Support you want. Help they need.

CLOZARIL® handbook for healthcare professionals

PrCLOZARIL® (clozapine) is indicated in the management of symptoms of treatment-resistant schizophrenia (TRS).[1]

Visit **www.clozaril.ca** for additional support and information

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

NOW AVAILABLE: CSAN® Pronto™ is a new point-of-care blood monitoring device to help simplify routine blood monitoring for your patients on CLOZARIL®. See inside for more information or visit www.CSANPronto.ca.

CSAN
"CLOZARIL" (clozapine) SUPPORT AND ASSISTANCE NETWORK
1-800-267-2726

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

Pr CLOZARIL®
Clozapine

Table of contents

Resources for patients and caregivers

Resources for patients and caregivers

Organizations—national

Canadian Mental Health Association, National
500-250 Dundas Street West
Toronto, ON M5T 2Z5
Tel.: (416) 646-5557
Email: info@cmha.ca
www.cmha.ca

Schizophrenia Society of Canada
100-4 Fort Street
Winnipeg, MB R3C 1C4
Tel.: (204) 786-1616 or 1-800-263-5545
Fax: (204) 783-4898
Email: info@schizophrenia.ca
www.schizophrenia.ca

Internet resources

Schizophrenia Society of Canada
www.schizophrenia.ca

BC Mental Health & Substance Use Services
www.bcmhsus.ca

Alberta

Schizophrenia Society of Alberta
Provincial Office
4809-48th Avenue
Red Deer, AB T4N 3T2
Tel.: (403) 986-9440
Fax: (403) 986-9442
Email: info@schizophrenia.ab.ca
www.schizophrenia.ab.ca

British Columbia

British Columbia Schizophrenia Society
Provincial Office
1100-1200 West 73rd Avenue
Vancouver, BC V6P 6G5
Tel.: (604) 270-7841 or 1-888-888-0029
Fax: (604) 270-9861
Email: prov@bcss.org
www.bcss.org

Manitoba

Manitoba Schizophrenia Society
100-4 Fort Street
Winnipeg, MB R3C 1C4
Tel.: (204) 786-1616
Fax: (204) 783-4898
Email: info@mss.mb.ca
www.mss.mb.ca

New Brunswick

Schizophrenia Society of New Brunswick
Mailing address: PO Box 562
Miramichi, NB E1V 3T7
Civic address: 1756 Water Street, Suite 103
Miramichi, NB E1N 1B5
Tel.: (506) 622-1595 or 1-877-240-4412
Fax: (506) 622-8927
Email: ssnbmiramichi@nb.aibn.com
www.schizophreniasociety.nb.ca

Newfoundland and Labrador

Schizophrenia Society of Newfoundland and Labrador
Main office: 18A-18B UB Waterford Hospital
Waterford Bridge Road
St. John's, NL A1E 4J8
Mail: 48 Kenmount Road
PO Box 28029
St. John's, NL A1B 4J8
Tel.: (709) 777-3335
Fax: (709) 777-3524
Email: info@ssnl.org
www.ssnl.org

Nova Scotia

Schizophrenia Society of Nova Scotia
5571 Cunard Street, Unit 101
Halifax, NS B3K 1C5
Tel.: (902) 465-2601 or 1-800-465-2601
Fax: (902) 465-5479
Email: contact@ssns.ca
www.ssns.ca

Ontario

Schizophrenia Society of Ontario
Provincial/Toronto Office
95 King Street East, Third Floor
Toronto, ON M5C 1G4
Tel.: 1-800-449-6367
Fax: (416) 449-8434
Email: info@schizophrenia.on.ca
www.schizophrenia.on.ca

Prince Edward Island

Schizophrenia Society of Prince Edward Island
PO Box 25020
Charlottetown, PE C1A 9N4
Tel.: (902) 368-5850
Fax: (902) 368-5467
Email: schizophreniapei@pei.aibn.com

Quebec

Société québécoise de la schizophrénie (SQS)
7401, rue Hochelaga
Montreal, QC H1N 3M5
Tel.: (514) 251-4125 or 1-866-888-2323
Fax: (514) 251-6347
Email: info@schizophrenie.qc.ca
www.schizophrenie.qc.ca

