Elecsys Digoxin

cobas®

REF		Σ	SYSTEM
			cobas e 411
11820796190	11820796500	100	**cobas e** 601
			cobas e 602

English

System information

For **cobas e** 411 analyzer: test number 620
For **cobas e** 601 and **cobas e** 602 analyzers: Application Code Number 115

Intended use

Immunoassay for the in vitro quantitative determination of digoxin in human serum and plasma. Measurements are used in the diagnosis and treatment of digoxin overdose and in monitoring levels of digoxin to ensure proper therapy.

The **e**lectro**c**hemi**l**uminescence **i**mmuno**a**ssay "ECLIA" is intended for use on Elecsys and **cobas e** immunoassay analyzers.

Summary

Digoxin is a widely prescribed steroidal cardio-active glycoside. It acts by binding and inhibiting the Na^+/K^+-ATPase which in the end increases the intracellular Ca^{2+} concentration.[1,2] This results in a positive inotrope effect which makes digoxin a beneficial drug for heart failure. It improves the strength of myocardial contraction and results in the beneficial effects of increased cardiac output, increased Left Ventricular Ejection Fraction, and decreased Pulmonary Capillary Wedge pressure.[3,4] Digoxin therapy also results in stabilized and slowed ventricular pulse rate.[5]

Although the availability of crystalline digoxin has permitted the standardization of drug dosage, therapeutic administration inadvertently, yet frequently, results in toxicity. Importantly, symptoms of digoxin toxicity often mimic the cardiac arrhythmias for which the drug was originally prescribed. Digoxin concentrations of 0.9-2.0 ng/mL in serum or plasma were considered to be therapeutic.[6,7] However, later studies observed an increased risk for mortality for digoxin concentrations of 1.2 ng/mL and higher.[8,9] The 2013 AHA/ACC guidelines mentioned that doses of digoxin that achieve a plasma concentration of drug in the range of 0.5 to 0.9 ng/mL are suggested, given the limited evidence currently available and that overt digoxin toxicity is commonly associated with serum digoxin levels > 2 ng/mL.[10]

Toxicity of digoxin may reflect several factors:

1. The drug has a low therapeutic ratio (i.e. a very small difference exists between therapeutic and toxic tissue levels);
2. Individuals vary in their response to digoxin;
3. Absorption of various tablet forms of digoxin may vary over a two-fold range;[11,12]
4. Susceptibility to digitalis toxicity apparently increases with age mainly associated with renal impairment.[4,13]

In combination with other clinical data, monitoring serum or plasma levels may provide the physician with useful information to aid in adjusting patient dosage, and achieving optimal therapeutic effect, while avoiding both subtherapeutic and harmful toxic drug levels.[14]

The Elecsys Digoxin assay employs a competitive test principle using a monoclonal antibody specifically directed against digoxin. Digoxin in the sample competes with the added digoxin derivative labeled with biotin for the binding sites on the ruthenylated antibody-complex[a].

a) Tris(2,2'-bipyridyl)ruthenium(II)-complex ($Ru(bpy)_3^{2+}$)

Test principle

Competition principle. Total duration of assay: 18 minutes.

- 1st incubation: By incubating the sample (10 µL) with a digoxin-specific ruthenium-labeled antibody, an immunocomplex is formed, the amount of which is dependent upon the analyte concentration in the sample.
- 2nd incubation: After addition of streptavidin-coated microparticles and a digoxin derivative labeled with biotin, the still-vacant sites of the ruthenium labeled antibodies become occupied, with formation of an antibody-hapten complex. The entire complex becomes bound to the solid phase via interaction of biotin and streptavidin.
- The reaction mixture is aspirated into the measuring cell where the microparticles are magnetically captured onto the surface of the electrode. Unbound substances are then removed with ProCell/ProCell M. Application of a voltage to the electrode then induces chemiluminescent emission which is measured by a photomultiplier.
- Results are determined via a calibration curve which is instrument-specifically generated by 2-point calibration and a master curve provided via the reagent barcode or e-barcode.

Reagents - working solutions

The reagent rackpack is labeled as DIGO.

