Elecsys Anti-HCV II

cobas®

REF		Σ	SYSTEM
09730788190	09730788500	100	**cobas e** 402 **cobas e** 801

English

System information

Short name	ACN (application code number)
AHCV 2	10189

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 **cobas e** immunoassay analyzers.

Summary

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

The hepatitis C virus (HCV), first identified in 1989, is a member of the Flaviviridae family and has a single-stranded, positive-sense RNA genome encoding 3 structural (Core, Envelope 1 and 2) and 7 non-structural (p7, NS2, NS3, NS4A, NS4B, NS5A, NS5B) proteins.[2,3,4,5] Currently 90 subtypes have been identified, which have been classified into 8 genotypes.[6] Globally, genotype 1 is the most common, accounting for 46 % of all infections, followed by genotype 3 (22 %), and genotypes 2 and 4 (13 % each).[7]

The total global seroprevalence of antibodies against HCV (indicating past exposure to HCV) was estimated to be 1.6 %, corresponding to approximately 115 million past infections.[7] The prevalence of HCV RNA positivity indicating active HCV infection was determined to be 1 %, corresponding to 71.1 million viremic infections.[8] 1.7 million new infections occur annually.[9] Prevalence of HCV infection shows considerable variation across the globe. The most affected regions are Eastern Europe, Northern Africa, and Central Asia, with the highest infection rate found in countries with a past or present history of infections due to the activity of a physician or medical therapy.

Transmission of HCV occurs by percutaneous exposure to blood, blood products, or organs from an infected person. In developed regions where blood donor screening programs have operated for many years the major mode of HCV transmission is through intravenous drug use. In less developed regions, the major routes of transmission are through medical treatment with unsterilized equipment or unscreened blood.[5,8,9]

Infection with HCV can lead to acute and chronic liver inflammation (hepatitis). Approximately 70-85 % of HCV infections progress to chronic disease, although this varies according to patient gender, age, ethnic group and immune status.[2,3,4,5,9] In acute infection, the average incubation period is 6-7 weeks and 70-85 % of patients exhibit no symptoms; in the remainder, non-specific symptoms and jaundice are observed around this time. Symptoms last for several weeks before spontaneous resolution, which occurs in 15-30 % of patients.[2,3,4,5,9,10] Patients who develop chronic HCV infection are much less likely to exhibit symptoms, but can develop long-term complications. If untreated, 20 % of patients develop liver cirrhosis, and a fraction of these progress to hepatocellular carcinoma (HCC). Annually, 400000 patients die globally due to HCV infection.[5,11,12] Advanced, highly efficacious direct-acting antivirals (DAAs) combination therapies cure more than 95 % of treated patients.[12]

HCV infection can be detected by measuring alanine aminotransferase (ALT), HCV-specific immunoglobulins (anti-HCV), HCV RNA and/or viral antigens in patient serum or plasma samples. This can also indicate if the infection is acute or chronic.[5,11,13] International guidelines recommend initial screening by anti-HCV testing. A positive result is recommended to be followed up by measuring HCV RNA or HCV antigen as markers of active infection.[3,14,15,16]

The Elecsys Anti-HCV II assay is a third-generation test.[17,18] 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: 30 µL of sample, a reagent containing biotinylated HCV-specific antigens and 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 II M. Application of a voltage to the electrode then induces chemiluminescent emission which is measured by a photomultiplier.
- Results are determined automatically by the software by comparing the electrochemiluminescence signal obtained from the reaction product of the sample with the signal of the cutoff value previously obtained by calibration.

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

Reagents - working solutions

The **cobas e** pack (M, R1, R2) is labeled as AHCV 2.

M Streptavidin-coated microparticles, 1 bottle, 7.2 mL:
Streptavidin-coated microparticles 0.72 mg/mL; preservative.

R1 HCV-specific antigens~biotin, 1 bottle, 14.8 mL:
Biotinylated HCV-specific antigens, HEPES[b)] buffer, pH 7.4; preservative.

R2 HCV-specific antigens~$Ru(bpy)_3^{2+}$, 1 bottle, 14.8 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

AHCV 2 Cal1 Negative calibrator 1, 1 bottle of 1.3 mL:
Human serum negative for anti-HCV Ab; preservative.