AMI-Quebec (anglophone association)
5800, boulevard Décarie
Montreal, QC H3X 2J5
Tel.: (514) 486-1448 or 1-877-303-0264
Email: info@amiquebec.org
www.amiquebec.org

Fédération des familles et amis de la personne atteinte de maladie mentale
1990, rue Cyrille-Duquet, bureau 203
Quebec, QC G1N 4K8
Tel.: (418) 687-0474 or 1-800-323-0474
Fax: (418) 687-0123
Email: info@ffapamm.com
www.ffapamm.com

Saskatchewan

Schizophrenia Society of Saskatchewan
Provincial Office
1311 Saskatchewan Drive
Regina, SK S4P 0C9
Mail: Box 305 Station Main
Regina, SK S4P 3A1
Tel.: (306) 584-2620 or 1-877-584-2620
Fax: (306) 584-0525
Email: info@schizophrenia.sk.ca
www.schizophrenia.sk.ca

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
- 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.

Treatment-resistant schizophrenia

In Canada, approximately one out of every 100 people will suffer from schizophrenia in their lifetime.[2]

Unfortunately, some patients may not respond to, or may be intolerant of, other antipsychotic drugs. If symptoms persist despite trials with two chemically unrelated antipsychotics, the illness is diagnosed as **treatment-resistant schizophrenia (TRS)**. The inability to achieve adequate benefit with different antipsychotic drugs because of dose-limiting, intolerable side effects is also considered to be treatment resistance.[1,3] **It is estimated that 25–30% of individuals with schizophrenia meet the criteria for TRS.[3] For these patients, the only treatment that is indicated and recommended by guidelines is clozapine.**[1,4]

CLOZARIL® (clozapine) is indicated in the management of symptoms of TRS.[1]

In controlled clinical trials, CLOZARIL® was found to improve both positive and negative symptoms of schizophrenia.[1] According to the Canadian Guidelines for the Pharmacotherapy of Schizophrenia in Adults, clozapine becomes the treatment of choice when treatment resistance has been demonstrated.[3]

How CLOZARIL® can help your patients with TRS

CLOZARIL® is an effective medication that has been available in Canada since 1991 for patients with schizophrenia who are unresponsive to other antipsychotics and deemed treatment resistant.[1,3]

It has demonstrated efficacy for positive and negative symptoms compared with conventional antipsychotic drugs (chlorpromazine,* fluphenazine,† and haloperidol;‡ primary endpoints across all studies).[5-7] In addition, CLOZARIL® treatment has resulted in improved social competence, social interest, and personal neatness vs. chlorpromazine (secondary endpoints).[5§]

Improvements may be gradual and continued therapeutic response can be expected beyond the first month of treatment. The need for continued treatment in patients exhibiting beneficial clinical response should be periodically evaluated.[1]

* CLOZARIL® (n=126; up to 900 mg/day) vs. chlorpromazine (n=142; up to 1800 mg/day) for 6 weeks. $p<0.001$ for each of the following BPRS-positive symptoms: conceptual disorganization, mannerisms/posturing, hostility, suspiciousness, hallucinatory behaviours, excitement, unusual thoughts, and grandiosity. $p<0.05$ for each of the following BPRS-negative symptoms: emotional withdrawal, uncooperativeness, blunted affect, disorientation, and motor retardation.

† CLOZARIL® (mean dose 543 mg/day) vs. fluphenazine (mean dose 29 mg/day); n=21 (100-day, crossover study). $p<0.05$ for BPRS-positive symptoms; $p<0.01$ for BPRS-negative symptoms. There was no significant difference between treatments for the schedule for assessment of negative symptoms.

‡ CLOZARIL® (n=19; 200–600 mg/day) vs. haloperidol (n=20; 10–30 mg/day) for 10 weeks. $p=0.05$ for BPRS-positive symptoms; $p=0.04$ for negative scale for the assessment of negative symptoms.

§ CLOZARIL® (n=126; up to 900 mg/day) vs. chlorpromazine (n=142; up to 1800 mg/day) for 6 weeks. For each of these comparisons, $p<0.001$ for CLOZARIL® vs. chlorpromazine.

