipsychotic drugs, clinical EEG studies have shown that CLOZARIL increases delta and theta activity and slows dominant alpha frequencies. Enhanced synchronization occurs, and sharp wave activity and spike and wave complexes may also develop.
Pharmacokinetics

The absorption of orally administered clozapine is 90 to 95%. Food does not affect either the rate or the extent of absorption. Clozapine is subject to first-pass metabolism, resulting in an absolute bioavailability of 50 to 60%.

Plasma concentrations show large inter-individual differences, with peak concentrations occurring approximately 2.5 hours (range: 1 to 6 hours) after dosing. In a dose range of 37.5 mg bid to 150 mg bid, the area under the curve (AUC) and the peak plasma concentration ($C_{\text{max}}$) increase linearly in a dose-related fashion.

Clozapine is approximately 95% bound to plasma proteins. The elimination of clozapine is biphasic with a mean terminal half-life of 12 hours (range: 6 to 30 hours, calculated from three steady-state in vivo studies). 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. Clozapine is almost completely metabolized prior to excretion. Only trace amounts of unchanged drug are detected in the urine and feces. Approximately 50% of the administered dose is excreted as metabolites in the urine and 30% in the feces.

Recent studies suggest that there is a significant correlation between clozapine plasma levels and clinical response. The concentrations of clozapine, and its major metabolite norclozapine, were significantly higher in responders than in nonresponders although the mean doses of clozapine did not differ between the two groups. Of the main metabolites, only norclozapine was found to be active. In patients who responded to treatment, plasma clozapine levels reached at least 350 to 370 ng/ml.
INDICATIONS AND CLINICAL USE

CLOZARIL® (clozapine) is indicated in the management of symptoms of treatment-resistant schizophrenia. In controlled clinical trials, CLOZARIL was found to improve both positive and negative symptoms.

Due to the significant risk of agranulocytosis and seizure associated with its use, CLOZARIL should be limited to treatment-resistant schizophrenic patients who are non-responsive to, or intolerant of, conventional antipsychotic drugs. Non-responsiveness is defined as the lack of satisfactory clinical response, despite treatment with appropriate courses of at least two marketed chemically-unrelated antipsychotic drugs. Intolerance is defined as the inability to achieve adequate benefit with conventional antipsychotic drugs because of dose-limiting, intolerable adverse effects.

Because of the significant risk of agranulocytosis and seizure, events which both present a continuing risk over time, the extended treatment of patients failing to show an acceptable level of clinical response to CLOZARIL should ordinarily be avoided. In addition, the need for continuing treatment in patients exhibiting beneficial clinical responses should be periodically reevaluated.

CLOZARIL can be used only if regular hematological examinations can be guaranteed, as specified under WARNINGS and DOSAGE AND ADMINISTRATION.

CLOZARIL is available only through a distribution system that ensures:

- weekly or every-two-week hematological testing prior to the delivery of the next period's supply of medication (see WARNINGS)
- maintenance of a central national database that monitors the hematological results of all patients on CLOZARIL and provides timely feedback to the treating physician.
- registration of the patient, treating physician, laboratory and dispensing pharmacist.
CONTRAINDICATIONS

CLOZARIL® (clozapine) is contraindicated in patients with myeloproliferative disorders, a history of toxic or idiosyncratic agranulocytosis or severe granulocytopenia (with the exception of granulocytopenia/ agranulocytosis from previous chemotherapy). [CLOZARIL should not be used simultaneously with other agents known to suppress bone marrow function.]

CLOZARIL is also contraindicated in patients with active liver disease associated with nausea, anorexia, or jaundice; progressive liver disease; hepatic failure.

Other contraindications include severe central nervous system depression or comatose states, severe renal or cardiac disease (eg. myocarditis), uncontrolled epilepsy, and previous hypersensitivity to clozapine or any other components of CLOZARIL.

WARNINGS

AGRANULOCYTOSIS

BECAUSE OF THE SIGNIFICANT RISK OF GRANULOCYTOPENIA AND AGRANULOCYTOSIS, A POTENTIALLY LIFE-THREATENING ADVERSE EVENT (SEE BELOW), CLOZARIL® (CLOZAPINE) SHOULD BE RESERVED FOR USE IN THE TREATMENT OF SCHIZOPHRENIC PATIENTS WHO FAIL TO SHOW AN ACCEPTABLE RESPONSE TO ADEQUATE COURSES OF CONVENTIONAL ANTIPSYCHOTIC DRUG TREATMENT, EITHER BECAUSE OF INSUFFICIENT EFFECTIVENESS OR THE INABILITY TO ACHIEVE AN EFFECTIVE DOSE DUE TO INTOLERABLE ADVERSE EFFECTS.

PATIENTS MUST HAVE A NORMAL WHITE BLOOD-CELL (WBC) COUNT AND DIFFERENTIAL COUNT PRIOR TO STARTING CLOZARIL THERAPY. SUBSEQUENTLY, A WBC COUNT AND DIFFERENTIAL COUNT MUST BE CARRIED OUT AT LEAST WEEKLY FOR THE FIRST 26 WEEKS OF TREATMENT AND AT
The change from a weekly to a "once every two weeks" schedule should be evaluated on an individual patient basis after 126 weeks of treatment. This decision should be made based upon the clinical judgement of the treating physician, and if he/she deems it appropriate, a consulting hematologist, as well as the patient’s willingness to pursue a given frequency of blood monitoring. In turn, the clinical evaluation should take into consideration possible factors that would place the patient in a higher risk group, as well as the hematological profile of the patient during the first 26 weeks of treatment.

CLOZARIL is available only through a distribution system that requires weekly or every-two-week hematological testing prior to the delivery of the next period’s supply of medication (see INDICATIONS).

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Granulocytopenia (defined as a granulocyte count of less than 1.5 x 10^9/L) and agranulocytosis (defined as a granulocyte count of less than 0.5 x 10^9/L, including polys + bands) have been estimated to occur in association with CLOZARIL use at an incidence of 3% and 0.7%, respectively. These incidences are derived from post-marketing data as per June 1993, covering over 60,000 patients treated with CLOZARIL for up to 3 years in USA, Canada and UK. Approximately 88% of the cases of agranulocytosis have occurred during the first 26 weeks of therapy.

