GenCAN Monitoring With Confidence

Gen-Clozapine Access Network

Getting Started on Gen-Clozapine

A guide for healthcare professionals

VIATRIS® Mental Health

GenCAN Monitoring With Confidence

Gen-Clozapine Access Network

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Gen-Clozapine Access Network

GenCAN CLINICAL SERVICES TEAM

- 7 Full Time Clinical Nurse Coordinators (Advanced Mental Health Registered Nurses)
- 120+ years combined of extensive experience and proven leadership, including 65+ years combined of clozapine practice
- Dedicated in providing exceptional evidence-based clinical monitoring and support, ensuring product monograph requirements, as per Health Canada, are met, maximizing patient safety across Canada
- Easily accessible and responsive
- GenCAN Clinical Services include:
  - ✓ Hematologist Consultant
  - ✓ Cardiologist Consultant
  - ✓ Psychiatrist and Pharmacist Consultants: Non-salaried psychiatrists and pharmacists available

GenCAN DATABASE

GenCAN is a sophisticated, continually improving monitoring program that is accessible to healthcare treatment teams

- All clinical safety alerts are addressed and followed up by a Clinical Nurse Coordinator, customized to each healthcare team
- In addition to monitoring ANC (absolute neutrophil count), GenCAN database also records: WBC (white blood cell count), Weight/BMI/Blood Glucose/Dose/Troponin/ C-Reactive Protein and Clozapine Serum Levels
- Non-Rechallengeable and Cardiac Adverse Reaction warnings
- eAlerts provide email notifications*
- Preliminary status notifications to increase registration turnaround
- Customizable e-LabLink

*Optional

GenCAN Monitoring With Confidence

Gen-Clozapine Access Network

VALUE-ADDED SERVICES AND RESOURCES

PATIENT PROGRAMS

- Sweet Dreams Pillow kits[1]
- Annual Balanced Health Calendar[2]
- Compassionate Use Program[3]
- Side Effects Abatement Program[4]
- GenMobile Lab Services

FORMS & RESOURCES

- Hematological Guidelines
- A Guide for Healthcare Professionals
- A Guide for Healthcare Professionals for Outpatient Starts
- A Guide for Patients and Families
- Gen-Clozapine Drug Interactions
- Discharge Checklist
- GenCAN Patient Care Funding Request

HCP PROGRAMS

- Accredited on-line CME for Pharmacists[5]
- Patient Journey Program[6]
- Global Educational Program[7]

1. Includes super absorbent pillow cases to assist with hypersalivation side effect
2. To promote patient well-being and healthy lifestyle via monthly reminders on diet, exercise and resting.
3. To help patients in special cases and/or not covered by public or private drug plans
4. To assist local treatment teams managing side effects caused by Gen-Clozapine treatment
5. Clozapine: Revisiting the Gold Standard. https://www.healthelearning.ca/#/online-courses/
6. Clinical presentations on safety monitoring available live or in webinar format
7. Visit https://cme.psychiatrist.com and enter MY20096.

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A guide for healthcare professionals

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Reference: Gen-Clozapine Product Monograph, Health Canada, July 18, 2022.

Objective: Treatment Initiation

Patient's treatment will be initiated safely as per Product Monograph Guidelines

Intervention	Rationale
PATIENT CONSENT	
• Patient consent is obtained and patient is advised of sharing blood work results and other safety data between Clozapine registries.	• **GenCAN** is within the 'Circle of Care' therefore when a patient consents to Clozapine treatment, they consent to the blood monitoring system. • The signature of the treating physician on the patient registration form is confirmation for **GenCAN** that consent has been obtained.
PRE-TREATMENT EXAMINATIONS	

Required:
• Absolute Neutrophil Count (ANC)
  • Mandatory for registration
  • Results within 28 days of start
	• As per Health Canada, treatment should not be initiated if the ANC is less than 2.0 x 10^9/L, or BEN - ANC is less than 1.0 x 10^9/L , or if the patient has a history of a myeloproliferative disorder, or toxic or idiosyncratic agranulocytosis or severe granulocytopenia (with the exception of granulocytopenia/agranulocytosis from previous chemotherapy).

Recommended:
• Complete Medical History
  • ECG
  • Weight/BMI
  • Lipid profile
  • Blood Glucose
  • Liver/Renal function tests
  • Serum creatinine
  • Creatine kinase
  • C-reactive protein/ Troponin
  • Glycated hemoglobin (HbA1c)
  • Na-K-Cl ions
  • Prolactin
	• ECG prior to treatment is recommended as Clozapine is associated with several cardiac complications, i.e. cardiomyopathy, myocarditis, pericarditis, pericardial effusion, heart failure, myocardial infarction and mitral insufficiency. Clozapine is contraindicated in patients with previous cardiac conditions.
	• Clozapine is also associated with metabolic changes that may increase cardiovascular/cerebrovascular risk. These metabolic changes may include hyperglycemia, dyslipidemia, and body weight gain. A pre-treatment evaluation will give the clinician a baseline to measure against while monitoring these values on treatment.
	• Use caution with patients with a history of seizures. Clozapine is contraindicated in patients with severe renal disease, active liver disease and or history of paralytic ileus. Patients must be able to undergo blood tests.
	• The **GenCAN database** allows for additional monitoring parameters (weight, BMI, blood glucose, troponin/c-reactive protein, and serum Clozapine levels).

