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Anti-HCV

cobas®

Antibody to hepatitis C virus (anti-HCV)

REF	Σ	SYSTEM
03290352 190	100	Elecsys 2010 MODULAR ANALYTICS E170 **cobas e** 411 **cobas e** 601 **cobas e** 602

English

Intended use

Anti-HCV is an in vitro diagnostic test for the qualitative detection of antibodies to hepatitis C virus (HCV) in human serum or 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.

Summary

Hepatitis C virus, first identified in 1989,[1] is the most common cause of posttransfusion and community-acquired non-A, non-B hepatitis worldwide. Infection with HCV frequently leads to chronic hepatitis and cirrhosis, and is associated with the development of hepatocellullar carcinoma.[2] Common extrahepatic manifestations comprise mixed cryoglobulinemia and other rheumatic diseases.[3]

Hepatitis C virus is an enveloped, positive-sense single-stranded RNA virus which has been classified as an own genus in the family of Flaviviridae. The genome consists of ~9.5 kb encoding for a 3000 amino acid polypeptide of structural and non-structural domains.[4] Like other RNA viruses, the HCV genome exhibits substantial heterogeneity as a result of mutations that occur during viral replication. Worldwide, at least 11 genetically distinct genotypes and multiple subtypes and virus variants have been described.[5] Infection with specific genotypes can affect disease severity and treatment response.[6,7]

Hepatitis C is primarily transmitted through contaminated blood and blood products and to a lower extent by human body secretions.[8]

Anti-HCV antibody tests are used alone or in combination with other tests (e.g. HCV-RNA) to detect an infection with hepatitis C virus and to identify blood and blood products of individuals infected with HCV.

The Elecsys Anti-HCV assay is a third-generation test.[9,10] The assay uses peptides and recombinant antigens representing core, NS3 and NS4 proteins for the determination of anti-HCV antibodies.

Test principle

Sandwich principle. Total duration of assay: 18 minutes.

- 1st incubation: 40 µL of sample, 60 µL of a reagent containing biotinylated HCV antigens and 60 µL of a reagent containing HCV 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, R1a, R2a, R1b, R2b) is labeled as A-HCV.

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

R1 Buffer (gray cap), 1 bottle, 7 mL: HEPES[b] buffer, pH 5.0.

R2 Buffer (black cap), 1 bottle, 7 mL: HEPES buffer, pH 5.0.

R1a Lyophilized HCV antigens, biotinylated (gray cap), 1 bottle for 1.2 mL solution.

R2a Lyophilized HCV antigens, ruthenylated (black cap), 1 bottle for 1.2 mL solution.

R1b Reconstitution medium for bottle R1a (gray cap), 1 bottle, 1.4 mL: Water, preservative.

R2b Reconstitution medium for bottle R2a (black cap), 1 bottle, 1.4 mL: Water, preservative.

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

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

A-HCV 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 Cal1 only) and HIV. The testing methods applied were FDA-approved or cleared in compliance with the European Directive 98/79/EC, Annex II, List A.

The serum containing anti-HCV (A-HCV 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).

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

Reagent handling

The reagents R1 and R2 are not ready for use and have to be prepared. See "Preparation of working solutions" section for further instructions. The reagents M, A-HCV Cal1 and A-HCV Cal2 are ready for use and are supplied in bottles compatible with the system.

Elecsys 2010 and **cobas e** 411 analyzers: The calibrators should only be left on the analyzers during calibration at 20-25 °C. After use, close the bottles as soon as possible and store 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.

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

Preparation of working solutions

The reagents R1 and R2 are not ready for use and have to be prepared by adding the reconstituted antigens.

