INTRODUCING 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

Medication for treatment-resistant schizophrenia (TRS)

Clozapine is the treatment of choice for TRS according to the Canadian Psychiatric Association.[1]

Consider AA-CLOZAPINE for TRS, defined as:[2]

- ☑ **Non-responsive** to treatment with appropriate courses of at least **two** different **antipsychotic drugs**
- ☑ **Intolerant:** treatment with conventional antipsychotic drugs causes **dose-limiting**, intolerable **adverse effects**

How common is TRS?

Despite adequate pharmacotherapy:*

≥20% At least 20% of multiple-episode patients have no positive-symptom response to antipsychotics.[1]

30% A further 30% respond only partially to antipsychotics.[1]

* An adequate trial of an antipsychotic prior to being deemed treatment-resistant is considered to be 4 to 8 weeks' duration on the maximum tolerated dosage within the recommended range.

If a patient is switched from one brand of clozapine to another, NO dosage adjustment is required.

Recommended dose and dosage adjustment[2]

	Dose	Important considerations
Day 1	12.5 mg OD or BID	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.
Day 2	25 mg OD or BID	Cautious titration and a divided dosage schedule are necessary to minimize the risks of hypotension, seizure, and sedation.
Weeks 1–2	Increase daily by 25–50 mg **Target:** 300–450 mg/day	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.
Following months	**Therapeutic dose:** 300–600 mg/day in divided doses	Patients must be given adequate time to respond to a given dose level before escalation to a higher dose is contemplated. Increased risk of adverse reactions at daily doses of 600 mg and higher. **The maximum dose of 900 mg/day should not be exceeded.**
Maintenance	Titrate downward to target 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 after treatment interruption (≥2 days since last dose)	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.

* When treatment is initiated 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 available in the following dosage strengths: 25 mg, 50 mg, 100 mg, and 200 mg tablets.

AA-CLOZAPINE treatment requires regular hematological monitoring[2]

Due to the significant risk of granulocytopenia* and agranulocytosis†, patients treated with AA-CLOZAPINE require regular hematological monitoring.[2]

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

ANC=absolute neutrophil count; WBC=white blood cell.
* Granulocytopenia is defined as a granulocyte count of <1.5 x 10^9/L.
† Agranulocytosis is defined as a granulocyte count of <0.5 x 10^9/L, including polys + bands.
‡ 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.[2]

AA-CLOZAPINE treatment requires regular hematological monitoring[2]

If treatment is interrupted, monitoring frequency may need to be adjusted.[2]

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.[2]

HEMATOLOGICAL MONITORING

Hematological guidelines for treatment with AA-CLOZAPINE

Hematological guidelines for treatment with AA-CLOZAPINE[2]

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

ANC=absolute neutrophil count; WBC=white blood cell.

* 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.

According to the Canadian Psychiatric Association, the duration of an adequate trial with clozapine is considered to be 4 to 6 months.[1]

Important safety considerations to note before prescribing AA-CLOZAPINE

Serious warnings and precautions[2]

- 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.
- 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.
- Use of AA-CLOZAPINE has been associated with potentially serious heart problems (e.g. myocarditis, pericarditis, pericardial effusion, and cardiomyopathy) and should not be used if the patient has a history of heart disease.

Do not prescribe AA-CLOZAPINE to patients with:[2]

- 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.
- Inability to undergo blood tests.
- Severe central nervous system depression or comatose states, severe renal or cardiac disease (e.g. myocarditis), paralytic ileus, uncontrolled epilepsy.

* Granulocytopenia is defined as a granulocyte count of <1.5 x 10^9/L.

† Agranulocytosis is defined as a granulocyte count of <0.5 x 10^9/L, including polys + bands.

Potential side effects of AA-CLOZAPINE

The most serious adverse reactions experienced with clozapine are agranulocytosis, seizure, cardiovascular effects, and fever. It is important to encourage your patients to notify you if any of these serious side effects occur while taking AA-CLOZAPINE.[2]

Adverse events observed in clinical trials (≥5%)[2]*

Central nervous system complaints

- Drowsiness/sedation (39%)
- Dizziness/vertigo (19%)
- Headache (7%)
- Tremor (6%)

Cardiovascular

- Tachycardia (25%)†
- Hypotension (9%)
- Syncope (6%)

Autonomic nervous system complaints

- Salivation (31%)
- Sweating (6%)
- Dry mouth (6%)
- Visual disturbances (5%)
- Fever (5%)

Gastrointestinal

- Constipation (14%)
- Nausea (5%)

* Adverse events experienced among patients taking clozapine in clinical trials (N = 842).
† Rate based on population of approximately 1,700 exposed during premarket clinical evaluation of clozapine.

The most common side effects are drowsiness/sedation, dizziness, hypersalivation, tachycardia, and constipation. Encourage your patients to report ANY side effects, no matter how minor. Also, advise your patients of the importance of adhering to their treatment. Stopping AA-CLOZAPINE can cause unwanted side effects.[1,2]

Concomitant medication and alcohol

Due to the possible drug-drug interactions associated with AA-CLOZAPINE, it is important for the physician to discuss the following with their patients:[1,2]

- The current medication (prescription and non-prescription) they are taking
- Before starting new medication (prescription and non-prescription)
- Past or present history with substance use or abuse

Drugs that should be avoided[2]

Drug	Interaction
Alcohol, monoamine oxidase inhibitors, CNS depressants (eg. narcotics, antihistamines, and benzodiazepines), anticholinergic and antihypertensive agents	AA-CLOZAPINE may enhance the effects of these substances.
Long-acting depot antipsychotic drugs	Potential to be myelosuppressive and cannot be rapidly removed from the body.
Valproic acid	May alter the plasma levels of clozapine. Rare but serious reports of seizures and isolated cases of delirium have been reported.
Cimetidine, erythromycin, azole antimycotics, protease inhibitors, fluvoxamine, ciprofloxacin, oral contraceptives, serotonin re-uptake inhibitors (e.g., paroxetine, sertraline, fluoxetine, citalopram), and caffeine	Inhibitors of cytochrome P450 isozymes may increase plasma levels of clozapine.
Carbamazepine, phenytoin, rifampicin, omeprazole, and tobacco smoking	Inducers of cytochrome P450 isozymes may decrease plasma levels of 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.

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.[2]

Important safety information

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

Consider AA-CLOZAPINE for your treatment-resistant patients

- TRS occurs in more than 50% of patients.[1]
- The Canadian Psychiatric Association recommends clozapine for TRS.[1]
- AA-CLOZAPINE is the only Canadian-made treatment indicated for the symptoms of TRS.
- AA-CLOZAPINE is available only through a special AA-CLOZAPINE Risk Management Program designed to ensure the required blood monitoring.

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.

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.

References: 1. Canadian Psychiatric Association (CPA). Clinical Practice Guidelines—Treatment of schizophrenia. *Can J Psychiatry.* 2005; 50(13): 1S–56S. https://ww1.cpa-apc.org/Publications/Clinical_Guidelines/schizophrenia/november2005/cjp-cpg-suppl1-05_full_spread.pdf. Accessed October 9, 2016. **2.** AA-CLOZAPINE Product Monograph, AA Pharma, December 2, 2016.

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SUMMARY

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