• Assess current medications for possible interactions.	• Refer to the **GenCAN Drug Interactions Guide.**
BENIGN ETHNIC NEUTROPENIA (BEN)	
• Additional evaluation may be needed to determine if baseline neutropenia is due to BEN. Consider a hematology consultation before initiating or during Gen-Clozapine treatment as necessary.	• Benign ethnic neutropenia (BEN) is a condition observed in certain ethnic groups whose average ANC (absolute neutrophil count) values are lower than standard laboratory ranges for neutrophils. It is most commonly observed in non-Caucasian individuals and is more common in men.

Cont...

Reference: Gen-Clozapine Product Monograph, Health Canada, July 18, 2022.

Objective: Treatment Initiation (continued)

Patient's treatment will be initiated safely as per Product Monograph Guidelines

Intervention	Rationale
BENIGN ETHNIC NEUTROPENIA (BEN)	
• BEN status to be indicated on the **GenCAN Patient Registration Form** and/or in consultation with your Clinical Nurse Coordinator.	• Patient with BEN have normal hematopoietic stem cell number and myeloid maturation, are healthy, and do not suffer from repeated or severe infections. They are not at increased risk for developing Gen-Clozapine-induced neutropenia.

• Patients with BEN have altered monitoring guidelines as follows:
  • ANC ≥ 1.0 x 10^9/L Green Status
  • ANC < 1.0 x 10^9/L Yellow Alert
  • ANC < 0.5 x 10^9/L Red Alert	

REGISTRATION FORM	
• The **GenCAN Patient Registration Form** is completed and signed by physician and pharmacy (where required), and includes baseline blood work: ANC (absolute neutrophil count). • Online form is available at www.gencan.ca	• A completed and signed patient registration form ensures all members of treatment team are aware that Gen-Clozapine treatment is being initiated and baseline blood work is completed.
	• The required information includes patient's initials, DOB, PHIN, testing lab, treatment location, prescribing physician and dispensing pharmacy.
REGISTRATION NOTIFICATION	
• Treatment should only be started upon receipt of final notification.	• Health Canada requires that a patient treated with Gen-Clozapine be registered with the Gen-Clozapine Access Network **(GenCAN)**. The physician and pharmacy will receive a preliminary registration notification confirming receipt of registration followed by a FINAL registration once processed. The FINAL registration notification fax is a confirmation for the treatment team that registration is complete and Gen-Clozapine treatment can be initiated.

• Contact your Clinical Nurse Coordinator to set-up **eAlerts** for notifications.	• **GenCAN eAlerts** provide email notifications for
	  • Preliminary and FINAL registration
	  • All clinical safety alerts, including return to green status
	  • Late blood work
	  • Patient modifications
	Pharmacies may register for Active Weekly Blood Work Reports.

Cont...

Reference: Gen-Clozapine Product Monograph, Health Canada, July 18, 2022.

Objective: Treatment Initiation (continued)

Patient's treatment will be initiated safely as per Product Monograph Guidelines

Intervention	Rationale
DOSE, TITRATION AND VITAL SIGNS	
Dose Titration: • Day 1: 12.5 mg (one-half of a 25 mg tab). • Day 2: 25 mg dose. • Day 3: Incremental doses 25-50 mg/day achieving a target dose of 300-450 mg/day by the end of Day 14. • Day 3 to 14: Subsequent dosage increases should be made no more than once or twice weekly, in increments not to exceed 100 mg.	• The dosage of Gen-Clozapine must be adjusted individually. For each patient the lowest effective dose should be used. Patients must be given adequate time to respond to a given dose level before escalation to a higher dose is contemplated. Patients should be periodically reassessed to determine the continued need for maintenance dose.
• In most patients, efficacy can be expected within the therapeutic range of 300-600 mg/day in divided doses. Can be divided unevenly with larger portion at bedtime. See Product Monograph for maintenance dosage.	• Cautious titration and a divided dosage schedule are necessary to minimize the risks of hypotension, seizure and sedation.
• 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.	• Seizure risk is dose-related and is more likely to occur with rapid dose increases.
• Vital signs to be monitored for a minimum of 6-8 hours after the initial 2-3 doses. This is a minimum requirement. Follow your organization's policy for more detailed instructions.	• Vital sign variances are more likely to occur during initial titration and in addition with rapid dose escalation and may even occur on first dose. In one report, initial doses as low as 12.5 mg were associated with circulatory collapse and respiratory arrest.