A fatality rate of 32% for Clozapine-induced agranulocytosis had been reported in association with clozapine use as of December 31, 1989. However, more than half of these deaths occurred before 1977, prior to the recognition of the risk of agranulocytosis and the need for routine blood monitoring. From February 1990 to August 21, 1997, among approximately 150,409 patients treated with CLOZARIL in the U.S.A., 585 new cases of agranulocytosis have been reported, of which 19 (3.2%) had a fatal outcome.

Fatalities occurring in association with CLOZARIL - induced granulocytopenia/agranulocytosis have generally resulted from infections due to compromised immune system responses. Therefore, patients should be advised to report immediately the appearance of lethargy, weakness, fever, sore throat, flu-like complaints or any other signs of infection.

CLOZARIL treatment should be initiated and carried out according to the following guidelines:

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1 The change from a weekly to a "once every two weeks" schedule should be evaluated on an individual patient basis after 26 weeks of treatment. This decision should be made based upon the clinical judgement of the treating physician, and if he/she deems it appropriate, a consulting hematologist, as well as the patient’s willingness to pursue a given frequency of blood monitoring. In turn, the clinical evaluation should take into consideration possible factors that would place the patient in a higher risk group, as well as the hematological profile of the patient during the first 26 weeks of treatment.
• Treatment should not be initiated if the WBC count is less than 3.5 x 10^9/L and/or the absolute neutrophil count (ANC) is less than 2.0 x 10^9/L, or if the patient has a history of a myeloproliferative disorder, or toxic or idiosyncratic agranulocytosis or severe granulocytopenia (with the exception of granulocytopenia/ agranulocytosis from previous chemotherapy).

• Independently of their blood monitoring regimen (weekly or at two-week intervals), patients should be evaluated immediately and WBC and differential counts checked at least twice weekly if after the initiation of treatment:
  
  I) the total WBC count falls to between 2.0 x 10^9/L and 3.5 x 10^9/L,
  
  ii) the ANC falls to between 1.5 x 10^9/L and 2.0 x 10^9/L,
  
  iii) a single fall or sum of falls in WBC count of 3.0 x 10^9/L or more is measured in the last four weeks, reaching a value below 4.0 x 10^9/L,
  
  iv) a single fall or sum of falls in ANC of 1.5 x 10^9/L or more is measured in the last four weeks, reaching a value below 2.5 x 10^9/L,
  
  and/or
  
  v) flu-like complaints or other symptoms appear which might suggest infection.

In the event of a fall in total WBC to below 2.0 x 10^9/L or in ANC to below 1.5 x 10^9/L, CLOZARIL therapy must be discontinued immediately and the patient closely monitored. CLOZARIL THERAPY MUST NOT BE RESUMED. Particular attention should be paid to any flu-like complaints or other symptoms which might suggest infection. If the patient should develop a further fall in the WBC count to below 1.0 x 10^9/L, or a decrease in ANC to below 0.5 x 10^9/L, it is recommended that patients be placed in protective isolation with close observation and be watched for signs of infection by their physician. Should evidence of infection develop, the appropriate cultures should be performed and an appropriate antibiotic regimen instituted.

The development of granulocytopenia and agranulocytosis does not appear to be dose dependent, nor is duration of treatment a reliable predictor. Approximately 88% of the cases have occurred in the first twenty-six weeks of treatment, but some cases have developed after years of clozapine use. The incidence of neutropenia and agranulocytosis associated with the use of CLOZARIL
increases as a function of age. Experience in the U.S. (approx. 58,000 patients, as per June 1993) reveals that patients over 50 years old would present an approximately two to three times higher incidence of agranulocytosis when compared with the overall incidence in patients treated with CLOZARIL.

Patients who have shown hematopoietic reactions to other medications may also be more likely to demonstrate such reactions with CLOZARIL. A disproportionate number of the U.S. cases of agranulocytosis occurred in patients of Jewish origin compared to the overall proportion of such patients exposed to the drug in pre-marketing clinical experience in the United States.

Agranulocytosis associated with other antipsychotic drugs has been reported to occur with a greater frequency in patients who are cachectic or have a serious underlying medical illness.

**Seizures**

Caution should be used in administering CLOZARIL to patients having a history of seizures or other predisposing factors.

Seizures have been estimated to occur in association with CLOZARIL use at a cumulative incidence at one year of approximately 5%, based on the occurrence of one or more seizures in the patients exposed to CLOZARIL during clinical trials in the United States. Dose appears to be an important predictor of seizure. At doses below 300 mg/day, seizure risk is comparable to that of other antipsychotic drugs (about 1-2%). At higher doses, seizure risk rises accordingly, reaching 5% at doses of 600 to 900 mg/day. Because of the risk of seizure associated with CLOZARIL use, patients should be advised not to engage in any activity where sudden loss of consciousness could cause serious risk to themselves or others (e.g. driving, operating machinery, swimming, climbing, etc.)
Adverse Cardiovascular Effects

CLOZARIL should be used with caution in patients with known cardiovascular and/or pulmonary disease, particularly in those with cardiac arrhythmias and conduction disturbances.

Orthostatic hypotension, with or without syncope, can occur with CLOZARIL and may represent a continuing risk in some patients. Rarely (approximately 1 case per 3,000 patients in the United States), collapse can be profound and can be accompanied by respiratory and/or cardiac arrest. Orthostatic hypotension is more likely to occur during initial titration in association with rapid dose escalation and may even occur on the first or second day of initial dosing. Therefore, upon initiation of CLOZARIL therapy or re-initiation of treatment in patients who have had even a brief interval off CLOZARIL, i.e. two days or more since the last dose, it is recommended that treatment be re-initiated with only 12.5 mg (one half of a 25 mg tablet) once or twice daily (See DOSAGE AND ADMINISTRATION).