For the reconstitution of the lyophilized antigens proceed as follows:

A. *Using adapters*

1a. Connect bottle R1a (lyophilized biotinylated antigens; gray cap) with bottle R1b (reconstitution medium for bottle R1a; gray cap) using one of the adapters. Transfer the volume of reconstitution medium. **Avoid foam formation!**

1b. Connect bottle R2a (lyophilized ruthenylated antigens; black cap) with bottle R2b (reconstitution medium for bottle R2a; black cap) using one of the adapters. Transfer the volume of reconstitution medium. **Avoid foam formation!**

2. Reconstitute the lyophilisates during 30 min ± 5 min by occasionally gently swirling until the lyophilisates are completely dissolved. **Avoid foam formation! Do not shake back and forth vigorously!**

3. Remove empty bottles from adapters.

4a. Transfer the volume of the reconstituted Bi-antigen solution R1a (gray cap) into the R1 of the rackpack (gray cap).

4b. Transfer the volume of the reconstituted Ru-antigen solution R2a (black cap) into the R2 of the rackpack (black cap).

5. Produce homogeneous solutions (R1 and R2) by occasionally gently swirling from time to time during a time period of 15 min. **Avoid foam formation!**

6a. Incubate the reconstituted reagent for at least 12 hours at 2-8 °C to finalize the reconstitution process. Overnight storage (e.g. 16 hours at 2-8 °C) is recommended. Reagent kit with R1 and R2 working solution is now ready for use.

6b. Alternatively, the solution prepared under 5. may be used without further incubation. In this case increased control frequency within the first 24 hours of use is recommended. A calibration should be performed after 12-24 hours.

7. **Always store the kit containing the working solution R1/R2 at 2-8 °C when not in use. A stability of 14 days can only be guaranteed if R1 and R2 containing the HCV antigens are stored at 2-8 °C, and are not subjected to heat stress.**

Note: When transferring the solutions using the adapter, a volume of < 200 µL remains. This remaining volume does not need to be transferred by additional pipetting.

B. *Or alternatively by pipetting:*

1a. Pipette 1.2 mL of R1b (reconstitution medium; gray cap) into R1a (lyophilized biotinylated antigens; gray cap).

1b. Pipette 1.2 mL of R2b (reconstitution medium; black cap) into R2a (lyophilized ruthenylated antigens; black cap).

2. Reconstitute the lyophilisates during 30 min ± 5 min by occasionally gently swirling until the lyophilisates are completely dissolved. **Avoid foam formation!**

3a. Pipette 1 mL of this reconstituted Bi-antigen solution R1a (gray cap) into R1 of the rackpack (gray cap).

3b. Pipette 1 mL of this reconstituted Ru-antigen solution R2a (black cap) into R2 of the rackpack (black cap).

4. Produce homogeneous solutions (R1 and R2) by occasionally gently swirling from time to time during a time period of 15 min. **Avoid foam formation!**

5a. Incubate the reconstituted reagent for at least 12 hours at 2-8 °C to finalize the reconstitution process. Overnight storage (e.g. 16 hours at 2-8 °C) is recommended. Reagent kit with R1 and R2 working solution is now ready for use.

5b. Alternatively, the solution prepared under 4. may be used without further incubation. In this case increased control frequency within the first 24 hours of use is recommended. A calibration should be performed after 12-24 hours.

6. **Always store the kit containing the working solution R1/R2 at 2-8 °C when not in use. A stability of 14 days can only be guaranteed if R1/R2 containing the HCV antigens are stored at 2-8 °C, and are not subjected to heat stress.**

Storage and stability

Store at 2-8 °C.

Return to storage after use. Ensure the reagents are at 20-25 °C prior to use.

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 kit and rackpack	
reagent kit unopened at 2-8 °C	up to the stated expiration date
rackpack (including reconstituted antigens) at 2-8 °C	2 weeks
on the analyzers	72 hours if continuously stored onboard (20-25 °C) or 2 weeks and up to 40 hours in total onboard (20-25 °C) if stored alternately in the refrigerator and on the analyzer

Stability of the calibrators	
after opening at 2-8 °C	8 weeks
on Elecsys 2010 and **cobas e** 411 at 20-25 °C	up to 5 hours
on MODULAR ANALYTICS E170, **cobas e** 601 and **cobas e** 602	use only once

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

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Specimen collection and preparation

Only the specimens listed below were tested in a sufficient number and found acceptable.

