

## Overview

### Useful For

Monitoring patient compliance of clozapine treatment

An aid to achieving desired serum levels

### Method Name

Liquid Chromatography Tandem Mass Spectrometry (LC-MS/MS)

### NY State Available

Yes

## Specimen

### Specimen Type

Serum Red

### Specimen Required

**Supplies:** Sarstedt Aliquot Tube, 5 mL (T914)

**Collection Container/Tube:** Red top (serum gel/SST are **not acceptable**)

**Submission Container/Tube:** Plastic vial

**Specimen Volume:** 1 mL

**Collection Instructions:**

1. Collect specimen immediately before next scheduled dose.
2. Within 2 hours of collection, centrifuge and aliquot serum into a plastic vial.

**Additional Information:** Therapeutic range (trough level) applies to specimens collected immediately prior to next dose.

### Forms

If not ordering electronically, complete, print, and send a [Therapeutics Test Request](#) (T831) with the specimen.

### Specimen Minimum Volume

0.6 mL

### Reject Due To

|                 |    |
|-----------------|----|
| Gross hemolysis | OK |
| Gross lipemia   | OK |
| Gross icterus   | OK |

**Specimen Stability Information**

| Specimen Type | Temperature              | Time    | Special Container |
|---------------|--------------------------|---------|-------------------|
| Serum Red     | Refrigerated (preferred) | 28 days |                   |
|               | Frozen                   | 28 days |                   |
|               | Ambient                  | 7 days  |                   |

**Clinical & Interpretive****Clinical Information**

Clozapine (Clozaril), a tricyclic dibenzodiazepine, is used for the symptomatic management of psychotic disorders and is considered an atypical antipsychotic drug. It is currently used primarily for the treatment of patients with schizophrenia or schizoaffective disorders who are at risk for recurrent suicidal behavior and who have encountered nonresponse or adverse, intolerable extrapyramidal side effects with more classical antipsychotics (chlorpromazine, haloperidol).

Although clozapine was developed about 30 years ago and the initial results were promising, the development of several fatal cases of agranulocytosis resulted in the discontinued use of this agent. Seizures, orthostatic hypotension, and an increased risk of fatal myocarditis have also been associated with the use of clozapine. The use of clozapine has regained interest for several reasons. Patients who did not respond to treatment with other antipsychotics improved when clozapine was administered. Also, agranulocytosis, which occurs in approximately 1% to 2% of patients, can be controlled with close hematologic monitoring. However, because of the significant risk of agranulocytosis and seizure associated with its use, clozapine should only be used in patients who have failed to respond adequately to treatment with appropriate courses of standard drug treatments, either because of insufficient effectiveness or the inability to achieve an effective dose because of intolerable adverse reactions from those drugs.

Treatment is usually started with dosages of 25 to 75 mg/day with a gradual increase to reach a final dose of 300 to 450 mg/day within approximately 2 weeks of the initiation of treatment. Once the desired effect is achieved, the dose may be gradually decreased to keep the patient on the lowest possible effective dose.

Patients being treated with clozapine should be closely monitored during treatment for adverse reactions. Treatment must include monitoring of white blood cell count and absolute neutrophil count. Clozapine treatment should be discontinued in patients failing to show an acceptable clinical response. In addition, the need for continuing treatment should be periodically reevaluated in patients exhibiting beneficial clinical responses.

Clozapine is metabolized to desmethylated and N-oxide derivatives. The desmethyl metabolite (norclozapine) has only limited activity, and N-oxide metabolite is inactive.

**Reference Values**

Clozapine

Therapeutic range: 350-600 ng/mL

Norclozapine

Therapeutic range: Not well established

Clozapine + Norclozapine

Therapeutic range: Not well established

### Interpretation

The effectiveness of clozapine treatment should be based on clinical response and treatment should be discontinued in patients failing to show an acceptable clinical response.

### Cautions

No significant cautionary statements

### Clinical Reference

1. Volpicelli SA, Centorrino F, Puopolo PR, et al.: Determination of clozapine, norclozapine, and clozapine-N-oxide in serum by liquid chromatography. *ClinChem*. 1993;39(8):1656-1659
2. Chung MC, Lin SK, Chang WH, Jann MW. Determination of clozapine and desmethylclozapine in human plasma by high-performance liquid chromatography with ultraviolet detection. *J Chromatogr*. 1993;613(1):168-173. doi:10.1016/0378-4347(93)80212-m
3. Perry PJ, Miller DD, Arndt SV, Cadoret RJ. Clozapine and norclozapine plasma concentrations and clinical response of treatment-refractory schizophrenia patients. *Am J Psychiatry*. 1991;148(2):231-235. doi:10.1176/ajp.148.2.231
4. Physicians' Desk Reference (PDR). 61st ed. Thomson PDR; 2007
5. Fitton A, Heel RC. Clozapine. A review of its pharmacological properties, and therapeutic use in schizophrenia. *Drugs*. 1990;40(5):722-747. doi:10.2165/00003495-199040050-00007
6. Clozaril. Package insert: Novartis Pharmaceuticals; 05/2005
7. Mitchell PB. Therapeutic drug monitoring of psychotropic medications. *Br J Clin Pharmacol*. 2001;52(Suppl 1):45S-54S. doi:10.1046/j.1365-2125.2001.0520s1045.x
8. Hiemke C, Bergemann N, Clement HW, et al. Consensus Guidelines for Therapeutic Drug Monitoring in Neuropsychopharmacology: Update 2017. *Pharmacopsychiatry*. 2018;51(1-02):9-62. doi:10.1055/s-0043-116492
9. Milone MC, Shaw LM: Therapeutic drugs and their management. In: Rifai N, Chiu RWK, Young I, Burnham CAD, Wittwer CT, eds. *Tietz Textbook of Laboratory Medicine*. 7th ed. Elsevier; 2023:420-453

### Performance

#### Method Description

Deuterated stable isotope of clozapine is added to the serum sample as an internal standard. Protein is precipitated from the mixture by the addition of acetonitrile. Clozapine, norclozapine, and the internal standard are extracted from the resulting supernatant by an online extraction utilizing high-throughput liquid chromatography. This is followed by conventional liquid chromatography and analysis on a tandem mass spectrometer equipped with a heated nebulizer ion source. (Unpublished Mayo method)

#### PDF Report

No

#### Day(s) Performed

Monday through Friday

**Report Available**

3 to 5 days

**Specimen Retention Time**

2 weeks

**Performing Laboratory Location**

Rochester

**Fees & Codes****Fees**

- Authorized users can sign in to [Test Prices](#) for detailed fee information.
- Clients without access to Test Prices can contact [Customer Service](#) 24 hours a day, seven days a week.
- Prospective clients should contact their account representative. For assistance, contact [Customer Service](#).

**Test Classification**

This test was developed and its performance characteristics determined by Mayo Clinic in a manner consistent with CLIA requirements. It has not been cleared or approved by the US Food and Drug Administration.

**CPT Code Information**

80159

**LOINC® Information**

| Test ID | Test Order Name | Order LOINC® Value |
|---------|-----------------|--------------------|
| CLZ     | Clozapine, S    | 65632-2            |

| Result ID | Test Result Name             | Result LOINC® Value |
|-----------|------------------------------|---------------------|
| 33841     | Norclozapine                 | 10992-6             |
| 33842     | Clozapine+Norclozapine Total | 12375-2             |
| 33840     | Clozapine                    | 6896-5              |