Warsaw, November 17th,2021

To Whom It May Concern

Roche Diagnostics Poland herby confirm that Instructions for Use (IFU) or Method Sheets of the following cobas e601 reagents:

1.Elecsys HBsAg II 08814856190
2. Elecsys Anti-HCV II 06368921190
3.Elecsys Syphilis 06923348190
4.Elecsys HIV combi PT 08924163190

are an official document, which are essential to perform conformity assessment in accordance to EU Directive 98/79/EC on In vitro Diagnostic Medical Device. The content of IFU reflects product's performance characteristics supported by the manufacturer's technical documentation.

In addition, for high-risk products (08814856190 HBsAg G2 Elecsys cobas e 100, 06368921190 Anti HCV G2 Elecsys cobas e 100, 08924163190 HIV combi PT Elecsys cobas e 100) conformity assessment was conducted by a Notified Body, which holds accreditation to check products compliance to EU Directive 98/79/EC on In vitro Diagnostic Medical Devices in European Union. For those products, EC Certificate finalizes products compliance.

Attachments:

1. EC Certificates and Declaration of Conformity for reagents;
2. Instructions for USE (Method Sheets) of reagents listed above;

Marta Czerniawska-Lech
Prokurent
Roche Diagnostics Polska Sp. z o.o.

Krzysztof Politowski
Prokurent
Roche Diagnostics Polska Sp. z o.o.

Digitally signed by Lazari Cristina
Date: 2022.07.25 11:22:00 EEST
Reason: MoldSign Signature
Location: Moldova

EG-Konformitätserklärung/*EC Declaration of Conformity*

gemäß Anhang IV der Richtlinie 98/79/EG des Europäischen Parlaments und des Rates vom 27. Oktober 1998 mit TÜV SÜD Product Service GmbH (Ridlerstraße 65, 80339 München, Germany) als Notified Body (Nr. 0123)
as per Annex IV of Directive 98/79/EC of the European Parliaments and Council of 27 October 1998 via TÜV SÜD Product Service GmbH (Ridlerstrasse 65, 80339 Munich, Germany) as the Notified Body (No. 0123)

Hersteller/*Manufacturer*:	Roche Diagnostics GmbH
Adresse/*Address:*	Sandhofer Strasse 116 D-68305 Mannheim

Die Roche Diagnostics GmbH erklärt, dass das Produkt/die Produktfamilie
Roche Diagnostics GmbH declares that the product/the product line

Produktname/*Product name*:	**Elecsys Anti-HCV II**
Art.-Nr./*Cat. No.*:	**06368921190**
Beschreibung/*Description*:	Der Elecsys Anti-HCV II Test ist ein diagnostischer In-vitro-Test für den qualitativen Nachweis von Antikörpern gegen Hepatitis-C-Virus (HCV) in Humanserum und -plasma. Der ElektroChemiLumineszenz ImmunoAssay "ECLIA" ist zur Durchführung an Elecsys und **cobas e** Immunoassay-Systemen vorgesehen. *The Elecsys Anti-HCV II assay is an in vitro diagnostic test for the qualitative detection of antibodies to hepatitis C virus (HCV) in human serum and plasma.* *The electrochemiluminescence immunoassay "ECLIA" is intended for use on Elecsys and **cobas e** immunoassay analyzers.*

auf das/die sich diese Erklärung bezieht, den Förderungen der Richtlinie 98/79/EG des Europäischen Parlaments und des Rates vom 27. Oktober 1998 über In-vitro-Diagnostica (bzw. seine Umsetzung in nationales Recht der Mitgliedsstaaten in welchen das Produkt vermarktet werden soll) entspricht.
to which this declaration relates fulfils the requirements of Directive 98/79/EC of the European Parliament and Council of 27 October 1998 on in-vitro diagnostic medical devices (and its relevant transposition into the national laws of the Member States in which the device is intended to be placed on the market).

Mannheim, 21 August 2018

Roche Diagnostics GmbH

ppa./*on behalf of the company*
ppa. Dr. Beate Ronefeld

Ralf Zielenski
Head of Quality
Centralised and Point of Care Solutions

ppa./*on behalf of the company*
i.V. Stefan Grigarczik

Dr. Stefan Scheib
Director Global Regulatory Affairs
Centralised and Point of Care Solutions

Kontaktadresse/*Contact address*: Roche Diagnostics GmbH
Abt./*Dept.* Global Regulatory Affairs
Sandhofer Strasse 116
D-68305 Mannheim

Roche Diagnostics GmbH; Sandhofer Strasse 116; D-68305 Mannheim; Telefon +49-621-759-0; Telefax +49-621-759-2890

ms_06368921190V8.0

Elecsys Anti-HCV II

cobas®

REF	Σ	SYSTEM
		MODULAR ANALYTICS E170
06368921 190	100	**cobas e** 411
		cobas e 601
		cobas e 602

English

System information

For **cobas e** 411 analyzer: test number 1020
For MODULAR ANALYTICS E170, **cobas e** 601 and **cobas e** 602 analyzers: Application Code Number 286

Intended use

The Elecsys Anti-HCV II assay is an in vitro diagnostic test for the qualitative detection of antibodies to hepatitis C virus (HCV) in human serum and plasma.

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

Regulatory approval

This assay has been CE marked according to Directive 98/79/EC. Test performance has been established and certified by a Notified Body according to the Common Technical Specifications (CTS) for diagnostic use and for screening of blood donations and, according to Paul-Ehrlich-Institut (PEI) recommendation[1], for use of cadaveric blood specimens (specimens collected post-mortem, non-heart-beating).

Summary

The hepatitis C virus (HCV), first identified in 1989, is a leading cause of liver disease and a major healthcare concern with over 170 million persons (roughly 3 % of the human population), infected worldwide.[2,3] The highest prevalence is found in Africa, the Eastern Mediterranean and Asian regions.[3,4] HCV is a member of the Flaviviridae family and has a single-stranded, positive-sense RNA genome.[5] Currently over 67 subtypes have been identified and these have been classified into 7 genotypes (1-7).[6]

Due to the high rate of asymptomatic infections, clinical diagnosis is difficult and screening assays are of major importance.[7] Infection with HCV can lead to acute and chronic hepatitis disease. Approximately 70-85 % of HCV infections progress to chronic disease, although this varies according to patient gender, age, race and immune status.[5,8] Chronic HCV infection may lead to cirrhosis and hepatocellular carcinoma,[9] therefore, early anti-HCV detection is the first step in the management of chronic hepatitis and in the selection of patients needing treatment.[7] HCV infection can be detected by measuring the amount of HCV RNA, alanine aminotransferase (ALT) and HCV-specific immunoglobulins (anti-HCV) in patient serum or plasma samples. This can also indicate if the infection is acute or chronic.[5,8]

Anti-HCV antibody tests are used alone or in combination with other tests (e.g. HCV RNA) to detect an infection with HCV and to identify blood and blood products of individuals infected with HCV. The Elecsys Anti-HCV II assay is a third-generation test.[10,11] The Elecsys Anti-HCV II assay uses peptides and recombinant proteins representing HCV core, NS3 and NS4 antigens for the determination of anti-HCV antibodies.

Test principle

Sandwich principle. Total duration of assay: 18 minutes.

- 1st incubation: 50 µL of sample, 55 µL of a reagent containing biotinylated HCV-specific antigens and 55 µL of a reagent containing HCV-specific 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/ProCell 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 reagent rackpack (M, R1, R2) is labeled as A-HCV II.

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

R1 HCV-specific antigens~biotin (gray cap), 1 bottle, 18 mL:
Biotinylated HCV-specific antigens, HEPES[b)] buffer, pH 7.4; preservative.

R2 HCV-specific antigens~$Ru(bpy)_3^{2+}$ (black cap), 1 bottle, 18 mL:
HCV-specific antigens labeled with ruthenium complex ≥ 0.3 mg/L, HEPES buffer, pH 7.4; preservative.

b) HEPES = [4-(2-hydroxyethyl)-piperazine]-ethane sulfonic acid

A-HCV II Cal1 Negative calibrator 1 (white cap), 2 bottles of 1.3 mL each:
Human serum, preservative.

A-HCV II Cal2 Positive calibrator 2 (black cap), 2 bottles of 1.3 mL each:
Human serum positive for anti-HCV Ab; preservative. Non-reactive for HBsAg, anti-HIV 1/2.

Precautions and warnings

For in vitro diagnostic use.
Exercise the normal precautions required for handling all laboratory reagents.
Disposal of all waste material should be in accordance with local guidelines.
Safety data sheet available for professional user on request.

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 (A-HCV II Cal1 only) and HIV.

The testing methods used assays approved by the FDA or cleared in compliance with the European Directive 98/79/EC, Annex II, List A.

The serum containing anti-HCV (A-HCV II Cal2) was inactivated using β-propiolactone and UV-radiation.

However, as no inactivation or 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.[12,13]

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

The Elecsys Anti-HCV II assay has a high dilution sensitivity. Avoid any sample cross-contamination during sample pre-analytics.

Reagent handling

The reagents in the kit are ready-for-use and are supplied in bottles compatible with the system.

cobas e 411 analyzer: The calibrators should only be left on the analyzer during calibration at 20-25 °C. After use, close the bottles as soon as possible and store upright at 2-8 °C.

Due to possible evaporation effects, not more than 5 calibration procedures per bottle set should be performed.

MODULAR ANALYTICS E170, **cobas e** 601 and **cobas e** 602 analyzers: Unless the entire volume is necessary for calibration on the analyzers, transfer aliquots of the ready-for-use calibrators into empty snap-cap bottles (CalSet Vials). Attach the supplied labels to these additional bottles. Store the aliquots at 2-8 °C for later use.

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

Elecsys Anti-HCV II

cobas®

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

Please note: Both the vial labels, and the additional labels (if available) contain 2 different barcodes. The barcode between the yellow markers is for **cobas** 8000 systems only. If using a **cobas** 8000 system, please turn the vial cap 180° into the correct position so the barcode can be read by the system. Place the vial on the instrument as usual.

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 of the reagent rackpack	
unopened at 2-8 °C	up to the stated expiration date
after first opening at 2-8 °C	8 weeks
on the analyzers	31 days if continuously stored onboard (20-25 °C) or 7 weeks and up to 80 hours in total onboard (20-25 °C) if stored alternately in the refrigerator and on the analyzer

Stability of the calibrators	
unopened at 2-8 °C	up to the stated expiration date
after opening at 2-8 °C	8 weeks
on **cobas e** 411 at 20-25 °C	up to 5 hours
on MODULAR ANALYTICS E170, **cobas e** 601 and **cobas e** 602 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.[14] 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, CPDA and Na-citrate plasma as well as plasma tubes containing separating gel.
Criterion: Correct assignment of positive and negative samples within a recovery of 80-120 % of serum value.

CPD and CP2D plasma.
Criterion: Correct assignment of positive and negative samples within a recovery of 80-130 % of serum value.

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, 3 months at -20 °C (± 5 °C). The samples may be frozen 6 times.
For cadaveric specimens: Stable for 3 days at 20-25 °C, 7 days at 2-8 °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 manufacturer.

Centrifuge samples containing precipitates before performing the assay.

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.

The performance of the Elecsys Anti-HCV II assay has not been established with body fluids other than serum and plasma.

Materials provided

See "Reagents – working solutions" section for reagents.

- 2 x 6 bottle labels

Materials required (but not provided)

- REF 03290379190, PreciControl Anti-HCV, for 16 x 1.3 mL
- General laboratory equipment
- MODULAR ANALYTICS E170 or **cobas e** analyzer

Accessories for **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

Accessories for MODULAR ANALYTICS E170, **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

Accessories 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.

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 (except for the **cobas e** 602 analyzer).

MODULAR ANALYTICS E170, **cobas e** 601 and **cobas e** 602 analyzers: PreClean M solution is necessary.

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.

Place the calibrators in the sample zone.

All the information necessary for calibrating the assay is automatically read into the analyzer.

