REF RSP-RGT

MyCare Psychiatry Total Risperidone 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 (Lot)		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 Total Risperidone Assay Kit is intended for the *in vitro* quantitative measurement of risperidone and paliperidone (9-hydroxyrisperidone) in human serum using automated clinical chemistry analysers. Measurements obtained are used for monitoring patient adherence to risperidone or paliperidone therapy to help ensure appropriate treatment.

SUMMARY AND EXPLANATION OF THE TEST

Risperidone (3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl] ethyl]-6,7,8,9-tetrahydro-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one) is a benzisoxazole derivative, atypical antipsychotic agent used in the treatment of schizophrenia, acute manic or mixed episodes associated with bipolar disorder 1, and irritability associated with autistic disorder.[1,2]

Paliperidone (3-[2-[4-(6-fluoro-1,2-benzoxazol-3-yl)piperidin-1-yl]ethyl]-9-hydroxy-2-methyl-6,7,8,9-tetrahydropyrido[1,2-a]pyrimidin-4-one) is a benzisoxazole derivative, atypical antipsychotic agent used in the treatment of schizophrenia and schizoaffective disorder.[3,4]

The major metabolite of risperidone, paliperidone, is also pharmaceutically active. The therapeutic effect of risperidone is due to the total exposure to both risperidone and the active metabolite i.e. total risperidone.[5] The total risperidone assay measures the total active risperidone in patient serum: risperidone plus paliperidone. Nonadherence to medication is well known for patients with severe mental illness.[6] While adherence to medication is critical to successful treatment outcomes, adherence is also least likely to be accurately assessed by clinicians.[7,8] Measurement of risperidone and paliperidone provides clinicians with objective evidence of concentrations that may be related to patient adherence.[9]

The total risperidone assay (US Patent 8,088,594) is a homogenous two reagent nanoparticle agglutination assay used for detection of risperidone and paliperidone 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 analysers.

REAGENTS

MyCare Total Risperidone Assay Kit REF RSP-RGT	Quantity x Volume
Reagent 1 R1 Reaction buffer that contains drug-conjugate, protein, and buffer	1 x 10.0mL
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 total risperidone 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 total risperidone 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 analyser.

Mix the reagents before pouring them into any analyser-specific (secondary) reagent carrier. Before placing analyser-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. 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.[9,10] After one week of treatment on the same dose, collect samples 20 – 24 hours (daily dosing) or 9 - 12 hours (twice daily dosing) after the last dose.[11,12] For long lasting injectables collect the sample before the next dose.[13]

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. Avoid repeated freezing and thawing of samples.

PROCEDURE

Materials Provided:

REF	RSP-RGT – MyCare Total Risperidone 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 analyser-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 analyser 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 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 total risperidone assay. 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.

RESULTS

The concentration result is automatically calculated from the non-linear calibration curve by the analyser. Report results in ng/mL or nmol/L. The conversion factor for risperidone from ng/mL is 2.44 x ng/mL = 1 nmol/L. The conversion factor for paliperidone from ng/mL is 2.35 x ng/mL = 1 nmol/L.

LIMITATIONS OF THE PROCEDURE

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

Haloperidol when tested at 25 ng/mL had a cross-reactivity in the assay of ≤ 28%. Fentanyl when tested at 100 ng/mL had a cross-reactivity of ≤ 9%. Trazodone tested at 6,000 ng/mL had a cross-reactivity of 1%. Therefore, high therapeutic concentrations of trazodone may cause a bias in results. Elevated levels of risperidone may be seen in patients administered haloperidol, fentanyl, or trazodone. Elevated levels of paliperidone may be seen in patients administered haloperidol, fentanyl, or trazodone.

Paliperidone is the active metabolite of risperidone. For patients co-administrated paliperidone and risperidone, paliperidone will be quantitated as total risperidone.

