# Elecsys HBsAg II Auto Confirm

cobas®

| REF | | Σ | SYSTEM |
|---|---|---|---|
| 08741034190 | 08741034500 | 300; equals to maximum 150 confirmation determinations | **cobas e** 402<br>**cobas e** 801 |

**English**

**System information**

| Short name | Assay type | To be used for |
|---|---|---|
| HBSAG2CL | **cobas e** flow | samples repeatedly reactive with the Elecsys HBsAg II assay, titer < 100 COI[a)] |
| HBSAG2CH | **cobas e** flow | samples repeatedly reactive with the Elecsys HBsAg II assay, titer ≥ 100 COI |
| HBSAG2C | **cobas e** flow | samples repeatedly reactive, independently of Elecsys HBsAg II assay titer |

a) COI = cutoff index

**Intended use**

Immunoassay for in vitro confirmation of the presence of hepatitis B surface antigen in human serum and plasma samples repeatedly reactive when tested with the Elecsys HBsAg II assay.

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

**Summary**

The external envelope of the hepatitis B virus (HBV) particle is composed by a polypeptide of varying size, namely hepatitis B surface antigen (HBsAg).[1] Detection of HBsAg in human serum or plasma is the standard serological test to confirm an acute or chronic HBV infection. Particularly, after an acute exposure to HBV, HBsAg appears in serum within 1 to 10 weeks.[2] After recovery from an acute HBV infection, the level of HBsAg becomes undetectable.[3] Persistence of HBsAg for more than 6 months implies chronic HBV infection, which is conventionally diagnosed by a repeat positive test for HBsAg, 6 months after the initial positive test.[4] Therefore, HBsAg assays are used within routine diagnostic procedures to identify persons with acute or chronic HBV infection as well as to monitor the course of their disease and the efficacy of the selected therapy.[1,2,3,4,5]

HBsAg assays are also used to detect HBV in blood donors in order to prevent the transmission of the virus by blood and blood products.[6] As part of prenatal care, HBsAg assays are additionally used to detect HBV in pregnant women in order to determine initiation of suitable measures for preventing as far as possible the transmission of the virus from the mother to the newborn child.[7]

The Elecsys HBsAg II Auto Confirm assay is a fully automated confirmatory assay, based on the principle of specific antibody neutralization, intended to be used for samples repeatedly reactive in the Elecsys HBsAg II assay. Polyclonal HBsAg-specific antibodies bind to the immunodominant epitopes of HBsAg and thereby block the binding sites for the antibodies used in the Elecsys HBsAg II assay. Automation of the confirmatory assay mitigates risks of manual sample pretreatment, sample handling and result calculation.

**Test principle**

The test principle is based on 2 parallel measurements that are implemented into a **cobas e** flow (see also section "**cobas e** flows"). All steps are automated by the analyzers.

For the first measurement the sample is treated with the control pretreatment (PT2) prior to immunoreaction. This measurement serves as a reference.

For the second measurement the sample is treated with the confirmatory pretreatment (PT1) prior to immunoreaction. During incubation with confirmatory pretreatment unlabeled polyclonal anti-HBsAg antibodies are bound to the sample HBsAg and thereby block the binding sites for the labeled antibodies used in the following immunoreaction. The confirmation result (%) is automatically assessed by determining the ratio of both measurements.

The Elecsys HBsAg II Auto Confirm assay is based on the Elecsys HBsAg II assay which uses the sandwich principle.

- 1st incubation: Depending on the used **cobas e** flow, the sample may be automatically pre-diluted with Diluent Universal. The sample is incubated with control pretreatment and confirmatory pretreatment. In case of confirmatory pretreatment, unlabeled polyclonal anti-HBsAg antibodies form a complex with the sample HBsAg, inhibiting binding of labeled antibodies in the 2nd incubation phase. See "**cobas e** flows" section for required sample volume.
- 2nd incubation: 2 biotinylated monoclonal anti-HBsAg antibodies, and a mixture of monoclonal anti-HBsAg antibody and polyclonal anti-HBsAg antibodies labeled with a ruthenium complex[b)] form a sandwich complex with accessible HBsAg.
- 3rd 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.

