REF ARI-RGT

MyCare Psychiatry Total Aripiprazole 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.

CUSTOMER SERVICE

Telephone: +1 610 419-6731
Fax: +1 484 547-0590
Email: Techsupport@saladax.com
116 Research Dr.
Bethlehem, PA 18015 USA
MyCareTests.com

EC REP
EMERGO EUROPE
Prinsessegracht 20
2514 AP The Hague
The Netherlands

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 Total Aripiprazole Assay Kit is intended for the *in vitro* quantitative measurement of total aripiprazole (aripiprazole plus dehydroaripiprazole) in human serum using automated clinical chemistry analyzers. Measurements obtained are used for monitoring patient adherence to aripiprazole therapy to help ensure appropriate treatment.

SUMMARY AND EXPLANATION OF THE TEST

Aripiprazole (7-[4-[4-(2,3-dichlorophenyl)-1-piperazinyl]butoxy]-3,4-di-hydrocarbostyril) is a quinolone derivative atypical anti-psychotic agent. It has partial agonistic activity at dopamine D2 receptors and serotonin 5-HT1A receptors and potent antagonistic activity on serotonin 5-HT2A receptors.[1,2] The oral medication is indicated for the treatment of schizophrenia, acute treatment of manic and mixed episodes associated with bipolar disorder, adjunctive treatment of major depressive disorder, irritability associated with autistic disorder, and Tourette's disorder. The injectable is indicated for agitation associated with schizophrenia or bipolar mania. The major metabolite of aripiprazole, dehydroaripiprazole, is also pharmaceutically active.[1] The therapeutic effect of aripiprazole is due to the total exposure to both aripiprazole and the active metabolite (dehydroaripiprazole).[3] The total aripiprazole assay measures the total active aripiprazole in patient serum: aripiprazole plus dehydroaripiprazole.

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 aripiprazole provides clinicians with objective evidence of concentrations that may be related to patient adherence.[7]

The total aripiprazole assay is a homogenous two reagent nanoparticle agglutination assay used for detection of total aripiprazole 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 Aripiprazole Assay Kit REF ARI-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 total aripiprazole 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 aripiprazole 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 analyzer, 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. Trough or C_{min} samples at steady state have been recommended for testing antipsychotics.[6] After two weeks of treatment on the same dose, collect samples before the next dose.[8] For long lasting injectables collect the sample before the next dose.[7]

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 ARI-RGT – MyCare Total Aripiprazole 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 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 aripiprazole 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 2.23 x ng/mL = 1 nmol/L.

LIMITATIONS OF THE PROCEDURE

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

For samples containing 150 and 500 ng/mL total aripiprazole, 50 ng/mL of cariprazine caused assay biases of 164% and 71% respectively. Elevated levels of aripiprazole may be seen in patients administered cariprazine.

EXPECTED VALUES

The therapeutic range for total aripiprazole in serum is not fully established. A therapeutic range from 150 to 500 ng/mL has been proposed for aripiprazole plus dehydroaripiprazole.[7] Measured concentrations for adherent patients at steady-state are expected to be in the measuring range of the assay. Therapeutic drug monitoring of total aripiprazole 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 aripiprazole 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 aripiprazole 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] Three Control Kit 2 controls (Control 1, 2, 3), two serum pools spiked with both aripiprazole and dehydroaripiprazole to mimic the metabolite ratio found in clinical samples (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	6.5%	8.3%
Control 2	80	198	2.3%	4.0%
Control 3	80	682	2.2%	3.9%
Serum 1	80	45	6.5%	9.5%
Serum 2	80	959	2.6%	4.3%
Clinical 1	80	150	3.5%	4.1%
Clinical 2	80	503	2.6%	4.1%

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 total aripiprazole assay is 45 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 aripiprazole assay is 22 ng/mL.

Result Reporting

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

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 total aripiprazole assay is 45 – 1,000 ng/mL.

Specificity

Metabolism

Aripiprazole is metabolized in the liver by CYP3A4 and CYP2D6. The major metabolite dehydroaripiprazole also has pharmacological activity.[1,3] At steady state, its concentration is ~40% of the parent drug.[1] The other major metabolite, the acid product of N-dealkylation (OPC-3373) is also present in serum. Another minor metabolite (DCPP) is found at < 20% of the parent drug.

