Elecsys Syphilis

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REF		Σ	SYSTEM
09015051190	09015051500	300	**cobas e** 402 **cobas e** 801

English

System information

Short name	ACN (application code number)
SYPHILIS	10212

Intended use

Immunoassay for the in vitro qualitative determination of total antibodies to *Treponema pallidum* in human serum and plasma. The test is intended as an aid in the diagnosis of syphilis infection.

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

Summary

The Elecsys Syphilis assay is intended to be used as an aid, in conjunction with other laboratory results and clinical information, in the diagnosis of and the screening for *Treponema pallidum* (TP) infection. In addition, the assay is intended to be used for screening as first-line assay of individual human donors of blood, blood components, cells, tissue, and organs, when donor samples are obtained while the donor's heart is still beating and of cadaveric blood specimens (specimens collected post-mortem, non-heart-beating). The use of cadaveric blood specimens has been established according to Paul-Ehrlich-Institut (PEI) recommendation.[1]

Syphilis is caused by the intracellular gram-negative spirochete bacterium *T. pallidum* subspecies pallidum.[2] Syphilis is mainly transmitted sexually, but can also be transmitted from mother to fetus during pregnancy or birth, or rarely via transfusion of blood or blood products or organ transplants.[3,4]

Based on prevalence data from 2009 to 2016, the estimated global prevalence of syphilis in both men and women was 0.5 %, with regional values ranging from 0.1 to 1.6 %, corresponding to 19.9 million syphilis cases.[5] In 2020, WHO estimated 7.1 million new syphilis infections globally.[6] In the US, 133945 cases of all stages of syphilis were reported in 2020. Since reaching a historic low in 2000 and 2001, the rate of primary and secondary syphilis has increased almost every year, increasing 6.8 % during 2019-2020.[7] Certain European countries have also seen increases in the rate of infection and large localized outbreaks.[8] Congenital syphilis is still common in the developing world, as many women do not receive antenatal care or the scheme does not include syphilis screening.[9] The estimated global maternal syphilis prevalence in 2016 was 0.69 %, resulting in 661000 total congenital syphilis cases, including 355000 adverse birth outcomes and 306000 non-clinical congenital syphilis cases (infants without clinical signs born to untreated mothers).[10] WHO and US Preventive Services Task Force recommend that all women be tested at their first antenatal visit and again in the third trimester.[11,12] If they are positive, sexual partners should be evaluated and offered treatment.[13]

Typically, symptoms of syphilis start with a painless ulcer at the site of entry to the body (primary syphilis) followed by a widespread rash as the bacteria disseminate (secondary syphilis). This is followed by a lengthy latent (asymptomatic) period. Eventually, tertiary syphilis ensues, characterized by the development of granulomatous dermal lesions, neurosyphilis, and/or cardiovascular syphilis (which can be fatal).[14] The immune response to *T. pallidum* is the main driver of lesion development.[14] The antibody response is directed not only against antigens specific to *T. pallidum* (treponemal antibodies), but antibodies are also generated against antigens which are not specific (non-treponemal antibodies); for example, antigens released during the cellular damage caused by the organism. Therefore, treponemal and non-treponemal tests co-exist for the diagnosis of syphilis.[2]

Non-treponemal tests detect antibodies against lecithin, cholesterol and cardiolipin, which are present in many syphilis patients.[2] Treponemal tests detect antibodies directed against *T. pallidum* antigens such as TpN47, TpN17 and TpN15, for IgM and IgG detection.[2] The Elecsys Syphilis assay is a treponemal test using recombinant antigens representing the lipoproteins TpN17, TpN15 and TpN47 for the detection of anti-TP antibodies. A positive treponemal antibody test result indicates exposure to *T. pallidum* but cannot distinguish between treated and untreated syphilis. Non-treponemal assays are useful to help distinguish between treated and untreated syphilis and are used for monitoring the progression of disease and treatment response as well.[15]

Treponemal (and/or non-treponemal) tests are furthermore used to screen donors of blood, blood components, cells, tissue, and organs when donor samples are obtained while the donor's heart is still beating, and in testing blood specimens to screen deceased (non-heart-beating) donors.[16,17,18,19,20,21,22,23,24]

Test principle

Sandwich principle. Total duration of assay: 18 minutes.