Elecsys Anti-HCV II

cobas®

After calibration has been performed, store the calibrators at 2-8 °C or discard (MODULAR ANALYTICS E170, **cobas e** 601 and **cobas e** 602 analyzers).

Calibration

No internationally accepted standard for anti-HCV exists.

Every Elecsys Anti-HCV II 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 A-HCV II Cal1 and A-HCV II Cal2.

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

Range for electrochemiluminescence signals (counts) for the calibrators:
Negative calibrator (A-HCV II Cal1): 400-3000 (all analyzers)
Positive calibrator (A-HCV II Cal2): 25000-350000 (all analyzers)

Quality control

For quality control, use PreciControl Anti-HCV.

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.

Note:
For technical reasons re-assigned target values valid only for a specific reagent and control lot combination must be entered manually on all analyzers (except for the **cobas e** 602 analyzer). Therefore always refer to the value sheet included in the reagent kit or PreciControl kit to make sure that the correct target values are used.
When a new reagent or control lot is used, the analyzer will use the original values encoded in the control barcodes.

Calculation

The analyzer automatically calculates the cutoff based on the measurement of A-HCV II Cal1 and A-HCV II Cal2.

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

Interpretation of the results

Samples with a cutoff-index < 0.9 are non reactive in the Elecsys Anti-HCV II assay.

Samples with a cutoff-index ≥ 0.9 and < 1.0 are considered borderline in the Elecsys Anti-HCV II assay.

Samples with a cutoff-index ≥ 1.0 are reactive in the Elecsys Anti-HCV II assay.

All initially reactive or borderline samples should be redetermined in duplicate using the Elecsys Anti-HCV II assay. If no reactivity is found in both cases, the sample is negative for anti-HCV. If the result from either of the two measurements is reactive or borderline then the sample is repeatedly reactive. Repeatedly reactive samples must be investigated by supplemental methods (e.g. immunoblot or detection of HCV RNA). If one or both measurements remain borderline the analysis of a follow-up sample is recommended.

Limitations - interference

The assay is unaffected by icterus (bilirubin < 1129 µmol/L or < 66 mg/dL), hemolysis (Hb < 0.621 mmol/L or < 1.00 g/dL), lipemia (Intralipid < 2000 mg/dL) and biotin (< 172 nmol/L or < 42 ng/mL).

Criterion: Recovery of positive samples within ± 20 % of initial value, cutoff-index for negative samples ± 0.2 of initial value.

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.

No interference was observed from rheumatoid factors up to a concentration of 1200 IU/mL.

In vitro tests were performed on 18 commonly used pharmaceuticals and 3 drugs used in HCV therapy. 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.

Studies have been performed to assess the high-dose hook effect. Out of 765 positive samples no false negative result was found. Occurrence of high-dose hook effect cannot be completely excluded.

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

Due to a long time period from infection to seroconversion, negative anti-HCV test results may occur during early infection. If acute hepatitis C infection is suspected, measuring of HCV RNA by reverse transcriptase polymerase chain reaction (RT-PCR e.g. by COBAS AMPLICOR) may give evidence of HCV infection.

The detection of anti-HCV antibodies indicates a present or past infection with hepatitis C virus, but does not differentiate between acute, chronic or resolved infection. It is recognized within the scientific community that presently available methods for anti-HCV detection are not sensitive enough to detect all potentially infectious units of blood or possible cases of HCV infection. The antibody concentration may be beneath the detection limit of this assay or the patient's antibodies do not react with the antigens used in this test. In addition, non-specific results cannot be ruled out with the Elecsys Anti-HCV II assay.

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 (EP5-A2) 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[c]			**Intermediate precision**[d]		
Sample	Mean COI[e]	SD COI	CV %	Mean COI	SD COI	CV %
HS[f], negative	0.071	0.001	1.6	0.071	0.003	4.1
HS, weakly positive	1.86	0.049	2.7	1.86	0.085	4.6
HS, positive	20.0	0.476	2.4	20.0	1.04	5.2
PreciControl A-HCV1	0.097	0.001	1.4	0.097	0.004	3.8
PreciControl A-HCV2	4.39	0.113	2.6	4.39	0.185	4.2

c) Repeatability = within-run precision

d) Intermediate precision = within-laboratory precision

e) COI = Cutoff index

f) HS = Human serum

MODULAR ANALYTICS E170, **cobas e** 601 and **cobas e** 602 analyzers						
	Repeatability			**Intermediate precision**		
Sample	Mean COI	SD COI	CV %	Mean COI	SD COI	CV %
HS, negative	0.034	0.006	16.3	0.034	0.007	20.4
HS, weakly positive	1.89	0.017	0.9	1.89	0.033	1.8

Elecsys Anti-HCV II

cobas®

MODULAR ANALYTICS E170, **cobas e** 601 and **cobas e** 602 analyzers						
	Repeatability			**Intermediate precision**		
Sample	Mean COI	SD COI	CV %	Mean COI	SD COI	CV %
HS, positive	20.9	0.138	0.7	20.9	0.339	1.6
PreciControl A-HCV1	0.055	0.001	1.1	0.055	0.001	2.3
PreciControl A-HCV2	4.00	0.028	0.7	4.00	0.160	4.0

Analytical specificity

1037 samples containing potentially interfering substances or derived from high-risk groups were tested with the Elecsys Anti-HCV II assay comprising specimens:

- containing antibodies against HBV, HAV, HEV, EBV, CMV, HSV, HIV, VZV, Parvovirus, Mumps, Dengue, tick-borne encephalitis virus (TBEV), Rubella, Toxoplasma gondii, Treponema pallidum
- containing autoantibodies and elevated titers of rheumatoid factor, IgG, IgM or IgA antibodies
- positive for HBsAg and E. coli
- after vaccination against HBV and Influenza
- non-viral liver diseases
- alcoholic liver disease
- high-risk groups: hemophiliacs, homosexuals and intravenous drug abusers

	N	Elecsys Anti-HCV II reactive	Positive by immunoblot or indeterminate	Negative by immunoblot
Specimens containing potentially interfering substances	1037	59	58 positive	1[g]

g) EBV IgM positive patients: 1 out of 69 samples

Clinical sensitivity

Of 765 samples from HCV infected patients with different stages of disease and infected with different HCV genotypes (type 1, 2, 3, 4, 5 and 6), all samples were found to be reactive with the Elecsys Anti-HCV II assay.

Group	N	Reactive
HCV infected persons with different stages of disease	224	224
HCV genotypes (type 1, 2, 3, 4, 5, 6)	541	541

In the above study the diagnostic sensitivity was 100 %. The 95 % lower confidence limit was 99.61 %.

Seroconversion sensitivity

Seroconversion sensitivity of the Elecsys Anti-HCV II assay has been shown by testing 60 commercial seroconversion panels. The Elecsys Anti-HCV II assay detected more positive bleedings than all other registered anti-HCV assays tested and was more sensitive in the recognition of early HCV infection than the Elecsys Anti-HCV assay and the other registered anti-HCV screening assays.

Clinical specificity

In a group of randomly selected European blood donors the specificity of the Elecsys Anti-HCV II assay was found 99.85 % (RR). The 95 % confidence interval (2-sided) was 99.73-99.93 %.

The diagnostic specificity of the Elecsys Anti-HCV II assay in a group of hospitalized patients was found 99.66 %. The 95 % confidence interval (2-sided) was 99.41-99.82 %.

	N	Elecsys Anti-HCV II IR[h] COI ≥ 1	Elecsys Anti-HCV II RR[i] COI ≥ 1	Positive or indeterminate by immunoblot and/ or HCV RNA
European blood donors	6850	15	15	2 confirmed positive, 3 indeterminate
Hospitalized patients	3922	153[j]	152[k]	128 confirmed positive, 8 indeterminate
Dialysis patients	731	19	18	12 confirmed positive
Pregnant women	629	3	3	2 confirmed positive

h) IR = Initially Reactive

i) RR = Repeatedly Reactive

j) 4 (positive) samples had to be excluded from calculation due to "qns" for immunoblot analysis; qns = quantity not sufficient

k) 4 (positive) samples had to be excluded from calculation due to "qns" for immunoblot analysis

References

1 Proposal for the Validation of Anti-HIV-1/2 or HIV Ag/Ab Combination Assays, anti-HCV-Assays, HBsAg and Anti-HBc assays for Use with Cadaveric Samples; PEI 08/05/2014.

2 Choo QL, Kuo G, Weiner AJ, et al. Isolation of a cDNA clone derived from a blood-borne non-A, non-B viral hepatitis genome. Science 1989;244:359-362.

3 Lavanchy D. The global burden of hepatitis C. Liver Int 2009;29(s1):74-81.

4 Hepatitis C WHO report WHO/SCD/SCR/LYO/2003 http://www.who.int/csr/disease/hepatitis/Hepc.pdf

5 Hoofnagle JH. Course and outcome of hepatitis C. Hepatology 2002;36:21-29.

6 Smith DB, Bukh J, Kuiken C, et al. Expanded classification of hepatitis C virus into 7 genotypes and 67 subtypes: updated criteria and assignment web resource. Hepatology 2013;59:318-327.

7 Strader DB, Wright T, Thomas DL, et al. Diagnosis, management, and treatment of hepatitis C. Hepatology 2004;39(4):1147-1171.

8 Lemon SM, Walker CM, Alter MJ, et al. Fields Virology. Lippincot Williams and Wilkins, Philadelphia. Hepatitis C virus; 2007:1253-1304.

9 Di Bisceglie AM. Hepatitis C and hepatocellular carcinoma. Hepatology 1997;26(Suppl 1):34-38.

10 Couroucé A-M. Development of Screening and Confirmation Tests for Antibodies to Hepatitis C Virus. In: Reesink HW (ed.): Hepatitis C Virus. Curr Stud Hematol Blood Transf. Basel, Karger, 1998;62:64-75.

11 Vernelen K, Claeys H, Verhaert H, et al. Significance of NS3 and NS5 antigens in screening for HCV antibody. The Lancet 1994;343(8901):853.

12 Occupational Safety and Health Standards: Bloodborne pathogens. (29 CFR Part 1910.1030). Fed. Register.

13 Directive 2000/54/EC of the European Parliament and Council of 18 September 2000 on the protection of workers from risks related to exposure to biological agents at work.

14 Commission Directive 2006/17/EC of 8 February 2006 implementing Directive 2004/23/EC of the European Parliament and of the Council as regards certain technical requirements for the donation, procurement and testing of human tissues and cells.

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.

Elecsys Anti-HCV II

cobas®

Symbols

Roche Diagnostics uses the following symbols and signs in addition to those listed in the ISO 15223-1 standard (for USA: see https://usdiagnostics.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

Roche Diagnostics GmbH, Sandhofer Strasse 116, D-68305 Mannheim
www.roche.com

Roche

EG-Konformitätserklärung/*EC Declaration of Conformity*

gemäß Anhang III der Richtlinie 98/79/EG des Europäischen Parlaments und des Rates vom 27. Oktober 1998
as per Annex III of Directive 98/79/EC of the European Parliaments and Council of 27 October 1998

Hersteller/*Manufacturer*:	Roche Diagnostics GmbH
Adresse/*Address:*	Sandhofer Strasse 116 D-68305 Mannheim

Die Roche Diagnostics GmbH erklärt, dass das Produkt/die Produktfamilie
Roche Diagnostics GmbH declares that the product/the product line

Produktname/*Product name*:	**Elecsys Syphilis**
Art.-Nr./*Cat. No.*:	**06923348190**
Beschreibung/*Description*:	Immunologischer In-vitro-Test zur qualitativen Bestimmung der Gesamt-Antikörper gegen *Treponema pallidum* in Humanserum und -plasma. Der Test dient als Hilfe bei der Diagnose einer Syphilis-Infektion. Der **E**lektro**C**hemi**L**umineszenz **I**mmuno**A**ssay "ECLIA" ist zur Durchführung an Elecsys und **cobas e** Immunoassay-Systemen vorgesehen. *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**lectrochemi**l**uminescence **i**mmuno**a**ssay "ECLIA" is intended for use on Elecsys and **cobas e** immunoassay analyzers.*

auf das/die sich diese Erklärung bezieht, den Forderungen der Richtlinie 98/79/EG des Europäischen Parlaments und des Rates vom 27. Oktober 1998 über In-vitro-Diagnostica (bzw. seine Umsetzung in nationales Recht der Mitgliedsstaaten in welchen das Produkt vermarktet werden soll) entspricht.
to which this declaration relates fulfils the requirements of Directive 98/79/EC of the European Parliament and Council of 27 October 1998 on in-vitro diagnostic medical devices (and its relevant transposition into the national laws of the Member States in which the device is intended to be placed on the market).

