CSAN
PrCLOZARIL® (clozapine) SUPPORT AND ASSISTANCE NETWORK
1-800-267-2726

CSAN PRONTO
PrCLOZARIL® (clozapine) SUPPORT AND ASSISTANCE NETWORK

Pr CLOZARIL®
Clozapine

CLOZARIL® is an effective medication that has been available in Canada since 1991 for patients with treatment-resistant schizophrenia.

Before you start a patient on CLOZARIL®, there are procedures and actions that must be taken, including enrolment into the CLOZARIL® Support and Assistance Network (CSAN®). CSAN® is a comprehensive support and blood monitoring program, available 24/7 to answer your questions and provide insight into your patients' blood monitoring status and results.

Please visit the CSAN® sections for detailed information on the CSAN® team, processes, and procedures.

This compendium helps clarify the processes involved in clozapine treatment and provides valuable information for treating patients with CLOZARIL®.

Also included in this compendium are:

1. A sample copy of the Patient Booklet to help your patients understand their medication
2. A sample copy of the Healthcare Professional Booklet for healthcare professionals prescribing CLOZARIL®
3. CSAN® forms to initiate or modify registration with the program

Additional copies of the booklets and form can be obtained from your HLS representative or downloaded from www.clozaril.ca. The CSAN® form is also available at www.csan.ca, or by contacting CSAN® at 1-800-267-2726.

For more information on CLOZARIL®, visit www.clozaril.ca.

Download the **T**reatment-**R**esistant **S**chizophrenia **ID**entifier **(TRS-ID), an app available for free on the App Store and Google Play.**

CLOZARIL®
treatment compendium for healthcare professionals

CLOZARIL® treatment compendium

Table of contents

For immediate assistance at any time, please call CSAN® at 1-800-267-2726, or refer to the complete Product Monograph for CLOZARIL®.

CSAN® "CLOZARIL® (clozapine) SUPPORT AND ASSISTANCE NETWORK"

1-800-267-2726

CSAN® PRONTO™ "CLOZARIL® (clozapine) SUPPORT AND ASSISTANCE NETWORK"

CLOZARIL® Clozapine

Treatment algorithm:

Pharmacotherapy for treatment-resistant schizophrenia

Canadian Schizophrenia Guidelines[2]

Guideline development process

The recommendations below are based on the 2017 Canadian Psychiatric Association Guidelines for the Pharmacotherapy of Schizophrenia in Adults.

The Canadian Guidelines were developed using the ADAPTE process, using recently published, existing guidelines from around the world. Recommendations were drawn from six guidelines: three from NICE, one from SIGN, one from the EPA, and one from the APA. For those specific to the pharmacotherapy of schizophrenia in adults, a working group selected between guidelines and recommendations to create an adapted guideline.

The recommendations below are an excerpt of the Canadian Guidelines, related specifically to treatment-resistant schizophrenia.

It is estimated that 25% to 30% of individuals with schizophrenia meet criteria for TRS.

When to consider clozapine

Clozapine should be considered for patients whose schizophrenia has not responded to an adequate trial of two antipsychotics.[2]

Antipsychotic trial 1

Oral AP:

At least 6 weeks at the midpoint or greater of the licensed therapeutic dose range

LAI AP:

At least 6 weeks following reaching steady state

Antipsychotic trial 2

Oral AP:

At least 6 weeks at the midpoint or greater of the licensed therapeutic dose range

LAI AP:

At least 6 weeks following reaching steady state

No response after two antipsychotics: patient defined as having TRS

Clozapine trial*

At least 8, but preferably 12, weeks at a dose of ≥400 mg/day; where available, obtaining trough levels ≥350 ng/mL (1,100 nM/L) for once-a-day dosing and ≥250 ng/mL for equally divided dosing are suggested

If persistence of **2 or more positive symptoms** with at least a **moderate level of severity**, or a **single positive symptom with severe or greater severity**,

proceed to next step.

Adapted from CPA Guidelines (2017)[2]

Note:

Tailor all treatment approaches to the individual patient. Consider assessment, pharmacotherapy, and psychosocial interventions at **ALL** stages of treatment.

- Psychosocial interventions are generally recognized as essential components of the effective treatment of schizophrenia in adults[3]
- Assessing adherence is an essential step in identifying resistance to antipsychotic medications. Documentation of adherence is advised, using approaches such as pill counts, dispensing chart reviews, and antipsychotic plasma level monitoring on at least 1 occasion, where available[2]

* Following an adequate trial with clozapine, if the criteria above continue to be met, the specifier *clozapine-resistant schizophrenia* should be added.
AP=antipsychotic; APA=American Psychiatric Association; CPA=Canadian Psychiatric Association; EPA=European Psychiatric Association; LAI=long-acting injection; NICE=National Institute for Health and Care Excellence; SIGN=Scottish Intercollegiate Guidelines Network; TRS=treatment-resistant schizophrenia.

Patient safety considerations

Patients who are to receive CLOZARIL® should be informed about the **significant risk of developing agranulocytosis**, a condition in which the body fails to produce white blood cells needed to fight infections. Agranulocytosis is a **rare** but potentially life-threatening adverse event, shown to occur at a rate of 0.7%.[1*]

In order to manage this risk:

1. Clozapine patients require regular hematological testing at least:

- **every week** for the first 6 months of treatment,
- **every 2 weeks** for the next 6 months,
- **every 4 weeks** thereafter, for the duration of treatment, and
- every week for a period of 4 weeks after discontinuation of treatment.[1]

2. Clozapine patients must be enrolled in a registry for tracking and monitoring of hematological status.[4]

- Registries are maintained by each of the clozapine manufacturers[4]
- If patients switch physician, pharmacy, or laboratory, a modification form must be submitted[4]
- Patients may not be switched from one brand of clozapine to another without the completion of a new registry-specific patient registration form signed by the prescribing physician

3. Pharmacists must verify the patient's status and eligibility for clozapine.

- Hematological status—testing done within the appropriate time frame[5]

Please also refer to the Treatment Protocol and the Adverse Events sections of this compendium.

Should you have any questions, CSAN® is available to assist you.

* These incidences are derived from postmarketing data as per June 1993, covering over 60,000 patients treated with CLOZARIL® for up to 3 years in the USA, Canada, and the UK.

CLOZARIL® Support and Assistance Network (CSAN®)—There for you since 1991

CSAN®'s primary goal is to **assure the safe use of CLOZARIL®** by ensuring that recommended hematological monitoring is conducted for every patient on CLOZARIL®.

CSAN®

- **Notifies the treatment team of adverse hematological trends within 24 hours of receiving** clinically relevant test results
- **Safeguards patients from being restarted on clozapine** if they have previously discontinued due to neutropenia and/or agranulocytosis

Since its inception, CSAN® has expanded, offering services that support the patient and their healthcare team through a wide array of value-added services designed for continuity of care and to help minimize the risk of agranulocytosis over time. **CSAN® Pronto™ is the newest addition to the CSAN® program.**

CSAN® Pronto™: Helping to simplify the routine bloodwork for patients on CLOZARIL®

- A new point-of-care blood monitoring system that offers capillary and K_2EDTA venous whole blood sampling for adult patients
- Accurately determines white blood cell counts and neutrophil percentages in minutes from a single drop of blood
- Results are automatically and securely uploaded to the CSAN Patient Care Portal® to be made readily available to the healthcare team

The CSAN® team: Professionals dedicated to patient-safety management

CSAN® is an expert team with over 25 years of partnering that includes:

- **A hematologist working with CSAN® since 1991, and a consulting cardiologist**
- **Two consulting psychiatrists** specialized in treatment-resistant schizophrenia
- A CSAN® team with a combined CLOZARIL® experience of more than **90 years**
- Personal follow-up by a field team of clinical/nurse educators on **every red alert within an hour** of receiving results
- Evaluation of patient non-rechallengeable status

CSAN® support

- CSAN® is **available 24/7** to answer questions and offer support
- **Offers the CSAN Patient Care Portal®** online hematological monitoring database
- Performs 200,000 blood test entries per year
- Follows up on 1,300 patients for non-compliance every week
- Expertly handles more than 38,000 customer calls yearly
- **Has experience in dealing with difficult cases** and manages over 6,000 yellow and red alerts per year

High compliance with venous blood testing:
>95% of patients registered with CSAN® complied with the clozapine monograph criterion for laboratory compliance.[6] CSAN® Pronto™ aims to streamline blood monitoring for patients on CLOZARIL®.

CSAN® specialist consultants

Same on-staff hematologist consultant with CLOZARIL® expertise since the launch of CSAN®

Dr. Jaroslav Prchal

Dr. Prchal is an Associate Professor of Medicine and Oncology at McGill University and the Chief of the Department of Oncology at St. Mary's Hospital in Montreal.

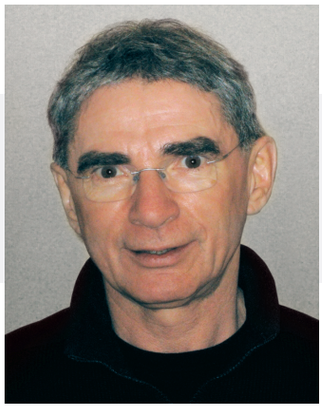
Dr. Prchal has been associated with CSAN® since its inception in 1991 and was involved in the original design of the hematological monitoring system. He has vast experience in the understanding and management of agranulocytosis. Dr. Prchal is available for direct consultation to the teams of nurses, pharmacists, and physicians caring for patients with treatment-resistant schizophrenia who are registered with CSAN®. He can be reached through the CSAN® line at 1-800-267-2726.

Experienced on-staff psychiatric consultants

Dr. Sean Flynn

Dr. Flynn is a Clinical Associate Professor of Psychiatry at the University of British Columbia and works on the Vancouver Assertive Community Treatment teams. He is a clinician and teacher with a special interest in the management of treatment-resistant psychotic conditions.

Dr. Flynn is a consultant to CSAN® and his advice can be sought for psychiatry and general medical questions related to treatment-resistant schizophrenia patients treated with CLOZARIL®. He can be reached through the CSAN® line at 1-800-267-2726.



Dr. Jean-Pierre Rodriguez

Dr. Rodriguez teaches in the residency program at the University of Montreal. He is based in the Hôpital Sacré-Cœur de Montréal, Pavillon Albert-Prévost, where he takes care of hospitalization services as well as the day hospital program for psychotic patients.

