



Elecsys HBsAg II quant II

cobas®

REF			SYSTEM
08814872190	08814872500	100	cobas e 402 cobas e 801

English

System information

Short name	ACN (application code number)
HBSAGQ2	10055

Intended use

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

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

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.^{1,2} In addition to the intact infectious viral particles, the blood of persons infected with HBV contains large amounts of non-infectious particles which consist only of an outer coat containing HBsAg.³ After infection, HBsAg is the first immunological marker detectable in serum and is usually present weeks to months before the onset of clinical symptoms and the appearance of other biochemical markers.⁴ In the case of acute HBV infection with recovery, HBsAg is detectable in serum for up to 6 months after its appearance.⁴ If HBsAg persists for more than 6 months after acute hepatitis, the presence of chronic hepatitis B (CHB) infection must be assumed.

Classifying the stage of CHB infection is essential for identifying patients who require treatment and monitoring, as well as assessing the likelihood of responding to treatment and risk of progression to more severe liver disease.^{5,6,7} A CHB patient with elevated aminotransferase levels, high HBV DNA viral load, and histological abnormalities will be considered for therapy and two different treatment strategies are applicable: treatment of finite duration with pegylated interferon alpha or long-term treatment with nucleoside/nucleotide analogs (NUCs).⁵ Monitoring HBsAg levels, in addition to HBV DNA, before^{8,9} and during pegylated interferon-based therapy can help physicians to predict the likely response and implement the response-guided therapy algorithms, as recommended in the guidelines, to achieve the optimal outcome, which is sustained HBsAg loss with or without seroconversion to anti-HBs.^{5,6,8,9,10,11} There is also some evidence suggesting that HBsAg quantification may have value for monitoring response to NUC therapy and identifying patients able to achieve a sustained response after terminating treatment.^{3,12,13,14,15} This is based on the suggestion that HBsAg levels decline during antiviral therapy with NUCs reflecting an improvement in the degree of host immune control of the virus, with lower HBsAg levels at end of treatment being associated with continued remission.^{11,16,17} However, further studies in larger cohorts are required.

For patients in the immune clearance phase of CHB, HBV DNA levels have traditionally been used to determine the disease progression risk. However, HBsAg monitoring can provide additional information and distinguish true inactive carriers (HBV DNA < 2000 IU/mL and HBsAg < 1000 IU/mL), who are at the lowest risk of progression from those at a higher risk of developing cirrhosis or hepatocellular carcinoma (HCC). An HBsAg level ≥ 1000 IU/mL in hepatitis B 'e' antigen negative patients with HBV DNA < 2000 IU/mL has been identified as an independent risk factor for progression to HCC.^{5,6,11,18,19,20}

Test principle

Sandwich principle. Total duration of assay: 18 minutes.

- 1st incubation: 30 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 II M. Application of a voltage to the electrode then induces chemiluminescent emission which is measured by a photomultiplier.
- Results are determined via a calibration curve which is instrument-specifically generated by 2-point calibration and a master curve provided via the **cobas link**.

a) Tris(2,2'-bipyridyl)ruthenium(II)-complex (Ru(bpy)₃²⁺)

Reagents - working solutions

The **cobas e** pack (M, R1, R2) is labeled as HBSAGQ2.

- M Streptavidin-coated microparticles, 1 bottle, 6.4 mL:
Streptavidin-coated microparticles 0.72 mg/mL; preservative.
- R1 Anti-HBsAg-Ab~biotin, 1 bottle, 7.2 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)₃²⁺, 1 bottle, 6.3 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.

- HBSAGQ2 Cal1 Negative calibrator 1, 2 bottles of 1.3 mL each:
Human serum, buffered, pH 6.5; preservative.
- HBSAGQ2 Cal2 Positive calibrator 2, 2 bottles of 1.3 mL each:
HBsAg approximately 50 IU/mL in human serum, buffered, pH 6.5; preservative.
- HBSAGQ2 Dil HepB **cobas e** pack with 2 bottles of 12.1 mL each and 1 bottle of 21 mL:
Human serum negative for HBsAg and anti-HBs, buffered, pH 6.5; 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.

Prevention:

- P261 Avoid breathing dust/fume/gas/mist/vapours/spray.
- P272 Contaminated work clothing should not be allowed out of the workplace.
- P280 Wear protective gloves.

Response:

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

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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.

The calibrators and HBSAGQ2 Dil HepB have been prepared exclusively from the blood of donors tested individually and shown to be free from HBsAg (HBSAGQ2 Cal1 and HBSAGQ2 Dil HepB 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 (HBSAGQ2 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.^{21,22}

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

Reagent handling

The reagents (M, R1, R2, Dil HepB) 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 packs (M, R1, R2, Dil HepB):	
unopened at 2-8 °C	up to the stated expiration date
on the analyzers	16 weeks

Stability of the calibrators:	
unopened at 2-8 °C	up to the stated expiration date
after opening at 2-8 °C	16 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

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, K₂-EDTA and Na-citrate plasma.

