ms_05572193190V5.0

HSV-2 IgG

cobas®

IgG antibodies to herpes simplex virus type 2

REF	Σ	SYSTEM
		Elecsys 2010
		MODULAR ANALYTICS E170
05572193 190	100	**cobas e** 411
		cobas e 601
		cobas e 602

English

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 Elecsys and **cobas e** immunoassay analyzers.

Summary

References[1,2,3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19,20,21,22,23]

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 %. Transmission of HSV-1 and HSV-2 depends on intimate, personal contact between a seronegative individual and someone excreting the virus. 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. 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.

Approximately 85 % of symptomatic primary genital HSV infections are caused by HSV-2, the rest is caused by HSV-1. 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. 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. In AIDS patients, HSV can produce persistent mucocutaneous disease.

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. In most cases the mothers have no reported history of HSV infection. Neonatal HSV infections may remain localized to the site of infection (skin, eye, mouth), extend to the CNS, or disseminate to multiple organs. Neonates have the highest frequency of visceral and CNS involvement of all HSV-infected patients.

HSV infection is frequently not recognized. Subclinical viral shedding and unrecognized infections seem to be major factors in transmission. Genital HSV infection is frequently not recognized and diagnosis based on the clinical presentation alone has a low sensitivity. Serologic tests have been recommended for pregnant women as well as for asymptomatic patients and patients at risk of HIV infection. 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. Testing algorithms have been described in guidelines.

Test principle

Sandwich principle. Total duration of assay: 18 minutes.

- 1st incubation: 20 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/ProCell 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 reagent rackpack (M, R1, R2) is labeled as HSV-2.

M Streptavidin-coated microparticles (transparent cap), 1 bottle, 6.5 mL:
Streptavidin-coated microparticles 0.72 mg/mL; preservative.

R1 HSV-2-Ag~biotin (gray cap), 1 bottle, 9 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~$Ru(bpy)_3^{2+}$ (black cap), 1 bottle, 9 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

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

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

All human material should be considered potentially infectious.

Both calibrators (HSV-2 Cal1, HSV-2 Cal2) have been prepared exclusively from the blood of donors tested individually and shown to be free from HBsAg and antibodies to HCV and HIV.

The serum containing HSV-2 IgG (HSV-2 Cal1, HSV-2 Cal2) was sterile filtrated.

The testing methods applied were FDA-approved or cleared in compliance with the European Directive 98/79/EC, Annex II, List A.

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.[24,25]

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

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Reagent handling

The reagents in the kit are ready for use (except for HSV-2 Cal1 and HSV-2 Cal2) and are supplied in bottles compatible with the system.

HSV-2 Cal1 and HSV-2 Cal2: Carefully dissolve the contents of one 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.

Elecsys 2010 and **cobas e** 411 analyzers: The reconstituted calibrators should only be left on the analyzers during calibration at 20-25 °C. After use, close the bottles as soon as possible and store upright at 2-8 °C.

Due to possible evaporation effects, not more than 5 calibration procedures per bottle set should be performed.

MODULAR ANALYTICS E170, **cobas e** 601 and **cobas e** 602 analyzers: Unless the entire volume is necessary for calibration on the analyzers, 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 for later use.

Perform **only one** calibration procedure per aliquot.

All information required for correct operation is read in from the respective reagent barcodes.

Storage and stability

Store at 2-8 °C.

Do not freeze.

Store the Elecsys reagent kit **upright** in order to ensure complete availability of the microparticles during automatic mixing prior to use.

Stability of the reagent rackpack	
unopened at 2-8 °C	up to the stated expiration date
after opening at 2-8 °C	8 weeks
on the analyzers	28 days

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	28 days (1 freeze/thaw cycle possible)
on Elecsys 2010 and **cobas e** 411 at 20-25 °C	up to 5 hours
on MODULAR ANALYTICS E170, **cobas e** 601 and **cobas e** 602	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 in a sufficient number and found acceptable.

Serum collected using standard sampling tubes or tubes containing separating gel.