Dr. Rodriguez is a CSAN® consultant. He is available for consultation on psychiatry and general medicine questions related to treatment-resistant schizophrenia patients treated with CLOZARIL®. He can be reached through the CSAN® line at 1-800-267-2726.

Experienced on-staff cardiology consultant

Dr. Richard Choi

Dr. Choi is a staff cardiologist at St. Joseph's Health Centre in Toronto. Moreover, he is an adjunct clinical faculty member and lecturer in the Faculty of Medicine at the University of Toronto.

Dr. Choi has a clinical interest in the cardiovascular effects of psychiatric medications and has collaborated with the Clozapine Program at the Centre for Addiction and Mental Health in Toronto. As a CSAN® consultant, he is available for consultation on the cardiovascular effects of CLOZARIL®. He can be reached through the CSAN® line at 1-800-267-2726.

Role of the caregiver team

The caregiver team is there to ensure the patient receives the best possible care throughout the course of CLOZARIL® therapy. In general:

- The physician or psychiatrist is responsible for the overall management of the patient's condition and progress
- The nurse is available to give guidance and support about issues that affect the patient's day-to-day living
- The pharmacist is responsible for dispensing CLOZARIL® and answering questions that the patient or caregiver has about taking the medication. Please note that the pharmacist is only authorized to dispense CLOZARIL® on an every-week, every-two-week, or every-four-week basis, as long as blood test results or confirmation that the blood work has been completed is available
- The social worker may help the patient get the basic things that they need, such as housing, money, transportation, or any other services to help normal functioning. Usually, the physician or nurse will help the patient get in touch with a social worker
- Services, such as patient/family education and counselling, may be offered within the community. Resources are listed at the front of the patient booklet
- Family and friends can also offer invaluable support

CSAN® is dedicated to assisting the healthcare team in the appropriate and effective use of CLOZARIL®. Please do not hesitate to contact us directly at 1-800-267-2726.

Introducing CSAN® Pronto™—The latest innovation of the CSAN® program

CSAN® PRONTO™ ®CLOZARIL® (clozapine) SUPPORT AND ASSISTANCE NETWORK

Now available in Canada!

CSAN® is offering a new way to help simplify the routine bloodwork for patients on CLOZARIL®.

CSAN® Pronto™ is a point-of-care blood monitoring system indicated for the quantitative determination of WBCs and NEUT% in capillary blood or K_2EDTA venous whole blood in adult patients only. Patients' results can be provided to the healthcare team in real time and are simultaneously auto-uploaded into your patients' CSAN® profiles using the CSAN Patient Care Portal®.[7]

CSAN® Pronto™ is equipped with technology that:

Provides laboratory-accurate WBC counts and NEUT% in real time[7]

Requires only 1 drop of capillary blood (about 3.5 µl) to run the test[7]

Offers one-step processing, while maintaining CSAN®'s privacy standards[7]

Is designed to address a barrier of CLOZARIL® use by offering the convenience of onsite testing

NEUT%=neutrophil percentages; WBC=white blood cell.

To learn more:

- Visit www.CSANPronto.ca to watch a video about this new addition to the CSAN® program and access the Instructions for Use
- Contact the CSAN® team at 1-800-267-2726

Call CSAN® at 1-800-267-2726 to obtain the CSAN® Pronto™ device for your practice.

CSAN® Pronto™ is a whole blood analyzer, which involves the collection of blood specimen. All patient samples should be treated as potentially infectious and handled appropriately. Standard precautions should be employed. Personal Protective Equipment should be worn when processing samples, testing quality control, and during maintenance procedures. During use, CSAN® Pronto™ should be placed on a stable surface, free from movements and any potential vibrations. Operators are not to move the device from one location to another while in operation. CSAN® Pronto™ is only to be used with CSAN® Pronto™ Test Strips. CSAN® Pronto™ Test Strips are single-use only.[7]

CLOZARIL® treatment protocol[1]

Physician or nurse practitioner with a patient starting treatment with CLOZARIL® **for the first time**

Prior to initiating CLOZARIL® treatment, the following steps should be followed:

1. **Physical examination:** Ensure no contraindications to treatment.
2. **Cardiac evaluation:** For patients with a family history of heart failure.
3. **Informed consent:** Consent to participate in the CLOZARIL® Support and Assistance Network (CSAN®) must be obtained from the patient or their legal representative (see CSAN® form).
4. **Complete blood count (CBC):** Perform a CBC and blood differential test to determine baseline values.
   - Alternatively, you may provide existing results that have been taken within 28 days
5. **CSAN® registration:** The form to complete is included in this compendium. An editable version is available at www.clozaril.ca. You may also call 1-800-267-2726 to have it faxed to you.
   - Complete section 4
   - Ask your pharmacist to complete section 3
   - The laboratory and institution must be identified
   - Fax the completed form to CSAN® at 1-800-465-1312 or email it to csan@hlstherapeutics.com
   - Include a copy of the CBC results
6. **Treatment initiation:** Follows the confirmation of CSAN® registration. Provide the patient with a standing lab requisition for a CBC with differential based on blood test monitoring frequency.
   - Fax a copy of the blood requisition to CSAN® at 1-800-465-1312
7. **Blood monitoring:**
   - **Every week** for the first 6 months
   - **Every 2 weeks** for the next 6 months*
   - **Every 4 weeks** thereafter*†

Blood monitoring should continue for as long as the patient is on the drug and for at least 4 weeks after discontinuation. CSAN® must receive the results.

With CSAN® Pronto™, patients can undergo their regular bloodwork onsite. CSAN® Pronto™ can determine white blood cell counts and neutrophil percentages from one drop of capillary blood. Read more about CSAN® Pronto™ on pages 8 and 25.

- Patients should also have baseline and periodic monitoring of:
  - Blood glucose
  - Body weight
  - Follow-up lipid evaluations

* If acceptable white blood cell (WBC) and neutrophil counts have been maintained during the prior 6 months.
† Unless the patient status warrants more frequent monitoring.

Physician, nurse practitioner, or pharmacist with an **existing CLOZARIL® patient** transferred to their care	**1. Call CSAN®** at 1-800-267-2726 to ascertain patient status and confirm: a) CSAN® number b) Blood monitoring frequency c) Last blood test date d) Next blood test date e) Last blood test result (green/yellow/red) **2. CSAN® registration:** The form to complete is included in this compendium. An editable version is available at www.clozaril.ca. You may also call 1-800-267-2726 to have it faxed to you. • Complete section 4 (physician or nurse practitioner) • Complete section 3 (pharmacist) • The laboratory and institution must be identified • Fax the completed form to CSAN® at 1-800-465-1312 or email it to csan@hlstherapeutics.com
Pharmacist for all patients on CLOZARIL®	**1. CSAN® registration:** The form to complete is included in this compendium. An editable version is available at www.clozaril.ca. You may also call 1-800-267-2726 to have it faxed to you. • Complete section 3 • Fax the completed form to CSAN® at 1-800-465-1312 or email it to csan@hlstherapeutics.com **2. CLOZARIL® dispensing:** The pharmacist must only give the patient a supply of CLOZARIL® on an: **a) every-week,** **b) every-two-week,** or **c) every-four-week** basis upon confirmation that hematological monitoring has been conducted for the current period. **3.** The **switching** of a patient from one brand of clozapine to another **must not be done** by a pharmacist unless they obtain a new registry-specific patient registration form filled out by the prescribing physician.[4]

CSAN® is available 24 hours a day, 7 days a week. Expert consultants in hematology, cardiology, and psychiatry can be reached through the service.

CLOZARIL® treatment protocol quick reference[1]

For additional details, please refer to the checklist on the following pages or the CLOZARIL® Product Monograph.

CSAN®-experienced consultants are also available at 1-800-267-2726 to assist you with any questions.

		New clozapine patient	Existing clozapine patient
Physician/ nurse practitioner	**Physical examination**	Ensure no contraindications[1]	Discretionary
	Cardiac evaluation	In patients with a family history of heart failure[1]	Discretionary
	Informed consent	Consent to participate in the CLOZARIL® Support and Assistance Network (CSAN®)[1]	
	Complete blood count (CBC)	Required: Baseline CBC Provide patient with a standing lab requisition for a weekly CBC with differential	Required: CBC Provide patient with a standing lab requisition for a CBC with differential based on blood monitoring frequency
	Other clinical monitoring	Discretionary: Blood glucose, lipid profile, and body weight/BMI[1]	
	CSAN® registration/ update	Editable online form can be found at www.clozaril.ca, or call CSAN® at 1-800-267-2726 to have one faxed to you Complete section 4 Treatment initiation follows registration	Editable online form can be found at www.clozaril.ca, or call CSAN® at 1-800-267-2726 to have one faxed to you Complete section 4 to update the prescriber
Pharmacist	**CLOZARIL® dispensing**	Upon confirmation that hematological monitoring has been conducted for the current period, dispense to the patient a supply of CLOZARIL® on an **every week**, **every-two-week**, or **every-four-week** basis[1]	
	Clozapine brands	Switching a patient from one brand of clozapine to another must not be done by a pharmacist unless they obtain a new, registry-specific patient registration form filled out by the prescribing physician[4]	
	CSAN® registration/ update	Editable online form can be found at www.clozaril.ca, or call CSAN® at 1-800-267-2726 to have one faxed to you Complete section 3	

CLOZARIL® treatment protocol checklist[1]

Prior to initiating your patient on CLOZARIL®:

- ☐ **Do a physical examination**
- ☐ **Patients with a family history of heart failure should have a cardiac evaluation**
- ☐ **Ensure there are no contraindications:**
  - ☐ Myeloproliferative disorders
  - ☐ A history of toxic or idiosyncratic agranulocytosis or severe granulocytopenia (unless due to previous chemotherapy)
  - ☐ Active liver disease associated with nausea, anorexia, or jaundice
  - ☐ Progressive liver disease
  - ☐ Hepatic failure
  - ☐ Severe central nervous system depression or comatose states
  - ☐ Severe renal or cardiac disease
  - ☐ Paralytic ileus
  - ☐ Uncontrolled epilepsy
  - ☐ Previous hypersensitivity to clozapine or other components of CLOZARIL®
  - ☐ Inability to undergo blood tests
- ☐ **Ask your patient what medications they are taking, including over-the-counter drugs, caffeine, tobacco, alcohol, and narcotics**
- ☐ **Perform a baseline complete blood count**
- ☐ **Blood glucose, lipid profile, and baseline body weight/BMI are recommended**
- ☐ **Consider the following conditions in the development of a treatment plan. Determine whether the patient:**
  - ☐ Suffers from enlargement of the prostate
  - ☐ Has a history of seizures
  - ☐ Has glaucoma
  - ☐ Suffers from diabetes
  - ☐ Has risk factors for developing blood clots, such as a family history of blood clots, age over 65 years, smoking, obesity, recent major surgery, immobility due to air travel or other reasons, or takes oral contraceptives
  - ☐ Has a history of bone marrow disorder
  - ☐ Has a paralytic ileus or other serious gastrointestinal problems
  - ☐ Suffers from constipation
  - ☐ Has or has had heart problems
  - ☐ Has heart disease or family history of prolongation of the QT interval
  - ☐ Has a history of stroke
  - ☐ Has or has had lung disease
  - ☐ Has Alzheimer's disease
  - ☐ Suffers from dementia
  - ☐ Plans to become pregnant or is currently pregnant
  - ☐ Is currently breastfeeding

CSAN® registration

- ☐ Obtain informed consent to authorize CSAN® to access hematological results
- ☐ Register with CSAN® by filling out the form found at **www.clozaril.ca**
- ☐ Review the CLOZARIL® titration schedule and arrange your patient's future blood monitoring appointments

CLOZARIL® patient discussion points

You are advised to discuss the following issues with your patients (and/or their caregivers) before starting CLOZARIL®:

☐ Patients who are to receive CLOZARIL® should be warned about the **significant risk of developing agranulocytosis**, a potentially life-threatening adverse event.

