

PRODUCT MONOGRAPH

Prpms-CLOZAPINE

(Clozapine Tablets)

25 mg and 100 mg

Antipsychotic Agent

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PRODUCT MONOGRAPH

Pr pms-CLOZAPINE

(Clozapine)

THERAPEUTIC CLASSIFICATION

Antipsychotic Agent

ACTION AND CLINICAL PHARMACOLOGY

pms-CLOZAPINE (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, clozapine produces little or no prolactin elevation. Clozapine exerts potent anticholinergic, adrenolytic, antihistaminic and antiserotonergic activity.

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

Patients on rare occasions may report an intensification of dream activity during clozapine 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 clozapine 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_{\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

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

Due to the significant risk of agranulocytosis and seizure associated with its use, clozapine 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 clozapine should ordinarily be avoided. In addition, the need for continuing treatment in patients exhibiting beneficial clinical responses should be periodically reevaluated.

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

pms-CLOZAPINE is available only through a distribution system (CSAN) that ensures weekly or every-two-week haematological testing prior to the dispensing of the next period's supply of pms-CLOZAPINE (see WARNINGS).

This requires:

- registration of the patient, their current location, treating physician, testing laboratory and dispensing pharmacist in the CSAN system.
- maintenance of a national PHARMASCIENCE-specific database that enables the monitoring of the haematological results of all patients on pms-CLOZAPINE and

provides timely feedback (within 24 hours of receipt of the blood test results) to the treating physician and dispensing pharmacist/or pharmacy.

- the ability to identify patients who have been assigned “Non-rechallengeable Status” (see WARNINGS). This requires that PHARMASCIENCE both provides to, and obtains from, all other approved suppliers* of clozapine, the Non-rechallengeable Status/Hematological Status of all patients (see DOSAGE AND ADMINISTRATION). The PHARMASCIENCE system must be able to provide this information within 24 hours of receiving a written request.

* :“approved supplier” is a manufacturer who holds a valid Notice of Compliance (NOC) for clozapine

Physicians should not prescribe pms-CLOZAPINE until the non-rechallengeable status and the hematological status of the patient has been verified.

For the distribution system to be effective, treating physicians must ensure that the hematological testing is performed at the required frequency (see WARNINGS) and that arrangements are made for the hematological results to be sent to CSAN.

Physicians may obtain details on the CSAN distribution system by calling a toll-free phone number (1-800-267-2726).

Other monitoring and distribution systems

Between 1991 and 2003, clozapine was distributed by a single manufacturer, and patients were monitored by this manufacturer’s specific registry and distribution system. The introduction of clozapine from other manufactures has now resulted in the establishment of manufacturer-specific registry and distribution systems.

In order to ensure the safe use and continued monitoring of all patients taking clozapine, the physician must have obtained consent from the patient for the potential sharing of hematological and other safety data between clozapine registries.

Patients may not be switched from one brand of clozapine to another without the completion of a new registry-specific patient registration form signed by the prescribing physician.

If a patient is switched from one brand of clozapine to another, the frequency of hematological monitoring may continue unaltered unless a change is clinically indicated.

CONTRAINDICATIONS

pms-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). [Clozapine should not be used simultaneously with other agents known to suppress bone marrow function.]

pms-CLOZAPINE 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 (e.g. myocarditis), uncontrolled epilepsy, and previous hypersensitivity to clozapine or any other components of pms-CLOZAPINE.

WARNINGS

AGRANULOCYTOSIS

BECAUSE OF THE SIGNIFICANT RISK OF GRANULOCYTOPENIA AND AGRANULOCYTOSIS, A POTENTIALLY LIFE-THREATENING ADVERSE EVENT (SEE BELOW), PMS-CLOZAPINE (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 CLOZAPINE THERAPY. SUBSEQUENTLY, A WBC COUNT AND DIFFERENTIAL COUNT MUST BE CARRIED OUT AT LEAST WEEKLY FOR THE FIRST 26 WEEKS OF TREATMENT WITH CLOZAPINE AND AT LEAST AT TWO-WEEK INTERVALS THEREAFTER¹. MONITORING MUST CONTINUE FOR AS LONG AS THE PATIENT IS ON THE DRUG. FURTHERMORE, MONITORING SHOULD OCCUR AT LEAST WEEKLY FOR A PERIOD OF 4 WEEKS FOLLOWING DISCONTINUATION OF CLOZAPINE THERAPY, IRRESPECTIVE OF THE CAUSE OF DISCONTINUATION.

pms-CLOZAPINE IS AVAILABLE ONLY THROUGH A DISTRIBUTION SYSTEM (CSAN) THAT REQUIRES WEEKLY OR EVERY-TWO-WEEK HAEMATOLOGICAL TESTING PRIOR TO THE DISPENSING OF THE NEXT PERIOD'S SUPPLY OF PMS-CLOZAPINE (SEE INDICATIONS).

¹THE 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 HAEMATOLOGIST, 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 HAEMATOLOGICAL PROFILE OF THE PATIENT DURING THE FIRST 26 WEEKS OF TREATMENT.

Granulocytopenia (defined as a granulocyte count of less than $1.5 \times 10^9/L$) and agranulocytosis (defined as a granulocyte count of less than $0.5 \times 10^9/L$, including polys + bands) have been estimated to occur in association with clozapine 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 clozapine 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 clozapine 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 clozapine-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.

All patients must be screened to ensure that they do not have a history of neutropenia/agranulocytosis associated with clozapine use (i.e., are not in the Non-rechallengeable databases of any of the currently approved suppliers of clozapine).

pms-CLOZAPINE treatment should be initiated and carried out according to the following guidelines:

- Treatment should not be initiated if the WBC count is less than $3.5 \times 10^9/L$ and/or the absolute neutrophil count (ANC) is less than $2.0 \times 10^9/L$, 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 the frequency 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 $2.0 \times 10^9/L$ and $3.5 \times 10^9/L$,
 - ii) the ANC falls to between $1.5 \times 10^9/L$ and $2.0 \times 10^9/L$,
 - iii) a single fall or sum of falls in WBC count of $3.0 \times 10^9/L$ or more is measured in the last four weeks, reaching a value below $4.0 \times 10^9/L$,
 - iv) a single fall or sum of falls in ANC of $1.5 \times 10^9/L$ or more is measured in the last four weeks, reaching a value below $2.5 \times 10^9/L$,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 $2.0 \times 10^9/L$ or in ANC to below $1.5 \times 10^9/L$, pms-CLOZAPINE therapy must be immediately withheld and the patient closely monitored.

