LI

cobas®

Lithium

Order information

REF		CONTENT		Analyzer(s) on which **cobas c** pack(s) can be used
04679598190	04679598500	Lithium (100 tests)	System-ID 07 6934 7	**cobas c** 311, **cobas c** 501/502

Materials required (but not provided):

10759350190	Calibrator f.a.s. (12 x 3 mL)	Code 401	
12149435122	Precinorm U plus (10 x 3 mL)	Code 300	
12149443122	Precipath U plus (10 x 3 mL)	Code 301	
05117003190	PreciControl ClinChem Multi 1 (20 x 5 mL)	Code 391	
05947626190	PreciControl ClinChem Multi 1 (4 x 5 mL)	Code 391	
05117216190	PreciControl ClinChem Multi 2 (20 x 5 mL)	Code 392	
05947774190	PreciControl ClinChem Multi 2 (4 x 5 mL)	Code 392	

English

System information

For **cobas c** 311/501 analyzers:

LI: ACN 136

For **cobas c** 502 analyzer:

LI: ACN 8136

Intended use

In vitro test for the quantitative determination of lithium in human serum and plasma on **cobas c** systems.

Summary

Lithium measurements, performed with this assay in human serum and plasma, are used in monitoring lithium levels to ensure appropriate therapy.

Lithium is a monovalent cation administered in oral formulations as carbonate or citrate salt. It is a mood-stabilizing agent indicated to treat manic episodes, bipolar disorder and is also useful as an adjunct for refractory depression and to control aggressive behavior or intentional self-harm.[1,2,3,4,5] The precise mechanism of action of lithium as a mood-stabilizing agent remains unknown, although many cellular actions of lithium have been characterized. It is believed that lithium can modulate several neurochemical systems, through ion channels, neurotransmitters (serotonin, dopamine and norepinephrine) and second messengers such as phosphoinositides and cyclic AMP (cAMP). It has been found to also influence brain glycogen synthase kinase 3β (GSK3-β), an enzyme that appears critical in the action of dopamine and serotonin in affecting behavior.[1,6]

A major cause of relapse for bipolar disorder patients is often nonadherence to the treatment.[7]

Serum lithium concentrations are measured essentially to ensure treatment adherence and to avoid toxicity. Since toxic serum concentrations of lithium are closely related to therapeutic serum lithium concentrations, clinicians are advised to ensure that facilities are available for rapid and accurate assessment of lithium concentrations when considering treatment. Some patients may be abnormally sensitive to lithium and exhibit toxic signs at concentrations within the therapeutic range. Patients should be monitored for signs and symptoms of lithium toxicity, including renal and thyroid toxicity, throughout treatment.[1,2,3,7,8,9,10,11,12,13] Early symptoms of intoxication include apathy, sluggishness, drowsiness, lethargy, speech difficulties, irregular tremors, myoclonic twitchings, muscle weakness and ataxia.[5]

Lithium is cleared through the kidneys, therefore reduced renal function can prolong clearance time and elderly patients as well as patients with renal impairment may have increased elimination half-life.[1,2,3,10] Lithium levels must be closely monitored in patients with mild and moderate renal insufficiency and the dose adjusted accordingly.[2]

In the diagnostic laboratory, lithium has traditionally been measured using either flame emission photometry, atomic absorption spectrometry, or ion selective electrodes. These methods require specific and often dedicated instrumentation. This lithium test is a colorimetric method.[14]

Test principle[14]

Colorimetric test.

Lithium present in the sample reacts with a substituted porphyrin compound at an alkaline pH, resulting in a change in absorbance which is directly proportional to the concentration of lithium in the sample.

Reagents - working solutions

R1 Sodium hydroxide: 0.5 mol/L; EDTA: 50 µmol/L; substituted porphyrin: 15 µmol/L; preservative; detergent

R1 is in position B.

Precautions and warnings

For in vitro diagnostic use for health care professionals. Exercise the normal precautions required for handling all laboratory reagents.

Infectious or microbial waste:
Warning: handle waste as potentially biohazardous material. Dispose of waste according to accepted laboratory instructions and procedures.

