Issue #1 - 2023

CSANewsletter

Your Patients. Our Priority.

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

There for you since 1991

CSAN® offers free consultations with our expert specialists in hematology, cardiology, psychiatry, nutrition, and general medicine.

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.[1]

Reference: 1. CLOZARIL® Product Monograph. HLS Therapeutics Inc. May 31, 2022.

CLOZARIL® Clozapine

What's Inside

Special Interest Articles

Capsules

CLOZARIL® is covered by the Non-Insured Health Benefits (NIHB) as an open benefit for all CLOZARIL® tablet strengths.[1]

What's new?

CSAN® is pleased to announce the first installation of **LabLink+**, a bi-directional interface which allows the CSAN® Pronto® blood test results to upload into the hospital information systems. Results are available to both the hospital and the CSAN Patient Care Portal®.

Updates to the CSAN Patient Care Portal®

The CSAN Patient Care Portal® has been updated to reflect the current CLOZARIL® Product Monograph.

What you can look for:

1. Updates to hematological follow-ups, Monitoring Schedule Guideline, and Monitoring Frequency after Interruption in Therapy. Please refer to the CLOZARIL® Product Monograph for complete information.[2]

2. Terminology has been modified and the post-discontinuation monitoring protocols have been outlined to assist in the healthcare professional's understanding of CLOZARIL® management.

3. The benign ethnic neutropenia (BEN) protocol has been elaborated upon. Please refer to the CLOZARIL® Product Monograph for complete information.[2]

4. Changes to the requirement for total white blood cell (WBC) monitoring. Please refer to the CLOZARIL® Product Monograph for complete information.[2]

Did you know?

The CSAN Patient Care Portal® lets you track clozapine levels within a patient's file.

Clozapine Levels

3 items • Sorted by Test Date • Updated a few seconds ago

	Clozapine Level	CLZ	Test Date ↓
1	CLZ-009644	3,506.00	3/4/2023
2	CLZ-002243	5,026.00	8/9/2018
3	CLZ-000474	2,399.00	9/20/2017

According to the Canadian Schizophrenia Guidelines, an estimated 25-30% of people diagnosed with schizophrenia meet guideline criteria for treatment-resistant schizophrenia.[3]

The Canadian Schizophrenia Guidelines recommend clozapine for these patients.[3] However, a side effect of taking clozapine is that it may cause neutropenia, and weekly, every-two-week or every-four-week bloodwork is required for monitoring neutrophil levels.[2]

For the full CLOZARIL® Product Monograph, please visit **https://www.hlstherapeutics.com/wp-content/uploads/monograph_pdf/HLS-Clozaril-PM-E.pdf**.

1. Express Scripts®. NIHB Drug Benefit List: CLOZARIL®. Accessed April 21, 2023 at: https://nihb-ssna.express-scripts.ca/en/0205140506092019/16/160407.
2. CLOZARIL® Product Monograph. HLS Therapeutics Inc. May 31, 2022.
3. Remington G, et al. Guidelines for the pharmacotherapy of schizophrenia in adults. *Can J Psychiatry.* 2017;62(9):604-616.

Cornwall Community Hospital — A first-hand experience with CSAN® Pronto®

Recently, our Assertive Community Treatment Team (a community-based, multi-disciplinary team that provides services to the residents who have a serious mental illness and require ongoing intensive treatment) introduced CSAN® Pronto®, a device which allows patients with treatment-resistant schizophrenia who take clozapine to have their neutrophil levels monitored using a drop of capillary blood.

The test is performed by appointment at our Community Addiction and Mental Health Centre, where we aim to provide a familiar, welcoming environment for clients, and offer new innovations into the patient journey.

Julie Dumoulin

Manager of the Assertive Community Treatment Team, next to the new CSAN® Pronto® device in the Community Addiction and Mental Health Centre

Assessments and treatment planning

In schizophrenia, the **duration of untreated psychosis** – the time from the onset of psychotic symptoms to the time of the first effective treatment – **has prognostic value**.[1]

The course of schizophrenia may be favorable in about 20% of patients, and a small number of individuals may experience remission. However, most patients require formal or informal daily living support and many remain chronically ill with exacerbations and remissions of active symptoms. Some patients experience progressive deterioration. Predictors of the course and outcomes of schizophrenia are largely unexplained and may not be reliable.[2]

When making treatment decisions, consider the following findings from the Canadian Schizophrenia Guidelines:

- Timely access to appropriate assessments and care are important in the first episode of psychosis.[1,3]
- The duration of untreated psychosis is an important predictor of outcomes.[1]
- Treatment resistance in schizophrenia is an important clinical concern and is associated with ongoing disability.[3]

Who is your treatment-resistant patient?[3]

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
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**, following **2 or more adequate trials** with different antipsychotic drugs defines antipsychotic treatment-resistant schizophrenia (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
Following an adequate trial with clozapine, if the criteria above continue to be met, the specifier “clozapine-resistant schizophrenia” should be added.	

