Elecsys S100

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REF		Σ	SYSTEM
08817324190	08817324500	100	**cobas e** 402 **cobas e** 801

English

System information

Short name	ACN (application code number)
S100	10118

Please note

The measured S100 value of a patient's sample can vary depending on the testing procedure used. The laboratory finding must therefore always contain a statement on the S100 assay method used. S100 values determined on patient samples by different testing procedures cannot be directly compared with one another and could be the cause of erroneous medical interpretations. If there is a change in the S100 assay procedure used while monitoring therapy, then the S100 values obtained upon changing over to the new procedure must be confirmed by parallel measurements with both methods.

Intended use

Immunoassay for the in vitro quantitative determination of S100 (S100 A1B and S100 BB) in human serum. This assay can be used

- to aid in the management of patients suffering from malignant melanoma (Elecsys S100 assay is not suitable for the diagnosis of malignant melanoma)
- to aid in the management of patients after potential brain injury in conjunction with clinical information and imaging techniques

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

Summary

S100 is a small dimeric protein with a molecular weight of approximately 10.5 kDa, and belongs to a multigenic family of calcium-binding proteins.[1,2]

S100 A1 (α) and S100 B (β) were the first members described, originally isolated as an unfractionated mixture by Moore[3] from bovine brain and named S100 after its solubility in a 100 % saturated ammonium sulfate solution. In the meantime, at least 21 different members of the S100 family have been identified.[4]

S100 A1 and S100 B are predominantly expressed by cells of the central nervous system, mainly astroglial cells, but are also expressed in melanoma cells and to some extent in other tissues. The functional protein, which is composed of hetero- or homodimers of A1 and B, is implicated in a variety of intra- and extracellular regulatory activities.[1,5,6]

In patients suffering from malignant melanoma, especially stage II, III, and IV, elevated S100 serum levels may indicate disease progression. Serial measurements can be useful for follow-up and monitoring therapy success in these patients.[7,8,9,10,11,12,13]

In addition, levels of S100 rise in the CSF (cerebrospinal fluid) and are released in peripheral blood after a variety of cerebral lesions.

S100 can be detected in patients with cerebral damage caused by several events, e.g. traumatic brain injuries[14,15,16,17,18,19,20,21] or stroke.[22,23,24]

Test principle

Sandwich principle. Total duration of assay: 18 minutes.

- 1st incubation: 12 µL of sample, a biotinylated monoclonal S100 B-specific antibody, and a monoclonal S100 B-specific antibody labeled with a ruthenium complex[a)] react to 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 is labeled as S100.

M Streptavidin-coated microparticles, 1 bottle, 5.8 mL:
Streptavidin-coated microparticles 0.72 mg/mL; preservative.

R1 Anti-S100 B-Ab~biotin, 1 bottle, 9.9 mL:
Biotinylated monoclonal anti-S100 antibody (mouse) 1.0 mg/L; phosphate buffer 50 mmol/L, pH 7.2; preservative.

R2 Anti-S100 B-Ab~$Ru(bpy)_3^{2+}$, 1 bottle, 9.9 mL:
Monoclonal anti-S100 antibody (mouse) labeled with ruthenium complex 1.0 mg/L; phosphate buffer 50 mmol/L, pH 7.2; 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.
Prevention:	
P261	Avoid breathing mist or vapours.
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.

Product safety labeling follows EU GHS guidance.

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

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

Reagent handling

The reagents in the kit have been assembled into a ready-for-use unit that cannot be separated.

All information required for correct operation is available via the **cobas** link.

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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:	
unopened at 2-8 °C	up to the stated expiration date
on the analyzers	16 weeks

Specimen collection and preparation

Only the specimen listed below was tested and found acceptable.

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

Do not use plasma.

Stable for 8 hours at 20-25 °C, 2 days at 2-8 °C, 3 months 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.

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.