Tachycardia, which may be sustained, has been observed in approximately 25% of patients taking CLOZARIL with patients having an average increase in pulse rate of 10 to 15 bpm. The sustained tachycardia is not simply a reflex response to hypotension and is present in all positions monitored. Tachycardia may be due to the anticholinergic effect of CLOZARIL and its ability to elevate plasma norepinephrine. Either tachycardia or hypotension may pose a serious risk for an individual with compromised cardiovascular function.

A minority of CLOZARIL-treated patients experience ECG repolarization changes similar to those seen with other antipsychotic drugs, including S-T segment depression and flattening or inversion of T waves. There have also been reports of ischemic changes, myocardial infarction, nonfatal arrhythmias, sudden unexplained deaths and congestive heart failure in association with CLOZARIL use. Causality assessment was difficult in many of these cases due to serious preexisting cardiac disease and plausible alternative causes. Rare instances of sudden, unexplained death have been reported in psychiatric patients, with or without associated antipsychotic drug treatment, and the relationship of these events to antipsychotic drug use is unknown.
Isolated cases of cardiac arrhythmias, pericarditis and myocarditis (with or without eosinophilia) have been reported, some of which have been fatal. The occurrence of tachycardia that persists at rest, accompanied by arrhythmias, shortness of breath, or signs and symptoms of heart failure (which may rarely occur during the first month of treatment and very rarely thereafter) necessitates an urgent diagnostic evaluation for myocarditis, especially during the titration period. If the diagnosis of myocarditis is confirmed, CLOZARIL should be discontinued.

**Neuroleptic Malignant Syndrome**

A potentially fatal symptom complex sometimes referred to as neuroleptic malignant syndrome (NMS) has been reported in association with antipsychotic drugs. Cases of NMS have been reported in patients treated with CLOZARIL, most of which have included the concomitant use of lithium or other CNS-active agents.

Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status (including catatonic signs) and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmias). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure.

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever and primary central nervous system (CNS) pathology.

The management of NMS should include: (1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy; (2) intensive symptomatic treatment and medical monitoring; and (3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS.
If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported.

**Tardive Dyskinesia**

A syndrome consisting of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with conventional antipsychotic drugs. Although the prevalence of tardive dyskinesia with conventional antipsychotics appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the beginning of treatment, which patients are likely to develop the syndrome.

Both the risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses. There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic drug treatment is withdrawn. Antipsychotic drug treatment itself, however, may suppress (or partially suppress) the signs and symptoms of tardive dyskinesia and thereby may possibly mask the underlying process. The effect that symptom suppression has upon the long-term course of the syndrome is unknown.

There are several reasons for predicting that CLOZARIL may be different from other antipsychotic drugs in its potential for inducing tardive dyskinesia. These include the preclinical finding that it has a relatively weak dopamine receptor blocking effect and the clinical finding that it is associated with a low incidence of extrapyramidal symptoms. Very rarely tardive dyskinesia has been reported in patients on CLOZARIL who had been previously treated with other antipsychotic agents, so that a causal relationship cannot be established. Nevertheless, it cannot be concluded, without more extended experience, that CLOZARIL will not induce this syndrome.

Given this consideration, CLOZARIL should be prescribed in a manner that is most likely to
minimize the risk of the occurrence of tardive dyskinesia. As with any antipsychotic drug, chronic CLOZARIL use should be reserved for patients who appear to be obtaining substantial benefit from the drug. In such patients, the smallest dose and the shortest duration of treatment should be sought. The need for continued treatment should be reassessed periodically.

Patients in whom tardive dyskinesia developed with other neuroleptics have improved on CLOZARIL.

If signs and symptoms of tardive dyskinesia appear in a patient on CLOZARIL, drug discontinuation should be considered. However, some patients may require treatment with CLOZARIL despite the presence of the syndrome.

**PRECAUTIONS**

Because of the significant risk of agranulocytosis and seizure, events which both present a continuing risk over time, the extended treatment of patients failing to show an acceptable level of clinical response to CLOZARIL (clozapine) should ordinarily be avoided. In addition, the need for continuing treatment in patients exhibiting beneficial clinical responses should be reassessed periodically.

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

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

**Fever**

During CLOZARIL therapy, patients may experience transient temperature elevations above 38º C (100.4º F) with the peak incidence within the first three weeks of treatment. This fever is
generally benign and self-limiting; however, on occasion there may be an associated increase or decrease in the white blood cell count. Patients should be carefully evaluated to rule out the possibility of an underlying infectious process or the development of blood dyscrasia. In the presence of high fever, the possibility of neuroleptic malignant syndrome must be considered (see WARNINGS).

Interference with Cognitive and Motor Performance

Because of the potential for initial sedation, CLOZARIL may impair mental and/or physical abilities especially during the first few days of therapy. The recommendation for gradual dose escalation should be carefully adhered to and patients should be cautioned about activities requiring alertness (e.g., driving, operating machinery, swimming, climbing, etc.). (See DOSAGE AND ADMINISTRATION).

Drug Interactions

CLOZARIL may enhance the central effects of alcohol, MAO inhibitors, CNS depressants including narcotics, antihistamines, and benzodiazepines, as well as the effects of anticholinergic and antihypertensive agents.

Caution is advised with patients who are receiving (or have recently received) benzodiazepines or other psychotropic drugs, as these patients may have an increased risk of circulatory collapse accompanied by respiratory and/or cardiac arrest.

Owing to its anti-α-adrenergic properties, CLOZARIL may reduce the blood pressure increasing effect of norepinephrine or other predominantly α-adrenergic agents and reverse the pressor effect of epinephrine.

CLOZARIL should not be used with other agents, such as carbamazepine, having a known potential to suppress bone marrow function. In particular, the concomitant use of long-acting depot antipsychotic drugs should be avoided because these medications, which may have the
potential to be myelosuppressive, cannot be rapidly removed from the body.

Concomitant use of valproic acid with CLOZARIL may alter the plasma levels of clozapine. Rare but serious reports of seizures, including onset of seizures in non-epileptic patients, and isolated cases of delirium where CLOZARIL 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.

