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 total risperidone (risperidone plus 9-hydroxyrisperidone) in human serum using automated clinical chemistry analyzers. Measurements obtained are used for monitoring patient adherence to risperidone 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] The major metabolite of risperidone, 9-hydroxyrisperidone, is also pharmaceutically active. The therapeutic effect of risperidone is due to the total exposure to both risperidone and the active metabolite (total risperidone).[3] The MyCare Total Risperidone Assay Kit measures the total active risperidone in patient serum: risperidone plus 9-hydroxyrisperidone.

Nonadherence to medication is well known for patients with severe mental illness.[4] While adherence to medication is critical to successful treatment outcomes, adherence is also least likely to be accurately assessed.[5,6] Measurement of total risperidone provides clinicians with objective evidence of concentrations that may be related to patient adherence.[7]

The MyCare Total Risperidone Assay Kit (US Patent 8,088,594) is a homogenous two reagent nanoparticle agglutination assay used for detection of total risperidone (risperidone + 9-hydroxyrisperidone) 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 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.
- All components of the MyCare Total Risperidone Assay Kit 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

MyCare Total Risperidone Assay Kit reagents are ready to use. Before use, 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 (35-46°F). 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.[7,8] 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.[9,10] For long lasting injectables collect the sample before the next dose.[11]

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 MCP1-CAL – MyCare Psychiatry Calibrator Kit 1

REF MCP1-CON - MyCare Psychiatry Control Kit 1

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 MyCare Psychiatry Calibrator Kit 1. Verify the calibration by testing the low, medium, and high controls in the MyCare Psychiatry Control Kit 1.

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 MyCare Total Risperidone 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.

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 2.44 x ng/mL = nmol/L.

LIMITATIONS OF THE PROCEDURE

The MyCare Total Risperidone Assay Kit 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 total risperidone may be seen in patients administered haloperidol, fentanyl or trazodone.

EXPECTED VALUES

The therapeutic range for total risperidone in serum is not fully established. A therapeutic range from 20 to 60 ng/mL has been proposed.[7] Measured concentrations for adherent patients at steady-state are expected to be in the measuring range of the assay.[12] Therapeutic drug monitoring of total risperidone has been recommended because of high interpatient variability, unpredictable response, and the importance of adherence for successful therapy.[7] The complexity of the clinical state, individual differences in sensitivity, and co-administered medications may contribute to different requirements for optimal total risperidone 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 PEFORMANCE DATA

Typical performance data for the MyCare Total Risperidone Assay Kit 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.[13] Three MyCare Psychiatry Control Kit 1 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.[14]

LoQ

The LoQ was determined with an accuracy goal at the LoQ of ≤ 35% total error (Westgard model). The LoQ of the MyCare Total Risperidone Assay Kit 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 MyCare Total Risperidone Assay Kit is 6 ng/mL.

Result Reporting

Each laboratory should determine reporting criteria for total risperidone concentrations. The following suggestion from CLSI EP17-A2 may be appropriate:[14]

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 MyCare Total Risperidone Assay Kit 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 CYP26D6 gives the major metabolite (±) 9-hydroxy-risperidone, 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 in serum. 7-hydroxyrisperidone occurs as 1-5% of parent drug.[15] The minor N-desalkyl-risperidone metabolite has been reported to occur at 10 – 13% of the parent drug.[15]

Specificity for the following metabolites and cross-reactants 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-hydroxrisperidone	10	<60%
N-desalkyl risperidone	20	< 5%

Cross-reactivity

The following compounds did not interfere with the MyCare Total Risperidone Assay Kit: cross reactivity was ≤ 3% or the assay bias was ≤ 10%.

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
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
Gentamycin 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

Compound	Tested at (ng/mL)	Compound	Tested at (ng/mL)
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	N-desalkyl risperidone	20
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 9-hydroxyrisperidone (9-OH RSP) in their serum. Therefore, to assess recovery of the MyCare Total Risperidone Assay Kit, risperidone and the active metabolite 9-hydroxyrisperidone 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 9-hydroxyrisperidone.

Mean Percent Recovery

Theoretical ng/mL	RSP:9-OH RSP ratio	Percent Recovery	RSP:9-OH RSP 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 MyCare Total Risperidone Assay Kit was verified according to CLSI guideline EP6-A.[13] Eleven linearity samples covering the measuring range were prepared in human serum spiked with risperidone. Deviation from linearity (n=5) was < 4%. The assay was linear across the measuring range from 16 – 120 ng/mL.

Method Comparison

Results of the MyCare Total Risperidone Assay Kit were compared to a validated LC-MS/MS according to CLSI guideline EP09-A3.[17] Deming regression analysis was performed with 146 patient samples. Results are shown for one lot.

Deming Regression statistics MyCare Total Risperidone Assay Kit vs. LC-MS/MS	
Slope	0.98
Intercept	1.23
Correlation Coefficient (R)	0.96
N	146
Concentration Range (LC-MS/MS)	16 – 118 ng/mL

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