BPRS=Brief Psychiatric Rating Scale.

Blood monitoring[1]

A rare but serious adverse event associated with clozapine is **agranulocytosis**, a condition in which the body fails to produce white blood cells needed to fight infections. If left undetected and unmanaged, a patient may develop serious or possibly fatal infections. Since there may be no clinical evidence of agranulocytosis before infection, it is mandatory that patients undergo regular hematological monitoring.

Current estimates of the rate of agranulocytosis are 0.7%. The development of granulocytopenia and agranulocytosis does not appear to be dose dependent, nor is the duration of treatment a reliable predictor. Approximately 88% of cases of agranulocytosis occurred during the first 6 months of treatment.

Blood tests must be done every week during the first 6 months of treatment with CLOZARIL® due to the increased risk of agranulocytosis during this time. If acceptable WBC counts and ANCs have been maintained during the first 6 months of treatment, testing can be extended to two-week intervals for the next 6 months, and then to four-week intervals thereafter. In addition, the patient should report to the physician the first signs of a cold, influenza, lethargy, weakness, fever, sore throat, or any other signs of infection. Blood testing should be increased to at least twice weekly while a patient is symptomatic.

First 6 months:
Blood tests are required **every week**

Next 6 months:
Blood tests are required **every 2 weeks**

After 1 year:
Blood tests are required **every 4 weeks**

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

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.

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 "CLOZARIL" (clozapine) SUPPORT AND ASSISTANCE NETWORK
1-800-267-2726

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

CSAN® support

- CSAN® is **available 24/7** to answer questions and offer support
- **Offers the CSAN Patient Care Portal®** online hematological monitoring database
- Integrated with the CSAN® Pronto™ point-of-care testing device to help reduce the burden of blood monitoring
- 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 blood testing:
>95% of patients registered with CSAN® complied with the clozapine monograph criterion for laboratory compliance.[8]
CSAN® Pronto™ aims to streamline blood monitoring for patients on CLOZARIL®.

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. 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®.[9]

CSAN® Pronto™ is equipped with technology that:

- Provides laboratory-accurate WBC counts and NEUT% in real time[9]
- Requires only 1 drop of capillary blood (about 3.5 µl) to run the test[9]
- Offers one-step processing, while maintaining CSAN®'s privacy standards[9]
- Is designed to address a barrier of CLOZARIL® use by offering the convenience of onsite testing[9,10]

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**

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.[9]

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

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.

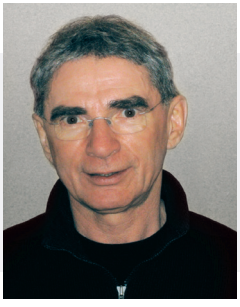
Dr. Prchal has been associated with CSAN® since its inception in 1991 and was involved in the original design of the hematological monitoring system. He has vast experience in the understanding and management of agranulocytosis. Dr. Prchal is available for direct consultation to the teams of nurses, 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

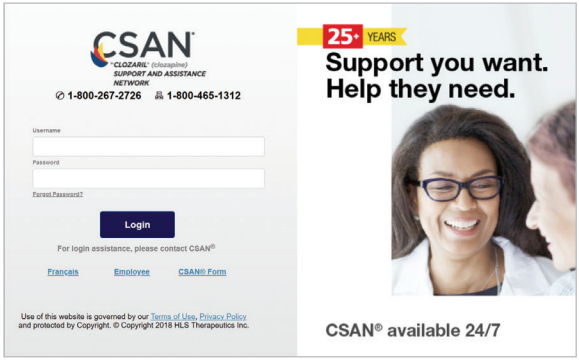
The caregiver team is there to ensure the patient receives the best possible care throughout the course of CLOZARIL® therapy. In general:

- 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.

The CSAN Patient Care Portal®

To access, visit 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.

