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Elecsys Prolactin II

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REF		Σ	SYSTEM
03203093190* 03203093214*	03203093500	100	**cobas e** 411 **cobas e** 601 **cobas e** 602

* Some kits shown may not be available in all countries.

English

System information

For **cobas e** 411 analyzer: test number 131
For **cobas e** 601 and **cobas e** 602 analyzers: Application Code Number 014

Intended use

Immunoassay for the in vitro quantitative determination of prolactin in human serum and plasma.

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

Summary

Prolactin measurements, performed with this assay, in human serum and plasma, are used in the diagnosis of hyperprolactinemia, associated with endocrine disorders and infertility.

Prolactin is synthesized in the anterior pituitary and is secreted in episodes by lactotroph cells. Prolactin appears in serum in three different forms: the monomeric form ("little" prolactin, 23 kDa), the dimeric form ("big" prolactin, 48 to 56 kDa) and the polymeric form ("big-big" prolactin, > 100 kDa).[1] Occasionally immunoglobulin G autoantibodies against prolactin can bind to prolactin, forming a macromolecular complex called macroprolactin. The presence of macroprolactin elevates the total serum concentration of prolactin.[2,3]

Prolactin secretion is predominantly controlled through suppression by dopamine. Factors inducing prolactin synthesis and secretion include estrogen, thyrotropin-releasing hormone, epidermal growth factor, and dopamine receptor antagonists. High concentrations of prolactin reduce luteinising hormone (LH) and follicle stimulating hormone (FSH) by inhibiting the secretion of gonadotropin releasing hormone (GnRH).[1]

Hyperprolactinemia (in men and women) is a cause of fertility disorders. Oligomenorrhea, amenorrhea and infertility in hyperprolactinemic women (premenopausal: > 30 ng/mL, postmenopausal: > 20 ng/mL), and impotence and oligospermia in hyperprolactinemic men (> 20 ng/mL), result from prolactin suppression of GnRH secretion.[1]

During pregnancy, the concentration of prolactin rises under the influence of sex hormones (predominantly estradiol).[1,4] In women, prolactin stimulates and sustains postpartum lactation; low postpartum levels of prolactin can be a cause of lactation failure after childbirth.[1,5,6]

Nonpuerperal hyperprolactinemia is one of the most common endocrine disorders and may be caused by lactotroph adenomas (prolactinomas, approximately 40 % of all pituitary tumors), by pharmacological or pathological interruption of hypothalamic-pituitary dopaminergic pathways or it can sometimes be idiopathic.[4]

Emotional stress, physical exercise and a protein-rich diet can all stimulate prolactin secretion.[1,4,7] Metabolic disorders related to gluco-insulinemic and lipid profile are commonly reported in patients with prolactin excess.[8,9] Pharmacological modulation of the hypothalamic dopamine system and/or the pituitary dopamine receptors can affect prolactin levels.[10,11,12,13,14,15]

Low circulating prolactin levels can be the consequence of: abnormal lactotroph cell development (genetic causes), destruction of pituitary tissue (Sheehan syndrome, inflammation or autoimmune lactotroph damage, tumor or surgery, tuberculosis infection), pseudohypoparathyroidism, idiopathic prolactin deficiency, medications (e.g. dopamine agonist).[15] Isolated prolactin deficiency is rare and mainly manifests clinically in women after childbirth with puerperal alactogenesis.[5,16] The incidence of severe prolactin deficiency in patients with acquired prolactin deficiency increases alongside an increase in the number of other anterior pituitary hormone defects.[15]

The Elecsys Prolactin II assay uses two monoclonal antibodies specifically directed against human prolactin.[17] Both antibodies show a low reactivity with most forms of macroprolactin.

Test principle

Sandwich principle. Total duration of assay: 18 minutes.

- 1st incubation: 10 µL of sample and a biotinylated monoclonal prolactin-specific antibody form a first complex.
- 2nd incubation: After addition of a monoclonal prolactin-specific antibody labeled with a ruthenium complex[a)] and streptavidin-coated microparticles, a sandwich complex is formed and 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 ($Ru(bpy)_3^{2+}$)

Reagents - working solutions

The reagent rackpack is labeled as PRL II.

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

R1 Anti-prolactin-Ab~biotin (gray cap), 1 bottle, 10 mL:
Biotinylated monoclonal anti-prolactin antibody (mouse) 0.7 mg/L; phosphate buffer 50 mmol/L, pH 7.0; preservative.