Cont...

Reference: Gen-Clozapine Product Monograph, Health Canada, July 18, 2022.

Objective: Treatment Initiation (continued)

Patient's treatment will be initiated safely as per Product Monograph Guidelines

Intervention	Rationale
DOSE, TITRATION AND VITAL SIGNS	
• Contact your Clinical Nurse Coordinator to set-up access to the **GenCAN database.**	• Utilizing the **GenCAN database** allows for additional monitoring parameters including dosage.
• For outpatient settings, please refer to the **Getting Started on Gen-Clozapine: A guide for healthcare professionals for outpatient starts.**	• The **Getting Started on Gen-Clozapine: A guide for healthcare professionals for outpatient starts** assists HCPs starting patients in an out-patient setting. Gen-Clozapine treatment may be initiated on an outpatient basis where medical supervision is available and vital signs can be monitored for a minimum of 6-8 hours after the initial 2 to 3 doses.

Reference: Gen-Clozapine Product Monograph, Health Canada, July 18, 2022.

Objective: Blood Monitoring

Patient will have blood monitoring as per Product Monograph

ABSOLUTE NEUTROPHIL COUNT (ANC)

Blood work should be done every week for the first 26 weeks of treatment, then every two weeks for the next 26 weeks and every four weeks for the duration of remaining treatment. The development of neutropenia and agranulocytosis does not appear to be dependent on the duration of treatment.

Intervention	Rationale
• Blood work results (ANC) collected as per monitoring frequency.	• The cumulative incidence of neutropenia on Gen-Clozapine use is 2.6%. This cumulative incidence can be further divided into moderate neutropenia (1.24%), severe neutropenia (0.62%) and agranulocytosis (0.76%). • Rare fatal cases of Clozapine-induced neutropenia have been reported in association with Gen-Clozapine. However, more than half of these deaths occurred before 1977, prior to the recognition of the risk of neutropenia and the need for routine blood monitoring. • The development of neutropenia and agranulocytosis does not appear to be dependent on the duration of treatment. Recent Canadian data indicate that approximately 51% of the cases of neutropenia have occurred during the first 26 weeks of therapy, and 41% occurred after ≥52 weeks of treatment, underscoring the need for continued monitoring. • Experience in Canada (38,996 patients ever exposed to April 2019) reveals that the mean age of patients treated with clozapine is 39.3 years while the mean age of patients experiencing a hematological event is 44 years and 47 years for those experiencing agranulocytosis.

• Arrangements made to have blood tests results sent to **GenCAN**:
  • Fax: 1-800-497-9592
  • Online: www.gencan.ca
  • Phone: 1-866-501-3338
  • Lab Req: Ensure to cc: **GenCAN** fax# on requisition
  • **Lablink:** Automatic lab upload	

• Contact your Clinical Nurse Coordinator to:
  • Access and enter results via the **GenCAN database.**
  • Set up a customizable **LabLink.**
  • Register for **eAlerts** to include late blood work notices.	

Cont...

Reference: Gen-Clozapine Product Monograph, Health Canada, July 18, 2022.

Objective: Blood Monitoring (continued)

Patient will have blood monitoring as per Product Monograph

Intervention	Rationale
'NO BLOOD NO DRUG' POLICY	
• Regular hematologic monitoring is required prior to medication dispensing. As per monograph guidelines, pharmacy will not dispense until confirmation is received that current blood work has been completed.	• Gen-Clozapine is available only through a distribution system the Gen-Clozapine Access Network **(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 (see Product Monograph).

• Contact your Clinical Nurse Coordinator to:
  • Set-up **GenCAN database** access.
  • Register for **eAlerts.**
  • Obtain **GenCAN Lab Stickers** and **GenCAN LabMinders.**
	• Utilizing the **GenCAN database** provides up-to-date blood work results.
	• Utilizing **GenCAN eAlerts** provides email notifications for late blood work.
	• Utilizing **GenCAN Lab Stickers** directs lab to cc: **GenCAN** blood work results.
	• Utilizing **GenCAN LabMinders** assist the patient in communicating with the pharmacy blood work has been completed.

TREATMENT BREAK	
• If a dose of Gen-Clozapine is missed and remembered within two hours, then it may be taken immediately. Otherwise, the missed dose should be skipped, and the regular dosing schedule is to be continued. Double doses should not be taken.	
• If dosing is missed or stopped for 48 hours or more, it is recommended that the patient's dose be re-initiated to 12.5 mg and re-titrated. The blood monitoring frequency may remain the same.	
• If Gen-Clozapine treatment is interrupted for more than 72 hours but less than 1 month, it is recommended that the patient's dose be re-initiated to 12.5 mg and re-titrated. Blood monitoring should return to weekly frequency for 6 weeks.	