Criterion: Slope 0.9-1.1 + intercept within ± 0.5 IU/mL + coefficient of correlation ≥ 0.95 .

Stable for 6 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.

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.

Do not use heat-inactivated samples.

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.

Materials provided

See "Reagents – working solutions" section for reagents.

- 2 x 6 bottle labels

Materials required (but not provided)

- [REF] 07143745190, PreciControl HBsAg II quant II, 15 x 1.3 mL
- [REF] 11776576322, CalSet Vials, 2 x 56 empty snap-cap bottles
- 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
- [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. **Pre-dilution of samples is mandatory according to the test algorithm (see "Dilution" section).** 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

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 predefined master curve is adapted to the analyzer using HBSAGQ2 Cal1 and HBSAGQ2 Cal2.

Calibration frequency: Calibration must be performed once per reagent lot using HBSAGQ2 Cal1, HBSAGQ2 Cal2 and fresh reagent (i.e. not more than 24 hours since the **cobas e** pack was registered on the analyzer).

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

Renewed calibration is recommended as follows:

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

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Quality control

For quality control, use PreciControl HBsAg II quant 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 **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 analyte concentration (IU/mL) based on the measurement of HBSAGQ2 Cal1 and HBSAGQ2 Cal2. In case of a manual pre-dilution, the dilution factor needs to be accounted for manual calculation of the final result.

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	≤ 0.311 mmol/L or ≤ 500 mg/dL
Intralipid	≤ 2000 mg/dL
Biotin	≤ 4912 nmol/L or ≤ 1200 ng/mL
Rheumatoid factors	≤ 1200 IU/mL
Albumin	≤ 7.0 g/dL

Criterion: For concentrations of 0.05-1 IU/mL the deviation is ≤ 0.2 IU/mL. For concentrations of 1-130 IU/mL the recovery is 80-120 %.

No high-dose hook effect was found with the Elecsys HBsAg II quant II assay up to a concentration of 250000 IU/mL when samples were analyzed according to instructions for use (predilution 1:900).

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 B therapy were tested. No interference with the assay was found.

Special drugs

Drug	Concentration tested mg/L
Peginterferon alfa-2a	≤ 0.036
Peginterferon alfa-2b	≤ 1.6
Lamivudine	≤ 300
Adefovir	≤ 10
Entecavir	≤ 1.0
Telbivudine	≤ 600
Tenofovir	≤ 245

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.

Limits and ranges

Measuring range

Measuring range for pre-diluted samples:

45-117000 IU/mL for 900-fold diluted samples.

Values below the measuring range are reported as < 45 IU/mL.

Values above the measuring range are reported as > 117000 IU/mL.

1350-3510000 IU/mL for 27000-fold diluted samples.

Values below the measuring range are reported as < 1350 IU/mL.

Values above the measuring range are reported as > 3510000 IU/mL.

Measuring range for undiluted samples:

0.05-130 IU/mL (defined by the Limit of Detection and the maximum of the master curve).

Values below the Limit of Detection are reported as < 0.05 IU/mL.

Values above the measuring range are reported as > 130 IU/mL.

Lower limits of measurement

Limit of Blank and Limit of Detection

Limit of Blank = 0.03 IU/mL

Limit of Detection = 0.05 IU/mL

The Limit of Blank and Limit of Detection were determined in accordance with the CLSI (Clinical and Laboratory Standards Institute) EP17-A2 requirements.

The Limit of Blank is the 95th percentile value from $n \geq 60$ measurements of analyte-free samples over several independent series. The Limit of Blank corresponds to the concentration below which analyte-free samples are found with a probability of 95 %.

The Limit of Detection is determined based on the Limit of Blank and the standard deviation of low concentration samples. The Limit of Detection corresponds to the lowest analyte concentration which can be detected (value above the Limit of Blank with a probability of 95 %).

Dilution

Initial onboard dilution of 1:900 with HBSAGQ2 Dil HepB is mandatory for every sample. Therefore every sample should first be run with a dilution step of 1:900 ordered by the user and performed by the analyzers.

After dilution by the analyzers, the software automatically takes the dilution into account when calculating the sample concentration.

If a result is found within the measuring range 45-117000 IU/mL for 900-fold diluted samples no further dilution is necessary.

If a result is found < 45 IU/mL for 900-fold diluted samples, the sample has to be run undiluted and should be found within 0.05-130 IU/mL.

If a result is found > 117000 IU/mL for 900-fold diluted samples the sample has to be run with a dilution step 1:27000 ordered by the user and performed by the analyzer.

