

REF



SYSTEM

08814848119

08814848500

300

cobas e 801

English

System information

Short name	ACN (application code number)
HBSAG 2	10049

Intended use

Immunoassay for the in vitro qualitative determination of hepatitis B surface antigen (HBsAg) in human serum and plasma. This assay is indicated as an aid in the diagnosis of infection with HBV. This assay is also indicated as a donor screening test to detect HBV in serum or plasma specimens from individual human blood donors. It may also be used in testing serum or plasma specimens to screen individual organ donors when specimens are obtained while the donor's heart is still beating.

The electrochemiluminescence immunoassay "ECLIA" is intended for use on the **cobas e 801** immunoassay analyzer.

Note: Please note that the catalogue number appearing on the package insert retains only the first 8 digits of the licensed 11-digit Catalogue Number: 08814848190 for the HBsAg II assay. The last 3 digits -190 have been replaced by -119 for logistic purposes.

Summary

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

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

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

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

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

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

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

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

- M Streptavidin-coated microparticles, 1 bottle, 14.1 mL:
Streptavidin-coated microparticles 0.72 mg/mL; preservative.
- R1 Anti-HBsAg-Ab-biotin, 1 bottle, 15.8 mL:
Two biotinylated monoclonal anti-HBsAg antibodies (mouse) > 0.5 mg/L; phosphate buffer 100 mmol/L, pH 7.5; preservative.
- R2 Anti-HBsAg-Ab-Ru(bpy)₃²⁺, 1 bottle, 13.9 mL:
Monoclonal anti-HBsAg antibody (mouse), polyclonal anti-HBsAg antibodies (sheep) labeled with ruthenium complex > 1.5 mg/L; phosphate buffer 100 mmol/L, pH 8.0; preservative.

HBSAG 2 Cal1 Negative calibrator 1, 1 bottle of 1.3 mL:
Human serum; preservative.

HBSAG 2 Cal2 Positive calibrator 2, 1 bottle of 1.3 mL:
HBsAg approximately 0.5 IU/mL in human serum;
preservative.

Precautions and warnings

For in vitro diagnostic use.

Exercise the normal precautions required for handling all laboratory reagents.

Disposal of all waste material should be in accordance with local guidelines. Safety data sheet available for professional user on request.

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

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

EUH 208 May produce an allergic reaction.

Product safety labeling follows EU GHS guidance.

All human material should be considered potentially infectious.

The calibrators have been prepared exclusively from the blood of donors tested individually and shown to be free from HBsAg (HBSAG 2 Cal1 only) and antibodies to HCV and HIV.

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

The serum containing HBsAg (HBSAG 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.^{11,12}

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

Reagent handling

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

Elecsys HBsAg II



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 cobas e 801 analyzer	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 cobas e 801 analyzer 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, K₃-EDTA, ACD, CPD, CP2D, CPDA and Na-citrate plasma.

Plasma tubes containing separating gel can be used.

Criterion: Correct assignment of negative and positive samples.

Stable for 7 days at 20-25 °C, 14 days at 2-8 °C, 6 months at -20 °C (± 5 °C). The samples may be frozen 6 times.

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

Centrifuge samples containing precipitates before performing the assay.

Do not use heat-inactivated samples.

Do not use samples and controls stabilized with azide.

Ensure the samples 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 HBsAg 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] 04687876190, PreciControl HBsAg II, 16 x 1.3 mL
- [REF] 11820648122, HBsAg Confirmatory Test, 2 x 1 mL each of confirmatory and control reagent or [REF] 08741034190, Elecsys HBsAg II Auto Confirm reagent kit
- [REF] 11776576322, CalSet Vials, 2 x 56 empty snap-cap bottles
- General laboratory equipment

- cobas e** 801 analyzer

Additional materials for the **cobas e** 801 analyzer:

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

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

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

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

Calibration frequency:

Calibration must be performed once per reagent lot using HBSAG 2 Cal1, HBSAG 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:

- 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

Range for electrochemiluminescence signals (counts) for the calibrators:

Negative calibrator (HBSAG 2 Cal1): 300-1500

Positive calibrator (HBSAG 2 Cal2): 2500-11000

Quality control

For quality control, use PreciControl HBsAg II.

