

Clozaril® (clozapine)

WARNING

1. AGRANULOCYTOSIS

Because of a significant risk of agranulocytosis, a potentially life-threatening adverse effect, clozapine should be reserved for the use in the treatment of severely ill patients with schizophrenia who fail to show an acceptable response to adequate courses of standard antipsychotics drug treatment.

Patients being treated with clozapine must have a baseline white blood cell (WBC) and differential count before initiation of treatment as well as regular WBC counts during treatment and for 4 weeks after discontinuation of treatment.

Clozapine is available only through a distribution system that ensures monitoring of WBC counts according to the schedule described below prior to delivery of the next supply of medication.

2. SEIZURES

Seizures have been associated with the use of clozapine. Dose appears to be an important predictor of seizure, with a greater risk at higher doses. Caution should be used when administering clozapine to patients with a history of seizures or other predisposing factors. Patients should be advised not to engage in any activity where sudden loss of consciousness could cause serious risk to themselves or others.

3. MYOCARDITIS

Clozapine may be associated with an increased risk of fatal myocarditis, an inflammation of the heart muscle, especially during, but not limited to, the first month of therapy. In patients in whom myocarditis is suspected, clozapine treatment should be promptly discontinued.

4. OTHER ADVERSE CARDIOVASCULAR AND RESPIRATORY EFFECTS

Dizziness on standing, with or without fainting, can occur with clozapine treatment. Rarely, collapse can be profound and be accompanied by respiratory and/or cardiac arrest. A drop in blood pressure related to a positional change is more likely to occur during initial titration in association with rapid increases in the dose. In patients who have had even a brief interval off clozapine (2 or more days since the last dose), treatment should be started with 12.5 mg once or twice daily.

Since collapse, respiratory arrest and cardiac arrest during initial treatment has occurred in patients who were being administered benzodiazepines or other psychiatric medications, caution is advised when clozapine is initiated in patients already taking these other medications.

5. INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS

Elderly patients with dementia-related psychosis treated with atypical antipsychotics are at an increased risk of death compared to placebo. Most deaths appeared to be either cardiovascular or infectious in nature. Clozapine is not approved for the treatment of patients with dementia-related psychosis.

6. At the beginning of 2004, the Food and Drug Administration had all manufacturers of atypical antipsychotics include new warnings about each medication being associated with a possible risk of increased blood sugar and diabetes. All adverse effects should be monitored routinely by the professional prescribing treatment and preventive lifestyle changes are often needed.

Brand and Generic Names:

- Brand Name: Clozaril®, FazaClo ODT®

- 25 mg

- 100 mg

- Generic name: clozapine

What is clozapine and what does it treat?

Clozapine is an atypical antipsychotic that is approved for schizophrenia that has not responded to other treatments.

In schizophrenia, clozapine is useful for treating positive symptoms such as hallucinations, delusions, bizarre behavior and hostility. It also treats the negative

symptoms such as withdrawal, blunted emotions, lack of motivation, and inability to experience pleasure or enjoyment.

Clozapine is effective for about 60 percent of those who try it. A person should try clozapine for at least four to six weeks. Some symptoms, such as hallucinations, anxiety, paranoia, and bizarre behavior, should improve within that time; other symptoms may take longer. Additional improvements may be noticed over six to twelve months.

What is the most important information I should know about Clozaril?

- Blood work to obtain a WBC count must be done before you start taking the medication, weekly for the first six months of treatment then every 2 weeks for the next 6 months. Thereafter, if blood counts have been acceptable, the WBC count can be done every 4 weeks. This is to watch for agranulocytosis, in which the WBC count drops and increases the risk of infection. This condition is rare but potentially fatal.
- Do not stop taking clozapine or change your dose without first talking with your health care provider.
- Clozapine treatment must be closely monitored by a healthcare provider. Be sure to keep all scheduled appointments.
- You should not use illegal drugs or drink alcohol while taking clozapine.
- Clozapine may reduce the incidence of alcohol and drug use possibly by reducing craving for substances of abuse.
- Clozapine may increase the chances of having: diabetes, seizures and other potentially serious adverse effects.
- Clozapine has been shown to reduce suicide in persons with schizophrenia. It is the only antipsychotic medication that has been demonstrated to have this effect to date. Schizophrenia carries a 10% rate of actual suicide so this is key for consumers and families to know as they make decisions.
- Clozapine is a unique medicine and has important possible benefits as well as risks. The most noteworthy risk is weight gain and the risk of diabetes. For many people, being physically active and eating a good diet can keep this risk to a minimum. If you have a family history of diabetes or are part of a group that has increased risk, (African American, Asian American, Native American) you should discuss this with your doctor.

