LITHIUM

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REF 8A1680	**1680**	**Tests**
REF 8A1681	**810**	**Tests**
REF BY1680	**1680**	**Tests**
REF BY1681	**810**	**Tests**
REF At125	**900**	**Tests**

Diagnostic reagent for determination of lithium concentration.
Liquid. Dual Reagents. Store at +2/+8°C. For in Vitro Diagnostic Use (IVD). **Do not freeze.**
8A1680/BY1680/8A1681/BY1681/At125 Products are Produced Specifically for Siemens Advia and Atellica Analyzer Series.

Changes made in the instructions for use are marked as grey.

INTENDED USE

This test is an in vitro assay used in clinical laboratories for the quantitative determination of lithium in human serum using auto analyzers.

GENERAL INFORMATION

Lithium (e.g. Eskalith, Lithane, Lithonate) is applied as lithium carbonate and is used in the treatment of affective disorders, mania and the manic phase of manic-depressive illness. Lithium's mechanism of action is not entirely clear. Early studies suggested that it acts by increasing the re-uptake of catecholamines, reducing their concentration at the neuronal junction and producing a sedating effect on the central nervous system.[1] In recent studies, lithium, along with other mood-affecting drugs such as valproic acid, carbamazepine and tricyclic antidepressants (TCAs), has been shown to inhibit GSK3-β, a protein at the center of the Wnt/β-catenin signaling pathway that affects gene expression, including many aspects of cellular behavior, neuronal polarity, plasticity and survival, and brain development.[2]

Absorption of lithium from the gastrointestinal tract is complete with a peak plasma concentration reached within 2 to 4 hours after the oral dose. This cation does not bind to protein. Lithium elimination is biphasic; in the first phase, 30 to 40% of the lithium dose is cleared, with an apparent half-life of 24 hours. In the second phase, the remainder of the lithium that has joined the cellular ion pool is cleared and exhibits a half-life of 48 to 72 hours. Clearance is predominantly a function of the kidneys where active reabsorption occurs. Decreased renal function results in prolonged clearance times.[1]

The optimal therapeutic response to lithium is not related to a specific serum concentration; however, toxicity is related to serum concentration. Serum lithium concentrations are monitored to ensure patient compliance and prevent intoxication. The use of a standardized 12-hour post-dose serum lithium concentration is recommended to assess the adequacy of treatment.[3]

Early symptoms of lithium poisoning include apathy, weakness, lethargy, drowsiness, somnolence, lethargy, speech difficulties, irregular tremors, myoclonic twitching, muscle weakness and ataxia. Although these symptoms are not life-threatening, they are uncomfortable for patients and indicate that life-threatening seizures are imminent. Signs of severe intoxication include muscle rigidity, hyperactive deep tendon reflexes and epileptic seizures. The potential for lithium intoxication is increased when patients are susceptible to dehydration (fever, watery stools, vomiting, anorexia, hot weather).[1]

TEST PRINCIPLE

Colorimetric measurement

Under strongly alkaline conditions, lithium in serum forms a complex with a chromophore compound that is porphyrin-like and forms a colored product that is easily detected spectrophotometrically after binding to lithium. The absorbance of the colored complex formed is directly proportional to the lithium concentration in the sample.

REAGENT COMPONENTS

Reagent 1

Sodium hydroxide	1.0 mmol/L
Ethylenediaminetetraacetic acid	0.05 mmol/L

Reagent 2

Sodium hydroxide	1.0 mmol/L
Porphyrin-like compounds	0.06 mmol/L

REAGENT PREPARATION

Reagents are ready to use.

REAGENT STABILITY AND STORAGE

Reagents are stable at +2/+8°C till the expiration date stated on the label which is only for closed and uncontaminated vials.

Once opened vials are stable for 28 days at +2/+8°C in optimum conditions. On board stability is strongly related to auto analyzers' cooling specification and carry-over values.

Reagent stability and storage data have been verified by using Clinical and Laboratory Standards Institute (CLSI) EP25-A protocol.[4]

SAMPLE REQUIREMENTS

Serum and plasma can be used and are collected according to the standard procedures. For plasma, sample collection tubes with Na-heparin should be preferred. Sample collection tubes with EDTA must not be preferred for plasma. Hemolyzed samples must not be used.