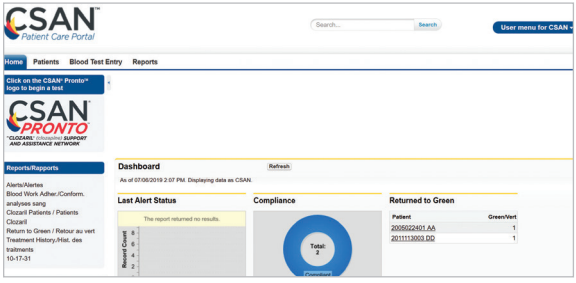
The CSAN Patient Care Portal® gives physicians, pharmacists, and nurse specialists instant access to real-time data for any patient registered with CSAN® anywhere in the world.

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. 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.

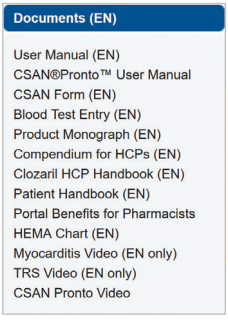
How easy is it?

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.

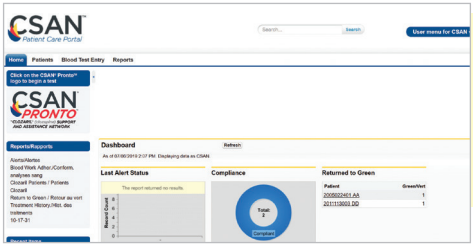
How the CSAN Patient Care Portal® can help you

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.

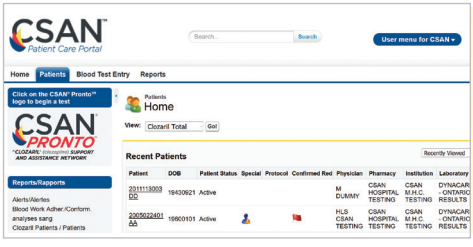
The CSAN Patient Care Portal® offers:



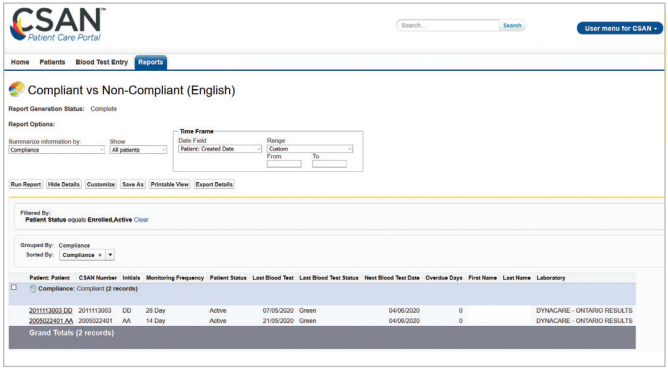
- Links to the User Manual, CLOZARIL® Product Monograph, editable CSAN® form, and additional resources via the navigation toolbar



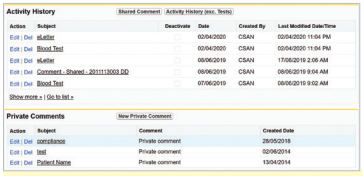
- Up-to-date, menu-driven daily, weekly, and monthly reports that enable you to identify patients who may need additional backup or immediate attention at a glance



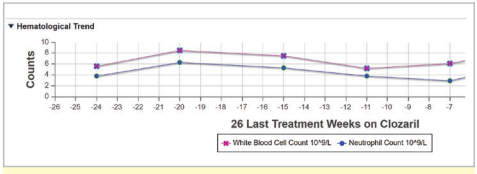
- Search capabilities within your patient's listing
- Ability to export patient data into Excel format
- Patient-grouping capabilities by initials, date of birth, and patient identifier



- 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

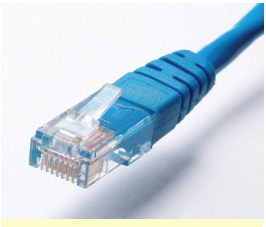
- Seamless integration with the CSAN® Pronto™ blood monitoring device

- 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.



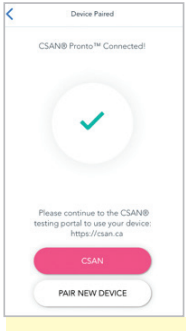
Option 1:
Plug an ethernet cable into CSAN® Pronto™ to connect to the Internet directly.