R2 Anti-prolactin-Ab~$Ru(bpy)_3^{2+}$ (black cap), 1 bottle, 10 mL:
Monoclonal anti-prolactin antibody (mouse) labeled with ruthenium complex 0.35 mg/L; phosphate buffer 50 mmol/L, pH 7.0; 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.

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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

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_2-EDTA and K_3-EDTA plasma.

Criterion: Slope 0.9-1.1 + intercept within ≤ ± 10 µIU/mL + 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.

Stability of serum obtained with separating tubes: 24 hours at 2-8 °C (note the data provided by the tube manufacturer).

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 03277356190, Prolactin II CalSet, for 4 x 1.0 mL
- REF 11731416190, PreciControl Universal, for 4 x 3.0 mL
- REF 11732277122, Diluent Universal, 2 x 16 mL sample diluent or REF 03183971122, Diluent Universal, 2 x 36 mL sample diluent
- 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 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.

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 3rd IRP WHO Reference Standard 84/500.

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

Use PreciControl Universal or other suitable controls for routine quality control procedures.

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.

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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 µIU/mL, ng/mL or in mIU/L).

Conversion factors: µIU/mL (mIU/L) x 0.047 = ng/mL

ng/mL x 21.2 = µIU/mL (mIU/L)

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	≤ 513 µmol/L or ≤ 30 mg/dL
Hemoglobin	≤ 0.932 mmol/L or ≤ 1500 mg/dL
Intralipid	≤ 1500 mg/dL
Biotin	≤ 164 nmol/L or ≤ 40 ng/mL
Rheumatoid factors	≤ 1100 IU/mL

Criterion: For concentrations of 1-50 µIU/mL the deviation is ≤ ± 10 µIU/mL. For concentrations > 50-100 µIU/mL the deviation is ± 20 %. For concentrations > 100 µIU/mL the deviation is ± 15 %.

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.

There is no high-dose hook effect at prolactin concentrations up to 270000 µIU/mL (12690 ng/mL).

Pharmaceutical substances

In vitro tests were performed on 16 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.

When determining prolactin it should be remembered that the measured concentration is dependent upon when the blood sample was taken, since the secretion of prolactin occurs in episodes and is also subject to a 24-hour cycle.[18,19]

The release of prolactin is inhibited by dopamine, L-dopa and ergotamine derivatives.

A number of publications report the presence of macroprolactin in the serum of female patients with various endocrinological diseases or during pregnancy. Differing degrees of detection of the serum macroprolactins relative to monomeric prolactin (22-23 kDa) by various immunoassays have also been described. This could lead to a false diagnosis of hyperprolactinemia depending on the immunoassay used.[17]

In case of implausible high prolactin values a precipitation by polyethylene glycol (PEG) is recommended in order to estimate the amount of the biological active monomeric prolactin.

See section “Sample pretreatment by polyethylene glycol (PEG) precipitation” for further details.

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

1.00-10000 µIU/mL or 0.0470-470 ng/mL (defined by the lower detection limit and the maximum of the master curve). Values below the lower detection limit are reported as < 1 µIU/mL or < 0.0470 ng/mL. Values above the measuring range are reported as > 10000 µIU/mL or > 470 ng/mL (or up to 100000 µIU/mL or 4700 ng/mL for 10-fold diluted samples).

Lower limits of measurement

Lower detection limit of the test

Lower detection limit: 1.00 µIU/mL (0.047 ng/mL)

The Lower Detection Limit represents the lowest analyte level that can be distinguished from zero. It is calculated as the value lying two standard deviations above that of the lowest standard (master calibrator, standard 1 + 2 SD, repeatability study, n = 21).

Dilution

Samples with prolactin concentrations above the measuring range can be diluted with Diluent Universal. The recommended dilution is 1:10 (either automatically by the analyzers or manually). The concentration of the diluted sample must be > 50 µIU/mL or > 2.4 ng/mL.

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

After dilution by the analyzers, the software automatically takes the dilution into account when calculating the sample concentration.