The confirmation result (%) is automatically calculated by the software by determining the ratio between the COI obtained for the measurement with confirmatory pretreatment (result displayed as "CFHBSAG2") and the COI obtained for the measurement with control pretreatment (result displayed as "CNHBSAG2").

b) Tris(2,2'-bipyridyl)ruthenium(II)-complex ($Ru(bpy)_3^{2+}$)

**Reagents - working solutions**

The **cobas e** pack (M, R1, R2) and the pretreatment **cobas e** pack (PT1, PT2) are labeled as HBSAG2AC.

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:
2 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, 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.

PT1 Confirmatory pretreatment, 1 bottle, 5.0 mL:
Anti-HBsAg (sheep) ≥ 500000 IU/L in sheep serum; MES[c)] buffer 85 mmol/L, pH 6.5; preservative.

PT2 Control pretreatment, 1 bottle, 5.0 mL:
Sheep serum negative for anti-HBsAg; MES buffer 80 mmol/L, pH 6.5; preservative.

c) MES = 2-morpholino-ethane sulfonic acid

HBSAG2AC Cal1 Negative calibrator 1, 1 bottle of 1.3 mL:
Human serum; preservative.

HBSAG2AC 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 (HBSAG2AC 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 (HBSAG2AC 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.[8,9]

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

**Reagent handling**

The reagents (M, R1, R2, PT1, PT2) 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.

60 µL of each calibrator are required for calibration per measuring cell.

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 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** pack and the pretreatment reagents: | |
|---|---|
| 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**

Samples that were repeatedly reactive in the Elecsys HBsAg II assay.

The conditions regarding stability and specimen collection described for the Elecsys HBsAg II assay also apply here.

**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 08741107190, PreciControl HBsAg Auto Confirm, 8 x 1.3 mL
- REF 07299001190, Diluent Universal, 45.2 mL sample diluent
- 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. 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: The Elecsys HBsAg II assay has been standardized against the NIBSC standard (code number: 00/588; WHO Second International Standard for HBsAg, subtype adw2, genotype A; IU/mL).

*Calibration frequency:*

Calibration must be performed once per reagent lot using HBSAG2AC Cal1, HBSAG2AC 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**

For quality control, use PreciControl HBsAg II and PreciControl HBsAg Auto Confirm.

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 cutoff based on the measurement of HBSAG2AC Cal1 and HBSAG2AC Cal2.

# Elecsys HBsAg II Auto Confirm

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The Elecsys HBsAg II Auto Confirm **cobas e** flows automatically calculate the confirmation result of the sample. The confirmation result (%) is shown as the main result, together with its qualitative interpretation (confirmed reactive/confirmed non-reactive/indeterminate/confirmation not valid).

The confirmation result is determined as follows:

$$\text{Confirmation result (\%)} = \frac{\text{COI confirmatory reaction (CFHBSAG2)}}{\text{COI control reaction (CNHBSAG2)}} \times 100$$

For traceability of the main result, the result of the control reaction CNHBSAG2 (COI), confirmatory reaction CFHBSAG2 (COI) and the corresponding qualitative interpretation (non-reactive/borderline/reactive) are shown as subresults. Due to dilution/pretreatment steps during the reaction, the subresults do not concur with the COI obtained for the sample tested with the Elecsys HBsAg II assay.

For samples with a COI of 0.81 to < 0.90 in the control reaction, the subresult is interpreted as “non-reactive”. These samples can have a “confirmed reactive” main result (see also section “Interpretation of the results”) if the confirmation result is ≤ 60 %.

Main result and subresults are also uploaded to the Laboratory Information System (LIS).