☐ They should be informed that **regular blood tests are required to monitor for the occurrence of agranulocytosis**, and that CLOZARIL® tablets will be made available only through a special program designed to ensure the required blood monitoring. They should also be informed that the blood tests will be performed according to the following monitoring schedule:

- Weekly blood tests will be required for the **first 6 months of their treatment** with CLOZARIL®
- Following this initial higher risk period, they could be allowed to change to an **every-two-week** schedule, provided that acceptable white blood cell (WBC) counts and absolute neutrophil counts (ANCs) **(WBC ≥3.5 x 10^9/L and ANC ≥2.0 x 10^9/L)** have been maintained during the first **6 months of continuous therapy**, and that their clinical condition permits such a change in monitoring regimen
- Thereafter, if acceptable WBC counts and ANCs have been maintained during the next 6 months of continuous therapy, **blood tests could be performed every 4 weeks**

To help simplify the regular blood tests required for the agranulocytosis monitoring of patients on CLOZARIL®, CSAN® Pronto™ offers onsite testing and can generate WBC counts/NEUT% from a drop of capillary-drawn blood. Results are automatically uploaded into the CSAN Patient Care Portal® and made available to the healthcare team in minutes for added convenience. Read more about CSAN® Pronto™ on pages 8 and 25.

☐ Patients should be advised to **report immediately the appearance of**:

- **Lethargy**
- **Weakness**
- **Fever**
- **Sore throat**
- **Malaise**
- **Mucous membrane ulceration or other possible signs of infection**

Particular attention should be paid to any flu-like complaints or other symptoms that might suggest infection.

☐ Patients should be advised to contact their physician immediately if they develop persistent **tachycardia** 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**). Other symptoms that may be present in addition to the above include:

- Fatigue
- Flu-like symptoms
- Fever that is otherwise unexplained
- Hypotension
- Raised jugular venous pressure (bulging neck veins when sitting or standing)

Patients should be advised to contact their physician before discontinuing any medication.

☐ Patients should be informed of the **significant risk of seizure** during CLOZARIL® treatment and should be advised to avoid activities that require alertness (e.g., driving, operating machinery, swimming, climbing, etc.)

☐ Patients should be advised of the **risk of orthostatic hypotension**, especially during the period of initial dose titration

☐ Patients should be advised of the **risk of severe constipation** during CLOZARIL® treatment and that they should tell their physician if constipation occurs or worsens, as they may need laxatives

☐ Patients should be informed that if they stop taking CLOZARIL® for 2 days or more, **they should not restart their medication** at the same dosage but **should contact their physician for dosage instructions**

☐ Patients should notify their physician if they are taking or plan to take **any prescription or over-the-counter drugs or drink alcohol**

☐ Patients should also notify their physician of any changes to their caffeine or nicotine use. Abrupt changes to coffee intake or smoking habits may change the effect of CLOZARIL®[1]

- Caffeine is known to inhibit the activity of cytochrome P450 isoenzyme 1A2 and may increase the plasma levels of CLOZARIL®*
- Smoking tobacco is known to induce the activity of cytochrome P450 isoenzyme 1A2 and may decrease the plasma levels of CLOZARIL®†

☐ Patients should notify their physician if **they become pregnant or intend to become pregnant during therapy**

☐ Patients **should not breastfeed** an infant if they are taking CLOZARIL®

* The plasma concentration of clozapine is increased by caffeine intake and decreased by nearly 50% following a 5-day caffeine-free period.
† In cases of sudden smoking cessation, the plasma clozapine concentration may be increased, and thus may lead to an increase in adverse effects.

Antipsychotic medication monitoring—Canadian Schizophrenia Guidelines[8]

Once established on CLOZARIL® treatment, your patients may require routine monitoring.

Canadian Schizophrenia Guidelines recommend the following monitoring schedule for antipsychotic medications:[8]

Note: These recommendations are general and not specific to CLOZARIL® or clozapine.

Test	Baseline	At 1 month	At 3 months	Annually
Individual and family history of physical illness	X			X
Smoking history	X		X	X
BMI/weight/waist circumference	X	X	X	X
Blood pressure	X	As clinically indicated	X	X
HbA1C/fasting glucose	X	As clinically indicated	X	X
Random lipids/fasting lipids	X	As clinically indicated	X	X
Prolactin	As clinically indicated			
History and examination for extrapyramidal symptoms	X	X	X	X

For information related to CLOZARIL®, please call CSAN® at 1-800-267-2726, or refer to the complete Product Monograph for CLOZARIL®.

Special considerations for starting outpatient treatment with CLOZARIL®

CLOZARIL® may only be used in an outpatient setting where medical supervision is available and vital signs can be monitored for a minimum of 6 to 8 hours after the initial 2 to 3 doses. Special caution is advised in patients who are receiving benzodiazepines or other psychotropic drugs as these patients may have an increased risk of circulatory collapse accompanied by respiratory and/or cardiac arrest. Extra caution is advised in patients with cardiovascular disease or a history of seizures.[1]

CLOZARIL® dosage titration

Recommended dosing schedule[1] (total mg/day)

(May be adjusted to a slower rate in order to minimize the risks of hypotension, seizure, and/or sedation.)

Day 1	12.5 mg O.D. or B.I.D.	Cautious titration and a divided dosage schedule are necessary to minimize the risks of hypotension, seizure, and sedation
Day 2	25 mg O.D. or B.I.D.	
Weeks 1–2	25–50 mg/day **increases**	Gradually titrate upward in 25–50 mg daily increments
	Target 300–450 mg/day	If well tolerated, target 300–450 mg/day by the end of week 2†
Following months	300–600 mg/day **in divided doses***	Gradually titrate in ≤100 mg daily increments, no more than once/twice weekly, over several weeks‡ Doses up to 900 mg/day may be required to obtain an acceptable therapeutic response‡§
Maintenance	Gradually decrease to target	After achieving maximum therapeutic benefit, many patients can be maintained effectively at lower doses Gradually titrate downward to 150–300 mg/day in divided doses
	Target 150–300 mg/day **in divided doses**	

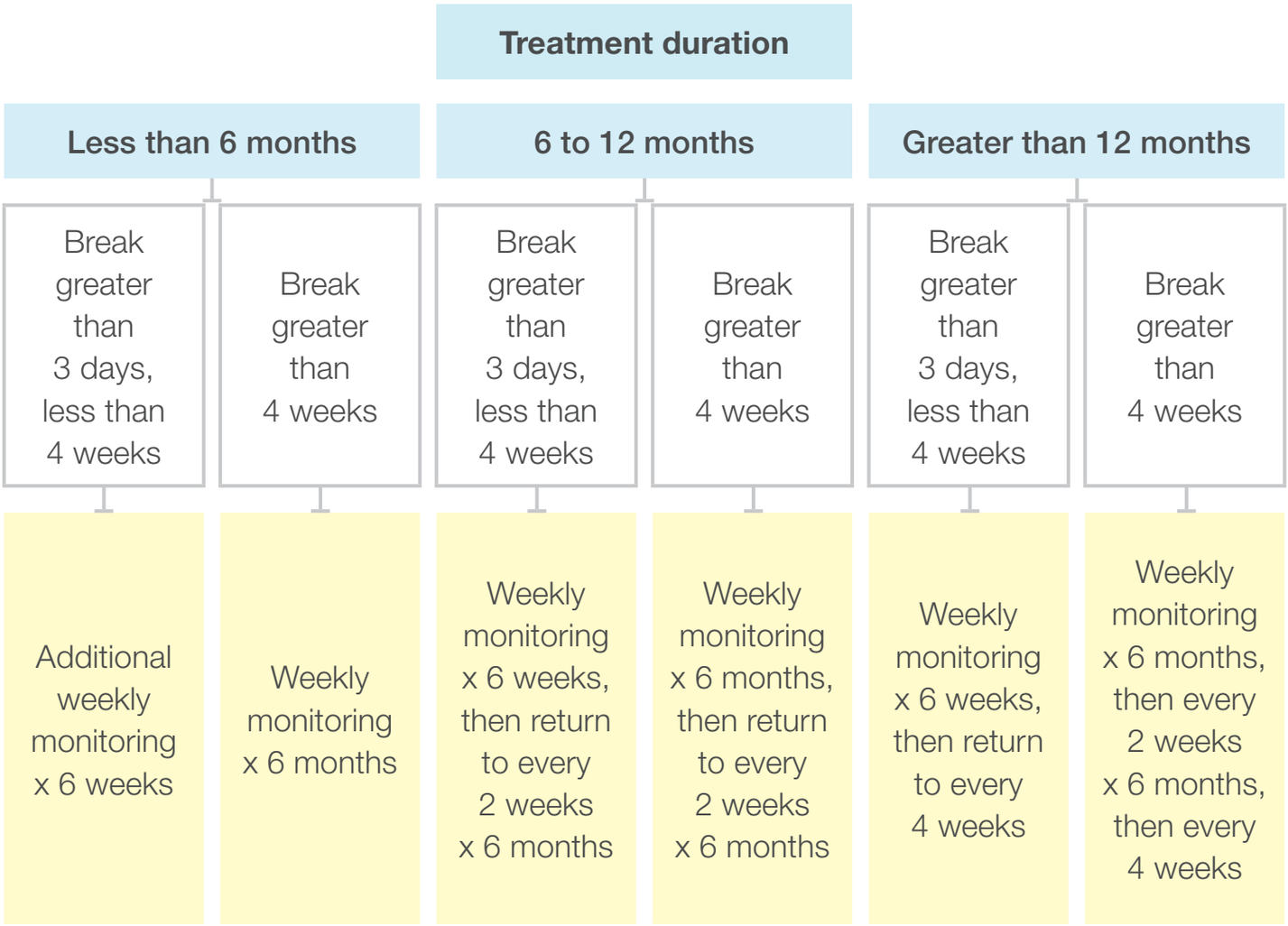
The maximum dose of 900 mg/day should not be exceeded§