A dilution algorithm can be performed automatically (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 automatically perform an initial 1:900 sample dilution and calculate the assay result. In case the result is found above the extended measuring range, another dilution of the sample is carried out (1:27000) and another result is calculated. In case the initial result is found below the extended measuring range, another measurement is carried out without dilution of the sample and the result is reported.

Expected values

Note: Where indicated, data have been generated using the Elecsys HBsAg II quant assay. Since the reagents (M, R1, R2) of the Elecsys HBsAg II quant assay are the same as those of the Elecsys HBsAg II quant II assay (only the controls and calibrators have been modified) the data generated with the Elecsys HBsAg II quant assay are transferable to the Elecsys HBsAg II quant II assay and no new data needed to be generated.

From 611 samples obtained from a multicenter evaluation the following values have been reported with the Elecsys HBsAg II quant assay.

IU/mL	MCE (n = 611)	% of total
< 1	17	2.78
1-< 10	20	3.27
10-< 100	35	5.73

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IU/mL	MCE (n = 611)	% of total
100-< 1000	127	20.8
1000-< 10000	239	39.1
10000-< 100000	147	24.1
100000-< 1000000	26	4.26

The final result was determined from the first measurement in 70.0 % of the samples on the **cobas e 411** analyzer (1:100 dilution) and 86.5 % of the samples on the **cobas e 601** and **cobas e 602** analyzers (1:400 dilution).

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					
Sample	Mean IU/mL	Repeatability ^{b)}		Intermediate precision ^{c)}	
		SD IU/mL	CV %	SD IU/mL	CV %
Human serum 1	0.150	0.004	2.7	0.006	4.2
Human serum 2	2.89	0.028	1.0	0.064	2.2
Human serum 3	61.0	0.595	1.0	1.27	2.1
Human serum 4	116	1.54	1.3	2.63	2.3
Human serum 5	329	4.31	1.3	8.99	2.7
Human serum 6	4668	82.7	1.8	138	3.0
PC ^{d)} HBsAg II quant II 1	3.80	0.027	0.7	0.075	2.0
PC HBsAg II quant II 2	90.3	0.646	0.7	2.01	2.2
PC HBsAg II quant II 3	86.0	1.83	2.1	3.19	3.7

b) Repeatability = within-run precision

c) Intermediate precision = between-run precision

d) PC = PreciControl

Method comparison

a) A comparison of the Elecsys HBsAg II quant II assay, [REF] 08814872190 (**cobas e 801** analyzer; y), with the Elecsys HBsAg II quant II assay, [REF] 07027443190 (**cobas e 801** analyzer; x), gave the following correlation (IU/mL):

Number of samples measured: 220

Passing/Bablok²³ $y = 1.04x + 0.000$

Pearson $r = 1.00$

The sample concentrations were between 0 and 25758 IU/mL.

b) A comparison of the Elecsys HBsAg II quant II assay, [REF] 08814872190 (**cobas e 402** analyzer; y), with the Elecsys HBsAg II quant II assay, [REF] 08814872190 (**cobas e 801** analyzer; x), gave the following correlation (IU/mL):

Number of samples measured: 217

Passing/Bablok²³ $y = 1.06x + 0.000$

Pearson $r = 0.996$

The sample concentrations were between 0 and 25696 IU/mL.

Quantitation of potentially cross reactive samples

1285 samples containing potentially interfering substances were tested with the Elecsys HBsAg II quant assay comprising specimens:

- containing antibodies against HAV, HCV, HIV, HTLV, CMV, EBV, HSV, Rubella, Parvo virus, VZV, Toxoplasma gondii, Treponema pallidum
- 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 results were found ≥ 0.05 IU/mL.

Quantitation of HBV mutants

A total of 50 samples comprising different HBsAg mutations were tested with the Elecsys HBsAg II quant assay. Results of observed concentrations are displayed.

Mutant panel	Elecsys HBsAg II quant (IU/mL) ^{e)}
Native mutant panel (strains displaying amino acid substitutions either linked to vaccine resistance, resistance to therapy with human HB immunoglobulin or impaired HBsAg reactivity)	< 0.05 (n = 2) 0.05-324 (n = 17)
Recombinant mutant panel	> 0.05-6.9 (n = 31)

e) Observed concentrations with HBV mutants might differ compared to competitor assays and are a characteristic of the individual assays.

Seroconversion panels

18 seroconversion panels were analyzed with the Elecsys HBsAg II quant assay. In all panels the Elecsys HBsAg II quant assay showed a significant increase in concentration upon seroconversion correlated to the shift as it is detectable in qualitative screening assays. Observed concentrations ranged from < Limit of Detection for negative samples, and 0.058-92300 IU/mL for conversion (confirmed positive) samples.

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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 (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

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