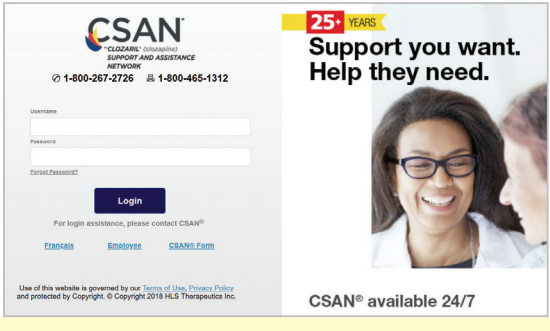
Option 2:
Download the CSAN® Pronto™ Application onto an authorized smartphone, computer, or tablet. Follow the steps within the application to connect the device to Wi-Fi.

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®.

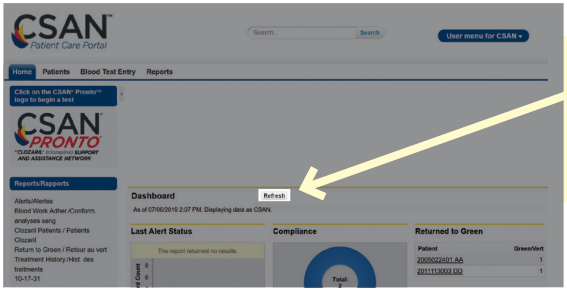
Running tests with CSAN® Pronto™

A[1]
Running a routine test Option 1

A[2]
Running a routine test Option 2

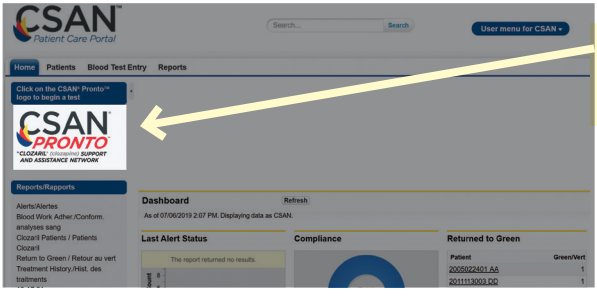
B
Running a baseline test

C
Completing the test

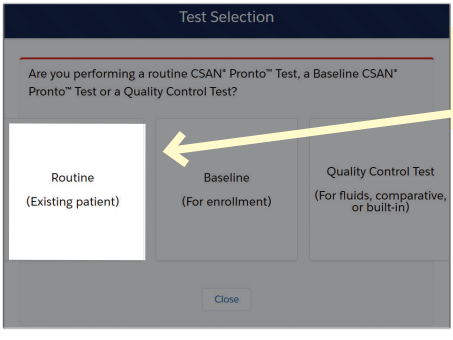


Before running a test, remember to click the “Refresh” button to ensure the most up-to-date information is being displayed in your dashboard.

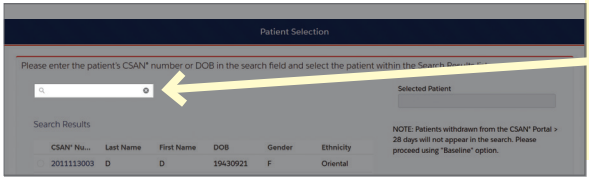
A1
Running a routine test
Option 1: From the CSAN® Pronto™ logo