- 1st incubation: 6 µL of sample, biotinylated TP-specific recombinant antigens and TP-specific recombinant antigens labeled with a ruthenium complex[a)] react to form a sandwich complex.
- 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 automatically by the software by comparing the electrochemiluminescence signal obtained from the reaction product of the sample with the signal of the cutoff value previously obtained by calibration.

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

Reagents - working solutions

The **cobas e** pack (M, R1, R2) is labeled as SYPHILIS.

M Streptavidin-coated microparticles, 1 bottle, 14.1 mL:
Streptavidin-coated microparticles 0.72 mg/mL; preservative.

R1 TP-specific recombinant antigens (E. coli)~biotin, 1 bottle, 19.7 mL:
Biotinylated TP-specific recombinant antigens (E. coli) 0.7 mg/L; MES[b)] buffer 50 mmol/L, pH 6.5; preservative.

R2 TP-specific recombinant antigens (E. coli)~$Ru(bpy)_3^{2+}$, 1 bottle, 19.7 mL:
TP-specific recombinant antigens labeled with ruthenium complex 0.7 mg/L; MES buffer 50 mmol/L, pH 6.5; preservative.

b) MES = 2-morpholino-ethane sulfonic acid

SYPHILIS Cal1 Negative calibrator 1 (lyophilized), 1 bottle for 1.0 mL:
Human serum, non-reactive for anti-TP antibodies; preservative.

SYPHILIS Cal2 Positive calibrator 2 (lyophilized), 1 bottle for 1.0 mL:
Human serum, reactive for anti-TP antibodies, 22000 - 140000 counts; preservative.

Precautions and warnings

For in vitro diagnostic use for laboratory 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

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H317	May cause an allergic skin reaction.
H412	Harmful to aquatic life with long lasting effects.

Prevention:

P261	Avoid breathing mist or vapours.
P273	Avoid release to the environment.
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.

Hazardous components:

- 2-methyl-2H-isothiazol-3-one hydrochloride

Product safety labeling follows EU GHS guidance.

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

All human material should be considered potentially infectious. All products derived from human blood are prepared exclusively from the blood of donors tested individually and shown to be free from HBsAg and antibodies to HCV and HIV. The testing methods use assays that have been approved or cleared by the FDA or that are in compliance with the legal rules of the European Union (IVDR 2017/746/EU, IVDD 98/79/EC, Annex II, List A). However, as no testing method can rule out the potential risk of infection with absolute certainty, the material should be handled with the same level of care as a patient specimen. In the event of exposure, the directives of the responsible health authorities should be followed.[25,26]

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

Reagent handling

The reagents (M, R1, R2) in the kit are ready-for-use and are supplied in **cobas e** packs.

Calibrators:

Carefully dissolve the contents of 1 bottle by adding exactly 1.0 mL of distilled or deionized water and allow to stand closed for 15 minutes to reconstitute. Mix carefully, avoiding foam formation.

Transfer the reconstituted calibrators into the supplied empty labeled snap-cap bottles.

Unless the entire volume is necessary for calibration on the analyzer, transfer aliquots of the reconstituted calibrators into empty snap-cap bottles (CalSet Vials). Attach the supplied labels to these additional bottles. Store the aliquots at 2-8 °C or -20 °C (± 5 °C) for later use.

Perform **only one** calibration procedure per aliquot.

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 of the **cobas e** pack:	
unopened at 2-8 °C	up to the stated expiration date
on the analyzers	16 weeks

Stability of the calibrators:	
unopened at 2-8 °C	up to the stated expiration date
reconstituted at 2-8 °C	28 days

Stability of the calibrators:	
reconstituted at -20 °C (± 5 °C)	6 months (3 freeze/thaw cycles possible)
on the analyzers at 20-25 °C	use only once

Store calibrators **upright** in order to prevent the calibrator solution from adhering to the snap-cap.

Specimen collection and preparation

Specimen collected from living patients, blood donors, or individual organ, tissue or cell donors may be used, including donor samples obtained while the donor's heart is still beating.
Performance for the use of cadaveric blood specimens (specimens collected post-mortem, non-heart-beating) was established according to Paul-Ehrlich-Institut recommendation[1] with samples obtained within 24 hours after death.[27] Qualitative differences of neat (non-reactive) or spiked (reactive) specimens from cadaveric compared to living donors were not observed.

Criterion: Mean value of cadaveric specimens compared to specimens from living donors within a recovery of 75-125 %.