Clozapine is a substrate for many CYP 450 isoenzymes, in particular 1A2 and 3A4. Caution is called for in patients receiving concomitant treatment with other drugs which are either inhibitors or inducers of these enzymes.

**CONCOMITANT ADMINISTRATION OF DRUGS KNOWN TO INHIBIT THE ACTIVITY OF CYTOCHROME P450 ISOZYMES MAY INCREASE THE PLASMA LEVELS OF CLOZAPINE:**

- Drugs known to inhibit the activity of the major isozymes involved in the metabolism of clozapine and with reported interactions include, cimetidine (2D6, 3A4), and erythromycin (3A4). Other potent inhibitors of CYP3A, such as azole antimycotics and protease inhibitors, could potentially also increase clozapine plasma concentrations; however, no interactions have been reported to date.

- Substantial elevation of the plasma concentration of clozapine has been reported in patients receiving the drug in combination with fluvoxamine (1A2). Smaller elevations in clozapine plasma concentrations have also been reported in patients receiving the drug in combination with other selective serotonin re-uptake inhibitors (SSRIs) such as paroxetine, sertraline and fluoxetine.

- The plasma concentration of clozapine is increased by caffeine (1A2) intake and decreased by nearly 50% following a 5-day caffeine-free period.
No clinically relevant interactions have been observed thus far with tricyclic antidepressants, phenothiazines and type Iβ anti-arrhythmics, known to bind to cytochrome P450 2D6.

CONCOMITANT ADMINISTRATION OF DRUGS KNOWN TO INDUCE CYTOCHROME P450 ENZYMES MAY DECREASE THE PLASMA LEVELS OF CLOZAPINE:

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

- Known inducers of 1A2 include, for instance, omeprazole and cigarette smoking. In cases of sudden smoking cessation, the plasma clozapine concentration may be increased, thus leading to an increase in adverse effects. Interactions with omeprazole have not been reported to date.

Anticholinergic Activity

CLOZARIL has potent anticholinergic effects, which may produce undesirable effects throughout the body. Great care should be exercised in using the drug in the presence of prostatic enlargement, narrow-angle glaucoma or paralytic ileus. Probably on account of its anticholinergic properties, CLOZARIL 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.

Deep Vein Thrombosis and Pulmonary Embolism

Deep vein thrombosis has been observed in association with CLOZARIL. Since CLOZARIL may cause sedation and weight gain, thereby increasing the risk of thromboembolism, immobilization of patients should be avoided.

Whether pulmonary embolism can be attributed to CLOZARIL or some characteristic(s) of its
users is not clear. However, the possibility of pulmonary embolism should be considered in patients receiving CLOZARIL who present with deep vein thrombosis, acute dyspnea, chest pain, or other respiratory symptoms.

**Eosinophilia**

In the event of eosinophilia, it is recommended to discontinue CLOZARIL if the eosinophil count rises above $3.0 \times 10^9$/L, and to re-start therapy only after the eosinophil count has fallen below $1.0 \times 10^9$/L.

**Thrombocytopenia**

In the event of thrombocytopenia, it is recommended to discontinue CLOZARIL therapy if the patient falls below $50.0 \times 10^9$/L.

**Hepatitis**

Patients with stable pre-existing liver disorders may receive CLOZARIL, but need regular liver function tests. In patients in whom, during CLOZARIL 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 these values is clinically relevant or if symptoms of jaundice occur, treatment with CLOZARIL must be discontinued. It may be resumed 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.

**Hyperglycemia**

On rare occasions, severe hyperglycemia, sometimes leading to ketoacidosis, has been reported during CLOZARIL treatment in patients with no prior history of hyperglycemia. While a causal relationship to CLOZARIL use has not been definitely established, glucose levels returned to normal in most patients after discontinuation of CLOZARIL, and rechallenge produced a
recurrence of hyperglycemia in a few cases. The effect of CLOZARIL on glucose metabolism in patients with diabetes mellitus has not been studied. The possibility of impaired glucose tolerance should be considered in patients receiving CLOZARIL who develop symptoms of hyperglycemia, such as polydipsia, polyuria, polyphagia or weakness. In patients with significant treatment-emergent hyperglycemia, discontinuation of CLOZARIL should be considered.

**Use in Patients with Concomitant Illness**

Clinical experience with CLOZARIL in patients with concomitant systemic diseases is limited. Nevertheless, caution is advised when using CLOZARIL in patients with hepatic, renal, or cardiac disease. For severe cases, see CONTRAINDICATIONS.

**Use in Pregnancy**

Reproduction studies, performed in rats and rabbits at doses of approximately 2 to 4 times the human dose, have revealed no evidence of impaired fertility or harm to the fetus due to clozapine. However, there has not been any adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response and in view of the desirability of keeping the administration of all drugs to a minimum during pregnancy, CLOZARIL should be used only if the benefits clearly outweigh the risks.

**Nursing Mothers**

Animal studies suggest that clozapine may be excreted in breast milk and have an effect on the nursing infant. Therefore, women receiving CLOZARIL should not breast-feed.

**Pediatric Use**

Safety and efficacy in children below age 16 have not been established.
Use in the Elderly

Orthostatic hypotension can occur with CLOZARIL treatment and there have been rare reports of tachycardia, which may be sustained, in patients taking CLOZARIL. 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 CLOZARIL, such as urinary retention and constipation.

Information to be Provided to the Patient

Physicians are advised to discuss the following issues with patients (and/or their guardians) for whom they prescribe CLOZARIL®:

- Patients who are to receive CLOZARIL® should be warned about the significant risk of developing agranulocytosis, a potentially life-threatening adverse event. They should be informed that regular blood tests are required to monitor for the occurrence of agranulocytosis, and that CLOZARIL® tablets will be made available only through a special program designed to ensure the required blood monitoring. They should also be informed that weekly blood tests will be required for the first 26 weeks of their treatment with CLOZARIL and that, following this initial higher risk period, they could be allowed to change to a "once every two weeks" schedule, provided that their clinical condition is permitting such a change in monitoring regimen. Patients should be advised to report immediately the appearance of lethargy, weakness, fever, sore throat, malaise, mucous membrane ulceration or other possible signs of infection. Particular attention should be paid to any flu-like complaints or other symptoms that might suggest infection.