1. Click on the CSAN® Pronto™ logo.

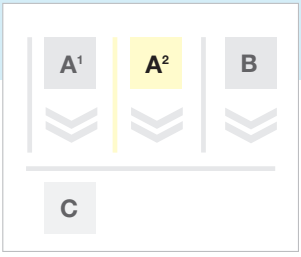


2. Click “Routine.”

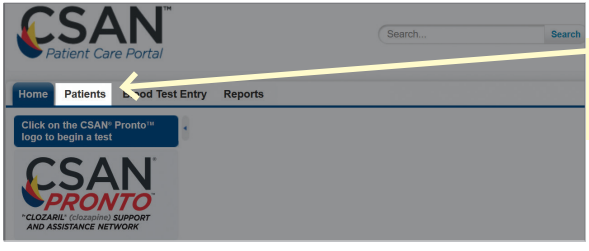


3. Patient selection: To select the patient, enter the CSAN® number or date of birth (DOB) (YYYY/MM/DD).

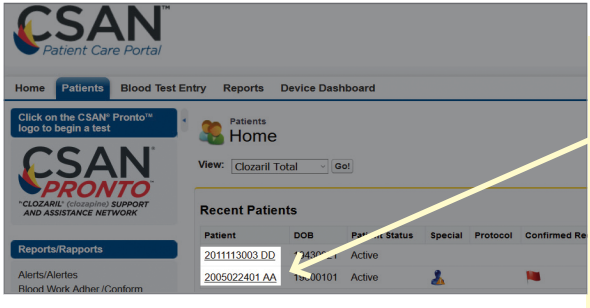
4. Proceed to step 5 on page 18.

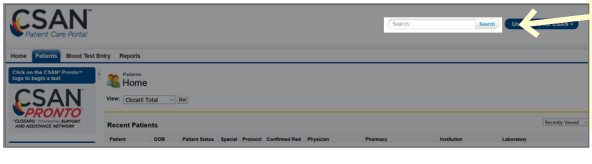


A2 Running a routine test
Option 2: From a patient file



1. Click on the “Patients” tab.

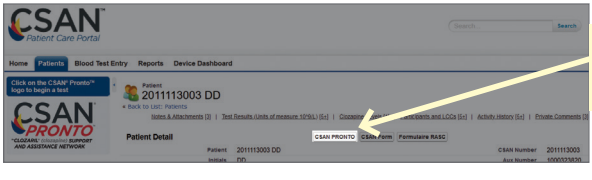




2. There are 2 ways to access a patient file:

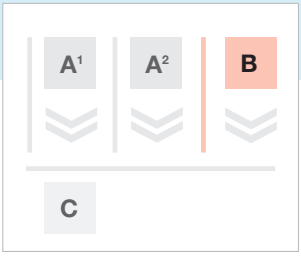
a. Choose “CLOZARIL® Total” view and click “Go!” to see a complete list of your patients. Click on a patient’s CSAN® number to access their patient file.

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

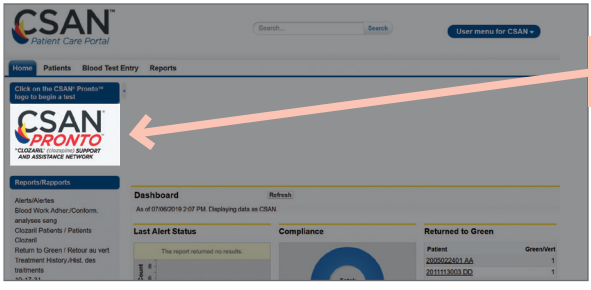


3. Click on the “CSAN PRONTO” button to begin a test.

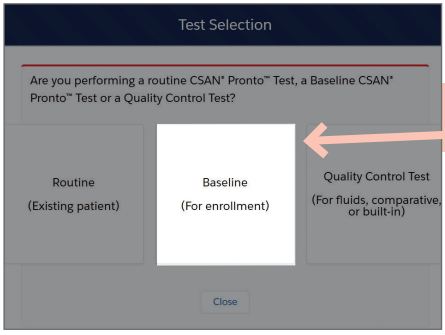
4. Proceed to step 5 on page 18.



B
Running a baseline test



1. Click on the CSAN® Pronto™ logo.

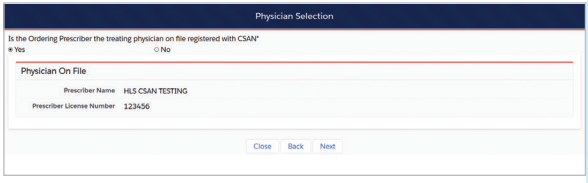


2. Click “Baseline.”

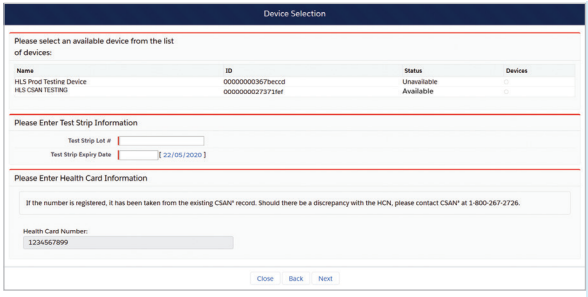
3. Patient selection: Enter the baseline patient information (red-line fields are mandatory), then click “Next.”