EXPECTED VALUES

The therapeutic range for total risperidone or paliperidone in serum is not fully established. A therapeutic range from 20 to 60 ng/mL has been proposed for both risperidone and paliperidone.[9] Measured concentrations for adherent patients at steady-state are expected to be in the measuring range of the assay.[14] Therapeutic drug monitoring of total risperidone or paliperidone has been recommended because of high interpatient variability, unpredictable response, and the importance of adherence for successful therapy.[9] The complexity of the clinical state, individual differences in sensitivity, and co-administered medications may contribute to different requirements for optimal total risperidone and paliperidone 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 total risperidone 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 EP5-A3.[15] Three control kit controls, three risperidone spiked pools (Serum 1, 2, 3) and two pools of clinical samples (Clinical 1, 2) were tested.

Sample	N	Mean (ng/mL)	Repeatability	Within-Laboratory
			CV	CV
Control 1	80	36	2.8%	3.7%
Control 2	80	65	2.1%	2.8%
Control 3	80	99	2.5%	3.3%
Serum 1	80	21	3.3%	5.0%
Serum 2	80	59	2.4%	4.2%
Serum 3	80	78	3.3%	6.0%
Clinical 1	80	22	3.0%	4.2%
Clinical 2	80	58	3.1%	3.8%

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

The lower limits of quantitation and detection were established using CLSI guideline EP17-A2.[16]

LoQ

The LoQ was determined with an accuracy goal at the LoQ of ≤ 35% total error (Westgard model). The LoQ of the total risperidone assay is 16 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 total risperidone assay is 7 ng/mL.

Result Reporting

Each laboratory should determine reporting criteria for total risperidone concentrations. The following suggestion from CLSI EP17-A2 may be appropriate:[16]

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 total risperidone assay is 16 – 120 ng/mL.

Specificity

Metabolism

Risperidone is extensively metabolized in the liver by CYP2D6 and to a lesser extent by CYP3A4.[1] The biotransformation by CYP2D6 gives the major metabolite (±) 9-hydroxyrisperidone (paliperidone), both enantiomers of which are as active as the parent drug. The therapeutic effect of risperidone is due to the total exposure to both risperidone and the active metabolite.

There are two minor metabolites of risperidone in serum. 7-hydroxyrisperidone occurs as 1-5% of parent drug.[17] The minor N-desalkyl-risperidone metabolite has been reported to occur at 10 – 13% of the parent drug.[17]

Paliperidone itself is not extensively metabolized.[18] No metabolites have been detected in plasma and paliperidone accounts for 97% of the area under the curve at 24 hours.[19]

Specificity for the following metabolites was tested in the absence and presence of risperidone at 20 and 60 ng/mL.

Risperidone metabolites

Compound	Tested at (ng/mL)	Cross-Reactivity
9-hydroxyrisperidone	with risperidone for total risperidone concentrations of 20, 60 and 120 ng/mL	101%
7-hydroxyrisperidone	10	< 60%
N-desalkyl risperidone	20	< 5%

Specificity for the following cross-reactants was tested in the absence and presence of risperidone and paliperidone at 20 and 60 ng/mL.

Cross-reactivity

The following compounds did not interfere with the total risperidone assay: cross reactivity was ≤ 3% or the assay bias was ≤ 13%.

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	10,000
Amikacin sulfate	100,000	Amiloride HCl dihydrate	500
Amisulpride	400	Amitriptyline	1,000
Amlodipine besylate	100	Amoxicillin	80,000
S (+)-amphetamine	1,000	Aripiprazole	500
L-ascorbic acid	60,000	Atomoxetine	5,000
Atorvastatin calcium	600	Baclofen	3,000
Benztropine	400	Betamethasone	100
Biotin	300	Biperiden	100
Budesonide	2.2	Bupropion	3,000
Buspirone	20	Caffeine	60,000
Calcium carbonate	300,000	Carbamazepine	30,000
Cefalexin	200,000	Celecoxib	1,000
Cetirizine dihydrochloride	3,500	8-chlorotheophylline	3,000
Chlorpromazine HCl	2,500	Cimetidine	20,000
Ciprofloxacin	10,000	Citalopram HBr	750
Clindamycin	50,000	Clonazepam	150
Clotrimazole	50	Clozapine	1,000
Codeine	2,000	Cortisol	300
(-)-cotinine	2,000	Desloratadine	600
Desvenlafaxine	400	Dextromethorphan	1,000
Diazepam	6,000	Diphenhydramine HCl	6,000