Lithium activity stability in serum[15]:

1 day at +20/+25°C
7 days at +2 /+8ºC
6 months at -20°C

Unit Conversion:
mmol/L x 0.6941 = mg/dL
mg/dL x 1.441 = mmol/L

CALIBRATION AND QUALITY CONTROL

Calibration: The assay requires the use of a Lithium Calibrator Set (5 Levels) Liquid. We recommend:

Lithium Calibrator Set (5 Levels)-Liquid
Ref.No: L168S

Calibration stability depends on the application characteristics and cooling capacity of the autoanalyzer used. Calibration stability is 7 days.

Control: Commercially available control material with established values determined by this method can be used. We recommend:

Lithium Control Set (2 Levels)-Liquid
Ref.No: LCN168

At least two level controls must be run once in every 24 hours. Each laboratory should determine its own quality control scheme and procedures. If quality control results are not within acceptable limits, calibration is required.

REFERENCE INTERVALS / MEDICAL DECISION LEVELS

mmol/L

Lithium[16]:	Therapeutic conc.:	0.6-1.2 mmol/L
	Toxic range:	>2.0 mmol/L

mg/dL

Lithium[16]:	Therapeutic conc.:	0.42-0.83 mg/dL
	Toxic range	>1.39 mg/dL

There are some important clinical decision levels for lithium:

- *1 to 1.2 mmol/L range:* Optimal therapeutic concentration
- *1.2 to 1.5 mmol range:* Indicates the warning range and a concentration exceeding 1.5 mmol/L in a sample taken 12 hours after the dose indicates a significant risk of poisoning.
- *>2.5 mmol/L:* Severe risk of poisoning.[1]

The analytical measurement range determined for lithium is: 0.05 mmol/L to 4.05 mmol/L.

Each laboratory should investigate the transferability of the expected values to its own patient population and if necessary, determine its own reference range.

Reference interval has been verified by using CLSI EP28-A3c protocol.[5]

PERFORMANCE CHARACTERISTICS

Measuring Interval

According to CLSI EP34-ED1:2018, "Measuring Interval" refers to the interval where the analyte concentration is measured with intended accuracy in terms of medical and laboratory requirements without dilution, concentrating or any kind of pre-treatment that is between the analyte's lower limit of quantitation (LLoQ) and upper limit of quantitation (ULoQ).[6]

The determined analytic measuring interval for Lithium is 0.05 – 4.05 mmol/L.

Detection Capability

Limit of Detection (LoD): 0.03 mmol/L

Limit of Quantitation (LoQ): 0.05 mmol/L

Note: LoQ values are based on Coefficient of Variation Percentage (CV) ≤ 20%.

LoD and LoQ values have been verified by using CLSI EP17-A2:2012 protocol.[7]

Linearity

This method shows measurement linearity in the activities up to 4,05 mmol/L.

Autoanaylzer's auto-dilution system can be used if the concentrations have higher values. See device manual for further information.

For manual dilution procedure, dilute the sample 10-fold using 0.90% isotonic. After the dilution, multiply the result of rerun sample by the dilution factor. Do not report the sample result after dilution if it is marked as lower than the linear lower limit. Rerun with a suitable dilution.

Linearity Studies data have been verified by using CLSI EP06-A:2003 protocol.[8]

Precision

Running system has been developed according to 20x2x2 "The Single Site" protocol. Repeatability and Within-Laboratory Precision/Within-Device values have been obtained according to the running results.
According to the protocol in use, 2 separate runs per day have been made for 20 days (no obligation for being consecutive days). This protocol has been applied to each low and high samples separately and 80 results have been

obtained for each one. Statistically, the results have been obtained using 2-factor Nested-ANOVA model.[9]
Repeatability (Within Run) and Repeatability (Day to Day) SD (standard deviation) and CV% values of Lithium have been given in the table 1 and 2 respectively.