THE PATIENT IS TO BE ASSIGNED “NON-RECHALLENGEABLE” STATUS UPON CONFIRMATION OF FALL IN WBC AND NEUTROPHIL COUNTS. pms-CLOZAPINE 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 $1.0 \times 10^9/L$, or a decrease in ANC to below $0.5 \times 10^9/L$, 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 clozapine 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 clozapine.

Patients who have shown hematopoietic reactions to other medications may also be more likely to demonstrate such reactions with clozapine. 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.

CARDIOTOXICITY

**IMPORTANT SAFETY INFORMATION REGARDING A CONSTELLATION OF CARDIOVASCULAR EVENTS
REPORTED IN PATIENTS TREATED WITH CLOZAPINE⁶⁰:**

CARDIOVASCULAR TOXICITY:

Analysis of safety databases suggests that the use of clozapine is associated with an increased risk of myocarditis especially during, but not limited to, the first month of therapy. Myocarditis has been reported in patients 19 years of age and older, at dosages within the approved dosage range and during titration of clozapine. In Canada, there have been 9 reported cases of myocarditis. Of these, three have been fatal. Given the estimated 15,600 Canadian clozapine-treated patients as of August 2001, this represents an estimated incidence of 0.06% for all reports of myocarditis (or 1/1667 patients) and 0.02% for myocarditis fatalities (or 1/5200).

Pericarditis, pericardial effusion and cardiomyopathy have also been reported in association with clozapine use, as have heart failure, myocardial infarction and mitral insufficiency; these reports include fatalities.

In patients who develop persistent tachycardia at rest accompanied by other signs and symptoms of heart failure (e.g. chest pain, tachypnoea (shortness of breath), or arrhythmias), the possibility of myocarditis, cardiomyopathy and/or other cardiovascular dysfunction must be considered. Other symptoms which may be present in addition to the above include fatigue, flu-like symptoms, fever that is otherwise unexplained, hypotension and/or raised jugular venous pressure.

The occurrence of such signs and symptoms necessitates an urgent diagnostic evaluation for myocarditis, cardiomyopathy and/or other cardiovascular dysfunction by a cardiologist. Patients with a family history of heart failure should have a cardiac evaluation prior to commencing treatment; clozapine is contraindicated in patients with severe cardiac disease.

In patients in whom myocarditis is suspected, clozapine treatment should be promptly discontinued. Patients with clozapine-induced myocarditis should not be re-exposed to clozapine.

If cardiomyopathy and/or other cardiovascular dysfunction is diagnosed, discontinuation of clozapine, based on clinical grounds, should be considered.

BACKGROUND INFORMATION FOR CARDIOTOXICITY BOXED WARNING (AS OF EARLY 2002):

A. Myocarditis, pericarditis and pericardial effusion

Canadian Reports

In Canada, a total of 16 post-marketing surveillance spontaneous reports of myocarditis/pericarditis/pericardial effusion have been received by Health Canada since marketing in 1991 (see also boxed warning regarding myocarditis cases). Information additional to the Boxed Warning: the age range was 19-37 years; the shortest known clozapine treatment duration was 2 weeks.

International Reports

Reporting incidences for myocarditis can be reliably calculated from the four countries with pms-CLOZAPINE national registries (USA, United Kingdom, Canada, Australia). The lowest rate is reported in the U.S. (1/20 000 person years) and the highest in Australia (1/800 person years). Of these 81 cases, 37% were fatal, with 80% of fatal cases showing evidence of myocarditis at autopsy. When all international reports of myocarditis are included (n = 213 cases), the myocarditis rate is 1/14000 patient years; 23% of cases had a fatal outcome and 85% occurred within the first two months of initiation of clozapine therapy. Recurrences of myocarditis upon rechallenge with clozapine have been documented.

Another analysis of clozapine and myocarditis revealed that 70% of patients were under 50 years of age; thus, clozapine-associated myocarditis can occur in younger patients. Dosages were mostly in accordance with current labelled dosage recommendations, with a third of patients taking less than therapeutic doses; this likely reflects the occurrence of myocarditis during dose titration.

There are also reports of pericarditis/pericardial effusion, some of which have been fatal. Eosinophilia has been co-reported in some cases, which may indicate that the carditis is a hypersensitivity reaction to clozapine; however, it is not known whether eosinophilia is a reliable predictor of carditis.

B. Cardiomyopathy/heart failure/mitral insufficiency

Canadian Reports

In Canada, seven cases of cardiomyopathy and 3 cases of heart failure/mitral insufficiency have been reported to Health Canada, with individual cases reported to have concomitant myo/endo carditis. The age range is 19-55 years; Two of the reports of heart failure are known to have been fatal (61y male, 46y male).

International Reports

A total of 178 cardiomyopathy reports (18% fatal), have been received by Novartis. Analysis of the reports revealed that four times as many men as women were diagnosed with cardiomyopathy. About 80% of the cases occurred in patients under the age of 50; the incidence rate of spontaneous reports of cardiomyopathy for this age range was greater in clozapine-treated patients than in the general population in established international market economies.

Diagnosis was confirmed (by echocardiography or autopsy) in 44% of the cases. Typically, the clozapine dose was within therapeutic range, with the duration of treatment more than 6 months in 65% of the patients. There was no other apparent cause of the cardiomyopathy in about 50% of all reported cases of cardiomyopathy and in 28% of fatalities (including history, concomitant medications, comorbidities), with an average age of approximately 37 years. Terms most commonly co-reported with cardiomyopathy were: congestive heart failure (21%), heart rate and rhythm disorders (10%), cardiomegaly (8%). In the 4 cases where follow-up was reported after withdrawal of clozapine, there was improvement of the cardiomyopathy.