- The Canadian Psychiatric Association Guidelines for the Pharmacotherapy of Schizophrenia in Adults state that the duration of an adequate trial with clozapine is at least 8, but preferably 12, weeks at a dose of ≥400 mg/day; where available, obtaining trough levels ≥350 ng/mL (1,100 nM/L) for once-a-day dosing and ≥250 ng/mL for equal divided dosing are suggested[2]

Previous oral neuroleptics should be discontinued by gradual tapering. CLOZARIL® should be initiated 24 hours after the previous neuroleptic is completely discontinued. CLOZARIL® should not be used in combination with other neuroleptics.[1]

* In most patients, antipsychotic efficacy can be expected within the therapeutic range of 300–600 mg/day in divided doses. The total daily dose may be divided unevenly, with the larger portion at bedtime. Improvements may be gradual and continued therapeutic response can be expected beyond the first month of treatment.
† If not well tolerated, a more gradual titration is recommended.
‡ As the possibility of increased adverse reactions may occur at daily doses ≥600 mg, provide patients with adequate response time to a given dose before considering a dose escalation.
§ The decision to treat in the range of 600–900 mg/day must be made cautiously, as increased dosage may increase adverse reactions (particularly seizures).
B.I.D.=twice a day; O.D.=once a day.

How to resume hematological monitoring frequency in the event of interruption in therapy greater than 3 days[1]



Hematological monitoring must continue for as long as the patient is on the drug. Monitoring frequency does not have to be modified if therapy is interrupted for 3 days or less; however, weekly hematological testing should be resumed for an additional 6 weeks if therapy is disrupted for more than 3 days. Furthermore, monitoring should occur at least once weekly for a period of 4 weeks following discontinuation of CLOZARIL® therapy, irrespective of the cause of discontinuation.

Adverse Events (AEs)[1]

Common AEs[1]

Cautious titration and a divided dosage schedule are necessary to minimize the risks of hypotension, seizure, and sedation. Some patients may contemplate discontinuing therapy with CLOZARIL® prematurely because of side effects. Consider whether a dosage adjustment may be required. If patients find that some of their side effects reduce their quality of life, then they should consult with their physician before stopping any medication.

Drowsiness/sedation (39%)	Hypotension (9%)	Tremor (6%)
Hypersalivation (31%)	Headache (7%)	Visual disturbances (5%)
Tachycardia (25%)	Sweating (6%)	Nausea (5%)
Dizziness/vertigo (19%)	Dry mouth (6%)	Fever (5%)
Constipation (14%)	Syncope (6%)	

In rare cases, CLOZARIL® may cause confusion (3%) and restlessness (4%). More serious side effects include seizures (3%) and cardiovascular toxicity.

Excessive thirst, dry mouth, and passing large amounts of urine may be signs of high sugar levels in the blood.

Patients may experience transient fever with the peak incidence within the first 3 weeks of treatment. In clinical trials, approximately 5% of patients experienced a temperature elevation. Although the fever is generally benign and self-limiting, it can be associated with changes in the WBC count. Patients should be evaluated to rule out an underlying infectious process or the development of a blood disorder. In case of a high fever, neuroleptic malignant syndrome (a potentially fatal symptom complex associated with antipsychotics) must be considered. If this diagnosis is confirmed, CLOZARIL® should be discontinued immediately and appropriate medical measures should be administered. Unexplained fever can accompany myocarditis.

IMPORTANT REMINDER: TELL THE PATIENT THAT ANY SIDE EFFECT, NO MATTER HOW MINOR, SHOULD BE REPORTED.

Serious AEs[1]

Agranulocytosis

- Agranulocytosis has been shown to occur at an incidence of 0.7%*
- Blood tests must be done every week during the first 6 months of treatment due to the increased risk of agranulocytosis. Approximately 88% of cases of agranulocytosis have occurred during this time
  - The physician will evaluate the possibility of reducing blood monitoring depending on the patient's status
- CSAN®'s primary goal is to assure the safe use of CLOZARIL® by ensuring that regular hematological monitoring is carried out

* These incidences are derived from postmarketing data as per June 1993, covering over 60,000 patients treated with CLOZARIL® for up to 3 years in the USA, Canada, and the UK.

Other common AEs[1,9]

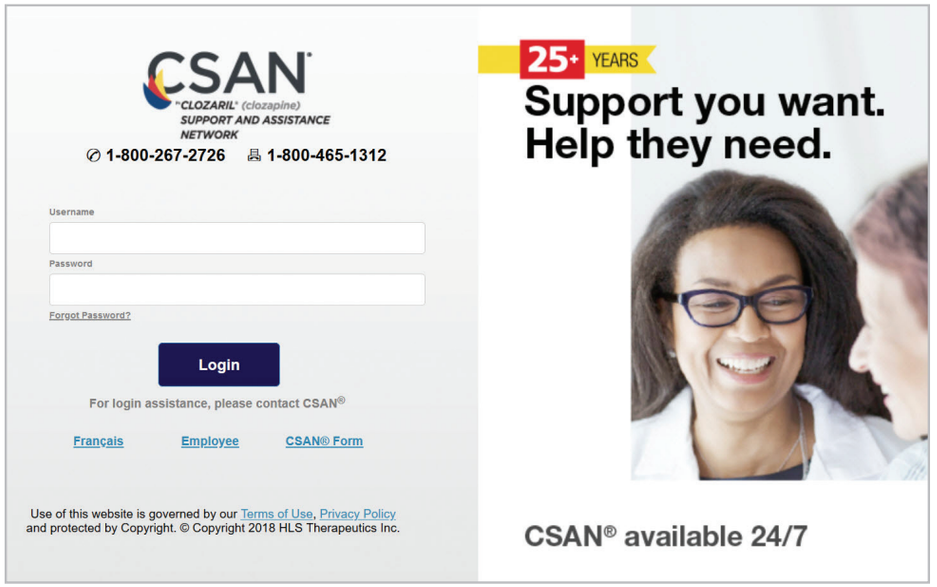
In order to help promote patient adherence, listed below are some of the potentially bothersome side effects of CLOZARIL®, along with suggestions for their management.

Side effect	Suggested non-medical intervention
Constipation[8]	• Recommend that patients eat more fruits and/or bran and drink plenty of water* • Exercise may also help* • Use caution when prescribing medications that can cause constipation
Drowsiness[8]	• This tends to subside with continued therapy or dose reduction • Recommend that patients do not drive a car or operate machinery if they feel drowsy • The total daily dose may be divided unevenly, with the larger portion taken at bedtime
Enuresis[8]	• Recommend that patients decrease their intake of liquids in the evening
Hypersalivation[8]	• This occurs most often during the night. • Suggest that patients place a soft towel over their pillow to feel more comfortable • During the day, patients can chew gum or suck on some ice to control their hypersalivation
Weight gain[8]	• Recommend that patients consult a dietitian about proper dietary measures*
Seizures (patients taking high doses)[1]	• This may affect 5% of patients taking doses of 600–900 mg daily • Caution should be used in patients who have a history of seizures or other predisposing factors • Patients should be advised to avoid activities where a sudden loss of consciousness could cause risk to themselves or others (e.g., driving, operating machinery, swimming, climbing, etc.)

* It is recommended that patients seek the advice of a dietitian or physician before changing their diet, and the advice of a physician before starting an exercise program.

The CSAN Patient Care Portal®

www.clozaril.ca



Online CLOZARIL® patient management that's fast, friendly, and secure

- Excellent performance and system reliability
- Exceptional end-user experience
- High level of security

User's guide

The CSAN Patient Care Portal® is a Canadian web-based, real-time, patient-management tool designed to assist healthcare professionals in the management of treatment-resistant schizophrenia.

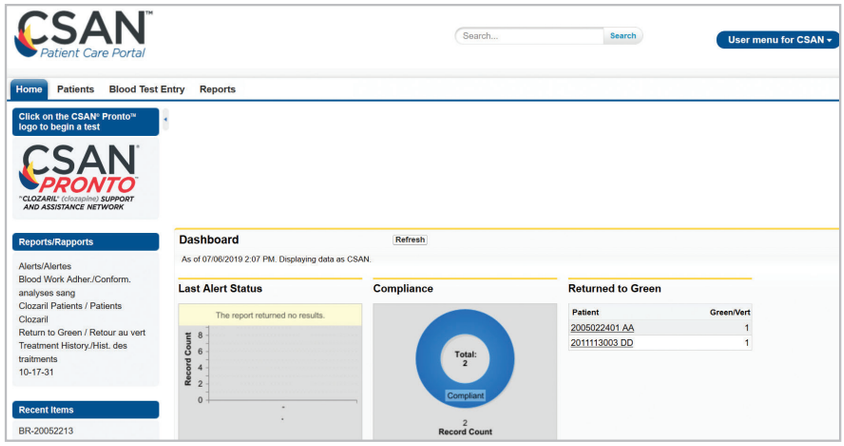
The CSAN Patient Care Portal® gives physicians, pharmacists, and nurse specialists instant access to real-time data for any patient registered with CSAN® anywhere in the world.

CSAN® is the longest-running clozapine hematological monitoring program in Canada (comparative clinical significance is unknown). Its range of services helps you manage the risk of agranulocytosis in patients who are taking CLOZARIL® by making sure that regular hematological monitoring is carried out according to the guidelines of the CLOZARIL® Product Monograph.