4. Proceed to step 5 on page 18.

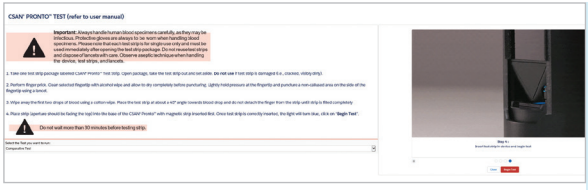
C
Completing the test



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.”

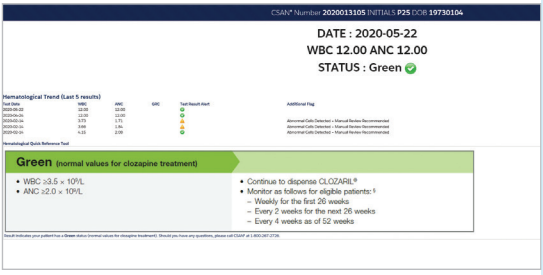


6. Device selection: Choose an available device, and enter the test strip lot # and expiry date. The health card number (HCN) will populate if it was provided to CSAN®. If it is blank, then it can be entered manually. If it is prepopulated but believed to be incorrect, then the user must call CSAN® to 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 26 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.

CSAN® procedures for initiating CLOZARIL® treatment

Prior to initiating CLOZARIL® treatment, the following steps should be followed:[1]

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:** Form to complete can be found at www.clozaril.ca.
   - The pharmacist and physician sections must be completed and signed
   - The laboratory and institution must be identified
   - A copy of the CBC results must be included

6. **Treatment initiation:** Follows the confirmation of CSAN® registration.

7. **Blood monitoring:**
   - **Every week** for the first 6 months
   - **Every 2 weeks** for the next 6 months*
   - **Every 4 weeks** thereafter*†

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. The CSAN® Pronto™ device can help simplify this process and reduce the burden of regular blood monitoring.

8. **CLOZARIL® dispensing:** The pharmacist must give the patient a supply of CLOZARIL® on an **every week, every-two-week,** or **every-four-week** basis only upon confirmation that hematological monitoring has been conducted for the current period.

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.

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

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

BMI=body mass index; CBC=complete blood count.

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.
Day 2	25 mg O.D. or B.I.D.
Weeks 1–2	25–50 mg/day **increases** **Target** 300–450 mg/day
Following months	300–600 mg/day **in divided doses***
Maintenance	Gradually decrease to target **Target** 150–300 mg/day **in divided doses**

- 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.[3]

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]

Cautious titration and a divided dosage schedule are necessary to minimize the risks of hypotension, seizure, and sedation

Note for outpatients: *CLOZARIL® may only be initiated 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.*†

Gradually titrate upward in 25–50 mg daily increments

If well tolerated, target 300–450 mg/day by the end of week 2‡

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§¶

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

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

* 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.

† 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.

‡ 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.

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. If blood work is processed at a laboratory that uses the LabLink automated reporting network, patient results will be immediately available online at the CSAN Patient Care Portal®.

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 on the following page).

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 with 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 the CSAN® criteria for BEN enrolment, the patient must have at least two ANC results greater than or equal to 1 x 10^9/L and less than 2 x 10^9/L (one within the past six months and another within the past 28 days). For patients not already on clozapine, at least 1 test must have been 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 them the medication. These provisions are supported by the Product Monograph.

