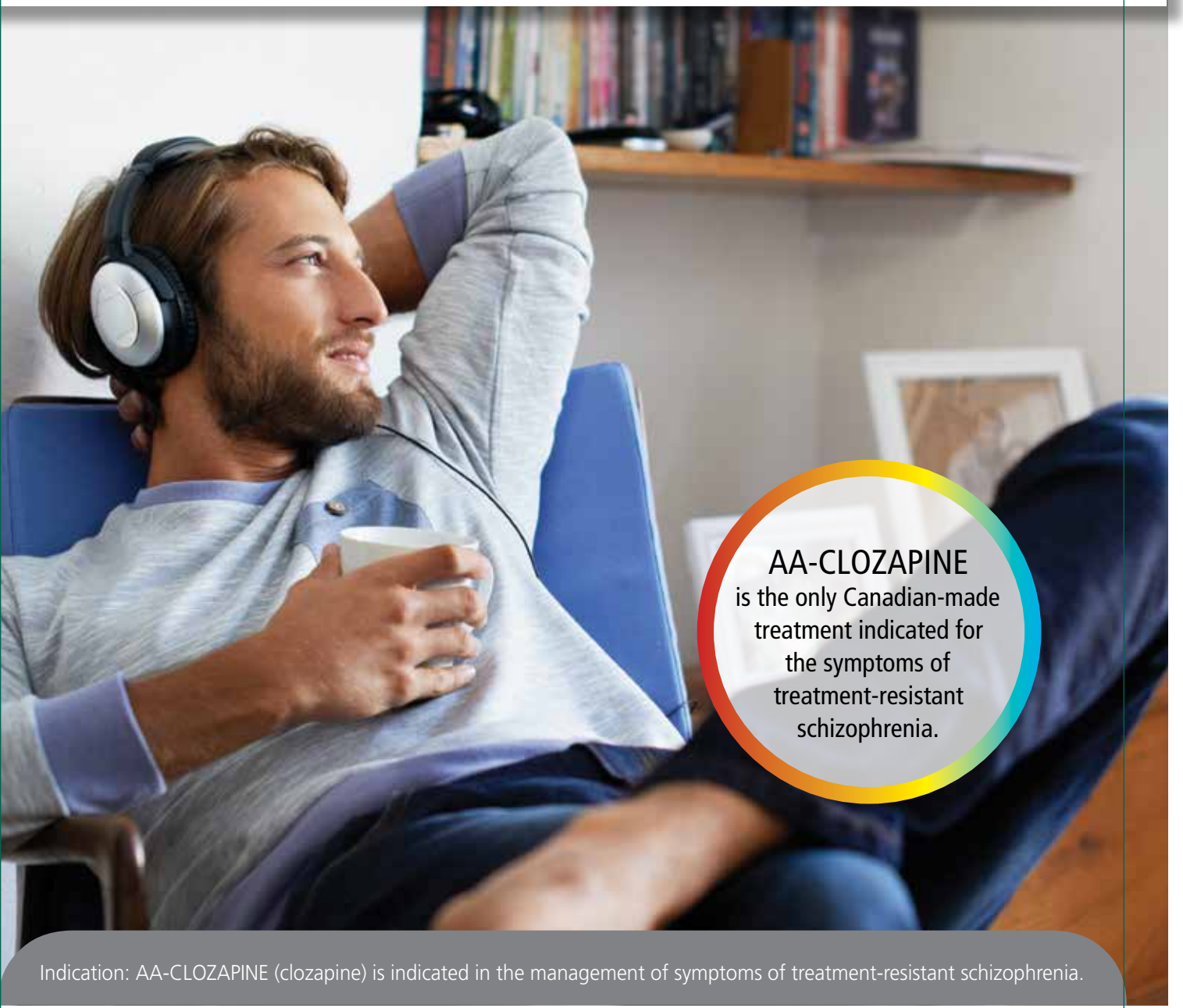
STARTING PATIENTS ON Pr AA Clozapine (CLOZAPINE)



AA-CLOZAPINE
is the only Canadian-made treatment indicated for the symptoms of treatment-resistant schizophrenia.