Environmental hazards:
Apply all relevant local disposal regulations to determine the safe disposal.

Safety data sheet available for professional user on request.

This kit contains components classified as follows in accordance with the Regulation (EC) No. 1272/2008:

Danger

H290	May be corrosive to metals.
H314	Causes severe skin burns and eye damage.

Prevention:

P280	Wear protective gloves/ protective clothing/ eye protection/ face protection/ hearing protection.

Response:

P301 + P330 + P331	IF SWALLOWED: Rinse mouth. Do NOT induce vomiting.
P303 + P361 + P353	IF ON SKIN (or hair): Take off immediately all contaminated clothing. Rinse skin with water.
P304 + P340 + P310	IF INHALED: Remove person to fresh air and keep comfortable for breathing. Immediately call a POISON CENTER/ doctor.

LI

Lithium

P305 + P351 + P338 + P310	IF IN EYES: Rinse cautiously with water for several minutes. Remove contact lenses, if present and easy to do. Continue rinsing. Immediately call a POISON CENTER/ doctor.
P390	Absorb spillage to prevent material damage.

Product safety labeling follows EU GHS guidance.

Contact phone: all countries: +49-621-7590

Reagent handling

Ready for use

Storage and stability

Shelf life at 2-8 °C:	See expiration date on **cobas c** pack label.
On-board in use and refrigerated on the analyzer:	4 weeks

Specimen collection and preparation[15,16,17]

For specimen collection and preparation only use suitable tubes or collection containers.

Only the specimens listed below were tested and found acceptable.
Serum.
Plasma: K_2-EDTA and Na-heparin plasma.

Do not use lithium heparinized plasma.

The specimen should be separated from cells if storage for more than 4 hours is anticipated.

The sample types listed were tested with a selection of sample collection tubes that were commercially available at the time of testing, i.e. not all available tubes of all manufacturers were tested. Sample collection systems from various manufacturers may contain differing materials which could affect the test results in some cases. When processing samples in primary tubes (sample collection systems), follow the instructions of the tube manufacturer.

Centrifuge samples containing precipitates before performing the assay.

See the limitations and interferences section for details about possible sample interferences.

Stability:[16]	1 day at 15-25 °C
	7 days at 2-8 °C
	6 months at (-15)-(-25) °C

Freeze only once.

Materials provided

See “Reagents – working solutions” section for reagents.

Materials required (but not provided)

See “Order information” section

General laboratory equipment

Assay

For optimum performance of the assay follow the directions given in this document for the analyzer concerned. Refer to the appropriate operator’s manual for analyzer-specific assay instructions.

The performance of applications not validated by Roche is not warranted and must be defined by the user.

Application for serum and plasma

cobas c 311 **test definition**

Assay type	1-Point	
Reaction time / Assay points	10 / 7	
Wavelength (sub/main)	480/505 nm	
Reaction direction	Decrease	
Unit	mmol/L (mg/dL)	
Reagent pipetting		Diluent
R1	100 µL	-
R2	-	-

Sample volumes	*Sample*	*Sample dilution*	
		Sample	Diluent (H_2O)
Normal	4 µL	5 µL	100 µL
Decreased	2 µL	5 µL	100 µL
Increased	4 µL	5 µL	100 µL

cobas c 501 **test definition**

Assay type	1-Point	
Reaction time / Assay points	10 / 11	
Wavelength (sub/main)	480/505 nm	
Reaction direction	Decrease	
Unit	mmol/L (mg/dL)	
Reagent pipetting		Diluent
R1	100 µL	-
R2	-	-

Sample volumes	*Sample*	*Sample dilution*	
		Sample	Diluent (H_2O)
Normal	4 µL	5 µL	100 µL
Decreased	2 µL	5 µL	100 µL
Increased	4 µL	5 µL	100 µL

cobas c 502 **test definition**

Assay type	1-Point	
Reaction time / Assay points	10 / 11	
Wavelength (sub/main)	480/505 nm	
Reaction direction	Decrease	
Unit	mmol/L (mg/dL)	
Reagent pipetting		Diluent
R1	100 µL	-
R2	-	-

