REF CLZ-MCI-32.2

MyCare Insite Clozapine Test

INDICATIONS FOR USE

The MyCare Insite Clozapine Test is intended for the *in vitro* quantitative measurement of clozapine in finger capillary blood using the automated MyCare Insite. The MyCare Insite Clozapine Test is designed to be used either in a clinical laboratory or in the near patient setting by trained health-care professionals.

SUMMARY AND EXPLANATION OF THE TEST

Clozapine 8-chloro-11-(4-methyl-1-piperazinyl)-5H-dibenzo [b,e] [1,4] diazepine is a tricyclic dibenzodiazepine derivative atypical antipsychotic agent used for treatment resistant schizophrenia and reducing suicidal behavior in schizophrenia and schizoaffective disorder.[1]

The utility of monitoring clozapine blood levels is supported by multiple studies suggesting an association between positive therapeutic response and a threshold blood concentration.[2-8] Improved clinical outcomes resulting from therapeutic blood concentrations have led to recommendations to measure clozapine levels for dose adjustment in practice guidelines,[9-11] clinical support tools,[12,13] and expert consensus recommendations.[14-16]

Nonadherence to medication is well known for patients with severe mental illness.[17] While adherence to medication is critical to successful treatment outcomes, adherence is also not accurately assessed by clinicians.[18,19] Measurement of clozapine provides objective evidence of concentrations to assist in the clinical evaluation of adherence.[12,15,20-22] The MyCare Insite Clozapine Test is a homogenous two reagent nanoparticle agglutination assay used for detection of clozapine in human blood. It is based on competition between drug and drug-conjugates for binding to drug specific antibodies that are covalently bound to nanoparticles. The extent of particle aggregation can be measured photometrically on the MyCare Insite.

TEST COMPONENTS

The Test components, Cuvettes, Reagent Caps, and RFID card are color-coded blue. Always match the Cuvette, Cap, and RFID colors. The RFID card should be used with the tests it comes with.

MyCare Insite Clozapine Test REF CLZ-MCI-32.2	Amount
MyCare Insite Cuvette – Single Use Reaction buffer that contains drug-conjugate, protein, and buffer	32 x 0.95 mL per test
MyCare Insite Reagent Cap - Single Use Nanoparticle component that contains monoclonal antibody bound to nanoparticles in a buffered solution	32 x 0.20 mL per test
MyCare Insite Clozapine RFID Card	1 per test box

WARNINGS AND PRECAUTIONS

- For *In Vitro* Diagnostic Use Only.
- For diagnostic purposes, the results should always be assessed with the patient's medical history, clinical examination, and other findings.

- Exercise normal precautions for handling laboratory tests.
- All components of the clozapine test contain less than 0.1% sodium azide. Do not swallow. Avoid contact with skin and mucous membranes. Flush affected areas with copious amounts of water. Seek immediate medical attention if tests are ingested or come into contact with eyes. When disposing of tests, always flush with large amounts of water to prevent accumulation of azide.

TEST HANDLING

IMPORTANT

Remove the Reagent Cap and Cuvette from the test box and place in the Test Rack to come to room temperature.

Reagent Cap and Cuvette must be at room temperature (20 - 25°C) to perform a test.

Allow the test(s) at least 10 minutes to come to room temperature (20 - 25°C).

If liquid is spilled from the Cuvette, DO NOT USE. Use a new Cuvette.

STORAGE AND STABILITY

Store the tests refrigerated at 2 – 8°C.

Cuvettes should be stored upright. If a closed Cuvette is tipped over, tap the Cuvette 2 – 3 times on the benchtop to ensure there is no liquid stuck to the Cuvette stopper.

Cuvettes and Reagent Caps may be used until their expiration date.

The RFID card may be used with the tests until the expiration date. The RFID card should only be used with the tests it comes with. Keep the RFID card with the test box.

Do not freeze.

SPECIMEN COLLECTION AND HANDLING

Capillary blood from a finger stick is required.

Trough or C_{min} samples at steady state have been recommended for testing antipsychotics and specifically for clozapine.[10,11,15,16] After one week of treatment on the same dose, collect samples 10 – 14 hours,[10,12,23] preferably 11 – 13 hours[10] after the last dose.

