PRODUCT MONOGRAPH

PrAA-CLOZAPINE

(Clozapine Tablets USP)
25 mg, 50 mg, 100 mg and 200 mg

Antipsychotic Agent

AA PHARMA INC.
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PrAA-CLOZAPINE
(Clozapine Tablets USP)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	All Nonmedicinal Ingredients
Oral	AA-CLOZAPINE 25 mg tablets; Each 25 mg tablet contains 25 mg of clozapine AA-CLOZAPINE 50 mg tablets; Each 50 mg tablet contains 50 mg of clozapine AA-CLOZAPINE 100 mg tablets; Each 100 mg tablet contains 100 mg of clozapine AA-CLOZAPINE 200 mg tablets; Each 200 mg tablet contains 200 mg of clozapine	anhydrous lactose, colloidal silicon dioxide, crospovidone, magnesium stearate, methylcellulose and sodium lauryl sulfate

INDICATIONS AND CLINICAL USE

AA-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 PRECAUTIONS and DOSAGE AND ADMINISTRATION.

AA-CLOZAPINE is available only through a distribution system AA-CLOZAPINE Risk Management Program that ensures: weekly, every-two-week or every-four-week hematological testing prior to the dispensing of the next period's supply of AA-CLOZAPINE (see WARNINGS AND PRECAUTIONS).

This requires:

- registration of the patient, their current location, treating physician, testing laboratory and dispensing pharmacist in the AA-CLOZAPINE Risk Management Program.
- maintenance of a national AA Pharma monitoring system of the hematological results of all patients on AA-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 AND PRECAUTIONS). This requires that AA Pharma Inc. both provide to, and obtain from, all other approved suppliers[†] of clozapine, the Non-rechallengeable Status / Hematological Status of all patients (see DOSAGE AND ADMINISTRATION). AA Pharma Inc. must be able to provide this information within 24 hours of receiving a written request.

Physicians should not prescribe AA-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 PRECAUTIONS) and that arrangements are made for the hematological results to be sent to AA-CLOZAPINE Risk Management Program. Physicians may obtain details on the AA-CLOZAPINE Risk Management

[†] **"approved supplier" is a manufacturer who holds a valid Notice of Compliance (NOC) for clozapine**

Program by calling a toll-free phone number (1-877-276-2569).

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.

Patients 60 years of age and older: See WARNINGS AND PRECAUTIONS – Serious Warnings and Precautions Box and Special populations.

AA-CLOZAPINE should be used with care in the elderly. (See DOSAGE AND ADMINISTRATION, Dosing Considerations in Special Populations)

Pediatrics (< 18 years of age): No pediatric studies have been performed. The safety and efficacy of AA-CLOZAPINE in children and adolescents have not been established. AA-CLOZAPINE is not indicated in pediatric patients and its use is not recommended.

CONTRAINDICATIONS

- Patients with known hypersensitivity to clozapine or any other components of AA-CLOZAPINE. For a complete listing, see DOSAGE FORMS, COMPOSITION AND PACKAGING section of the product monograph.
- 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.]
- Patients with active liver disease associated with nausea, anorexia, or jaundice; progressive liver disease; hepatic failure.
- Patients unable to undergo blood tests.

Other contraindications include severe central nervous system depression or comatose states, severe renal or cardiac disease (e.g. myocarditis), paralytic ileus, uncontrolled epilepsy.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

Elderly Patients with Dementia

Elderly patients with dementia treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. Analyses of thirteen placebo-controlled trials with various atypical antipsychotics (modal duration of 10 weeks) in these patients showed a mean 1.6 fold increase in the death rate in the drug-treated patients. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. Clozapine has not been studied in elderly patients with dementia and therefore no such data were included in this analysis.

AA-CLOZAPINE is not indicated in elderly patients with dementia (see WARNINGS AND PRECAUTIONS, Special populations).

AGRANULOCYTOSIS

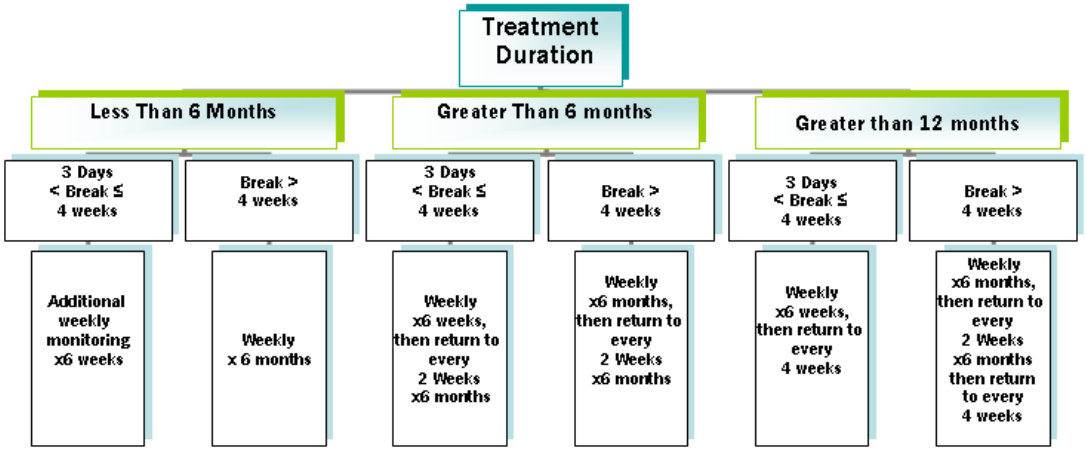
Because of the significant risk of granulocytopenia and agranulocytosis, a potentially life-threatening adverse event (see below), AA-CLOZAPINE should be reserved for use in the treatment of schizophrenic patients who fail to show an acceptable response to adequate courses of conventional antipsychotic 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. Thereafter, if acceptable WBC counts and absolute neutrophil counts (ANC) (WBC $\geq$3500/mm^3 and ANC $\geq$2000/mm^3) have been maintained during the first 26 weeks of continuous therapy, the WBC count and differential count can be performed at least at two-week intervals for the next 26 weeks. Thereafter, if acceptable WBC counts and ANCs (WBC $\geq$3500/mm^3 and ANC $\geq$2000/mm^3) have been maintained during the second 26 weeks of continuous therapy, the WBC count and differential count can be performed at least every four weeks throughout treatment.

The change from a weekly to a "once every two weeks", or from a “once every two weeks” to a “once every four weeks” schedule should be evaluated on an individual patient basis after 26 and 52 weeks of treatment, respectively. This decision should be made based upon the hematological profile of the patient during the first 26 or 52 weeks of treatment (as appropriate), as well as on the clinical judgement of the treating physician, and if he/she deems it appropriate, a consulting hematologist, and on 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.