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

Li-, Na-heparin, K_3-EDTA and sodium citrate plasma.

Criterion: Correct assignment of negative and positive samples within a recovery of 80-120 % of serum value.

Stable for 21 days at 2-8 °C, 3 days at 25 °C, 3 months at -20 °C. Only freeze 6 times.

The sample types listed were tested with a selection of sample collection tubes that were commercially available at the time of testing, i.e. not all available tubes of all manufacturers were tested. Sample collection systems from various manufacturers may contain differing materials which could affect the test results in some cases. When processing samples in primary tubes (sample collection systems), follow the instructions of the tube manufacturer.

Centrifuge samples containing precipitates before performing the assay.

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

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

Materials provided

See "Reagents – working solutions" section for reagents.

- 2 x 6 bottle labels
- 2 adapters

Materials required (but not provided)

- REF 03290379190, PreciControl Anti-HCV, for 8 x 1.3 mL each of PreciControl Anti-HCV 1 and 2
- General laboratory equipment
- Elecsys 2010, MODULAR ANALYTICS E170 or **cobas e** analyzer

Accessories for Elecsys 2010 and **cobas e** 411 analyzers:

- 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, Elecsys 2010 AssayCup, 60 x 60 reaction vessels
- REF 11706799001, Elecsys 2010 AssayTip, 30 x 120 pipette tips

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 Combimagazine M, 48 magazines x 84 reaction vessels or pipette tips, waste bags
- REF 03023150001, WasteLiner, waste bags
- REF 03027651001, SysClean Adapter M

Accessories for all analyzers:

- REF 11298500316, 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.

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

Bring the cooled reagents to approx. 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.

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

Calibration frequency:

Every Elecsys Anti-HCV rackpack must be calibrated using A-HCV Cal1 and A-HCV Cal2. **Lot calibrations are not allowed** for the Elecsys Anti-HCV assay.

Renewed calibration for each Elecsys Anti-HCV rackpack is recommended as follows:

- after 7 days (when the same reagent kit is alternately used on the analyzer and refrigerated)
- after 12-24 hours if the preparation of working solutions is performed according to 6b. (using adapters) or 5b. (by pipetting)
- as required: e.g. quality control findings outside the defined limits
- more frequently when this is required by pertinent regulations

Range for electrochemiluminescence signals (counts) for the calibrators:

Negative calibrator (A-HCV Cal1): 350-1200 (Elecsys 2010 and **cobas e** 411 analyzers) or 350-1600 (MODULAR ANALYTICS E170, **cobas e** 601 and **cobas e** 602 analyzers).

Positive calibrator (A-HCV Cal2): 10000-38000 (Elecsys 2010 and **cobas e** 411 analyzers) or 10000-60000 (MODULAR ANALYTICS E170, **cobas e** 601 and **cobas e** 602 analyzers).

No internationally accepted standard for anti-HCV exists.

Quality control

For quality control, use PreciControl Anti-HCV.

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 rackpack 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 Cal1 and A-HCV 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 < 0.9 are non reactive in the Elecsys Anti-HCV assay.

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

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

All initially reactive or borderline samples should be redetermined in duplicate using the Elecsys Anti-HCV 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 < 855 µmol/L or < 50 mg/dL), hemolysis (Hb < 1.09 mmol/L or < 1.75 g/dL), lipemia (Intralipid < 2100 mg/dL) and biotin (< 50 ng/mL or < 205 nmol/L).

Criterion: Recovery of positive samples within ± 20 % of initial value, cutoff-index for negative samples ≤ 0.5.

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 1000 IU/mL.

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

In vitro tests were performed on 18 commonly used pharmaceuticals and 2 drugs used in HCV therapy. No interference with the assay was found.