C. Myocardial infarction

In Canada, 30 reports of myocardial infarction in patients receiving clozapine have been received by Health Canada with 50% of cases known to be fatal.

Other Adverse Cardiovascular and Respiratory Effects

pms-CLOZAPINE should be used with caution in patients with known cardiovascular and/or pulmonary disease, particularly in those with cardiac arrhythmias and conduction disturbances and the recommendation for gradual titration of dose should be carefully observed.

Orthostatic hypotension, with or without syncope, can occur with pms-CLOZAPINE 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 dose. In one report, initial doses as low as 12.5 mg were associated with collapse and respiratory arrest. When restarting patients who have had even a brief interval off pms-CLOZAPINE, i.e. two days or more since the last dose, it is recommended that treatment be re-initiated with one-half of a 25 mg tablet (12.5 mg) once or twice daily (See DOSAGE AND ADMINISTRATION).

Cases of collapse/ respiratory arrest/ cardiac arrest during initial clozapine treatment occurred in patients administered clozapine by itself and in patients administered clozapine in combination with benzodiazepines or other psychotropic drugs. Although it has not been established that there is an interaction between pms-CLOZAPINE and benzodiazepines or other psychotropics, caution is advised when clozapine is initiated in patients taking a benzodiazepine or any other psychotropic drug.

Tachycardia, which may be sustained, has been observed in approximately 25% of patients taking pms-CLOZAPINE 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 pms-CLOZAPINE 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 pms-CLOZAPINE-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. The clinical significance of these changes is unclear. However, in clinical trials with clozapine, several patients experienced significant cardiac events, including ischemic changes, myocardial infarction, arrhythmias and sudden death. In addition, there have been post-marketing reports of congestive heart failure. 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.

SEIZURES

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

Seizures have been estimated to occur in association with pms-CLOZAPINE 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 pms-CLOZAPINE 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 pms-CLOZAPINE 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.)

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 clozapine, 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 pms-CLOZAPINE 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 clozapine 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 pms-CLOZAPINE will not induce this syndrome.

Given this consideration, pms-CLOZAPINE 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 pms-CLOZAPINE 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 clozapine.

If signs and symptoms of tardive dyskinesia appear in a patient on pms-CLOZAPINE, drug discontinuation should be considered. However, some patients may require treatment with pms-CLOZAPINE 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 pms-CLOZAPINE (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 pms-CLOZAPINE.

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

FEVER

During pms-CLOZAPINE therapy, patients may experience transient temperature elevations above 38°C (100.4°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). Fever that is otherwise unexplained can accompany myocarditis (see WARNINGS).

INTERFERENCE WITH COGNITIVE AND MOTOR PERFORMANCE

Because of the potential for initial sedation, pms-CLOZAPINE 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

pms-CLOZAPINE 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, pms-CLOZAPINE may reduce the blood pressure increasing effect of noradrenaline or other predominantly α -adrenergic agents and reverse the pressor effect of epinephrine.

pms-CLOZAPINE 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 pms-CLOZAPINE 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 pms-CLOZAPINE was co-administered with valproic acid have been reported. These effects are possibly due to a pharmacodynamic interaction, the mechanism of which has not been determined.

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 I_c 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

pms-CLOZAPINE 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, pms-CLOZAPINE has been associated with varying degrees of impairment of intestinal peristalsis, ranging from constipation to intestinal obstruction, faecal impaction and paralytic ileus. On rare occasions, these cases have been fatal.

Deep Vein Thrombosis and Pulmonary Embolism

Deep vein thrombosis has been observed in association with pms-CLOZAPINE. Since pms-CLOZAPINE 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 pms-CLOZAPINE or some characteristic(s) of its users is not clear. However, the possibility of pulmonary embolism should be considered in patients receiving pms-CLOZAPINE 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 pms-CLOZAPINE 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 $1.0 \times 10^9/L$. Eosinophilia has been co-reported in some cases of myocarditis and thus such cardiovascular adverse events associated with clozapine use may represent hypersensitivity reactions to clozapine.

Patients with both eosinophilia and clozapine-induced myocarditis should not be re-exposed to clozapine.

Thrombocytopenia

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

Hepatitis

Patients with stable pre-existing liver disorders may receive pms-CLOZAPINE, but need regular liver function test. In patients in whom, during pms-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 these values is clinically relevant or if symptoms of jaundice occur, treatment with pms-CLOZAPINE 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/hyperosmolar coma, has been reported during pms-CLOZAPINE treatment in patients with no prior history of hyperglycemia. While a causal relationship to clozapine use has not been definitely established, glucose levels returned to normal in most patients after discontinuation of pms-CLOZAPINE, and rechallenge produced a recurrence of hyperglycemia in a few cases. The effect of clozapine on glucose metabolism in patients with diabetes mellitus has not been studied. The possibility of impaired glucose tolerance should be considered in patients receiving clozapine who develop symptoms of hyperglycemia, such as polydipsia, polyuria, polyphagia or weakness. In patients with significant treatment-emergent hyperglycemia, discontinuation of clozapine should be considered.

Use in Patients with Concomitant Illness

Clinical experience with pms-CLOZAPINE in patients with concomitant systemic diseases is limited. Nevertheless, caution is advised when using pms-CLOZAPINE 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, pms-CLOZAPINE 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 pms-CLOZAPINE should not breast-feed.

Pediatric Use

Safety and efficacy in children below age 18 have not been established.

Use in the Elderly

Orthostatic hypotension can occur with pms-CLOZAPINE treatment and there have been rare reports of tachycardia, which may be sustained, in patients taking clozapine. 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 pms-CLOZAPINE 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 pms-CLOZAPINE:

- Patients who are to receive pms-CLOZAPINE 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 pms-CLOZAPINE 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 clozapine 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 advised to contact their physician immediately if they develop persistent tachycardia (rapid heart rate) at rest accompanied by other signs and symptoms of heart failure (e.g. chest pain, shortness of breath, swelling of the ankles and feet, or arrhythmias (abnormal heart rhythms). Other symptoms which may be present in addition to the above include fatigue, flu-like symptoms, fever that is otherwise unexplained, hypotension (low blood pressure) and/or raised jugular venous pressure (bulging neck veins when sitting or standing). Patients are advised to contact their physician before discontinuing any medication.
- Patients should be informed of the significant risk of seizure during pms-CLOZAPINE 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 pms-CLOZAPINE 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 pms-CLOZAPINE.

