REF OLZ-RGT

MyCare Psychiatry Olanzapine Assay Kit

This package insert must be read carefully prior to product use. Package insert instructions must be followed accordingly. Reliability of assay results cannot be guaranteed if there are any deviations from the instructions in this package insert.

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IVD	*in vitro* Diagnostic Device		Consult Instructions for Use
REF	Catalog Number		Use By
LOT	Batch Code		Temperature Limitation
EC REP	Authorized Representative in the European Community		Manufacturer
Rx only	For Prescription Use Only	R1 R2	Reagent 1 Reagent 2

INTENDED USE

Rx only

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

SUMMARY AND EXPLANATION OF THE TEST

Olanzapine (2-methyl-4-(4-methyl-1-piperazinyl)-10*H*-thieno[2,3-b][1,5]benzodiazepine) is an atypical antipsychotic in the thienobenzodiazepine class.[1] It is a serotonin and dopamine receptor antagonist with anticholinergic properties indicated for the treatment of schizophrenia and acute treatment of manic or mixed episodes associated with bipolar I disorder (given alone or as an adjunct to valproate or lithium),[1] while an injectable form is indicated for treatment of acute agitation associated with schizophrenia and bipolar I mania.[2] Used in conjunction with fluoxetine, olanzapine is used for the treatment of depressive episodes associated with bipolar I disorder and also for treatment resistant depression.[1]

Nonadherence to medication is well known for patients with severe mental illness.[3] While adherence to medication is critical to successful treatment outcomes, adherence is also least likely to be accurately assessed.[4,5] Measurement of olanzapine provides clinicians with objective evidence of concentrations that may be related to patient adherence.[6]

The olanzapine assay is a homogenous two reagent nanoparticle agglutination assay used for detection of olanzapine 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 Olanzapine Assay Kit REF OLZ-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 olanzapine 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 olanzapine assay reagents are ready to use.

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

Mix the reagents before pouring them into any analyzer-specific (secondary) reagent carrier. Before placing analyzer-specific (secondary) reagent carriers on the analyser, mix the reagents by gently inverting three to 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. Olanzapine is taken in the evening or at bedtime, making a twelve-hour concentration a practical option, one that has been used in multiple studies.[6-8] Olanzapine reaches steady state after 7 days on the sa rme dose.[1] For long lasting injectables collect the sample before the next dose.[6]

Prepare serum from whole blood at room temperature within 8 hours of blood collection. If whole blood is stored at 2 - 8°C, prepare serum within 3 days. Serum samples may be stored at room temperature or 2 - 8°C. Serum may be stored up to 7 days before measuring. Freeze (≤ -20°C) for longer storage. Avoid repeated freezing and thawing of samples.

PROCEDURE

Materials Provided:

REF OLZ-RGT – MyCare Olanzapine 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 five calibrators CAL A, B, C, D and E from the Calibrator Kit 2. Verify the calibration by testing the low and medium controls from the Control Kit 2.

Calibration Frequency - Calibration is recommended:

- After a calibrator or 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 olanzapine assay kit. All quality control 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 olanzapine in concentrations greater than 114 ng/mL can be diluted 1:2 (1-part sample plus two parts water) to give an upper range of 342 ng/mL. Refer to the instrument specific operation manual for an automatic dilution protocol (by cuvette only) of olanzapine samples with water. Alternatively, specimens out of range can be manually diluted 1:2 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 3.20 x ng/mL = nmol/L.

LIMITATIONS OF THE PROCEDURE

The olanzapine 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 olanzapine results, which are inconsistent with the patient's clinical profile.

For samples containing 20 ng/mL olanzapine, the addition of asenapine (500 ng/mL) or donepezil (50,000 ng/mL) caused assay biases ≥ 35%. Elevated levels of olanzapine may be seen in patients administered asenapine or donepezil.

Elevated levels of olanzapine may be seen in patients co-administered clozapine. Patients taking clozapine should not be tested with the MyCare Olanzapine Assay Kit.