Before collecting the sample remove the stopper from the Cuvette; discard the stopper. If the Cuvette cracks, discard and use a new Cuvette. Return Cuvette to the Test Rack provided with the MyCare Insite.

Use standard capillary blood collection techniques to produce a blood drop on the patient's finger.[24,25]

Collect 20 µL of capillary blood using a 20 µL capillary. Hold the capillary at an angle below the drop of blood (Figure 1). When the capillary is completely filled it contains exactly 20 µL.

Ensure that the capillary is completely filled (Figure 2) with blood and there is no blood on the outside of the capillary. The capillary may be wiped with a clean lint-free cloth to remove excess blood on the outside of the capillary.

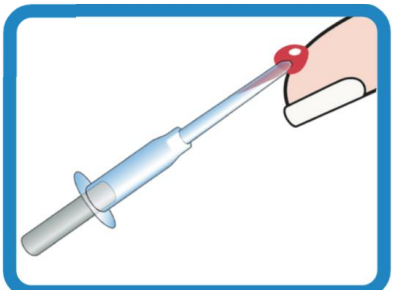

Figure 1

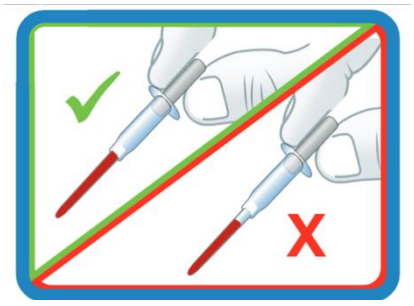

Figure 2

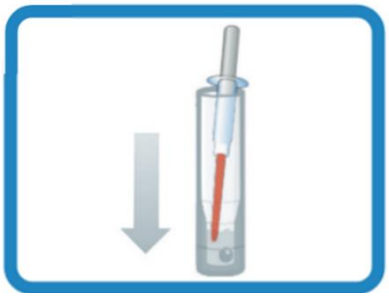

Figure 3

Immediately (within 15 seconds) add the blood from the capillary into the Cuvette (Figure 3). Place the capillary just in the liquid and dispense by slowly depressing the capillary plunger. Ensure all blood is transferred.

Place the Reagent Cap on the Cuvette immediately (within 15 seconds) of adding the sample. Firmly snap the Reagent Cap in place to tightly close the Cuvette. The Cuvette containing sample and sealed with the Reagent Cap is used as a test cartridge. The test cartridge must be measured within 6 hours of collection.

Place the cartridge in the Analyser Chamber and immediately (within 10 seconds) close the door to start the measurement.

PROCEDURE

Materials Provided:

REF CLZ-MCI-32.2 – MyCare Insite Clozapine Test with Clozapine RFID Card

Materials Required – Provided Separately:

REF MCP2-CON – MyCare Psychiatry Control Kit 2

REF MCI-EUR– MyCare Insite (MyCare Insite Analyser laboratory photometer and MyCare Insite Touch Screen)

Materials Required – Not Provided

Finger stick lancets (e.g. 21 G x 2.0 mm, single use safety lancet)

20 µL (neutral, white) Sarstedt Minivette® POCT capillary for blood collection (Order No. 17.2111.020)

Pipette for 20 µL

Calibration

The manufacturer's calibration is stored on the RFID card that is included in the test box.

Quality Control (QC)

All quality control requirements and testing should be performed in accordance with local, state and/or federal regulations or accreditation requirements.

QC testing ensures that the calibration stored on the RFID card is valid.

QC testing is recommended when:

- Testing patient samples (at least once a week)
- A new test box is opened
- A new shipment or lot is used
- There is an unexpected patient result
- New users are trained
- The Insite is installed

Preparing to measure

1. For each test to be performed, place a Cuvette and Reagent Cap in the Test Rack.
2. Allow at least 10 minutes to warm to room temperature.
3. Refer to the MyCare Insite User Manual PI MCI-EUR-ML-PKG for steps to prepare the MyCare Insite to measure a patient sample.
4. Remove the stopper from the Cuvette, discard the stopper, and place the Cuvette back into the Test Rack.

Collecting a sample - See Specimen Collection and Handling

Testing a sample - Refer to the MyCare Insite User Manual PI MCI-EUR-ML-PKG for steps to test a patient sample on the MyCare Insite.