M Streptavidin-coated microparticles (transparent cap), 1 bottle, 6.5 mL:
Streptavidin-coated microparticles 0.72 mg/mL; preservative.

R1 Anti-digoxin-Ab~$Ru(bpy)_3^{2+}$ (gray cap), 1 bottle, 10 mL:
Monoclonal anti-digoxin antibody (mouse) labeled with ruthenium complex 15 µg/L; phosphate buffer 100 mmol/L, pH 7.0; preservative.

R2 Digoxin-derivative~biotin (black cap), 1 bottle, 10 mL:
Biotinylated digoxigenin 1.06 ng/mL; biotin 15 µg/L; phosphate buffer 100 mmol/L, pH 7.0; preservative.

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:

Warning

H317	May cause an allergic skin reaction.
Prevention:	
P261	Avoid breathing dust/fume/gas/mist/vapours/spray.
P272	Contaminated work clothing should not be allowed out of the workplace.
P280	Wear protective gloves.
Response:	
P333 + P313	If skin irritation or rash occurs: Get medical advice/attention.
P362 + P364	Take off contaminated clothing and wash it before reuse.
Disposal:	
P501	Dispose of contents/container to an approved waste disposal plant.

Product safety labeling follows EU GHS guidance.

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

Avoid foam formation in all reagents and sample types (specimens, calibrators and controls).

Reagent handling

The reagents in the kit have been assembled into a ready-for-use unit that cannot be separated.

All information required for correct operation is read in from the respective reagent barcodes.

Storage and stability

Store at 2-8 °C.

Do not freeze.

Store the Elecsys reagent kit **upright** in order to ensure complete availability of the microparticles during automatic mixing prior to use.

Stability:	
unopened at 2-8 °C	up to the stated expiration date
after opening at 2-8 °C	12 weeks
on the analyzers	8 weeks

Specimen collection and preparation

Blood samples for digoxin analyses should be collected at trough levels which is just prior to the next drug dose or at least 12 hours, and preferably 24 hours after the previous digoxin dose. Considering a blood elimination half-life of 1.5 days for digoxin, steady state blood concentrations require approximately 1 week after initiation of therapy – or longer in case of abnormal kidney function.[15]

Only the specimens listed below were tested and found acceptable.

Serum collected using standard sampling tubes or tubes containing separating gel.

Li-heparin, K_2-EDTA and K_3-EDTA plasma. Li-heparin plasma tubes containing separating gel can be used.

Criterion: Slope 0.9-1.1 + intercept within < ± 1x Limit of Blank + coefficient of correlation ≥ 0.95.

Stable for 7 days at 15-25 °C, 14 days at 2-8 °C, 6 months at -20 °C (± 5 °C). Freeze only once.

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.

Heat-inactivated serum can be used.

Ensure the samples, calibrators and controls are at 20-25 °C prior to measurement.

Due to possible evaporation effects, samples, calibrators and controls on the analyzers should be analyzed/measured within 2 hours.

Materials provided

See "Reagents – working solutions" section for reagents.

Materials required (but not provided)

- REF 11820907322, Digoxin CalSet, 4 x 1.5 mL
- REF 04917049190, PreciControl Cardiac II, for 4 x 2.0 mL
- REF 11732277122, Diluent Universal, 2 x 16 mL sample diluent or
  REF 03183971122, Diluent Universal, 2 x 36 mL sample diluent
- General laboratory equipment
- **cobas e** analyzer

Additional materials for the **cobas e** 411 analyzer:

- REF 11662988122, ProCell, 6 x 380 mL system buffer
- REF 11662970122, CleanCell, 6 x 380 mL measuring cell cleaning solution
- REF 11930346122, Elecsys SysWash, 1 x 500 mL washwater additive
- REF 11933159001, Adapter for SysClean
- REF 11706802001, AssayCup, 60 x 60 reaction cups
- REF 11706799001, AssayTip, 30 x 120 pipette tips
- REF 11800507001, Clean-Liner

Additional materials for **cobas e** 601 and **cobas e** 602 analyzers:

- REF 04880340190, ProCell M, 2 x 2 L system buffer
- REF 04880293190, CleanCell M, 2 x 2 L measuring cell cleaning solution
- REF 03023141001, PC/CC-Cups, 12 cups to prewarm ProCell M and CleanCell M before use
- REF 03005712190, ProbeWash M, 12 x 70 mL cleaning solution for run finalization and rinsing during reagent change
- REF 03004899190, PreClean M, 5 x 600 mL detection cleaning solution
- REF 12102137001, AssayTip/AssayCup, 48 magazines x 84 reaction cups or pipette tips, waste bags
- REF 03023150001, WasteLiner, waste bags
- REF 03027651001, SysClean Adapter M

Additional materials for all analyzers:

- REF 11298500316, ISE Cleaning Solution/Elecsys SysClean, 5 x 100 mL system cleaning solution

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.

cobas e 601 and **cobas e** 602 analyzers: PreClean M solution is necessary.

Resuspension of the microparticles takes place automatically prior to use. Read in the test-specific parameters via the reagent barcode. If in exceptional cases the barcode cannot be read, enter the 15-digit sequence of numbers.

Bring the cooled reagents to approximately 20 °C and place on the reagent disk (20 °C) of the analyzer. Avoid foam formation. The system automatically regulates the temperature of the reagents and the opening/closing of the bottles.

Calibration

Traceability: This method has been standardized by weighing United States Pharmacopoeia (USP) digoxin reference material into analyte free human serum.

Every Elecsys reagent set has a barcoded label containing specific information for calibration of the particular reagent lot. The predefined master curve is adapted to the analyzer using the relevant CalSet.

Calibration frequency: Calibration must be performed once per reagent lot using fresh reagent (i.e. not more than 24 hours since the reagent kit was registered on the analyzer).

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

Renewed calibration is recommended as follows:

- after 1 month (28 days) when using the same reagent lot
- after 7 days (when using the same reagent kit on the analyzer)
- as required: e.g. quality control findings outside the defined limits

Quality control

For quality control, use PreciControl Cardiac II.

In addition, other suitable control material can be used.

Controls for the various concentration ranges should be run individually at least once every 24 hours when the test is in use, once per reagent kit, and following each calibration.

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.

If necessary, repeat the measurement of the samples concerned.

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

Calculation

The analyzer automatically calculates the analyte concentration of each sample (either in nmol/L or ng/mL).

Conversion factors: nmol/L x 0.78 = ng/mL
ng/mL x 1.28 = nmol/L

Limitations - interference

The effect of the following endogenous substances and pharmaceutical compounds on assay performance was tested. Interferences were tested up to the listed concentrations and no impact on results was observed.

Endogenous substances

Compound	Concentration tested
Bilirubin	≤ 1129 µmol/L or ≤ 66 mg/dL
Hemoglobin	≤ 0.621 mmol/L or ≤ 1000 mg/dL
Intralipid	≤ 1500 mg/dL
Biotin	≤ 409 nmol/L or ≤ 100 ng/mL
Rheumatoid factors	≤ 1630 IU/mL
IgG	≤ 7.00 g/dL
Albumin	≤ 7.00 g/dL

Criterion: For concentrations ≤ 0.8 ng/mL (≤ 1.02 nmol/L) the deviation is ≤ ± 0.08 ng/mL (± 0.10 nmol/L). For concentrations > 0.8-4.0 ng/mL (> 1.02-5.12 nmol/L) the deviation is ≤ 10 %. For concentrations > 4.0 ng/mL (> 5.12 nmol/L) the deviation is ≤ 12 %.

Samples should not be taken from patients receiving therapy with high biotin doses (i.e. > 5 mg/day) until at least 8 hours following the last biotin administration.

Pharmaceutical substances

In vitro tests were performed on 16 commonly used pharmaceuticals. No interference with the assay was found.

In addition, the following special cardiac drugs were tested. No interference with the assay was found.

Special cardiac drugs

Drug	Concentration tested mg/L
Carvedilol	37.5
Clopidogrel	75.0
Epinephrine (adrenaline)	0.50
Insulin	1.60
Lidocaine	80.0
Lisinopril	10.0
Methylprednisolone	7.50
Metoprolol	150
Nifedipine	30.0
Phenprocoumon	3.00
Propafenone	300
Reteplase	33.3
Simvastatin	30.0
Spironolactone	15.0
Tolbutamide	1500
Torasemide	15.0
Verapamil	240

Spironolactone was identified to cause falsely elevated digoxin values when exceeding the concentration mentioned in the table above.