Only the specimens listed below were tested and found acceptable.

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

Li-heparin, Na-heparin, K_2-EDTA, K_3-EDTA, ACD, CPD, CP2D, CPDA and Na-citrate plasma.

K_2-EDTA plasma tubes containing separating gel can be used.

Criterion: Mean recovery of positive samples within ± 20 % of serum value. Absolute deviation of samples with COI (cutoff index) values from 0.0-1.00 within ± 0.2 COI.

Sampling devices containing liquid anticoagulants have a dilution effect resulting in lower COI values for individual patient specimens. In order to minimize dilution effects it is essential that respective sampling devices are filled completely according to manufacturer's instructions.

Stability:
For living patients and donor specimens obtained while the donor's heart is still beating: Stable for 7 days at 20-25 °C, 14 days at 2-8 °C, 12 months at -20 °C (± 5 °C). The samples may be frozen 5 times.
For cadaveric specimens: Stable for 2 days at 20-25 °C, 7 days at 2-8 °C, 1 month at -20 °C (± 5 °C). The samples may be frozen 3 times.

The sample types listed were tested with a selection of sample collection tubes or systems 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/collection system manufacturer.

Centrifuge samples containing precipitates and thawed samples before performing the assay.

Do not use heat-inactivated samples.

Do not use post-mortem samples collected later than 24 hours after last heart beat.

Do not use samples and controls stabilized with azide.

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

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

The performance of the Elecsys Syphilis assay has not been established with body fluids other than serum and plasma.

Specimens should not be subsequently altered with additives (e.g. biocides, anti-oxidants or substances that could possibly change the pH or ionic strength of the sample) in order to avoid erroneous findings.

Materials provided

See "Reagents – working solutions" section for reagents.

- 2 x 6 bottle labels
- 4 empty labeled snap-cap bottles

Materials required (but not provided)

- REF 06923364190, PreciControl Syphilis, for 4 x 2.0 mL
- REF 11776576322, CalSet Vials, 2 x 56 empty snap-cap bottles

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- General laboratory equipment
- **cobas e** analyzer
- Distilled or deionized water

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

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.

Calibrators:

Place the reconstituted calibrators in the sample zone.

Read in all the information necessary for calibrating the assay.

Calibration

Traceability: No internationally accepted standard for anti-*Treponema pallidum* antibodies exists.

Calibration frequency: Calibration must be performed once per reagent lot using SYPHILIS Cal1, SYPHILIS Cal2 and 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

Use PreciControl Syphilis or other suitable controls for routine quality control procedures.

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 cutoff based on the measurement of SYPHILIS Cal1 and SYPHILIS Cal2.

The result of a sample is given either as reactive or non-reactive as well as in the form of a cutoff index (signal sample/cutoff).

Interpretation of the results

Numeric result	Result message	Interpretation/ further steps
COI < 1.00	Non-reactive	Negative for anti-TP antibodies, no further testing needed.
COI ≥ 1.00	Reactive	Reactive in the Elecsys Syphilis assay. Redetermine initially reactive samples in duplicate with the Elecsys Syphilis assay.[c)]

c) Optional, or if required by specific local testing guidelines; redetermination of samples with an initial COI ≥ 1.00 can be performed automatically (see section **cobas e** flows).

Numeric result	Final result	Interpretation/ further steps
One or both of the duplicate retests have a COI ≥ 1.00	Repeatedly reactive	Must be confirmed according to recommended confirmatory algorithms.
Both of the duplicate retests have a COI < 1.00	Non-reactive	Negative for anti-TP antibodies.

cobas e flows

cobas e flows are procedures programmed into the system to enable a fully automated sequence of measurements and the calculation of assay combinations to perform decision algorithms.

A **cobas e** flow is available to perform a repetition of measurements in duplicate automatically for samples with an initial cutoff index ≥ 1.00 (short name SYPH R).

Both sub-results and the overall result message will be reported.

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	≤ 0.310 mmol/L or ≤ 500 mg/dL
Intralipid	≤ 2000 mg/dL
Biotin	≤ 4912 nmol/L or ≤ 1200 ng/mL
Rheumatoid factors	≤ 1500 IU/mL
IgG	≤ 3.2 g/dL
IgA	≤ 2.8 g/dL
IgM	≤ 1.0 g/dL
Human serum albumin	≤ 10 g/dL

Criterion: Mean recovery of positive samples within ± 15 %. Absolute deviation of samples with COI values from 0.0-1.00 within ± 0.2 COI.