Table 1. Lithium Repeatability (Within Run) results obtained from samples in two different concentrations

Mean Concentration	SD	CV%	n
0.75 mmol/L	0.0157	2.1	80
1.90 mmol/L	0.0342	1.8	80

Note: This working system has been named "Within-Run Precision" in the previous CLSI - EP05-A2 manual.[10]

Table 2. Lithium Repeatability (Day to Day) results obtained from samples in two different concentrations

Mean Concentration	SD	CV%	n
0.75 mmol/L	0.0187	2.5	80
1.90 mmol/L	0.0380	2.0	80

Note: This working system has been named "Total Precision" in the previous CLSI - EP05-A2 manual.[10]

Method Comparison

As a result of the statistical evaluation of the method comparison data:

Passing-Bablock equation:[11]
y= 1.0x + 0.01 mmol/L
r=0.99

Interference

Endogenous interferant and analyte concentrations that have been used in the Lithium scanning tests has been determined according to "CLSI EP37-ED1:2018" and "CLSI EP07-ED3:2018" manuals.[12,13]

The total acceptable error rate, which is going to be used to detect whether the observed differential value obtained from Lithium interference scanning test is appropriate, is determined as ±25%.[14]

In Lithium test results, no significant interaction has been observed in the determined endogenous interferant and analyte concentrations or between interferants and analyte.

Interferent and Concentration	Lithium Target (mmol/L)	N*	%Observed Recovery
Bilirubin Total 36 mg/dL	1.05	5	%107
Trigliserit 1350 mg/dL	1.07	5	%103
Hemoglobin 500 mg/dL	1.02	5	%102

** Total acceptable error rate determined as interference limit and repeatability (within run) pre-detected for the related method were used for the calculations of how many times the control and test samples prepared as a serum pool are going to be run repetitively. In the calculations, the accepted error rate for type 1 (α error) was 5% and for type 2 (β error) was 10% (90% power).*[13]

It should be noted that endogenous interferants, as well as various medicines and metabolites, anticoagulants (e.g. Heparin, EDTA, citrate, oxalate) and preservatives (e.g. sodium floride, iodoacetate, hydrochloride acide) such as additives, materials that may contact with samples during collection and processing (serum separator devices, sample collection containers and contents, catheters, catheter wash solutions, skin disinfectants, hand cleaners and lotions, glass washing detergents, powder gloves), dietary substances known to affect some specific tests (caffeine, beta-carotene, poppy seeds, etc.), or some substances present in a sample that cause foreign proteins (heterophilic antibodies, etc.), autoimmune response (autoantibodies, etc.), or due to malignancy (for example, interference by paraproteins with phosphate testing and indirect ion selective electrode methods) may show some negative effects that will cause various attempts and some misjudgements.[13]

These performance characteristics have been obtained using an autoanalyzer. Results may vary slightly when using different equipment or manual procedures.

WARNINGS AND PRECAUTIONS

IVD: For in Vitro Diagnostic use only.
Do not use expired reagents.
Reagents with two different lot numbers should not be interchanged.
For professional use.
Follow Good Laboratory Practice (GLP) guidelines.
Contains sodium azide.

CAUTION: Human source samples are processed with this product. All human source samples must be treated as potentially infectious materials and must be handled in accordance with OSHA standards.

Danger

EUH032 :Releases a very toxic gas if contacts with acid.
H317 :May cause allergic skin reaction.

Precaution

P280 :Use protective gloves / clothes / glasses / mask.
P264 :Wash your hands properly after using.
P272 :Contaminated work clothes should not be allowed to be used outside of the workplace.

Intervention

P302+P352 :Wash with plenty of water and soap if it contacts with skin.
P333+P313 :Seek medical help if it irritates your skin or develops rash.
P362+P364 :Remove contaminated clothes and wash properly before using.

Disposal

P501 :Dispose the vials and contents according to the local regulations.

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SYMBOLS

IVD	In Vitro Diagnostic Medical Device
LOT	Lot Number
R1	Reagent 1
R2	Reagent 2
GTIN	Global Trade Item Number
REF	Reference Number
GLP	Good Laboratory Practice
FOR USE WITH	Identifies Products to Be Used Together
PRODUCT OF TURKEY	Product of Turkey
	Manufacturer
	Expiration Date
	Temperature Limits
	Consult Instructions for Use
	Caution
	Number Of Tests

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