Hydrocortisone was identified to cause falsely elevated digoxin values above (drug) levels of 10 mg/L.

Uzara, nabumetone, pentoxifylline and canrenone were identified to cause falsely elevated digoxin values at concentrations of the recommended daily dose.

Digoxin-like immunoreactive substances (DLIS) have been identified in blood from patients in renal failure, liver failure, and pregnant women in their third trimester. Studies have shown that the presence of DLIS in a sample can result in a false elevation of digoxin when assayed by commercially available immunoassays.[16,17,18]

As stated by the manufacturers of digitalis antidotes, the therapeutic antibody fragments against digitalis (e.g. DigiFab, DigiBind) will interfere with digitalis immunoassay measurements.[19] Therefore, the manufacturer of DigiFab recommends to obtain samples for determination of digoxin concentration prior to antidote administration.[19] As a consequence Elecsys Digoxin concentrations may be falsely elevated if measured in the presence of the antidote until the Fab fragments are eliminated from the body.[19]

In rare cases, interference due to extremely high titers of antibodies to analyte-specific antibodies, streptavidin or ruthenium can occur. These effects are minimized by suitable test design.

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

Limits and ranges

Measuring range

0.2-5.0 ng/mL or 0.26-6.4 nmol/L (defined by the Limit of Detection and the maximum of the master curve). Values below the Limit of Detection are reported as < 0.2 ng/mL or < 0.26 nmol/L. Values above the measuring range are reported as > 5.0 ng/mL or > 6.4 nmol/L (or up to 10.0 ng/mL or 12.8 nmol/L for 2-fold diluted samples).

Lower limits of measurement

Limit of Blank, Limit of Detection and Limit of Quantitation

Limit of Blank = 0.15 ng/mL (0.19 nmol/L)

Limit of Detection = 0.2 ng/mL (0.26 nmol/L)

Limit of Quantitation = 0.4 ng/mL (0.51 nmol/L)

The Limit of Blank, Limit of Detection and Limit of Quantitation were determined in accordance with the CLSI (Clinical and Laboratory Standards Institute) EP17-A2 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 %).

The Limit of Quantitation is defined as the lowest amount of analyte in a sample that can be accurately quantitated with a total allowable error of ≤ 20 %.

Dilution

Samples with digoxin concentrations above the measuring range can be diluted with Diluent Universal. The recommended dilution is 1:2 (either automatically by the analyzers or manually). The concentration of the diluted sample must be > 2.5 ng/mL or > 3.2 nmol/L.

After manual dilution, multiply the result by the dilution factor.

After dilution by the analyzers, the software automatically takes the dilution into account when calculating the sample concentration.

Expected values

The recommended therapeutic range for digoxin is 0.6-1.2 ng/mL (0.77-1.5 nmol/L) (ESC Guideline 2008[20]) or even 0.5-1.0 ng/mL (0.64-1.3 nmol/L).[21] Particularly the upper end of the therapeutic range is controversial and concentrations up to 2.0 ng/mL (2.6 nmol/L) may still be applied.[6,7] Concentrations > 2.0 ng/mL are generally considered toxic.[10,22]

Therefore, clinical diagnosis should be based on clinical and laboratory data. Each laboratory should establish an acceptable reporting format and identify procedures for the reporting of abnormal results.

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

Elecsys Digoxin

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Specific performance data

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

Precision

Precision was determined using Elecsys reagents, samples and controls in a protocol (EP05-A3) of the CLSI (Clinical and Laboratory Standards Institute): 2 runs per day in duplicate each for 21 days (n = 84). The following results were obtained:

cobas e 411 analyzer					
		Repeatability		**Intermediate precision**	
Sample	Mean nmol/L	SD nmol/L	CV %	SD nmol/L	CV %
Human serum 1	0.724	0.025	3.4	0.046	6.4
Human serum 2	1.39	0.035	2.5	0.080	5.8
Human serum 3	2.37	0.049	2.1	0.106	4.5
Human serum 4	3.05	0.071	2.3	0.117	3.8
Human serum 5	5.98	0.152	2.5	0.382	6.4
PC[b)] CARDII1	1.54	0.045	2.9	0.066	4.3
PC CARDII2	3.51	0.131	3.7	0.143	4.1