EXPECTED VALUES

The therapeutic range for olanzapine in serum is not fully established. A therapeutic range from 20 to 80 ng/mL has been proposed for olanzapine.[6] Measured concentrations for adherent patients at steady-state are expected to be in the measuring range of the assay. Therapeutic drug monitoring of olanzapine has been recommended because of high interpatient variability, unpredictable response, and the importance of adherence for successful therapy.[6] The complexity of the clinical state, individual differences in sensitivity, and co-administered medications may contribute to different requirements for optimal olanzapine 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 olanzapine 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.[9] Two Control Kit 2 controls and two olanzapine 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	49	3.1%	4.6%
Control 2	80	106	1.7%	1.9%
Serum 1	80	48	2.9%	3.7%
Serum 2	80	101	1.5%	2.4%
Clinical 1	80	20	5.6%	9.0%
Clinical 2	80	76	2.4%	3.7%

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

The lower limits of quantitation and detection were established using CLSI guideline EP17-A2.[10]

LoQ

The LoQ was determined with an accuracy goal at the LoQ of ≤ 35% total error (Westgard model). The LoQ of the olanzapine assay is 22 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 olanzapine assay is 18 ng/mL.

Result Reporting

Each laboratory should determine reporting criteria for olanzapine concentrations. The following suggestion from CLSI EP17-A2 may be appropriate:[10]

Result < LoD - report "not detected; concentration < LoD"

LoD < Result < LoQ - report "analyte detected; concentration < LoQ"

Result ≥ LoQ - report the result as measured

Measurement Range

The measurement range of the olanzapine assay is 22 – 114 ng/mL.

Specificity

Metabolism

Olanzapine is extensively metabolized in the liver. The major metabolites N-desmethyl-olanzapine and N-glucuronide are inactive at circulating concentrations and occur at lower concentrations than the parent compound,[11] as do the minor metabolites olanzapine N-oxide and 2-hydroxymethyl olanzapine.[12] When the following metabolites were tested with 80 ng/mL olanzapine the assay bias was ≤ 18%. This should not introduce a clinically relevant bias given the low concentration of these minor metabolites.[11]

Compound	Tested at (ng/mL)	% Bias
N-desmethyl-olanzapine	50	4%
Olanzapine N-oxide	50	18%
2-hydroxymethyl olanzapine	50	4%

Specificity for the following cross-reactants was tested in the absence and presence of olanzapine at 20 and 80 ng/mL.

Cross-reactivity

The following compounds did not interfere with the olanzapine assay: assay bias was ≤ 27% at 20 ng/mL of olanzapine and ≤ 18% at 80 ng/mL olanzapine.

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	Amoxapine	2,900
Amoxicillin	80,000	S (+)-amphet-amine	1,000
Aripiprazole	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
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
Dextro-methorphan	1,000	Diazepam	6,000
Diphenhydramine HCl	6,000	Divalproex Sodium	50,000
Docosahexaenoic acid ethyl ester	150,000	Doxycycline HCl	35,000
Droperidol	100	Duloxetine	200
Erythromycin	60,000	Escitalopram	100
Eszopiclone	200	Ethanol	4,000,000

Compound	Tested at (ng/mL)	Compound	Tested at (ng/mL)
Famotidine	600	Fenofibrate	50,000
Fentanyl	600	Fluoxetine HCl	4,000
Fluticasone propionate	1	Fluvoxamine	2,000
Folic acid	15	Furosemide	60,000
Galantamine	100	Gentamicin sulfate	30,000
Glyburide	2,000	Haloperidol	1,000
Heparin sodium salt	50 U/mL	Hydrochloro-thiazide	6,000
Hyoscine (Scopolamine HBr)	100	Ibuprofen	500,000
Iloperidone	10	Imipramine	700
Indinavir Sulfate	400	K_2EDTA	1,000
Lactulose	10,000	Lamivudine	2,000
Lamotrigine	15,000	Lansoprazole	1,000
L-ascorbic acid	60,000	L-Carnosine	50,000
Lisinopril dihydrate	350	Lithium carbonate	250,000
Lorazepam	1,000	Lovastatin	500
Loxapine	150	Lurasidone	100
Meclizine dihydrochloride	500	Metformin	40,000
Methotri-meprazine	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	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	Pravastatin sodium	150
Prednisolone	3,000	Pregabalin	5,000
Procyclidine	1,000	Promethazine	1,200
R,R-(-)-pseudo-ephedrine	10,000	S,S-(+)-pseudo-ephedrine	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
D-Serine	100,000	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	Topiramate	10,000
Trazodone HCl	6,000	Triamcinolone acetonide	10
Triamterene	9,000	Triazolam	40
Valproic acid	500,000	Vancomycin HCl	100,000
Venlafaxine HCl	400	Vitamin B12	50
Vitamin D2	40	Vitamin K1	50
Warfarin	10,000	Ziprasidone	200
Zolpidem hemitartrate	5,000	Zopiclone	100
Zonisamide	40,000	Zuclopenthixol	250

Interfering Substances

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

Interferent	Level	
Rheumatoid Factor	508 IU/mL	
Total Protein Matrix Effect	13.4 g/dL	134 g/L
Icteric Interference	21 mg/dL	359 µmol/L
Lipemic Interference	756 mg/dL	8.54 mmol/L
Hemolysate	1050 mg/dL	

Recovery

The recovery of olanzapine was assessed for the 2 controls and two spiked serum 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 added olanzapine. The percent recovery ranged from 90 to 105%.