Mannheim, 21 November 2017

Roche Diagnostics GmbH

ppa./*on behalf of the company*

Ralf Zielenski
Head of Quality
Centralised and Point of Care Solutions

ppa./*on behalf of the company*
i.V. Dr. Stefan Scheib

Dr. Peter Martin
Senior Director Global Regulatory Affairs
Centralised and Point of Care Solutions

Kontaktadresse/*Contact address*: Roche Diagnostics GmbH
Abt./*Dept.* Global Regulatory Affairs
Sandhofer Strasse 116
D-68305 Mannheim

Roche Diagnostics GmbH; Sandhofer Strasse 116; D-68305 Mannheim; Telefon +49-621-759-0; Telefax +49-621-759-2890

06923348500V7.0

Elecsys Syphilis

cobas®

REF		Σ	SYSTEM
			cobas e 411
06923348190	06923348500	100	**cobas e** 601
			cobas e 602

English

System information

For **cobas e** 411 analyzer: test number 1360
For **cobas e** 601 and **cobas e** 602 analyzers: Application Code Number 160

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 **electrochemiluminescence immunoassay** "ECLIA" is intended for use on Elecsys and **cobas e** immunoassay analyzers.

Regulatory status

This assay has been CE marked according to Directive 98/79/EC. Test performance has been established for diagnostic use and for screening of blood donations and, according to Paul-Ehrlich-Institut (PEI) recommendation,[1] for use of cadaveric blood specimens (specimens collected post-mortem, non-heart-beating).

Summary

Syphilis is caused by the intracellular gram-negative spirochete bacterium Treponema pallidum (TP) subspecies pallidum.[2]

Syphilis is mainly transmitted sexually, but can also be transmitted from mother to fetus during pregnancy or birth. The global incidence of infection in 2008 was approximately 10.6 million and the total number of infections during that year was estimated to be 36.4 million.[3] In the USA the national infection rate rose to 6.3 cases per 100000 people, the highest rate since 1994.[4] Certain European countries have also seen increases in the rate of infection[5,6] and large localized outbreaks.[7] Each year, globally, an estimated 2 million pregnancies are affected.[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] Up to 80 % of syphilis infected pregnant women show adverse pregnancy outcomes.[8] The World Health Organization recommends all women to be tested at their first antenatal visit and again in the third trimester.[8] If they are positive, the recommendation also includes treatment of the partner.

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).[10]

The immune response to T. pallidum is the main driver of lesion development.[10] 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] 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 also used for monitoring the progression of disease and treatment response.

Test principle

Sandwich principle. Total duration of assay: 18 minutes.

- 1st incubation: 10 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/ProCell 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 reagent rackpack (M, R1, R2) is labeled as Syphilis.

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

R1 TP-specific recombinant antigens (E. coli)~biotin (gray cap), 1 bottle, 9 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)~$Ru(bpy)_3^{2+}$ (black cap), 1 bottle, 9 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 (white cap), 2 bottles (lyophilized) for 1.0 mL each:
Human serum, non reactive for anti-TP antibodies; preservative.

Syphilis Cal2 Positive calibrator (black cap), 2 bottles (lyophilized) for 1.0 mL each:
Human serum, reactive for anti-TP antibodies; preservative.

Precautions and warnings

For in vitro diagnostic use.
Exercise the normal precautions required for handling all laboratory reagents.
Disposal of all waste material should be in accordance with local guidelines.
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.
H412	Harmful to aquatic life with long lasting effects.

Prevention:

P261	Avoid breathing dust/fume/gas/mist/vapours/spray.
P273	Avoid release to the environment.
P280	Wear protective gloves.

Elecsys Syphilis

cobas®

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

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 used assays approved by the FDA or cleared in compliance with the European Directive 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.[11,12]

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 bottles compatible with the system.

Calibrators

Syphilis Cal1 and Syphilis Cal2: Carefully dissolve the contents of one 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.

cobas e 411 analyzer: The reconstituted calibrators should only be left on the analyzer during calibration at 20-25 °C. After use, close the bottles as soon as possible and store upright at 2-8 °C.

Due to possible evaporation effects, not more than 5 calibration procedures per calibrator bottle set should be performed.

If necessary, freeze in aliquots; see section on **cobas e** 601 and **cobas e** 602 analyzers.

cobas e 601 and **cobas e** 602 analyzers: Unless the entire volume is necessary for calibration on the analyzers, 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 -20 °C (± 5 °C) for later use.

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

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

Please note: Both the vial labels, and the additional labels (if available) contain 2 different barcodes. The barcode between the yellow markers is for **cobas** 8000 systems only. If using a **cobas** 8000 system, please turn the vial cap 180° into the correct position so the barcode can be read by the system. Place the vial on the instrument as usual.

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 of the reagent rackpack	
unopened at 2-8 °C	up to the stated expiration date
after opening at 2-8 °C	56 days
on the analyzers	28 days

The lyophilized calibrators are stable up to the stated expiration date.

Stability of the reconstituted calibrators	
either at -20 °C (± 5 °C)	6 months (3 freeze/thaw cycles possible)
or at 2-8 °C	28 days
on **cobas e** 411 at 20-25 °C	up to 6 hours
on **cobas e** 601 and **cobas e** 602 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.[13] 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 as well as K_2-EDTA plasma tubes containing separating gel.

Criterion: Mean recovery of positive samples within ± 20 % of serum value. Absolute deviation of samples with COI (cutoff index) values from 0.00-1.0 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. 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 samples and controls stabilized with azide.

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.

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

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

Elecsys Syphilis

cobas®

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

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.

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.

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

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.

Place the reconstituted calibrators in the sample zone.

All the information necessary for calibrating the assay is automatically read into the analyzer.

After calibration has been performed, store the calibrators at 2-8 °C or discard (**cobas e** 601 and **cobas e** 602 analyzers).

Calibration

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 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

Range for the electrochemiluminescence signals (counts) for the calibrators:
Negative calibrator (Syphilis Cal1): 450-4000
Positive calibrator (Syphilis Cal2): 22000-140000

Quality control

For quality control, use PreciControl Syphilis.

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 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 (COI; signal sample/cutoff).

Interpretation of the results

Samples with a cutoff index < 1.00 are non-reactive in the Elecsys Syphilis assay. These samples are considered negative for syphilis-specific antibodies and do not need further testing.

Samples with a cutoff index ≥ 1.00 are considered reactive in the Elecsys Syphilis assay.

All initially reactive samples should be redetermined in duplicate with the Elecsys Syphilis assay. If cutoff index values < 1.00 are found in both cases, the samples are considered negative for syphilis-specific antibodies.

Initially reactive samples giving cutoff index values of ≥ 1.00 in either of the redeterminations are considered repeatedly reactive. Repeatedly reactive samples must be confirmed according to recommended confirmatory algorithms.

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	≤ 246 nmol/L or ≤ 60 ng/mL
Rheumatoid factors	≤ 1500 IU/mL
Human serum albumin	≤ 10 g/dL
IgG	≤ 3.2 g/dL
IgA	≤ 2.8 g/dL
IgM	≤ 1.0 g/dL

Criterion: Mean recovery of positive samples within ± 15 %. Absolute deviation of samples with COI values from 0.00-1.0 within ± 0.2 COI.

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.

No false negative result due to high-dose hook effect was found with the Elecsys Syphilis assay.

Pharmaceutical substances
In vitro tests were performed on 16 commonly used pharmaceuticals. 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.

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

Elecsys Syphilis

cobas®

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, samples and controls in a protocol (EP5-A2) 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 COI	SD COI	CV %	SD COI	CV %
HS[c], negative	0.103	0.002	1.6	0.003	3.2
HS, positive 1	1.01	0.028	2.8	0.033	3.2
HS, positive 2	1.12	0.018	1.6	0.022	1.9
HS, positive 3	9.99	0.171	1.7	0.262	2.6
HS, positive 4	50.2	0.986	2.0	1.24	2.5
PC[d] Syphilis1	0.106	0.003	2.4	0.004	4.1
PC Syphilis2	4.95	0.101	2.1	0.161	3.2

c) HS = human serum

d) PC = PreciControl

cobas e 601 and **cobas e** 602 analyzers					
		Repeatability		**Intermediate precision**	
Sample	Mean COI	SD COI	CV %	SD COI	CV %
HS, negative	0.062	0.001	2.0	0.002	3.6
HS, positive 1	1.10	0.017	1.5	0.055	5.0
HS, positive 2	1.19	0.014	1.2	0.055	4.6
HS, positive 3	11.1	0.146	1.3	0.508	4.6
HS, positive 4	54.6	0.910	1.7	2.69	4.9
PC Syphilis1	0.064	0.001	1.8	0.002	2.5
PC Syphilis2	5.36	0.082	1.5	0.138	2.6

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. Four 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[h] and other anti-TP assays). Two samples were found to be indeterminate. Overall, 922 samples were found to be repeatedly reactive (RR) with the Elecsys Syphilis assay. The two 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[e]	Sensitivity[f] %
Primary syphilis	101	101	0	0	100
Secondary syphilis	124	124	0	0	100
Latent syphilis	470	470	0	0	100
Syphilis, stage of the disease unknown	229	227	2	0	100
Total[g]	**924**	**922**	**2**	**0**	**100**

e) Elecsys Syphilis assay (RR)

f) Sensitivity of confirmed positive samples

g) Four additional samples were excluded due to probable handling errors with banked samples.

h) 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[i]	Specificity %
Diagnostic routine samples	3500	14	3486	7	99.80
Blood donor samples	4579	0	4577*	3	99.93
Overall specificity for all samples (routine cohorts and blood donations)	**8079**	**14**	**8063***	**10**	**99.88**

i) Elecsys Syphilis assay (RR)

* Two samples were excluded due to indeterminate confirmation results.

References

1 Proposal for the Validation of Anti-HIV-1/2 or HIV Ag/Ab Combination Assays, anti-HCV-Assays, HBsAg and Anti-HBc assays for Use with Cadaveric Samples; PEI 08/05/2014.

2 Seña AC, White BL, Sparling PF. Novel Treponema pallidum serologic tests: a paradigm shift in syphilis screening for the 21st century. Clin Infect Dis 2010:51(6);700-708.

3 World Health Organization. Global incidence and prevalence of selected curable sexually transmitted infections – 2008, http://apps.who.int/iris/bitstream/10665/43782/1/9789241595858_eng.pdfpdf, 2012.

4 Centers for Disease Control and Prevention. Sexually Transmitted Disease Surveillance 2014, http://www.cdc.gov/std/stats14/surv-2014-print.pdf.

5 European Centre for Disease Prevention and Control. Sexually transmitted infections in Europe 2013, http://ecdc.europa.eu/en/publications/Publications/sexual-transmitted-infections-europe-surveillance-report-2013.pdf, 2015.

6 Jebbari H, Simms I, Conti S, et al. Variations in the epidemiology of primary, secondary and early latent syphilis, England and Wales: 1999 to 2008. Sex Transm Infect 2011;87(3):191-198.

Elecsys Syphilis

cobas®

7 Righarts AA, Simms I, Wallace L, et al. Syphilis surveillance and epidemiology in the United Kingdom. Euro Surveill 2004;9(12):21-25.