Sample volumes	*Sample*	*Sample dilution*	
		Sample	Diluent (H_2O)
Normal	4 µL	5 µL	100 µL
Decreased	2 µL	5 µL	100 µL
Increased	4 µL	10 µL	100 µL

Calibration

Calibrators	S1: H_2O
	S2: C.f.a.s.
Calibration mode	Linear
Calibration frequency	2-point calibration • every 7 days on-board • after **cobas c** pack change • after reagent lot change • as required following quality control procedures

Calibration interval may be extended based on acceptable verification of calibration by the laboratory.

Traceability: The lithium calibrator C.f.a.s. is traceable against AAS.

LI

Lithium

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Quality control

For quality control, use control materials as listed in the "Order information" section.

In addition, other suitable control material can be used.

The control intervals and limits should be adapted to each laboratory's individual requirements. Values obtained should fall within the defined limits. Each laboratory should establish corrective measures to be taken if values fall outside the defined limits.

Follow the applicable government regulations and local guidelines for quality control.

Calculation

cobas c systems automatically calculate the analyte concentration of each sample.

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

Limitations – interference

Criterion: Recovery within ± 10 % of initial values at therapeutic concentrations.[18]

Icterus:[19] No significant interference up to an I index of 43 for conjugated and 37 for unconjugated bilirubin (approximate conjugated bilirubin concentration: 735 µmol/L or 43 mg/dL and approximate unconjugated bilirubin concentration: 633 µmol/L or 37 mg/dL).

Hemolysis:[19] No significant interference up to an H index of 1000 (approximate hemoglobin concentration: 621 µmol/L or 1000 mg/dL).

Lipemia (Intralipid):[19] No significant interference up to an L index of 2000. There is poor correlation between the L index (corresponds to turbidity) and triglycerides concentration.

Drugs: No interference was found at therapeutic concentrations using common drug panels.[20,21]

Key interferences:

Criterion: Recovery within ± 5 % of initial values at therapeutic concentrations.[20]

NH_4Cl (19.8 µmol/L), NaCl (140 mmol/L), KCl (4 mmol/L),

$CaCl_2$ (2.4 mmol/L), $MgCl_2$ (0.9 mmol/L), $FeCl_3$ (1.04 mg/L),

$Cu(NO_3)_2$ (1.15 mmol/L), $ZnCl_2$ (1.07 mmol/L).

No significant interference was found in the physiological key interference range.

In very rare cases, gammopathy, in particular type IgM (Waldenström's macroglobulinemia), may cause unreliable results.[22]

For diagnostic purposes, the results should always be assessed in conjunction with the patient's medical history, clinical examination and other findings.

ACTION REQUIRED

Special Wash Programming: The use of special wash steps is mandatory when certain test combinations are run together on **cobas c** systems. The latest version of the carry-over evasion list can be found with the NaOHD-SMS-SmpCln1+2-SCCS Method Sheets. For further instructions refer to the operator's manual. **cobas c** 502 analyzer: All special wash programming necessary for avoiding carry-over is available via the **cobas** link, manual input is required in certain cases.

Where required, special wash/carry-over evasion programming must be implemented prior to reporting results with this test.

Limits and ranges

Measuring range

0.05-3.00 mmol/L (0.03-2.08 mg/dL)

Determine samples having higher concentrations via the rerun function. Dilution of samples via the rerun function is a 1:2 dilution. Results from samples diluted using the rerun function are automatically multiplied by a factor of 2.

Lower limits of measurement

Limit of Blank and Limit of Detection

Limit of Blank:	= 0.03 mmol/L (0.02 mg/dL)
Limit of Detection:	= 0.05 mmol/L (0.03 mg/dL)

The Limit of Blank and Limit of Detection were determined in accordance with the CLSI (Clinical and Laboratory Standards Institute) EP17-A requirements.