Expected values

A study with the Elecsys Prolactin II assay was performed using samples from 300 apparently healthy blood donors. The following results were obtained:

		Percentiles			
		50th	2.5-97.5th	50th	2.5-97.5th
	N	µIU/mL		ng/mL	
Men	102	155	86-324	7.30	4.04-15.2
Women (not-pregnant)	198	225	102-496	10.6	4.79-23.3

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								
			Repeatability			Intermediate precision		
Sample	Mean		SD		CV	SD		CV
	µIU/mL	ng/mL	µIU/mL	ng/mL	%	µIU/mL	ng/mL	%
HS[b] 1	10.2	0.48	0.27	0.013	2.7	0.32	0.015	3.1
HS 2	74.9	3.52	1.82	0.086	2.4	2.17	0.10	2.9
HS 3	567	26.6	19.3	0.91	3.4	25.7	1.21	4.5
HS 4	5333	251	199	9.35	3.7	278	13.1	5.2
HS 5	8083	380	266	12.5	3.3	423	19.9	5.2
PC U[c]1	243	11.4	4.75	0.22	1.9	5.79	0.27	2.4
PC U2	859	40.4	18.2	0.86	2.1	27.3	1.28	3.2

b) HS = human serum

c) PC U = PreciControl Universal

cobas e 601 and **cobas e** 602 analyzers								
			Repeatability			Intermediate precision		
Sample	Mean		SD		CV	SD		CV
	µIU/mL	ng/mL	µIU/mL	ng/mL	%	µIU/mL	ng/mL	%
HS 1	9.96	0.47	0.15	0.007	1.5	0.32	0.015	3.2
HS 2	71.6	3.37	0.91	0.043	1.3	1.73	0.081	2.4
HS 3	5233	246	157	7.38	3.0	271	12.7	5.2

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cobas e 601 and **cobas e** 602 analyzers								
			Repeatability			**Intermediate precision**		
Sample	Mean		SD		CV	SD		CV
	µIU/mL	ng/mL	µIU/mL	ng/mL	%	µIU/mL	ng/mL	%
HS 4	529	24.9	14.4	0.68	2.7	23.4	1.10	4.4
HS 5	7524	354	180	8.46	2.4	394	18.5	5.2
PC U1	229	10.8	3.53	0.17	1.5	4.76	0.22	2.1
PC U2	806	37.9	10.7	0.50	1.3	15.0	0.71	1.9

Method comparison

A comparison of the Elecsys Prolactin II assay (y) with the Elecsys Prolactin assay (x) using clinical samples containing no significant amounts of macroprolactin gave the following correlations (µIU/mL):

Number of samples measured: 227

Passing/Bablok[20]	Linear regression
y = 0.74x - 10.36	y = 0.76x - 21.21
τ = 0.942	r = 0.998

The sample concentrations were between 10 and 9063 µIU/mL (0.47 and 426 ng/mL).

Analytical specificity

The monoclonal antibodies used are highly specific against prolactin. No cross reaction with hGH, hCG, hPL, TSH, FSH and LH has been observed.

Sample pretreatment by polyethylene glycol (PEG) precipitation

Test principle

Macroprolactin and oligomers can be precipitated by using a 25 % aqueous PEG solution (ratio 1+1). After centrifugation, the supernatant containing monomeric prolactin is used in the Elecsys Prolactin II assay in the same way as a native sample. The dilution effect which occurs during sample pretreatment and the coprecipitation of monomeric prolactin must be taken into consideration.

Reagents (not provided)

- Polyethylene glycol 6000 (e.g. available from Serva, Cat. No. 33137)
- Distilled or deionized water

Precautions and warnings

See instructions provided by the manufacturer of the polyethylene glycol 6000.

Reagent handling

To prepare a 25 % PEG solution, dissolve 25 g polyethylene glycol 6000 in approximately 60 mL of distilled or deionized water at 18-25 °C (magnetic stirrer, 15 minutes) and fill up to 100 mL.

Storage and stability

Store the original substance according to the instructions of the manufacturer.
Store the 25 % PEG solution at 20-25 °C.
Stability of the solution: 7 days.

Materials required (but not provided)

- Magnetic stirrer
- Rotating shaker (vortex)
- Centrifuge (1500 g to 10000 g)

Assay

Sample pretreatment (18-25 °C):

- Mix appropriate volume of sample (at least 180 µL) with PEG solution at a ratio of 1+1
- Mix well for approximately 10 seconds in a rotating shaker (vortex)
- Centrifuge for 5 minutes between 1500 g and 10000 g (within 1-30 minutes)

Analyze the supernatant in the same way as the native samples.

Calculation

Approximately 14 % (range: 0-40 %) of monomeric prolactin is coprecipitated by PEG.[21] The dilution effect which occurs during PEG treatment and the coprecipitation of monomeric prolactin must be taken into consideration when calculating the results.

After precipitation by PEG each laboratory should investigate the transferability of the expected values to its own patient population and if necessary determine its own reference ranges.

References

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For further information, please refer to the appropriate user guide or 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 navifyportal.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
Rx only	For USA: Caution: Federal law restricts this device to sale by or on the order of a physician.

CE 0123

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