- Patients should be informed of the significant risk of seizure during CLOZARIL® treatment and should be advised to avoid activities that require alertness (e.g. driving, operating machinery, swimming, climbing, etc.)

- Patients should be advised of the risk of orthostatic hypotension, especially during the period of initial dose titration.

- Patients should be informed that if they stop taking CLOZARIL for 2 days or more, they
should not restart their medication at the same dosage, but should contact their physician for dosage instructions.

- Patients should notify their physician if they are taking, or plan to take, any prescription or over-the-counter drugs or alcohol.
- Patients should notify their physician if they become pregnant or intend to become pregnant during therapy.
- Patients should not breast feed an infant if they are taking CLOZARIL®.

**ADVERSE REACTIONS**

The most serious adverse reactions experienced with CLOZARIL® (clozapine) are agranulocytosis, seizure, cardiovascular effects and fever (see WARNINGS and PRECAUTIONS). The most common side effects are drowsiness, hypersalivation, tachycardia and sedation.

**Central Nervous System**

Initially, drowsiness and sedation may be encountered, especially where relatively large doses of CLOZARIL are given. Generally, this effect tends to subside with continued therapy or dose reduction. CLOZARIL may cause EEG changes, including the occurrence of spike and wave complexes and may lower the seizure threshold and may induce myoclonic jerks or generalized seizures. These symptoms are more likely to occur with rapid dose increase and in patients with pre-existing epilepsy. On rare occasions it may induce episodes of delirium. **Extrapyramidal symptoms** are limited mainly to tremor, akathisia and rigidity and if such effects occur, they tend to be mild and transient.
Autonomic Nervous System

Hypersalivation is a relatively common adverse reaction associated with CLOZARIL therapy which may be profuse, especially during sleep, but may be diminished by dose reduction or the use of peripherally-acting anticholinergic medication. Dry mouth, blurred vision and an increase in body temperature may occur.

Cardiovascular System

Rare cases of thromboembolism have been reported.

Endocrine System

In contrast to conventional antipsychotics, CLOZARIL produces little or no prolactin response in humans. Consequently, prolactin dependent effects such as decreased libido, impotence, galactorrhea and amenorrhea are seldom associated with CLOZARIL therapy. With continued treatment, considerable weight gain has been seen in some patients. Therapeutic doses of CLOZARIL, to date, even on long-term treatment, have not been associated with symptoms of thyroid dysfunction. On rare occasions, severe hyperglycemia, sometimes leading to ketoacidosis, has been reported during CLOZARIL treatment in patients with no prior history of hyperglycemia.

Gastrointestinal

Constipation and nausea have been reported occasionally. Very rarely, ileus has been reported. 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, CLOZARIL should be discontinued (see PRECAUTIONS).

As a rare event, CLOZARIL treatment may be associated with dysphagia, a possible cause of aspiration. There have also been very rare reports of parotid gland enlargement.
In rare cases, acute pancreatitis has been reported.

**Genital**

In a few cases, priapism has been reported. Isolated cases of acute interstitial nephritis have been reported in association with CLOZARIL therapy.

**Hemic/Lymphatic**

Isolated cases of various types of leukemia have been reported in patients treated with CLOZARIL. However, there is no evidence to suggest a causal relationship between the drug and any type of leukemia. The reported occurrence rate is in the range of the background incidence of these diseases in the general population.

Unexplained leucocytosis may occur, especially in the initial weeks of treatment.

Very rarely, CLOZARIL may cause thrombocytopenia.

**Respiratory System**

Rarely, aspiration of ingested food may occur in patients presenting with dysphagia or as a consequence of acute overdosage.

**Musculoskeletal System**

Rarely, increases in CPK values have occurred.
**PERCENT OF PATIENTS REPORTING ADVERSE REACTIONS (≥1%)**
**DURING CLOZARIL THERAPY (N=842)**

