REF QTP-RGT

MyCare Psychiatry Quetiapine Assay Kit

INDICATIONS FOR USE

The MyCare Psychiatry Quetiapine Assay Kit is intended for the *in vitro* quantitative measurement of quetiapine in human serum using automated clinical chemistry analyzers. Measurements obtained are used for monitoring patient adherence to quetiapine therapy to help ensure appropriate treatment.

SUMMARY AND EXPLANATION OF THE TEST

Quetiapine (2-[2-(4-dibenzo [b,f] [1,4]thiazepin-11-yl-1-piperazinyl)-ethoxy]-ethanol is a dibenzopthiazepine derivative atypical antipsychotic agent used in the treatment of schizophrenia, manic episodes associated with bipolar I disorder, and depressive episodes associated with bipolar disorder.[1]

Nonadherence to medication is well known for patients with severe mental illness.[2] While adherence to medication is critical to successful treatment outcomes, adherence is also least likely to be accurately assessed.[3,4] Measurement of quetiapine provides clinicians with objective evidence of concentrations that may be related to patient adherence.[5]

The quetiapine assay is a homogenous two reagent nanoparticle agglutination assay used for detection of quetiapine in human serum. It is based on competition between drug and drug-conjugates for binding to drug specific antibodies covalently bound to nanoparticles. The extent of particle aggregation can be followed spectrophotometrically on clinical chemistry analyzers.

REAGENTS

MyCare Psychiatry Quetiapine Assay Kit REF QTP-RGT	Quantity x Volume
Reagent 1 R1 Reaction buffer that contains drug-conjugate, protein and buffer	1 x 10.0 mL
Reagent 2 R2 Nanoparticle reagent that contains monoclonal antibody bound to nanoparticles in a buffered solution	1 x 5.0 mL

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 required for handling all laboratory reagents.
- Follow reagent handling instructions. Improper mixing of reagents can affect assay performance.
- All components of the quetiapine assay contain less than 0.1% sodium azide. Avoid contact with skin and mucous membranes. Flush affected areas with copious amounts of water. Seek immediate medical attention if reagents are ingested or come into contact with eyes. When disposing of such reagents, always flush with large amounts of water to prevent accumulation of azide.

REAGENT HANDLING

The quetiapine assay reagents are ready to use.

Mix the reagents (R1 and R2) by gently inverting five times, avoiding the formation of bubbles then place them on the analyzer.

Mix the reagents (R1 and R2) before pouring them into any analyzer-specific (secondary) reagent carrier. Before placing analyzer-specific (secondary) reagent carriers on the analyzer, mix the reagents (R1 and R2) by gently inverting five times, avoiding the formation of bubbles.

STORAGE AND STABILITY

Store reagents refrigerated at 2 - 8°C. Do not freeze.

When stored and handled as directed unopened reagents are stable until the expiration date on the label. Improper storage of reagents can affect assay performance.

SPECIMEN COLLECTION AND HANDLING

Serum is required. Trough or C_{min} samples at steady state have been recommended for testing antipsychotics.[5] After one week of treatment on the same dose, collect samples before the next dose.[6]

Prepare serum within 3 days of blood collection. Blood and serum samples may be stored at room temperature or 2 - 8°C. Store serum for up to 7 days before measuring. Freeze (≤ -20°C) for longer storage. Ensure the sample is thawed and thoroughly mixed before measuring. Avoid repeated freezing and thawing of samples.

PROCEDURE

Materials Provided:

REF QTP-RGT – MyCare Psychiatry Quetiapine Assay Kit

Materials Required – Provided Separately:

REF MCP2-CAL – MyCare Psychiatry Calibrator Kit 2

REF MCP2-CON - MyCare Psychiatry Control Kit 2

Instruments

Reagents may need to be transferred to analyzer-specific reagent containers.

The performance of applications not validated by Saladax Biomedical, Inc. is not warranted and must be user defined.

Assay

To run the assay, see the instrument specific application sheet and appropriate analyzer operator's manual.

Calibration

Perform a full calibration using the six calibrators in the Calibrator Kit 2. Verify the calibration by testing the low, medium, and high controls in the Control Kit 2.

Calibration Frequency - Calibration is recommended:

- After a reagent kit lot change,
- After performance of major instrument maintenance,
- As required following quality control procedures.