Indication: AA-CLOZAPINE (clozapine) is indicated in the management of symptoms of treatment-resistant schizophrenia.

AA pharma

Dosing considerations

Initial 2 to 3 doses must be monitored.

- AA-CLOZAPINE treatment must be initiated on an in-patient basis or in an outpatient 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.

Caution advised in outpatients receiving benzodiazepines or other psychotropic drugs.

- In outpatients, 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. Extra caution is advised in patients with cardiovascular disease or a history of seizures.

AA-CLOZAPINE is restricted to patients with a normal WBC count and ANC.

- AA-CLOZAPINE is restricted to patients who have a normal white blood cell (WBC) count and absolute neutrophil count (ANC), and patients in whom a WBC count and ANC can be carried out:
  - At least weekly for the first 26 weeks of treatment
  - At least at two-week intervals for the next 26 weeks
  - At least at four-week intervals thereafter

  Monitoring must continue for as long as the patient is on the drug, and for at least four weeks after discontinuing treatment.

AA-CLOZAPINE treatment necessitates regular hematological monitoring.

- 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.

The lowest effective dose of AA-CLOZAPINE should be used.

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

Important note about hematological monitoring

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.

AA-CLOZAPINE is available in the following dosage strengths: 25 mg, 50 mg, 100 mg, and 200 mg tablets.

Recommended dose and dosage adjustment

DAY 1	DAY 2	WEEKS 1–2	FOLLOWING MONTHS	MAINTENANCE
12.5 mg OD or BID	**25 mg** OD or BID	Increase daily by **25–50 mg** Target: 300–450 mg/day	**300–600 mg/day** in divided doses	Titrate downward to target of **150–300 mg/day** in divided doses
	Cautious titration and a divided dosage schedule are necessary to minimize the risks of hypotension, seizure, and sedation.	After the first two weeks, subsequent dosage increases should be made no more than once or twice weekly, in increments not to exceed 100 mg.	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.**	

Therapeutic dose range

In most patients, antipsychotic efficacy can be expected within the therapeutic range of 300–600 mg/day in divided doses. The total daily dose may be divided unevenly, with the larger portion at bedtime. Since improvement may be gradual, continued therapeutic response can be expected beyond the first month of treatment.

Maximum dose

Occasionally, patients may require doses higher than 600 mg/day to obtain an acceptable therapeutic response. Because of the possibility of increased adverse reactions (particularly seizures) at daily doses of 600 mg and higher, the decision to treat in the range of 600–900 mg/day must be taken prudently. THE MAXIMUM DOSE OF 900 MG/DAY SHOULD NOT BE EXCEEDED.

Maintenance dose

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

Re-initiation of treatment in patients previously discontinued

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. 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.

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, i.e., non-rechallengeable status) or severe leukopenia (WBC <2.0 x 10^9/L, i.e., non-rechallengeable status), or in patients with clozapine-induced myocarditis.

AA-CLOZAPINE treatment requires regular hematological monitoring

Due to the significant risk of granulocytopenia and agranulocytosis, patients treated with AA-CLOZAPINE require regular hematological monitoring.

Patients should be monitored:*	
Before starting treatment	Must have a normal WBC count and ANC
Weekly	For the first 26 weeks (6 months) of treatment
Every two weeks	For the next 26 weeks (6 months) of treatment
Every four weeks	Thereafter

* 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 based upon the hematological profile of the patient as well as the clinical judgment of the treating physician, and if deemed appropriate, a consulting hematologist, and on the patient's willingness to pursue a given frequency of blood monitoring. 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, and for at least four weeks after discontinuing treatment.