Cont...

Reference: Gen-Clozapine Product Monograph, Health Canada, July 18, 2022.

Objective: Blood Monitoring (continued)

Patient will have blood monitoring as per Product Monograph

Intervention	Rationale
• If Gen-Clozapine treatment is interrupted for more than 1 month, the patient should be treated as a 'new start'.	• Certain additional precautions seem prudent when re-initiating treatment. The mechanisms underlying some of the Gen-Clozapine - induced adverse reactions are unknown. It is conceivable that re-exposure of a patient might enhance the risk of an untoward event's occurrence and increase its severity. Such phenomena, for example, occur when immune-mediated mechanisms are responsible. Therefore, any patient who has previously experienced respiratory or cardiac arrest with initial dosing, but was then able to be successfully titrated to a therapeutic dose, should be re-titrated with extreme caution after even 24 hours of discontinuation.
DISCONTINUATION	
• Discontinuation due to neutropenia, monitoring **twice a week** until ANC is **normal** (ANC is ≥ 2.0 x 10^9/L) (BEN-ANC is ≥ 1.0 x 10^9/L).	• Of 1,080 patients who received Clozapine in pre-marketing clinical trials, 16% discontinued treatment due to an adverse event, including both those that could be reasonably attributed to Clozapine treatment and those that might more appropriately be considered intercurrent illness.
• Discontinuation unrelated to neutropenia, **weekly** monitoring until ANC is **normal** (ANC is ≥ 2.0 x 10^9/L) (BEN-ANC is ≥ 1.0 x 10^9/L).	• The more common events considered to be causes of discontinuation included: CNS (psychotic disorder), primarily drowsiness/sedation, somnolence, seizures, dizziness (excluding vertigo)/syncope; cardiovascular, primarily tachycardia, hypotension and ECG changes; gastrointestinal, primarily nausea/vomiting; hematologic, primarily neutropenia and fever.
• In the event of planned termination of Gen-Clozapine treatment, gradual reduction in dose is recommended over a 1 to 2-week period.	
• Patients should be carefully observed for the recurrence of psychotic symptoms and symptoms related to cholinergic rebound such as profuse sweating, headache, nausea, vomiting and diarrhea.	

Reference: Gen-Clozapine Product Monograph, Health Canada, July 18, 2022.

Objective: Side Effect Management

Patient to be evaluated and treated for possible drug induced side effects as outlined in the Gen-Clozapine Product Monograph and as per treating physician's orders. The following are the most common or most dangerous side effects. (Consult Product Monograph for full side effect profile.) For all drug interactions refer to the Product Monograph and or the **Gen-Clozapine Drug Interaction Guide**

AGRANULOCYTOSIS

Severe Neutropenia (Agranulocytosis) Gen-Clozapine treatment has caused severe neutropenia, defined as an absolute neutrophil count (ANC) less than 500/µL. Severe neutropenia can lead to serious infection and death. Regular hematologic monitoring is required prior to dispensing, because of the significant risk of this potentially life-threatening adverse event.

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. **GenCAN** provides clinical safety alerts to healthcare professionals maximizing patient safety and ensuring monograph requirements are met.

Intervention	Rationale

• Continue Gen-Clozapine treatment
  • ANC blood work twice weekly.
  • Carefully monitor for flu-like symptoms or other symptoms that might suggest infection.
  • Pharmacy to continue to dispense once weekly, every two weeks or every four weeks.
	• **YELLOW** ALERT
	  • ANC < 2.0×10^9/L
	  • BEN - ANC < 1.0×10^9/L

• Place Gen-Clozapine on-hold
  • Repeat ANC within 24hrs to confirm results.
  • Carefully monitor for flu-like symptoms or other symptoms suggestive of infection.
  • Pharmacy to consult with physician for dispensing direction.
  • Upon confirmation of repeat ANC RED alert result, STOP Gen-Clozapine treatment. Patient to be assigned NON-RECHALLENGEABLE status for Clozapine associated neutropenia and Gen-Clozapine therapy must not be resumed.
	• **RED** ALERT
	  • ANC < 1.5×10^9/L
	  • BEN - ANC < 0.5×10^9/L

Cont...

Reference: Gen-Clozapine Product Monograph, Health Canada, July 18, 2022.

