Gen-Clozapine (clozapine)

Drug Interactions Guide

GenCAN Monitoring With Confidence
Gen-Clozapine Access Network

Drug	Potential Drug Interactions
Alcohol, MAO inhibitors, CNS depressants (including narcotics, antihistamines, and benzodiazepines), anticholinergic and antihypertensive agents	Gen-Clozapine may enhance the central effects of these drugs.
Benzodiazepines or other psychotropic drugs	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.
Norepinephrine or other predominantly α-adrenergic agents, epinephrine	Owing to its anti-α-adrenergic properties, Gen-Clozapine may reduce the blood pressure increasing effect of norepinephrine or other predominantly α-adrenergic agents and reverse the pressor effect of epinephrine.
Bone Marrow Suppressants (eg. Carbamazepine, long-acting depot antipsychotic drugs)	Gen-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.
Valproic Acid	Concomitant use of valproic acid with Gen-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 Gen-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 Gen-Clozapine is prescribed with medicines known to increase the QTc interval, or causing electrolyte imbalance.
Tricyclic antidepressants, phenothiazines and type I_C anti-arrhythmics	No clinically relevant interactions have been observed.
Drugs known to inhibit the activity of cytochrome P450 isozymes: • Potent inhibitors of CYP3A (eg. azole antimycotics and protease inhibitors)[1] • Cimetidine (2D6, 3A4) • Erythromycin (3A4) • Caffeine (1A2)[2] • Fluvoxamine (1A2)[3] • SSRIs[4] • Ciprofloxacin (1A2) • Oral contraceptives (1A2, 3A4, 2C19)	May increase the plasma levels of Gen-Clozapine.
Drugs known to induce cytochrome P450 enzymes: • Carbamazepine (3A4) • Phenytoin (3A4) • Rifampicin (3A4) • Omeprazole (1A2)[1] • Tobacco Smoking (1A2)[5]	May decrease the plasma levels of Gen-Clozapine.

[1]No interactions have been reported to date.

[2]The plasma concentration of clozapine is increased by caffeine (1A2) intake and decreased by nearly 50% following a 5-day caffeine-free period.

[3]Substantial elevation of the plasma concentration of clozapine has been reported in patients receiving the drug in combination with fluvoxamine (1A2).

[4]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.

[5]In cases of sudden smoking cessation, the plasma clozapine concentration may be increased, thus leading to an increase in adverse effects.

Due to the significant risk of agranulocytosis and seizure with the active ingredient, Gen-Clozapine(clozapine) is indicated for the management of symptoms of treatment-resistant schizophrenia (non-responsive to, or intolerant of conventional antipsychotics). It can only be used if regular hematological testing can be guaranteed as specified in the Product Monograph.
Please consult prescribing information for important warnings, precautions and adverse events.

Please consult product monograph for complete information.

Gen-Clozapine
25 mg, 50 mg, 100 mg, 200 mg tablets

VIATRIS® Mental Health

Gen-Clozapine (clozapine)

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Indications and clinical use:

GEN-CLOZAPINE (clozapine) tablet 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 significant risk of neutropenia and seizure, 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 neutropenia 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. Seizure risk is dose-related and is more likely to occur with rapid dose increases. Titrate gradually and use divided doses. Use with caution in patients with history of seizure or risk factors for seizure.

Clozapine can be used only if regular hematological examinations can be guaranteed.

GEN-CLOZAPINE is available only through a distribution system GenCAN™ that ensures: weekly, every-two-week or every-four-week hematological testing prior to the dispensing of the next period's supply of GEN-CLOZAPINE.

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

Contraindications:

- Patients who are hypersensitive to clozapine or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container.
- Patients with myeloproliferative disorders, a history of toxic or idiosyncratic agranulocytosis or severe granulocytopenia.
- Patients with active liver disease associated with nausea, anorexia, or jaundice; progressive liver disease; hepatic failure.
- Patients unable to undergo blood tests.
- Other contraindications including severe central nervous system depression or comatose states, severe renal or cardiac disease, paralytic ileus, uncontrolled epilepsy.

Most serious warnings and precautions:

Severe Neutropenia (Agranulocytosis): GEN-CLOZAPINE treatment has caused severe neutropenia, defined as an absolute neutrophil count less than 500/µL. Severe neutropenia can lead to serious infection and death. Prior to initiating treatment with GEN-CLOZAPINE a baseline ANC must be at least 1500/µL for the general population; and must be at least 1000/µL for patients with documented Benign Ethnic Neutropenia (BEN). Regular hematologic monitoring is required prior to dispensing, because of the significant risk of this potentially life-threatening adverse event. Advise patients to immediately report the appearance of lethargy, weakness, fever, sore throat, flu-like complaints or any other signs of infection. Because of the risk of severe neutropenia, GEN-CLOZAPINE is available only through a distribution system ("GenCAN™") that ensures weekly, every-two-week or every-four-week hematological testing prior to the dispensing of the next period's supply of GEN-CLOZAPINE.

