

PART III: CONSUMER INFORMATION

P AA-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 enroll 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. myocarditis, 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

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- 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

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drugs effective against fungal or viral infections, and birth-control pills.

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

- Carbamazepine
- 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 heart beat, constipation, and increased production of saliva. Other possible side effects include weight gain and urinary retention (less frequent urination).

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

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 erythematosus); 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 healthcare professional		Stop taking drug and get immediate medical help
		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		√	

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
Symptom / effect		Talk to your healthcare professional		Stop taking drug and get immediate medical help
		Only if severe	In all cases	
	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, 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		√	

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SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help	
	Only if severe	In all cases		
	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 the blood): Excessive thirst, dry mouth and passing large amounts of urine.		√	
Very rare	Chest pain, difficulty breathing or			√

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help	
	Only if severe	In all cases		
	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			√

IMPORTANT: PLEASE READ

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

Symptom / effect		Talk to your healthcare professional		Stop taking drug and get immediate medical help
		Only if severe	In all cases	
	or painful, difficulty in breathing.			
	Inflammation of the kidney		√	
	Long lasting (more than 4 hours of duration) and 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 -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 help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.

3 ways to report:

- Online at [MedEffect](http://www.healthcanada.gc.ca/medeffect) (www.healthcanada.gc.ca/medeffect);
- By calling 1-866-234-2345 (toll-free);
- By completing a Consumer Side Effect Reporting Form and sending it by:
 - Fax to 1-866-678-6789 (toll-free), or
 - Mail to: Canada Vigilance Program
Health Canada, Postal Locator 1908C
Ottawa, ON
K1A 0K9

Postage paid labels and the Consumer Side Effect Reporting Form are available at [MedEffect](http://www.healthcanada.gc.ca/medeffect) (www.healthcanada.gc.ca/medeffect).

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

For more information, please contact your doctor, pharmacist or other healthcare professional.

This leaflet plus the full product monograph, prepared for health professionals, can be obtained by contacting the sponsor, AA Pharma Inc. at:

1-877-998-9097

This leaflet was prepared by AA Pharma Inc.

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