Objective: Side Effect Management (continued)

Patient to be evaluated and treated for possible drug induced side effects as outlined in the Gen-Clozapine Product Monograph and as per treating physician's orders. The following are the most common or most dangerous side effects. (Consult Product Monograph for full side effect profile.) For all drug interactions refer to the Product Monograph and or the **Gen-Clozapine Drug Interaction Guide**

Intervention	Rationale
• Daily ANC monitoring encouraged until Red Alert resolved. • Continue with blood monitoring (ANC) at least twice weekly until ANC is ≥ 2.0×10^9 (≥ 1.0×10^9 for BEN patients).	
• Protective isolation is recommended with close observation for signs of infection by physician. Should evidence of infection develop, the appropriate cultures should be performed, and an appropriate antibiotic regimen instituted.	• Further fall of ANC < 0.5×10^9/L.
• Refer to the **GenCAN Hematological Guidelines** for more details. • Contact your Clinical Nurse Coordinator to register for **GenCAN eAlerts** for all clinical safety alerts, including return to green status. • Refer to Product Monograph for more details.	• Contacting your Clinical Nurse Coordinator will provide additional support and/or opportunity for consultation. For CNCs call 1-866-501-3338.

MYOCARDITIS, CARDIOMYOPATHY & MITRAL VALVE INCOMPETENCE

Fatal myocarditis and cardiomyopathy have occurred with the use of Gen-Clozapine. Pericarditis, and pericardial effusion have also been reported in association with clozapine use, as have heart failure, myocardial infarction and mitral insufficiency; these reports include fatalities.

Intervention	Rationale
• Use Gen-Clozapine with caution in patients with known cardiovascular and or pulmonary disease. Patients with a history/family history should have a cardiac evaluation prior to commencing treatment.	• Clozapine is contraindicated in patients with severe cardiac disease.

Cont...

Reference: Gen-Clozapine Product Monograph, Health Canada, July 18, 2022.

Objective: Side Effect Management (continued)

Patient to be evaluated and treated for possible drug induced side effects as outlined in the Gen-Clozapine Product Monograph and as per treating physician's orders. The following are the most common or most dangerous side effects. (Consult Product Monograph for full side effect profile.) For all drug interactions refer to the Product Monograph and or the **Gen-Clozapine Drug Interaction Guide**

Intervention	Rationale
• Recommend gradual titration of dose should be carefully observed (initial dose should be 12.5 mg given once on the first day), and dosage increase should be slow and in small increments.	
• Consider the possibility of myocarditis or cardiomyopathy if chest pain, dyspnea, persistent tachycardia at rest, palpitations, fever that is otherwise unexplained, fatigue, flu-like symptoms, hypotension, other signs or symptoms of heart failure (e.g. chest pain, tachypnea (shortness of breath), or arrhythmias), or ECG changes occur.	• Myocarditis most frequently presents within the first 2 months of clozapine treatment. Symptoms of cardiomyopathy generally occur later than clozapine-associated myocarditis and usually after 8 weeks of treatment. However, myocarditis and cardiomyopathy can occur at any period during treatment. • Typical laboratory findings include elevated troponin I or T, elevated creatinine kinase-MB, peripheral eosinophilia, and elevated C-reactive protein (CRP). Chest x-ray may demonstrate cardiac silhouette enlargement, and cardiac imaging (echocardiogram, radionucleotide studies, or cardiac catheterization) may reveal evidence of left ventricular dysfunction. • Eosinophilia has been co-reported in some cases, which may indicate that the carditis is a hypersensitivity reaction to clozapine; however, it is not known whether eosinophilia is a reliable predictor of carditis.
• Discontinue Gen-Clozapine and obtain a cardiac evaluation upon suspicion of myocarditis or cardiomyopathy or other significant cardiotoxicity.	• In general, patients with a history of clozapine-associated myocarditis or cardiomyopathy should not be rechallenged with Gen-Clozapine.
• Advise **GenCAN** for assigning 'Cardiac Adverse Reaction' to patient status.	• 'Cardiac Adverse Reaction' status alerts HCPs during future treatment of such patients.
• Utilize the **GenCAN database** for additional monitoring parameters.	• The **GenCAN database** allows for additional monitoring parameters of dose, troponin/c-reactive protein, and serum Clozapine levels.

Cont...

Reference: Gen-Clozapine Product Monograph, Health Canada, July 18, 2022.