CSAN® supplies healthcare teams with notification of adverse hematological trends within 24 hours. It also ensures that any patients who have been discontinued from CLOZARIL® treatment due to blood dyscrasias are not retreated.

CSAN® helps save you time

The CSAN Patient Care Portal® helps enhance your patient-management capabilities while trying to minimize demands on your valuable time. With the integration of the **new CSAN® Pronto™ device**, your patients' results are automatically uploaded to the CSAN Patient Care Portal® and made readily available to their healthcare teams. The experts at CSAN® assist with the monitoring, blood work entries, and coordination for the CSAN Patient Care Portal® site, as the site is kept continually up to date in real time. Reliable patient data are therefore accessible online within minutes, 24/7, 365 days a year.



Integrated LabLink data

Blood work data generated by laboratories using the LabLink automated reporting network will be available online at the CSAN Patient Care Portal® immediately. For laboratories not using LabLink, data can be forwarded to CSAN® for the CSAN Patient Care Portal® database entry. For additional general information or for information related to software installation, please contact CSAN® at 1-800-267-2726.

User friendly

Not keen on computers? Don't worry—the CSAN Patient Care Portal® is simple to use. Just a few simple keystrokes, and you'll be able to access the full range of critical patient database information and enter hematological data yourself. The CSAN Patient Care Portal® can be customized for your unique individual needs and workflow.

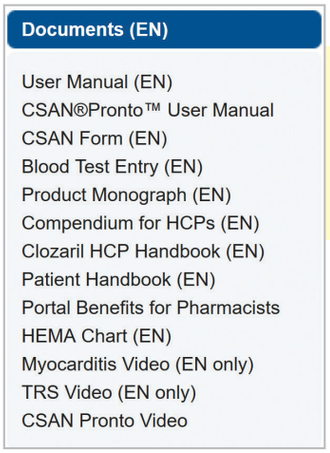
How easy is it?

Once you are registered with CSAN® and provided with a CSAN Patient Care Portal® secure user ID and password, simply go to www.clozaril.ca and log in—it's that simple. As soon as you're logged in, you'll have instant access to white blood cell (WBC)/absolute neutrophil count (ANC) histories of all your registered, active CSAN® patients. Real-time records will be accessible from this single comprehensive online source.

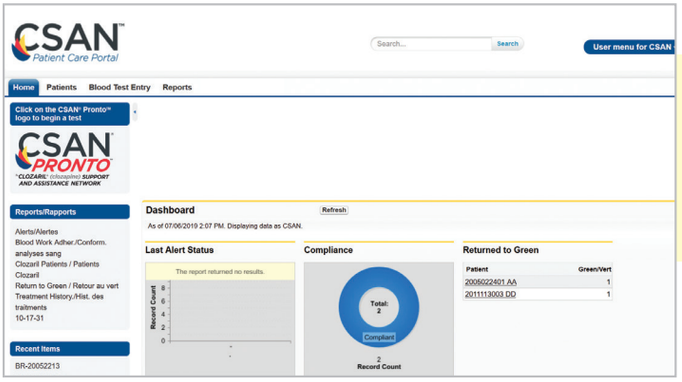
How the CSAN Patient Care Portal® can help you

The online CSAN Patient Care Portal® gives you a wide range of monitoring features and options designed to enhance patient-safety management. The CSAN Patient Care Portal® is a real-time, web-based system that will help you identify adverse hematological trends quickly, offering high reporting speed and monitoring efficiency across Canada and around the world.

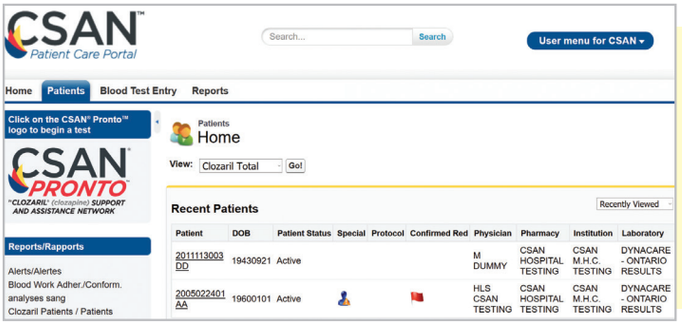
The CSAN Patient Care Portal® offers:



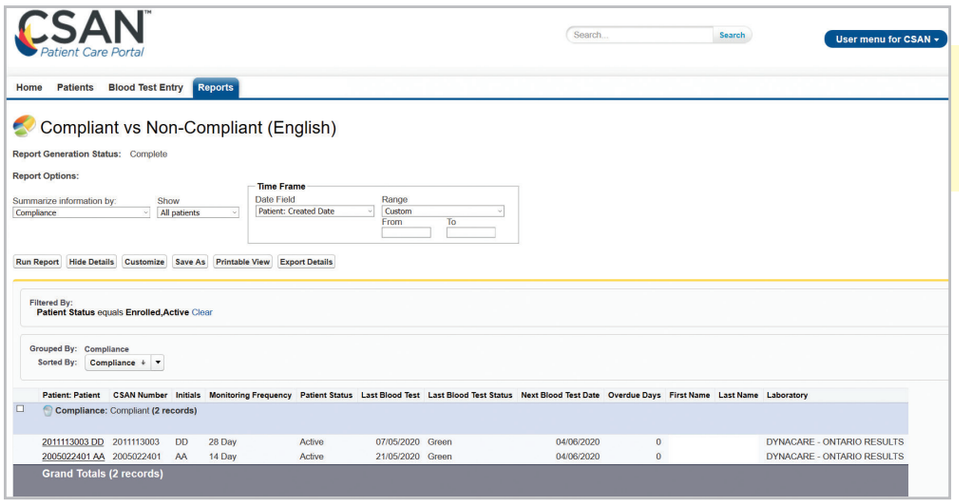
- Links to the User Manual, CLOZARIL® Product Monograph, editable CSAN® form, and additional resources via the navigation toolbar



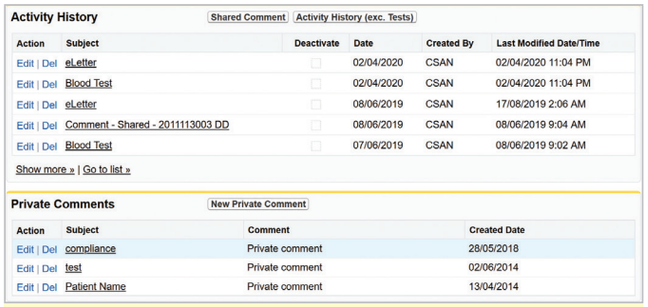
- Up-to-date, menu-driven daily, weekly, and monthly reports that enable you to identify patients who may need additional backup or immediate attention at a glance



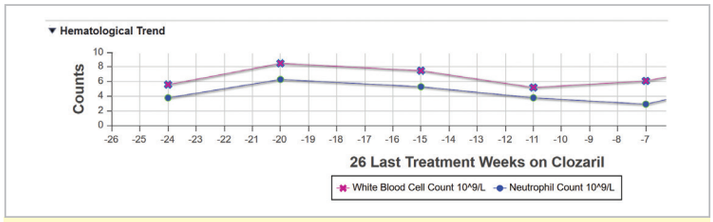
- Search capabilities within your patient's listing
- Ability to export patient data into Excel format
- Patient-grouping capabilities by initials, date of birth, and patient identifier



- Reports to aid in managing blood monitoring compliance



- Secure and confidential comments section for your clinical notes



- Patient blood monitoring history available to view trends

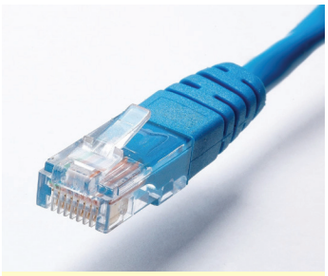
- Seamless integration with the CSAN® Pronto™ blood monitoring device

- Customizable reports available to fit your workflow
  - Please contact 1-800-267-2726 to learn more
- Continued storage in Canada of patient information, ensuring patient confidentiality

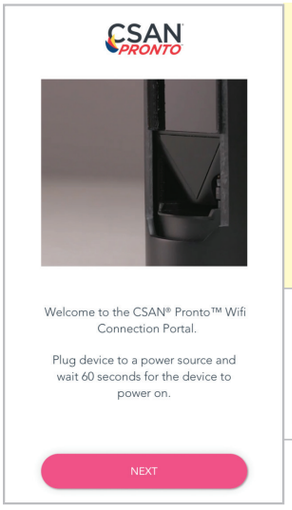
How to use CSAN® Pronto™

Connecting CSAN® Pronto™ to the Internet

1. Connect your CSAN® Pronto™ device to the Internet using either of the options below.



Option 1:
Plug an ethernet cable into CSAN® Pronto™ to connect to the Internet directly.

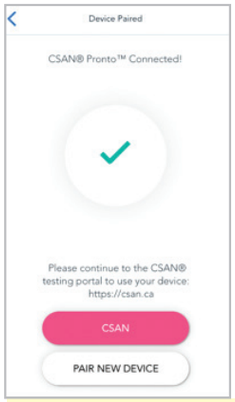


Option 2:
Download the CSAN® Pronto™ Application onto an authorized smartphone, computer, or tablet. Follow the steps within the application to connect the device to Wi-Fi.

GET IT ON Google Play

Download on the App Store

When the device is connected to the Internet successfully, the light under the slide tray will turn green.