ADVERSE REACTIONS

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

Adverse Reactions Associated with Discontinuation of Treatment

Sixteen percent of 1080 patients who received clozapine in premarketing clinical trials discontinued treatment due to an adverse event, including both those that could be reasonably attributed to clozapine-treatment and those that might more appropriately be considered intercurrent illness. The more common events considered to be causes of discontinuation included: CNS, primarily drowsiness/sedation, seizures, dizziness/syncope; cardiovascular, primarily tachycardia, hypotension and ECG changes; gastrointestinal, primarily nausea/vomiting; hematologic, primarily leukopenia/granulocytopenia/ agranulocytosis; and fever. None of the events enumerated accounts for more than 1.7% of all discontinuations attributed to adverse clinical events.

Commonly Observed Adverse Reactions

Adverse events observed in association with the use of clozapine in clinical trials at an incidence of greater than 5% were: central nervous system complaints, including drowsiness/sedation,

dizziness/vertigo, headache and tremor; autonomic nervous system complaints, including salivation, sweating, dry mouth and visual disturbances; cardiovascular findings, including tachycardia, hypotension and syncope; and gastrointestinal complaints, including constipation and nausea; and fever. Complaints of drowsiness/sedation tend to subside with continued therapy or dose reduction. Salivation may be profuse, especially during sleep, but may be diminished with dose reduction.

Incidence in Clinical Trials

The following table enumerates adverse events that occurred at a frequency of 1% or greater among (clozapine) patients who participated in clinical trials. These rates are not adjusted for duration of exposure.

**Treatment-Emergent Adverse Experience Incidence
Among Patients Taking clozapine in Clinical Trials
(N = 842)
(Percentage of Patients Reporting)**

Body System Adverse Event^a	Percent
Central Nervous System	
Drowsiness/Sedation	39
Dizziness/Vertigo	19
Headache	7
Tremor	6
Syncope	6
Disturbed sleep/Nightmares	4
Restlessness	4
Hypokinesia/Akinesia	4
Agitation	4
Seizures (convulsions)	3 ^b
Rigidity	3
Akathisia	3
Confusion	3
Fatigue	2
Insomnia	2
Hyperkinesia	1

Weakness	1	
Lethargy	1	
Ataxia	1	
Slurred speech	1	
Depression	1	
Epileptiform movements/Myoclonic jerks	1	
Anxiety	1	
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Cardiovascular		
Tachycardia	25 ^b	
Hypotension	9	
Hypertension	4	
Chest pain/Angina	1	
ECG change/Cardiac abnormality	1	
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Gastrointestinal		
Constipation	14	
Nausea	5	
Abdominal discomfort/Heartburn	4	
Nausea/Vomiting		3
Vomiting	3	
Diarrhea	2	
Liver test abnormality	1	
Anorexia	1	
<hr/>		
Urogenital		
Urinary abnormalities	2	
Incontinence	1	
Abnormal ejaculation	1	
Urinary urgency/frequency	1	
Urinary retention	1	
<hr/>		
Autonomic Nervous System		
Salivation	31	
Sweating	6	
Dry mouth	6	
Visual disturbances	5	
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Integumentary (Skin)

Rash	2
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Musculoskeletal

Muscle weakness	1
Pain (back, neck, legs)	1
Muscle spasm	1
Muscle pain, ache	1

Respiratory

Throat discomfort	1
Dyspnea, shortness of breath	1
Nasal congestion	1

Hemic/Lymphatic

Leukopenia/Decreased WBC/Neutropenia	3
Agranulocytosis	1 ^b
Eosinophilia	1

Miscellaneous

Fever	5
Weight gain	4
Tongue numb/sore	1

^aEvents reported by at least 1% of clozapine patients are included.

^bRate based on population of approximately 1700 exposed during premarket clinical evaluation of clozapine.

Other Events Observed During the Premarketing Evaluation of pms-CLOZAPINE (clozapine)

This section reports additional, less frequent adverse events which occurred among the patients taking clozapine in clinical trials. Various adverse events were reported as part of the total experience in these clinical studies; a causal relationship to clozapine treatment cannot be determined in the absence of appropriate controls in some of the studies. The table above enumerates adverse events that occurred at a frequency of at least 1% of patients treated with clozapine. The list below includes all additional adverse experiences reported as being temporally associated with the use of the drug which occurred at a frequency less than 1%, enumerated by organ system.

Central Nervous System: loss of speech, amentia, tics, poor coordination, delusions/hallucinations, involuntary movement, stuttering, dysarthria, amnesia/memory loss, histrionic movements, libido increase or decrease, paranoia, shakiness, Parkinsonism, and irritability.

Cardiovascular System: edema, palpitations, phlebitis/thrombophlebitis, cyanosis, premature ventricular contraction, bradycardia, and nose bleed; ischemic changes, arrhythmias, myocardial infarction, and sudden death.

Gastrointestinal System: abdominal distention, gastroenteritis, rectal bleeding, nervous stomach, abnormal stools, hematemesis, gastric ulcer, bitter taste, and eructation.

Urogenital System: dysmenorrhea, impotence, breast pain/discomfort, and vaginal itch/infection.

Autonomic Nervous System: numbness, polydipsia, hot flashes, dry throat, and mydriasis.

Integumentary (Skin): pruritus, pallor, eczema, erythema, bruise, dermatitis, petechiae, and urticaria.

Musculoskeletal System: twitching and joint pain.

Respiratory System: coughing, pneumonia/pneumonia-like symptoms, rhinorrhea, hyperventilation, wheezing, bronchitis, laryngitis, and sneezing.

Hemic and Lymphatic System: anemia and leukocytosis.