b) PC = PreciControl

cobas e 411 analyzer					
		Repeatability		**Intermediate precision**	
Sample	Mean ng/mL	SD ng/mL	CV %	SD ng/mL	CV %
Human serum 1	0.565	0.019	3.4	0.036	6.4
Human serum 2	1.09	0.027	2.5	0.063	5.8
Human serum 3	1.85	0.039	2.1	0.083	4.5
Human serum 4	2.38	0.055	2.3	0.092	3.8
Human serum 5	4.67	0.119	2.5	0.299	6.4
PC CARDII1	1.20	0.035	2.9	0.051	4.3
PC CARDII2	2.74	0.102	3.7	0.111	4.1

cobas e 601 and **cobas e** 602 analyzers					
		Repeatability		**Intermediate precision**	
Sample	Mean nmol/L	SD nmol/L	CV %	SD nmol/L	CV %
Human serum 1	0.712	0.045	6.3	0.058	8.2
Human serum 2	1.36	0.038	2.8	0.058	4.3
Human serum 3	2.33	0.058	2.5	0.084	3.6
Human serum 4	2.94	0.069	2.4	0.111	3.8
Human serum 5	5.49	0.147	2.7	0.276	5.0
PC CARDII1	1.55	0.037	2.4	0.056	3.6
PC CARDII2	3.50	0.047	1.3	0.082	2.3

cobas e 601 and **cobas e** 602 analyzers					
		Repeatability		**Intermediate precision**	
Sample	Mean ng/mL	SD ng/mL	CV %	SD ng/mL	CV %
Human serum 1	0.556	0.035	6.3	0.046	8.2
Human serum 2	1.07	0.030	2.8	0.045	4.3
Human serum 3	1.82	0.045	2.5	0.066	3.6
Human serum 4	2.29	0.054	2.4	0.087	3.8
Human serum 5	4.29	0.115	2.7	0.216	5.0
PC CARDII1	1.21	0.029	2.4	0.044	3.6
PC CARDII2	2.74	0.037	1.3	0.064	2.3

Analytical specificity

For the Co-analytes tested, the following relative Co-analyte reactivities were found:

Co-analyte	**Concentration ED50 ng/mL**	**Relative Co-analyte reactivity %**
α-acetyldigoxin	1.18	77.9
β-acetyldigoxin	1.09	84.4
β-methyldigoxin	1.05	87.9
Lanatoside C	1.31	65.2
Deslanoside	1.08	85.6
Digoxigenin-bis-digitoxoside	0.853	108
Digoxigenin-mono-digitoxoside	0.603	141

For the substances tested, the following cross-reactivities were found:

Substances	**Concentration tested ng/mL**	**Cross-reactivity %**
Digitoxin	250	0.522
Digitoxigenin	250	0.529
Digoxigenin	6.00	31.3
Dihydrodigoxin	1000	0.201
K-strophanthine	1250	0.137

No significant cross-reactivity (< 0.01 %) was found for the following substances (tested concentration 5000 ng/mL; 10000 ng/mL for Cortisol):

Cortisol, prednisone, β-estradiol, d-aldosterone, DHEA, dexamethasone, furosemide, sulthiame, quinidine (free base) and oleandrin. For testosterone and ouabain a cross-reactivity of < 0.1 % was found at 5000 ng/mL. For progesterone a cross-reactivity of < 0.05 % was found at 5000 ng/mL.

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For further information, please refer to the appropriate operator's manual for the analyzer concerned, the respective application sheets, the product information and the Method Sheets of all necessary components (if available in your country).

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 (for USA: see dialog.roche.com for definition of symbols used):

CONTENT	Contents of kit
SYSTEM	Analyzers/Instruments on which reagents can be used
REAGENT	Reagent
CALIBRATOR	Calibrator
→	Volume after reconstitution or mixing
GTIN	Global Trade Item Number

CE 0123

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