**cobas e flows**

**cobas e** flows are procedures to enable a fully automated sequence of measurements and the calculation of assay combinations to perform decision algorithms.

The following **cobas e** flows are available to perform the Elecsys HBsAg II Auto Confirm assay:

| cobas e flow | Time to result | Sample volume | Function |
|---|---|---|---|
| HBSAG2CL | 27 minutes | 108 µL | “HBsAg II Auto Confirm - low titer” performs a fully automated confirmation for samples with a COI < 100. The sample is measured undiluted. Samples with a COI ≥ 100 in the control reaction are not processed any further. |
| HBSAG2CH | 27 minutes | 24-36 µL | “HBsAg II Auto Confirm - high titer” performs a fully automated confirmation for samples with a COI ≥ 100. It triggers an automated 1:50 dilution with Diluent Universal and confirmation reaction. In the rare case that the sample is not confirmed, it is re-run with a 1:400 dilution to ensure confirmation of very high titer samples (time to result 54 minutes). Samples initially diluted 1:50 with a COI < 2 in the control reaction are not processed any further. |
| HBSAG2C | 27-54 minutes | 24-132 µL | “HBsAg II Auto Confirm - all titer” performs a fully automated confirmation independently of sample HBsAg titer. It triggers an automated 1:50 dilution with Diluent Universal and confirmation reaction. A re-run of the sample is performed: a) if the sample COI is too low for the 1:50 dilution (COI < 2 in the control reaction). It is re-run undiluted. b) if the sample is not confirmed in the 1:50 dilution. It is re-run with a 1:400 dilution to ensure confirmation of very high titer samples. Use of "HBSAG2C" reduces average device throughput and increases average reagent consumption compared to the use of the titer dependent "HBSAG2CL" and "HBSAG2CH". |

## Interpretation of the results

| Numeric result | | Result message | Further action |
|---|---|---|---|
| Control reaction CNHBSAG2 (subresult) | Confirmation result (main result) | | |
| COI ≥ 0.81 | ≤ 60 % | Confirmed reactive | None |
| COI ≥ 0.81 | > 60 % | Confirmed non-reactive | None |
| COI < 0.81 | ≤ 60 % | Indeterminate | “Indeterminate” results should be repeated. In case the result remains “Indeterminate”, a follow-up sample should be examined. |
| COI < 0.81 | > 60 % | Confirmation not valid | “Confirmation not valid” results should be repeated. In case the result remains “Confirmation not valid”, a follow-up sample should be examined. |

Recommendations in case the following result messages are obtained:

| Result message | Subresult | Used cobas e flow | Further action |
|---|---|---|---|
| Dilution recommended | Control reaction CNHBSAG2 COI ≥ 100 | HBSAG2CL | Sample HBsAg titer is too high. Repeat confirmation with “HBSAG2CH” or “HBSAG2C”. |
| Below measuring range | Control reaction CNHBSAG2 COI < 2 | HBSAG2CH | Sample HBsAg titer is too low. Repeat confirmation with “HBSAG2CL” or “HBSAG2C”. |
| Implausible | - | HBSAG2CL, HBSAG2CH, HBSAG2C | Recalibrate using a fresh aliquot of calibrators. Repeat quality control measurement and repeat confirmation for this sample. |
| Inconsistent result in **cobas e** flow | - | HBSAG2C | a) for samples with a COI < 100 repeat measurement with “HBSAG2CL” b) for samples with a COI ≥ 100 repeat measurement with “HBSAG2CH” c) or repeat sample measurement with “HBSAG2C” |

## Limitations - interference

Due to the high-dose hook effect, a sample with a very high HBsAg concentration (> 1.5 x $10^6$ IU/mL) can have a COI < 100 in the Elecsys HBsAg II assay. Such samples are not adequately neutralized by the confirmatory reagent with the “HBSAG2CL” (low titer) **cobas e** flow. Suspected very high titer samples must be re-confirmed with the “HBSAG2CH” or “HBSAG2C” **cobas e** flow.

