Elecsys Cyclosporine

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REF		Σ	SYSTEM
07251246190	07251246500	300	**cobas e** 402 **cobas e** 801

English

System information

Short name	ACN (application code number)
CSA	10109

Intended use

Immunoassay for the in vitro quantitative determination of cyclosporine in human whole blood. The assay is used as an aid in the management of heart, liver, kidney, lung and bone marrow transplant patients receiving cyclosporine therapy.

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

Summary

Cyclosporine is a cyclic undecapeptide of fungal origin and a potent immunosuppressive agent. The introduction of cyclosporine in human kidney transplantation in the late 1970s was a major step forward in transplantation medicine, and substantially improved patient and graft survival in patients receiving e.g. heart, kidney, liver, pancreas, lung or bone marrow transplants.[1,2,3]

Cyclosporine was the first drug identified to specifically and reversibly inhibit the activation and proliferation of lymphocytes and represents the prototype of a class of drugs called calcineurin inhibitors.[4]

The main mechanism through which cyclosporine exerts its immunosuppressive effect is believed to be via the inhibition of T cell activation and proliferation. Intracellular cyclosporine binds to both cyclophilin A and B and these complexes then inhibit the enzymatic activity of calcineurin.[3,5,6]

The inhibition of calcineurin restricts the dephosphorylation and nuclear translocation of nuclear factor of activated T cells (NFAT), which regulates transcription of several cytokines, including IL-2, IL-4, TNF-α, and interferon-γ, and therefore limits lymphocyte activation and proliferation.[7,8,9,10,11,12]

Cyclosporine is highly lipophilic and absorption from the gastrointestinal tract is incomplete and variable. Approximately 90 % of the cyclosporine within the plasma is bound to proteins.[13]

The bioavailability and metabolism of cyclosporine are predominantly influenced by the activity of the cytochrome P450 isozymes CYP3A4 and CYP3A5, as well as the efflux pump p-glycoprotein, which show significant inter- and intra-individual variability in expression and function.[14,15,16]

Cyclosporine displays significant inter- and intra-patient pharmacokinetic variability, as well as potentially severe side effects from doses that are either too low or too high. Inadequate cyclosporine concentrations might result in rejection of the transplanted organ. High levels may lead to severe adverse effects. The most significant and well recognized side effect of cyclosporine therapy is nephrotoxicity, which can manifest as both reversible acute manifestations and as irreversible chronic manifestations.[3,17] The use of cyclosporine is also associated with renal dysfunction, tremor, hirsutism, hypertension, and gum hyperplasia.[13]

Therefore the application of therapeutic drug monitoring (TDM) and concentration-controlled dosing in order to maintain each patient's drug exposure within a narrow therapeutic window is clearly required and part of standard clinical practice for many years.[18,19,20]

Monitoring is most effective when there is a measurement that is a good surrogate for total drug exposure (measured as area under the time-concentration curve AUC 0-12). Advantages of monitoring cyclosporine concentrations based on predose trough (C0) concentrations versus two hours after administration (C2) are still under discussion and more multicenter studies are required to demonstrate a clinical benefit of C2 monitoring.[18,21]

Test principle

Manual precipitation:

Before testing with the Elecsys Cyclosporine assay, samples, calibrators and controls must be **pretreated** with Elecsys ISD Sample Pretreatment.

The reagent lyses the cells, extracts cyclosporine, and precipitates most of the blood proteins. The **pretreated** samples are centrifuged, and an aliquot of the resulting supernatant containing cyclosporine is then assayed using the Elecsys Cyclosporine assay.

Competition principle. Total duration of assay: 18 minutes.

- 1st incubation: 12 µL of pretreated sample is incubated with a cyclosporine-specific biotinylated antibody and a ruthenium complex[a)] labeled cyclosporine-derivate. Depending on the analyte concentration in the sample and the formation of the respective immune complex, the labeled antibody binding site is occupied in part with sample analyte and in part with ruthenylated hapten.
- 2nd incubation: After addition of streptavidin-coated microparticles, the 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 II 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 **cobas** link.

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

Reagents - working solutions

The **cobas e** pack is labeled as CSA.

M Streptavidin-coated microparticles, 1 bottle, 12.4 mL:
Streptavidin-coated microparticles 0.72 mg/mL; preservative.

R1 Anti-cyclosporine Ab~biotin, 1 bottle, 19.7 mL:
Biotinylated monoclonal anti-cyclosporine antibody (mouse) 25 µg/L; phosphate buffer 50 mmol/L, pH 6.0; preservative.