Miscellaneous: chills/chills with fever, malaise, appetite increase, ear disorder, hypothermia, eyelid disorder, bloodshot eyes, and nystagmus.

Postmarketing Clinical Experience

Postmarketing experience has shown an adverse experience profile similar to that presented above. Voluntary reports of adverse events temporally associated with clozapine not mentioned above that have been received since market introduction and that may have no causal relationship with the drug include the following:

Central Nervous System: delirium; EEG abnormal; exacerbation of psychosis; myoclonus; overdose; paresthesia; possible mild cataplexy; and status epilepticus.

Cardiovascular System: analysis of safety databases suggests that the use of clozapine is associated with an increased risk of myocarditis especially during, but not limited to, the first month of therapy (see **WARNINGS**); atrial or ventricular fibrillation, periorbital edema, pericarditis, pericardial effusion, cardiomyopathy, heart failure, mitral insufficiency and myocardial infarction.

Gastrointestinal System: acute pancreatitis; dysphagia; fecal impaction; intestinal obstruction/paralytic ileus; and salivary gland swelling.

Hepatobiliary System: cholestasis; hepatitis; jaundice.

Hepatic System: cholestasis.

Urogenital System: acute interstitial nephritis and priapism.

Integumentary (Skin): hypersensitivity reactions: photosensitivity, vasculitis, erythema multiforme, and Stevens-Johnson Syndrome.

Metabolic and Nutritional Disorders: hyperglycemia, ketoacidosis/ hyperosmolar coma, hyperuricemia, hyponatremia, and weight loss.

Musculoskeletal System: myasthenic syndrome and rhabdomyolysis.

Respiratory System: aspiration, pleural effusion and respiratory arrest

Hemic and Lymphatic System: deep vein thrombosis; elevated hemoglobin/hematocrit; ESR increased; pulmonary embolism; sepsis; thrombocytosis; and thrombocytopenia.

Vision Disorders: narrow angle glaucoma

Miscellaneous: CPK elevation.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

The signs and symptoms associated with clozapine (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 clozapine overdose, 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 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.

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 overdose. 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 pms-CLOZAPINE. Forced diuresis, dialysis, hemoperfusion and exchange transfusion are unlikely to be of benefit.

In managing overdose, the physician should consider the possibility of multiple drug involvement.

DOSAGE AND ADMINISTRATION

pms-CLOZAPINE (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).

pms-CLOZAPINE 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 with clozapine and at least at two-week intervals thereafter². 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.

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

²THE 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 HAEMATOLOGIST, 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 HAEMATOLOGICAL 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 INTERRUPTED FOR MORE THAN 3 DAYS. IF CLOZAPINE IS INTERRUPTED FOR 4 WEEKS OR LONGER, WEEKLY MONITORING IS REQUIRED FOR AN ADDITIONAL 26 WEEKS.

PHARMASCIENCE will provide the Non-rechallengeable Status/Hematological Status of patients to the requesting approved suppliers* of clozapine within 24 hours of receipt of a written request (see INDICATIONS).

* “approved supplier” is a manufacturer who holds a valid Notice of Compliance (NOC) for clozapine

The dosage of pms-CLOZAPINE must be adjusted individually. For each patient the lowest effective dose should be used.

Other monitoring and distribution systems

The introduction of clozapine from other manufacturers has resulted in the establishment of manufacturer-specific registry and distribution systems.

In order to ensure the safe use and continued monitoring of all patients taking clozapine, the physician must have obtained consent from the patient for the potential sharing of hematological and other safety data between clozapine registries.

Patients may not be switched from one brand of clozapine to another without the completion of a new registry-specific patient registration form signed by the prescribing physician.

If a patient is switched from one brand of clozapine to another, the frequency of hematological monitoring may continue unaltered unless a change is clinically indicated

INITIAL DOSE

On the first day, clozapine 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 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 pms-CLOZAPINE 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, pms-CLOZAPINE treatment can be started as described above. It is generally recommended that pms-CLOZAPINE 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 pms-CLOZAPINE 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, cardiovascular toxicity), 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

pms-CLOZAPINE THERAPY MUST NOT BE RESUMED IN:

- **Patients who have been discontinued from treatment due to neutropenia (ANC < 1.5 x 10⁹/L) or severe leukopenia (WBC < 2.0 x 10⁹/L, i.e. Non-rechallengeable Status).**
- **Patients with clozapine-induced myocarditis.**

When restarting patients who have had even a brief interval off pms-CLOZAPINE, 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.

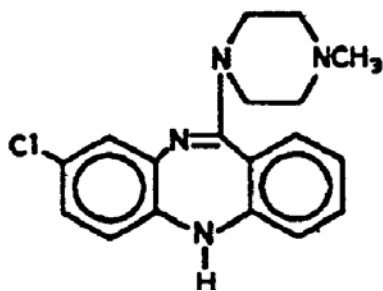
Certain additional precautions seem prudent when re-initiating treatment. The mechanisms underlying some of the pms-CLOZAPINE-induced adverse reactions are unknown. It is conceivable that re-exposure of a patient might enhance the risk of an untoward event's occurrence and increase its severity. Such 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.

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:

Molecular Weight: 326.83

Description: Clozapine is a yellow, crystalline powder with a melting range of 182.0°-186.0°C. The values for pKa (I) and pKa (II) are 3.69 and 7.57 respectively. At 25°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 30°C.

AVAILABILITY OF DOSAGE FORMS

Pr pms-CLOZAPINE Tablets 25 mg - Each round, pale yellow, uncoated, easy-to-break, scored tablet, embossed "CLOZAPINE" on one side and "P Logo/ 25 " on the other, contains clozapine 25 mg. Bottles of 100.

Pr pms-CLOZAPINE Tablets 100 mg - Each round, pale yellow, uncoated, easy-to-break, scored tablet embossed "CLOZAPINE" on one side and "P Logo/100 " on the other, contains clozapine 100 mg. Bottles of 100.

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

INFORMATION FOR THE CONSUMER/GUARDIAN

WHAT IS PMS-CLOZAPINE AND WHAT IS IT USED FOR?

pms-CLOZAPINE 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.

pms-CLOZAPINE can only be taken if prescribed by a doctor.