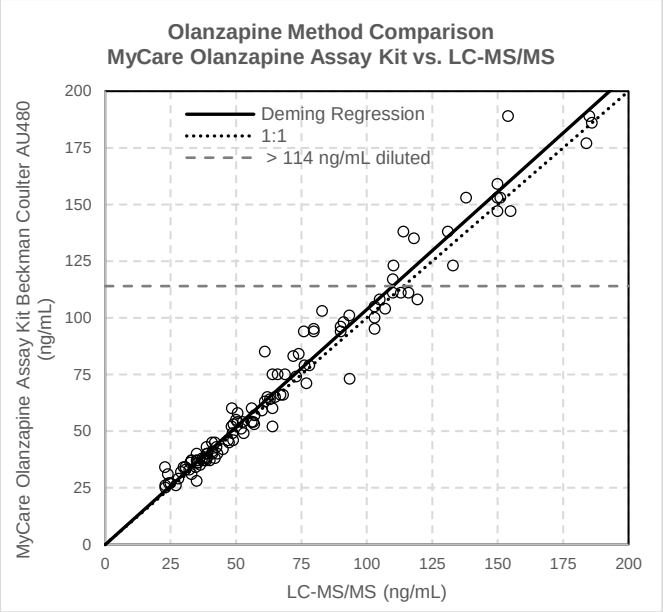
Linearity

The linearity of the olanzapine assay was verified according to CLSI guideline EP6-A.[13] Eleven linearity samples covering the measuring range were prepared in human serum spiked with olanzapine. The assay was linear across the measuring range from 22 – 114 ng/mL. Deviation from linearity (n=5) was ≤ 5% in the measuring range.

Method Comparison

Results of the olanzapine assay were compared to a validated LC-MS/MS according to CLSI guideline EP09-A3.[14] Deming regression analysis was performed with 113 patient samples. Patient samples above the test range of the olanzapine assay kit were diluted as described under Specimen Dilution Procedure. Results are shown for one lot.

Deming Regression Statistics Olanzapine Assay vs. LC-MS/MS	
Slope	1.038
Intercept	-0.1
Correlation Coefficient (R)	0.98
N	113
Concentration Range (LC-MS/MS)	23 - 186



References

1. Eli Lilly USA, LLC. Zyprexa® (olanzapine) Prescribing Information. Product Insert. 2017.
2. Lilly USA, LLC. Zyprexa® Relprevv™ (olanzapine). Prescribing information. Product Insert. 2017.
3. 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.
4. 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.
5. Haddad PM, Brain C, Scott J. Nonadherence with antipsychotic medication in schizophrenia: challenges and management strategies. Patient Relat Outcome Meas. 2014;5:43-62.
6. Hiemke C, Bergemann N, Clement HW, et al. Consensus Guidelines for Therapeutic Drug Monitoring in Neuropsychopharmacology: Update 2017. Pharmacopsychiatry. 2018:51:9-62.
7. Taylor DM, Barnes TRE, Young AH. The Maudsley Prescribing Guidelines in Psychiatry. 13th ed. Great Britain: Wiley Blackwell; 2018.
8. Perry PJ, Lund BC, Sanger T, Beasley C. Olanzapine plasma concentrations and clinical response: acute phase results of the North American Olanzapine Trial. Journal of clinical psychopharmacology. 2001;21(1):14-20.
9. 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.
10. 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.
11. Kassahun K, Mattiuz E, Nyhart E, et al. Disposition and Biotransformation of the Antipsychotic Agent Olanzapine in Humans. Drug Metabolism and Disposition. 1997;25(1):81.
12. Spina E, de Leon J. Metabolic drug interactions with newer antipsychotics: a comparative review. Basic & clinical pharmacology & toxicology. 2007;100(1):4-22.
13. NCCLS. Evaluation of the Linearity of Quantitative Measurement Procedures: A Statistical Approach; Approved Guideline. NCCLS document EP6-A. Wayne, PA: NCCLS; 2003.
14. 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.