2. Once CSAN® Pronto™ has successfully connected to the Internet, log in to the CSAN Patient Care Portal®.

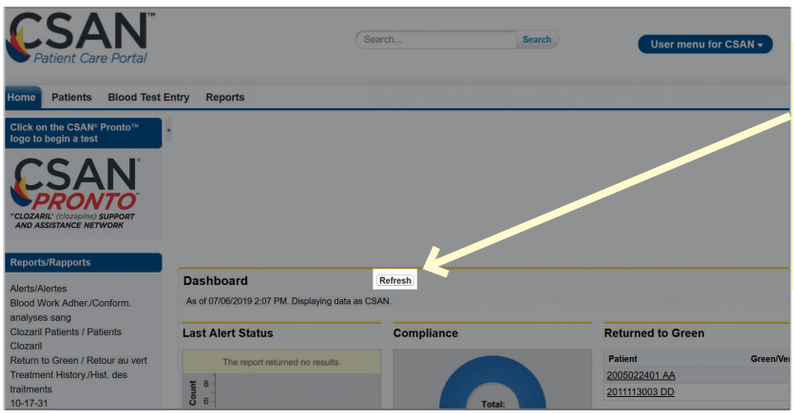
Running a test with CSAN® Pronto™

A¹
Running a routine test Option 1

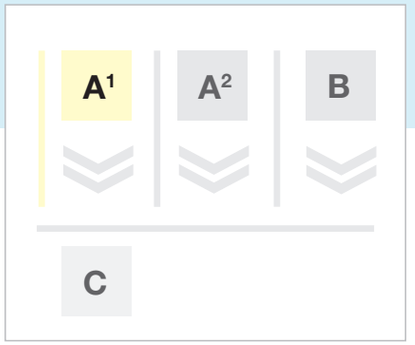
A²
Running a routine test Option 2

B
Running a baseline test

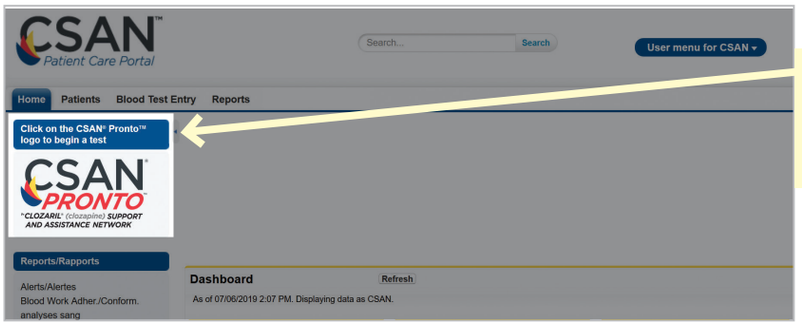
C
Completing the test



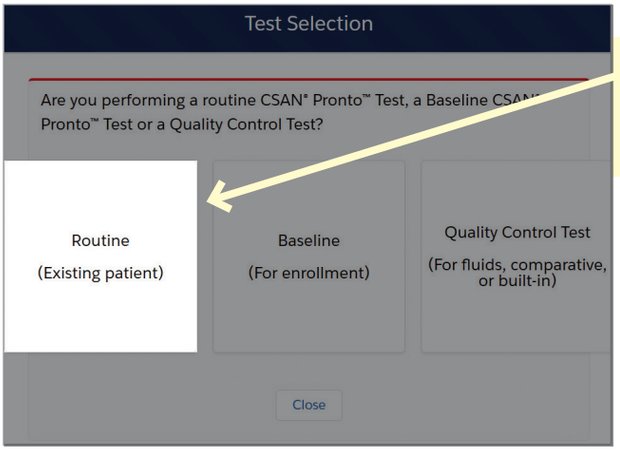
Before running a test, remember to click the “Refresh” button to ensure the most up-to-date information is being displayed in your dashboard.



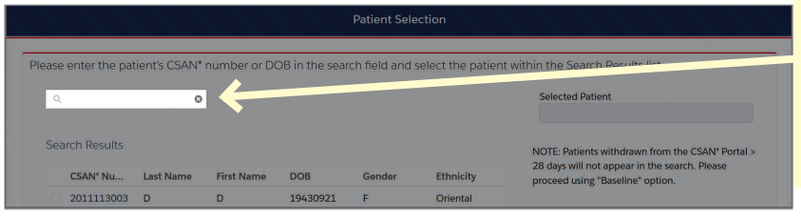
A1
Running a routine test
Option 1: From the CSAN® Pronto™ logo



1. Click on the CSAN® Pronto™ logo.

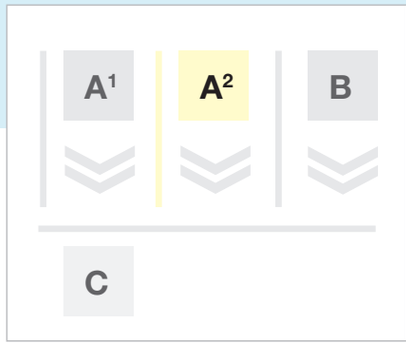


2. Click “Routine.”

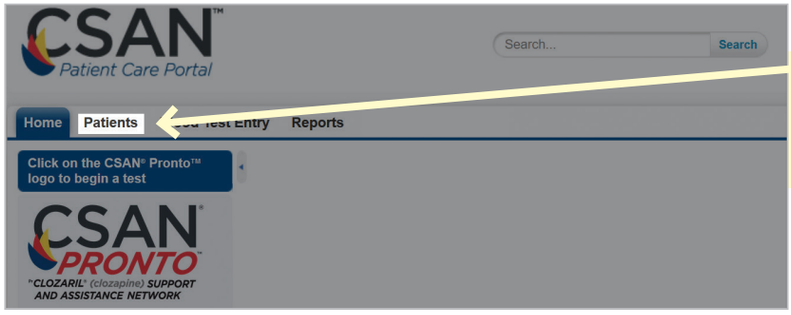


3. Patient selection: To select the patient, enter the CSAN® number or date of birth (DOB) (YYYY/MM/DD).

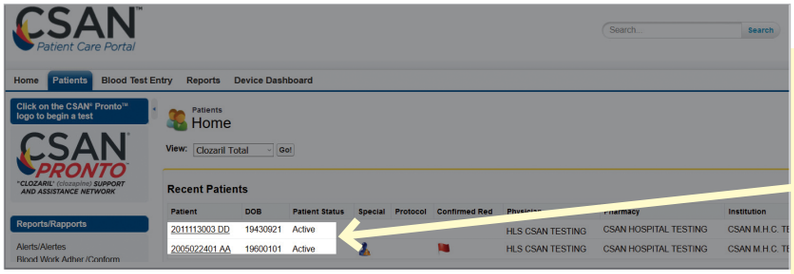
4. Proceed to step 5 on page 30.



A2
Running a routine test
Option 2: From a patient file

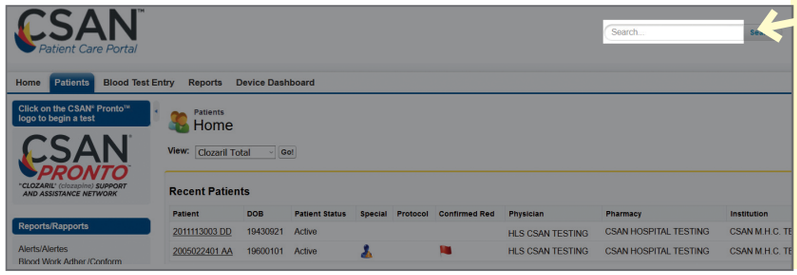


1. Click on the “Patients” tab.

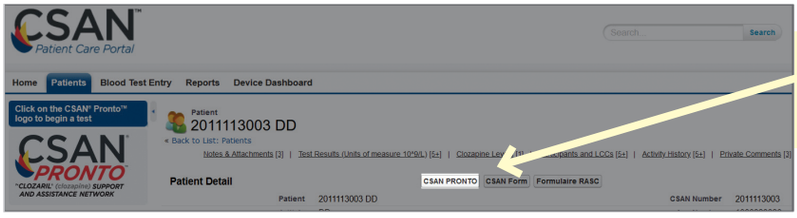


2. There are 2 ways to access a patient file:

a. Choose “CLOZARIL® Total” view and click “Go!” to see a complete list of your patients. Click on a patient’s CSAN® number to access their patient file.

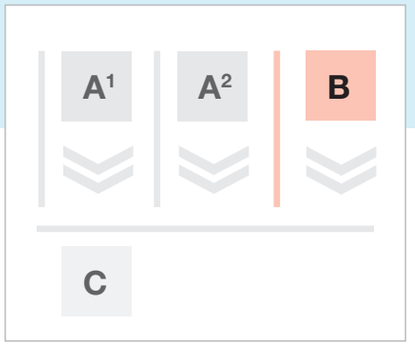


b. Use the Global Search bar to find a patient using their CSAN® number or date of birth (DOB) (YYYY/MM/DD).

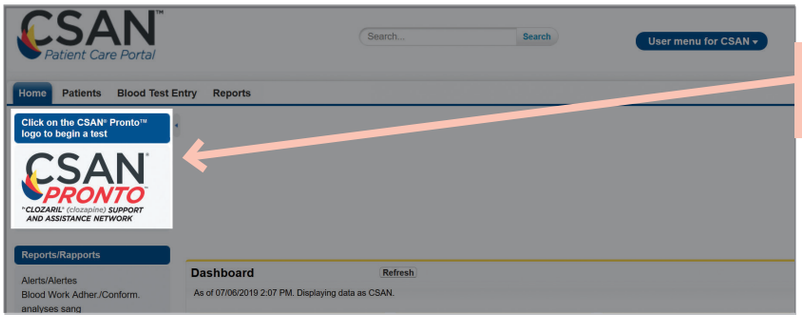


3. Click on the “CSAN PRONTO” button to begin a test.

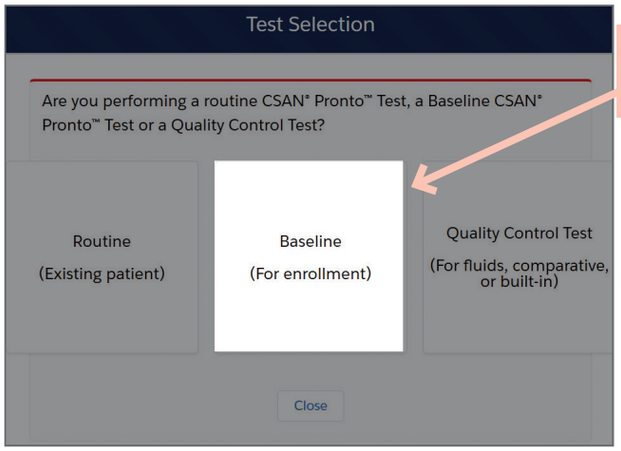
4. Proceed to step 5 on page 30.



B
Running a baseline test



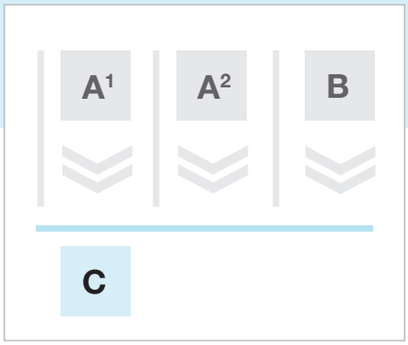
1. Click on the CSAN® Pronto™ logo.