Materials required (but not provided)

- REF 03289834190, S100 CalSet, for 4 x 1.0 mL
- REF 11731416190, PreciControl Universal, for 4 x 3.0 mL
- 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.

Calibration

Traceability: This method has been standardized against weighed-out S100 B protein.

The predefined master curve is adapted to the analyzer using the relevant CalSet.

Calibration frequency: Calibration must be performed once per reagent lot using 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 Universal.

In addition, other suitable control material can be used.

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 of each sample (either in µg/L, ng/mL or pg/mL).

Interpretation of the results

Samples with S100 values ≥ 0.105 µg/L are considered to have elevated levels of S100 protein. This cutoff value is defined by the 95th percentile of S100 concentrations observed in a cohort of apparently healthy individuals.

The following should be taken into consideration when interpreting S100 measurements for patient management:

In patients with malignant melanoma:

- S100 levels alone, regardless of the value, should not be interpreted as absolute evidence for the presence or absence of disease, its progression or recurrence.
- The level of S100 < 0.105 µg/L cannot be interpreted as the absence of disease progression or relapse.
- In patients with known malignant melanoma, elevated S100 results may be indicative of disease progression or relapse, though final decisions regarding appropriate patient management must always be made in conjunction with other clinical data, e.g. imaging results, clinical signs, symptoms or results of other tests.

In patients with mild traumatic brain injury:

- S100 should be measured in serum up to 3 hours after the trauma occurred.
- S100 levels alone, regardless of the value, should not be interpreted as absolute evidence for the presence or absence of intracranial bleeding, and overall patient management should combine measurement of serum S100 with clinical information and neuroimaging.
- Serum S100 values < 0.105 µg/L are considered to be indicative of absence of intracranial injury. In this case, physicians may avoid recommending patients to undergo a CT scan.
- Patients presenting serum S100 levels > 0.105 µg/L may have an intracranial injury, which should be confirmed with a CT scan.

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.

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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	≤ 1200 IU/mL
IgG	≤ 5.0 g/dL
IgA	≤ 1.6 g/dL
IgM	≤ 1.0 g/dL

Criterion: For concentrations ≤ 0.05 µg/L the deviation is ≤ 0.005 µg/L. For concentrations > 0.05 µg/L the deviation is ≤ 10 %.

There is no high-dose hook effect at S100 concentrations up to 10 µg/mL.

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

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

Special cancer drugs

Drug	Concentration tested
Cisplatin	50 mg/L
Doxorubicin	200 mg/L
Dacarbazine	5000 mg/L
Interferon α	15 Mio IU/L

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

0.015-30 µg/L (defined by the Limit of Detection and the maximum of the master curve). Values below the Limit of Detection are reported as < 0.015 µg/L. Values above the measuring range are reported as > 30 µg/L.

Lower limits of measurement

Limit of Blank, Limit of Detection and Limit of Quantitation

Limit of Blank = 0.005 µg/L

Limit of Detection = 0.015 µg/L

Limit of Quantitation = 0.02 µg/L

The Limit of Blank, Limit of Detection and Limit of Quantitation 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 %).

The Limit of Quantitation is the lowest analyte concentration that can be reproducibly measured with an intermediate precision CV of ≤ 20 %.

Dilution

Samples with S100 concentrations above the measuring range can be diluted with Elecsys S100 CalI or S100 negative human serum. Diluent Universal is not recommended. The recommended dilution is 1:5 (manually). The concentration of the diluted sample must be ≥ 1.0 µg/L.

After manual dilution, multiply the result by the dilution factor.