For further information on limitations and interferences, please refer to the Elecsys HBsAg II Method Sheet.

No false confirmation of samples containing human anti-sheep antibodies up to 1000 µg/mL.

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 confirmation sensitivity of the Elecsys HBsAg II Auto Confirm assay, 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 in human HBV-negative serum. All dilutions ≥ 0.1 IU/mL were confirmed for NIBSC standard (code number: 00/588; WHO Second International Standard for HBsAg, subtype adw2, genotype A) and NIBSC standard (code number: 12/226; WHO Third International Standard for HBsAg, HBV genotype B4, HBsAg subtypes ayw1/adw2).

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### Dilution

Samples with a COI ≥ 100 in the Elecsys HBsAg II assay should be analyzed with "HBSAG2CH" or "HBSAG2C". In these **cobas e** flows, the sample is automatically pre-diluted with Diluent Universal. Please make sure to provide Diluent Universal on the analyzer if running "HBSAG2CH" or "HBSAG2C".

### 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:

| Repeatability (within-run precision) | | | | | | | |
|---|---|---|---|---|---|---|---|
| **cobas e** 402 and **cobas e** 801 analyzers | | Control reaction (CNHBSAG2) | | | Confirmatory reaction (CFHBSAG2) | | |
| Sample (original COI) | Mean confirmation result, %* | Mean COI | SD COI | CV % | Mean COI | SD COI | CV % |
| HS** 1, weakly positive COI 1.19 | 33.0 | 0.997 | 0.044 | 4.5 | 0.321 | 0.029 | 8.9 |
| HS 2, positive COI 76.9 | 0.443 | 66.5 | 2.48 | 3.7 | 0.294 | 0.027 | 9.2 |
| HS 3, high positive COI 4246 | 0.071 | 2494 | 61.8 | 2.5 | 1.77 | 0.113 | 6.4 |
| PC*** HBSAGAC COI 4.17 | 8.97 | 3.99 | 0.083 | 2.1 | 0.358 | 0.026 | 7.4 |

* Mean confirmation result in % over n = 84 determinations; all n = 84 determinations per sample were found "Confirmed reactive" for all samples tested.

** HS = human serum

*** PC = PreciControl

| Intermediate precision (between-run precision) | | | | | | | |
|---|---|---|---|---|---|---|---|
| **cobas e** 402 and **cobas e** 801 analyzers | | Control reaction (CNHBSAG2) | | | Confirmatory reaction (CFHBSAG2) | | |
| Sample (original COI) | Mean confirmation result, %* | Mean COI | SD COI | CV % | Mean COI | SD COI | CV % |
| HS 1, weakly positive COI 1.19 | 33.0 | 0.997 | 0.074 | 7.5 | 0.321 | 0.034 | 10.7 |
| HS 2, positive COI 76.9 | 0.443 | 66.5 | 2.65 | 4.0 | 0.294 | 0.032 | 10.9 |
| HS 3, high positive COI 4246 | 0.071 | 2494 | 130 | 5.2 | 1.77 | 0.129 | 7.3 |
| PC HBSAGAC COI 4.17 | 8.97 | 3.99 | 0.098 | 2.5 | 0.358 | 0.027 | 7.6 |

* Mean confirmation result in % over n = 84 determinations; all n = 84 determinations per sample were found "Confirmed reactive" for all samples tested.

### Analytical specificity

50 potentially cross-reacting HBsAg-negative samples were spiked with ≤ 10 % of an Elecsys HBsAg II confirmed reactive sample. The resulting HBsAg-positive samples containing the potential cross-reactants were confirmed by the Elecsys HBsAg II Auto Confirm assay, demonstrating that the potential cross-reactants do not interfere with sample confirmation.