Compound	Tested at (ng/mL)	Compound	Tested at (ng/mL)
Docosahexaenoic acid ethyl ester	150,000	Doxycycline HCl	35,000
Duloxetine	200	Erythromycin	60,000
Escitalopram	100	Estradiol	1.2
Eszopiclone	200	Ethanol	4,000,000
Famotidine	600	Fenofibrate	50,000
Fluoxetine HCl	4,000	Fluticasone propionate	1
Folic acid	15	Furosemide	60,000
Gentamicin sulfate	30,000	Glyburide	2,000
Haloperidol decanoate	1,500	Heparin sodium salt	3 U/mL
Hydrochlorothiazide	6,000	Ibuprofen	500,000
Iloperidone	10	Indinavir sulfate	400
Lamivudine	2,000	Lamotrigine	15,000
Lansoprazole	1,000	Lisinopril dihydrate	350
Lithium carbonate	250,000	Lorazepam	1,000
Lovastatin	500	Meclizine	500
Metformin	40,000	Methotrimeprazine	200
Methylphenidate HCl	350	Metoclopramide HCl	500
Metoprolol tartrate	5,000	Metronidazole	120,000
Mirtazapine	300	Mometasone furoate	1
Morphine	500	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
Pantothenic acid	150	Paroxetine	1,000
Penicillin V	6,000	Perphenazine	100
Phentermine	500	Pimozide	20
Pipamperone dihydrochloride	400	Potassium EDTA	1,000
Pravastatin sodium	150	Prednisolone	3,000
Pregabalin	5,000	Promethazine	1,200
R,R (-)-pseudoephedrine	10,000	S,S (+)-pseudoephedrine	10,000
Pyridoxine HCl	100	Quetiapine	500
Quinidine	12,000	Ranitidine	6,000
Retinol	4,000	Riboflavin	200
Rosuvastatin calcium	50	Salicylic acid	500,000
Sertraline hydrochloride	600	Simvastatin	30
Sodium fluoride	150	Spironolactone	600
Sulfamethoxazole	400,000	Temazepam	5,000
Theophylline	40,000	Thiamine HCl	50
Topiramate	10,000	Triamcinolone acetonide	10
Triamterene	9,000	Triazolam	40
Valproic acid	500,000	Vancomycin HCl	100,000
Venlafaxine HCl	400	Vitamin B12	1
Vitamin D2	40	Vitamin K1	1
Warfarin	10,000	Ziprasidone	200
Zolpidem hemitartrate	5,000	Zonisamide	40,000
Zopiclone	100		

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	11.0 g/dL	110 g/L
Icteric Interference	18.32 mg/dL	313 µmol/L
Lipemic Interference	1,828 mg/dL	20 mmol/L
Hemolysate	210 mg/dL	

Recovery

Patients on risperidone therapy have both risperidone (RSP) and the active metabolite paliperidone (PAL) in their serum. Therefore, to assess recovery of the total risperidone assay, risperidone and the active metabolite paliperidone were spiked together into four individual normal risperidone-free sera. The percent recovery was determined by dividing the observed concentration of each sample by the expected concentration of added risperidone plus paliperidone.