Sample calculations

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

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

Hematological quick reference chart[1*]

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

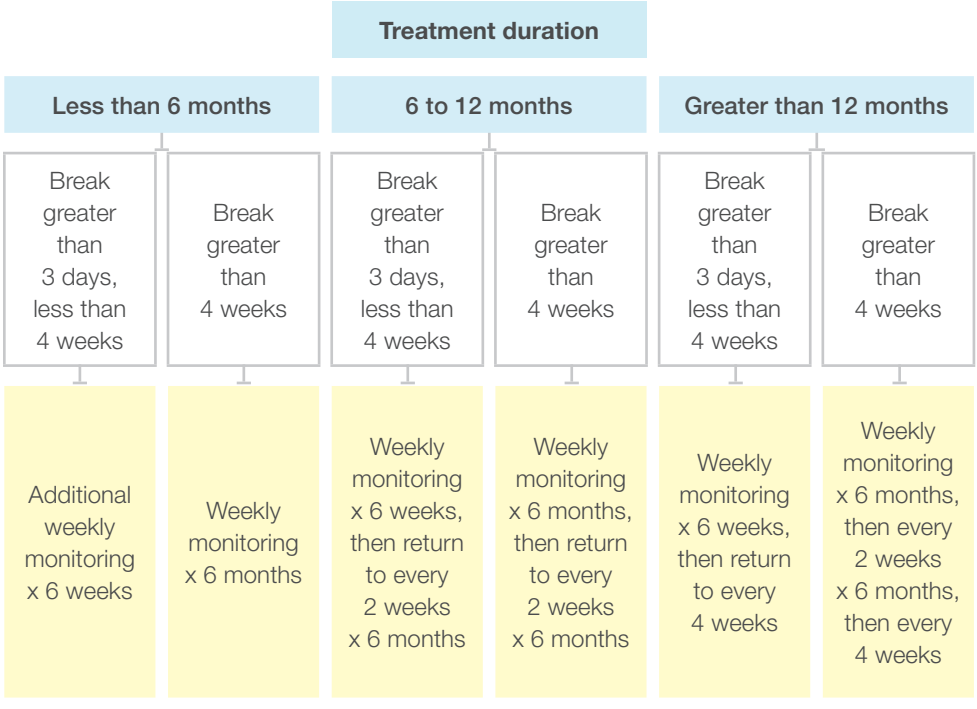
Green (normal values for clozapine treatment)	
• WBC ≥3.5 × 10^9/L • ANC ≥2.0 × 10^9/L	• Continue to dispense CLOZARIL® • Monitor as follows for eligible patients:† – Every week for the first 6 months – Every 2 weeks for the next 6 months – Every 4 weeks thereafter
Yellow Alert(s)	
WBC or ANC in the 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 schedule, 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.

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 weekly for a period of 4 weeks following discontinuation of CLOZARIL® therapy, irrespective of the cause of discontinuation.

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

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 – 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[1,11]

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[11]	• 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[11]	• 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[11]	• Recommend that patients decrease their intake of liquids in the evening
Hypersalivation[11]	• 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[11]	• 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.

Please refer to the Product Monograph for contraindications to CLOZARIL® and to read the warnings regarding agranulocytosis and cardiovascular toxicity.

Please do not hesitate to contact our experienced on-staff psychiatric consultants if you wish to have further guidance in the management of CLOZARIL® side effects.

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.

Additional useful information[1]

Visit **www.clozaril.ca** for additional support and information

What the patient should do if they are planning to move or go on vacation

If the patient is planning to move or take a vacation, they should notify the treating team with details as soon as possible (at least 2 to 3 weeks prior to departure). CSAN® can assist in making arrangements for continuation of blood monitoring and dispensing of CLOZARIL®. This facilitates the continuity of treatment and access to care.

Concomitant medication and alcohol

The treating physician should always be consulted before the patient takes other medications (including nonprescription drugs, such as cold and allergy remedies) because of possible drug interactions. Alcohol should be avoided due to its potential to increase drowsiness and dizziness.

Pregnancy and nursing

Should the patient miss a menstrual period, think she is pregnant, or plan on becoming pregnant, she must contact her physician as soon as possible. As CLOZARIL® can pass through breast milk, mothers receiving CLOZARIL® should not breastfeed.

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Questions?
Don't hesitate to contact us.

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