WHAT SHOULD BE BORNE IN MIND ABOUT PMS-CLOZAPINE?

WHY IS THE TESTING OF YOUR BLOOD BY YOUR DOCTOR NECESSARY?

In rare instances (approximately 0.7% of cases), pms-CLOZAPINE 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, pms-CLOZAPINE is only available through a special program.

Blood testing must be done weekly during the first 26 weeks of treatment with clozapine, 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 pms-CLOZAPINE.

In addition, you should consult your doctor immediately at the first signs of a cold, flu-like symptoms, 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.

Why does my doctor need my consent?

The medication you are taking, clozapine, is produced by several different suppliers. Each supplier has a different monitoring system to ensure patient safety. Should your doctor and/or pharmacist (with the approval of your doctor) change the brand of clozapine you are

taking, you will be transferred to a different monitoring system. If this happens, it is very important that your new supplier is able to access your past white blood cell counts results in order to help your doctor ensure that you are properly monitored.

It is also important to check with all registries at the start of the treatment that you have not experienced in the past a decrease of your white blood cell count with clozapine. Your consent is needed to allow this verification and sharing of information to take place.

Why is personal information such as my initials, birth date, gender and health card number being collected and used for identification purposes?

This information will be collected and used for several reasons. Since this information is specific to you, it helps to ensure that your test results are not mixed up with those of another person on the same medication. Using this information also avoids the need to use your full name and therefore protects your privacy.

Can my personal information be used for other purposes?

No. Your information will only be used to ensure that you are properly monitored while using any brand of clozapine.

Where can I find information on the protection of health related personal information in the private sector?

Information on this topic can be found on the website of Industry Canada, at the following address:

<http://e-com.ic.gc.ca/epic/internet/inecic-ceac.nsf/vwGeneratedInterE/gv00235e.html>

WHEN SHOULD PMS-CLOZAPINE NOT BE USED?

You should not take pms-CLOZAPINE if you already have too few white blood cells, or if you have ever had a disease affecting blood cell formation. pms-CLOZAPINE 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, (e.g. myocarditis, cardiomyopathy, heart failure), or uncontrolled epilepsy, or have ever had a bad, unusual or allergic reaction to pms-CLOZAPINE, or any of its components (see “**What does pms-CLOZAPINE contain**” at the bottom of this leaflet)..

WHEN TAKING PMS-CLOZAPINE, 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.

You should inform your physician immediately if you develop persistent tachycardia (rapid heart rate) at rest accompanied by other signs and symptoms of heart failure (e.g. chest pain, shortness of breath, swelling of the ankles and feet, or arrhythmias (abnormal heart rhythms). Other symptoms which you may also experience include fatigue, flu-like symptoms, fever that is otherwise unexplained, hypotension (low blood pressure) and/or raised jugular venous pressure (bulging neck veins when sitting or standing). You should contact your physician before discontinuing any medication.

(Reference: Canadian Public Advisory, dated January 18, 2002, regarding pms-CLOZAPINE cardiotoxicity)^{6f}.

Due to the risk of convulsions during pms-CLOZAPINE 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 pms-CLOZAPINE.

pms-CLOZAPINE 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 pms-CLOZAPINE 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.

pms-CLOZAPINE may lower your blood pressure, especially at the start of treatment. This may result in light-headedness or fainting.

SHOULD PMS-CLOZAPINE BE TAKEN DURING PREGNANCY OR BREAST-FEEDING?

pms-CLOZAPINE 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 pms-CLOZAPINE can pass into breast milk, mothers receiving pms-CLOZAPINE should not breast-feed.

HOW SHOULD PMS-CLOZAPINE 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 pms-CLOZAPINE, 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 pms-CLOZAPINE 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 PMS-CLOZAPINE?

The most serious side effects of pms-CLOZAPINE are a possible fall in the white blood cell count, (leading to an increased risk of infection, convulsions, fall in blood pressure, and fever) and heart problems.

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, chest pain, fatigue, flu-like symptoms, fever that is otherwise unexplained, low blood pressure and/or raised jugular venous pressure (bulging neck veins when sitting or standing), 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, pms-CLOZAPINE 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, pms-CLOZAPINE should be kept out of the reach of children.

Further information can be obtained from your doctor or pharmacist.

WHAT DOES PMS-CLOZAPINE CONTAIN?

The active ingredient of pms-CLOZAPINE is clozapine. Inactive ingredients are: colloidal silicon dioxide, lactose, magnesium stearate, povidone, starch and talc.

PHARMACOLOGY

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), *in vitro* (isolated tissue - Acetylcholine-induced contractions), and binding (^3H -QNB) studies.

Clozapine has potent antihistaminic activity as shown in *in vivo* (histamine - induced bronchoconstriction) and *in vitro* (isolated ileum - histamine-induced contractions) studies.

Clozapine has potent antiserotonergic activity as shown in *in vivo* (5-HTP-induced behaviours) and *in vitro* (isolated uterus - 5-HT-induced contractions) studies.

Clozapine binds to several types of receptors, especially serotonergic (S_2), α_1 -adrenergic, and histaminergic (H_1) receptors. It has weak dopamine receptor blocking activity at D_1 , D_2 , D_3 and D_5 , but shows high potency for the D_4 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.

TOXICOLOGY

ACUTE TOXICITY

The acute toxicity of clozapine is as follows:

Species	Sex	Route	LD ₅₀ (mg/kg)
Mouse	M,F	IV	61
	M,F	IP	90
	M	Oral	210
	F	Oral	190
Rat	M,F	IV	58
	M	IM	228
	F	IM	198
	M	Oral	325
	F	Oral	225
Guinea Pig	M	Oral	510
	F	Oral	681
Dog	M,F	Oral	145

LONG-TERM TOXICITY - Rats

26-Week Oral Toxicity Study in Rats: Clozapine was given to rats in a solution by gavage daily, 5 days a week, for 26 weeks. The doses used were 10, 20 and 40 mg/kg/day. Parameters examined included clinical signs, body weights, hematology, clinical chemistry, urinalysis as well as full necropsy (with organ weights) and histological examination.