<table>
<thead>
<tr>
<th>Organ System/Adverse Reaction</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Central Nervous System:</strong></td>
<td></td>
</tr>
<tr>
<td>Drowsiness</td>
<td>39</td>
</tr>
<tr>
<td>Dizziness</td>
<td>19</td>
</tr>
<tr>
<td>Headache</td>
<td>7</td>
</tr>
<tr>
<td>Tremor</td>
<td>6</td>
</tr>
<tr>
<td>Syncope</td>
<td>6</td>
</tr>
<tr>
<td>Agitation</td>
<td>4</td>
</tr>
<tr>
<td>Restlessness</td>
<td>4</td>
</tr>
<tr>
<td>Hypokinesia</td>
<td>4</td>
</tr>
<tr>
<td>Disturbed Sleep</td>
<td>4</td>
</tr>
<tr>
<td>Seizures</td>
<td>4*</td>
</tr>
<tr>
<td>Akathisia</td>
<td>3</td>
</tr>
<tr>
<td>Confusion</td>
<td>3</td>
</tr>
<tr>
<td>Rigidity</td>
<td>3</td>
</tr>
<tr>
<td>Fatigue</td>
<td>2</td>
</tr>
<tr>
<td>Insomnia</td>
<td>2</td>
</tr>
<tr>
<td>Hyperkinesia</td>
<td>1</td>
</tr>
<tr>
<td>Weakness</td>
<td>1</td>
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<tr>
<td>Lethargy</td>
<td>1</td>
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<tr>
<td><strong>Autonomic Nervous System:</strong></td>
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</tr>
<tr>
<td>Hypersalivation</td>
<td>31</td>
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<tr>
<td>Hyperhidrosis (Sweating)</td>
<td>6</td>
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<tr>
<td>Dry Mouth</td>
<td>6</td>
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<tr>
<td>Visual Disturbance</td>
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<tr>
<td><strong>Cardiovascular:</strong></td>
<td></td>
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<tr>
<td>Tachycardia</td>
<td>25*</td>
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<tr>
<td>Hypotension</td>
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<tr>
<td>Hypertension</td>
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<tr>
<td>Chest Pain (Angina)</td>
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<tr>
<td>ECG Changes</td>
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<tr>
<td><strong>Gastrointestinal:</strong></td>
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<tr>
<td>Constipation</td>
<td>14</td>
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<tr>
<td>Nausea</td>
<td>5</td>
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<tr>
<td>Abdominal Discomfort</td>
<td>4</td>
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<tr>
<td>Nausea/Vomiting</td>
<td>3</td>
</tr>
<tr>
<td>Vomiting</td>
<td>3</td>
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<tr>
<td>Diarrhea</td>
<td>2</td>
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<tr>
<td>Liver Test Abnormality</td>
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<tr>
<td><strong>Urogenital:</strong></td>
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<tr>
<td>Urinary Abnormalities</td>
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<tr>
<td>Urinary Urgency/Frequency</td>
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<tr>
<td>Urinary Incontinence</td>
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<tr>
<td>Urinary Retention</td>
<td>1</td>
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<tr>
<td><strong>Respiratory:</strong></td>
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<tr>
<td>Nasal Congestion</td>
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<tr>
<td>Throat Discomfort</td>
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<tr>
<td><strong>Integumentary (Skin):</strong></td>
<td></td>
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<tr>
<td>Rash</td>
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<tr>
<td><strong>Musculoskeletal:</strong></td>
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<tr>
<td>Muscle Weakness</td>
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<tr>
<td><strong>Hemic/Lymphatic:</strong></td>
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<tr>
<td>Decreased WBC</td>
<td>3</td>
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<tr>
<td>Agranulocytosis</td>
<td>1***</td>
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<tr>
<td>Eosinophilia</td>
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<tr>
<td><strong>Miscellaneous:</strong></td>
<td></td>
</tr>
<tr>
<td>Fever (Pyrexia)</td>
<td>5</td>
</tr>
<tr>
<td>Weight Gain</td>
<td>4**</td>
</tr>
</tbody>
</table>

* Rate based on population of approximately 1700 exposed during the premarket clinical evaluation of CLOZARIL
** Recently published literature suggests that the incidence of weight gain may be higher than 4%.
***Rate based on premarket clinical evaluation of CLOZARIL; postmarket data on population of approximately 60,000 patients exposed, indicate an incidence of 0.7%.
SYMPTOMS AND TREATMENT OF OVERDOSAGE

The signs and symptoms associated with CLOZARIL® (clozapine) overdose are: drowsiness, lethargy, coma, areflexia, confusion, agitation, delirium, hyperreflexia, convulsions, hypersalivation, mydriasis, blurred vision, thermolability, tachycardia, hypotension, collapse, cardiac arrhythmias, heart block, respiratory depression or failure, hallucinations, extrapyramidal symptoms, aspiration pneumonia and dyspnea.

In cases of acute intentional or accidental CLOZARIL overdosage, for which information on the outcome is available, to date the mortality is about 12%. Most of the fatalities were associated with cardiac failure or pneumonia caused by aspiration and occurred at doses above 2,000 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 CLOZARIL, 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 mg to 200 mg resulted in strong sedation or coma without being lethal.

Treatment of Overdosage

Establish and maintain an airway; ensure adequate oxygenation and ventilation. Perform gastric lavage and/or the administration of activated charcoal within the first 6 hours after the ingestion of the drug. Activated charcoal, which may be used with sorbitol, may be as or more effective than emesis or lavage, and should be considered in treating overdosage. Cardiac and vital signs monitoring is recommended along with general symptomatic and supportive measures. Surveillance should be continued for several days because of the risk of delayed effects. Avoid epinephrine when treating hypotension, and quinidine and procainamide when treating cardiac arrhythmia.

There are no specific antidotes for CLOZARIL. Forced diuresis, dialysis, hemoperfusion and exchange transfusion are unlikely to be of benefit.
In managing overdosage, the physician should consider the possibility of multiple drug involvement.

**DOSAGE AND ADMINISTRATION**

CLOZARIL® (clozapine) treatment must be initiated on an in-patient basis or in an out-patient setting where medical supervision is available and vital signs can be monitored for a minimum of 6 to 8 hours after the initial 2 to 3 doses.

When treatment is initiated in out-patients, special caution is advised in patients who are receiving benzodiazepines or other psychotropic drugs as these patients may have an increased risk of circulatory collapse accompanied by respiratory and/or cardiac arrest (see Drug Interactions). Extra caution is advised in patients with cardiovascular disease or a history of seizures (see WARNINGS).

CLOZARIL is restricted to patients who have a normal white blood cell (WBC) count and differential cell (DC) count and in whom a WBC count and DC count can be carried out at least weekly for the first 26 weeks of treatment and at least at two-week intervals thereafter\(^2\). Monitoring must continue for as long as the patient is on the drug, as well as for at least four weeks after discontinuation of treatment.

CLOZARIL is available only through a distribution system that requires weekly or every-two-week hematological testing prior to the delivery of the next period's supply of medication (see INDICATIONS).

\(^2\)The change from a weekly to a "once every two weeks" schedule should be evaluated on an individual patient basis after 26 weeks of treatment. This decision should be made based upon the clinical judgement of the treating physician, and if he/she deems it appropriate, a consulting hematologist, as well as the patient’s willingness to pursue a given frequency of blood monitoring. In turn, the clinical evaluation should take into consideration possible factors that would place the patient in a higher risk group, as well as the hematological profile of the patient during the first 26 weeks of treatment. Weekly hematological testing should be resumed for an additional 6 weeks if therapy is disrupted for more than 3 days. If CLOZARIL is interrupted for 4 weeks or longer, weekly monitoring is required for an additional 26 weeks.
The dosage of CLOZARIL must be adjusted individually. For each patient the lowest effective dose should be used.