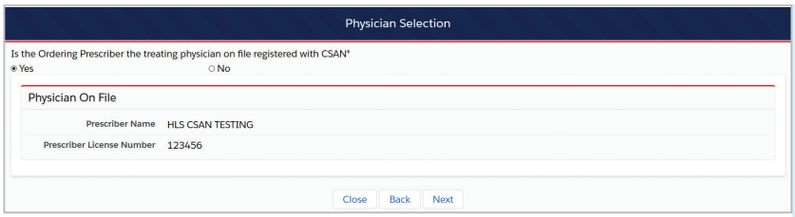
2. Click “Baseline.”

3. Patient selection: Enter the baseline patient information (red-line fields are mandatory), then click “Next.”

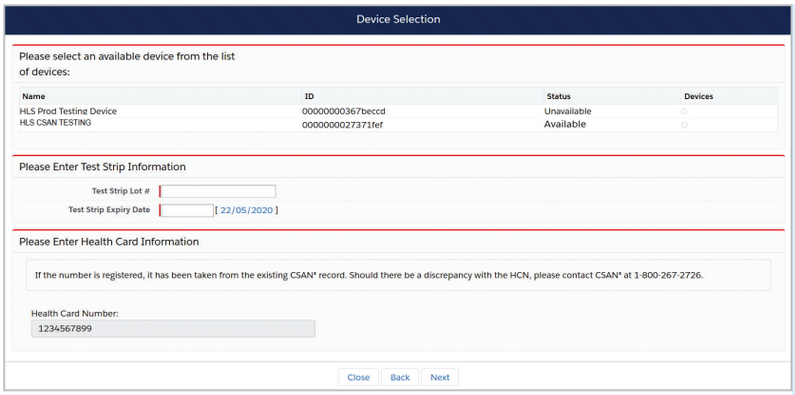
4. Proceed to step 5 on page 30.



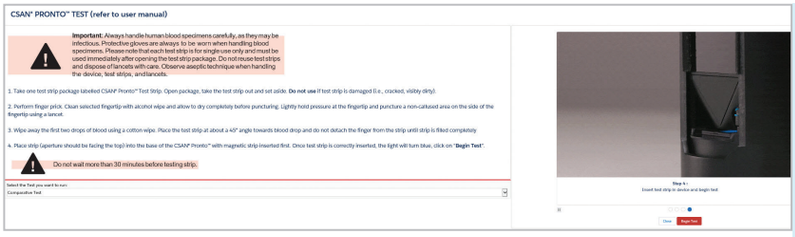
C
Completing the test



5. Physician selection: The treating physician on file will appear by default. You can also choose a different ordering physician by clicking on “No” and entering the name and licence number manually. Then, click “Next.”

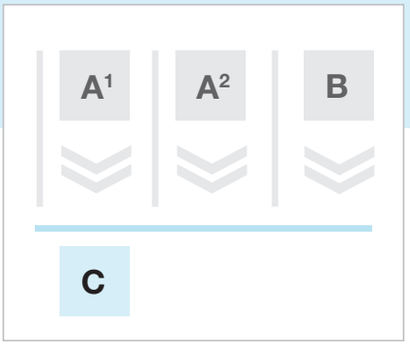


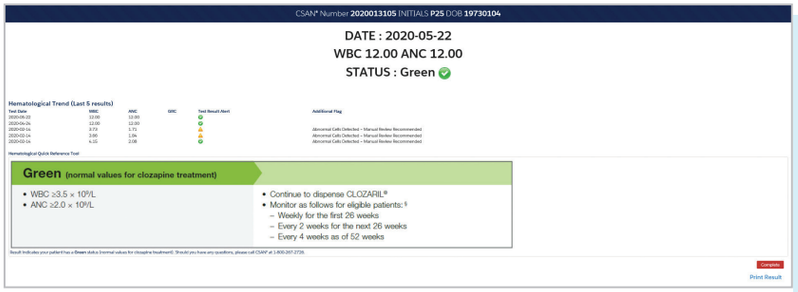
6. Device selection: Choose an available device, and enter the test strip lot # and expiry date. The health card number (HCN) will populate if it was provided to CSAN®. If it is blank then it can be entered manually. If it is prepopulated but believed to be incorrect, then the user must call CSAN® to have it corrected. Click “Next.”



7. Follow the instructions that appear on-screen to collect the sample and insert the test strip into the device. For more information, please refer to the Instructions for Use.

8. Next, click on “Begin Test."





9. CSAN® Pronto™ will now analyse the test strip and render the results on-screen after just a few minutes. The results will also be automatically uploaded into the CSAN Patient Care Portal® and shared with the healthcare team via fax or email. Text messages will also be sent in the event that there are red or yellow alerts.

Refer to the hematological quick reference chart on page 32 for more information on potential results.

For more details, please refer to the Instructions for Use at www.CSANPronto.ca.

To learn more or for additional support, visit www.CSANPronto.ca to watch a video about this new addition to the CSAN® program or contact the CSAN® team at 1-800-267-2726.

To order additional CSAN® Pronto™ Test Strips or QC test fluid (CP WBC Quality Control Fluid), please contact CSAN® Order Desk at 1-866-669-2313.

To order additional CSAN® Pronto™ Optical Swabs (to clean the optical parts of CSAN® Pronto™), please contact CSAN® at 1-800-267-2726.

Hematological quick reference chart[1]*

How CSAN® defines results associated with WBC and ANC laboratory values

CLOZARIL® (clozapine) is indicated in the management of symptoms of treatment-resistant schizophrenia.

Green (normal values for clozapine treatment)

- WBC ≥3.5 × 10^9/L
- ANC ≥2.0 × 10^9/L

- Continue to dispense CLOZARIL®
- Monitor as follows for eligible patients:†
  - Every week for the first 6 months
  - Every 2 weeks for the next 6 months
  - Every 4 weeks thereafter

Yellow Alert(s)

WBC or ANC in the range of:

- 2.0 × 10^9/L ≤WBC <3.5 × 10^9/L
- 1.5 × 10^9/L ≤ANC <2.0 × 10^9/L

Flashing Yellow

Indicates a significant fall in WBC or ANC:

- Single fall or sum of falls in WBC or ANC measured in the **last 4 weeks**
  - Fall of WBC of ≥3.0 × 10^9/L, reaching a value <4.0 × 10^9/L
  - Fall of ANC of ≥1.5 × 10^9/L, reaching a value <2.5 × 10^9/L

Particular attention should be paid if patient presents with the following:

- Any flu-like complaints or other symptoms that might suggest infection (i.e., fever, sore throat, or any other signs of infection)

- Hematological monitoring at least twice a week
- Continue to dispense CLOZARIL®

Red Alert

- WBC <2.0 × 10^9/L
- ANC <1.5 × 10^9/L

Consider protective isolation when:

- WBC <1.0 × 10^9/L
- ANC <0.5 × 10^9/L

- Notify CSAN® at 1-800-267-2726
- Confirm laboratory results by drawing another sample within 24 hours
- **STOP CLOZARIL® THERAPY IMMEDIATELY IF RESULTS ARE CONFIRMED.** Monitoring should occur at least once weekly for a period of 4 weeks following discontinuation.
  - Particular attention should be paid to any flu-like complaints or other symptoms that might suggest infection (i.e., fever, sore throat, or any other signs of infection)
- **DO NOT RESUME CLOZARIL® THERAPY**
- **A non-rechallengeable status is immediately assigned to the patient's profile**
- **Consult with a CSAN® hematologist**

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

* Please consult the prescribing information for complete hematological monitoring information.

† The change from an every-week to an every-two-week or from an every-two-week to an every-four-week schedule should be based on the hematological profile of the patient, the clinical judgement of the treating physician, and if deemed appropriate, a consulting hematologist, and on the patient's willingness to pursue a given frequency of blood monitoring. The clinical evaluation should take into consideration possible factors that would place the patient in a higher risk group.

Hematological reporting

Using CSAN® Pronto™

CSAN® Pronto™ provides lab results in minutes after testing. After providing a readout of the results, the device will automatically use the total WBC count and neutrophil percentage to determine ANC and report the values to CSAN®. Once you have received the CSAN® Pronto™-generated results, please follow the steps outlined below:

Step 1 Refer to the **lowest** value between the WBC and ANC to determine appropriate hematological monitoring or action. For example, if either the WBC or ANC score is in the RED area, then this represents a RED ALERT, and patient management is described on the chart provided and in detail in the CLOZARIL® Product Monograph.

Using venous blood draw labs

Once you have received the lab report from the testing centre, please follow the steps outlined below:

Step 1 Locate the total WBC (leukocytes) and the neutrophil counts.

Step 2 Determine whether this neutrophil count is expressed as an absolute number, a percentage, or a fraction of the total WBC.

Step 3 If the absolute value of neutrophils is given, then report it along with the total WBC to CSAN®.

Step 4 If the absolute value of neutrophils is not reported, then it can be calculated from the total WBC. Multiply the fraction (or percentage) of neutrophils by the total WBC. This number will represent the ANC (see examples below).

Step 5 Refer to the **lowest** value between the WBC and ANC to determine appropriate hematological monitoring or action. For example, if either the WBC or ANC score is in the RED area, then this represents a RED ALERT, and patient management is described on the chart provided and in detail in the CLOZARIL® Product Monograph.

Patients who have low WBC counts because of benign ethnic neutropenia (BEN) should be given special consideration and may be started on CLOZARIL® after agreement by a hematologist.

In order to meet CSAN® criteria for BEN enrolment, the patient must have at least two ANC results greater than or equal to 1 x10^9/L and less than 2 x10^9/L (one within the past 6 months and another within the past 28 days). For patients not already on clozapine, at least one test must be within the past 28 days.

Patients with a history of primary bone marrow disorders or concurrent conditions may be treated with CLOZARIL® on a compassionate basis and, therefore, may not need to follow the regular monitoring guidelines if the benefit outweighs the risk. These patients should be carefully evaluated by a hematologist. In such cases, it is in the patient's best interest to relieve their pain and suffering by continuing to provide the medication. These provisions are supported by the Product Monograph.

Sample calculations

ANC=absolute neutrophil count; WBC=white blood cell.
Please note: All cell counts are expressed in units of 10^9/L.