No false negative result due to high-dose hook effect was found with the Elecsys Syphilis assay but occurrence of high-dose hook effect cannot be completely excluded.

Pharmaceutical substances

In vitro tests were performed on 17 commonly used pharmaceuticals. In addition, 5 pharmaceuticals representing different HIV antiretroviral drug classes were tested due to the high prevalence of syphilis infection in HIV patients. No interference with the assay was found.

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.

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

A negative test result does not completely rule out the possibility of an infection with *Treponema pallidum*. Serum or plasma samples from the very early (pre-seroconversion) phase or the late phase of a syphilis infection can occasionally yield negative findings.

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, pooled human sera 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 COI	SD COI	CV %	SD COI	CV %
HS[d], negative	0.125	0.00192	1.5	0.00210	1.7
HS, positive 1	1.09	0.0173	1.6	0.0260	2.4
HS, positive 2	4.11	0.0983	2.4	0.126	3.1
HS, positive 3	6.88	0.198	2.9	0.249	3.6
HS, positive 4	15.8	0.395	2.5	0.574	3.6
PC[e] Syphilis 1	0.0951	0.00107	1.1	0.00130	1.4
PC Syphilis 2	5.90	0.126	2.1	0.155	2.6

d) HS = human serum

e) PC = PreciControl

Analytical specificity

236 samples containing antibodies against Borrelia, EBV, Rubella, HAV, HBV, HCV, HIV, CMV, HSV, E. coli, Toxoplasma gondii, ANA and rheumatoid factor, respectively, were tested with the Elecsys Syphilis assay. 227 samples were tested negative, 9 samples were tested positive for anti-TP antibodies (confirmed by Western Blot and other anti-TP assays). No cross-reactivity was found.

Clinical sensitivity

A total of 924 samples from patients with suspected syphilis infection (diagnostic routine and blood screening) from Europe and Asia were tested with the Elecsys Syphilis assay. 4 additional samples were excluded due to probable handling errors with banked samples. 922 samples were found to be positive for anti-TP antibodies (either clinically defined or confirmed by FTA-Abs[i] and other anti-TP assays). 2 samples were found to be indeterminate. Overall, 922 samples were found to be repeatedly reactive (RR) with the Elecsys Syphilis assay. The 2 indeterminate samples were found to be non-reactive with the Elecsys Syphilis assay. The resulting sensitivity of confirmed positive samples is 100 %. The 95 % lower confidence limit was 99.60 %.

Cohort	N	Confirmed positive samples	Indeterminate samples	False negative samples[f]	Sensitivity[g] %
Primary syphilis	101	101	0	0	100
Secondary syphilis	124	124	0	0	100
Latent syphilis	470	470	0	0	100
Syphilis, stage unknown	229	227	2	0	100
Total[h]	**924**	**922**	**2**	**0**	**100**

f) Elecsys Syphilis assay (RR)

g) Sensitivity of confirmed positive samples

h) 4 additional samples were excluded due to probable handling errors with banked samples.

i) FTA (Fluorescent Treponemal Antibody) - Abs (absorption)

Clinical specificity

A total of 8079 samples (diagnostic routine and blood screening) from Europe and Asia were tested with the Elecsys Syphilis assay. 14 samples were found to be positive for anti-TP antibodies (confirmed by FTA-Abs and other anti-TP assays), 8063 samples were found to be negative and 10 samples were found to be repeatedly false reactive with the Elecsys Syphilis assay (negative in FTA-Abs and other anti-TP assays). The resulting specificity in the study is 99.88 %. The 95 % lower confidence limit was 99.77 %.

Cohort	N	Confirmed positive samples	Confirmed negative samples	False positive samples[j]	Specificity %
Diagnostic routine samples	3500	14	3486	7	99.80
Blood donor samples	4579	0	4577*	3	99.93
Overall specificity	**8079**	**14**	**8063***	**10**	**99.88**

j) Elecsys Syphilis assay (RR)

* 2 samples were excluded due to indeterminate confirmation results.

References

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For further information, please refer to the appropriate user guide or operator's manual for the analyzer concerned, the respective application sheets 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 navifyportal.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 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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