The Limit of Blank is the 95th percentile value from n ≥ 60 measurements of analyte-free samples over several independent series. The Limit of Blank corresponds to the concentration below which analyte-free samples are found with a probability of 95 %.

The Limit of Detection is determined based on the Limit of Blank and the standard deviation of low concentration samples.

The Limit of Detection corresponds to the lowest analyte concentration which can be detected (value above the Limit of Blank with a probability of 95 %).

Values below the Limit of Detection (< 0.05 mmol/L or 0.03 mg/dL) will not be flagged by the instrument.

Expected values

Lithium[18]	Therapeutic conc.:	0.6-1.2 mmol/L (0.42-0.83 mg/dL)
	Toxic range:	> 2.0 mmol/L (> 1.39 mg/dL)

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

Expected values reflect the data and information provided in the reference and do not necessarily represent therapeutic recommendations and/or dosage instructions. For therapeutic recommendations and dosage instructions refer to applicable guidelines and the full prescription information of the drug.

Specific performance data

Representative performance data on the analyzers are given below. Results obtained in individual laboratories may differ.

Precision

Precision was determined using human samples and controls in an internal protocol with repeatability (n = 21) and intermediate precision (3 aliquots per run, 1 run per day, 21 days). The following results were obtained on the **cobas c** 501 analyzer:

Repeatability	*Mean*	*SD*	*CV*
	mmol/L (mg/dL)	*mmol/L (mg/dL)*	*%*
Precinorm U	0.77 (0.534)	0.01 (0.007)	1.7
Precipath U	2.38 (1.65)	0.02 (0.01)	1.0
Human serum 1	0.46 (0.319)	0.01 (0.007)	1.9
Human serum 2	1.40 (0.972)	0.02 (0.014)	1.2

Intermediate precision	*Mean*	*SD*	*CV*
	mmol/L (mg/dL)	*mmol/L (mg/dL)*	*%*
Precinorm U	0.79 (0.548)	0.02 (0.014)	2.2
Precipath U	2.42 (1.68)	0.03 (0.02)	1.3
Human serum 1	0.64 (0.444)	0.01 (0.007)	2.3
Human serum 2	1.62 (1.12)	0.03 (0.02)	1.6

The data obtained on **cobas c** 501 analyzer(s) are representative for **cobas c** 311 analyzer(s).

Method comparison

Lithium values for human serum samples obtained with the lithium reagent on a **cobas c** 501 analyzer (y) were compared with those determined using the corresponding reagent on a Roche/Hitachi 917 analyzer (x).

Sample size (n) = 50

Passing/Bablok[23]	Linear regression
y = 1.034x - 0.013	y = 1.032x - 0.016
τ = 0.959	r = 0.996

The sample concentrations were between 0.434 and 1.36 mmol/L (0.301 and 0.944 mg/dL).

Lithium values for human serum samples obtained with the lithium reagent on a **cobas c** 501 analyzer (y) were compared with those determined using the lithium ion-selective electrode on a COBAS INTEGRA 400 analyzer (x).

Sample size (n) = 78

Passing/Bablok[23]	Linear regression
y = 0.989x + 0.037	y = 0.961x + 0.060
τ = 0.958	r = 0.998

The sample concentrations were between 0.120 and 3.35 mmol/L (0.083 and 2.323 mg/dL).

The data obtained on **cobas c** 501 analyzer(s) are representative for **cobas c** 311 analyzer(s).

References

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A point (period/stop) is always used in this Method Sheet as the decimal separator to mark the border between the integral and the fractional parts of a decimal numeral. Separators for thousands are not used.

Any serious incident that has occurred in relation to the device shall be reported to the manufacturer and the competent authority of the Member State in which the user and/or the patient is established.

The Summary of Safety & Performance Report can be found here: https://ec.europa.eu/tools/eudamed

Symbols

Roche Diagnostics uses the following symbols and signs in addition to those listed in the ISO 15223-1 standard:

CONTENT	Contents of kit
→	Volume for reconstitution
GTIN	Global Trade Item Number
Rx only	For USA: Caution: Federal law restricts this device to sale by or on the order of a physician.

CE 0123

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