Measuring QC

Controls are run in the same way as patient samples. Transfer exactly 20 µL of control into a Cuvette with a pipette. Place the Reagent Cap in the Cuvette. Firmly snap the Reagent Cap in place to close the test cartridge. The Cuvette containing sample and sealed with the Reagent Cap is used as a test cartridge. The test cartridge is now ready to measure.

Compare the QC result to the range in the MyCare Psychiatry Control Kit 2 package insert (MCP2-CON). If the result is not in range, perform the following:

1. Verify that the control materials have been stored according to the directions and that the open vial stability duration and expiration date have not been exceeded.
2. Verify that the handling and testing procedures were performed according to the directions in the package insert, instructional wall chart, or video at MyCareInsite.com.
3. Verify that the operator had passing control results during training.
4. Repeat the control test, using a new control from the same lot.

If all instructions have been followed but control results are still not within range, please contact your Official Saladax Distributor for assistance before testing any patient samples.

RESULTS

The concentration result is automatically calculated from the manufacturer's calibration on the RFID card. Results are reported from 0 to 1,390 ng/mL (1.390 mg/L). Below the LoQ, the Total Error of the test is > 35%; consider this when evaluating results.

Test results > 1,390 ng/mL should be repeated. If the second result is in the assay range, report the second result. If the repeat result is > 1,390 ng/mL, report result as > 1,390 ng/mL.

Interpret results in accordance with recommendations in the published literature.[9-16]

For diagnostic purposes the test findings should always be assessed in conjunction with the patient's medical history, clinical examinations, and other findings.

The reference range for clozapine is not fully established. Therapeutic ranges of 350 to 600 ng/mL[10,15,16] and 350 to 500 ng/mL[10] have been proposed. A minimum effective concentration of 350 ng/mL is frequently mentioned.[11] Clinicians using reference ranges should be aware that patients may achieve therapeutic benefit with drug concentrations outside of these ranges and may experience toxicity with levels below the lower limit of the reference range.

Clinicians should carefully monitor patients during therapy initiation and dose adjustments. It may be necessary to obtain multiple samples, including establishing a baseline, to determine expected optimal (steady-state) concentrations for individual patients.[9,12,26]

Compare test results to expected results based on previous measurements, subject's baseline, suggested therapeutic range, or values expected for the individual. Consult the references above for guidance.

LIMITATIONS OF THE PROCEDURE

Use only capillary whole blood obtained by finger stick.

As with any test utilizing mouse antibodies, the possibility exists for interference by human anti-mouse antibodies (HAMA) in the sample. Samples containing such antibodies can potentially produce erroneous clozapine results, which are inconsistent with the patient's clinical profile.

SPECIFIC PERFORMANCE DATA

Typical performance data for the clozapine test using multiple MyCare Insites and operators are shown below. Results obtained by individual users may differ from these data.

Precision

Within-laboratory precision and repeatability were verified throughout the measuring range according to CLSI Guideline EP05-A3.[27] The MCP2 medium control and four clozapine spiked whole blood samples (Whole Blood (WB) spikes 1, 2, 3, 4) were tested. Testing included 5 different operators and 34 MyCare Insites.

Sample	N	Mean (ng/mL)	Repeatability	Within-Laboratory
			CV	CV
Control	80	518	7.7%	11.8%
Whole Blood Spike 1	80	244	6.8%	12.6%
Whole Blood Spike 2	80	407	7.3%	12.9%
Whole Blood Spike 3	80	555	7.2%	10.6%
Whole Blood Spike 4	80	734	10.1%	15.6%

Limit of Quantitation (LoQ) and Limit of Detection (LoD)

The lower limits of quantitation and detection were established using CLSI guideline EP17-A2.[28]

LoQ

The LoQ was determined with an accuracy goal at the LoQ of ≤ 35% total error (Westgard model). The LoQ of the MyCare Insite Clozapine Test is 170 ng/mL.

LoD

The LoD is the lowest amount of analyte that can be reliably detected (≥ 95% of results greater than the limit of blank). The LoD of the MyCare Insite Clozapine Test is 76 ng/mL.