Objective: Side Effect Management (continued)

Patient to be evaluated and treated for possible drug induced side effects as outlined in the Gen-Clozapine Product Monograph and as per treating physician's orders. The following are the most common or most dangerous side effects. (Consult Product Monograph for full side effect profile.) For all drug interactions refer to the Product Monograph and or the **Gen-Clozapine Drug Interaction Guide**

Intervention	Rationale
TACHYCARDIA	
• Assess patients for persistent tachycardia. It can be related to rapid dose escalation, consider reducing dosage and then increasing it slowly.	• Tachycardia, which may be sustained, has been observed in approximately 25% of patients taking Gen-Clozapine with patients having an average increase in pulse rate of 10 to 15 bpm. • The sustained tachycardia is not simply a reflex response to hypotension and is present in all positions monitored. • Tachycardia may be due to the anticholinergic effect of Gen-Clozapine and its ability to elevate plasma norepinephrine. • Either tachycardia or hypotension may pose a serious risk for an individual with compromised cardiovascular function.
• If persistent after 4 weeks of therapy, consider pharmacological intervention, and if continues to persist thereafter with greater than 120 bpm heart rate, stop Gen-Clozapine treatment.	
ORTHOSTATIC HYPOTENSION	
• Cautious titration and a divided dosage schedule are necessary to minimize the risks of hypotension.	• Orthostatic hypotension can occur with Gen-Clozapine treatment in 9% of cases. It may be associated with other conditions like myocarditis or cardiomyopathy. • Orthostatic hypotension, with or without syncope, can occur with Gen-Clozapine treatment and may represent a continuing risk in some patients. Rarely (approximately 1 case per 3,000 patients in the United States), collapse can be profound and can be accompanied by respiratory and/or cardiac arrest. • Orthostatic hypotension is more likely to occur during initial titration in association with rapid dose escalation and may even occur on first dose. In one report, initial doses as low as 12.5 mg were associated with collapse and respiratory arrest. Hypotension may pose a serious risk for an individual with compromised cardiovascular function.
• Patient's sitting and standing blood pressure should be taken for a minimum of 6-8 hours after the initial 2-3 doses.	

Cont...

Reference: Gen-Clozapine Product Monograph, Health Canada, July 18, 2022.

Objective: Side Effect Management (continued)

Patient to be evaluated and treated for possible drug induced side effects as outlined in the Gen-Clozapine Product Monograph and as per treating physician's orders. The following are the most common or most dangerous side effects. (Consult Product Monograph for full side effect profile.) For all drug interactions refer to the Product Monograph and or the **Gen-Clozapine Drug Interaction Guide**

Intervention	Rationale
SEIZURES	
• Caution should be used in administering Gen-Clozapine to patients having a history of seizures or other predisposing factors.	• Seizures have been estimated to occur in association with Gen-Clozapine use at a cumulative incidence at one year of approximately 5%, based on the occurrence of one or more seizures in the patients exposed to Gen-Clozapine during clinical trials in the United States.
• Cautious titration and a divided dosage schedule are necessary to minimize the risk of seizures.	• Gen-Clozapine may lower the seizure threshold. Dose appears to be an important predictor of seizure and is more likely to occur with rapid dose increases. • At doses below 300 mg/day, seizure risk is comparable to that of other antipsychotic drugs (about 1-2%). • The risk for seizure increases to 5% if the Gen-Clozapine dose exceeds 600 mg/day.
• Patients should be advised not to engage in any activity where sudden loss of consciousness could cause serious risk to themselves or others (e.g., driving, operating machinery, swimming, climbing, etc.).	
HYPERGLYCEMIA, DYSLIPIDEMIA AND WEIGHT GAIN	
• In patients using Gen-Clozapine, clinical monitoring is recommended to include baseline and periodic follow-up on fasting blood glucose levels, lipid evaluations and body weight.	• Undesirable alterations in lipids and weight gain have been observed in patients treated with atypical antipsychotics, including Gen-Clozapine.
• In patients receiving Gen-Clozapine who developed symptoms of hyperglycemia, such as polydipsia, polyuria, polyphagia or weakness, discontinuation should be considered.	• On rare occasions, severe hyperglycemia, sometimes leading to ketoacidosis/hyperosmolar coma including some fatal cases, has been reported during Gen-Clozapine treatment in patients with no prior history of hyperglycemia. While a causal relationship to clozapine use has not been established definitively, glucose levels returned to normal in most patients after discontinuation of Gen-Clozapine and rechallenge produced a recurrence of hyperglycemia in a few cases. The effect of clozapine on glucose metabolism in patients with diabetes mellitus has not been studied. Impaired glucose tolerance, severe hyperglycemia, ketoacidosis and hyperosmolar coma have been reported in patients with no prior history of hyperglycemia.

Cont...

Reference: Gen-Clozapine Product Monograph, Health Canada, July 18, 2022.