8 World Health Organization. The global elimination of congenital syphilis: rationale and strategy for action, http://apps.who.int/iris/bitstream/10665/43782/9789241595858_eng.pdf, 2007.

9 Schmid G. Economic and programmatic aspects of congenital syphilis prevention. Bull World Health Organ 2004;82(6):402-409.

10 Lafond RE, Lukehart SA. Biological basis for syphilis. Clin Microbiol Rev 2006;19(1):29-49.

11 Occupational Safety and Health Standards: Bloodborne pathogens. (29 CFR Part 1910.1030). Fed. Register.

12 Directive 2000/54/EC of the European Parliament and Council of 18 September 2000 on the protection of workers from risks related to exposure to biological agents at work.

13 Commission Directive 2006/17/EC of 8 February 2006 implementing Directive 2004/23/EC of the European Parliament and of the Council as regards certain technical requirements for the donation, procurement and testing of human tissues and cells.

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.

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 for reconstitution
GTIN	Global Trade Item Number

CE

Roche Diagnostics GmbH, Sandhofer Strasse 116, D-68305 Mannheim
www.roche.com

Roche

EG-Konformitätserklärung/*EC Declaration of Conformity*

gemäß Anhang IV der Richtlinie 98/79/EG des Europäischen Parlaments und des Rates vom 27. Oktober 1998 mit TÜV SÜD Product Service GmbH (Ridlerstraße 65, 80339 München, Germany) als Notified Body (Nr. 0123)
as per Annex IV of Directive 98/79/EC of the European Parliaments and Council of 27 October 1998 via TÜV SÜD Product Service GmbH (Ridlerstrasse 65, 80339 Munich, Germany) as the Notified Body (No. 0123)

Hersteller/*Manufacturer*:	Roche Diagnostics GmbH
Adresse/*Address:*	Sandhofer Strasse 116 D-68305 Mannheim

Die Roche Diagnostics GmbH erklärt, dass das Produkt/die Produktfamilie
Roche Diagnostics GmbH declares that the product/the product line

Produktname/*Product name*:	**Elecsys HBsAg II**
Art.-Nr./*Cat. No.*:	**08814856190**
Beschreibung/*Description*:	Immunologischer In-vitro-Test zur qualitativen Bestimmung von Hepatitis B Oberflächen-Antigen (HBsAg) in Humanserum und -plasma. Der **E**lektro**C**hemi**L**umineszenz **I**mmuno**A**ssay "ECLIA" ist zur Durchführung an **cobas e** Immunoassay-Systemen vorgesehen. *Immunoassay for the in vitro qualitative determination of hepatitis B surface antigen (HBsAg) in human serum and plasma.* *The electrochemiluminescence immunoassay "ECLIA" is intended for use on **cobas e** immunoassay analyzers.*

auf das/die sich diese Erklärung bezieht, den Forderungen der Richtlinie 98/79/EG des Europäischen Parlaments und des Rates vom 27. Oktober 1998 über In-vitro-Diagnostica (bzw. seine Umsetzung in nationales Recht der Mitgliedsstaaten in welchen das Produkt vermarktet werden soll) entspricht.
to which this declaration relates fulfils the requirements of Directive 98/79/EC of the European Parliament and Council of 27 October 1998 on in-vitro diagnostic medical devices (and its relevant transposition into the national laws of the Member States in which the device is intended to be placed on the market).

Mannheim, 16 October 2019

Roche Diagnostics GmbH

ppa./*on behalf of the company*
Ralf Zielenski
Head of Quality
Centralised and Point of Care Solutions

ppa./*on behalf of the company*
Dr. Stefan Scheib
Director Global Regulatory Affairs
Centralised and Point of Care Solutions

Kontaktadresse/*Contact address*: Roche Diagnostics GmbH
Abt./*Dept.* Global Regulatory Affairs
Sandhofer Strasse 116
D-68305 Mannheim

Roche Diagnostics GmbH; Sandhofer Strasse 116; D-68305 Mannheim; Telefon +49-621-759-0; Telefax +49-621-759-2890

08814856500V2.0

Elecsys HBsAg II

cobas®

REF		Σ	SYSTEM
08814856190	08814856500	100	**cobas e** 411 **cobas e** 601 **cobas e** 602

English

System information

For **cobas e** 411 analyzer: test number 2080
For **cobas e** 601 and **cobas e** 602 analyzers: Application Code Number 515

Intended use

Immunoassay for the in vitro qualitative determination of hepatitis B surface antigen (HBsAg) in human serum and plasma.

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

Regulatory approval

This assay has been CE marked according to Directive 98/79/EC. Test performance has been established and certified by a Notified Body according to the Common Technical Specifications (CTS) for diagnostic use and for screening of blood donations and, according to Paul-Ehrlich-Institut (PEI) recommendation,[1] for use of cadaveric blood specimens (specimens collected post-mortem, non-heart-beating).

Summary

The hepatitis B surface antigen (HBsAg), a polypeptide of varying size, is a component of the external envelope of the hepatitis B virus (HBV) particle.[2,3] The blood of persons infected with HBV contains, in addition to intact infectious HBV particles, an excess of smaller non-infectious 'empty' envelope particles, or filaments, formed from HBsAg.[4]

The HBsAg determinant 'a', against which the immune response is mainly directed, is common to all HBsAg particles. Within this 'a' determinant several HBsAg subtype determinants could be defined as d, y, w1-w4, r and q.[5] Under selective pressure (caused by antiviral therapy or by the action of the immune system itself) the virus can express many different viable HBsAg mutants (so-called 'escape mutants'). Some mutants might lead to a loss of detection in commercially available HBsAg assays.[3,6]

The Elecsys HBsAg II assay was specifically developed to detect a multitude of these mutants. HBsAg is the first immunologic marker of HBV infection and is generally present some days or weeks before clinical symptoms begin to appear. Detection of HBsAg in human serum or plasma indicates the presence of acute or chronic HBV infection.[7]

HBsAg assays are used within the scope of diagnostic procedures to identify persons infected with HBV and prevent the transmission of the virus by blood and blood products.[4,8]

HBsAg assays can also be used to monitor the course of the disease and the efficacy of therapy in persons with acute or chronic HBV infections.[9]

In addition, HBsAg assays are recommended as part of prenatal care, in order to initiate suitable measures for preventing as far as possible the transmission of an HBV infection to the newborn child.[10]

The Elecsys HBsAg II assay uses monoclonal and polyclonal anti-HBs antibodies (mouse and sheep) to detect HBsAg.

Test principle

Sandwich principle. Total duration of assay: 18 minutes.

- 1st incubation: 50 µL of sample, two biotinylated monoclonal anti-HBsAg antibodies, and a mixture of monoclonal anti-HBsAg antibody and polyclonal anti-HBsAg antibodies labeled with a ruthenium complex[a)] 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/ProCell 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 reagent rackpack (M, R1, R2) is labeled as HBSAG II.

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

R1 Anti-HBsAg-Ab~biotin (gray cap), 1 bottle, 8 mL: Two biotinylated monoclonal anti-HBsAg antibodies (mouse) > 0.5 mg/L; phosphate buffer 100 mmol/L, pH 7.5; preservative.

R2 Anti-HBsAg-Ab~$Ru(bpy)_3^{2+}$ (black cap), 1 bottle, 7 mL: Monoclonal anti-HBsAg antibody (mouse), polyclonal anti-HBsAg antibodies (sheep) labeled with ruthenium complex > 1.5 mg/L; phosphate buffer 100 mmol/L, pH 8.0; preservative.

HBSAG II Cal1 Negative calibrator 1 (white cap), 2 bottles of 1.3 mL each: Human serum; preservative.

HBSAG II Cal2 Positive calibrator 2 (black cap), 2 bottles of 1.3 mL each: HBsAg approximately 0.5 IU/mL in human serum; preservative.

Precautions and warnings

For in vitro diagnostic use.
Exercise the normal precautions required for handling all laboratory reagents.
Disposal of all waste material should be in accordance with local guidelines.
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:

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

EUH 208 May produce an allergic reaction.

Product safety labeling follows EU GHS guidance.

All human material should be considered potentially infectious.

The calibrators have been prepared exclusively from the blood of donors tested individually and shown to be free from HBsAg (HBSAG II Cal1 only) and antibodies to HCV and HIV.

The testing methods used assays approved by the FDA or cleared in compliance with the European Directive 98/79/EC, Annex II, List A.

The serum containing HBsAg (HBSAG II Cal2) was inactivated using β-propiolactone and UV-radiation.

However, as no inactivation or 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.[11,12]

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

Reagent handling

The reagents in the kit are ready-for-use and are supplied in bottles compatible with the system.

cobas e 411 analyzer: The calibrators should only be left on the analyzer during calibration at 20-25 °C. After use, close the bottles as soon as possible and store upright at 2-8 °C.

Due to possible evaporation effects, not more than 5 calibration procedures per calibrator bottle set should be performed.

cobas e 601 and **cobas e** 602 analyzers: Unless the entire volume is necessary for calibration on the analyzers, transfer aliquots of the

Elecsys HBsAg II

cobas®

ready-for-use calibrators into empty snap-cap bottles (CalSet Vials). Attach the supplied labels to these additional bottles. Store the aliquots at 2-8 °C for later use.

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

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

Please note: Both the vial labels, and the additional labels (if available) contain 2 different barcodes. The barcode between the yellow markers is for **cobas** 8000 systems only. If using a **cobas** 8000 system, please turn the vial cap 180° into the correct position so the barcode can be read by the system. Place the vial on the instrument as usual.

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 of the reagent rackpack	
unopened at 2-8 °C	up to the stated expiration date
after opening at 2-8 °C	8 weeks
on **cobas e** 601 and **cobas e** 602	4 weeks
on **cobas e** 411	4 weeks
on **cobas e** 411	6 weeks if stored alternately in the refrigerator and on the analyzers (up to 42 hours at 20-25 °C)

Stability of the calibrators	
unopened at 2-8 °C	up to the stated expiration date
after opening at 2-8 °C	8 weeks
on **cobas e** 411 at 20-25 °C	up to 5 hours
on **cobas e** 601 and **cobas e** 602 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.[13] 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.

Plasma tubes containing separating gel can be used.

Criterion: Correct assignment of negative and positive samples.

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, 6 months at -20 °C (± 5 °C). The samples may be frozen 6 times.
For cadaveric specimens: Stable for 3 days at 20-25 °C, 7 days at 2-8 °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 before performing the assay.

Do not use heat-inactivated samples.

Do not use samples and controls stabilized with azide.

Ensure the samples, calibrators and controls 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 HBsAg II assay has not been established with body fluids other than serum and plasma.

Materials provided

See "Reagents – working solutions" section for reagents.

- 2 x 6 bottle labels

Materials required (but not provided)

- REF 04687876190, PreciControl HBsAg II, for 16 x 1.3 mL
- REF 11820648122, HBsAg Confirmatory Test, 2 x 1.0 mL each of confirmatory and control reagent
- REF 11776576322, CalSet Vials, 2 x 56 empty snap-cap bottles
- 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 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.

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.

Place the calibrators in the sample zone.

All the information necessary for calibrating the assay is automatically read into the analyzer.

Elecsys HBsAg II

cobas®

After calibration has been performed, store the calibrators at 2-8 °C or discard (**cobas e** 601 and **cobas e** 602 analyzers).

Calibration

Traceability: This method has been standardized against the NIBSC standard (code number: 00/588; WHO Second International Standard for HBsAg, subtype adw2, genotype A; IU/mL).