Recovery

The recovery of clozapine was assessed in the two controls, and in the four clozapine spiked whole blood samples that were measured for the EP05-A3 precision performance study. The percent recovery was determined by dividing the mean measured concentration of each sample by the expected concentration of clozapine. The percent recovery ranged from 83 to 104%.

Linearity

The linearity of the clozapine test was verified according to CLSI guideline EP06-Ed2.[29] In the study with 11 levels and seven replicates for each level, the maximum observed percent deviation from linearity was 15%. The test was linear across the measuring range from 170 to 1,390 ng/mL**.**

Specificity

Metabolism

Clozapine is extensively metabolized in the liver by CYP1A2 and to a lesser extent by CYP2D6 and CYP3A4. There are two major metabolites in blood: norclozapine and clozapine N-oxide, which have limited and no activity respectively.[1] The antibody formulation in the Reagent Cap was tested for selectivity to

metabolites. Specificity for the following metabolites and cross-reactants was tested in the absence and presence of clozapine at 350 and 600 ng/mL.[30]

Clozapine metabolites

Compound	Tested at (ng/mL)	Bias
Clozapine N-oxide	250	3%
Norclozapine	2,700	1%

Cross-reactivity

The antibody formulation in the Reagent Cap was tested for selectivity. The following compounds did not interfere with the MyCare Psychiatry Clozapine Assay Kit: the test bias was -15 to 8%.[30]

In addition, ethanol was tested at 10 mg/mL in the presence (350 and 500 ng/mL) and absence of clozapine. Test bias introduced by 10 mg/mL of ethanol in whole blood was < 10%.

Compound	Tested at (ng/mL)	Compound	Tested at (ng/mL)	Compound	Tested at (ng/mL)
Acetaminophen	200,000	Acetazolamide	60,000	Acetylsalicylic acid	500,000
Albuterol	1,000	Alendronate sodium	1,000	Alpha - tocopherol	40,000
Alprazolam	2,000	Amantadine Hydrochloride	10,000	Amikacin sulfate	100,000
Amiloride HCl dihydrate	500	Amisulpride	400	Amitriptyline	1,000
Amlodipine besylate	100	S (+)-amphetamine	1,000	Amoxapine	2,900
Amoxicillin	80,000	Aripiprazole	500	L-ascorbic acid	60,000
Asenapine	500	Atomoxetine	5,000	Atorvastatin calcium	600
Baclofen	3,000	Benztropine	400	Betamethasone	100
Biotin	300	Biperiden	100	Blonanserin	100
Brexpiprazole	1,000	Bromperidol	100	Budesonide	50
Bupropion	3,000	Buspirone	200	Caffeine	60,000
Calcium carbonate	300,000	Cannabidiol	100	Cannabinol	100
Carbamazepine	30,000	Cariprazine	50	L-Carnosine	50,000
Cefalexin	200,000	Celecoxib	1,000	Cetirizine dihydrochloride	3,500
8-chloro-theophylline	3,000	Chlorpromazine HCl	2,500	Cimetidine	20,000
Ciprofloxacin	10,000	Citalopram HBr	750	Clindamycin	50,000
Clonazepam	150	Clotiapine	500	Clotrimazole	50
Codeine	2,000	Cortisol	300	(-)-Cotinine	2,000
Cyclosporin A	9,000	Desloratadine	600	Desvenlafaxine	400
Dextromethorphan	1,000	Diazepam	6,000	Diphenhydramine HCl	6,000
Divalproex Sodium	50,000	Docosahexaenoic acid ethyl ester	150,000	Donepezil	50,000
Doxycycline HCl	35,000	Droperidol	100	D-Serine	100,000
Duloxetine	200	Erythromycin	60,000	Escitalopram	100
Eszopiclone	200	Ethanol	10,000,000	Famotidine	600
Fenofibrate	50,000	Fentanyl	600	Fluoxetine HCl	4,000