Mean Percent Recovery

Theoretical ng/mL	RSP:PAL ratio	Percent Recovery	RSP:PAL ratio	Percent Recovery
20	4:1	90 – 120	1:4	90 – 120
60	4:1	90 – 108	1:4	92 – 115
120	4:1	90 – 110	1:4	95 – 115

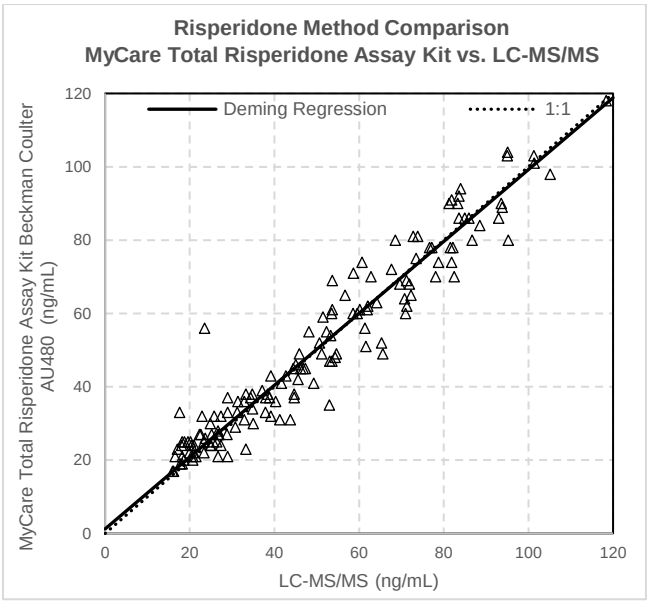
Linearity

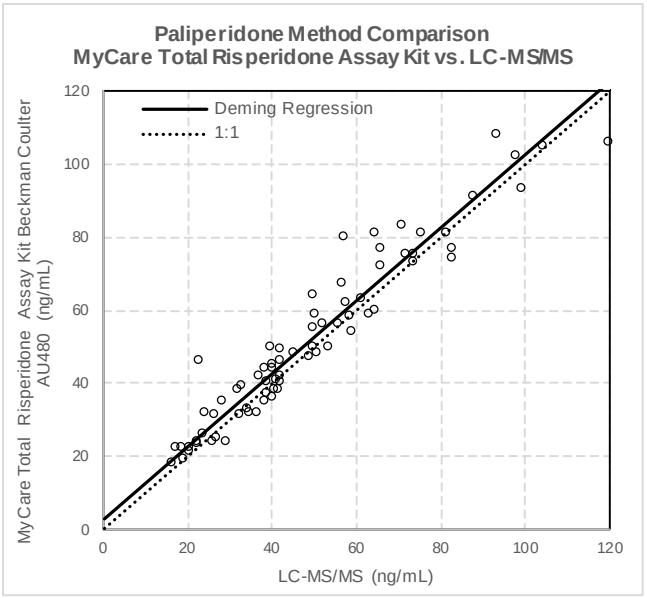
The linearity of the total risperidone assay was verified according to CLSI guideline EP6-A.[20] Eleven linearity samples covering the measuring range were prepared in human serum spiked with risperidone and eleven linearity samples covering the measuring range were prepared in human serum spiked with paliperidone. Deviation from linearity (n=5) for eleven sample with risperidone or paliperidone was < 6%. The assay was linear across the measuring range from 16 – 120 ng/mL.

Method Comparison

Results of the total risperidone assay were compared to a validated LC-MS/MS, using samples from patients taking risperidone or paliperidone according to CLSI guideline EP09-A3.[21] Deming regression analysis was performed with 146 risperidone patient samples and 119 paliperidone patient samples. Results are shown for one lot.

Deming Regression Statistics Total Risperidone Assay vs. LC-MS/MS		
Statistic	Risperidone Samples	Paliperidone Samples
Slope	0.98	1.00
Intercept	1	3
Correlation Coefficient (R)	0.96	0.94
N	146	119
Concentration Range (LC-MS/MS)	16 – 118 ng/mL	16 – 120 ng/mL





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