

REF		$\Sigma$	SYSTEM
08932352190	08932352500	100	<b>cobas e 411</b> <b>cobas e 601</b> <b>cobas e 602</b>

## English

### System information

For **cobas e 411** analyzer: test number 2350

For **cobas e 601** and **cobas e 602** analyzers: Application Code Number 99

### Intended use

Immunoassay for the in vitro quantitative determination of follicle-stimulating hormone in human serum and plasma.

The **electrochemiluminescence immunoassay** "ECLIA" is intended for use on **cobas e** immunoassay analyzers.

### Summary

Follicle stimulating hormone (FSH) measurements, performed with this assay, in human serum and plasma are used as an aid in the diagnosis and monitoring of dysfunction of the hypothalamic-pituitary-gonadal system, primary causes of male and female infertility.

FSH is a glycoprotein consisting of two subunits,  $\alpha$ - and  $\beta$ -chains. Together with LH (luteinizing hormone), FSH belongs to the gonadotropin family, regulates and stimulates the growth and function of the gonads (ovaries and testes).<sup>1</sup> FSH is released in pulses from the gonadotropic cells of the anterior pituitary. The levels of the circulating hormone are controlled via negative feedback to the hypothalamus and pituitary by estrogens (especially estradiol) and inhibins. In women, FSH stimulates biosynthesis and secretion of estrogens and ovulation. The FSH levels show a mid-menstrual cycle peak, although less prominent than LH. Due to changes in ovarian function and reduced estrogen secretion, high FSH concentrations occur during menopause.<sup>1,2,3</sup> In men, FSH acts on Sertoli cells to support spermatogenesis.<sup>1,2,3</sup>

Altered FSH concentrations are measured in cases of disorders of the hypothalamic-pituitary-gonadal system, which often impact male and female fertility.<sup>4,5</sup> The determination of FSH in conjunction with LH is therefore utilized for clinical indications such as congenital diseases with chromosome aberrations (e.g. Turner's syndrome), polycystic ovary syndrome (PCOS), amenorrhea (clarify causes), menopausal syndrome.<sup>4</sup> In men, FSH measurements can be used to distinguish different types of azoospermia: primary non-obstructive azoospermia (elevated FSH, suggesting Sertoli cell lesions), secondary non-obstructive azoospermia (low FSH, suggesting hypothalamic and pituitary disorders), obstructive azoospermia (normal FSH, suggesting obstruction in the reproductive tract).<sup>6</sup>

The Elecsys FSH assay employs two different monoclonal antibodies specifically directed against human FSH. Cross-reactivity with LH, TSH (thyroid stimulating hormone), hCG (human chorionic gonadotropin), hGH (human growth hormone), and hPL (human placental lactogen) is negligible.

### Test principle

Sandwich principle. Total duration of assay: 18 minutes.

- 1st incubation: 40  $\mu$ L of sample, a biotinylated monoclonal FSH-specific antibody, and a monoclonal FSH-specific antibody labeled with a ruthenium complex<sup>a)</sup> 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 via a calibration curve which is instrument-specifically generated by 2-point calibration and a master curve provided via the reagent barcode or e-barcode.

a) Tris(2,2'-bipyridyl)ruthenium(II)-complex (Ru(bpy)<sub>3</sub><sup>2+</sup>)

### Reagents - working solutions

The reagent rackpack is labeled as FSH.

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

R1 Anti-FSH-Ab~biotin (gray cap), 1 bottle, 10 mL:  
Biotinylated monoclonal anti-FSH antibody (mouse) 0.5 mg/L, MES buffer 50 mmol/L, pH 6.0; preservative.

R2 Anti-FSH-Ab~Ru(bpy)<sub>3</sub><sup>2+</sup> (black cap), 1 bottle, 10 mL:  
Monoclonal anti-FSH antibody (mouse) labeled with ruthenium complex 0.8 mg/L, MES buffer 50 mmol/L, pH 6.0; 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 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:	
unopened at 2-8 °C	up to the stated expiration date
after opening at 2-8 °C	12 weeks
on the analyzers	8 weeks

## 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<sub>2</sub>-EDTA and K<sub>3</sub>-EDTA plasma.

Criterion: Slope 0.9-1.1 + bias at 10 mIU/mL ≤ 10 % + coefficient of correlation ≥ 0.95.