Li-heparin, K_2-EDTA and K_3-EDTA plasma.

Criterion: Correct assignment of negative samples and recovery of positive samples ± 20 % of serum value.

Stable for 7 days at 2-8 °C, 48 hours at 20-25 °C, 12 weeks at -20 °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 (biocides, anti-oxidants or substances that could possibly change the pH 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 frozen samples before performing the assay.

Do not use heat-inactivated samples.

Do not use samples and controls stabilized with azide.

Ensure the samples, calibrators and controls 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, 2 x 3 mL each of PreciControl HSV level 1 and 2
- REF 11776576322, CalSet Vials, 2 x 56 empty snap-cap bottles
- General laboratory equipment
- Elecsys 2010, MODULAR ANALYTICS E170 or **cobas e** analyzer
- Distilled or deionized water

Accessories for Elecsys 2010 and **cobas e** 411 analyzers:

- REF 11662988122, ProCell, 6 x 380 mL system buffer
- REF 11662970122, CleanCell, 6 x 380 mL measuring cell cleaning solution
- REF 11930346122, Elecsys SysWash, 1 x 500 mL washwater additive
- REF 11933159001, Adapter for SysClean
- REF 11706802001, Elecsys 2010 AssayCup, 60 x 60 reaction vessels
- REF 11706799001, Elecsys 2010 AssayTip, 30 x 120 pipette tips

Accessories for MODULAR ANALYTICS E170, **cobas e** 601 and **cobas e** 602 analyzers:

- REF 04880340190, ProCell M, 2 x 2 L system buffer
- REF 04880293190, CleanCell M, 2 x 2 L measuring cell cleaning solution
- REF 03023141001, PC/CC-Cups, 12 cups to prewarm ProCell M and CleanCell M before use
- REF 03005712190, ProbeWash M, 12 x 70 mL cleaning solution for run finalization and rinsing during reagent change
- REF 03004899190, PreClean M, 5 x 600 mL detection cleaning solution
- REF 12102137001, AssayTip/AssayCup Combimagazine M, 48 magazines x 84 reaction vessels or pipette tips, waste bags
- REF 03023150001, WasteLiner, waste bags
- REF 03027651001, SysClean Adapter M

Accessories for all analyzers:

- REF 11298500316, 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. Read in the test-specific parameters via the reagent barcode. If in exceptional cases the barcode cannot be read, enter the 15-digit sequence of numbers.

MODULAR ANALYTICS E170, **cobas e** 601 and **cobas e** 602 analyzers: PreClean M solution is necessary.

Bring the cooled reagents to approximately 20 °C and place on the reagent disk (20 °C) of the analyzer. Avoid foam formation. The system automatically regulates the temperature of the reagents and the opening/closing of the bottles.

Place the reconstituted calibrators (in the system-compatible bottles with barcoded labels) in the sample zone.

All the information necessary for calibrating the assay is automatically read into the analyzer.

After calibration has been performed, store the calibrators at 2-8 °C or discard (MODULAR ANALYTICS E170, **cobas e** 601 and **cobas e** 602 analyzers).

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 HSV-2 Cal1, HSV-2 Cal2 and fresh reagent (i.e. not more than 24 hours since the reagent kit was registered on the analyzer).

Renewed calibration is recommended as follows:

- after 12 weeks when using the same reagent lot
- after 7 days (when using the same reagent kit on the analyzer)
- as required: e.g. quality control findings with PreciControl HSV outside the defined limits
- more frequently when this is required by pertinent regulations

Range for the electrochemiluminescence signals (counts) for the calibrators:

Negative calibrator (HSV-2 Cal1): 600-6500 (Elecsys 2010 and **cobas e** 411 analyzers), 400-4000 (MODULAR ANALYTICS E170, **cobas e** 601 and **cobas e** 602 analyzers).

Positive calibrator (HSV-2 Cal2): 28000-300000 (Elecsys 2010 and **cobas e** 411 analyzers), 24000-260000 (MODULAR ANALYTICS E170, **cobas e** 601 and **cobas e** 602 analyzers).