Are there specific concerns about clozapine and pregnancy?

If you are planning on becoming pregnant, notify your healthcare provider so that he/she can best manage your medications. People living with schizophrenia who wish to become pregnant face important decisions, each with risks and benefits as it relates to how the illness, medications and the risks to the fetus may interact. This is complex, as untreated schizophrenia also has risk to the mother and fetus. There are many dimensions to these choices, so be sure to confer with your doctor and caregivers.

Studies done in animals have not shown any evidence of harm to the fetus but there are no adequate and well-controlled studies in pregnant women. Because animal studies are not always predictive of human response, all medications should be kept to a minimum if possible, during pregnancy, and only used if clearly needed.

What should I discuss with my healthcare provider before taking Clozaril?

- The symptoms of schizophrenia that are most bothersome to you.
- The medications you have taken in the past for schizophrenia. It would be helpful for your provider to know which medications were effective and which were not.
- If you had any serious side effects to other antipsychotic medications like dystonia, tardive dyskinesia, neuroleptic malignant syndrome, weight gain, or diabetes, tell your healthcare provider.
- If you have ever had seizures.
- All other medications you are currently taking.
- If you smoke cigarettes, use illegal drugs, or drink alcohol.
- About any medication allergies you have.
- If you are pregnant, plan to get pregnant, or are breast feeding.
- Tell your doctor if you have thoughts of suicide.

How should I take Clozaril?

Clozaril is usually taken once or twice daily. It is usually started at a low dose and then gradually increased to prevent some of the side effects from developing. While many people may be treated with between 300–500 mg/day, the highest FDA approved dose is 900 mg/day.

What happens if I miss a dose of clozapine?

If a dose of clozapine is missed, take it as soon as you remember to, if it is not too close to when your next dose is due. Do not double up on your next dose. If you have been off of the medication for 2 or more days, don't start taking the full dose again. Talk to your healthcare professional about how to restart your clozapine. You may need to start at the initial dose and gradually increase it again, to prevent side effects.

What happens if I overdose with clozapine?

You may experience drowsiness, delirium or coma; low blood pressure, increased heart rate, or an abnormal heart rhythm; trouble breathing; and drooling. You should immediately go to the nearest emergency department or call 911.

What should I avoid while taking Clozaril?

- Please check with your healthcare provider before taking any other prescription, over-the-counter, or herbal/nutritional supplements.
- Avoid smoking cigarettes, using illegal drugs, or drinking alcohol.
- Some people get drowsy on clozaril, avoid driving a car until you are sure how the medication will affect you.

What are the possible side effects of clozapine?

Common adverse effects of clozapine usually include sleepiness, dizziness, rapid heart beat, constipation, excess saliva production and weight gain. Another important adverse effect that occurs commonly is orthostatic hypotension (a lowering of your blood pressure when you are sitting up or standing up). Occasionally this can lead to fainting and falling down, therefore, people taking clozapine should be careful when they change positions. These adverse effects are usually mild and usually go away after the first several days of starting treatment or increasing a dose.

One to two percent of patients who take clozapine develop a condition called agranulocytosis, in which the white blood cell count drops dramatically. The patient becomes extremely vulnerable to infections and unable to fight them off. This condition is dangerous and potentially fatal. Fortunately, if agranulocytosis does occur, most patients can be successfully treated by stopping clozapine. In addition to stopping clozapine, hospitalization and treatment with a drug that increases white blood cell production are available. To maintain safety, the white blood cell count for all patients taking clozapine must be checked each week for the first six months and then every other week after that. The results are sent to the patient's pharmacy before the next week's supply can be picked up. If detected early enough, the condition can be reversed by simply withdrawing the patient from clozapine. Hospitalization and treatment with medication to stimulate production of white blood cells may be necessary in some cases.