In rare cases, interference due to extremely high titers of antibodies to streptavidin and ruthenium can occur.

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 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, human sera and controls.

The following results were obtained by preparation of the working solutions via adapters. Comparable results were obtained when using the pipetting method.

Elecsys 2010 and **cobas e** 411 analyzers						
	Repeatability[c]			**Intermediate precision**[d]		
Sample	Mean COI[e]	SD COI	CV %	Mean COI	SD COI	CV %
HS[f], negative	0.11	0.01	-	0.10	0.01	-
HS, weakly positive	4.15	0.14	3.3	4.82	0.14	3.0
HS, positive	34.7	0.38	1.1	39.7	1.37	3.5
PreciControl A-HCV1	0.14	0.01	-	0.14	0.01	-
PreciControl A-HCV2	8.67	0.11	1.2	11.1	0.47	4.2

c) Repeatability = within-run precision (n = 21)

d) Intermediate precision = between-run (n = 10)

e) COI = Cutoff index

f) HS = Human serum

MODULAR ANALYTICS E170, **cobas e** 601 and **cobas e** 602 analyzers						
	Repeatability[g]			**Intermediate precision**[h]		
Sample	Mean COI	SD COI	CV %	Mean COI	SD COI	CV %
HS, negative	0.084	0.020	-	0.127	0.014	-
HS, weakly positive	3.14	0.143	4.6	2.30	0.103	4.5
HS, positive	72.8	2.23	3.1	260	10.5	4.0
PreciControl A-HCV1	0.052	0.007	-	0.134	0.015	-
PreciControl A-HCV2	11.7	0.241	2.1	11.3	0.415	3.7

g) Repeatability = within-run precision (n = 21)

h) Intermediate precision = within-laboratory (modified protocol (EP5-A) of the CLSI (Clinical and Laboratory Standards Institute): 6 times daily for 10 days (n = 60))

Analytical specificity

774 samples containing potentially interfering substances were tested with the Elecsys Anti-HCV assay comprising specimens:

- containing antibodies against HBV, HAV, HEV, EBV, CMV, HSV, HIV, 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

	N	Elecsys Anti-HCV reactive	Positive by immunoblot or indeterminate	Negative by immunoblot
Specimens containing potentially interfering substances	774	29	21 positive 3 indeterminate	5[i]

i) Patients with autoantibodies: 1 out of 164 samples, HBV infected: 2 out of 87 samples, EBV infected: 1 out of 61 samples, non viral liver diseases: 1 out of 24 samples

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Clinical sensitivity

Of 1057 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 assay.

Group	N	Reactive
HCV infected persons with different stages of disease	813	813
HCV genotypes (type 1, 2, 3, 4, 5, 6)	244	244

In the study above the diagnostic sensitivity was found 100 %. The 95 % lower confidence limit was 99.72 %.

Seroconversion sensitivity

Seroconversion sensitivity of the Elecsys Anti-HCV assay has been shown by testing 50 commercial seroconversion panels in comparison to other registered anti-HCV immunoassays.

Clinical specificity

In a group of randomly selected European blood donors the specificity of the Elecsys Anti-HCV assay was found 99.71 % (RR). The 95 % lower confidence limit was 99.58 %.

The diagnostic specificity of the Elecsys Anti-HCV assay in a group of hospitalized patients, dialysis patients and pregnant women was found 99.17 %. The 95 % lower confidence limit was 98.76 %.

	N	Elecsys Anti-HCV IR COI ≥ 1	Elecsys Anti-HCV RR COI ≥ 1	Positive or indeterminate by immunoblot and/or HCV RNA
European Blood donors	6317	26	20	3 indeterminate
Hospitalized patients	1770	189	186	164 positive 9 indeterminate
Dialysis patients	217	14	13	11
Pregnant women	259	2	2	1

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

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

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 after reconstitution or mixing

CE 0123

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