Quality Control (QC)

Each laboratory should establish its own QC procedures for the quetiapine assay kit. All quality control requirements and testing should be performed in accordance with local, state and/or federal regulations or accreditation requirements. Good laboratory practice suggests that at least two QC concentrations be tested each day patient samples are measured, and each time calibration is performed. Ensure that the quality control results meet the acceptance criteria before reporting patient results.

Specimen Dilution Procedure

Samples containing quetiapine in concentrations greater than 700 ng/mL can be diluted 1:2 (1-part sample plus two parts water) to give an upper range of 2,100 ng/mL. Refer to the instrument specific operation manual for an automatic dilution protocol (by cuvette only) of quetiapine samples with water. Alternatively, specimens out of range can be manually diluted 1:2 or 1:3 with deionized water and placed in the sample rack for analysis.

RESULTS

The concentration result is automatically calculated from the non-linear calibration curve by the analyzer. Report results in ng/mL or nmol/L. The conversion factor from ng/mL is 2.61 x ng/mL = 1 nmol/L.

LIMITATIONS OF THE PROCEDURE

The quetiapine assay has been validated for serum. Do not use serum separator tubes.

As with any assay 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 quetiapine results, which are inconsistent with the patient's clinical profile.

For samples containing quetiapine, addition of amoxapine (200 ng/mL), clotiapine (175 ng/mL), or loxapine (200 ng/mL) caused assay biases of ≥ 19%. Elevated levels of quetiapine may be seen in patients administered amoxapine, clotiapine, or loxapine.

EXPECTED VALUES

The therapeutic range for quetiapine in serum is not fully established. A therapeutic range from 100 to 500 ng/mL has been proposed.[5] Measured concentrations for adherent patients at steady state are expected to be in the measuring range of the assay. Therapeutic drug monitoring of quetiapine has been recommended because of high interpatient variability, unpredictable response, and the importance of adherence for successful therapy.[5] The complexity of the clinical state, individual differences in sensitivity, and co-administered medications may contribute to different requirements for optimal quetiapine blood levels. Users should investigate the transferability of the expected values to their own patient population and if necessary determine their own reference range. For diagnostic purposes the test findings should always be assessed in conjunction with the patient's medical history, clinical examinations, and other findings. Clinicians should carefully monitor patients during therapy initiation and dose adjustments. It may be necessary to obtain multiple samples to determine expected variation of optimal (steady state) concentrations for individual patients.

SPECIFIC PERFORMANCE DATA

Typical performance data for the quetiapine assay obtained on a Beckman Coulter AU480 are shown below. Results obtained in individual laboratories may differ from these data.

Precision

Within-laboratory precision and repeatability were verified throughout the measuring range according to CLSI Guideline EP05-A3.[7] Three Control Kit 2 controls, two total quetiapine spiked pools (Serum 1, 2) and two pools of clinical samples (Clinical 1, 2) were tested.

Sample	N	Mean (ng/mL)	Repeatability	Within-Laboratory
			CV	CV
Control 1	80	59	3.4%	7.4%
Control 2	80	317	1.3%	3.7%
Control 3	80	574	1.5%	3.7%
Serum 1	80	51	3.0%	7.9%
Serum 2	80	1002	1.6%	4.6%
Clinical 1	80	91	2.3%	5.6%
Clinical 2	80	506	1.7%	3.5%

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

The lower limits of quantitation and detection were established using CLSI guideline EP17-A2.[8]

LoQ

The LoQ was determined with an accuracy goal at the LoQ of ≤ 35% total error (Westgard model). The LoQ of the quetiapine assay is 34 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 quetiapine assay is 10 ng/mL.

Result Reporting

Each laboratory should determine reporting criteria for quetiapine concentrations. The following suggestion from CLSI EP17-A2 may be appropriate:[8]

Result ≤ LoB - report “not detected; concentration < LoD”

LoB < Result < LoQ - report “analyte detected; concentration < LoQ”

Result ≥ LoQ - report the result as measured

Measurement Range

The measurement range of the quetiapine assay is 34 – 700 ng/mL.