**Initial Dose**

On the first day, CLOZARIL should be given at a 12.5 mg dose (one-half of a 25 mg tablet) once or twice, followed by one or two 25 mg tablets on the second day. If well tolerated, the dosage may be increased in daily increments of 25 mg to 50 mg, achieving a target dose of 300-450 mg/day by the end of two weeks. Subsequent dosage increases should be made no more than once or twice weekly, in increments not to exceed 100 mg. Cautious titration and a divided dosage schedule are necessary to minimize the risks of hypotension, seizure and sedation.

**Switching from Previous Neuroleptics**

When CLOZARIL therapy is initiated in a patient undergoing oral neuroleptic therapy, it is generally recommended that the other neuroleptic should first be discontinued by tapering the dosage downwards. Once the neuroleptic is completely discontinued for at least 24 hours, CLOZARIL treatment can be started as described above. It is generally recommended that CLOZARIL should not be used in combination with other neuroleptics.

**Therapeutic Dose Range**

In most patients, antipsychotic efficacy can be expected within the therapeutic range of 300-600 mg/day in divided doses. The total daily dose may be divided unevenly, with the larger portion at bedtime.

Since improvement may be gradual, continued therapeutic response can be expected beyond the first month of treatment.
Maximum Dose

Occasionally, patients may require doses higher than 600 mg/day to obtain an acceptable therapeutic response. Because of the possibility of increased adverse reactions (particularly seizures) at daily doses of 600 mg and higher, the decision to treat in the range of 600-900 mg/day must be taken prudently. Patients must be given adequate time to respond to a given dose level before escalation to a higher dose is contemplated. **THE MAXIMUM DOSE OF 900 MG/DAY SHOULD NOT BE EXCEEDED.**

Maintenance Dose

After achieving maximum therapeutic benefit, many patients can be maintained effectively at lower doses. Careful downward titration is recommended to the level of 150-300 mg/day in divided doses. At daily doses not exceeding 200 mg, a single administration in the evening may be appropriate.

Discontinuation of Therapy

In the event of planned termination of CLOZARIL therapy, gradual reduction in dose is recommended over a 1 to 2 week period. However, should a patient's medical condition require abrupt discontinuation (e.g. severe leukopenia), the patient should be carefully observed for the recurrence of psychotic symptoms and symptoms related to cholinergic rebound such as headache, nausea, vomiting and diarrhoea.

Re-Initiation of Treatment in Patients Previously Discontinued

When restarting patients who have had even a brief interval off CLOZARIL, i.e. two days or more since the last dose, it is recommended that treatment be re-initiated with 12.5 mg (one half of a 25 mg tablet) once or twice on the first day. (see DOSAGE AND ADMINISTRATION for hematological testing conditions). If that dose is well tolerated, it may be feasible to titrate patients back to a therapeutic dose more quickly than is recommended for initial treatment.
Certain additional precautions seem prudent when re-initiating treatment. The mechanisms underlying some of the CLOZARIL-induced adverse reactions are unknown. It is conceivable that re-exposure of a patient might enhance the risk of an untoward event's occurrence and increase its severity. Such phenomena, for example, occur when immune mediated mechanisms are responsible. Therefore, 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, should be re-titrated with extreme caution after even 24 hours of discontinuation.

CLOZARIL THERAPY MUST NOT BE RESUMED IN PATIENTS WHO HAVE BEEN DISCONTINUED FROM TREATMENT DUE TO NEUTROPENIA (ANC<1.5 X 10^9/L) OR SEVERE LEUKOPENIA (WBC <2.0 X 10^9/L).

**PHARMACEUTICAL INFORMATION**

Drug Substance

**Proper Name:** Clozapine

**Chemical Name:** 8-Chloro-11-(4-methyl-1-piperazinyl)-5H-dibenzo[b,e][1,4]-diazepine

![Structural Formula: Clozapine](image)

**Molecular Weight:** 326.83
**Description:** Clozapine is a yellow, crystalline powder with a melting range of 182.0º -186.0º C. The values for pKa (I) and pKa (II) are 3.69 and 7.57 respectively. At 25º C, the solubility of clozapine is <0.01% in water and >20% in chloroform.

**Composition**

Each 25 mg and 100 mg tablet contains 25 mg and 100 mg of clozapine respectively, and the inactive ingredients colloidal silicon dioxide, lactose, magnesium stearate, povidone, starch and talc.

**Stability and Storage Recommendation**

Store below 30º C.

**AVAILABILITY OF DOSAGE FORMS**

**P**r**CLOZARIL**® Tablets 25 mg - Each round, pale yellow, uncoated, easy-to-break, scored tablet, embossed "CLOZARIL" on one side and "25 mg" on the other, contains clozapine 25 mg. Bottles of 100.

**P**r**CLOZARIL** Tablets 100 mg - Each round, pale yellow, uncoated, easy-to-break, scored tablet embossed "CLOZARIL" on one side and "100 mg" on the other, contains clozapine 100 mg. Bottles of 100.

CLOZARIL is available only through a distribution system that requires weekly or every-two-week hematological testing prior to the delivery of the next period's supply of medication (see INDICATIONS).
WHAT IS CLOZARIL® AND WHAT IS IT USED FOR?

CLOZARIL® is a drug for the treatment of symptoms of schizophrenia in patients who do not respond to, or who experience serious side-effects with other drugs used for the same purpose.

CLOZARIL® can only be taken if prescribed by a doctor.

WHAT SHOULD BE BORNE IN MIND ABOUT CLOZARIL®? WHY IS THE TESTING OF YOUR BLOOD BY YOUR DOCTOR NECESSARY?

In rare instances (approximately 0.7% of cases), CLOZARIL® can cause a suppression of white blood cells, necessary to help the body fight infection. Because this condition is potentially life-threatening, it is important to have regular blood testing done. To ensure that the required blood tests are performed, CLOZARIL is only available through a special program.

Blood testing must be done weekly during the first 26 weeks of treatment with CLOZARIL, because the risk for developing a deficiency of white blood cells is highest during this initial period. Thereafter, your doctor will evaluate with you the possibility of limiting blood checks to two-week intervals, depending on your health condition. Regular blood testing must be done for as long as you are taking CLOZARIL®.