AP=antipsychotic; **CPA**=Canadian Psychiatric Association; **LAI**=long-acting injection

Adapted from Remington, et al. *Can J Psychiatry* 2017.[2]

How the CLOZARIL® Product Monograph defines **non-responsiveness** and **intolerance** to conventional antipsychotic drugs:[4]

Non-responsiveness is the lack of satisfactory clinical response, despite treatment with appropriate courses of at least two marketed chemically unrelated antipsychotic drugs.

Intolerance is the inability to achieve adequate benefit with conventional antipsychotic drugs because of dose-limiting, intolerable adverse effects.

The Canadian Schizophrenia Guidelines cites that established guidelines have identified clozapine as the only indicated treatment in TRS.[3]

Recommendation 1:	Recommendation 2:
Clozapine should be offered to patients who have TRS. (Grade A)*	Clozapine should be considered for patients whose schizophrenia has not responded to 2 antipsychotics. (Grade B)†

Please refer to the Canadian Schizophrenia Guidelines for complete information.

*Grade A: At least one meta-analysis, systematic review, or randomized controlled trial rated as "1++" and directly applicable to the target population or a body of evidence consisting principally of studies rated as "1+", being directly applicable to the target population, and demonstrating overall consistency of results.

†Grade B: A body of evidence including studies rated as "2++", being directly applicable to the target population, and demonstrating overall consistency of results or extrapolated evidence from studies rated as 1++ or 1+.

1++: High-quality meta-analyses, systematic reviews of randomized controlled trials, or randomized controlled trials with a very low risk of bias.

1+: Well-conducted meta-analyses, systematic reviews, or randomized controlled trials with a low risk of bias.

2++: High-quality systematic reviews of case control or cohort studies or high-quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal.

1. Addington D, et al. Canadian guidelines for the assessment and diagnosis of patients with schizophrenia spectrum and other psychotic disorders. *Can J Psychiatry*. 2017;62(9):594-603.
2. American Psychiatric Association. Schizophrenia spectrum and other psychotic disorders. *Diagnostic and Statistical Manual of Mental Disorders*. Fifth edition. 2013.
3. Remington G, et al. Guidelines for the pharmacotherapy of schizophrenia in adults. *Can J Psychiatry*. 2017;62(9):604-616.
4. CLOZARIL® Product Monograph. HLS Therapeutics Inc. May 31, 2022.

CLOZARIL® recommended dosing and titration[1]

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	If well tolerated, 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 Subsequent dosage increases should be made no more than once or twice weekly in increments not to exceed 100 mg
Therapeutic dose range	300-600 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
Since improvement may be gradual, continued therapeutic response can be expected beyond the first month of treatment.		
Maximum dose	600-900 mg/day **Maximum dose of 900 mg/day should not be exceeded**	Doses up to 900 mg/day may be required to obtain an acceptable therapeutic response Patients must be given adequate time to respond to a given dose level before escalation to a higher dose Note: An increase in adverse reactions (particularly seizures) at daily doses ≥600 mg may occur.
Maintenance	Gradually decrease to target Target 150-300 mg/day in divided doses	After achieving maximum therapeutic benefit, many patients can be maintained effectively at lower doses At daily doses not exceeding 200 mg, a single administration in the evening may be appropriate Patients should be periodically reassessed to determine the continued need for maintenance treatment

CLOZARIL® should be initiated once the neuroleptic is completely discontinued for at least 24 hours. CLOZARIL® should not be used in combination with other neuroleptics.

Patients 60 years of age and older: It is recommended that treatment in patients 60 years and older is initiated at a particularly low dose of CLOZARIL® (12.5 mg given once on the first day) with subsequent dose increments restricted to 25 mg/day.