Monitoring must continue for as long as the patient is on the drug. Monitoring frequency does not have to be modified if therapy is interrupted for 3 days or less. However, weekly hematological testing should be resumed for an additional 6 weeks if therapy is disrupted for more than 3 days (see Figure 1). Furthermore, monitoring should occur at least weekly for a period of 4 weeks following discontinuation of clozapine therapy, irrespective of the cause of discontinuation.

Figure 1: Resuming Monitoring Frequency after Interruption in Therapy



AA-CLOZAPINE is available only through a distribution system (AA-CLOZAPINE risk management program) that requires weekly, every-two-week, or every-four-week hematological testing prior to the dispensing of the next period's supply of AA-CLOZAPINE (see INDICATIONS AND CLINICAL USE).

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 shown 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 current approved suppliers of clozapine).

AA-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 x 10^9/L and/or the ANC count 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 the frequency of their blood monitoring regimen (weekly, at two-week, or at four-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, AA-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. AA-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 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 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.

General

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 AA-CLOZAPINE should ordinarily be avoided. In addition, the need for continuing treatment in patients exhibiting beneficial clinical responses should be reassessed periodically.

Fever: During AA-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 AND PRECAUTIONS). If the diagnosis of neuroleptic malignant syndrome is confirmed, AA-CLOZAPINE should be discontinued immediately and appropriate medical measures should be administered.

Fever that is otherwise unexplained can accompany myocarditis (see WARNINGS AND PRECAUTIONS - Cardiovascular).

Interference with Cognitive and Motor Performance: Because of the potential for initial sedation, AA-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).

Anticholinergic Activity: 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, clozapine has been associated with varying degrees of impairment of intestinal peristalsis, ranging from constipation to intestinal obstruction, faecal impaction, paralytic ileus, megacolon and intestinal infarction/ischemia. On rare occasions, these cases have been fatal. Careful monitoring during treatment with Clozapine to identify early the onset of constipation, followed by effective management of constipation are recommended to prevent complications. Particular care is necessary in patients who are receiving concomitant medications known to cause constipation (especially those with anticholinergic properties such as some antipsychotics, antidepressants and antiparkinsonian treatments), have a history of colonic disease or a history of lower abdominal surgery as these may exacerbate the situation. It is vital that constipation is recognized and actively treated.

Rebound, withdrawal effects: If abrupt discontinuation of AA-CLOZAPINE is necessary (e.g. because of leukopenia), the patient should be carefully observed for the recurrence of psychotic symptoms and symptoms related to cholinergic rebound such as profuse sweating, headache, nausea, vomiting and diarrhea.

Cardiovascular

CARDIOTOXICITY

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

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, tachypnea (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 to 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 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 1/14,000 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 to 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. 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

Canadian Reports

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.

International Reports

There have been post-marketing reports of myocardial infarction which may be fatal. Causality assessment was difficult in the majority of these cases because of serious pre-existing cardiac disease and plausible alternative causes.

Other Adverse Cardiovascular and Respiratory Effects

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 [initial dose should be 12.5 mg given once on the first day, and dosage increase should be slow and in small increments (see DOSAGE AND ADMINISTRATION)].

Orthostatic hypotension, with or without syncope, can occur during AA-CLOZAPINE treatment 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 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 of clozapine, i.e. 2 days or more since the last dose, it is recommended that treatment be reinitiated 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 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 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 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 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.

QT interval prolongation: As with other antipsychotics, caution is advised in patients with known cardiovascular disease, a family history of QT prolongation, or when clozapine is prescribed with medicines known to increase the QTc interval.

Venous Thromboembolism: Venous thromboembolism (VTE), including fatal pulmonary embolism, has been reported with antipsychotic drugs including clozapine, in case reports and/or observational studies. When prescribing AA-CLOZAPINE all possible risk factors for VTE should be identified before and during treatment with AA-CLOZAPINE and preventative measures undertaken.

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

Neurologic

Seizures: Clozapine may lower seizure threshold. Caution should be used in administering AA-CLOZAPINE to patients having a history of seizures or other predisposing factors.

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

Falls: Clozapine, like other antipsychotics, may cause somnolence, postural hypotension, motor and sensory instability, which may lead to falls and, consequently, fractures or other injuries. For patients with diseases, conditions, or medications that could exacerbate these effects, complete fall risk assessments when initiating antipsychotic treatment and recurrently for patients on long-term antipsychotic therapy.

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 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 clozapine will not induce this syndrome.

Given this consideration, AA-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 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 AA-CLOZAPINE, drug discontinuation should be considered. However, some patients may require treatment with AA-CLOZAPINE despite the presence of the syndrome.

Hematologic

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 AA-CLOZAPINE.

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

Eosinophilia: In the event of eosinophilia, it is recommended to discontinue AA-CLOZAPINE if the eosinophil count rises above 3.0 x 10^9/L, and to re-start therapy only after the eosinophil count has fallen below 1.0 x 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. Post market cases of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) have been reported in association with 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 AA-CLOZAPINE therapy if the platelet count falls below 50.0 x 10^9/L.

Endocrine and Metabolism

Metabolic Changes

Atypical antipsychotic drugs, including clozapine, have been associated with metabolic changes that may increase cardiovascular/cerebrovascular risk. These metabolic changes may include hyperglycemia, dyslipidemia, and body weight gain. While atypical antipsychotic drugs may produce some metabolic changes, each drug in the class has its own specific risk profile.

Hyperglycemia: On rare occasions, severe hyperglycemia, sometimes leading to ketoacidosis/hyperosmolar coma including some fatal cases, has been reported during 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 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. Impaired glucose tolerance, severe hyperglycemia, ketoacidosis and hyperosmolar coma have been reported in patients with no prior history of hyperglycaemia. Patients should have baseline and periodic monitoring of blood glucose and body weight. In patient receiving AA-CLOZAPINE who developed symptom of hyperglycaemia, such as polydipsia, polyuria, polyphagia or weakness discontinuation should be considered.

There is a risk of altering the metabolic balance resulting in slight impairment of glucose homeostasis and a possibility of unmasking a pre-diabetic condition or aggravating pre-existing diabetes.

Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. However, epidemiological studies suggest an increased

risk of treatment-emergent hyperglycemia-related adverse events in patients treated with the atypical antipsychotics. Precise risk estimates for hyperglycemia-related adverse events in patients treated with atypical antipsychotics are not available.

Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug. Patients with risk factors for diabetes mellitus (e.g., obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control.

Dyslipidemia: Undesirable alterations in lipids have been observed in patients treated with atypical antipsychotics, including clozapine. Clinical monitoring, including baseline and periodic follow-up lipid evaluations in patients using clozapine, is recommended.

Weight Gain: Weight gain has been observed with atypical antipsychotic use, including clozapine. Clinical monitoring of weight is recommended.

Respiratory

Dysphagia: Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of morbidity and mortality in elderly patients, in particular those with advanced Alzheimer's dementia. AA-CLOZAPINE and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia.

Hepatic

Hepatotoxicity: Severe, life threatening, and in some cases fatal hepatotoxicity including hepatic failure, hepatic necrosis, and hepatitis have been reported in post marketing studies in patients treated with clozapine. Monitor for the appearance of signs and symptoms of hepatotoxicity such as fatigue, malaise, anorexia, nausea, jaundice, bilirubinemia, coagulopathy, and hepatic

encephalopathy. Perform serum tests for liver injury and consider permanently discontinuing treatment if hepatitis or transaminase elevations combined with other systemic symptoms are due to clozapine.

Sexual Function/Reproduction

Genitourinary: Very rare cases of priapism have been reported with clozapine. This adverse reaction, as with other psychotropic drugs, did not appear to be dose-dependent and did not correlate with the duration of treatment.

Special populations

Use in Patients with Concomitant Illnesses: Clinical experience with clozapine in patients with concomitant systemic diseases is limited. Nevertheless, caution is advised when using AA-CLOZAPINE in patients with hepatic, renal, or cardiac disease. For severe cases, see CONTRAINDICATIONS.

Hepatic impairment: Patients with stable pre-existing liver disorders may receive AA-CLOZAPINE, but need regular liver function tests. In patients in whom, during AA-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 AA-CLOZAPINE must be discontinued. It may be resumed (see DOSAGE AND ADMINISTRATION, Re-Initiation of Treatment in Patients Previously Discontinued) 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.

Renal impairment: In patients suffering from mild to moderate renal impairment, an initial dose of 12.5 mg/day (half a 25 mg tablet) is recommended (see DOSAGE AND ADMINISTRATION).

Vascular disease: AA-CLOZAPINE should be used with caution in patients with risk factors for stroke or with a history of stroke.

Pregnant women: 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 have 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, AA-CLOZAPINE should be used only if the benefits clearly outweigh the risks.

Women of Childbearing Potential and Contraceptive Measures: Some female patients treated with antipsychotics other than clozapine may become amenorrheic. A return to normal menstruation may occur as a result of switching from other antipsychotics to clozapine. Adequate contraceptive measures must therefore be ensured in women of childbearing potential.

Non-Teratogenic Effects: Neonates exposed to antipsychotic drugs, during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms following delivery. There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress and feeding disorder in these neonates. These complications have varied in severity; while in some cases symptoms have been self-limited, in other cases neonates have required intensive care unit support and prolonged hospitalization.

Antipsychotic drugs, including AA-CLOZAPINE, should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing women: Animal studies suggest that clozapine may be excreted in breast milk and has an effect in the suckling offspring. Therefore, women receiving AA-CLOZAPINE should not breast-feed.

Pediatrics (< 18 years of age): No pediatric studies have been performed. Safety and efficacy of clozapine in children and adolescents below age 18 have not been established and its use is not recommended.

Weight gain has been observed with atypical antipsychotic use in pediatric and adolescent patient populations. Independent of any drug-specific effects, weight gain can be associated with adverse changes in other metabolic parameters (e.g. glucose and lipid metabolism).

Abnormal childhood weight and metabolic status can have adverse effects on cardiovascular outcomes in adulthood. Weight gain and adverse effects on other metabolic parameters associated

with atypical antipsychotics can be more frequent or more severe in pediatric and adolescent patients than in the adult patients.

The long-term safety, including cardiometabolic effects and effects on growth, maturation and behavioural development in patients under 18 years of age has not been systematically evaluated.

Patients aged 60 years and older:

Orthostatic hypotension can occur with AA-CLOZAPINE treatment and there have been rare reports of tachycardia, which may be sustained, in patients taking clozapine. Patients aged 60 years and older, particularly those with compromised cardiovascular function, may be more susceptible to these effects.

Patients aged 60 years and older may also be particularly susceptible to the anticholinergic effects of AA-CLOZAPINE, such as urinary retention and constipation.

Use in Patients aged 60 years and older with Dementia: Overall Mortality

Patients aged 60 years and older with dementia treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. Clozapine has not been studied in patients aged 60 years and older with dementia. AA-CLOZAPINE is not indicated for the treatment of patients with dementia (see WARNINGS AND PRECAUTIONS, boxed Serious Warnings and Precautions). In the published literature, risk factors that may predispose this patient population to increased risk of death when treated with antipsychotics include sedation, the presence of cardiac conditions (e.g. cardiac arrhythmias) or pulmonary conditions (e.g. pneumonia, with or without aspiration).

Cerebrovascular Adverse Events (CVAEs), Including Stroke in Elderly Patients with Dementia

In placebo-controlled trials with some atypical antipsychotics, there was a higher incidence of cerebrovascular adverse events (cerebrovascular accidents and transient ischemic attacks) including fatalities compared to placebo-treated subjects. There are insufficient data with clozapine to know if there is an increased risk of cerebrovascular events associated with clozapine. AA-CLOZAPINE is not indicated for the treatment of patients with dementia-related psychosis (see also WARNINGS AND PRECAUTIONS, boxed Serious Warnings and Precautions).

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 AA-CLOZAPINE:

- Patients who are to receive AA-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 AA-CLOZAPINE tablets will be made available only through a special program designed to ensure the required blood monitoring. They should also be informed that the blood tests will be performed according to the following monitoring schedule:
  - Weekly blood tests will be required for the first 26 weeks of their treatment with clozapine.
  - Following this initial higher risk period, they could be allowed to change to a "once every two weeks" schedule, provided that acceptable WBC counts and ANCs (WBC $\geq$3500/mm^3 and ANC $\geq$2000/mm^3) have been maintained during the first 26 weeks of continuous therapy, and that their clinical condition is permitting such a change in monitoring regimen.
  - Thereafter, if acceptable WBC counts and ANCs have been maintained during the second 26 weeks of continuous therapy, blood tests could be performed every four weeks.
- 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 AA-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 advised of the risk of severe constipation during AA-CLOZAPINE treatment, and that they should tell their doctor if constipation occurs or worsens, as they may need laxatives.
- Patients should be informed that if they stop taking AA-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 AA-CLOZAPINE.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

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

Adverse Events Leading to Discontinuation

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 (psychotic disorder), primarily drowsiness/sedation, somnolence, seizures, dizziness (excluding vertigo)/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 event.