The following reference materials from the Paul-Ehrlich-Institute, Langen (Germany), were also measured (U/mL) and compared with the WHO standard:

PEI Standard AD (information sheet 1985, subtype AD; 1000 U/mL; inactivated)

PEI Standard AY (information sheet 1985, subtype AY; 1000 U/mL; inactivated)

(1 IU/mL WHO Standard corresponds to 0.34 U/mL PEI Standard AY and 1 IU/mL WHO Standard corresponds to 0.44 U/mL PEI Standard AD)

Calibration frequency:

Calibration must be performed once per reagent lot using HBSAG II Cal1, HBSAG II Cal2 and 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

Range for the electrochemiluminescence signals (counts) for the calibrators:
Negative calibrator (HBSAG II Cal1): 600-1700
Positive calibrator (HBSAG II Cal2): 3000-11000

Quality control

For quality control, use PreciControl HBsAg II.

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.

Note:
For technical reasons re-assigned target values valid only for a specific reagent and control lot combination must be entered manually on all analyzers (except for the **cobas e** 602 analyzer). Therefore always refer to the value sheet included in the reagent kit or PreciControl kit to make sure that the correct target values are used.
When a new reagent or control lot is used, the analyzer will use the original values encoded in the control barcodes.

Calculation

The analyzer automatically calculates the cutoff based on the measurement of HBSAG II Cal1 and HBSAG II 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

Samples with a cutoff index < 0.90 are non-reactive in the Elecsys HBsAg II assay. These samples are considered negative for HBsAg and do not need further testing.

Samples having a cutoff index in the range ≥ 0.90 to < 1.0 are considered borderline in the Elecsys HBsAg II assay.

Samples with a cutoff index ≥ 1.0 are considered reactive.

All initially reactive or borderline samples should be redetermined in duplicate using the Elecsys HBsAg II assay. If cutoff index values < 0.90 are found in both cases, the sample is considered negative for HBsAg. Initially reactive or borderline samples giving cutoff index values of ≥ 0.90 in either of the redeterminations are considered repeatedly reactive.

Repeatedly reactive samples must be investigated using an independent neutralization test (Elecsys HBsAg Confirmatory Test).

Samples confirmed by neutralization with human anti-HBs are regarded as positive for HBsAg.

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	≤ 684 µmol/L or ≤ 40 mg/dL
Hemoglobin	≤ 1.24 mmol/L or ≤ 2000 mg/dL
Intralipid	≤ 2000 mg/dL
Biotin	≤ 4912 nmol/L or ≤ 1200 ng/mL
Rheumatoid factors	≤ 6210 IU/mL
IgG	≤ 3817 mg/dL
IgA	≤ 3250 mg/dL
IgM	≤ 3678 mg/dL

Criterion for all substances but biotin: Correct assignment of negative and positive samples.

Criterion for biotin: Correct assignment of negative and positive samples. Samples with a COI (cutoff index) < 0.7: recovery < COI + 0.3; samples with a COI ≥ 0.7: recovery 80-140 %.

No false negative result due to high-dose hook effect was found with the Elecsys HBsAg II assay up to a concentration of 1.5 million IU/mL.

No significant interfering effects of 21 commonly used therapeutic drugs could be detected.

According to the present state of knowledge, it can be assumed that available assays for the detection of HBsAg cannot identify all infected blood samples or persons. A negative test result does not exclude with certainty a possible exposure to or an infection with the hepatitis B virus. Negative test results obtained for persons with a past exposure may be caused by an antigen concentration below the detection limit of this assay or the lack of reactivity of the antigens to the antibodies used in this assay.

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.

cobas e 601 and **cobas e** 602 analyzers:

Make sure that in the Special Wash List (Screen → Utility → Special Wash → Immune) the Elecsys HBsAg II assay is combined with all assays performed on the analyzer - including the Elecsys HBsAg II assay itself:

From test	Step	To test	Step 0	Step 1	Step 2
Elecsys HBsAg II	1	Elecsys HBsAg II	x	x	x
Elecsys HBsAg II	1	each other assay	x	x	x

If new tests are installed make sure that the Special Wash List is updated accordingly.

For the Elecsys Anti-HBs II assay make sure that "Step 1" and "Step 2" are activated:

From test	Step	To test	Step 0	Step 1	Step 2
Elecsys Anti-HBs II	1	Elecsys HBsAg II	-	x	x

The described additions to the Special Wash List have to be entered manually. Please refer to the operator's manual.

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

Elecsys HBsAg II

cobas®

Limits and ranges

Detection limit

In order to determine the sensitivity, the HBsAg concentration which corresponds to the measuring signal of the cutoff value was read off the standard curves of serial dilutions of HBsAg standards (ad and ay) in human HBV-negative serum.

	Paul-Ehrlich-Institute standards				WHO standard 00/588	
	Subtype ad, 1985		Subtype ay, 1985		Subtype ad	
Sample	COI	U/mL	COI	U/mL	COI	IU/mL
1	88.4	1.999	566	10.0	39.4	2.00
2	44.7	1.005	289	5.04	19.9	0.998
3	3.09	0.047	12.7	0.200	1.64	0.052
4	0.396	0.000	0.421	0.000	0.409	0.000
Cutoff sensitivity (cutoff = 0.9)	≤ 0.04 U/mL		≤ 0.04 U/mL		≤ 0.1 IU/mL	

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[b]		**Intermediate precision**[c]	
Sample	Mean COI	SD COI	CV %	SD COI	CV %
HS[d], negative	0.267	0.033	12.5	0.060	22.5
HS, high negative	0.695	0.035	5.0	0.066	9.6
HS, weakly positive	1.00	0.039	3.9	0.076	7.6
HS, positive	7.74	0.147	1.9	0.432	5.6
PreciControl HBsAg II 1	0.454	0.045	9.9	0.066	14.4
PreciControl HBsAg II 2	3.14	0.060	1.9	0.206	6.6

b) Repeatability = within-run precision

c) Intermediate precision = between-run precision

d) HS = human serum

cobas e 601 and **cobas e** 602 analyzers					
		Repeatability		**Intermediate precision**	
Sample	Mean COI	SD COI	CV %	SD COI	CV %
HS[d], negative	0.235	0.024	10.3	0.043	18.2
HS, high negative	0.899	0.040	4.5	0.077	8.6
HS, weakly positive	1.01	0.035	3.4	0.082	8.1
HS, positive	8.00	0.253	3.2	0.589	7.4
PreciControl HBsAg II 1	0.353	0.029	8.2	0.052	14.6
PreciControl HBsAg II 2	3.01	0.085	2.8	0.245	8.1

Analytical specificity

1596 samples containing potentially interfering substances were tested with the Elecsys HBsAg II assay comprising specimens:

- containing antibodies against HAV, HCV, HIV, HTLV, CMV, EBV, HSV, Rubella, Parvo virus, VZV, Toxoplasma gondii, Treponema pallidum, Borrelia, Listeriosis
- containing autoantibodies (ANA, SLE), elevated titers of rheumatoid factor or HAMA antibodies
- positive for Mumps, Measles, Malaria
- after vaccination against HBV and influenza
- from patients with monoclonal gammopathy and multiple myeloma/lymphoma, patients undergoing dialysis or patients suffering from alcoholic liver disease
- from pregnant women

No false positive result was found. 14 samples were found to be positive for HBsAg (1 out of each group of the HAV, HIV, HTLV and EBV antibody positive patients; 1 from a patient undergoing dialysis and 9 from pregnant women). 2 samples (1 after HBV vaccination and 1 with elevated RF) were initially positive, but negative after performing a second measurement. The overall specificity was 100 % (lower confidence limit 95 %, one-sided: 99.81 %).

Clinical sensitivity

A total of 1025 selected HBsAg confirmed positive samples in various stages of the disease were tested with the Elecsys HBsAg II assay. 1024 samples were correctly identified (1 sample was repeatedly negative (COI 0.81-0.88), positively neutralized with the Elecsys HBsAg Confirmatory Test; negative in a 3rd HBsAg assay, anti-HBs negative, anti-HBe negative, HBeAg negative, anti-HBc positive). The sensitivity in that group of 1025 samples is 99.9 %.

A total of 156 genotyped samples (genotype A (30), B (8), C (11), C/E (1), D (68), E (17), F (17), G (3), not assigned (1)) and all known HBsAg subtypes (CNTS "Centre National de la Transfusion Sanguine", n = 9 subtype panels) were tested with the Elecsys HBsAg II assay. All of them were positive except for 6 samples (2 of genotype A, 1 of genotype D and 3 of genotype E) with negative or low HBV-DNA (also negative in other HBsAg tests). A total of 115 samples comprising different HBsAg mutations were tested with the Elecsys HBsAg II assay and compared to 3 registered HBsAg assays.

Mutant panel	Elecsys HBsAg II tested/positive
Native mutant panel 1 (strains displaying amino acid substitutions either linked to vaccine resistance, resistance to therapy with human HB immunoglobulin or impaired HBsAg reactivity)	41/40[e]
Native mutant panel 2 (strains displaying other amino acid changes)	24/24
Native mutant panel 3	19/17[f]
Recombinant mutant panel	31/31
Total	115/112

e) sample (mutation G145R) negative in all assays (COI 0.1-0.8); all measurements were performed in 1:40 dilution (FCS: fetal calf serum)

f) samples (mutation M133L/M143T/G145R and mutation T45S/I49R/113T114/I186P, respectively) negative in all assays tested; 1st mutation tested in 3 assays (COI 0.03-0.76), 2nd mutation tested in 4 assays (COI 0.03-0.78)

For 8 performance panels (Boston Biomedica, Inc.) the Elecsys HBsAg II assay shows a very good concordance with the data given in the respective product information (140 positives out of 150 samples tested). All positive assigned samples were positive with the Elecsys HBsAg II assay, resulting in a 100 % sensitivity.

Clinical specificity

The specificity of the Elecsys HBsAg II assay in a group of 6360 blood donors was found to be as follows: initially reactive (IR) specificity 99.91 %; repeatedly reactive (RR) specificity 99.98 %.

Elecsys HBsAg II

cobas®

In the group of the 3593 daily routine samples (hospitalized patients, outpatients, pre-surgery, health care workers and anonymous testing), the specificity (IR and RR) was 99.88 %.

Group	Number	Initially reactive	Repeatedly reactive	Confirmed positive
Blood donors	6360	8	3	2
Hospitalized patients	3593	181	176[g)]	122[h)]

g) 5 samples could not be repeated due to insufficient sample volume

h) 55 samples could not be neutralized due to insufficient sample volume; 1 sample was negative with the Elecsys HBsAg II assay

Seroconversion panels

Seroconversion sensitivity of the Elecsys HBsAg II assay has been shown by testing 56 commercial seroconversion panels in comparison to registered HBsAg assays. In all panels the Elecsys HBsAg II assay shows detection of seroconversion equal to or earlier than other HBsAg assays.

References

1 Proposal for the Validation of Anti-HIV-1/2 or HIV Ag/Ab Combination Assays, anti-HCV-Assays, HBsAg and Anti-HBc assays for Use with Cadaveric Samples; PEI 08/05/2014.

2 Seeger C, Zoulim F, Mason WS. Hepadnaviruses. In: Field's Virology, Knipe DM, Howley RM (eds), 2007 5th edition, Lippincott Williams and Wilkins, Philadelphia, USA. Chapter 76, pp2977-3029.

3 Lee JM, Ahn SH. Quantification of HBsAg: basic virology for clinical practice. World J Gastroenterol 2011;17:283-289.

4 Liaw YF. Clinical utility of hepatitis B surface antigen quantification in patients with chronic hepatitis B: a review. Hepatology 2011;54:W1-E9.

5 Norder H, Couroucé AM, Coursaget P, et al. Genetic diversity of hepatitis B virus strains derived worldwide: genotypes, subgenotypes and HBsAg subtypes. Intervirology 2004;47:289-309.

6 Gerlich W. Diagnostic problems caused by HBsAg mutants – a consensus report of an expert meeting. Intervirology 2004;47:310-313.

7 Liaw YF, Chu CM. Hepatitis B infection. Lancet 2009;373:582-592.

8 WHO. Hepatitis B. Fact sheet N°204. Available at: http://www.who.int/mediacentre/factsheets/fs204/en, accessed March 2015.