Cardiovascular disorders: Severe cardiovascular disorders are contraindications. CLOZARIL® should be used with caution in patients with known cardiovascular and/or pulmonary disease, particularly in those with cardiac arrhythmias and conduction disturbances, and the recommendation for gradual titration of dose should be carefully observed.

Renal impairment: In patients with mild to moderate renal impairment the initial dose of CLOZARIL® should be 12.5 mg given once on the first day, and dosage increase should be slow and in small increments.

Hepatic impairment: Patients with hepatic impairment should receive CLOZARIL® with caution along with regular monitoring of liver function tests.

Please refer to the CLOZARIL® Product Monograph for complete dosing and administration information.

1. CLOZARIL® Product Monograph. HLS Therapeutics Inc. May 31, 2022.

Nutritional Psychiatry
The connection between diet, nutrition and mental health

Encouraging food choices and eating habits that are realistic, accessible, and achievable

Marilyn Rabin,
RD, ODNQ

The groundwork for evoking change is embedded in a meaningful conversation. Nearly 40 years ago, William Miller and Steve Rollnick began developing a way of engaging with vulnerable people to enhance their autonomy that has evolved into what is now known as motivational interviewing (MI). One thousand eight hundred published trials have demonstrated that simply telling others what to do is usually not enough to motivate them to do it; you get better outcomes if you put less pressure on people to change.[1] Just as the way we eat is as important as what we eat, the way we speak is as important as what we say. At the core of MI is the spirit (partnership, acceptance, compassion, empowerment) along with an ability to navigate ambivalence (the struggle between the willingness to change and the reasons to sustain the behaviour). MI is not a panacea but is beneficial for people who are given the opportunity to chart their own trajectory. It is considered a component of best practices in translating and applying nutritional psychiatry and assuring nutrition literacy.

The Mediterranean dietary pattern promotes cardiometabolic health and is achievable.[2,3] Guiding an individual toward improving nutrient density rather than restricting calories offers the opportunity to explore foods that enhance diet quality over time. This is the hallmark of the Mediterranean dietary pattern – it embraces all foods and is compatible with Canada's Food Guide.[4] The practitioner can determine what their client knows, what they are willing to do and how confident they are to fulfil their own objectives. The important debriefing component reviews how the discussion went and what can be added or deleted for future meetings. This can be a convenient segue to address critical food-medication interactions and the advantages of pertinent goals of reducing caffeine, alcohol, and highly processed foods.

Food insecurity prevalence for people living with severe mental illness (SMI) and schizophrenia. Food security is described as the consistent and assured access to and availability of safe sufficient food to support nutritional adequacy and a healthy life. It is deemed a right for all humans by the United Nations.[5,6] Regrettably, people living with SMI do not always have regular access to nutritious foods in recommended quantities for a variety of reasons. While there are some obvious solutions (food banks, lower costing foods such as grains, legumes, frozen, canned, dried fruit and vegetables, and foods priced lower when short-dated), this delicate topic can be discussed by first affirming the person's ability to cope with this severe circumstance and then asking what steps the person is taking to acquire food and prepare meals.[5]

Summary. Motivational interviewing may be valuable in mental health settings as a way of guiding a conversation that engages people by looking together at their experiences, strengths, values, skills and goals.[7] The Mediterranean dietary pattern emerges most often in the nutrition care for SMI. It embraces all foods in proportions and portions, achievable in a slow and progressive process.

When examining ways to encourage food choices and eating habits that are realistic, accessible, and achievable, MI combined with mindfulness may lead to desired outcomes.

ODNQ: *Ordre des diététistes nutritionnistes du Québec* (Quebec Order of Dietitians-Nutritionists)

1. Rollnick, Miller and Butler. Motivational Interviewing in Healthcare, Helping Patients Change Behavior. 2nd edition. 2023. The Guilford Press. p1 & p5.
2. Khalil M et al. The potential of the Mediterranean Diet to improve mitochondrial function in experimental models of obesity and metabolic syndrome. *Nutrients*. 2022;14, 3112-3143. https://doi.org/10.3390/nu14153112.
3. Hoffman, Richard. Implementing the Mediterranean Diet. Nutrition in Practice and Public Health. 2023. John Wiley & Sons Ltd. Page vii.
4. Government of Canada. Canada's Food Guide. Accessed February 1, 2023 at: https://food-guide.canada.ca/en/.
5. Tripodi E et al. Prevalence of food insecurity in community-dwelling people living with severe mental illness. *Nutrition & Dietetics*. 2022;79(3):374-379.
6. Food and Agriculture Organization. The Right to Adequate Food. Geneva: United Nations; 2010.
7. Frey J and Hall A. 2021. Motivational interviewing for mental health clinicians – A toolkit for skills enhancement. PESI Publishing.