Ten mg/kg/day produced a slight increase in liver weights in the males. The 20 and 40 mg/kg/day doses caused sedation during the early weeks, and aggression during the later

weeks of the study. Weight gain was somewhat impaired, and absolute and relative liver weights were slightly increased. The fore-stomach was slightly dilated in males.

100-Week Oral Toxicity Study in Rats: Rats were given clozapine mixed in their feed at concentrations corresponding to 15, 31 and 74 mg/kg/day for 100 weeks. A control group received unmedicated feed. The primary purpose of the study was to detect any possible carcinogenic potential of the drug in rats (see Carcinogenicity). In addition, the following parameters were studied: body weight, food intake, clinical signs, hematology, blood chemistry, urinalysis, urine chemistry, full necropsy (including organ weights) and histology of 30 organs.

During the study, a dose- and time-dependent occurrence of increased lipopigment was observed in various organs. With the 31 and 74 mg/kg/day doses, increased lipopigment was seen in the thyroid, brain, kidney, liver, heart, spleen and skeletal muscle of animals dying or sacrificed after one year. At the terminal examination (100 weeks) pigment was also seen in the thyroid, heart and brain at the 15 mg/kg/day dose. The presence of increased amounts of pigment was not associated with significant adverse changes.

The liver showed microscopic changes at all three dose levels, namely centro-lobular vacuolization and hepatocyte swelling, in addition to increased liver weights. The effects were dose-dependent. At the 31 mg/kg/day dose urine was reddened (probably due to a metabolite). BUN and SGPT levels were slightly increased at 26 and 100 weeks, and degenerative changes were seen in the testes and skeletal muscle. These findings were more intense at the high dose. Overall mortality was marginally increased in the treated rats, compared with the controls, but no dose-dependence was seen.

24-Month Oral Toxicity Study in Rats: Rats were given clozapine mixed in their feed at concentrations corresponding to 3, 10 and 35 mg/kg/day for 108 weeks. A control group received unmedicated feed. The purpose of the study was to detect any chronic toxic effects including carcinogenic potential of the drug in rats (see Carcinogenicity). The following parameters were studied: body weight, food intake, clinical signs, hematology, blood chemistry,

full necropsy (including organ weights) and histology of 33 organs.

Mortality of clozapine-treated rats was comparable to control rats at all time intervals.

With the exception of lipofuscin pigmentation similar to that observed in the 100-week oral toxicity study there was no evidence that the treatments had affected the occurrence of diseases anticipated to occur spontaneously in laboratory rats.

LONG-TERM TOXICITY - Mice

78-Week Oral Toxicity Study in Mice: Mice were given clozapine mixed in their feed for 78 weeks at an initial dose of approximately 40 mg/kg/day. From 32 weeks onwards, half of the treated mice were given a dose of approximately 75 mg/kg/day. Although the purpose of the study was primarily to detect any carcinogenic potential of the drug (see Carcinogenicity), the following parameters were also studied: body weight, food intake, hematology, blood chemistry, urinalysis, full necropsy (including organ weights) and histology of all major organs.

During the early weeks of treatment up to 40% of the mice (including controls) had occasional skin lesions of unknown etiology, which were treated for short periods with antibiotic and antimycotic drugs. Clinical pathology results were unremarkable except for slightly increased serum glutamic oxaloacetic transaminase levels in treated mice at week 78. However, histology of the liver revealed no evidence of hepatotoxicity.

LONG-TERM TOXICITY - Dogs

13-Week Oral Toxicity Study in Dogs: Clozapine was given in gelatin capsules to beagles 7 days a week for 13 weeks. Doses of 5, 10 and 20 mg/kg/day were used. Parameters studied included body weight, food intake, clinical signs, physical and neurological examinations, electrocardiography, hematology, clinical chemistry, urinalysis, as well as full necropsy (including organ weights) and histology.

At all dose levels the following signs were observed (with evidence of dose-dependency): sedation, muscular relaxation, miosis, lacrimation, salivation, muscular tremors, prolapse of nictitating membranes, irritability and emesis. All signs disappeared within 12 hours after drug administration with the exception of salivation, which persisted in some instances for 24 hours. No toxicological changes were observed with the exception of some increases in liver weights in some dogs compared with the controls, but there was no evidence of dose-dependence. One female at the mid dose level died after 25 days of treatment. Necropsy revealed that death was due to acute pneumonia, and was not related to medication. No other deaths occurred at any dose level.

Oral Toxicity in Dogs Using Escalating Doses: Clozapine was given orally in gelatin capsules to beagle dogs at dose levels that increased daily, 7 days a week for 13 weeks. During the administration period the dose was gradually increased from 20 to 90 mg/kg/day. This high dosage was maintained from weeks 9 to 13. Thereafter, half of the dogs were sacrificed, while the remainder were entered into an 8-week drug-free recovery period before being sacrificed.

Initially, with doses of 20 to 30 mg/kg/day, the dogs showed slight paresis, prolapse of the nictitating membrane, salivation, tremor and distinct dacryorrhea. With increasing doses these signs became progressively accentuated. In addition, miosis, unnatural posture, tachypnea and aggression developed. In two dogs convulsions and ataxia were seen. All adverse signs disappeared within two weeks after ending drug administration. ECG tracings revealed decreased heart rate, prolonged QT intervals and twin-peaked T-waves in some leads. The ECG

changes disappeared 4 weeks after the withdrawal of clozapine. All other clinical and postmortem examinations yielded changes that were probably not drug-induced, with the possible exception of increased kidney weights. Microscopic examinations were unremarkable. The final dose reached was roughly 60% of the acute LD₅₀.

One-year Oral Toxicity Study in Dogs: Clozapine was given orally in gelatin capsules to beagle dogs at doses of 5, 10 and 20 mg/kg/day for 4 weeks, and thereafter at doses of 7.5, 15 and 30 mg/kg/day. The drug was administered 7 days a week. A control group received empty gelatin capsules. The parameters measured were the same as those described before.