Seizures may occur in roughly one to five percent of patients. The higher the dose, the greater the risk of seizures. Cardiovascular and respiratory side effects are also possible but extremely rare. Lowered blood pressure and increased heart rate can usually be managed by gradually increasing a patient's clozapine dosage from an initially low level. Some patients may notice weight gain, drooling, and initial lethargy but these can be managed by dose adjustment or other interventions.

Clozapine has virtually no incidence of extrapyramidal symptoms such as muscle spasms, cramps, or posturing movements common to other antipsychotic medications, and a low incidence of side effects such as restlessness, muscle rigidity, and tremor. Clozapine does not seem to cause tardive dyskinesia (TD), a potentially permanent side effect of standard antipsychotic medications. TD is characterized by involuntary movements such as grimacing, sucking/smacking of lips, and spasmodic movements of the extremities. It usually begins after several months of treatment and may be irreversible. There have been no confirmed cases of TD directly caused by clozapine alone.

Although rare, there are some additional, serious adverse effects that may occur with clozapine treatment. Specifically, these are: myocarditis (a swelling of the heart muscle), cardiomyopathy (a widening of the lower heart chambers with weak contraction of the heart muscle that surrounds these two chambers), pulmonary embolism (a clot that blocks blood flow through the lungs) and respiratory depression (a decrease in breathing).

If you experience being extremely tired all of the time, changes in your breathing, a rapid heart beat, chest pain, or if you develop pain or discomfort in your legs, contact your doctor right away.

Are there any risks for taking this medication for long periods of time?

Long term treatment with antipsychotics has caused TD in some patients. There have been no confirmed cases of TD directly caused by clozapine alone, but patients should be regularly monitored for the development of TD. While agranulocytosis usually occurs most commonly within the first 4–6 months of treatment, you are at risk of this rare adverse effect for as long as you take clozapine. In most of the cases reported, cardiac enlargement occurred in those people who had been treated with clozapine for more than six months.

What other drugs interact with clozapine?

There are many other medications that may interact with clozapine. Any other medication that causes sleepiness or low blood pressure may increase the same side effects of clozapine and increase your chances of falling.

- Medications that may **increase** levels of clozapine in your body: ciprofloxacin (Cipro®), cimetidine (Tagamet®), erythromycin, lopinavir/ritonavir (Kaletra®), ritonavir (Norvir®), fluoxetine (Prozac®), fluvoxamine (Luvox®), citalopram (Celexa®), and sertraline (Zoloft®)
- Medications that may **decrease** levels of clozapine in your body: carbamazepine (Tegretol®), phenobarbital, phenytoin (Dilantin®), rifampin (Rifadin®), omeprazole (Prilosec®), and oxcarbazepine (Trileptal®).
- Combining clozapine with some seizure medications (especially carbamazepine [Tegretol®]) may increase the risk of agranulocytosis.

How long does it take for Clozaril to work?

A patient should try clozaril for at least four to six weeks. Some symptoms such as hallucinations, anxiety, paranoia, and bizarre behavior should improve within that time. Other symptoms may take longer. Additional improvements may be noticed over six to twelve months.

*Updated by Carla Cobb, Pharm.D., BCPP
December 2006*



For further more information please contact the pharmaceutical company listed below.

Teva Pharmaceuticals	50 NW 176th St Butler Building, Second Floor Miami, FL 33169	Clozapine Patient Registry: 800-507-8334	www.clozapineregistry.com
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Free or low-cost medications provided by pharmaceutical companies

Some pharmaceutical companies offer medication assistance programs to low-income individuals and families. These programs typically require a doctor's consent and proof of financial status. They may also require that you have either no health insurance, or no prescription drug benefit through your health insurance. Please contact the pharmaceutical company directly for specific eligibility requirements and application information.

Clozapine Rx Assistance: 1-800-507-8334