AHCV 2 Cal2 Positive calibrator 2, 1 bottle of 1.3 mL:
Human serum positive for anti-HCV Ab; preservative. Non-reactive for HBsAg, anti-HIV 1/2.

Precautions and warnings

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

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

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

Safety data sheet available for professional user on request.

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

Warning

H317 May cause an allergic skin reaction.

Elecsys Anti-HCV II

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H319	Causes serious eye irritation.

Prevention:

P261	Avoid breathing mist or vapours.
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.

Disposal:

P501	Dispose of contents/container to an approved waste disposal plant.

Hazardous components:

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

Product safety labeling follows EU GHS guidance.

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

All human material should be considered potentially infectious.

All products derived from human blood are prepared exclusively from the blood of donors tested individually and shown to be free from HBsAg and antibodies to HCV (AHCV 2 Cal1 only) and HIV.

The testing methods use assays that have been approved or cleared by the FDA or that are in compliance with the legal rules of the European Union (IVDR 2017/746/EU, IVDD 98/79/EC, Annex II, List A).

The serum containing anti-HCV (AHCV 2 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.[19,20]

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 pouch should remain sealed until immediately prior to use.

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

Calibrators:

The calibrators are supplied ready-for-use in bottles compatible with the system.

Unless the entire volume is necessary for calibration on the analyzer, 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.

All information required for correct operation is available via the **cobas** link.

Storage and stability

Store at 2-8 °C.

Do not freeze.

Store the **cobas e** pack **upright** in order to ensure complete availability of the microparticles during automatic mixing prior to use.

Stability of the **cobas e** pack:	
unopened at 2-8 °C	up to the stated expiration date
on the analyzers	31 days

Stability of the calibrators:	
unopened at 2-8 °C	up to the stated expiration date
after opening at 2-8 °C	8 weeks
on the analyzers at 20-25 °C	use only once

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

Specimen collection and preparation

Specimen collected from living patients, blood donors, or individual organ, tissue or cell donors may be used, including donor samples obtained while the donor's heart is still beating.
Performance for the use of cadaveric blood specimens (specimens collected post-mortem, non-heart-beating) was established according to Paul-Ehrlich-Institut recommendation[1] with samples obtained within 24 hours after death.[21] 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, CPD, CP2D and Na-citrate plasma.

Plasma tubes containing separating gel can be used.

Criterion: Correct assignment of positive and negative samples within a recovery of 80-120 % of serum value for positive samples and within ± 0.2 COI for negative 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, 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/collection system manufacturer.

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

Centrifuge samples containing precipitates before performing the assay.

Do not use heat-inactivated samples.

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

Do not use samples and controls stabilized with azide.

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

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

The performance of the Elecsys 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, 16 x 1.3 mL
- General laboratory equipment
- **cobas e** analyzer

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

- REF 06908799190, ProCell II M, 2 x 2 L system solution
- REF 04880293190, CleanCell M, 2 x 2 L measuring cell cleaning solution

Elecsys Anti-HCV II

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

Assay

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

Resuspension of the microparticles takes place automatically prior to use.

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

Calibrators:

Place the calibrators in the sample zone.

Read in all the information necessary for calibrating the assay.

Calibration

No internationally accepted standard for anti-HCV exists.

Calibration frequency: Calibration must be performed once per reagent lot using AHCV 2 Cal1, AHCV 2 Cal2 and fresh reagent (i.e. not more than 24 hours since the **cobas e** pack was registered on the analyzer).

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

Renewed calibration is recommended as follows:

- every 12 weeks when using the same reagent lot
- every 28 days when using the same **cobas e** pack on the analyzer
- as required: e.g. quality control findings outside the defined limits

Quality control

Use PreciControl Anti-HCV or other suitable controls for routine quality control procedures.

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

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

If necessary, repeat the measurement of the samples concerned.

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

Calculation

The analyzer automatically calculates the cutoff based on the measurement of AHCV 2 Cal1 and AHCV 2 Cal2.