Compound	Tested at (ng/mL)	Compound	Tested at (ng/mL)	Compound	Tested at (ng/mL)
Fluticasone propionate	1	Fluvoxamine	2,000	Folic acid	15
Furosemide	60,000	Galantamine	100	Gentamycin sulfate	30,000
Glyburide	2,000	Haloperidol	1,000	Heparin sodium salt	50 U/mL
Hydrochlorothiazide	6,000	Hyoscine (Scopolamine HBr)	100	Ibuprofen	500,000
Iloperidone	10	Imipramine	700	Indinavir sulfate	400
Lactulose	10,000	Lamivudine	2,000	Lamotrigine	15,000
Lansoprazole	1,000	Lisinopril dihydrate	350	Lithium carbonate	250,000
Lorazepam	1,000	Lovastatin	500	Loxapine	150
Lurasidone	100	Meclizine dihydrochloride	500	Metformin	40,000
Methotrimeprazine	200	Methylphenidate HCl	350	Metoclopramide HCl	500
Metoprolol tartrate	5,000	Metronidazole	120,000	Midazolam	1,000
Milnacipran	10,000	Mirtazapine	300	Mometasone furoate	50
Morphine	500	Naltrexone	50	Naproxen sodium	500,000
Nateglinide	20,000	Nefazodone HCl	3,500	Nicotinic acid	20,000
Nordiazepam	5,000	Nortriptyline	1,000	Olanzapine	300
Omeprazole	6,000	Oxazepam	5,000	Oxcarbazepine	35,000
Oxycodone	500	Paliperidone	60	Pantothenic acid	150
Paroxetine	1,000	Penicillin V	6,000	Perazine	1,000
Perlapine	150	Perphenazine	100	Phenobarbital	50,000
Phentermine	500	Phenytoin	50,000	Pimozide	20
Pipamperone dihydrochloride	400	Potassium EDTA	1,000	Pravastatin sodium	150
Prednisolone	3,000	Pregabalin	5,000	Procyclidine	1,000
Promethazine	1,200	R,R-(-)-pseudoephedrine	10,000	S,S-(+)-pseudoephedrine	10,000
Pyridoxine HCl	100	Quetiapine	500	Quinidine	12,000
Raloxifene	50	Ranitidine	6,000	Retinol	4,000
Riboflavin	200	Rifampicin	65,000	Risperidone	60
Rosuvastatin calcium	50	Salicylic acid	500,000	Sarcosine	1,000
Sertindole	50	Sertraline hydrochloride	600	Simvastatin	30
Sodium benzoate	400,000	Sodium fluoride	150	Spironolactone	600
Sulfamethoxazole	400,000	Sulpiride	50,000	Temazepam	5,000
Theophylline	40,000	Thiamine HCl	50	Topiramate	10,000
Trazodone HCl	6,000	Triamcinolone acetonide	10	Triamterene	9,000
Triazolam	40	Valproic acid	500,000	Vancomycin HCl	100,000
Varenicline	50	Venlafaxine HCl	400	Vitamin B12	50
Vitamin D2	40	Vitamin K1	50	Warfarin	10,000
Ziprasidone	200	Zolpidem hemitartrate	5,000	Zonisamide	40,000
Zopiclone	100	Zuclopenthixol	250		

Interfering Substances

No significant test bias was observed from samples with the following endogenous interferents at the given levels:

Interferent	Level	
Rheumatoid Factor	510 IU/mL	
Human Serum Albumin	6.1 g/dL	61 g/L
Human IgG	6.1 g/dL	61 g/L
Icteric Interference	44 mg/dL	753 µmol/L
Lipemic Interference	1,600 mg/dL	18.08 mmol/L
Hemolysate	1,050 mg/dL	
Hematocrit	11.5 – 18.5 g/dL	35% – 55%

Method Comparison

Results of MyCare Insite Clozapine Test CLZ-MCI-32.2 were compared to the first generation of MyCare Insite Clozapine Test CLZ-MCI according to CLSI guideline EP09c.[31] Passing-Bablok regression analysis was performed with 88 patient samples.

Regression Statistics CLZ-MCI-32.2 vs. CLZ-MCI	
Slope	0.94
Intercept	22
Correlation Coefficient (R)	0.9482
N	88
Concentration Range (CLZ-MCI)	14 – 999 ng/mL

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SYMBOLS USED

IVD	*in vitro* Diagnostic Device	LOT	Batch Code
	Consult Instructions for Use		Manufacturer
	Contains sufficient for <n> tests		Use By Date
	Temperature Limitation		Caution
REF	Catalog Number	EC REP	Authorized Representative in the European Community
	Do not re-use		Near Patient Testing
CE	CE mark		

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