08948909500V1.0

Elecsys HSV-2 IgG

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REF		Σ	SYSTEM
08948909190	08948909500	100	**cobas e** 402 **cobas e** 801

English

System information

Short name	ACN (application code number)
HSV2	10099

Intended use

Immunoassay for the in vitro qualitative determination of IgG class antibodies to HSV-2 in human serum and plasma. The test is intended for use as an aid in the assessment of immune status and as an aid in the diagnosis of HSV infection.

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

Summary

Herpes simplex viruses 1 and 2 (HSV-1 and HSV-2) are two members of the family Herpesviridae. The prevalence of HSV-1 infections in the general population is estimated to be around 70-80 %, for HSV-2 around 17-25 %.[1,2] Transmission of HSV-1 and HSV-2 depends on intimate, personal contact between a seronegative individual and someone excreting the virus.[3] Infection with HSV-1 and HSV-2 can produce a wide spectrum of symptoms, e.g. mucous membrane and skin lesions and ocular, visceral, and central nervous system (CNS) disease. In immunosuppressed patients HSV infection can be associated with severe and extensive lesions.[4] Although HSV-1 and HSV-2 are usually transmitted by different routes and involve different areas of the body, much overlap is seen between the epidemiology and clinical manifestations of these two viruses.[2,5,6,7]

Primary HSV-2 infections are mainly acquired through sexual contact. The risk of HSV-2 infection is correlated with sexual promiscuity, including early age of first intercourse, history of other sexually transmitted diseases and large number of sexual partners. Initial HSV-2 replication takes place at genital sites with colonization of the sacral ganglia. Symptoms of primary infection include itching, pain, and lymphadenopathy. In females, infection is manifested by vesicles on the mucous membranes of the labia and the vagina. In males, the shaft of the penis, the prepuce, and the glans of the penis are common sites of HSV-2 infection. Systemic symptoms often accompany the appearance of primary lesions and include fever, headache, photophobia, malaise, and generalized myalgias.[8] Atypical genital herpes is often described in immunocompromised patients and can present as large hyperkeratotic ulcers. HSV-2 infection is a risk factor for HIV transmission and is associated with an increased risk of acquisition of HIV.[9] In AIDS patients, HSV can produce persistent mucocutaneous disease.

Genital herpes can be induced by either HSV-1 or HSV-2.[10] Approximately 85 % of symptomatic primary genital HSV infections are caused by HSV-2, the rest is caused by HSV-1. Genital HSV-1 results from self-inoculation or from oral sexual practices.[11]

Neonatal herpes – which can be caused by HSV-1 as well as HSV-2 – has the most severe implications and is usually acquired during the intrapartum period through exposure in the genital tract.[7,12] In most cases the mothers have no reported history of HSV infection.[13] Neonatal HSV infections may remain localized to the site of infection (skin, eye, mouth), extend to the CNS, or disseminate to multiple organs.[14] Neonates have the highest frequency of visceral and CNS involvement of all HSV-infected patients.[15,16,17]

HSV infection is frequently not recognized. Subclinical viral shedding and unrecognized infections seem to be major factors in transmission.[13] Genital HSV infection is frequently not recognized and diagnosis based on the clinical presentation alone has a low sensitivity.[8] Serologic tests have been recommended for pregnant women with active HSV lesions at delivery in order to guide patient management and when there is a high risk for infection.[18,19] Type-specific serologic tests allow the identification of silent carriers of HSV-2 infection in patients with or without pre-existing antibodies to HSV-1.[20,21] Testing algorithms have been described in guidelines.[22,23,24,25,26]

Test principle

Sandwich principle. Total duration of assay: 18 minutes.

- 1st incubation: 12 µL of sample, biotinylated recombinant HSV-2-specific antigens, and HSV-2-specific recombinant antigens 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 ($Ru(bpy)_3^{2+}$)

Reagents - working solutions

The **cobas e** pack (M, R1, R2) is labeled as HSV2.

M Streptavidin-coated microparticles, 1 bottle, 6.4 mL:
Streptavidin-coated microparticles 0.72 mg/mL; preservative.

R1 HSV-2-Ag~biotin, 1 bottle, 9.5 mL:
Biotinylated HSV-2-specific antigen (recombinant, E. coli) > 150 µg/L, MES[b)] buffer 50 mmol/L, pH 6.5; preservative.