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 reagent kit, 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.

Note: The controls are not barcode-labeled and therefore have to be run like external controls. All values and ranges have to be entered manually. Please refer to the section "QC" in the operator's manual or to the online help of the instrument software.

The exact lot-specific target values and ranges are printed on the value sheet which is included in the control kit or reagent kit (or electronically available).

Calculation

The analyzer automatically calculates the cutoff based on the measurement of HSV-2 Cal1 and HSV-2 Cal2. The result of a sample is given either as reactive or non-reactive as well as in the form of a cutoff index (signal sample/cutoff).

Interpretation of the results

Non-reactive: < 0.51 COI

Gray-zone: ≥ 0.51 - < 1.0 COI

Reactive: ≥ 1.0 COI

Samples with a cutoff index < 0.51 are non-reactive in the Elecsys HSV-2 IgG assay. These samples are considered negative for HSV-2 IgG-specific antibodies and do not need further testing.

Samples with a cutoff index between ≥ 0.51 and < 1.0 are considered as gray-zone samples. The samples should be retested. In case the result is still gray-zone, a second sample should be tested e.g. within the following 2-3 weeks.

Samples with a cutoff index ≥ 1.0 are considered reactive in the Elecsys HSV-2 IgG assay.

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

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).[26]

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.

The assay is unaffected by icterus (bilirubin < 1130 µmol/L or < 66 mg/dL), hemolysis (Hb < 0.621 mmol/L or < 1.0 g/dL), lipemia (Intralipid < 2000 mg/dL) and biotin (< 205 nmol/L or < 50 ng/mL).

Criterion: Mean recovery of positive samples within ± 20 % of serum value. Correct assignment of negative samples and recovery of positive samples ± 20 %.

Samples should not be taken from patients receiving therapy with high biotin doses (i.e. > 5 mg/day) until at least 8 hours following the last biotin administration.

No interference was observed from rheumatoid factors up to a concentration of 1500 IU/mL.

In vitro tests were performed on 18 commonly used pharmaceuticals and in addition on Famciclovir, Aciclovir and Valaciclovir. No interference with the assay was found.

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, human sera and controls (repeatability n = 21) in a modified protocol (EP5-A) of the CLSI (Clinical and Laboratory Standards Institute): 4 times daily for 21 days (n = 84). The following results were obtained:

Elecsys 2010 and **cobas e** 411 analyzers					
		Repeatability		**Intermediate precision**	
Sample	Mean COI	SD COI	CV %	SD COI	CV %
HS[c], negative	0.11	0.001	1.1	0.002	1.8
HS, near cutoff	0.80	0.010	1.2	0.024	3.0
HS, positive	5.70	0.090	1.6	0.206	3.6
PC[d] HSV_1	0.34	0.005	1.3	0.010	2.9
PC HSV_2	7.04	0.110	1.6	0.231	3.3

c) HS = human serum

d) PC = PreciControl

HSV-2 IgG

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MODULAR ANALYTICS E170, **cobas e** 601 and **cobas e** 602 analyzers					
		Repeatability		**Intermediate precision**	
Sample	Mean COI	SD COI	CV %	SD COI	CV %
HS, negative	0.08	0.001	1.6	0.001	1.8
HS, near cutoff	0.86	0.009	1.0	0.015	1.7
HS, positive	6.18	0.064	1.0	0.111	1.8
PC HSV_1	0.32	0.004	1.1	0.005	1.7
PC HSV_2	7.59	0.080	1.0	0.150	2.0

Method comparison

A total of 800 frozen samples (sexually active adults, pregnancy routine, and request for herpes testing) analyzed by 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 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[e)]	1	300	98.4	100
	1[f)]	2	300	100	99.6
Pregnancy screening	2[g)]	3	400	92.6	99.7
Request for herpes testing	2[h)]	3	100	100	98.7

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

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

g) 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.

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

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

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

Symbols

Roche Diagnostics uses the following symbols and signs in addition to those listed in the ISO 15223-1 standard.

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

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