Most Frequent Adverse Events

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.

Clinical Trials Adverse Drug Reactions

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
Nervous System disorders	
Drowsiness/Sedation	39
Dizziness/Vertigo	19
Headache	7
Tremor	6
Disturbed sleep/Nightmares	4
Hypokinesia/Akinesia	4
Seizures (convulsions)	3[b]
Rigidity	3
Akathisia	3
Confusion	3
Insomnia	2
Hyperkinesia	1
Weakness	1
Lethargy	1
Ataxia	1
Slurred speech	1
Depression	1
Epileptiform movements/Myoclonic jerks	1
Anxiety	1
Psychiatric disorders	
Agitation	4
Restlessness	4
Cardiac disorders	
Tachycardia	25[b]
Chest pain/Angina	1
ECG changes/Cardiac abnormality	1
Vascular disorders	
Syncope	6
Hypotension	9

Hypertension	4
Gastrointestinal disorders	
Constipation	14
Nausea	5
Abdominal discomfort/Heartburn	4
Nausea/Vomiting	3
Vomiting	3
Dry mouth	6
Diarrhea	2
Anorexia	1
Hepatobiliary disorders	
Liver test abnormality	1
Renal and urinary disorders	
Urinary abnormalities	2
Urinary incontinence	1
Urinary urgency/frequency	1
Urinary retention	1
Reproductive system disorders	
Abnormal ejaculation	1
Autonomic Nervous System	
Salivation	31
Sweating	6
Visual disturbances	5
Skin and subcutaneous tissue disorders	
Rash	2
Musculoskeletal	
Muscle weakness	1
Pain (back, neck, legs)	1
Muscle spasm	1
Muscle pain, ache	1
Respiratory disorders	
Throat discomfort	1
Dyspnea, shortness of breath	1
Nasal congestion	1
Blood and lymphatic disorders	
Leukopenia/Decreased WBC/Neutropenia	3
Agranulocytosis	1[b]
Eosinophilia	1
Metabolism and nutrition disorders	
Weight gain	4
Miscellaneous	
Fever	5
Fatigue	2
Tongue numb/sore	1

[a] Events reported by at least 1% of clozapine patients are included.

[b] Rate based on population of approximately 1700 exposed during premarket clinical evaluation of clozapine.

Adverse Events Observed During the InterSePT Study

Adverse events reported during the InterSePT study were consistent with the known safety profiles for clozapine and olanzapine. The ten most frequently reported adverse events in the clozapine treatment group were: salivary hypersecretion, somnolence, weight increase, anxiety, depression, dizziness (excluding vertigo), psychotic disorder, suicidal ideation, constipation, and insomnia.

Other Adverse Events Observed during Clinical Trials

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.

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

Psychiatric disorders: dysarthria, dysphemia (stuttering).

Eye disorders: eyelid disorder, bloodshot eyes, and nystagmus.

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

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

Reproductive system disorders: dysmenorrhea, impotence, breast pain/discomfort, and vaginal itch/infection.

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

Skin and subcutaneous tissue disorders: pruritus, pallor, eczema, erythema, bruise, dermatitis, petechiae, and urticaria.

Musculoskeletal and connective tissue disorders: twitching and joint pain.

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

Blood and lymphatic system disorders: anemia and leukocytosis.

General disorders: chills/chills with fever, malaise, appetite increase, ear disorder, hypothermia.

Post-Market Adverse Drug Reactions

Post-marketing experience has shown an adverse experience profile similar to that presented above. In Post-marketing experience, cases of hepatic, cholestatic or mixed liver injury, hepatic failure, including fatalities, has been reported with the use of clozapine.

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

Sleep walking (SW) and sleep-related eating disorder (SRED) have been associated with the use of atypical antipsychotics, including cases reported with clozapine.

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:

Immune system disorders: angioedema, leukocytoclastic vasculitis (sometimes fatal).
Endocrine disorders: pseudophaeochromocytoma
Nervous system disorders: delirium, cholinergic syndrome, EEG abnormal, exacerbation of psychosis, myoclonus, overdose, paresthesia, possible mild cataplexy, obsessive compulsive symptoms, status epilepticus, pleurothotonus.
Cardiac disorders: analysis of safety databases suggests that the use of clozapine is associated with an increased risk of myocarditis (which may be fatal) especially during, but not limited to, the first month of therapy (see WARNINGS AND PRECAUTIONS); atrial or ventricular fibrillation, periorbital edema, pericarditis, pericardial effusion, cardiomyopathy, heart failure, mitral insufficiency, and myocardial infarction which may be fatal. Very rare events of ventricular tachycardia, cardiac arrest and QT prolongation which may be associated with torsades de pointes have been observed.
Gastrointestinal disorders: dysphagia, dyspepsia, fecal impaction, intestinal obstruction/paralytic ileus, parotid gland enlargement, colitis (sometimes fatal), megacolon (which may be fatal), intestinal infarction/ischaemia (which may be fatal), intestinal necrosis (sometimes fatal), ulceration

(sometimes fatal) and perforation (sometimes fatal).

Hepatobiliary disorders: acute pancreatitis, cholestasis, hepatitis, jaundice, fulminant hepatic necrosis, hepatic steatosis, hepatic necrosis, hepatotoxicity, hepatic fibrosis, hepatic cirrhosis, liver disorders including those hepatic events leading to life-threatening consequences such as liver failure, liver injury, liver transplant.

Renal and urinary disorders: acute interstitial nephritis, renal failure, nocturnal enuresis.

Reproductive system disorders: priapism, retrograde ejaculation.

Skin and subcutaneous tissue disorders: hypersensitivity reactions: photosensitivity, vasculitis, erythema multiforme, Stevens-Johnson Syndrome, pigmentation disorder.

Post market cases of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) have been reported in association with clozapine.

Metabolism and nutritional Disorders: hyperglycemia, ketoacidosis, hyperosmolar coma, hyperuricemia, hyponatremia, weight loss, impaired glucose tolerance, new onset diabetes, diabetes aggravated, hypercholesterolemia, hypertriglyceridemia, obesity.

Musculoskeletal and connective tissue disorders: myasthenic syndrome, rhabdomyolysis, systemic lupus erythematosus.

Respiratory disorders: aspiration, pneumonia and lower respiratory tract infection which may be fatal, pleural effusion, respiratory arrest.