Compound	Tested at (ng/mL)	% Bias
3,4-dihydro-7-(3’carboxy) propoxy-2(1H) quinolinone (OPC-3373)	475	3%
1-(2,3-dichlorophenyl) piperazine (DCPP)	50	6%

Structurally related

Compound	Tested at (ng/mL)	% Bias
Brexpiprazole	1,000	3%

Specificity for the following cross-reactants was tested in the absence and presence of total aripiprazole at 150 and 500 ng/mL.

Cross-reactivity

The following compounds did not interfere with the total aripiprazole 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	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
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
Bromperidol	100	Budesonide	50
Bupropion	3,000	Buspirone	200
Caffeine	60,000	Calcium carbonate	300,000
Cannabidiol	100	Cannabinol	100
Carbamazepine	30,000	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
Clozapine	1,000	Codeine	2,000
Cortisol	300	(-)-cotinine	2,000
Cyclosporin A	9,000	Desloratadine	600

Compound	Tested at (ng/mL)	Compound	Tested at (ng/mL)
Desvenlafaxine	400	Dextro-methorphan	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	4,000,000	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
Lactulose	10,000	Lamivudine	2000
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
Metho-trimeprazine	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	1000	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 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	10.8 g/dL	108 g/L
Icteric Interference	18.5 mg/dL	315 µmol/L
Lipemic Interference	614 mg/dL	6.95 mmol/L
Hemolysate	210 mg/dL	

Recovery

The recovery of total aripiprazole 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 total aripiprazole. All mean recoveries were within 88% to 114%.

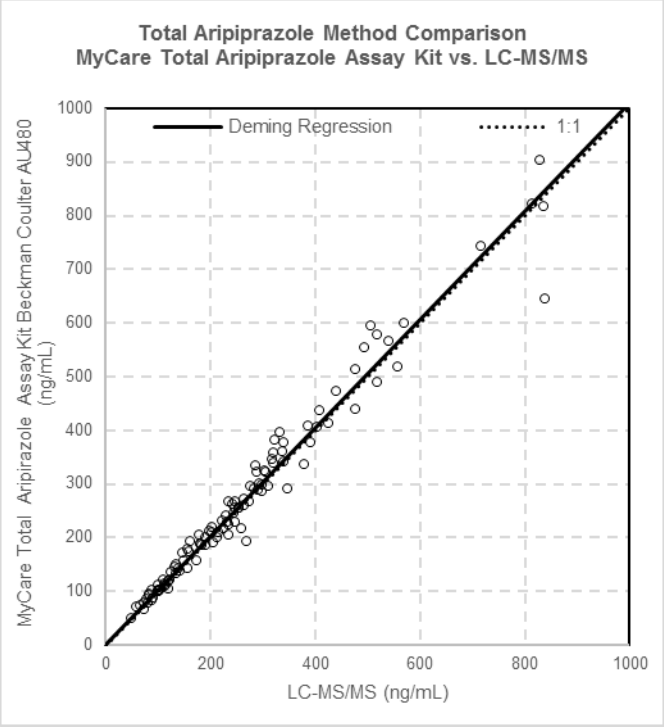
Linearity

The linearity of the total aripiprazole assay was verified according to CLSI guideline EP6-A.[11] Eleven linearity samples covering the measuring range were prepared in human serum spiked with aripiprazole. Deviation from linearity (n=5) was ≤ 10%. The assay was linear across the measuring range from 45 – 1,000 ng/mL.

Method Comparison

Results of the total aripiprazole assay were compared to a validated LC-MS/MS according to CLSI guideline EP09-A3.[12] Deming regression analysis was performed with 110 patient samples. Results are shown for one lot.

Deming Regression Statistics Total Aripiprazole Assay vs. LC-MS/MS	
Slope	1.01
Intercept	2.56
Correlation Coefficient (R)	0.98
N	110
Concentration Range (LC-MS/MS)	48 - 839



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