Specificity

Metabolism

Quetiapine is extensively metabolized by the liver. Metabolic pathways of quetiapine include sulfoxidation (quetiapine sulfoxide), N-dealkylation (N-desalkylquetiapine, O-desalkylquetiapine), and 7-hydroxylation (7-hydroxyquetiapine).[9] N-desalkylquetiapine, also known as nor-quetiapine, is quetiapine’s major active metabolite.[10] Norquetiapine is further metabolized to N-desalkylquetiapine sulfoxide, 7-hydroxy-N-desalkylquetiapine and an unidentified molecule. The metabolite 7-hydroxy-N-desalkylquetiapine also has pharmacological activity.[11]

Interfering Substances

Testing of interferents was conducted according to CLSI guidelines for interferences.[12-14] No significant assay bias was observed from samples with the following endogenous interferents at the given levels:

Interferent	Level	
Rheumatoid Factor	508 IU/mL	
Human Serum Albumin	10.8 g/dL	108 g/L
Human Immunoglobulin G	12.7 g/dL	127 g/L
Icteric Interference	34.7 mg/dL	592 µmol/L
Lipemic Interference	662 mg/dL	7.4 mmol/L
Hemolysate	1,050 mg/dL	

Cross-reactivity

Specificity for the following cross-reactants was tested in the absence and presence of quetiapine at 100, 500, and 1,000 ng/mL.

Cross-reactivity was tested according to CLSI guidelines for interferences.[12-14] The following compounds did not interfere with the quetiapine assay: assay bias was ≤ 11%.

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	130,000
Alprazolam	2,000	Amantadine Hydrochloride	10,000
Amikacin sulfate	144,000	Amiloride HCl dihydrate	500
Amisulpride	1,200	Amitriptyline	1,000
Amlodipine besylate	100	S (+)-amphetamine	1,000
Amoxicillin	80,000	Aripiprazole	1,400
L-ascorbic acid	60,000	Asenapine	500
Atomoxetine	7,900	Atorvastatin calcium	800
Baclofen	3,000	Benztropine	600

Compound	Tested at (ng/mL)	Compound	Tested at (ng/mL)
Betamethasone	400	Biotin	3,600
Biperiden	300	Blonanserin	100
Brexpiprazole	1,000	Bromperidol	100
Budesonide	50	Bupropion	3,000
Buspirone	200	Caffeine	108,000
Calcium carbonate	315,000	Cannabidiol	100
Cannabinol	100	Carbamazepine	45,000
Cariprazine	50	L-Carnosine	100,000
Cefalexin	200,000	Celecoxib	8,800
Cetirizine dihydrochloride	4,400	8-chloro-theophylline	3,000
Chlorpromazine HCl	3,300	Cimetidine	30,000

Compound	Tested at (ng/mL)	Compound	Tested at (ng/mL)
Ciprofloxacin	12,000	Citalopram HBr	5,500
Clindamycin	51,000	Clonazepam	300
Clotrimazole	50	Clozapine	1,800
Codeine	2,000	Cortisol	300
(-)-Cotinine	2,000	Cyclosporin A	9,000
Desloratadine	600	Desvenlafaxine	800
Dextro-methorphan	1,000	Diazepam	30,000
Diphenhydramine HCl	6,000	Divalproex Sodium	400,000
Docosahexaenoic acid ethyl ester	150,000	Donepezil	50,000
Doxycycline HCl	35,000	Droperidol	200
D-Serine	100,000	Duloxetine	200
Erythromycin	138,000	Escitalopram	200
Estradiol	10	Eszopiclone	200
Ethanol	10,000,000	Famotidine	2,500
Fenofibrate	50,000	Fentanyl	600
Fluoxetine HCl	4,000	Fluticasone propionate	50
Fluvoxamine	2,000	Folic acid	15
Furosemide	60,000	Galantamine	200
Gentamicin sulfate	30,000	Glyburide	2,000
Haloperidol	1,000	Heparin sodium salt	50 U/mL
Hydro-chlorothiazide	6,000	Hyoscine (Scopolamine HBr)	100
Hyperforin (St. John's Wort)	200	Hypericin (St. John's Wort)	100
Ibuprofen	500,000	Iloperidone	100
Imipramine	700	Indinavir sulfate	400
Lactulose	10,000	Lamivudine	10,500
Lamotrigine	42,000	Lansoprazole	9,400
Levonorgestrel	100	Lisinopril dihydrate	350
Lithium carbonate	250,000	Lorazepam	1,000
Lovastatin	500	Lurasidone	400
Meclizine dihydrochloride	500	Metformin	40,000
Methotrimeprazine	600	Methylphenidate HCl	350
Metoclopramide HCl	500	Metoprolol tartrate	5,000
Metronidazole	123,000	Midazolam	3,800
Milnacipran	10,000	Mirtazapine	900
Mometasone furoate	50	Morphine	7,800
Naltrexone	200	Naproxen sodium	500,000