Objective: Side Effect Management (continued)

Patient to be evaluated and treated for possible drug induced side effects as outlined in the Gen-Clozapine Product Monograph and as per treating physician's orders. The following are the most common or most dangerous side effects. (Consult Product Monograph for full side effect profile.) For all drug interactions refer to the Product Monograph and or the **Gen-Clozapine Drug Interaction Guide**

Intervention	Rationale
• Encourage health lifestyle to include a healthy diet and active living. • Refer to the **GenCAN Annual Balanced Health Calendar,** available through your Clinical Nurse Coordinator.	• The **GenCAN Annual Balanced Health Calendar** promotes patient well-being and healthy lifestyle via staying fit and eating well options.
• Utilize the **GenCAN database** for additional monitoring parameters.	• The **GenCAN database** allows for additional monitoring parameters that include weight, BMI and blood glucose.
FEVER	
• Assess for possible causes of fever.	• During Gen-Clozapine therapy, patients may experience transient temperature elevations above 38°C (100.4°F) with the peak incidence within the first three weeks of treatment. This fever is generally benign and self-limiting; however, on occasion there may be an associated increase or decrease in the white blood cell count. • Patients should be carefully evaluated to rule out the possibility of an underlying infectious process or the development of blood dyscrasia.
• Monitor temperature on Day 1 and Day 2, then follow up at clinician's discretion.	• In the presence of high fever, the possibility of neuroleptic malignant syndrome must be considered. If the diagnosis of neuroleptic malignant syndrome is confirmed, Gen-Clozapine should be discontinued immediately, and appropriate medical measures should be administered. • Fever that is otherwise unexplained can accompany myocarditis, cardiomyopathy, pancreatitis, severe cutaneous adverse reaction.
DROWSINESS AND SEDATION	
• Advise patients to be cautious about their activities.	• Increased drowsiness/sedation is common during initial treatment (39%). This tends to subside with continued therapy or dose reduction. • Because of the potential for initial sedation, Gen-Clozapine may impair mental and/or physical abilities especially during the first few days of therapy. The recommendation for gradual dose escalation should be carefully adhered to and patients should be cautioned about activities requiring alertness (e.g., driving, operating machinery, swimming, climbing, etc.).

Cont...

Reference: Gen-Clozapine Product Monograph, Health Canada, July 18, 2022.

Objective: Side Effect Management (continued)

Patient to be evaluated and treated for possible drug induced side effects as outlined in the Gen-Clozapine Product Monograph and as per treating physician's orders. The following are the most common or most dangerous side effects. (Consult Product Monograph for full side effect profile.) For all drug interactions refer to the Product Monograph and or the **Gen-Clozapine Drug Interaction Guide**

Intervention	Rationale
DIZZINESS	
• Assess patient for dizziness.	• Dizziness can be a common side effect (19%). • Tolerance may develop beyond 4 to 6 weeks of treatment. However, on occasion it may be associated with other conditions (hypotension, myocardial infarction, anemia, thrombocytosis).
• Gradual titration starting with a low dose is important.	
HYPERSALIVATION	
• Encourage patients to place a towel on their pillow and consider pharmacological treatments.	• Clozapine is associated with sialorrhea. Mechanism of action is unknown. • Hypersalivation is a common side effect (31%) and may be profuse, especially during sleep. It may be diminished with dose reduction.
• Utilize the **GenCAN Sweet Dream Pillow Kit** available through your Clinical Nurse Coordinator.	• The **GenCAN Sweet Dream Pillow Kit** provides super absorbent pillow cases assisting with hypersalivation.
GASTROINTESTINAL SIDE EFFECTS	
• Assess patient for history of paralytic ileus, severe constipation, an obstruction of the bowel, or any other condition which has affected large bowel.	• Constipation is a common side effect (14%). • Gen-Clozapine has been associated with varying degrees of impairment of intestinal peristalsis, ranging from constipation to intestinal obstruction, fecal impaction and paralytic ileus, megacolon and intestinal infarction/ischemia. On rare occasions, these cases have been fatal. Careful monitoring during treatment with Gen-Clozapine to identify early the onset of constipation, followed by effective management of constipation are recommended to prevent. It is vital that constipation is recognized and actively treated.
• Assess for medication use known to cause constipation.	• Gen-Clozapine has potent anticholinergic effects, which may produce undesirable effects throughout the body.
• Assess regularly for nausea, vomiting and/or bowel irregularities.	• Incidence of nausea (5%) and vomiting (3%) often develops after 6-8 weeks treatment.
• Promote high fiber diet, exercise, increased fluids and monitoring of bowel movement.	

Cont...

Reference: Gen-Clozapine Product Monograph, Health Canada, July 18, 2022.

Objective: Side Effect Management (continued)

Patient to be evaluated and treated for possible drug induced side effects as outlined in the Gen-Clozapine Product Monograph and as per treating physician's orders. The following are the most common or most dangerous side effects. (Consult Product Monograph for full side effect profile.) For all drug interactions refer to the Product Monograph and or the **Gen-Clozapine Drug Interaction Guide**

Intervention	Rationale
• Refer to the **GenCAN Annual Balanced Health Calendar** available through your Clinical Nurse Coordinator.	• The **GenCAN Annual Balanced Health Calendar** promotes patient well-being and healthy lifestyle via staying fit and eating well options.
NEUROLEPTIC MALIGNANT SYNDROME (NMS)	
• Assess patient for clinical manifestations of NMS such as hyperpyrexia, muscle rigidity, altered mental status (including catatonic signs) and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmias). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure.	• Cases of NMS have been reported in patients treated with clozapine, most of which have included the concomitant use of lithium or other CNS-active agents. • NMS can also be related to rapid dose escalation.