R2 Cyclosporine~$Ru(bpy)_3^{2+}$, 1 bottle, 19.7 mL:
Cyclosporine labeled with ruthenium complex 5 µg/L; phosphate buffer 50 mmol/L, pH 6.0; 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.

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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 available via the **cobas** link.

Storage and stability

Store at 2-8 °C.

Do not freeze.

Store the **cobas e** pack **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
on the analyzers	16 weeks

Specimen collection and preparation

Only the specimens listed below were tested and found acceptable.

K_2-EDTA and K_3-EDTA whole blood.

Specimens collected in EDTA tubes may be stored for up to 5 days at 15-25 °C or 7 days at 2-8 °C prior to being tested. If testing will be delayed by more than 7 days, store frozen at -20 °C (± 5 °C) or lower for up to 6 months. Freeze only once. Specimens must be mixed thoroughly after thawing to ensure consistency of the results.

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.

Mix thawed specimens thoroughly by hand or on a roller mixer or rocker. Visually inspect the specimens. If layering or stratification is observed, continue mixing until specimens are visibly homogeneous.

Do not use heat-inactivated samples.

Do not use samples and controls stabilized with azide.

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

Use caution when handling patient specimens to prevent cross contamination. Use of disposable pipettes or pipette tips is recommended.

Pretreated samples can be stored in closed tubes for up to 4 hours at 20-25 °C.

Due to evaporation effects, pretreated samples should be analyzed/measured within 30 minutes after opening the vials and loading the samples on the analyzer. Avoid delays between loading and measurement to ensure the 30 minute stability of pretreated samples.

A re-run requires repeating of the manual pretreatment procedure.

Materials provided

See "Reagents – working solutions" section for reagents.

Materials required (but not provided)

- REF 05889073190, ISD Sample Pretreatment, 1 x 30 mL
- REF 05889022190, Cyclosporine CalSet, for 6 x 1.0 mL
- REF 05889081190, PreciControl ISD, for 3 x 3.0 mL
- REF 11776576322, CalSet Vials, 2 x 56 empty snap-cap bottles
- REF 07299001190, Diluent Universal, 45.2 mL sample diluent
- General laboratory equipment
- Precision pipettes (use only positive displacement pipettes for ISD Sample Pretreatment reagent handling)
- Microcentrifuge tubes (2.0 mL capacity)
- Microcentrifuge (at least 10000 g)
- Vortex mixer
- Roller mixer or rocker
- **cobas e** analyzer

Additional materials for **cobas e** 402 and **cobas e** 801 analyzers:

- REF 06908799190, ProCell II M, 2 x 2 L system solution
- REF 04880293190, CleanCell M, 2 x 2 L measuring cell cleaning solution
- REF 07485409001, Reservoir Cup, 8 cups to supply ProCell II M and CleanCell M
- REF 06908853190, PreClean II M, 2 x 2 L wash solution
- REF 05694302001, Assay Tip/Assay Cup tray, 6 magazines x 6 magazine stacks x 105 assay tips and 105 assay cups, 3 wasteliners
- REF 07485425001, Liquid Flow Cleaning Cup, 2 adaptor cups to supply ISE Cleaning Solution/Elecsys SysClean for Liquid Flow Cleaning Detection Unit
- REF 07485433001, PreWash Liquid Flow Cleaning Cup, 1 adaptor cup to supply ISE Cleaning Solution/Elecsys SysClean for Liquid Flow Cleaning PreWash Unit
- REF 11298500316, ISE Cleaning Solution/Elecsys SysClean, 5 x 100 mL system cleaning solution

Manual specimen pretreatment

Follow the steps listed below to pretreat calibrators, controls and/or specimens. **The technical notes hereafter, are an essential part of the instructions and must be read thoroughly before completing each step.** Follow steps 1 through 7 to pretreat calibrators, controls and/or specimens.

Steps	Technical notes
1. Equilibrate all reagents, calibrators, controls and specimens to 20-25 °C. Mix all calibrators, controls and specimens gently but thoroughly just before use.	Do not vortex. The liquids may be mixed by hand or on a roller mixer or rocker. The calibrators and controls are a whole-blood hemolysate and may be slightly different in appearance from whole-blood samples.
2. Label one microcentrifuge tube for each calibrator, control and/or specimen to be pretreated.	none
3. Using a precision pipette, transfer 300 µL of each calibrator, control and/or specimen to the appropriately labeled micro-centrifuge tube.	Use a fresh pipette tip for each calibrator, control and/or specimen.
4. Using a precision pipette, add 300 µL of ISD Sample Pretreatment reagent to each microcentrifuge tube. Immediately cap each tube and immediately proceed to step 5.	Note: ISD Sample Pretreatment is highly volatile. Keep tightly closed when not in use to prevent evaporation.