Myocarditis and Cardiomyopathy and Mitral Valve Incompetence: Fatal myocarditis and cardiomyopathy have occurred with the use of GEN-CLOZAPINE. Discontinue GEN-CLOZAPINE and obtain a cardiac evaluation upon suspicion of myocarditis or cardiomyopathy. Consider the possibility of myocarditis or cardiomyopathy if chest pain, tachycardia, palpitations, dyspnea, fever, flu-like symptoms, hypotension, or ECG changes occur.

Generally, patients with a history of clozapine-associated myocarditis or cardiomyopathy should not be rechallenged with GEN-CLOZAPINE.

Increased Mortality in Elderly Patients with Dementia: Elderly patients with dementia treated with antipsychotic drugs are at an increased risk of death compared to those treated with placebo. GEN-CLOZAPINE is not approved for use in elderly patients with dementia.

Other relevant warnings and precautions:

- Fever: may be associated with increase or decrease in the white blood cell count, rule out the possibility of an underlying infectious process or the development of blood dyscrasia, possibility of neuroleptic malignant syndrome must be considered, otherwise unexplained can accompany myocarditis. Anticholinergic activity: prostatic enlargement, narrow-angle glaucoma paralytic ileus; intestinal peristalsis, constipation, intestinal obstruction, fecal impaction, paralytic ileus, megacolon, intestinal infarction/ischemia; careful monitoring to identify early the onset of constipation, and effective management to prevent complications; concomitant medications known to cause constipation history of colonic disease or lower abdominal surgery, vital that constipation is recognized and actively treated
- Rebound, withdrawal effects: if abrupt discontinuation necessary, should be carefully observed for recurrence of psychotic related to cholinergic rebound symptoms, profuse sweating, headache, nausea, vomiting, diarrhea
- Cardiotoxicity: myocarditis, cardiomyopathy, pericarditis, pericardial effusion, heart failure, myocardial infarction, mitral insufficiency, eosinophilia. Patients with a family history of heart failure should have a cardiac evaluation prior to commencing treatment; contraindicated in patients with severe cardiac disease
- Other adverse cardiovascular and respiratory effects: patients with known cardiovascular and/or pulmonary disease, cardiac arrhythmias and conduction disturbances, recommendation for gradual titration of dose should be carefully observed; orthostatic hypotension, with or without syncope; collapse/ respiratory arrest/ cardiac arrest in combination or not with benzodiazepines or other psychotropic drugs; tachycardia; ECG repolarization changes including ischemic changes, myocardial infarction, arrhythmias, sudden death, congestive heart failure
- QT interval prolongation: caution advised when known cardiovascular disease, family history of QT prolongation, or when prescribed with medicines known to increase the QTc interval
- Venous Thromboembolism including fatal pulmonary embolism
- Sedation and weight gain: immobilization of patients should be avoided
- Driving and Operating Machinery: risk of convulsions, activities where a sudden loss of consciousness could occur should be avoided (e.g., driving, using machines, swimming, climbing)
- Impaired mental and/or physical ability
- Metabolic Changes: cardiovascular/cerebrovascular risk, hyperglycemia, dyslipidemia, and body weight gain
- Hyperglycemia: severe, sometimes leading to ketoacidosis/hyperosmolar coma; baseline and periodic monitoring of blood glucose and body weight; slight impairment of glucose homeostasis and a possibility of unmasking a pre-diabetic condition or aggravating pre-existing diabetes; any patient should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness
- Dyslipidemia: Clinical monitoring, baseline and periodic follow-up lipid evaluations recommended
- Weight Gain: Clinical monitoring of weight is recommended
- Priapism
- Hematologic Severe Neutropenia: 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 should be advised to report immediately the appearance of lethargy, weakness, fever, sore throat, flu-like complaints or any other signs of infection; patients must have a normal absolute neutrophil count prior to starting clozapine therapy
- Monitoring Schedule Guideline: monitoring must continue for as long as the patient is on the drug
- Eosinophilia: recommended to discontinue 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. Patients with both eosinophilia and clozapine-induced myocarditis should not be re-exposed to clozapine
- Thrombocytopenia: recommended to discontinue therapy if the platelet count falls below 50.0 x 10^9/L
- Hepatotoxicity: fatigue, malaise, anorexia, nausea, jaundice, bilirubinemia, coagulopathy, and hepatic encephalopathy
- Hepatic impairment: nausea, vomiting and/or anorexia, jaundice
- Seizures: may lower threshold
- Falls: somnolence, postural hypotension, motor and sensory instability, may lead to falls and, fractures or other injuries
- Neuroleptic Malignant Syndrome: hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmias), elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure
- Tardive Dyskinesia: potentially irreversible, involuntary, dyskinetic movements
- Renal impairment
- Severe Cutaneous Adverse Reactions Stevens-Johnson syndrome, toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms, acute generalized exanthematous pustulosis; combination of extensive cutaneous rash or exfoliative dermatitis, fever, lymphadenopathy and possible eosinophilia

For more information:

Consult the Product Monograph at https://health-products.canada.ca/dpd-bdpp/index-eng.jsp for more information about conditions of clinical use, contraindications, warnings, precautions, adverse reactions, interactions and dosing.

The Product Monograph is also available by calling Mylan Pharmaceuticals ULC at 1-844-596-9526 or the GenCAN Gen-Clozapine Access Network at 1-866-501-3338.

CLZ-2022-0129E - SE2022

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