Blood and lymphatic system disorders: deep vein thrombosis, elevated hemoglobin/haematocrit, ESR increased, pulmonary embolism, sepsis, thrombocytosis, thrombocytopenia, thombocythaemia.

Eye disorders*:* narrow angle glaucoma.

Investigations**:** CPK elevation.

General disorders: polyserositis

DRUG INTERACTIONS

<u>Drug-Drug Interactions</u>

AA-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-alpha-adrenergic properties, AA-CLOZAPINE may reduce the blood pressure increasing effect of norepinephrine or other predominantly alpha-adrenergic agents and reverse the pressor effect of epinephrine.

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

As with other antipsychotics, caution should be exercised when AA-CLOZAPINE is prescribed with medicines known to increase the QTc interval, or causing electrolyte imbalance.

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), ciprofloxacin (1A2) and oral contraceptives (1A2, 3A4, 2C19). 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, fluoxetine and citalopram (possibly a weak inhibitor of CYP1A2 and possibly the least likely among SSRIs to cause a clinically significant interaction with clozapine).

- 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, or type 1_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 tobacco smoking. In cases of sudden smoking cessation, the plasma clozapine concentration may be increased, thus leading to an increase in adverse effects.

DOSAGE AND ADMINISTRATION

Dosing considerations

AA-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, Drug-Drug Interactions). Extra caution is advised in patients with cardiovascular disease or a history of seizures (see WARNINGS AND PRECAUTIONS).

AA-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, at least at two-week intervals for the next 26 weeks, and at least at four-week intervals thereafter. 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.

The change from a weekly to a "once every two weeks", or from a “once every two weeks” to a “once every four weeks” schedule should be evaluated on an individual patient basis after 26 and 52 weeks of treatment, respectively. This decision should be made based upon the hematological profile of the patient during the first 26 or 52 weeks of treatment (as appropriate) (see WARNINGS AND PRECAUTIONS), 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. Weekly hematological testing should be resumed for an additional 6 weeks if therapy is disrupted for more than 3 days. If clozapine is interrupted for 4 weeks or longer, weekly monitoring is required for an additional 26 weeks.

AA-CLOZAPINE is available only through a distribution system that requires weekly, every-two-week or every-four-week hematological testing prior to the dispensing of the next period's supply of medication (see INDICATIONS AND CLINICAL USE).

AA Pharma Inc. 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 AND CLINICAL USE).

The dosage of AA-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

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

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.

Recommended Dose and Dosage Adjustment

Initial Dose

On the first day, AA-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 mg to 50 mg, achieving a target dose of 300to 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 (see also DRUG INTERACTIONS).

Switching from Previous Neuroleptics

When AA-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, AA-CLOZAPINE treatment can be started as described above. It is generally recommended that AA-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 to 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 to 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 to 300 mg/day in divided doses. At daily doses not exceeding 200 mg, a single administration in the evening may be appropriate.

Dosing Considerations in Special Populations

Patients 60 years of age and older: It is recommended that treatment in patients 60 years and older is initiated at a particularly low dose of AA-CLOZAPINE (12.5 mg given once on the first day) with subsequent dose increments restricted to 25 mg/day.

Pediatrics (< 18 years of age): No pediatric studies have been performed. The safety and efficacy of clozapine in children and adolescents have not been established.

Cardiovascular disorders: In patients suffering from cardiovascular disorders (note: severe cardiovascular disorders are contraindications) the initial dose of AA-CLOZAPINE should be 12.5 mg given once on the first day, and dosage increase should be slow and in small increments.

Renal impairment: In patients with mild to moderate renal impairment the initial dose of AA-CLOZAPINE should be 12.5 mg given once on the first day, and dosage increase should be slow and in small increments.

Hepatic impairment: Patients with hepatic impairment should receive AA-CLOZAPINE with caution along with regular monitoring of liver function tests (see WARNINGS AND PRECAUTIONS).

Discontinuation of Therapy

In the event of planned termination of AA-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 diarrhea (see WARNINGS AND PRECAUTIONS).

Re-Initiation of Treatment in Patients Previously Discontinued

AA-CLOZAPINE 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, i.e. Non-rechallengeable Status).**
- **Patients with clozapine-induced myocarditis**

When restarting patients who have had even a brief interval off AA-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 AA-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.

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

The signs and symptoms associated with 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 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 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 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 clozapine. 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.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

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 antiserotoninergic activity.

Pharmacodynamics

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

Absorption: 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%.

Distribution: 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.

Biotransformation/metabolism: Clozapine is almost completely metabolized prior to excretion. Clozapine is converted to norclozapine (desmethyl clozapine) by CYP1A2 and 3A4, and to clozapine-N-oxide by 3A4, and metabolized to some extent by CYP2C19 and 2D6. 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.

Elimination: 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.

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.

STORAGE AND STABILITY

Store at room temperature 15°C to 30°C. Protect from moisture.

DOSAGE FORMS, COMPOSITION AND PACKAGING

AA-CLOZAPINE Tablets 25 mg - Light yellow, round tablets. Engraved “C” over bisect “25” on one side, other side plain. Available in bottles of 100 and 500.

AA-CLOZAPINE Tablets 50 mg - Light yellow, flat face bevelled edge round tablets. Engraved “C” over bisect “50” on one side, other side plain. Available in bottles of 100 and 500.

AA-CLOZAPINE Tablets 100 mg - Light yellow, round tablets. Engraved “C” over bisect “100” on one side, other side plain. Available in bottles of 100.

AA-CLOZAPINE Tablets 200 mg - Light yellow, capsule shape biconvex tablets. Engraved "C" bisect "200" on one side, bisect on the other side. Available in bottles of 100 and 500.

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

Composition

Each 25 mg, 50 mg, 100 mg and 200 mg tablet contains 25 mg, 50 mg, 100 mg and 200 mg of clozapine respectively, and the inactive ingredients anhydrous lactose, colloidal silicon dioxide, crospovidone, magnesium stearate, methylcellulose and sodium lauryl sulfate.

PART II: SCIENTIFIC INFORMATION

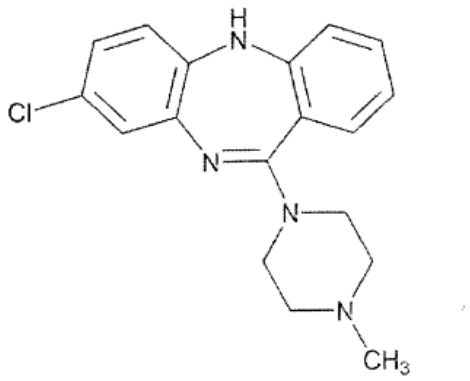
PHARMACEUTICAL INFORMATION

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 g/mol

Description: Clozapine is a yellow, crystalline powder with a melting range of 182.0°Cto 186.0°C. The values for pKa (I) and pKa (II) are 3.70 and 7.60 respectively. At 25°C, the solubility of clozapine is <0.01% in water and >20% in chloroform.