The following specimens were tested:

- containing antibodies against HAV, HCV, HIV, EBV, Rubella
- containing autoantibodies (ANA)
- after vaccination against HBV and influenza
- risk group homosexuals and patients suffering from non-viral induced liver diseases

### Confirmation of seroconversion panels

16 commercial seroconversion panels were tested. At least the first sample (first bleeding) in each panel was negative for HBsAg. All samples positive with the Elecsys HBsAg II assay in each seroconversion were confirmed by the Elecsys HBsAg II Auto Confirm assay.

### Confirmation of common HBsAg mutants and HBV genotypes

20 recombinant HBsAg proteins with mutations and 41 native samples with HBsAg mutations in the immunodominant "a" determinant region (amino acids 124-147) were tested. All samples with HBsAg mutations were positive with the Elecsys HBsAg II assay and were confirmed with the Elecsys HBsAg II Auto Confirm assay.

1st WHO International Reference Panel for Hepatitis B Virus (HBV) Genotypes for Hepatitis B Surface Antigen (HBsAg) Assays (PEI code 6100/09) representing subgenotypes A1, A2, B2, C2, D1, D2, D3, E, F2 and H was evaluated. All samples were positive with the Elecsys HBsAg II assay and confirmed with the Elecsys HBsAg II Auto Confirm assay.

### Sensitivity

309 confirmed HBsAg-positive samples, including samples from acute and chronic hepatitis B infection, were tested with the Elecsys HBsAg II Auto Confirm assay at an external site.

| Elecsys HBsAg II assay titer | Elecsys HBsAg II Auto Confirm Samples tested/confirmed reactive |
|---|---|
| Low titer, COI ≤ 10 | 25/25 |
| COI > 10 to < 600 | 80/80 |
| High titer, COI ≥ 600 | 204/204 |

The presence of HBsAg was confirmed in all 309 samples, resulting in a 100 % sensitivity. The 95 % lower confidence limit was 99.04 %.

### Specificity

2 native samples, known to be false positive in the Elecsys HBsAg II assay, were tested at an external site. The Elecsys HBsAg II Auto Confirm assay correctly did not confirm those samples.

5 native false positive samples and 7 artificial interfering false positive samples were tested with the Elecsys HBsAg II Auto Confirm assay in-house. The Elecsys HBsAg II Auto Confirm assay correctly did not confirm those samples.

### References


1 Trépo C, Chan HL, Lok A. Hepatitis B virus infection. Lancet 2014;384(9959):2053-2063.

2 Song JE, Kim DY. Diagnosis of hepatitis B. Ann Transl Med 2016;4(18):338. doi:10.21037/atm.2016.09.11

3 Yuen MF, Chen DS, Dusheiko GM, et al. Hepatitis B virus infection. Nature Reviews Disease Primers 2018;18035. doi: 10.1038/nrdp.2018.35.

4 European Association for Study of Liver & Asociacion Latinoamericana para el Estudio del Higado. EASL-ALEH Clinical Practice Guidelines: Non-invasive tests for evaluation of liver disease severity and prognosis. Journal of Hepatology 2015;63:237-264.

5 Seto WK, Wong DKH, Fung J, et al. Linearized hepatitis B surface antigen and hepatitis B core-related antigen in the natural history of chronic hepatitis B. Clin Microbiol Infect 2014;20:1173-1180.

6 World Health Organization. (2009). Screening donated blood for transfusion-transmissible infections: recommendations. https://apps.who.int/iris/handle/10665/44202

7 Schillie S, Vellozzi C, Reingold A., et al. Prevention of Hepatitis B Virus Infection in the United States: Recommendations of the Advisory Committee on Immunization Practices. Morbidity and Mortality Weekly Report, Recomm Rep 2018;67(1):1-31. DOI: http://dx.doi.org/10.15585/mmwr.rr6701a1.

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

9 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):

| | |
|---|---|
| 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 |



CE 0123

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