Elecsys HBsAg II quant II

cobas®

REF		Σ	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 **e**lectro**c**hemi**l**uminescence **i**mmuno**a**ssay "ECLIA" is intended for use on **cobas e** immunoassay analyzers.

Summary

The Elecsys HBsAg II quant II assay is intended to be used as an aid, in conjunction with other laboratory results and clinical information, in the management of patients with chronic Hepatitis B virus (HBV) infection. The test may be used in the assessment of the stage of HBV infection, monitoring of patients with chronic HBV infection and in predicting and assessing treatment response. Moreover, the test may be used as an aid in the monitoring of patients who are currently not on antiviral therapy.

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.[5,6,7,8,9,10,11,12,13,14,15,16,17,18,19] 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.[3,20,21,22,23,24,25,26] 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.[11,27,28] 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.[5,6,11,29,30,31]

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 ($Ru(bpy)_3^{2+}$)

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~$Ru(bpy)_3^{2+}$, 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 for laboratory professionals. Exercise the normal precautions required for handling all laboratory reagents.

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

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

Safety data sheet available for professional user on request.

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

Warning

H317	May cause an allergic skin reaction.

Prevention:

P261	Avoid breathing mist or vapours.

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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.

Disposal:

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

Hazardous components:

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

Product safety labeling follows EU GHS guidance.

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

All human material should be considered potentially infectious.

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

The serum containing 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.[32,33]

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, K_2-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.

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

Centrifuge samples containing precipitates before performing the assay.

Do not use heat-inactivated samples.

Do not use 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.

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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

Quality control

Use PreciControl HBsAg II quant II or other suitable controls for routine quality control procedures.

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

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

If necessary, repeat the measurement of the samples concerned.

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

Calculation

The analyzer automatically calculates the 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 ≥ 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

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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
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					
		Repeatability[b]		**Intermediate precision**[c]	
Sample	Mean IU/mL	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/Bablok[34]	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/Bablok[34]	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.

References

1 Seeger C, Zoulim F, Mason WS. Hepadnaviruses. In: Field's Virology, Knipe DM, Howley RM (eds), 2007 5th edition, Lippincott Williams and Wilkins, Philadelphia, USA. Chapter 76, pp2977–3029.

2 Lee JM, Ahn SH. Quantification of HBsAg: basic virology for clinical practice. World J Gastroenterol 2011;17:283-289.

3 Liaw YF. Clinical utility of hepatitis B surface antigen quantification in patients with chronic hepatitis B: a review. Hepatology 2011;54:E1-E9.

4 Liaw YF, Chu CM. Hepatitis B infection. Lancet 2009;373:582-592.

5 European Association for the Study of the Liver. EASL clinical practice guidelines: management of chronic hepatitis B virus infection. J Hepatol 2017;67:370-398.

6 Liaw YF, Kao JH, Piratvisuth T, et al. Asian-Pacific consensus statement on the management of chronic hepatitis B: a 2012 update. Hepatol Int 2012;6:531-561.

7 Terrault NA, Lok ASF, McMahon BJ, et al. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. Hepatology 2018;67(4):1560-1599.

8 Piratvisuth T, Marcellin P, Popescu M, et al. Hepatitis B surface antigen: association with sustained response to peginterferon alfa-2a in hepatitis B e antigen positive patients. Hepatol Int 2013;7:429-436.

9 Marcellin P, Bonino F, Yurdaydin C, et al. Hepatitis B surface antigen levels: association with 5 year response to peginterferon alfa-2a in hepatitis B e antigen-negative patients. Hepatol Int 2013;7:88-97.

10 Sonneveld MJ, Hansen BE, Piratvisuth T, et al. Response-guided peginterferon therapy in hepatitis B e antigen-positive chronic hepatitis B using serum hepatitis B surface antigen levels. Hepatology 2013;58:872-880.

11 Martinot-Peignoux M, Lapalus M, Asselah T, et al. The role of HBsAg quantification for monitoring natural history and treatment outcomes. Liver Int 2013;33 Suppl1:125-132.

12 Wang ML, Liao J, Wei B, et al. Comparison of hepatitis B virus core-related antigen and hepatitis B surface antigen for predicting HBeAg seroconversion in chronic hepatitis B patients with pegylated interferon therapy. Infect Dis (Lond) 2018;50(7):522-530.