If treatment is interrupted, monitoring frequency may need to be adjusted

Resuming monitoring frequency after interruption in therapy

Treatment duration less than 6 months		Treatment duration greater than 6 months		Treatment duration greater than 12 months	
If break is >3 days, but ≤4 weeks	Break >4 weeks	If break is >3 days, but ≤4 weeks	Break >4 weeks	If break is >3 days, but ≤4 weeks	Break >4 weeks
Additional weekly monitoring x6 weeks	Weekly x6 months	Weekly x6 weeks, then return to every 2 weeks x6 months	Weekly x6 months, then return to every 2 weeks x6 months	Weekly x6 weeks, then return to every 4 weeks	Weekly x6 months, then every 2 weeks x6 months, then return to every 4 weeks

If patients switch from one brand of clozapine to another…

- The **frequency of hematological monitoring may continue unaltered**, unless a change is clinically indicated.
- Patients may NOT be switched without the completion of a new registry-specific patient registration form signed by the prescribing physician and the dispensing pharmacy/pharmacist.

Hematological guidelines for treatment with AA-CLOZAPINE

Treatment status	Course of action
BASELINE Hematological requirements for initiation of treatment: • WBC ≥3.5 x 10^9/L • ANC ≥2.0 x 10^9/L	• Begin treatment with AA-CLOZAPINE
GREEN If WBC ≥3.5 x 10^9/L and ANC ≥2.0 x 10^9/L	• Continue treatment with AA-CLOZAPINE • Monitor patient as follows:* – Weekly for the first 26 weeks – Every 2 weeks for the next 26 weeks – Every 4 weeks thereafter
FLASHING YELLOW • 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 <4.0 x 10^9/L • 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 <2.5 x 10^9/L	• Patient should be evaluated immediately • Check WBC count and ANC twice weekly • Continue treatment with AA-CLOZAPINE
YELLOW If any of the following: • WBC count falls to between 2.0 x 10^9/L and 3.5 x 10^9/L • ANC falls to between 1.5 x 10^9/L and 2.0 x 10^9/L	• Patient should be evaluated immediately • Check WBC count and ANC twice weekly • Continue treatment with AA-CLOZAPINE
RED If any of the following: • Total WBC count falls to below 2.0 x 10^9/L • ANC falls to below 1.5 x 10^9/L	• Immediately stop treatment with AA-CLOZAPINE and confirm results within 24 hours • Patient must be closely monitored • Attention must be paid to any flu-like complaints or other symptoms which might suggest infection • AA-CLOZAPINE therapy must NOT be resumed if results are confirmed and the patient should be assigned a non-rechallengeable status
CRITICAL If any of the following: • WBC count continues to fall below 1.0 x 10^9/L • ANC drops below 0.5 x 10^9/L	• Place the patient in protective isolation with close observation • Physician must watch for signs of infection

* 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 based upon the hematological profile of the patient as well as the clinical judgment of the treating physician, and if deemed appropriate, a consulting hematologist, and on the patient's willingness to pursue a given frequency of blood monitoring. The clinical evaluation should take into consideration possible factors that would place the patient in a higher risk group.

Please note: Waivers are available to treating physicians, which allow them to adjust and modify hematologic monitoring frequency as they deem appropriate.

Although rare, agranulocytosis is a concern

The facts on granulocytopenia/agranulocytosis

When does a patient have granulocytopenia or agranulocytosis?

Granulocytopenia is defined as a granulocyte count <1.5 x 10^9/L; agranulocytosis is defined as a granulocyte count <0.5 x 10^9/L, including polys + bands.

The overall incidence of granulocytopenia and agranulocytosis is low.

Granulocytopenia and agranulocytosis have been shown to occur in association with clozapine use at an incidence of 3% and 0.7%, respectively.*

Duration of treatment is not *always* a reliable predictor.

Approximately 88% of cases of agranulocytosis have occurred during the first 26 weeks of therapy, but some have occurred after years of clozapine use.

The risk of neutropenia and agranulocytosis increases with age.

50+

Patients over 50 years old are shown to present an approximately two- to three-times higher incidence of agranulocytosis vs. the overall incidence in clozapine-treated patients.

The development of granulocytopenia and agranulocytosis does not appear to be dose dependent.

Patients can develop granulocytopenia or agranulocytosis at any clozapine dose, and at any point in treatment, although the risk appears to be higher in the first 26 weeks of therapy.

* 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 the USA, Canada and the UK.