• If the diagnosis of neuroleptic malignant syndrome is confirmed, Gen-Clozapine should be discontinued immediately and appropriate medical measures administered:
  • Immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy.
  • Intensive symptomatic treatment and medical monitoring.
  • Treatment of any concomitant serious medical problems for which specific treatments are available.
	• The diagnostic evaluation of patients with NMS syndrome is complicated. In arriving at a diagnosis, it is important to identify cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS).
	• Other important considerations in the differential diagnosis include central anti-cholinergic toxicity, heat stroke, drug fever, and primary central nervous system (CNS) pathology.

• There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS.	• If a patient requires antipsychotic treatment regime after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported.

Reference: Gen-Clozapine Product Monograph, Health Canada, July 18, 2022.

Objective: Patient and Family Education

Patient and family to be involved and aware of all aspects of treatment.

Intervention	Rationale
PATIENT CONSENT	
• Ensure patient has consented to treatment and the exchange of information between the treatment team and **GenCAN** (i.e. blood test results). Patient advised that no personal information will be disclosed to **GenCAN.**	• **GenCAN** is a registry designed to help reduce the risk of developing agranulocytosis. • **GenCAN** informs the physician, pharmacist and other health team members of low blood test results (ANC). • In the event that the treatment team decides to change the brand of Clozapine and the patient is transferred to a different blood monitoring system or registry, patient consent is important for sharing historical blood counts and confirming with registries that there have not been any hematological issues in the past on another brand of clozapine.
SIGNS AND SYMPTOMS OF INFECTION AND SIDE EFFECTS	
• Patient and family advised to evaluate for signs or symptoms of infection (i.e. tiredness, weakness, fever, sore throat or flu-like complaints) and or any other side effects (i.e. rapid heart rate when resting, chest pain, shortness of breath, nausea, vomiting).	
• Patient and family encouraged to notify the treatment team of the same.	
• Patient and family advised of the most common side effects such as drowsiness/ sedation, dizziness, hypersalivation, tachycardia, and constipation.	• See Side Effect Management section of this guide.
• Patient and family encouraged to advise treatment team of any changes in habits with caffeine intake and/or smoking.	• It is important for patient and family to understand that abrupt changes in habits may change the effect of Gen-Clozapine.
• Refer to the **Getting Started on Gen-Clozapine: A guide for patients and families.**	• The **guide for patients and families** is designed to assist patients, their relatives, and caregivers to better understand the risks associated with Gen-Clozapine and monitoring requirements.

Cont...

Reference: Gen-Clozapine Product Monograph, Health Canada, July 18, 2022.

Objective: Patient and Family Education (continued)

Patient and family to be involved and aware of all aspects of treatment.

Intervention	Rationale
COMPLIANCE	
• Patient and family advised that a blood test is required every week for the first 26 weeks of treatment because the risk of a low absolute neutrophil count is highest during this time. After 26 weeks of treatment, doctor may recommend that patient would require a blood test every two weeks. After 52 weeks of treatment, doctor may then recommend that patient would require a blood test every four weeks.	• A rare (approximately 0.7% of cases) condition called "agranulocytosis" can occur when taking Gen-Clozapine. This is a condition, which causes a low absolute neutrophil count, and makes it difficult to fight off infections. Early detection is important to prevent or reverse this condition. Because this condition is life-threatening it is important to have regular blood tests done.
• Patient and family advised of the importance of treatment compliance and blood-monitoring requirements during treatment break.	• It is important for patient and family to understand that if the treatment is to be successful, the patient must follow exactly prescribed dosage instructions, and under no circumstances take more or less than the prescribed dose. If patient and or family think the dosage is too weak or too strong, they need to discuss this matter with the prescribing physician.
• Patient and family advised if Gen-Clozapine dose is missed and remembered within two hours, then it may be taken immediately. Otherwise, the missed dose is skipped, and the regular dosing schedule is continued. Double doses should not be taken.	
TRAVEL	
• Patient and Family advised to notify treatment team of any travel plans in advance.	• This will facilitate planning between **GenCAN** and the treatment team to make alternate lab and pharmacy arrangements for this period.

Reference: Gen-Clozapine Product Monograph, Health Canada, July 18, 2022.

NOTES:

Reference: Gen-Clozapine Product Monograph, Health Canada, July 18, 2022.

GenCAN Monitoring With Confidence

Gen-Clozapine Access Network

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.

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CLZ-2022-0131E - SE2022

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