9 Sonneveld MJ, Zoutendijk R, Janssen HLA. Hepatitis B surface antigen monitoring and management of chronic hepatitis B. J Viral Hepat 2011;18:449-457.

10 US Preventative Services Task Force. Screening for hepatitis B virus infection in pregnancy: US Preventative Services Task Force Reaffirmation Recommendation Statement. Ann Int Med 2009;150:569-873.

11 Occupational Safety and Health Standards: Bloodborne pathogens. (29 CFR Part 1910.1030). Fed. Register.

12 Directive 2000/54/EC of the European Parliament and Council of 18 September 2000 on the protection of workers from risks related to exposure to biological agents at work.

13 Commission Directive 2006/17/EC of 8 February 2006 implementing Directive 2004/23/EC of the European Parliament and of the Council as regards certain technical requirements for the donation, procurement and testing of human tissues and cells.

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.

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

Roche Diagnostics GmbH, Sandhofer Strasse 116, D-68305 Mannheim
www.roche.com

Roche

EG-Konformitätserklärung/*EC Declaration of Conformity*

gemäß Anhang IV der Richtlinie 98/79/EG des Europäischen Parlaments und des Rates vom 27. Oktober 1998 mit TÜV SÜD Product Service GmbH (Ridlerstraße 65, 80339 München, Germany) als Notified Body (Nr. 0123)
as per Annex IV of Directive 98/79/EC of the European Parliaments and Council of 27 October 1998 via TÜV SÜD Product Service GmbH (Ridlerstrasse 65, 80339 Munich, Germany) as the Notified Body (No. 0123)

Hersteller/*Manufacturer*:	Roche Diagnostics GmbH
Adresse/*Address:*	Sandhofer Strasse 116 D-68305 Mannheim

Die Roche Diagnostics GmbH erklärt, dass das Produkt/die Produktfamilie
Roche Diagnostics GmbH declares that the product/the product line

Produktname/*Product name*:	**Elecsys HIV combi PT**
Art.-Nr./*Cat. No.*:	**08924163190** **08924180190**
Beschreibung/*Description*:	Immunologischer In-vitro-Test zur qualitativen Bestimmung von HIV-1 p24-Antigen und Antikörper gegen HIV-1, einschließlich Gruppe O, und HIV-2 in Humanserum und -plasma. Der **E**lektro**C**hemi**L**umineszenz **I**mmuno**A**ssay "ECLIA" ist zur Durchführung an **cobas e** Immunoassay-Systemen vorgesehen. *Immunoassay for the in vitro qualitative determination of HIV-1 p24 antigen and antibodies to HIV-1, including group O, and HIV-2 in human serum and plasma.* *The **electrochemiluminescence immunoassay** "ECLIA" is intended for use on **cobas e** immunoassay analyzers.*

auf das/die sich diese Erklärung bezieht, den Forderungen der Richtlinie 98/79/EG des Europäischen Parlaments und des Rates vom 27. Oktober 1998 über In-vitro-Diagnostica (bzw. seine Umsetzung in nationales Recht der Mitgliedsstaaten in welchen das Produkt vermarktet werden soll) entspricht.
to which this declaration relates fulfils the requirements of Directive 98/79/EC of the European Parliament and Council of 27 October 1998 on in-vitro diagnostic medical devices (and its relevant transposition into the national laws of the Member States in which the device is intended to be placed on the market).

Roche Diagnostics GmbH; Sandhofer Strasse 116; D-68305 Mannheim; Telefon +49-621-759-0; Telefax +49-621-759-2890

Sitz der Gesellschaft: Mannheim - Registergericht: AG Mannheim HRB 3962 - Geschäftsführung: Claus Haberda; Andreas Schmitz - Aufsichtsratsvorsitzender: Dr. Thomas Schinecker

Mannheim, 29 May 2020

Roche Diagnostics GmbH

ppa./*on behalf of the company*

DocuSigned by:
R Zielenski
A45CC19E27A04F3...

Ralf Zielenski
Head of Quality
Centralised and Point of Care Solutions

ppa./*on behalf of the company*

DocuSigned by:
Stefan Scheib
FC5EDEC1054B44C...

Dr. Stefan Scheib
Director Global Regulatory Affairs
Centralised and Point of Care Solutions

Kontaktadresse/*Contact address*: Roche Diagnostics GmbH
Abt./*Dept.* Global Regulatory Affairs
Sandhofer Strasse 116
D-68305 Mannheim

08924163500V1.0

Elecsys HIV combi PT

cobas®

REF		Σ	SYSTEM
08924163190	08924163500	100	**cobas e** 411 **cobas e** 601 **cobas e** 602

English

System information

For **cobas e** 411 analyzer: test number 2250
For **cobas e** 601 and **cobas e** 602 analyzers: Application Code Number 225

Intended use

Immunoassay for the in vitro qualitative determination of HIV-1 p24 antigen and antibodies to HIV-1, including group O, and HIV-2 in human serum and plasma.

The electrochemiluminescence immunoassay "ECLIA" is intended for use on **cobas e** immunoassay analyzers.

Regulatory approval

This assay has been CE marked according to Directive 98/79/EC. Test performance has been established and certified by a Notified Body according to the Common Technical Specifications (CTS) for diagnostic use and for screening of blood donations and, according to Paul-Ehrlich-Institut (PEI) recommendation,[1] for use of cadaveric blood specimens (specimens collected post-mortem, non-heart-beating).

Summary

The human immunodeficiency virus (HIV), the causative agent of Acquired Immunodeficiency Syndrome (AIDS), belongs to the family of retroviruses. HIV can be transmitted through sexual contact, contaminated blood and blood products or from an HIV-infected mother to her child before, during and after birth.

Two types of HIV, called HIV-1 and HIV-2, have been identified to date.[2,3,4,5] HIV-1 can be divided into 4 distantly related groups: group M (for main), group N (for non-M, non-O), group O (for outlier) and group P.[6,7,8] Based on their genetic relationship, 9 different subtypes (A to D, F to H, J, K) as well as several circulating recombinant forms (CRFs) have been identified within HIV-1 group M.[9] The large majority of HIV-1 infections are caused by viruses belonging to group M, while geographical distribution of subtypes and CRFs within this group varies strongly.[10] Due to differences in the sequence of immunodominant epitopes, especially in the envelope proteins of HIV-1 group M, HIV-1 group O and HIV-2, specific antigens are necessary to avoid failure in the detection of an HIV infection by immunoassays.[11,12]

HIV p24 antigen in blood specimen of recently infected patients can be detected as early as 2-3 weeks after infection.[13,14] Anti-HIV antibodies are detectable in serum from around 4 weeks post infection.[13,15] The combined detection of HIV p24 antigen and anti-HIV antibodies in 4th generation HIV screening assays leads to improved sensitivity and therefore a shorter diagnostic window compared to traditional anti-HIV assays.[16,17]

With the Elecsys HIV combi PT assay the HIV-1 p24 antigen and antibodies to HIV-1 and HIV-2 can be detected simultanously within one determination. The assay uses recombinant antigens derived from the *env*- and *pol*-region of HIV-1 (including group O) and HIV-2 to determine HIV-specific antibodies. For the detection of HIV-1 p24 antigen specific monoclonal antibodies are used. Repeatedly reactive samples must be confirmed according to recommended confirmatory algorithms. Confirmatory tests include Western Blot and HIV RNA tests.

Test principle

Sandwich principle. Total duration of assay: 27 minutes.

- 1st incubation: Pretreatment of 40 µL of sample with detergent agent.
- 2nd incubation: Biotinylated monoclonal anti-p24 antibodies/HIV-specific recombinant antigens/HIV-specific peptides, and monoclonal anti-p24 antibodies/HIV-specific recombinant antigens/HIV-specific peptides labeled with a ruthenium complex[a)] react to form a sandwich complex.
- 3rd 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/ProCell 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 reagent rackpack (M, R0, R1, R2) is labeled as HIVCOMPT.

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

R0 MES[b)] buffer 50 mmol/L, pH 5.5; 1.5 % Nonidet P40; preservative (white cap), 1 bottle, 4 mL.

R1 Anti-HIV p24-Ab~, HIV-1/2-specific recombinant antigens (E. coli)~, HIV-1/2-specific peptides~biotin (gray cap), 1 bottle, 7 mL: Biotinylated monoclonal anti-p24 antibodies (mouse), biotinylated HIV-1/2-specific recombinant antigens (E. coli), biotinylated HIV-1/2-specific peptides > 1.3 mg/L; TRIS[c)] buffer 50 mmol/L, pH 7.5; preservative.

R2 Anti-HIV p24-Ab~, HIV-1/2-specific recombinant antigens (E. coli)~, HIV-1/2-specific peptides~$Ru(bpy)_3^{2+}$ (black cap), 1 bottle, 7 mL: Monoclonal anti-p24 antibodies (mouse), HIV-1/2-specific recombinant antigens, HIV-1/2-specific peptides labeled with ruthenium complex > 1.5 mg/L; TRIS buffer 50 mmol/L, pH 7.5; preservative.

b) MES = 2-morpholino-ethane sulfonic acid

c) TRIS = Tris(hydroxymethyl)-aminomethane

HIVCOMPT Cal1 Negative calibrator (white cap; lyophilized), 2 bottles for 1.0 mL each:
Human serum, non reactive for anti-HIV-1 and anti-HIV-2.

HIVCOMPT Cal2 Positive calibrator (black cap; lyophilized), 2 bottles for 1.0 mL each:
Anti-HIV-1 positive human serum (inactivated) in human serum negative for anti-HIV-1 and anti-HIV-2.

Precautions and warnings

For in vitro diagnostic use.
Exercise the normal precautions required for handling all laboratory reagents.
Disposal of all waste material should be in accordance with local guidelines.
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:

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

EUH 208 May produce an allergic reaction.

Warning

H317 May cause an allergic skin reaction.

Elecsys HIV combi PT

cobas®

H319	Causes serious eye irritation.
H412	Harmful to aquatic life with long lasting effects.

Prevention:

P261	Avoid breathing dust/fume/gas/mist/vapours/spray.
P273	Avoid release to the environment.
P280	Wear protective gloves/ eye protection/ face protection.

Response:

P333 + P313	If skin irritation or rash occurs: Get medical advice/attention.
P337 + P313	If eye irritation persists: Get medical advice/attention.
P362 + P364	Take off contaminated clothing and wash it before reuse.

Product safety labeling follows EU GHS guidance.

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

All human material should be considered potentially infectious.

The negative calibrator (HIVCOMPT Cal1) has been 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 used assays approved by the FDA or cleared in compliance with the European Directive 98/79/EC, Annex II, List A.

The serum containing anti-HIV-1 (HIVCOMPT Cal2) was inactivated using β-propiolactone and UV-radiation.

However, as no inactivation or 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.[18,19]

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

Reagent handling

The reagents (M, R0, R1, R2) in the kit are ready-for-use and are supplied in bottles compatible with the system.

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.

cobas e 411 analyzer: The reconstituted calibrators should only be left on the analyzer during calibration at 20-25 °C. After use, close the bottles as soon as possible and store upright at 2-8 °C.

Due to possible evaporation effects, not more than 5 calibration procedures per calibrator bottle set should be performed.

cobas e 601 and **cobas e** 602 analyzers: Unless the entire volume is necessary for calibration on the analyzers, 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 for later use.

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

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

Please note: Both the vial labels, and the additional labels (if available) contain 2 different barcodes. The barcode between the yellow markers is for **cobas** 8000 systems only. If using a **cobas** 8000 system, please turn the vial cap 180° into the correct position so the barcode can be read by the system. Place the vial on the instrument as usual.

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 of the reagent rackpack	
unopened at 2-8 °C	up to the stated expiration date
after opening at 2-8 °C	12 weeks
on the analyzers	28 days

Stability of the calibrators	
lyophilized	up to the stated expiration date
reconstituted at 2-8 °C	12 weeks
on **cobas e** 411 at 20-25 °C	up to 5 hours
on **cobas e** 601 and **cobas e** 602 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.[20] 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 as well as Li-heparin plasma tubes containing separating gel.

