

Anti-HCV II

Antibody to hepatitis C virus (anti-HCV)

cobas[®]

| REF | | SYSTEM |
|--------------|-----|--|
| 06427405 190 | 200 | Elecsys 2010 MODULAR ANALYTICS E170 cobas e 411 cobas e 601 cobas e 602 |

English

Intended use

Anti-HCV II 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.

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

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.^{1,2} The highest prevalence is found in Africa, the Eastern Mediterranean and Asian regions.^{2,3} HCV is a member of the Flaviviridae family and has a single-stranded, positive-sense RNA genome.⁴ Currently over 50 subtypes have been identified and these have been classified into 6 genotypes (1-6).⁵

Due to the high rate of asymptomatic infections, clinical diagnosis is difficult and screening assays are of major importance.⁶ 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.^{4,7} Chronic HCV infection may lead to cirrhosis and hepatocellular carcinoma,⁸ therefore, early anti-HCV detection is the first step in the management of chronic hepatitis and in the selection of patients needing treatment.⁶ HCV infection can be detected by measuring the amount of HCV RNA, alanine aminotransferase (ALT) and HCV-specific immunoglobulins (anti-HCV) in patient serum samples. This can also indicate if the infection is acute or chronic.^{4,7}

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 II assay is a third-generation test.^{9,10} The Elecsys Anti-HCV II 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: 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)₃²⁺)

Reagents - working solutions

The reagent rackpack (M, R1, R2) is labeled as A-HCV II.

- M Streptavidin-coated microparticles (transparent cap), 1 bottle, 12 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)₃²⁺ (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 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 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).

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.

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 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.

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

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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 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 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

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-heparin, Na-heparin, K₂-EDTA, K₃-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.

Stable for 7 days at 2-8 °C, 3 days at 25 °C, 3 months at -20 °C. Freeze no more than 6 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 cadaveric samples or 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 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, 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.

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.

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). Renewed calibration is recommended as follows:

- after 1 month (28 days) when using the same reagent lot

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- 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 (Elecsys 2010, **cobas e 411**, MODULAR ANALYTICS E170, **cobas e 601** and **cobas e 602** analyzers).
 Positive calibrator (A-HCV II Cal2): 25000-350000 (Elecsys 2010, **cobas e 411**, MODULAR ANALYTICS E170, **cobas e 601** and **cobas e 602** 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 (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 duplication each for 21 days (n = 84). The following results were obtained:

| Elecsys 2010 and cobas e 411 analyzers | | | | | | |
|---|-----------------------------|--------|------|--------------------------------------|--------|------|
| Sample | Repeatability ^{c)} | | | Intermediate precision ^{d)} | | |
| | 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 | | | | | | |
|---|---------------|--------|------|------------------------|--------|------|
| Sample | Repeatability | | | Intermediate precision | | |
| | 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 |
| 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

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- 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. Elecsys Anti-HCV II detected more positive bleedings than all other registered anti-HCV assays tested and was more sensitive in the recognition of early HCV infection than Elecsys Anti-HCV 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 99.84 % (RR). The 95 % lower confidence limit (2-sided) was 99.71-99.92 %.

The diagnostic specificity of the Elecsys Anti-HCV II assay in a group of hospitalized patients was found 99.66 %. The 95 % lower confidence limit (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

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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 |
| GTIN | Global Trade Item Number |

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