13 Sun J, Ding H, Chen G, et al. Sustained serological and complete responses in HBeAg-positive patients treated with Peginterferon alfa-2b: a 6-year long-term follow-up of a multicenter, randomized, controlled trial in China. BMC Gastroenterol 2019;19(1):65.

14 Yang S, Xing H, Wang Y, et al. HBsAg and HBeAg in the prediction of a clinical response to peginterferon α-2b therapy in Chinese HBeAg-positive patients. Virol J 2016;13(1):180.

15 Cao Z, Liu Y, Ma L,et al. A potent hepatitis B surface antigen response in subjects with inactive hepatitis B surface antigen carrier treated with pegylated-interferon alpha. Hepatology 2017;66(4):1058-1066.

16 Cornberg M, Wong VW, Locarnini S, et al. The role of quantitative hepatitis B surface antigen revisited. J Hepatol 2017;66(2):398-411.

17 Sarin SK, Kumar M, Lau GK, et al. Asian-Pacific clinical practice guidelines on the management of hepatitis B: a 2015 update. Hepatol Int 2016;10(1):1-98.

18 Korean Association for the Study of the Liver (KASL). KASL clinical practice guidelines for management of chronic hepatitis B. Clin Mol Hepatol 2019;25(2):93-159.

19 US Food and Drug Administration (FDA). Center for Drug Evaluation and Research. Chronic hepatitis B virus infection: developing drugs for treatment. Guidance for Industry. April 2022. Available at: https://www.fda.gov/media/117977/download. Accessed 15 September 2023.

20 Janssen HLA, Sonneveld MJ, Brunetto MR. Quantification of serum hepatitis B surface antigen: is it useful for the management of chronic hepatitis B? Gut 2012;61:641-645.

21 Chan HL, Thompson A, Martinot-Peignoux M, et al. Hepatitis B surface antigen quantification: why and how to use it in 2011 – a core report. J Hepatol 2011;55:1121-1131.

22 Wang CC, Tseng TC, Wang PC, et al. Baseline hepatitis B surface antigen quantitation can predict virologic response in entecavir-treated chronic hepatitis B patients. J Formos Med Assoc Epub ahead of print Aug 1 2013.

23 Liang Y, Jiang J, Su M, et al. Predictors of relapse in chronic hepatitis B after discontinuation of anti-viral therapy. Aliment Pharmacol Ther 2011;34:344-352.

24 Zheng Z, Liao W, Liu L, et al. Effect of nucleos(t)ide analogue on serum HBsAg level in chronic hepatitis B patients: A 3-years study. Biomed Pharmacother 2020;122:109698.

25 Lai J, Sun HX, Jie YS, et al. Serum HBsAg level and its clinical significance in lamivudine treatment for patients with HBeAg-negative acute-on-chronic liver failure. Int J Infect Dis 2014;22:78-82.

26 Wang ML, Chen EQ, Tao CM, et al. Pronounced decline of serum HBsAg in chronic hepatitis B patients with long-term effective nucleos(t)ide analogs therapy. Scand J Gastroenterol 2017;52(12):1420-1426.

27 Tseng T-C, Kao J-H. Clinical utility of quantitative HBsAg in natural history and nucleos(t)ide analogue treatment of chronic hepatitis B: new trick of old dog. J Gastroenterol 2013;48:13-21.

28 Pérez-Cameo C, Pons M, Esteban R. New therapeutic perspectives in HBV: when to stop NAs. Liver Int 2014;34 Suppl 1:146-153.

29 Tseng TC, Liu CJ, Yang HC, et al. High levels of hepatitis B surface antigen increase risk of hepatocellular carcinoma in patients with low HBV load. Gastroenterology 2012;142:1140-1149.

30 Chen CJ, Lee MH, Liu J, et al. Quantitative serum levels of hepatitis B virus DNA and surface antigen are independent risk predictors of hepatocellular carcinoma. Hepatology 2011;54:881A (abstract 1095).

31 Tseng TC, Liu CJ, Yang HC, et al. Serum hepatitis B surface antigen levels help predict disease progression in patients with low hepatitis B virus loads. Hepatology 2013;57:441-450.

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

33 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.

34 Bablok W, Passing H, Bender R, et al. A general regression procedure for method transformation. Application of linear regression procedures for method comparison studies in clinical chemistry, Part III. J Clin Chem Clin Biochem 1988 Nov;26(11):783-790.

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

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

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

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

Symbols

Roche Diagnostics uses the following symbols and signs in addition to those listed in the ISO 15223-1 standard (for USA: see navifyportal.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

CE 0123

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