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 neutropenia and seizure associated with its use, clozapine should be limited to treatment-resistant schizophrenic patients who are non-responsive to, or intolerant of, conventional antipsychotic drugs. Non-responsiveness is defined as the lack of satisfactory clinical response, despite treatment with appropriate courses of at least two marketed chemically-unrelated antipsychotic drugs. Intolerance is defined as the inability to achieve adequate benefit with conventional antipsychotic drugs because of dose-limiting, intolerable adverse effects.
- Because of the significant risk of neutropenia and seizure, events which both present a continuing risk over time, the extended treatment of patients failing to show an acceptable level of clinical response to clozapine should ordinarily be avoided. Seizure risk is dose-related and is more likely to occur with rapid dose increases. Titrate gradually and use divided doses. Use with caution in patients with history of seizure or risk factors for seizure.
- Can be used only if regular hematological examinations through CSAN® can be guaranteed.
- Should not be prescribed until the non-rechallengeable status and the hematological status of the patient has been verified.
- Consent from the patient for the potential sharing of hematological and other safety data between clozapine registries must be obtained.
- Completion of a new registry-specific patient registration form signed by the prescribing physician for patients switching from one brand of clozapine to another.
- Not indicated in pediatrics (<18 years of age).
- Use with care in the elderly (>60 years of age).

Contraindications:

- 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
- Patients unable to undergo routine blood tests
- 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:

Severe Neutropenia (Agranulocytosis): CLOZARIL® treatment has caused severe neutropenia, defined as an absolute neutrophil count (ANC) less than 0.5 x 10^9/L. Severe neutropenia can lead to serious infection and death. Prior to initiating treatment with CLOZARIL® a baseline ANC must be at least ≥2.0 x 10^9/L for the general population; and must be at least ≥1.0 x 10^9/L for patients with documented Benign Ethnic Neutropenia (BEN). Regular hematologic monitoring is required prior to dispensing, because of the significant risk of this potentially life-threatening adverse event. Advise patients to immediately report the appearance of lethargy, weakness, fever, sore throat, flu-like complaints or any other signs of infection. Because of the risk of severe neutropenia, CLOZARIL® is available only through a distribution system (“CSAN”) that ensures weekly, every-two-week or every-four-week hematological testing prior to the dispensing of the next period’s supply of CLOZARIL®.

Myocarditis and Cardiomyopathy and Mitral Valve Incompetence: Fatal myocarditis and cardiomyopathy have occurred with the use of CLOZARIL®. Discontinue CLOZARIL® and obtain a cardiac evaluation upon suspicion of myocarditis or cardiomyopathy. Consider the possibility of myocarditis or cardiomyopathy if chest pain, tachycardia, palpitations, dyspnea, fever, flu-like symptoms, hypotension, or ECG changes occur. Generally, patients with a history of clozapine-associated myocarditis or cardiomyopathy should not be rechallenged with CLOZARIL®.

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

SUBSCRIBE

CSANewsletter@hlstherapeutics.com

You may update your information or unsubscribe to the CSANewsletter by contacting HLS Privacy Officer privacy@hlstherapeutics.com

1. CLOZARIL® Product Monograph. HLS Therapeutics Inc. May 31, 2022.

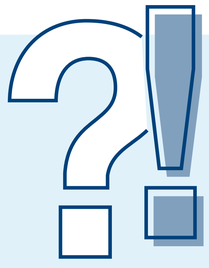
Safety information

Other relevant warnings and precautions:

- Risk of fever, possibility of an underlying infectious process or the development of blood dyscrasia
- Anticholinergic activity, caution in the presence of prostatic enlargement, narrow-angle glaucoma or paralytic ileus. Monitor for early onset of constipation
- Rebound/withdrawal effects
- Other adverse cardiovascular and respiratory effects
- QT interval prolongation
- Venous thromboembolism
- Driving and operating machinery
- Metabolic changes (hyperglycemia, dyslipidemia, and body weight gain); monitor blood glucose, body weight and lipid evaluations
- Priapism
- Eosinophilia
- Thrombocytopenia: Discontinue CLOZARIL® if platelet count falls below 50.0 x 10^9/L
- Hepatotoxicity: monitor for signs and symptoms of hepatotoxicity, and serum test for liver injury. Permanently discontinue CLOZARIL® if hepatitis or transaminase elevations combined with other systemic symptoms are due to clozapine
- Hepatic impairment: Regular liver function tests (LFTs). Discontinue CLOZARIL® if LFTs are elevated or symptoms of jaundice occur
- Seizures
- Falls
- Neuroleptic malignant syndrome
- Tardive dyskinesia
- Renal impairment
- Severe cutaneous adverse reactions (SCARs): Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), and acute generalized exanthematous pustulosis (AGEP); discontinue CLOZARIL® if SCAR occurs
- Pregnant women, breastfeeding women, and women with childbearing potential
- Should not be used for elderly patients with dementia
- Caution in patients at risk for aspiration pneumonia
- Cerebrovascular adverse events (including stroke) in elderly patients with dementia)
- Concomitant administration of drugs known to inhibit or induce the activity of cytochrome P450 isozymes

For more information:

Please consult the CLOZARIL® Product Monograph at https://www.hlstherapeutics.com/wp-content/uploads/monograph_pdf/HLS-Clozaril-PM-E.pdf for important information on adverse reactions, drug interactions (particularly CYP 450 isoenzymes inhibitors or inducers drugs), and dosing information which have not been discussed in this piece. The Product Monograph is also available by calling 1-800-267-2726.



QUESTIONS? Don't hesitate to contact us.

Available 24/7/365

1-800-267-2726 1-800-465-1312

1. CLOZARIL® Product Monograph. HLS Therapeutics Inc. May 31, 2022.

The MyCare™ psychiatry clozapine assay kit

Dr. Vincent De Guire

Clinical Biochemist,
Maisonneuve-Rosemont Hospital, OPTILAB-CHUM Laboratory Network

Clinical Assistant Professor
at the University of Montreal and Research Associate at CRHMR

Patients prescribed clozapine must be monitored for as long as they are on the drug.[1] For the Maisonneuve-Rosemont Hospital (HMR) laboratory in Montreal, the available technologies for clozapine drug monitoring were located at another hospital.

Through a collaboration with psychiatrists and pharmacists at the Montreal Mental Health University Institute (IUSMM), the HMR lab has now implemented the MyCare™ Psychiatry Clozapine Assay.

The MyCare™ Psychiatry Clozapine Assay Kit is intended for the *in vitro* quantitative measurement of any clozapine molecule in human serum and plasma using automated clinical chemistry analyzers.[2] It was added to the lab's Atellica (Siemens) clinical chemistry analyzer.

HMR: Hôpital Maisonneuve-Rosemont

The Montreal Mental Health University Institute (IUSMM) group are:

- Alain Lesage, psychiatrist, MD, Mphil, full professor, department of psychiatry, University of Montreal, CRIUSMM researcher and CIUSSS EMTL psychiatrist.
- Philippe Vincent, pharmacist, M.Sc., BCPP, associate clinical professor, associate researcher CRIUSMM
- Pierre Lalonde, psychiatrist, MD, professor emeritus, department of psychiatry, University of Montreal and CIUSSS EMTL psychiatrist.
- Olivier Lipp, psychiatrist, MD, PhD, associate clinical professor, department of psychiatry, University of Montreal, CRIUSMM associate researcher and CIUSSS EMTL psychiatrist.
- Luigi De Benedictis, psychiatrist, MD, MSc, assistant clinical professor, department of psychiatry, University of Montreal, CRIUSMM associate researcher and CIUSSS EMTL psychiatrist.
- Jean-Pierre Melun, psychiatrist, MD, assistant clinical professor, department of psychiatry, University of Montreal, CIUSSS EMTL psychiatrist.
- Valérie Tourjman, psychiatrist, MD, PhD, associate clinical professor, department of psychiatry, University of Montreal, CRIUSMM researcher, CIUSSS EMTL psychiatrist.

1. CLOZARIL® Product Monograph. HLS Therapeutics Inc. May 31, 2022.
2. Saladax Biomedical. MyCare Psychiatry Clozapine Assay Kit Package Insert. 2019.

HLS Therapeutics Inc.
10 Carlson Court, Suite 701
Etobicoke, Ontario M9W 6L2
www.hlstherapeutics.com

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