Compound	Tested at (ng/mL)	Compound	Tested at (ng/mL)
Nateglinide	30,000	Nefazodone HCl	6,000
Nicotine	1,000	Nicotinic acid	27,900
Nordiazepam	5,000	Nortriptyline	1,200
Olanzapine	300	Omeprazole	8,400
Oxazepam	5,000	Oxcarbazepine	105,000
Oxycodone	500	Paliperidone	60
Pantothenic acid	1,800	Paroxetine	1,200
Penicillin V	42,000	Perazine	1,400
Perlapine	150	Perphenazine	100
Phenobarbital	690,000	Phentermine	500
Phenytoin	60,000	Pimozide	100
Pipamperone dihydrochloride	1,200	Potassium EDTA	1000
Pravastatin sodium	300	Prednisolone	3,000
Pregabalin	22,500	Procyclidine	1,900
Promethazine	1,200	R,R-(-)-pseudoephedrine	10,000
S,S-(+)-pseudoephedrine	10,000	Pyridoxine HCl	100
Quinidine	15,000	Raloxifene	50
Ranitidine	10,500	Retinol	4,000
Riboflavin	200	Rifampicin	65,000
Risperidone	200	Rosuvastatin calcium	200
Salicylic acid	500,000	Sarcosine	1,500
Sertindole	300	Sertraline hydrochloride	1,000
Simvastatin	1,700	Sodium benzoate	400,000
Sodium fluoride	900	Spironolactone	600
Sulfamethoxazole	400,000	Sulpiride	50,000
Temazepam	5,000	Terbinafine	9,000
Theophylline	60,000	Thiamine HCl	500
Topiramate	75,000	Trazodone HCl	14,000
Triamcinolone acetonide	300	Triamterene	9,000
Triazolam	40	Valproic acid	500,000
Vancomycin HCl	120,000	Varenicline	50
Venlafaxine HCl	700	Vitamin B12	50
Vitamin D2	200	Vitamin K1	50
Warfarin	75,000	Ziprasidone	600
Zolpidem hemitartrate	1,000	Zonisamide	120,000
Zopiclone	200	Zuclopenthixol	300

Recovery

The recovery of total quetiapine was assessed in the 3 controls, two spiked serum pools and two clinical pools 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 quetiapine. The mean percent recoveries were all within 78% to 105%.

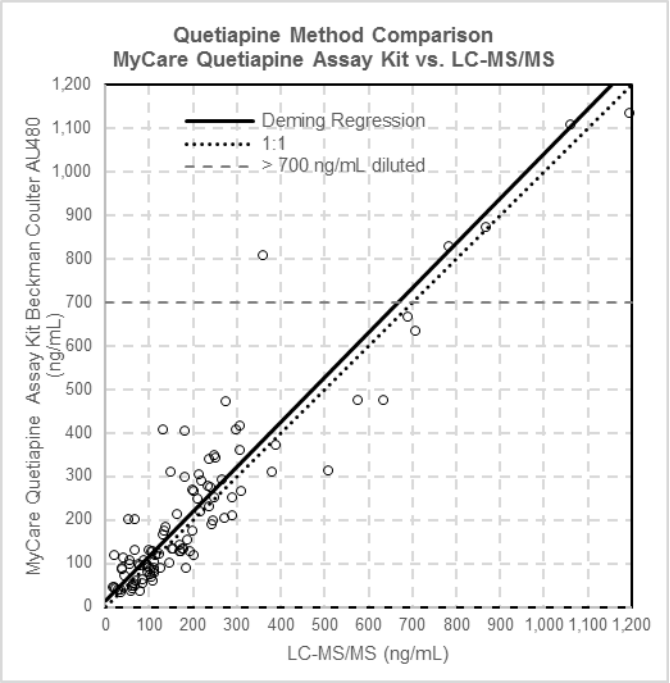
Linearity

The linearity of the quetiapine assay was verified according to CLSI guideline EP6-A.[15] Eleven linearity samples covering the measuring range were prepared in human serum spiked with quetiapine. Deviation from linearity (n=5) was ≤ 12%. The assay was linear across the measuring range from 34 – 700 ng/mL.

Method Comparison

Results of the quetiapine assay were compared to a validated LC-MS/MS according to CLSI guideline EP09-A3.[16] Deming regression analysis was performed with 103 patient samples. Patient samples above the test range of the quetiapine assay kit were diluted as described under Specimen Dilution Procedure. Results are shown for one lot.