Expected values

- *Apparently healthy adults and patients with malignant melanoma*

Measurements using the Elecsys S100 assay in samples from apparently healthy persons and patients suffering from malignant melanoma in different tumor stages under follow-up investigation revealed the following values:

Group	Subgroup	No. of samples (patients)	Median µg/L	95th percentile	No. of samples above cutoff (> 0.105 µg/L)b)
Apparently healthy adults		206 (206)	0.046	0.105	10 of 206 (4.9 %)
Malignant melanoma patients (all stages under follow-up investigation)	NEDc)	821 (408)	0.044	0.109	45 of 821 (5.5 %)
	Regional lymph node metastases	32 (24)	0.047	0.120	4 of 32 (12.5 %)
	Skin/distant lymph node metastases	21 (15)	0.093	0.511	10 of 21 (47.6 %)
	Distant/visceral metastases	70 (48)	0.077	0.759	30 of 70 (42.9 %)

b) Number of samples > 95th percentile of apparently healthy adults

c) No evidence of disease, tumor free

- *Adult patients with potential brain injury*

Elecsys S100 values were assessed within 3 hours after traumatic event in patients presenting with mild traumatic brain injury (GCS 13-15 - Glasgow Coma Score) and at least one symptom. CCT (cranial computer tomography) was performed within 6 hours after traumatic event. When using the 95th percentile value of the apparently healthy persons (0.105 µg/L) as the cutoff, the following results were obtained for the Elecsys S100 assay compared to the CCT reference:

NPV (negative predictive value) 99.7 %, PPV (positive predictive value) 11 %, sensitivity 98.8 %, and specificity 32.9 % (confidence interval 95 %: NPV 99.1-100 %, PPV 8.7-13.3 %, sensitivity 96.4-100 %, specificity 30-35.8 %).

	CCT positive	CCT negative	Total
Elecsys S100 positive	83	670	753
Elecsys S100 negative	1[d)]	329	330
Total	84	999	1083

d) 0.098 µg/L

Each laboratory should investigate the transferability of the expected values to its own patient population and if necessary determine its own reference ranges.

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 µg/L	SD µg/L	CV %	SD µg/L	CV %
Human serum 1	0.030	0.001	4.1	0.002	7.8
Human serum 2	0.035	0.001	3.6	0.002	6.9
Human serum 3	0.122	0.003	2.4	0.005	4.1
Human serum 4	16.0	0.356	2.2	0.720	4.5

cobas e 402 and **cobas e** 801 analyzers					
		Repeatability		**Intermediate precision**	
Sample	Mean µg/L	SD µg/L	CV %	SD µg/L	CV %
Human serum 5	25.2	0.502	2.0	1.24	4.9
PC[e)] Universal 1	0.198	0.002	1.2	0.007	3.4
PC Universal 2	2.39	0.022	0.9	0.070	2.9

e) PC = PreciControl

Method comparison

a) A comparison of the Elecsys S100 assay, REF 07027800190 (**cobas e** 801 analyzer, y), with the Elecsys S100 assay, REF 03175243190 (**cobas e** 601 analyzer, x), gave the following correlations (µg/L):

Number of samples measured: 383

Passing/Bablok[25]	Linear regression
y = 0.958x + 0.0008	y = 0.952x + 0.0811
τ = 0.971	r = 0.998

The sample concentrations were between 0.0184 and 29.6 µg/L.

b) A comparison of the Elecsys S100 assay, REF 08817324190 (y), with the Elecsys S100 assay, REF 07027800190 (x), gave the following correlations (µg/L):

Number of samples measured: 162

Passing/Bablok[25]	Linear regression
y = 1.007x + 0.0011	y = 0.991x + 0.0950
τ = 0.979	r = 0.999

The sample concentrations were between 0.0154 and 29.6 µg/L.

c) A comparison of the Elecsys S100 assay, REF 08817324190 (**cobas e** 402 analyzer, y), with the Elecsys S100 assay, REF 08817324190 (**cobas e** 801 analyzer, x), gave the following correlations (µg/L):

Number of samples measured: 158

Passing/Bablok[25]	Linear regression
y = 1.016x + 0.0001	y = 1.014x + 0.002
τ = 0.991	r = 1.00

The sample concentrations were between 0.0163 and 28.9 µg/L.

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For further information, please refer to the appropriate 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.

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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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