Criterion: Correct assignment of negative and positive samples.

Sampling devices containing liquid anticoagulants have a dilution effect resulting in lower cutoff index (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, 4 weeks at 2-8 °C, 3 months at -20 °C (± 5 °C). The samples may be frozen 5 times.
For cadaveric specimens: Stable for 3 days at 20-25 °C, 7 days at 2-8 °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 samples and controls stabilized with azide.

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.

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

Materials provided

See "Reagents – working solutions" section for reagents.

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

Elecsys HIV combi PT

cobas®

Materials required (but not provided)

- REF 06924107190, PreciControl HIV Gen II, for 6 x 2.0 mL
- REF 06924115190, PreciControl HIV; HIV-2+GrpO, for 4 x 2.0 mL (optional use)
- REF 11776576322, CalSet Vials, 2 x 56 empty snap-cap bottles
- General laboratory equipment
- **cobas e** analyzer
- Distilled or deionized water

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.

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.

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

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.

Calibrators:

Place the reconstituted calibrators in the sample zone.

All the information necessary for calibrating the assay is automatically read into the analyzer.

After calibration has been performed, store the calibrators at 2-8 °C or discard (**cobas e** 601 and **cobas e** 602 analyzers).

Calibration

Traceability: No internationally accepted standard for anti-HIV-1 and anti-HIV-2 exists.

This method has been standardized against the Human Immunodeficiency Virus Type 1 (HIV-1 p24 Antigen) - 1st International Reference Reagent 1992, code 90/636 - available from NIBSC (National Institute for Biological Standards and Control).

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

Range for the electrochemiluminescence signals (counts) for the calibrators:

Negative calibrator (HIVCOMPT Cal1):
1200-3500 (**cobas e** 411 analyzer)
550-2200 (**cobas e** 601 and **cobas e** 602 analyzers)

Positive calibrator (HIVCOMPT Cal2):
17000-75000 (**cobas e** 411 analyzer)
14000-70000 (**cobas e** 601 and **cobas e** 602 analyzers)

Quality control

For quality control, use PreciControl HIV Gen II. The use of PreciControl HIV; HIV-2+GrpO is optional. Note that all HIV results are sufficiently controlled if only PreciControl HIV Gen II is used.

All controls 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.

Note:
For technical reasons re-assigned target values valid only for a specific reagent and control lot combination must be entered manually on all analyzers (except for the **cobas e** 602 analyzer). Therefore always refer to the value sheet included in the reagent kit or PreciControl kit to make sure that the correct target values are used.
When a new reagent or control lot is used, the analyzer will use the original values encoded in the control barcodes.

Calculation

The analyzer automatically calculates the cutoff based on the measurement of HIVCOMPT Cal1 and HIVCOMPT 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

Samples with a cutoff index < 0.90 are non-reactive in the Elecsys HIV combi PT assay. These samples are considered negative for HIV-1 Ag and HIV-1/-2 specific antibodies and do not need further testing. Samples having a cutoff index in the range ≥ 0.90 to < 1.0 are considered borderline in the Elecsys HIV combi PT assay.

Samples with a cutoff index ≥ 1.0 are considered reactive in the Elecsys HIV combi PT assay.

All initially reactive or borderline samples should be redetermined in duplicate with the Elecsys HIV combi PT assay. If cutoff index values < 0.90 are found in both cases, the samples are considered negative for HIV-1 Ag and HIV-1/-2 specific antibodies.

Initially reactive or borderline samples giving cutoff index values of ≥ 0.90 in either of the redeterminations are considered repeatedly reactive. Repeatedly reactive samples must be confirmed according to recommended confirmatory algorithms. Confirmatory tests include Western Blot and HIV RNA tests.

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.

Elecsys HIV combi PT

cobas®

Endogenous substances

Compound	Concentration tested
Bilirubin	≤ 1026 µmol/L or ≤ 60 mg/dL
Hemoglobin	≤ 0.310 mmol/L or ≤ 500 mg/dL
Intralipid	≤ 1500 mg/dL
Biotin	≤ 4912 nmol/L or ≤ 1200 ng/mL
Rheumatoid factors	≤ 1500 IU/mL

Criterion: Correct assignment of negative and positive samples.

No false negative result due to high-dose hook effect was found with the Elecsys HIV combi PT assay.

Pharmaceutical substances

In vitro tests were performed on 18 commonly used pharmaceuticals. 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.

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 HIV. Serum or plasma samples from the very early (pre-seroconversion) phase or the late phase of HIV infection can occasionally yield negative findings. Yet unknown HIV variants can also lead to a negative HIV finding. The presence of HIV antigen or antibodies to HIV is not a diagnosis of AIDS.

Limits and ranges

Antigen detection

Detection limit: ≤ 2 IU/mL

The stated sensitivity was determined by reading off the HIV Ag concentration corresponding to the signal of the cutoff value from standard curves obtained by serial dilutions of the Human Immunodeficiency Virus Type 1 (HIV-1 p24 Antigen) - 1st International Reference Reagent 1992, code 90/636 - in human HIV-negative serum.

Antibody detection

No internationally accepted standard for HIV-specific antibody detection exists.

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[d]		**Intermediate precision**[e]	
Sample	Mean COI	SD COI	CV %	SD COI	CV %
HS[f], negative	0.141	0.022	-	0.041	-
HS, positive for HIV Ag	1.65	0.040	2.4	0.058	3.5
HS, positive for anti-HIV-1	1.85	0.044	2.4	0.056	3.0
HS, positive for anti-HIV-1	41.7	0.602	1.4	0.861	2.1
HS, positive for anti-HIV-2	1.80	0.044	2.4	0.065	3.6
HS, positive for anti-HIV-1 group O	1.63	0.034	2.1	0.060	3.7
PreciControl HIV1	0.205	0.020	-	0.036	-
PreciControl HIV2	4.66	0.074	1.6	0.103	2.2
PreciControl HIV3	4.55	0.065	1.4	0.124	2.7
PreciControl HIV4	4.25	0.062	1.5	0.080	1.9
PreciControl HIV5	4.99	0.101	2.0	0.118	2.4

d) Repeatability = within-run precision

e) Intermediate precision = between-run

f) HS = human serum

cobas e 601 and **cobas e** 602 analyzers					
		Repeatability		**Intermediate precision**	
Sample	Mean COI	SD COI	CV %	SD COI	CV %
HS, negative	0.104	0.007	-	0.010	-
HS, positive for HIV Ag	1.65	0.037	2.2	0.047	2.9
HS, positive for anti-HIV-1	1.93	0.045	2.3	0.057	3.0
HS, positive for anti-HIV-1	46.0	0.762	1.7	0.995	2.2
HS, positive for anti-HIV-2	1.94	0.054	2.8	0.070	3.6
HS, positive for anti-HIV-1 group O	1.79	0.037	2.1	0.056	3.2
PreciControl HIV1	0.163	0.009	-	0.011	-
PreciControl HIV2	4.85	0.090	1.9	0.120	2.5
PreciControl HIV3	4.52	0.088	1.9	0.115	2.5
PreciControl HIV4	4.57	0.090	2.0	0.133	2.9
PreciControl HIV5	4.74	0.089	1.9	0.127	2.7

Analytical specificity

1182 samples containing potentially interfering substances were tested with the Elecsys HIV combi PT assay comprising specimens:

- containing antibodies against HAV, HBV, HCV, HTLV, CMV, EBV, HSV, VZV, Toxoplasma gondii, Treponema pallidum, Borrelia, Parvovirus B19
- containing autoantibodies and elevated titers of rheumatoid factor
- positive for Candida, E. coli, Plasmodium falciparum/vivax, Mycobacterium tuberculosis
- after vaccination against HAV, HBV, and influenza
- from patients with monoclonal gammopathy and multiple myeloma/lymphoma

	N	Elecsys HIV combi PT assay		Western Blot[g]	Analytical specificity
		IR[h] COI ≥ 1	RR[i] COI ≥ 1		
Specimens containing potentially interfering substances	1182	1[j]	1	0	99.92 % 95 % lower confidence limit: 99.53 %

g) Western Blot confirmed positive/indeterminate

h) IR = initially reactive

i) RR = repeatedly reactive

j) Patients with monoclonal gammopathy: 1 out of 21

Clinical sensitivity

Of 179 HIV samples from early seroconversion phase (according to CTS definition), 172 samples were found positive with the Elecsys HIV combi PT assay.

Elecsys HIV combi PT

cobas®

Of 1532 samples from HIV infected patients in different stages of the disease and infected with HIV-1 group M, O and HIV-2, 1532 were found to be reactive with the Elecsys HIV combi PT assay. The sensitivity of the Elecsys HIV combi PT assay in this study was 100 %.

The 95 % lower confidence limit was 99.76 %.

Group	N	Reactive
HIV-1 infected persons from various stages of disease	338	338
Infection with HIV-1 group M (subtypes A-J)	629	629
Infection with HIV-1 group O	8	8
Infection with HIV-2	472	472
HIV Ag positive specimens	85	85

53 lysates of cell culture supernatants including different HIV-1 group M subtypes (A-H), HIV-1 group O, and HIV-2 were tested and found reactive in the Elecsys HIV combi PT assay.

In 46 follow-ups of very early HIV infections, 100 out of 105 samples were detected positive with the Elecsys HIV combi PT assay.

Clinical specificity

In a group of 7343 randomly selected blood donors from Europe and Asia the specificity of the Elecsys HIV combi PT assay was found 99.88 % (RR). The 95 % lower confidence limit was 99.77 %.

In a group of 4103 samples from unselected daily routine, dialysis patients and pregnant women the specificity of the Elecsys HIV combi PT assay was found 99.81 % (RR). The 95 % lower confidence limit was 99.62 %.

	N	Elecsys HIV combi PT assay		Western Blot[k)]	Clinical specificity (95 % lower confidence limit)
		IR COI ≥ 1	RR COI ≥ 1		
Blood donors	7343	13	11	1/1	99.88 % (99.77 %)
Unselected samples from daily routine	2721	33	33	26	99.74 % (99.47 %)
Dialysis patients	251	1	1	0	99.60 % (97.80 %)
Pregnant women	1131	1	1	1	100 % (99.67 %)

k) Western Blot (WB) confirmed positive/indeterminate. Samples with indeterminate WB were excluded from calculation.

Seroconversion panels

Seroconversion sensitivity of the Elecsys HIV combi PT assay has been shown by testing 102 commercial seroconversion panels in comparison to registered HIV combi assays or anti-HIV immunoassays and/or HIV Ag assays.

References

1 Proposal for the Validation of Anti-HIV-1/2 or HIV Ag/Ab Combination Assays, anti-HCV-Assays, HBsAg and Anti-HBc assays for Use with Cadaveric Samples; PEI 08/05/2014.

2 Barré-Sinoussi F, Chermann JC, Rey F, et al. Isolation of a T-lymphotrophic Retrovirus from a Patient at Risk for Acquired Immune Deficiency Syndrome (AIDS). Science 1983;220:868-871.

3 Popovic M, Sarngadharan MG, Read E, et al. Detection, Isolation and Continuous Production of Cytopathic Retroviruses (HTLV-III) from Patients with AIDS and Pre-AIDS. Science 1984;224:497-500.

4 Gallo RC, Salahuddin SZ, Popovic M, et al. Frequent Detection and Isolation of cytopathic Retroviruses (HTLV-III) from Patients with AIDS and RISk for AIDS. Science 1984;224:500-503.

5 Clavel F, Guétard D, Brun-Vézinet F, et al. Isolation of a New Human Retrovirus from West Africa Patients with AIDS. Science 1986;233:343-346.

6 Guertler LG, Hauser PH, Eberle J, et al. A New Subtype of Human Immunodeficiency Virus Type 1 (MVP-5180) from Cameroon. J Virol 1994;68(3):1581-1585.