Deming Regression Statistics Quetiapine Assay vs. LC-MS/MS	
Slope	1.03
Intercept	13.55
Correlation Coefficient (R)	0.92
N	103
Concentration Range (LC-MS/MS)	16 – 1192 ng/mL



References

1. AstraZeneca. Seroquel (Quetiapine Fumarate) Prescribing Information. 2017.
2. Velligan DI, Weiden PJ, Sajatovic M, et al. Assessment of adherence problems in patients with serious and persistent mental illness: recommendations from the Expert Consensus Guidelines. J Psychiatr Pract. 2010;16(1):34-45.
3. Higashi K, Medic G, Littlewood KJ, Diez T, Granstrom O, De Hert M. Medication adherence in schizophrenia: factors influencing adherence and consequences of nonadherence, a systematic literature review. Ther Adv Psychopharmacol. 2013;3(4):200-218.
4. Haddad PM, Brain C, Scott J. Nonadherence with antipsychotic medication in schizophrenia: challenges and management strategies. Patient Relat Outcome Meas. 2014;5:43-62.
5. Hiemke C, Bergemann N, Clement HW, et al. Consensus Guidelines for Therapeutic Drug Monitoring in Neuropsychopharmacology: Update 2017. Pharmacopsychiatry. 2018:51:9-62.
6. Grundmann M, Kacirova I, Urinovska R. Therapeutic drug monitoring of atypical antipsychotic drugs. *Acta Pharm.* 2014;64(4):387-401
7. CLSI. Evaluation of Precision Performance of Quantitative Measurement Methods; Approved Guideline-Second Edition. CLSI document EP05-A3. Wayne, PA: Clinical and Laboratory Standards Institute, 2014.
8. CLSI. Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures; Approved Guideline – Second Edition. CLSI document EP17-A2. Wayne, PA: Clinical and Laboratory Standards Institute; 2012.
9. Grimm SW, Richtand NM, Winter HR, Stams KR, Reele SB. Effects of cytochrome P450 3A modulators ketoconazole and carbamazepine on quetiapine pharmacokinetics. Br J Clin Pharmacol. 2006;61(1):58-69.
10. Lopez-Munoz F, Alamo C. Active metabolites as antidepressant drugs: the role of norquetiapine in the mechanism of action of quetiapine in the treatment of mood disorders. Front Psychiatry. 2013;4:102.macokinetics. Br J Clin Pharmacol. 2006;61(1):58-69.
11. Bakken GV, Molden E, Knutsen K, Lunder N, Hermann M. Metabolism of the active metabolite of quetiapine, N-desalkylquetiapine in vitro. Drug Metab Dispos. 2012;40(9):1778-1784.
12. CLSI. Interference Testing in Clinical Chemistry; Approved Guideline – Second Edition CLSI document EP7-A2. Wayne, PA: Clinical and Laboratory Standards Institute; 2005.
13. CLSI. Interference Testing in Clinical Chemistry. 3rd ed. CLSI guideline EP07. Wayne PA: Clinical and Laboratory Standards Institute; 2018.
14. CLSI. Supplemental Tables for Interference Testing in Clinical Chemistry. 1st ed. CLSI supplement EP37. Wayne PA: Clinical and Laboratory Standards Institute; 2018.
15. NCCLS. Evaluation of the Linearity of Quantitative Measurement Procedures: A Statistical Approach; Approved Guideline. NCCLS document EP6-A. Wayne, PA: NCCLS; 2003.
16. CLSI. Measurement Procedure and Bias Estimation Using Patient Samples; Approved Guideline-Third Edition. CLSI document EP09-A3. Wayne, PA: Clinical and Laboratory Standards Institute; 2013.

SYMBOLS USED

IVD	*in vitro* Diagnostic Device		Consult Instructions for Use
REF	Catalog Number		Use By
LOT	Batch Code		Temperature Limitation
	Manufacturer	**Rx only**	For Prescription Use Only
R1 R2	Reagent 1 Reagent 2	(N) x	Gently invert reagents (R1 and R2) N number of times prior to use
CE	CE mark	EC REP	Authorized Representative in the European Community
CH REP	Authorized Representative in Switzerland		

Saladax Biomedical, Inc.
116 Research Dr.
Bethlehem, PA 18015 USA
MyCareTests.com

EMERGO EUROPE
Westervoortsedijk 60,
6827 AT Arnhem
The Netherlands

Casus Switzerland GmbH
Hinterbergstrasse 49
6312 Steinhausen
Switzerland

Customer Service
Telephone: +1 (610) 419-6731
Fax: +1 (484) 547-0590
Email: Techsupport@saladax.com