Clinical effects due to the pharmacological action of the drug (e.g., salivation, apathy, slight tremor and diarrhea) occurred at all dose levels in a dose-dependent fashion. However, no specific toxic effect or nonspecific evidence of overdosage was encountered. Minor coincidental lesions were seen in some dogs but no relationship to drug administration could be established.

LONG-TERM TOXICITY - Monkeys

Two-year Oral Toxicity Study in Rhesus Monkeys: Clozapine was given in gelatin capsules 7 days a week for 104 weeks. The dose levels used were 3 and 20 mg/kg/day (the high dose level was between 15 and 30 mg/kg/day during the early weeks). Parameters measured included clinical observation, body weights, hematology, blood chemistry, electrocardiography, ophthalmoscopy, as well as full necropsy with histological work-up of two monkeys per dose after 52 weeks and two further monkeys per dose after 104 weeks.

Three mg/kg/day produced slight transient clinical signs (sedation and ptosis on day 1) and minor hematologic changes in the early weeks (slight falls in red and white blood cell counts without development of anemia or leukopenia). ECG tracings showed slightly prolonged QT intervals in individual monkeys at sporadic intervals, mostly in the first year. This dose is regarded as being a "no-toxic effect" level for the monkey. With 20 mg/kg/day the following clinical signs were seen: sedation, ptosis and salivation. Weight gain was impaired, and slight

depressions of red and white cell counts were noted, although no cases of anemia or leukopenia occurred. The ECG changes were similar to those seen at the low dose level, although there was a decrease in the incidence of these changes during the second year. After one year, slightly increased lipopigment deposition in myocardial fibres was noted on postmortem examination. After two years there was a distinct brown discoloration of the heart and urinary bladder mucosa associated with pigment deposition. Similar pigment was also seen microscopically in the neurons of the CNS and the mucosa of the gallbladder. Splenic weights were slightly increased. However, no specific organ toxicity was seen.

CARCINOGENICITY

Rats: In the 100-week and 24-month oral toxicity studies described above, there was no increased incidence of tumors in treated animals, tumors did not occur earlier in treated animals than in controls, and there was no difference in the pattern of tumors found in control and treated rats.

Mice: A 78-week oral carcinogenicity study was carried out as described above (see Long-Term Toxicity). In a second study, mice were given clozapine mixed in their feed for 18 months at levels yielding average doses of 6, 21 and 61 mg/kg/day. The parameters studied were body weight, food intake, terminal hematology, and full necropsy and microscopy of all major organs. In both studies the incidence of tumors was similar in treated and control mice, and there was no shift in the preponderance of one particular type of tumor in any treatment group.

MUTAGENICITY

No evidence of mutagenic effects of clozapine was detected in four assays: 1. Ames Salmonella; 2. DNA repair synthesis (UDS) *in vitro* rat hepatocytes; 3. V79 Chinese hamster cells *in vitro*; and 4. *In vivo* mouse micronucleus.

REPRODUCTION AND TERATOLOGY

Teratology Studies in Rats and Rabbits: Pregnant rats and rabbits were given clozapine orally during organogenesis (days 5 to 16 of pregnancy in rats, days 6 to 18 of pregnancy in rabbits). Doses of 20 and 40 mg/kg/day were dissolved in water and given by gavage. The control groups received water. The dams were sacrificed at term and examined with their fetuses. Maternal, litter and fetal parameters were evaluated.

Clozapine in the doses used had no apparent effect on the maternal, litter or fetal parameters. In rabbits, treatment attenuated weight gain during drug administration, which was not compensated for during the remainder of pregnancy. Nevertheless, no drug-related change in pregnancy, litter, or fetal data was observed, apart from a slight reduction in mean fetal weights (within normal limits).

Fertility Study in Rats: Male and female rats were treated before mating with clozapine for 70 and 14 days, respectively. Doses of 20 and 40 mg/kg/day dissolved in water were given by gavage. Control groups were given plain water by gavage. On day 13 of pregnancy half of the dams were sacrificed. Their genital tract and the condition of the fetuses were inspected. The remaining dams were allowed to litter and the young were sacrificed on day 21 postpartum and examined for abnormalities.

At the end of the treatment period, treated males, at both dose levels, had impaired weight gain as compared to the controls. Sedation was seen at 40 mg/kg/day, and excitation at 20 mg/kg/day. Fertility was not impaired. Pregnancy, fetal and postnatal development of the young were normal throughout the study.

In the females, the 2-week treatment period had no adverse effect on weight gain. The pharmacological effects observed were similar to those seen in the males. Pregnancy rate was remarkably high in the 40 mg/kg group but was associated with a slightly increased number of intrauterine deaths. No abnormalities were observed in fetuses or newborn animals. Birth and

postnatal development were normal throughout the study.

Perinatal Study in Rats: Mated female rats were given clozapine by gavage at doses of 20 and 40 mg/kg/day over the last third of pregnancy until day 21 post partum. Controls received water. Observations of the fetuses were made at birth and during the postnatal period.

A dose-dependent impairment of weight gain was apparent in the dams. With 40 mg/kg/day there was actually a weight loss. Litter size and litter weights were within normal limits, although a slight dose-dependent reduction was seen. Survival rates and mean weights of the offspring were reduced by the end of lactation compared to that of the controls. The offspring showed evidence of increased excitability.

Generation Study in Rats: The offspring of the three groups of the above study (controls, 20 and 40 mg/kg/day) were allowed to reach sexual maturity and mated, six possible combinations between groups being used (control males with 40 mg/kg females, control males with 20 mg/kg females, 40 mg/kg males with control females, 20 mg/kg males with control females, 20 mg/kg males with same dose females, 40 mg/kg males with same dose females). Pregnancy rates and litter data as well as the postnatal development of the F₂-generation were studied.

In none of the 6 groups was a deviation from normal values detected, nor was any intra-group difference noted. From these results, it may be concluded that clozapine administration had no effect on the F₂-generation.

OTHER STUDIES

In several test systems employing animal bone marrow cells, clozapine, as well as certain other drugs with a potential to cause agranulocytosis, were shown to have a suppressant effect on cell division. However, the relevance of these models for predicting potential bone marrow toxicity remains to be fully established.

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