CLINICAL TRIALS

A randomized, single dose, blinded, 2-way crossover comparative bioavailability study, conducted under fasting conditions, was performed on healthy male volunteers. The results obtained from 28 volunteers who completed the study are summarized in the following table. The rate and extent of absorption of clozapine was measured and compared following a single oral dose (12.5 mg [1/2 x 25 mg] tablet) of AA-CLOZAPINE (clozapine) 25 mg tablet (AA Pharma Inc.) and Clozaril* (clozapine) 25 mg tablet (HLS Therapeutics Inc.).

Clozapine (12.5 mg [1/2 x 25 mg]) From Measured Data Geometric Mean[#] Arithmetic Mean (CV%)				
Parameter	Test*	Reference[†]	Ratio of Geometric Means (%)	90% Confidence Interval (%)
AUC_t (ng•h/mL)	301.74 334.93 (51)	278.40 322.91 (61)	108.4	102.4 – 114.7
AUC_{inf} (ng•h/mL)	324.13 366.96 (59)	298.25 353.27 (67)	108.7	102.6 – 115.1
C_{max} (ng/mL)	23.90 25.50 (36)	21.89 24.24 (44)	109.2	102.6 – 116.1
T_{max}[§] (h)	2.11 (23)	2.13 (51)		
T_{half}[§] (h)	19.68 (26)	19.08 (24)		

* AA–Clozapine (clozapine) 25 mg tablets (AA Pharma Inc.)

[†] Clozaril* (clozapine) 25 mg tablets (HLS Therapeutics Inc.) were purchased in Canada.

[#] For balanced treatment sequence, results are based on Geometric means. For unbalanced treatment sequence, results are based on Least Squares Means (LSM).

[§] Expressed as arithmetic means (CV%) only.

Clinical Trial Data on Suicidal Behaviour (InterSePT Study)

The International Suicide Prevention Study (InterSePT) Study ABA 451 was a prospective, open-label randomized, international, parallel-group comparison of clozapine vs. olanzapine of two years duration, with approximately 490 patients per treatment group.

Trial Design

Patients were diagnosed with schizophrenia or schizoaffective disorder using DSM-IV criteria, and meeting at least one of the following criteria in order to be deemed at high risk for suicide: a) a suicide attempt, or hospitalization to prevent an attempt, within the last three years; or b) moderate to severe suicidal ideation with either a depressive component or command hallucinations, within the last week. One fourth (27%) of the patient population was considered "treatment-resistant".

Due to the high-risk nature of the study population, the principle investigators (PIs) were permitted to treat patients as they judged necessary, including concomitant medications, non-drug treatments, and hospitalizations. Both the PIs and the patients were aware of the treatment group assignment.

Efficacy Measures

The primary efficacy measure was time to the first occurrence of either a Type I or Type II event.

The unblinded PIs were responsible for identifying Type I events: a suicide attempt, or the judgement of need for hospitalization/increased surveillance to prevent an attempt. In the case of the Type I events, all relevant information from the PIs was blinded and forwarded to a blinded group of experts (the Suicide Monitoring Board) for final confirmation of each potential Type I event. Blinded psychiatrists, who assessed the patients at pre-determined intervals, were responsible for identifying Type II events: "much worsening" or "very much worsening" from baseline in the Clinical Global Impression of Severity of Suicidality-Blinded Psychiatrist (CGI-SS-BP) scale.

Results

Analysis using the Cox's proportional hazard regression model demonstrates that within the context of the InterSePT trial there was a 26% reduced risk for a suicide attempt or hospitalization to prevent suicide (Type 1 event) for clozapine-treated patients compared to olanzapine treated-patients ($p=0.02$, hazard ratio 0.74 [95% C.I.:0.57,0.96].

Factors that preclude regulatory endorsement of an indication for clozapine for the risk of recurrent suicidal behaviour in patients with schizophrenia or schizoaffective disorder:

1. The heavy reliance of the endpoints on clinical judgement, when combined with the fact that

the principle investigators were not blinded to the treatment group, creates the potential for bias in the results.

2. Separate indications for the domain of recurrent suicidal behaviour versus that of psychosis require a conclusion that the two domains are independent; currently, there is insufficient evidence to allow such a conclusion.
3. The usual concerns with generalizability of study results to individual patients in clinical practice are magnified in this therapeutic area. Given that schizophrenia is associated with long-term increased risk of suicide, the two year duration of the study limits generalizability. Many patients in this study had multiple suicide risk factors; the variable and dynamic nature of risk and protective factors, and the unpredictability of interaction with unique life circumstances also limit generalizability, as do the unusual efforts made in the study to prevent a suicide attempt, including frequent patient-clinician contact.
4. Because decisions about concomitant treatment were made by unblinded PIs, the post-hoc finding that the clozapine group received significantly less psychotropic medication than did the olanzapine group is not readily interpretable.
5. This is the sole prospective randomized trial.

Conclusion

Under the currently approved Canadian indication, clozapine is already available to a substantial percentage of psychotic patients at risk of suicide, given the frequency of tolerability issues and the fact that a complete response to an anti-psychotic is rare. The InterSePT study is a source of further information with regards to these patients.

While the InterSePT results are hypothesis-generating, they fail to provide sufficient evidence to support the safety and efficacy of the use of clozapine in patients who are naive to anti-psychotics, or have schizoaffective disorder.

DETAILED 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 (^{3}H-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 antiserotoninergic 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 serotoninergic (S_2), alpha-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 M,F	IV IP Oral	61
	M	Oral	90
	F		210
			190
Rat	M,F M	IV IM IM	58
	F M F	Oral Oral	228
			198
			325
			225
Guinea Pig	M F	Oral	510
		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 LD_{50}.

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 F_2-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 F_2-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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PART III: CONSUMER INFORMATION

PrAA-CLOZAPINE
Clozapine Tablets USP

This leaflet is part III of a three-part "Product Monograph" published when AA-CLOZAPINE was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about AA-CLOZAPINE. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
AA-CLOZAPINE is a drug for the treatment of symptoms of schizophrenia in adults over 18 years old who do not respond to, or who experience serious side-effects with other drugs used for the same purpose.