7 Simon F, Mauclère P, Roques P, et al. Identification of a new human immunodeficiency virus type 1 distinct from group M and group O. Nature Medicine 1998;4(9):1032-1037.

8 Plantier JC, Leoz M, Dickerson JE, et al. A new human immunodeficiency virus derived from gorillas. Nature Medicine 2009;15(8):871-872.

9 Robertson DL, Anderson JP, Bradac JA, et al. HIV-1 nomenclature Proposal. Science 2000;288(5463):55-56.

10 Taylor BS, Hammer SM. The challenge of HIV-1 subtype diversity. N Engl J Med 2008;358:1590-1602.

11 Guertler LG. Difficulties and strategies of HIV diagnosis. Lancet 1996;348:176-179.

12 Verdier M, Denis F, Leonard G, et al. Comparison of 10 Enzyme Immunoassays for Detection of Antibody to Human Immunodeficiency Virus Type 2 in West African Sera. J Clin Microbiol 1988;26:1000-1004.

13 Fiebig EW, Wright DJ, Rawal BD, et al. Dynamics of HIV viremia and antibody seroconversion in plasma donors: implications for diagnosis and staging of primary HIV infection. AIDS 2003;17(13):1871-1879.

14 Busch MP, Lee LL, Satten GA, et al. Time course of detection of viral and serologic markers preceding human immunodeficiency virus type 1 seroconversion: implications for screening of blood and tissue donors. Transfusion 1995;35:91-97.

15 Busch MP, Satten GA. Time course of viremia and antibody seroconversion following human immunodeficiency virus exposure. Am J Med 1997;102(5B):117-124.

16 Weber B, Fall EH, Berger A, et al. Reduction of Diagnostic Window by New Fourth-generation Human immunodeficiency Virus Screening Assays. Clin Microbiol 1998;36(8):2235-2239.

17 Guertler L, Mühlbacher A, Michl U, et al. Reduction of the diagnostic window with a new combined p24 antigen and human immunodeficiency virus antibody screening assay. Journal of Virological Methods 1998;75:27-38.

18 Occupational Safety and Health Standards: Bloodborne pathogens. (29 CFR Part 1910.1030). Fed. Register.

19 Directive 2000/54/EC of the European Parliament and Council of 18 September 2000 on the protection of workers from risks related to exposure to biological agents at work.

20 Commission Directive 2006/17/EC of 8 February 2006 implementing Directive 2004/23/EC of the European Parliament and of the Council as regards certain technical requirements for the donation, procurement and testing of human tissues and cells.

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.

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

08924163500V1.0

Elecsys HIV combi PT

cobas®

CE 0123

Roche Diagnostics GmbH, Sandhofer Strasse 116, D-68305 Mannheim
www.roche.com

Roche

ZERTIFIKAT ◆ CERTIFICATE ◆ 認證證書 ◆ СЕРТИФИКАТ ◆ CERTIFICADO ◆ CERTIFICAT

Benannt durch/Designated by
Zentralstelle der Länder für Gesundheitsschutz bei Arzneimitteln und Medizinprodukten
www.zlg.de
ZLG-BS-245.10.07

Product Service

EC Certificate

EC Design-Examination Certificate
Directive 98/79/EC on In Vitro Diagnostic Medical Devices (IVDD), Annex IV (4) (List A)

No. V7 010283 0630 Rev. 01

Manufacturer:

Roche Diagnostics GmbH
Sandhofer Strasse 116
68305 Mannheim
GERMANY

Product: **Screening test for Hepatitis C marker**

The Certification Body of TÜV SÜD Product Service GmbH declares that a design examination has been carried out on the respective devices in accordance with IVDD Annex IV (4). The design of the devices conforms to the requirements of this Directive. All applicable requirements of the testing and certification regulation of TÜV SÜD Group have to be complied with. For details and certificate validity see: www.tuvsud.com/ps-cert?q=cert:V7 010283 0630 Rev. 01

Report No.: 713223907-2_20

Valid from: 2021-09-16
Valid until: 2024-05-26

Date, 2021-09-14

Christoph Dicks
Head of Certification/Notified Body

TÜV SÜD Product Service GmbH is Notified Body with identification no. 0123

TÜV SÜD Product Service GmbH • Certification Body • Ridlerstraße 65 • 80339 Munich • Germany

Benannt durch/Designated by
Zentralstelle der Länder für Gesundheitsschutz bei Arzneimitteln und Medizinprodukten
www.zlg.de
ZLG-BS-245.10.07

TÜV SÜD Product Service

EC Certificate

EC Design-Examination Certificate
Directive 98/79/EC on In Vitro Diagnostic Medical Devices (IVDD), Annex IV (4) (List A)

No. V7 010283 0630 Rev. 01

Model(s):

Elecsys Anti-HCV II
PreciControl Anti-HCV
Elecsys and cobas e analyzers

Facility(ies):

Roche Diagnostics GmbH
Nonnenwald 2, 82377 Penzberg, GERMANY

Roche Diagnostics GmbH
Sandhofer Strasse 116, 68305 Mannheim, GERMANY

Roche Diagnostics International Ltd
Forrenstrasse 2, 6343 Rotkreuz, SWITZERLAND

Parameters:

Model Name:	Model No.:
Elecsys Anti-HCV II	06368921190
Elecsys Anti-HCV II	06427405190
Elecsys Anti-HCV II	07026889190
PreciControl Anti-HCV	03290379190
Elecsys and cobas e analyzers	

TÜV SÜD Product Service GmbH is Notified Body with identification no. 0123

TÜV SÜD Product Service GmbH • Certification Body • Ridlerstraße 65 • 80339 Munich • Germany

TÜV®

ZERTIFIKAT ◆ CERTIFICATE ◆ 認證證書 ◆ СЕРТИФИКАТ ◆ CERTIFICADO ◆ CERTIFICAT

Benannt durch/Designated by
Zentralstelle der Länder für Gesundheitsschutz bei Arzneimitteln und Medizinprodukten
www.zlg.de
ZLG-BS-245.10.07

Product Service

EC Certificate

EC Design-Examination Certificate
Directive 98/79/EC on In Vitro Diagnostic Medical Devices (IVDD), Annex IV (4) (List A)

No. V7 010283 0621 Rev. 02

Manufacturer:

Roche Diagnostics GmbH
Sandhofer Strasse 116
68305 Mannheim
GERMANY

Product: **Screening test for HIV-1/-2 marker**

The Certification Body of TÜV SÜD Product Service GmbH declares that a design examination has been carried out on the respective devices in accordance with IVDD Annex IV (4). The design of the devices conforms to the requirements of this Directive. All applicable requirements of the testing and certification regulation of TÜV SÜD Group have to be complied with. For details and certificate validity see: www.tuvsud.com/ps-cert?q=cert:V7 010283 0621 Rev. 02

Report No.: 713223907-2_13

Valid from: 2021-09-16
Valid until: 2024-05-26

Date, 2021-09-14

Christoph Dicks
Head of Certification/Notified Body

TÜV SÜD Product Service GmbH is Notified Body with identification no. 0123

TÜV SÜD Product Service GmbH • Certification Body • Ridlerstraße 65 • 80339 Munich • Germany

TÜV®

ZERTIFIKAT ◆ CERTIFICATE ◆ 認證證書 ◆ СЕРТИФИКАТ ◆ CERTIFICADO ◆ CERTIFICAT

Benannt durch/Designated by
Zentralstelle der Länder für Gesundheitsschutz bei Arzneimitteln und Medizinprodukten
www.zlg.de
ZLG-BS-245.10.07

Product Service

EC Certificate

EC Design-Examination Certificate
Directive 98/79/EC on In Vitro Diagnostic Medical Devices (IVDD), Annex IV (4) (List A)

No. V7 010283 0621 Rev. 02

Model(s):

Elecsys HIV combi PT
Elecsys and cobas e analyzers

Facility(ies):

Roche Diagnostics GmbH
Nonnenwald 2, 82377 Penzberg, GERMANY

Roche Diagnostics GmbH
Sandhofer Strasse 116, 68305 Mannheim, GERMANY

Roche Diagnostics International Ltd
Forrenstrasse 2, 6343 Rotkreuz, SWITZERLAND

Parameters:

Model Name:	Model No.:
Elecsys HIV combi PT	05390095190 08924163190
Elecsys HIV combi PT	07914504190 08924180190
Elecsys and cobas e analyzers	

TÜV SÜD Product Service GmbH is Notified Body with identification no. 0123

TÜV SÜD Product Service GmbH • Certification Body • Ridlerstraße 65 • 80339 Munich • Germany

TÜV®

ZERTIFIKAT ◆ CERTIFICATE ◆ 認證證書 ◆ СЕРТИФИКАТ ◆ CERTIFICADO ◆ CERTIFICAT

Benannt durch/Designated by
Zentralstelle der Länder für Gesundheitsschutz bei Arzneimitteln und Medizinprodukten
www.zlg.de
ZLG-BS-245.10.07

Product Service

EC Certificate

EC Design-Examination Certificate
Directive 98/79/EC on In Vitro Diagnostic Medical Devices (IVDD), Annex IV (4) (List A)

No. V7 010283 0610 Rev. 04

Manufacturer:

Roche Diagnostics GmbH
Sandhofer Strasse 116
68305 Mannheim
GERMANY

Product:

Screening and Confirmatory Test for Hepatitis B marker

The Certification Body of TÜV SÜD Product Service GmbH declares that a design examination has been carried out on the respective devices in accordance with IVDD Annex IV (4). The design of the devices conforms to the requirements of this Directive. All applicable requirements of the testing and certification regulation of TÜV SÜD Group have to be complied with. For details and certificate validity see: www.tuvsud.com/ps-cert?q=cert:V7 010283 0610 Rev. 04

Report No.: 713223907-2_04

Valid from: 2021-09-16
Valid until: 2024-05-26

Date, 2021-09-14

Christoph Dicks
Head of Certification/Notified Body

TÜV SÜD Product Service GmbH is Notified Body with identification no. 0123

TÜV SÜD Product Service GmbH • Certification Body • Ridlerstraße 65 • 80339 Munich • Germany

ZERTIFIKAT ◆ CERTIFICATE ◆ 認證證書 ◆ СЕРТИФИКАТ ◆ CERTIFICADO ◆ CERTIFICAT

Benannt durch/Designated by
Zentralstelle der Länder für Gesundheitsschutz bei Arzneimitteln und Medizinprodukten
www.zlg.de
ZLG-BS-245.10.07

Product Service

EC Certificate

EC Design-Examination Certificate
Directive 98/79/EC on In Vitro Diagnostic Medical Devices (IVDD), Annex IV (4) (List A)

No. V7 010283 0610 Rev. 04

Model(s):

Elecsys HBsAg II
PreciControl HBsAg II
Elecsys HBsAg Confirmatory Test
Elecsys HBsAg II Auto Confirm
PreciControl HBsAg Auto Confirm
Elecsys and cobas e analyzers

Facility(ies):

Roche Diagnostics GmbH
Nonnenwald 2, 82377 Penzberg, GERMANY

Roche Diagnostics GmbH
Sandhofer Strasse 116, 68305 Mannheim, GERMANY

Roche Diagnostics International Ltd
Forrenstrasse 2, 6343 Rotkreuz, SWITZERLAND

Parameters:

Model Name:	Model No.:
Elecsys HBsAg II	04687787190
	08814856190
Elecsys HBsAg II	07914482190
	08814864190
Elecsys HBsAg II	07251076190
	08814848190
PreciControl HBsAg II	04687876190
Elecsys HBsAg Confirmatory Test	11820648122
	09127127190
Elecsys HBsAg II Auto Confirm	08741034190
PreciControl HBsAg Auto Confirm	08741107190
Elecsys and cobas e analyzers	

TÜV SÜD Product Service GmbH is Notified Body with identification no. 0123

TÜV SÜD Product Service GmbH • Certification Body • Ridlerstraße 65 • 80339 Munich • Germany

TÜV®