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Steps	Technical notes
5. Vortex each microcentrifuge tube for at least 10 seconds. Failure to perform this step may result in a supernatant that appears red. See step 6, technical note.	Note: Failure to vortex each tube immediately after addition of the ISD Sample Pretreatment reagent will lead to erroneous assay results. Sample and reagent mixture should be completely homogeneous immediately after vortexing. Visual inspection is required.
6. Centrifuge the samples for at least 4 minutes in a micro-centrifuge (≥ 10000 g).	The centrifuged samples should have well-defined pellets and clear supernatant. The supernatant should not appear cloudy or red. If the supernatant is red, discard and replace it with a newly extracted sample.
7. Transfer each supernatant directly into an appropriate vial and immediately cap each vial. The samples are ready to be assayed.	Pretreated samples can be stored in closed tubes for up to 4 hours at 20-25 °C. **Please note:** **Due to evaporation effects, pre-treated samples should be analyzed/measured within 30 minutes after opening the vials and loading the samples on the system. Avoid delays between loading and measurement to ensure the 30 minutes stability of pretreated samples.** **This is supported by running the cyclosporine samples in batch mode:** **Based on average system sample processing time, no more than 35 cyclosporine samples may be loaded per calibrated measuring cell onto the analyzers at the same time.**

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.

Resuspension of the microparticles takes place automatically prior to use.

Place the cooled (stored at 2-8 °C) **cobas e** pack on the reagent manager. Avoid foam formation. The system automatically regulates the temperature of the reagents and the opening/closing of the **cobas e** pack.

Calibration

Traceability: This method has been standardized against reference standards traceable to cyclosporine reference material by weight.

The predefined master curve is adapted to the analyzer using the relevant CalSet.

Cyclosporine CalSet must be pretreated freshly before calibration.

Calibration frequency: Calibration must be performed once per reagent lot using fresh reagent (i.e. not more than 24 hours since the **cobas e** pack 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 12 weeks when using the same reagent lot
- after 28 days when using the same **cobas e** pack on the analyzer
- as required: e.g. quality control findings outside the defined limits

Quality control

For quality control, use PreciControl ISD.

PreciControl ISD must be pretreated freshly before measurement.

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 **cobas e** pack, 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 ng/mL, nmol/L, µg/L).

Conversion factors: ng/mL x 1.0 = µg/L

ng/mL x 0.832 = 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
Albumin	≤ 12.0 g/dL
Bilirubin	≤ 1026 µmol/L or ≤ 60.0 mg/dL
Biotin	≤ 123 nmol/L or ≤ 30.0 ng/mL
Cholesterol	≤ 500 mg/dL
HAMA	≤ 50.0 µg/mL
Hematocrit	15-60 %
IgG	≤ 12.0 g/dL
Intralipid	≤ 1500 mg/dL
Rheumatoid factors	up to 500 IU/mL
Uric acid	≤ 20.0 mg/dL

Criterion: For concentrations of 30.0-90.0 ng/mL the deviation is ≤ 18.0 ng/mL. For concentrations > 90.0 ng/mL the deviation is ≤ 20 %.

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 pharmaceutical compounds. No interference with the assay was found.

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

Special drugs

Drug	Concentration tested
Acyclovir	3.2 µg/mL
Amphotericin B	5.8 µg/mL
Ciprofloxacin	7.4 µg/mL
K_2-EDTA	6 mg/mL
K_3-EDTA	6 mg/mL
Erythromycin	20 mg/dL
Everolimus	60 ng/mL
Fluconazile	30 µg/mL

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Drug	Concentration tested
Flucytosine	40 µg/mL
Gancyclovir	1000 µg/mL
Gentamicin	12 mg/dL
Itraconazole	10 µg/mL
Kanamycin	100 µg/mL
Ketoconazole	50 µg/mL
Lidocaine	6 mg/dL
MPA (mycophenolic acid) glucuronide	1800 µg/mL
Mycophenolic acid	500 µg/mL
Nitrofurantoin	6 µg/mL
Phenobarbital	15 mg/dL
Sirolimus	60 ng/mL
Spectinomycin	100 µg/mL
Sulfomethoxazole	200 µg/mL
Tacrolimus	60 ng/mL
Tobramycin	2 mg/dL
Trimethoprim	40 µg/mL
Vancomycin	6 mg/dL

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

30.0-2000 ng/mL (defined by the Limit of Detection and the maximum of the master curve). Values below the Limit of Detection are reported as < 30.0 ng/mL. Values above the measuring range are reported as > 2000 ng/mL.