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

Interpretation of the results

Numeric result	Result message	Interpretation/ further steps
COI[c)] < 0.9	Non-reactive	Negative for anti-HCV, no further testing needed.
COI ≥ 0.9 to < 1.0	Borderline	All initially reactive or borderline samples should be retested in duplicate using the Elecsys Anti-HCV II assay.
COI ≥ 1.0	Reactive	

c) COI = cutoff index

Retest result	Final result/ interpretation	Further steps
One or both of the duplicate retests have a COI ≥ 0.9.	Repeatedly reactive	Confirmation via 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.
Both of the duplicate retests have a COI < 0.9.	Negative for anti-HCV	No further testing needed.

Retesting of samples with an initial cutoff index ≥ 0.9 can be automatically performed (see section "**cobas e** flows").

cobas e flows

cobas e flows are procedures programmed into the system to enable a fully automated sequence of measurements and the calculation of assay combinations to perform decision algorithms.
A **cobas e** flow is available to perform a repetition of measurements in duplicate automatically for samples with an initial cutoff index ≥ 0.9.
Both sub-results and the overall result message will be reported.

Limitations - interference

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

Endogenous substances

Compound	Concentration tested
Bilirubin	≤ 1129 µmol/L or ≤ 66 mg/dL
Hemoglobin	≤ 0.621 mmol/L or ≤ 1000 mg/dL
Intralipid	≤ 2000 mg/dL
Biotin	≤ 4912 nmol/L or ≤ 1200 ng/mL
Rheumatoid factors	≤ 1200 IU/mL
Albumin	≤ 7 g/dL
IgG	≤ 7 g/dL
IgA	≤ 1.6 g/dL
IgM	≤ 1 g/dL

Criterion: Samples with a COI ≥ 1.0: ± 20 % recovery; samples with a COI < 1.0: ± 0.2 COI recovery.

Pharmaceutical substances

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

In addition, the following special drugs used in hepatitis C therapy were tested. No interference with the assay was found.

Special drugs

Drug	Concentration tested
Peginterferon alfa-2a	≤ 0.18 mg/L
Interferon alfa	3000000 IU/L
Ribavirin	1200 mg/L

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In rare cases, interference due to extremely high titers of antibodies to 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 the **cobas** HCV Test for use on the **cobas** 6800/8800 Systems) may give evidence of HCV infection.

The detection of anti-HCV antibodies indicates a present or past infection with HCV, 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 (EP05-A3) of the CLSI (Clinical and Laboratory Standards Institute): 2 runs per day in duplicate each for 21 days (n = 84). The following results were obtained:

cobas e 402 and **cobas e** 801 analyzers					
		Repeatability[d]		**Intermediate precision**[e]	
Sample	Mean COI	SD COI	CV %	SD COI	CV %
HS[f], negative	0.035	0.0005	1.4	0.0005	1.5
HS, negative	0.885	0.012	1.3	0.016	1.8
HS, weakly positive	1.12	0.016	1.4	0.025	2.3
HS, weakly positive	1.36	0.014	1.0	0.018	1.3
HS, positive	7.66	0.089	1.2	0.146	1.9
PC[g] Anti-HCV1	0.045	0.0007	1.5	0.001	2.3
PC Anti-HCV2	3.46	0.088	2.5	0.235	6.8

d) Repeatability = within-run precision

e) Intermediate precision = within-laboratory precision

f) HS = Human serum

g) PC = PreciControl

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 or indeterminate by immunoblot**	**Negative by immunoblot**
Specimens containing potentially interfering substances	1037	59	58 positive	1[h]

h) 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 99.85 % (RR[l]). 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 99.66 %. The 95 % confidence interval (2-sided) was 99.41-99.82 %.

	N	**Elecsys Anti-HCV II IR[i] COI ≥ 1**	**Elecsys Anti-HCV II RR 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

i) IR = Initially 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

l) RR = Repeatedly Reactive

References

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Elecsys Anti-HCV II

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

20 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.

21 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 user guide or operator's manual for the analyzer concerned, the respective application sheets and the Method Sheets of all necessary components (if available in your country).

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

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

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

Symbols

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

CONTENT	Contents of kit
SYSTEM	Analyzers/Instruments on which reagents can be used
REAGENT	Reagent
CALIBRATOR	Calibrator
→	Volume for reconstitution
GTIN	Global Trade Item Number
Rx only	For USA: Caution: Federal law restricts this device to sale by or on the order of a physician.

CE 0123

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