If WBC = 10.0 ANC = 5.3 Then no calculation required	If WBC = 10.0 Neutrophil count (fraction) = 0.53 Then ANC = WBC × fraction = 10.0 × 0.53 = 5.3	If WBC = 10.0 Neutrophil count (percentage) = 53% Then ANC = WBC × percentage = 10.0 × 53% = 5.3

Please consult the CLOZARIL® Product Monograph at clozaril.ca/clozaril_monograph for important information on contraindications, warnings, precautions, adverse reactions, drug interactions, dosing, and conditions of clinical use. The Product Monograph is also available by calling 1-800-267-2726.

Drug interactions[1*]

Drugs	Interaction
Alcohol, monoamine oxidase (MAO) inhibitors, central nervous system (CNS) depressants (including narcotics, antihistamines and benzodiazepines), and anticholinergic and antihypertensive agents[1]	CLOZARIL® may enhance the central effects of these products.
Benzodiazepines or other psychotropic drugs[1]	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 and epinephrine[1]	Owing to its anti-α-adrenergic properties, CLOZARIL® 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 (e.g., carbamazepine, long-acting depot antipsychotic drugs)[1]	CLOZARIL® 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[1]	Concomitant use of valproic acid may alter the plasma levels of CLOZARIL®. Rare but serious reports of seizures, including onset of seizures in non-epileptic patients, and isolated cases of delirium where CLOZARIL® 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.
Medications known to lower seizure threshold[1]	Caution should be exercised when CLOZARIL® is prescribed with drugs known to lower seizure threshold.
Medicines known to increase the QTc interval or cause electrolyte imbalance[1]	As with other antipsychotics, caution should be exercised when CLOZARIL® is prescribed with medicines known to increase QTc interval or cause electrolyte imbalance.

Drugs	Interaction
Drugs known to inhibit the activity of cytochrome P450 isozymes:[1] • Cimetidine (2D6, 3A4) • Erythromycin (3A4) • Potent inhibitors of CYP3A (e.g., azole antimycotics,† protease inhibitors†) • Fluvoxamine (1A2), ciprofloxacin (1A2), and oral contraceptives (1A2, 3A4, 2C19)‡ • Paroxetine, sertraline, fluoxetine, and citalopram (selective serotonin reuptake inhibitors [SSRIs])§ • Caffeine (1A2)¶ • Tricyclic antidepressants and type 1_c anti-arrhythmics (2D6)**	May increase the plasma levels of CLOZARIL®.
Drugs known to induce cytochrome P450 enzymes:[1] • Carbamazepine (3A4) • Phenytoin (3A4) • Rifampicin (3A4) • Omeprazole (1A2) • Tobacco smoking (1A2)††	May decrease the plasma levels of CLOZARIL®.

* Please note that this list is not exhaustive.
† No interactions have been reported to date.
‡ Substantial elevation of the plasma concentration of clozapine has been reported in patients receiving the drug in combination with fluvoxamine (1A2), ciprofloxacin (1A2), and oral contraceptives (1A2, 3A4, 2C19).
§ Smaller elevations in clozapine plasma concentrations have also been reported in patients receiving the drug in combination with other SSRIs such as paroxetine, sertraline, fluoxetine, and citalopram (possibly a weak inhibitor of CYP1A2 and possibly the least among SSRIs to cause a clinically significant interaction with clozapine).
¶ The plasma concentration of clozapine is increased by caffeine (1A2) intake and decreased by nearly 50% following a 5-day caffeine-free period.
** No clinically relevant interactions have been observed thus far with tricyclic antidepressants, or type 1_c anti-arrhythmics, known to bind to cytochrome P450 2D6.
†† In cases of sudden smoking cessation, the plasma clozapine concentration may be increased, thus leading to an increase in adverse effects.
Abrupt changes to coffee intake or smoking habits may change the effect of CLOZARIL®.
Refer to the Product Monograph for a detailed list of drug interactions.

Are clozapine brands interchangeable?

The switching of a patient from one brand of clozapine to another must not be done by a pharmacist unless they obtain a new, registry-specific patient registration form filled out by the prescribing physician.[4]

Patient safety points to consider:

1. Clozapine patients require regular hematological testing.
   - **At lease every week** for the first 6 months of treatment, **every 2 weeks** for the next 6 months, and **every 4 weeks** thereafter, for the duration of treatment, and at least every week for 4 weeks after discontinuation of treatment[1]
2. Clozapine patients **must** be enrolled in a registry for tracking and monitoring of hematological status[4]
   - Registries are maintained by each of the clozapine manufacturers[4]
   - If patients switch physician, pharmacy, or laboratory, a modification form **must** be submitted[4]
   - Patients may not be switched from one brand of clozapine to another without the completion of a new registry-specific patient registration form signed by the prescribing physician
3. Pharmacists **must** verify the patients' status and eligibility for clozapine.
   - Hematological status—testing done within the appropriate time frame[5]

Clozapine registry support programs are not identical. When patients switch registries, their access to registry support programs changes accordingly.

Safety information

Indication and clinical use:

CLOZARIL® (clozapine) is indicated in the management of symptoms of treatment-resistant schizophrenia. In controlled clinical trials, clozapine was found to improve both positive and negative symptoms. Due to the significant risk of agranulocytosis and seizure associated with its use, clozapine should be limited to treatment-resistant patients suffering from schizophrenia who are non-responsive to, or intolerant of, conventional antipsychotic drugs. Non-responsiveness is defined as the lack of satisfactory clinical response, despite treatment with appropriate courses of at least two marketed, chemically-unrelated antipsychotic drugs. Intolerance is defined as the inability to achieve adequate benefit with conventional antipsychotic drugs because of dose-limiting, intolerable adverse effects. Because of the significant risk of agranulocytosis and seizure, events which both present a continuing risk over time, the extended treatment of patients failing to show an acceptable level of clinical response to clozapine should ordinarily be avoided. In addition, the need for continuing treatment in patients exhibiting beneficial clinical responses should be periodically reevaluated. Clozapine can be used only if regular hematological examinations can be guaranteed. Physicians should not prescribe CLOZARIL® until the non-rechallengeable status and the hematological status of the patient have been verified.

CLOZARIL® should be used with care in the elderly.

CLOZARIL® is not indicated in pediatric patients and its use is not recommended. The safety and efficacy of CLOZARIL® in children and adolescents have not been established.

Contraindications:

- Previous hypersensitivity to clozapine or any other components of CLOZARIL®
- Patients unable to undergo routine blood tests
- Myeloproliferative disorders, a history of toxic or idiosyncratic agranulocytosis, or severe granulocytopenia (with the exception of granulocytopenia/agranulocytosis from previous chemotherapy); clozapine should not be used simultaneously with other agents known to suppress bone marrow function
- Active liver disease associated with nausea, anorexia, or jaundice; progressive liver disease; hepatic failure
- Severe central nervous system depression or comatose states
- Severe renal or cardiac disease (e.g., myocarditis)
- Paralytic ileus
- Uncontrolled epilepsy

Most serious warnings and precautions:

Elderly patients with dementia: Elderly patients with dementia treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. CLOZARIL® is not indicated in elderly patients with dementia.

Agranulocytosis: Because of the significant risk of granulocytopenia and agranulocytosis, a potentially life-threatening adverse event, CLOZARIL® should be reserved for use in the treatment of patients suffering from schizophrenia who fail to show an acceptable response to adequate courses of conventional antipsychotic drug treatment. Patients must have a normal white blood cell (WBC) count and differential count prior to starting clozapine therapy. Subsequently, a WBC count and differential count must be carried out at least weekly for the first 26 weeks of treatment with clozapine. Thereafter, if acceptable WBC counts and absolute neutrophil counts (ANC) (WBC ≥3,500/mm^3 and ANC ≥2,000/mm^3) have been maintained during the first 26 weeks of continuous therapy, the WBC count and differential count can be performed at least at two-week intervals for the next 26 weeks. Thereafter, if acceptable WBC counts and ANCs (WBC ≥3,500/mm^3 and ANC ≥2,000/mm^3) have been maintained during the second 26 weeks of continuous therapy, the WBC count and differential count can be performed at least every four weeks throughout treatment.

Cardiovascular toxicity: The use of clozapine is associated with an increased risk of myocarditis, especially during, but not limited to, the first month of therapy.

Other relevant warnings and precautions:

- Fever
- Cognitive and motor performance
- Anticholinergic activity
- Rebound/withdrawal
- Other adverse cardiovascular and respiratory effects
- QT interval prolongation
- Venous thromboembolism
- Seizures
- Falls
- Neuroleptic Malignant Syndrome
- Tardive dyskinesia
- Hematologic disorders
- Eosinophilia/thrombocytopenia/Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)
- Metabolic changes (hyperglycemia, dyslipidemia, and body weight gain)
- Dysphagia
- Hepatotoxicity
- Genitourinary
- Patients with hepatic and renal impairment, and vascular disease
- Pregnant women, nursing women, and women with childbearing potential
- Cerebrovascular adverse events
- Concomitant administration of drugs known to inhibit or induce the activity of cytochrome P450 isozymes

For more information:

Please consult the Product Monograph at clozaril.ca/clozaril_monograph for important information on adverse reactions, drug interactions, and dosing information. The Product Monograph is also available by calling 1-800-267-2726.

For additional support and information on CLOZARIL®, visit **www.clozaril.ca.**

To learn more about CSAN® Pronto™, the latest offering from the CSAN® program, visit **www.CSANPronto.ca.**

References:

1. CLOZARIL® Product Monograph. HLS Therapeutics Inc. January 23, 2020. **2.** Remington G, et al. Guidelines for the pharmacotherapy of schizophrenia in adults. *Can J Psychiatry.* 2017;62(9):604-616. **3.** Norman R, et al. Canadian treatment guidelines on psychosocial treatment of schizophrenia in adults. *Can J Psychiatry.* 2017;62(9):617-623. **4.** Health Canada. Press release, monitoring of patients taking clozapine. Accessed October 23, 2019. http://www.healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2004/14249a-eng.php. **5.** CCHCS/DHCS care guide: Clozapine. March 2016. Accessed October 23, 2019. https://cchcs.ca.gov/wp-content/uploads/sites/60/2017/08/Clozapine-Care-Guide.pdf. **6.** Data on file. **7.** HLS Therapeutics Inc. CSAN® Pronto™ Device Monograph. 2019. **8.** Pringsheim T, et al. Physical health and drug safety in individuals with schizophrenia. *Can J Psychiatry.* 2017;62(9):673-683. **9.** Young CR, et al. Management of the adverse effects of clozapine. *Schizophr Bull.* 1998;24(3):381-390.

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Questions?
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CLOZARIL® Clozapine

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