Stable for 5 days at 20-25 °C, 14 days at 2-8 °C, 6 months at -20 °C (± 5 °C). Freeze only once.

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, calibrators and controls are at 20-25 °C prior to measurement.

Due to possible evaporation effects, samples, calibrators and controls 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] 08932417190, FSH CalSet II, for 4 x 1.0 mL
- [REF] 09557440190, FSH CalSet II, 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 the **cobas e** 411 analyzer:

- [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, AssayCup, 60 x 60 reaction cups
- [REF] 11706799001, AssayTip, 30 x 120 pipette tips
- [REF] 11800507001, Clean-Liner

Additional materials for **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, 48 magazines x 84 reaction cups or pipette tips, waste bags

- [REF] 03023150001, WasteLiner, waste bags

- [REF] 03027651001, SysClean Adapter M

Additional materials for all analyzers:

- [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.

**cobas e** 601 and **cobas e** 602 analyzers: PreClean M solution is necessary.

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.

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.

## Calibration

**Traceability:** This method has been standardized against the Enzymun-Test FSH method. This in turn has been standardized against the 2nd IRP WHO reference standard 78/549.

Every Elecsys reagent set has a barcoded label containing specific information for calibration of the particular reagent lot. 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 reagent kit 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 1 month (28 days) 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 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 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.

## Calculation

The analyzer automatically calculates the analyte concentration of each sample (either in mIU/mL or in IU/L).

## Limitations - interference

### Endogenous substances

Compound	Concentration tested
Bilirubin	≤ 1112 µmol/L or ≤ 65 mg/dL
Hemoglobin	≤ 0.621 mmol/L or ≤ 1000 mg/dL
Intralipid	≤ 1900 mg/dL
Biotin	≤ 4912 nmol/L or ≤ 1200 ng/mL
Rheumatoid factors	≤ 1200 IU/mL

Criterion: For concentrations from 0.3-20 mIU/mL the deviation is  $\pm 2.5$  mIU/mL. For concentrations from 20-200 mIU/mL the deviation is  $\pm 10$  %.

There is no high-dose hook effect at FSH concentrations up to 2000 mIU/mL.

In vitro tests were performed on 17 commonly used pharmaceuticals. 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.

## Limits and ranges

### Measuring range

0.3-200 mIU/mL (defined by the Limit of Detection and the maximum of the master curve). Values below the Limit of Detection are reported as  $< 0.3$  mIU/mL. Values above the measuring range are reported as  $> 200$  mIU/mL.

### Lower limits of measurement

Limit of Blank, Limit of Detection and Limit of Quantitation

Limit of Blank = 0.1 mIU/mL

Limit of Detection = 0.3 mIU/mL

Limit of Quantitation = 1 mIU/mL

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 95<sup>th</sup> percentile value from  $n \geq 60$  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  $\leq 20$  %.

### Dilution

Not necessary due to the broad measuring range.

### Expected values

Studies with the Elecsys FSH assay have revealed the following FSH values:

Test subjects	N	FSH (mIU/mL)		
		Percentile		
		50 <sup>th</sup>	5 <sup>th</sup>	95 <sup>th</sup>
Men	319	4.6	1.5	12.4
Women				
• Follicular phase	376	6.9	3.5	12.5
• Ovulation phase	56	12.3	4.7	21.5
• Luteal phase	349	3.6	1.7	7.7
• Postmenopause	181	67.0	25.8	134.8

**LH/FSH quotient:** Quotients have been calculated from the results obtained with the Elecsys LH assay and the Elecsys FSH assay in the samples of healthy women of child-bearing age. The following medians have been calculated:

Follicular phase: 0.82 ( $n = 315$ )

Luteal phase: 1.12 ( $n = 279$ )