Lower limits of measurement

Limit of Blank, Limit of Detection and Limit of Quantitation

Limit of Blank = 20.0 ng/mL

Limit of Detection = 30.0 ng/mL

Limit of Quantitation = 50.0 ng/mL

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 relative error of ≤ 20 %.

Dilution

Samples with cyclosporine concentrations above the measuring range can be manually diluted 1:3 with Diluent Universal prior to the manual pretreatment procedure. The concentration of the diluted sample must be > 500 ng/mL.

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

Expected values

No firm therapeutic range exists for cyclosporine in whole blood. The complexity of the clinical state, individual differences in sensitivity to immunosuppressive and nephrotoxic effects of cyclosporine, coadministration of other immunosuppressants, type of transplant, time post-transplant, and a number of other factors contribute to different requirements for optimal blood levels of cyclosporine. Individual cyclosporine values cannot be used as the sole indicator for making changes in the treatment regimen. Each patient should be thoroughly evaluated clinically before treatment adjustments are made, and each assay user must establish his or her ranges based on clinical experience.

These ranges will vary according to the commercial in vitro diagnostic test used. Ranges must be established for each commercial test used.

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 402 and **cobas e** 801 analyzers					
		Repeatability		**Intermediate precision**	
Sample	Mean ng/mL	SD ng/mL	CV %	SD ng/mL	CV %
HSP[b)] 1	36.2	1.33	3.7	2.22	6.1
HSP 2	213	4.19	2.0	5.91	2.8
HSP 3	472	13.5	2.9	16.3	3.4
HSP 4	1042	22.8	2.2	28.4	2.7
HSP 5	1867	28.2	1.5	38.9	2.1
PreciControl ISD 1	83.9	1.96	2.3	2.87	3.4
PreciControl ISD 2	349	5.63	1.6	7.54	2.2
PreciControl ISD 3	1243	18.8	1.5	22.4	1.8

b) HSP = Human Sample Pool

Method comparison

a) A comparison of the Elecsys Cyclosporine assay, REF 05889014190 (y) with an automated immunoassay (x) using clinical samples gave the following correlations:

Number of samples measured: 339

Passing/Bablok[22]	Weighted linear regression
y = 1.01x - 15.5	y = 0.946x - 8.95
τ = 0.857	r = 0.977

The sample concentrations were between 30.7 and 1770 ng/mL.

b) A comparison of the Elecsys Cyclosporine assay, REF 05889014190 (y) with an LC-MS-MS method (x) using clinical samples gave the following correlations:

Number of samples measured: 352

Passing/Bablok[22]	Weighted linear regression
y = 1.091x + 2.08	y = 1.092x + 1.87
τ = 0.900	r = 0.997

The sample concentrations were between 30.7 and 1912 ng/mL.

c) A comparison of the Elecsys Cyclosporine assay, REF 07251246190 (**cobas e** 801 analyzer; y) with the Elecsys Cyclosporine assay, REF 05889014190 (**cobas e** 601 analyzer; x) gave the following correlations (ng/mL):

Number of samples measured: 157

Passing/Bablok[22]	Linear regression

y = 0.968x - 1.27	y = 0.974x - 2.34
τ = 0.950	r = 0.999

The sample concentrations were between 32.1 and 1976 ng/mL.

d) A comparison of the Elecsys Cyclosporine assay, REF 07251246190 (**cobas e** 402 analyzer; y) with the Elecsys Cyclosporine assay, REF 07251246190 (**cobas e** 801 analyzer; x) gave the following correlations (ng/mL):

Number of samples measured: 148

Passing/Bablok[22]	Linear regression
y = 1.03x + 2.56	y = 1.03x + 0.391
τ = 0.966	r = 1.00

The sample concentrations were between 34.2 and 1906 ng/mL.

Analytical specificity

A study was performed with the Elecsys Cyclosporine assay based on guidance from the CLSI document EP7-A2.

Metabolite	Maximum concentration of metabolite added ng/mL	Cross-reactivity %
AM1	2000	2
AM19	2000	n. d.[c)]
AM1c	2000	n. d.
AM1c9	2000	n. d.
AM4n	2000	2
AM9	2000	6

c) n. d. = not detectable

Cross-reactivity was designated as „not detectable“ if the obtained value was less than the sensitivity of the assay.

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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

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