R2 HSV-2-Ag~$Ru(bpy)_3^{2+}$, 1 bottle, 9.5 mL:
HSV-2-specific antigen (recombinant, E. coli) labeled with ruthenium complex > 150 µg/L; MES buffer 50 mmol/L, pH 6.5; preservative.

b) MES = 2-morpholino-ethane sulfonic acid

HSV2 Cal1 Negative calibrator 1 (lyophilized), 2 bottles for 1.0 mL each:
Human serum, non-reactive for HSV-2 IgG; preservative.

HSV2 Cal2 Positive calibrator 2 (lyophilized), 2 bottles for 1.0 mL each:
Human serum, reactive for HSV-2 IgG; preservative.

Precautions and warnings

For in vitro diagnostic use for health care 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.
H412	Harmful to aquatic life with long lasting effects.

Prevention:

P261	Avoid breathing dust/fume/gas/mist/vapours/spray.
P273	Avoid release to the environment.
P280	Wear protective gloves.

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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.

Product safety labeling follows EU GHS guidance.

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

All human material should be considered potentially infectious. All products derived from human blood are prepared exclusively from the blood of donors tested individually and shown to be free from HBsAg and antibodies to HCV and HIV. The testing methods use assays that have been approved by the FDA or that are in compliance with the legal rules applicable to placing in vitro diagnostic medical devices for human use on the market in the European Union.
However, as no 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.[27,28]

The sera containing HSV-2 IgG (HSV2 Cal1, HSV2 Cal2) were 0.2 micron filtrated.

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:

Carefully dissolve the contents of 1 bottle by adding exactly 1.0 mL of distilled or deionized water and allow to stand closed for 15 minutes to reconstitute. Mix carefully, avoiding foam formation.

Transfer the reconstituted calibrators into the supplied empty labeled snap-cap bottles.

Unless the entire volume is necessary for calibration on the analyzer, transfer aliquots of the freshly reconstituted calibrators into empty snap-cap bottles (CalSet Vials). Attach the supplied labels to these additional bottles. Store the aliquots at 2-8 °C or -20 °C (± 5 °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:	
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 reconstitution at 2-8 °C	14 days
after reconstitution at -20 °C (± 5 °C)	12 weeks (1 freeze/thaw cycle possible)
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, K_2-EDTA and K_3-EDTA plasma.

Li-heparin plasma tubes containing separating gel can be used.

Criterion: For non-reactive samples the deviation is ≤ 0.20 COI (cutoff index), for reactive samples the deviation is ≤ 20 % of serum value.

Stable for 48 hours at 20-25 °C, 7 days at 2-8 °C, 12 weeks at -20 °C (± 5 °C). The samples may be frozen 5 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.

Pooled samples and other artificial material may have different effects on different assays and thus may lead to discrepant findings.

Centrifuge samples containing precipitates and thawed samples 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
- 4 empty labeled snap-cap bottles

Materials required (but not provided)

- REF 05572207190, PreciControl HSV, for 4 x 3.0 mL
- REF 11776576322, CalSet Vials, 2 x 56 empty snap-cap bottles
- General laboratory equipment
- **cobas e** analyzer
- Distilled or deionized water

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 reconstituted 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 a Roche standard. The units have been selected arbitrarily.

Calibration frequency: Calibration must be performed once per reagent lot using HSV2 Cal1, HSV2 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 (HSV2 Cal1): 400-4000
Positive calibrator (HSV2 Cal2): 24000-260000

Quality control

For quality control, use PreciControl HSV.

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 HSV2 Cal1 and HSV2 Cal2. The result of a sample is given either as non-reactive, borderline (gray-zone) or 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 < 0.51	Non-reactive	Negative for HSV-2 IgG-specific antibodies, no further testing needed.
COI ≥ 0.51 to < 1.0	Borderline	Samples should be retested. In case the result is still borderline, a second sample should be collected (e.g. within 2-3 weeks) and testing should be repeated.
COI ≥ 1.0	Reactive	Positive for HSV-2 IgG-specific antibodies.

The HSV-2 IgG results for a given specimen, as determined by assays from different manufacturers, can vary due to differences in reagents and assay methods.

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	≤ 1130 µmol/L or ≤ 66 mg/dL
Hemoglobin	≤ 0.621 mmol/L or ≤ 1000 mg/dL
Intralipid	≤ 2000 mg/dL
Biotin	≤ 4912 nmol/L or ≤ 1200 ng/mL
Rheumatoid factors	≤ 1500 IU/mL
IgG	≤ 7 g/dL
IgA	≤ 1.6 g/dL
IgM	≤ 1 g/dL

Criterion: For samples with a COI ≤ 0.8 the deviation is ≤ 0.20 COI. For samples with a COI > 0.8 the deviation is ≤ 20 %.