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

What it does:
AA-CLOZAPINE helps manage your symptoms of treatment-resistant schizophrenia. In controlled clinical trials, clozapine was found to improve both positive and negative symptoms.

If you have any questions about how **AA-CLOZAPINE** works or why this medicine has been prescribed to you, ask your doctor.

When it should not be used:
Do not take **AA-CLOZAPINE**:
- If you are allergic (hypersensitive) to clozapine or any of the other ingredients listed in "**What the non-medicinal ingredients are**".
- If you are unable to undergo regular blood tests
- If you have ever been diagnosed as having a low number of white blood cells, except if this was following a treatment for cancer
- If you suffer or have ever suffered from bone marrow disease or disease affecting blood cell formation
- If you have liver, kidney or heart problems (e.g. myocarditis, cardiomyopathy, heart failure)
- If you suffer from uncontrolled seizures
- If you have problems with alcohol or drug abuse
- If you suffer or have ever suffered from severe constipation, obstruction of the bowel or any other condition which has affected your large bowel

If you think you are allergic to AA-CLOZAPINE ask your doctor for advice before taking AA-CLOZAPINE.

What the medicinal ingredient is:
The active substance of AA-CLOZAPINE is clozapine.

What the non-medicinal ingredients are:
The non-medicinal ingredients are: anhydrous lactose, colloidal silicon dioxide, crospovidone, magnesium stearate, methylcellulose and sodium lauryl sulfate.

What dosage forms it comes in:
AA-CLOZAPINE is available in 25 mg, 50 mg, 100 mg and 200 mg tablets.

WARNINGS AND PRECAUTIONS

- **Studies with various medications of the group to which AA-CLOZAPINE belongs have shown an association with an increased rate of death when used in elderly patients with dementia. AA-CLOZAPINE is not indicated in elderly patients with dementia.**
- **AA-CLOZAPINE may cause a potentially life-threatening decrease in your white blood cell count (agranulocytosis or granulocytopenia) and should not be used if you have a history of bone marrow disorder. While you are using AA-CLOZAPINE, you will undergo regular blood tests to ensure you have healthy white blood cell levels. For this reason, your doctor will also enrol you in a patient registry program (see Proper Use of this Medication for more information).**
- **Use of AA-CLOZAPINE has been associated with potentially serious heart problems (e.g. mycocarditis, pericarditis, pericardial effusion or cardiomyopathy) and should not be used if you have a history of heart disease.**

BEFORE you use AA-CLOZAPINE be sure to tell your doctor or pharmacist if you:
- Suffer from enlargement of the prostate
- Have a history of seizures (e.g. epilepsy)
- Have glaucoma (an eye condition)
- Suffer from diabetes
- Have risk factors for developing blood clots such as: a family history of blood clots, age over 65, smoking, obesity, recent major surgery (such as hip or knee replacement), immobility due to air travel or other reasons, or take oral contraceptives ("The Pill").
- Have a history of bone marrow disorder
- Have a paralytic ileus or other serious gastrointestinal problems
- Suffer from constipation
- Have or have had heart problems

- Have heart disease or family history of abnormal conduction in the heart called "prolongation of the QT interval"
- Have had a stroke
- Have or have had lung disease
- Have Alzheimer's disease
- Suffer from a condition called dementia
- Are pregnant or planning to become pregnant
- Are breast-feeding

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

Your doctor should check your body weight before starting AA-CLOZAPINE and continue to monitor it for as long as you are being treated.

Your doctor should take blood tests before starting AA-CLOZAPINE and for as long as you are being treated to monitor your blood sugar.

Pregnancy and breast-feeding
AA-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.

Effects on Newborns
In some cases, babies born to a mother taking AA-CLOZAPINE during pregnancy may experience symptoms that sometimes resolve on their own, or in other cases may be severe and require the newborn to be hospitalized. Seek immediate emergency medical attention for your newborn if they have difficulty breathing, are overly sleepy, have muscle stiffness, floppy muscles (like a rag doll), are shaking, or are having difficulty feeding.

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

Driving and using machines
Due to the risk of convulsions during AA-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).

Further safety measures
WHY IS THE TESTING OF YOUR BLOOD BY YOUR DOCTOR NECESSARY?
In rare instances (approximately 0.7% of cases), AA-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, AA-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. Following this initial period, your doctor will evaluate with you the possibility of limiting blood checks to two-week intervals for the next 26 weeks, depending on your health condition. Thereafter, following 52 weeks of continuous therapy, if your clinical condition permits it, blood tests could be performed every four weeks. Regular blood testing must be done for as long as you are taking AA-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 from the Office of the Privacy Commissioner of Canada, at the following address:
https://www.priv.gc.ca/resource/fs-fi/02_05_d_15_e.asp

INTERACTIONS WITH THIS MEDICATION

AA-CLOZAPINE may intensify the effect of alcohol, sleeping pills, tranquilizers, and anti-allergy (antihistamine) medications. Other medicines which may change the way AA-CLOZAPINE works include, for instance, certain antibiotics, medicines used to treat depression, convulsions or ulcers of the stomach, certain drugs effective against fungal or viral infections, and birth-control pills.

You should inform your doctor before taking any other medications, including:

- Carbamazapine
- Phenytoin
- Omeprazole
- Rifampicin
- Erythromycin
- Cimetidine
- Valproic acid
- Antifungals (fluconazole, miconazole, clotrimazole, etc.)
- SSRI antidepressants (fluvoxamine, paroxetine, sertraline, fluoxetine, citalopram)
- Ciprofloxacin
- Caffeine
- Tobacco smoke
- Narcotics
- Benzodiazepines
- Norepinephrine
- Epinephrine
- MAO (monoamine oxidase) inhibitors
- Any drugs for bone marrow suppression

Tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

PROPER USE OF THIS MEDICATION

Usual dose:

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

How much AA-CLOZAPINE to take

Treatment is usually started with one half of a 25 mg tablet once or twice on the first day. Your doctor will then gradually increase your dose, until the ideal dose for you is established.

Your treatment will continue with a daily dose of AA-CLOZAPINE between 300 and 450 mg. Some people may require doses up to a maximum of 900 mg per day.

When to take AA-CLOZAPINE

Taking AA-CLOZAPINE at the same time each day will help you remember when to take your medicine.

How to take AA-CLOZAPINE

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.

How long to take AA-CLOZAPINE

Continue taking AA-CLOZAPINE as your doctor tells you.

If you have questions about how long to take AA-CLOZAPINE, talk to your doctor or your pharmacist.