Controls for the various concentration ranges should be run individually at least once every 24 hours when the test is in use, once per **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

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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 HBSAG 2 Cal1 and HBSAG 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 ^{b)} < 0.90	Non-reactive	Negative for HBsAg, no further testing needed.
COI ≥ 0.90 to < 1.0	Borderline	All initially reactive or borderline samples should be retested in duplicate using the Elecsys HBsAg II assay.
COI ≥ 1.0	Reactive	

b) COI = cutoff index

Retest result	Final result/ interpretation	Further steps
One or both of the duplicate retests have a COI ≥ 0.90.	Repeatedly reactive	Sample must be investigated using a neutralization test (Elecsys HBsAg Confirmatory Test or Elecsys HBsAg II Auto Confirm). Results confirmed by neutralization with anti-HBs are regarded as positive for HBsAg.
Both of the duplicate retests have a COI < 0.90.	Negative for HBsAg	No further testing needed.

Retesting of samples with an initial cutoff index ≥ 0.90 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 ≥ 0.90. 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	≤ 428 µmol/L or ≤ 25 mg/dL
Hemoglobin	≤ 0.621 mmol/L or ≤ 1000 mg/dL
Intralipid	≤ 1500 mg/dL
Biotin	≤ 4912 nmol/L or ≤ 1200 ng/mL
Rheumatoid factors	≤ 1000 IU/mL
Albumin	≤ 7.0 g/dL
IgG	≤ 4.0 g/dL
IgA	≤ 1.6 g/dL

Compound	Concentration tested
IgM	≤ 1.0 g/dL

Criterion for all substances but biotin: Correct assignment of negative and positive samples. Samples with a COI < 0.7: recovery < COI + 0.3; samples with a COI ≥ 0.7: recovery ± 20 %.

Single samples with a COI > 1: recovery 60-140 %.

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

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

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	≤ 0.18
Peginterferon alfa-2b	≤ 1.6
Lamivudine	≤ 300
Adefovir	≤ 10
Entecavir	≤ 10
Telbivudine	≤ 600
Tenofovir	≤ 245

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

In rare cases, interference due to extremely high titers of antibodies to analyte-specific antibodies, streptavidin or ruthenium can occur. These effects are minimized by suitable test design.

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

Detection limit

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

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

Specific performance data

Representative performance data on the analyzer is 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 801 analyzer					
Sample	Mean COI	Repeatability ^{c)}		Intermediate precision ^{d)}	
		SD COI	CV %	SD COI	CV %
HS ^{e)} , negative	0.254	0.018	7.1	0.030	11.7
HS, high negative	0.784	0.030	3.8	0.038	4.8
HS, weakly positive	1.12	0.038	3.3	0.043	3.9
HS, positive	10.8	0.295	2.7	0.365	3.4
PC ^{f)} HBsAg II 1	0.363	0.036	9.9	0.040	11.0
PC HBsAg II 2	4.17	0.091	2.2	0.125	3.0

c) Repeatability = within-run precision

d) Intermediate precision = between-run precision

e) HS = human serum

f) PC = PreciControl

Analytical specificity

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

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

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

Clinical sensitivity

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

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

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

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

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

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

Clinical specificity

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

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

Group	Number	Initially reactive	Repeatedly reactive	Confirmed positive
Blood donors	6360	8	3	2
Hospitalized patients	3593	181	176 ⁱ⁾	122 ^{j)}

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

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

Seroconversion panels

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

References

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- 9 Sonneveld MJ, Zoutendijk R, Janssen HLA. Hepatitis B surface antigen monitoring and management of chronic hepatitis B. *J Viral Hepat* 2011;18:449-457.
- 10 US Preventative Services Task Force. Screening for hepatitis B virus infection in pregnancy: US Preventative Services Task Force Reaffirmation Recommendation Statement. *Ann Int Med* 2009;150:569-873.
- 11 Occupational Safety and Health Standards: Bloodborne pathogens. (29 CFR Part 1910.1030). Fed. Register.
- 12 Directive 2000/54/EC of the European Parliament and Council of 18 September 2000 on the protection of workers from risks related to exposure to biological agents at work.

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):

	Contents of kit
	Analyzers/Instruments on which reagents can be used
	Reagent
	Calibrator
	Volume after reconstitution or mixing
	Global Trade Item Number

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