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, pooled human sera 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 411 analyzer					
Sample	Mean mIU/mL	Repeatability		Intermediate precision	
		SD mIU/mL	CV %	SD mIU/mL	CV %
Human serum 1	1.40	0.021	1.5	0.055	3.9
Human serum 2	10.7	0.205	1.9	0.401	3.7
Human serum 3	41.5	0.547	1.3	1.31	3.2
Human serum 4	107	1.52	1.4	3.69	3.4
Human serum 5	180	3.17	1.8	7.32	4.1
PC <sup>b)</sup> Universal 1	20.6	0.259	1.3	0.805	3.9
PC Universal 2	50.2	0.950	1.9	2.06	4.1

b) PC = PreciControl

cobas e 601 and cobas e 602 analyzers					
Sample	Mean mIU/mL	Repeatability		Intermediate precision	
		SD mIU/mL	CV %	SD mIU/mL	CV %
Human serum 1	1.29	0.017	1.3	0.039	3.0
Human serum 2	10.0	0.162	1.6	0.358	3.6
Human serum 3	79.9	1.41	1.8	2.99	3.7
Human serum 4	128	1.49	1.2	4.98	3.9
Human serum 5	184	2.40	1.3	7.63	4.1
PC <sup>b)</sup> Universal 1	18.2	0.252	1.4	0.784	4.3
PC Universal 2	44.0	0.932	2.1	1.85	4.2

### Method comparison

A comparison of the Elecsys FSH assay, [REF](#) 08932352190 (cobas e 601 analyzer; y) with the Elecsys FSH assay, [REF](#) 11775863122 (cobas e 601 analyzer; x) gave the following correlations (mIU/mL):

Number of samples measured: 170

Passing/Bablok<sup>7</sup> Linear regression

$y = 0.979x + 0.092$

$y = 1.01x - 1.69$

$\tau = 0.983$

$r = 0.998$

The sample concentrations were between 1.46 and 182 mIU/mL.

### Analytical specificity

For the monoclonal antibodies used, the following cross-reactivities were found:

Substance	Cross-reactivity %	Additive concentration mIU/mL
LH	0.022	5000
TSH	n.d. <sup>c)</sup>	5000
hCG	0.004	5000
hGH	n. d.	2000
hPL	n. d.	5000

c) n. d. = not detectable

## References

- 1 Cole TJ. Hormones. In: Rifai N, Chiu RWK, Young I, Burnham CAD, Wittwer CT, editors. Tietz Textbook of Laboratory Medicine, Saunders Elsevier, Philadelphia, 7th edition, 2023, chapter 38, p. 416-16.e14.
- 2 Padmanabhan V, Cardoso RC. Neuroendocrine, autocrine, and paracrine control of follicle-stimulating hormone secretion. Mol Cell Endocrinol 2020 Jan 15;500:110632. doi: 10.1016/j.mce.2019.110632.
- 3 Holmes DT, Bertholf RL, Winter WE. Pituitary Function and Pathophysiology. In: Rifai N, Chiu RWK, Young I, Burnham CAD, Wittwer CT, editors. Tietz Textbook of Laboratory Medicine, Saunders Elsevier, Philadelphia, 7th edition, 2023, chapter 55, p. 767-804.e10.
- 4 Nerenz RD, Boh B. Reproductive endocrinology and related disorders. In: Rifai N, Chiu RWK, Young I, Burnham CAD, Wittwer CT, editors. Tietz Textbook of Laboratory Medicine, Saunders Elsevier, Philadelphia, 7th edition, 2023, chapter 58, p. 846-884.e11.
- 5 Carson SA, Kallen AN. Diagnosis and Management of Infertility: A Review. JAMA 2021 Jul 6;326(1):65-76. doi: 10.1001/jama.2021.4788.
- 6 Adamopoulos DA, Koukkou EG. 'Value of FSH and inhibin-B measurements in the diagnosis of azoospermia'--a clinician's overview. Int J Androl 2010 Feb;33(1):e109-13. doi: 10.1111/j.1365-2605.2009.00980.x.
- 7 Bablok W, Passing H, Bender R, et al. A general regression procedure for method transformation. Application of linear regression procedures for method comparison studies in clinical chemistry, Part III. J Clin Chem Clin Biochem 1988 Nov;26(11):783-790.







For further information, please refer to the appropriate 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.

## 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](http://dialog. Roche.com) for definition of symbols used):

	Contents of kit
	Analyzers/Instruments on which reagents can be used
	Reagent
	Calibrator
	Volume for reconstitution
	Global Trade Item Number


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