A negative test result does not completely rule out the possibility of an infection with HSV-2. Individuals may not exhibit any detectable IgG antibodies at the early stage of acute infection.

False negative results may occur when the HSV virus is glycoprotein G (gG) deficient (0.2 % HSV isolates were gG deficient).[29]

The detection of HSV-2-specific IgG antibodies in a single sample indicates a previous exposure to HSV-2 but does not give any information of the time point of an exposure.

Elecsys HSV-2 IgG results should be used in conjunction with the patient's medical history and clinical symptoms.

The results in HIV patients, in patients undergoing immunosuppressive therapy, or in patients with other disorders leading to immune suppression, should be interpreted with caution.

Specimens from neonates, cord blood, pretransplant patients or body fluids other than serum and plasma, such as urine, saliva or amniotic fluid have not been tested.

Pharmaceutical substances
In vitro tests were performed on 17 commonly used pharmaceuticals. No interference with the assay was found.

In addition, the following special drugs were tested. No interference with the assay was found.

Special drugs

Drug	Concentration tested mg/mL
Famciclovir	≤ 0.25
Aciclovir	≤ 1.2
Valaciclovir	≤ 3

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.

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		Intermediate precision	
Sample	Mean COI	SD COI	CV %	SD COI	CV %
HS[c], negative	0.09	0.001	1.3	0.001	1.7
HS, near cutoff	0.90	0.011	1.2	0.023	2.6
HS, positive	12.7	0.214	1.7	0.347	2.7
PreciControl HSV 1	0.28	0.004	1.4	0.007	2.3
PreciControl HSV 2	7.89	0.083	1.1	0.206	2.6

c) HS = human serum

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Method comparison

A total of 800 frozen samples (sexually active adults, pregnancy routine, and request for herpes testing) analyzed by a commercially available HSV-2 IgG assay were tested with the Elecsys HSV-2 IgG assay at 2 sites. Resolution of discordant samples was done using a commercially available immunoblot assay. 12 gray-zone (borderline) results were excluded from the calculation of relative* sensitivity and relative* specificity.

* The word "relative" refers to comparing the results of this assay with those of the comparison assay.

	Site	Comparison assay	N	Relative sensitivity %	Relative specificity %
Sexually active adults	1[d)]	1	300	98.4	100
	1[e)]	2	300	100	99.6
Pregnancy screening	2[f)]	3	400	92.6	99.7
Request for herpes testing	2[e)]	3	100	100	98.7

d) 1 inconclusive sample was excluded from calculation. 1 discordant sample found negative by the Elecsys HSV-2 IgG assay was found positive by immunoblot.

e) 1 inconclusive sample was excluded from calculation. 1 discordant sample found positive by the Elecsys HSV-2 IgG assay was found negative by immunoblot.

f) 2 inconclusive samples were excluded from calculation. 1 discordant sample found positive by the Elecsys HSV-2 IgG assay was found negative by immunoblot. 2 discordant samples found negative by the Elecsys HSV-2 IgG assay were found positive by immunoblot.

Analytical specificity

130 potentially cross-reactive samples, characterized to be non-reactive for HSV-2 IgG with a commercially available assay but containing antibodies to HSV-1, were tested with the Elecsys HSV-2 IgG assay.

Gray-zone (borderline) results were excluded from the calculation of overall agreement.

An overall agreement of 100 % (130/130) was found in these specimens with the Elecsys HSV-2 IgG assay and the comparison test.

In addition, 180 potentially cross-reactive samples, characterized to be non-reactive for HSV-2 IgG with a commercially available assay, were tested with the Elecsys HSV-2 IgG assay. The potentially cross-reactive samples contained

- antibodies against CMV, EBV, VZV, Toxoplasma gondii, Rubella, HIV, Chlamydia trachomatis, Neisseria gonorrhea, Candida albicans, Syphilis (Treponema pallidum)
- E. coli antigens
- autoantibodies (ANA)

Gray-zone (borderline) results were excluded from the calculation of overall agreement.

An overall agreement of 100 % (180/180) was found in these specimens with the Elecsys HSV-2 IgG assay and the comparison test.

References

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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).

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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 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

CE 0123

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