Routine blood monitoring has drastically reduced the risk of agranulocytosis

The AA-CLOZAPINE Risk Management Program helps to:

Promote the appropriate use of AA-CLOZAPINE

Ensure that every AA-CLOZAPINE patient undergoes regular hematological monitoring

Alert the prescribing physician ***within 24 hours*** of a blood test if there's been a drop in a patient's granulocyte count

Prevent or reverse agranulocytosis by detecting it early on

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.

AA-CLOZAPINE is supported by a web-based Risk Management Program and patient registry

- Overseen by an experienced medical team including a hematologist
- Fully certified and compliant with all Canadian and provincial safety and privacy regulations
- Secure and informative

STEP 1

Complete patient registration form including their current treatment location, testing laboratory, and SIGNATURES of PHYSICIAN and PHARMACIST, then fax it to the AA-CLOZAPINE Risk Management Program at 1-866-836-6778.

STEP 2

The pharmacist receives a confirmation of patient registration. This confirms that the pharmacist may dispense the first prescription of AA-CLOZAPINE.

STEP 3

Prior to dispensing subsequent prescriptions of AA-CLOZAPINE, the pharmacist must verify patient colour-coded lab results. These results are faxed to the pharmacy each time the registry receives blood results. Furthermore, the pharmacist can access the patient registry by logging in at www.aaclozapine.ca, or calling 1-877-276-2569.

Important safety information

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

Contraindications:

- Previous hypersensitivity to clozapine or any other components of AA-CLOZAPINE
- 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.
- Active liver disease associated with nausea, anorexia, or jaundice; progressive liver disease; hepatic failure
- Severe central nervous system depression or comatose states
- Severe renal or cardiac disease (e.g. myocarditis)
- Paralytic ileus
- Uncontrolled epilepsy
- Patients unable to undergo routine blood tests

Most 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. AA-CLOZAPINE is not indicated in elderly patients with dementia.

Agranulocytosis: Because of the significant risk of granulocytopenia and agranulocytosis, a potentially life-threatening adverse event, AA-CLOZAPINE should be reserved for use in the treatment of patients suffering from schizophrenia who fail to show an acceptable response to adequate courses of conventional antipsychotic drug treatment. Patients must have a normal White Blood Cell (WBC) count and differential cell 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.

Cardiovascular toxicity: The use of clozapine is associated with an increased risk of myocarditis especially during, but not limited to, the first month of therapy.

Other relevant warnings and precautions:

- Other adverse cardiovascular and respiratory effects
- QT interval prolongation
- Seizures
- Neuroleptic malignant syndrome
- Tardive dyskinesia
- Fever
- Cognitive and motor performance
- Drug interactions
- Concomitant CYP450 inhibitors and inducers
- Anticholinergic activity
- Venous thromboembolism
- Cerebrovascular adverse events
- Eosinophilia/thrombocytopenia
- Metabolic changes (hyperglycemia, dyslipidemia, and body weight gain)
- Dysphagia
- Patients with concomitant illness
- Patients with hepatic impairment
- Patients with renal impairment
- Patients with vascular disease
- Genitourinary
- Pregnancy, breast-feeding, and childbearing potential
- Not recommended for use under 18 years of age
- Not recommended for use in patients aged 60 years and older
- Rebound/withdrawal

For more information:

Please consult the Product Monograph at https://health-products.canada.ca/dpd-bdpp/index-eng.jsp for important information relating to adverse reactions, drug interactions, and dosing information which have not been discussed in this piece.

The Product Monograph is also available by calling AA Pharma at: 1-877-998-9097.

Important safety information

SAFETY INFORMATION

Keep AA-CLOZAPINE in mind for your treatment-resistant patients

- The only Canadian-made treatment indicated for the symptoms of treatment-resistant schizophrenia.
- Available in the following dosage strengths: 25 mg, 50 mg, 100 mg, and 200 mg tablets.
- Available only through a special AA-CLOZAPINE Risk Management Program, to ensure routine blood monitoring and safety.

For more information about the AA-CLOZAPINE Risk Management Program, please visit **www.aaclozapine.ca**, or call the registry at **1-877-276-2569**.

Reference: AA-CLOZAPINE Product Monograph, AA Pharma, December 2, 2016.

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SUMMARY