In addition, you should consult your doctor immediately at the first signs of a cold, influenza, fever, sore throat, or any other signs of infection, as well as weakness or a general feeling of unwellness. The doctor may check your blood cell count and take further measures if necessary.
WHEN SHOULD CLOZARIL® NOT BE USED?

You should not take CLOZARIL® if you already have too few white blood cells, or if you have ever had a disease affecting blood cell formation. CLOZARIL® should not be taken with other drugs known to affect blood cell formation. The same restrictions apply if you are suffering from severe liver, kidney, or heart disease, or uncontrolled epilepsy, or have ever had a bad, unusual or allergic reaction to CLOZARIL, or any of its components.

WHEN TAKING CLOZARIL®, WHAT PARTICULAR PRECAUTIONS ARE RECOMMENDED?

It is essential to inform your doctor if you suffer from enlargement of the prostate, history of seizures, glaucoma (a condition in which the pressure of fluid in the eye is generally too high), allergy, or any other serious medical condition.

Due to the risk of convulsions during CLOZARIL® treatment, you should avoid activities where a sudden loss of consciousness could cause risk to yourself or others (e.g. driving, using machines, swimming, climbing).

Tell your doctor or pharmacist what your coffee intake is and if you smoke. Abrupt changes in your habits may change the effect of CLOZARIL.

CLOZARIL® may intensify the effects of alcohol, sleeping pills, tranquilizers and anti-allergy drugs. You should inform your doctor before taking any other medications (including the ones you may buy without a doctor's prescription).

Other medicines which may change the way CLOZARIL works include, for instance, certain antibiotics, medicines used to treat depression, convulsions or ulcers of the stomach and certain drugs effective against fungal or viral infections.

CLOZARIL® may lower your blood pressure, especially at the start of treatment. This may result in light-headedness or fainting.
SHOULD CLOZARIL® BE TAKEN DURING PREGNANCY OR BREAST-FEEDING?

CLOZARIL® should only be taken during pregnancy if your doctor specifically prescribes it. Therefore, you should consult your doctor if you are or intend to become pregnant.

As CLOZARIL® can pass into breast milk, mothers receiving CLOZARIL® should not breast-feed.

HOW SHOULD CLOZARIL® BE TAKEN?

The dosage in each individual case is decided by the doctor according to the severity of the disease.

For the treatment to be successful, you must follow exactly your doctor's dosage instructions, and under no circumstances should you take more or less than the prescribed dose. If you think the dosage is too weak or too strong, you should discuss this matter with your doctor.

If you miss a dose of CLOZARIL®, and remember within two hours, take the dose right away. Otherwise, skip the missed dose and continue with your regular dosing schedule. Do not take double doses. If you have stopped taking CLOZARIL® for more than two days, do not re-start taking the drug, but contact your doctor for dosing instructions.

WHAT ARE THE POSSIBLE SIDE EFFECTS OF CLOZARIL®?

The most serious side effects of CLOZARIL® are a possible fall in the white blood cell count, leading to an increased risk of infection, convulsions, fall in blood pressure, and fever.

The most frequent side effects are drowsiness, dizziness, increased or decreased production of saliva and rapid heartbeat. If you experience fast and irregular heart beat that persists when you are at rest, possibly accompanied by shortness of breath and swelling of the feet or legs, consult your doctor immediately.
Other side effects include: constipation, headache, tremor, fainting, sweating, weight gain, problems in passing or retaining urine, and abnormal movement behaviour. Check with your doctor if constipation gets worse. In rare cases, CLOZARIL may cause confusion, restlessness, difficulties in swallowing or impairment of heart function. These side effects are not generally persistent.

Excessive thirst, dry mouth and passing large amounts of urine may be signs of high sugar levels in the blood. If you experience any of these, tell your doctor as soon as possible.

**WHAT ELSE SHOULD BE BORNE IN MIND?**

Like all medicines, CLOZARIL® should be kept out of the reach of children.

Further information can be obtained from your doctor or pharmacist.

**WHAT DOES CLOZARIL® CONTAIN?**

The active ingredient of CLOZARIL® is clozapine.

**PHARMACOLOGY**

CLOZARIL® (clozapine) is distinguished from classical neuroleptics by its failure to induce the characteristic effects of dopamine (DA) receptor blockade, e.g. antagonism of apomorphine- or amphetamine-induced stereotyped behaviour, catalepsy, and DA receptor supersensitivity following repeated administration.

Clozapine inhibits conditioned avoidance response albeit at doses somewhat higher than those which attenuate locomotor activity. Clozapine induces hypothermia and exerts potent antiaggressive activity against isolation - induced fighting behaviour.

Clozapine has potent anticholinergic activity as shown in *in vivo* (oxotremorine-induced tremors),
Clozapine has potent antihistaminic activity as shown in \textit{in vivo} (histamine - induced bronchoconstriction) and \textit{in vitro} (isolated ileum - histamine-induced contractions) studies.

Clozapine has potent antiserotoninergic activity as shown in \textit{in vivo} (5-HTP-induced behaviours) and \textit{in vitro} (isolated uterus - 5-HT-induced contractions) studies.

Clozapine binds to several types of receptors, especially serotoninergic (S₂), α₁-adrenergic, and histaminergic (H₁) receptors. It has weak dopamine receptor blocking activity at D₁, D₂, D₃ and D₅, but shows high potency for the D₄ receptor.

Most neuroleptics increase dopamine (DA) turnover in the nigrostriatum to the same or greater extent than occurs in the mesolimbic system. Clozapine is atypical, in that it produces higher DA turnover in the mesolimbic than in the nigrostriatal system. Since dopamine receptor blockade in the corpus striatum is considered to be responsible for extrapyramidal symptoms observed in patients, this differential effect of clozapine may account for the low profile of extrapyramidal side effects exhibited by the drug.
SELECTED BIBLIOGRAPHY

PRECLINICAL


CLINICAL


54. Small JG, Milstein V, Marhenke JD et al. Treatment outcome with clozapine in tardive