Do not stop taking AA-CLOZAPINE suddenly as it may cause unwanted side effects. If it is necessary, discuss with your doctor how to slowly stop the medication

Overdose:

Should you take more than the recommended dose of AA-CLOZAPINE, contact your doctor immediately.

If you think you have taken too much AA-CLOZAPINE, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:

If you miss a dose of AA-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 AA-CLOZAPINE for more than two days, do not re-start taking the drug, but contact your doctor for dosing instructions.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

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 clozapine cardiotoxicity).

Tell your doctor or pharmacist as soon as possible if you get unexpected symptoms while you are using AA-CLOZAPINE, even if you do not think that they are connected with the medicine.

Common side effects
The most common side effects are drowsiness, dizziness, a rapid heartbeat, constipation, and increased production of saliva. Other possible side effects include weight gain and urinary retention (less frequent urination).

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

AA-CLOZAPINE may cause muscle weakness, somnolence and low blood pressure which may lead to fall and injuries.

Other possible side effects include: headache, tremor, repetitive and ritualized behaviour (obsessive compulsive symptoms), obsessive thoughts and compulsive behaviours, high blood pressure, decrease in blood pressure, fainting, sweating, weight gain, problems in passing or retaining urine, speech disorders (e.g. stuttering, slurred speech), nausea, vomiting, dry mouth; muscle stiffness; abnormal movements, inability to initiate movement, inability to remain motionless, inner feeling of restlessness, stiff limbs, trembling hands; blurred vision, difficulty in reading; change in ECG heart machine; elevated liver enzymes; increased muscle enzymes; confusion; irregular heartbeat; difficulty swallowing; high cholesterol; high fatty acids in the blood; involuntary purposeless movements such as grimacing, lip smacking, rapid eye blinking; swelling of the glands in the cheeks; skin reactions; changes in brain waves machine (Electroencephalogram /EEG); stomach discomfort, heartburn; muscle weakness, muscle spasms; muscle pain; diarrhea; stuffy nose; nighttime bedwetting; rash, purplish-red spots, itching; diarrhea, abdominal pain, fever; change in skin colour; “butterfly” facial rash, joint pain, muscle pain, fever and fatigue (lupus erythematous); sudden, uncontrollable increase in blood pressure (pseudophaeochromocytoma), uncontrolled bending of the body to one side (pleurothotonus), if you are a male, ejaculatory disorder in which semen enters the bladder instead of ejaculating through the penis (dry orgasm or retrograde ejaculation). Tell your doctor if you have constipation, or if your constipation becomes severe (gets worse). You may require laxatives.
If any of these affects you severely, **tell your doctor.**

If you notice any other side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
Symptom / effect		Talk to your doctor or pharmacist		Stop taking drug and seekimmediate emergency medical treatment
		Only if severe	In all cases	
Very common	New or worsening constipation		√	
Common	**Low blood pressure**: weakness, dizziness, fainting.		√	
	High level of a specific type of white blood cells, increased white blood cell count		√	
	Sudden weakness or numbness of the face, arms or legs and speech or vision problems.			√
	Rigid/stiff muscles, high fever, rapid or irregular heartbeat, sweating,			√

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk to your doctor or pharmacist		Stop taking drug and seekimmediate emergency medical treatment
		Only if severe	In all cases	
	state of confusion or reduced consciousness			
	Seizures: loss of consciousness with uncontrollable shaking			√
Uncommon	**Signs of infection:** such as fever, severe chills, sore throat or mouth ulcers (sign of reduced number of white cells in your blood, leading to a higher sensitivity to infection).		√	
Rare	**Blood clots**: swelling, pain and redness in an arm or leg that can be warm to touch. You may develop sudden chest pain, difficulty breathing and heart palpitations		√	
	Chest pain due to inflammation of the heart muscle or the outer lining of the heart		√	
	Food getting into the lung		√	
	Abdominal pain due to inflammation of the pancreas		√	
	Low level of red blood cells		√	
	Liver Disorder: yellowing of the skin or eyes, dark urine, abdominal pain, nausea, vomiting, loss of appetite	√		
	Signs of respiratory tract infection or pneumonia: such as fever, coughing, difficulty breathing or wheezing.		√	
	Diabetes (signs of high sugar levels in		√	

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk to your doctor or pharmacist		Stop taking drug and seekimmediate emergency medical treatment
		Only if severe	In all cases	
	the blood): Excessive thirst, dry mouth and passing large amounts of urine.			
Very rare	Chest pain, difficulty breathing or other respiratory symptoms.			√
	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.		√	
	Thrombocytopenia (signs of low level of blood platelets): Spontaneous bleeding or bruising		√	
	High platelet levels in the blood	√		
	Impaired orientation/ confusion, nausea/ vomiting, excessive urination, abdominal pain with high blood sugar			
	Feeling sick, vomiting with severe/ prolonged constipation		√	
	Allergic reaction: swelling mainly of the face, mouth, and throat, as well as, the tongue, which may be itchy or painful, difficulty in breathing.			√
	Serious skin reactions: if you develop a skin rash or redness developing into widespread rash with blisters and peeling skin, swollen lymph nodes and fever.			√
	Inflammation of the kidney		√	
	Long lasting (more than 4 hours of duration) and			√

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk to your doctor or pharmacist		Stop taking drug and seekimmediate emergency medical treatment
		Only if severe	In all cases	
	painful erection of the penis.			

Other serious side effects include:
Very rare: sudden unexplained death
Unknown: profuse sweating, headache, nausea, vomiting, diarrhea (symptoms of cholinergic syndrome); heart attack which may cause death; crushing chest pain (signs of insufficient blood flow and oxygen to the heart muscle); kidney failure; liver disorders including fatty liver disease, death of liver cells; liver toxicity/injury and liver disorders that involve replacement of normal liver tissue with scar tissue leading to loss of liver function, including those liver events leading to life-threatening consequences such as liver failure (which may lead to death), liver injury (injury of liver cells, bile duct in the liver, or both) and liver transplant.

This is not a complete list of side effects. For any unexpected effects while taking AA-CLOZAPINE, contact your doctor or pharmacist.

HOW TO STORE IT

- Store at room temperature (15° C to 30° C).
- Protect from moisture.
- Do not use after the expiry date shown on the bottle.
- Keep out of the reach and sight of children.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

If you want more information about AA-CLOZAPINE:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Consumer Information by visiting the Health Canada website (https://health-products.canada.ca/dpd-bdpp/index-eng.jsp). Find the Consumer Information on the manufacturer's website http://www.aapharma.ca/products, or by calling 1-877-998-9097.

This leaflet was prepared by AA Pharma Inc.

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