

| REF | | SYSTEM |
|--------------|-----|---|
| 12017547 122 | 100 | MODULAR ANALYTICS E170 cobas e 411 cobas e 601 cobas e 602 |

For USA: Elecsys Insulin

English

System information

For **cobas e 411** analyzer: test number 650
For MODULAR ANALYTICS E170, **cobas e 601** and **cobas e 602** analyzers: Application Code Number 120

Intended use

Immunoassay for the in vitro quantitative determination of human insulin in human serum and plasma. The determination of insulin is utilized in the diagnosis and therapy of various disorders of carbohydrate metabolism, including diabetes mellitus and hypoglycemia.

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

Summary

Insulin is a 51-residue peptide hormone with a molecular weight of 5808 Da. It is secreted by the β -cells of the islets of Langerhans in the pancreas, and passes into circulation via the portal vein and the liver. Insulin is generally released in pulses.^{1,2}

The biologically active insulin molecule is monomeric and consists of two polypeptide chains, the 21 amino acid α -chain and the 30 amino acid β -chain joined by disulphide bridges. Insulin is the biosynthetic product of the single-chain precursor proinsulin, which is subsequently cleaved to give proinsulin.^{2,3,4,5} Specific proteases further cleave proinsulin to produce insulin and the connecting (C)-peptide which pass into the bloodstream simultaneously in equimolar concentrations. Circulating insulin has a half-life of 3-5 minutes and is preferentially retained and degraded in the liver. Therefore only about half of the insulin reaches the systemic circulation. Inactivation or excretion of proinsulin and C-peptide mainly takes place in the kidney and virtually none of the C-peptide is retained in the liver. As a result, C-peptide has a higher plasma concentration than insulin.⁶

The amino acid sequence of insulin is extremely well conserved, with the result that prior to the development of genetically engineered human insulin it was possible to successfully use porcine or bovine insulin in the therapy of diabetes mellitus.⁷

The action of insulin is mediated by specific receptors and primarily consists of facilitation of glucose uptake by the cells of the liver, fatty tissue and musculature; this is the basis of its hypoglycemic action.^{2,8}

Serum insulin determinations are mainly performed on patients with symptoms of hypoglycemia and may be useful in classifying the different types of diabetes.^{9,10} They are used to ascertain the glucose/insulin quotients and for clarification of questions concerning insulin secretion and β -cell function, e.g. in the evaluation of oral glucose tolerance tests or hunger provocation tests.¹¹

A disorder in insulin metabolism can have a significant impact on a number of metabolic processes. Low concentrations of free, biologically active insulin can lead to the development of diabetes mellitus. Possible causes of this include destruction of the β -cells (type I diabetes), reduced activity of insulin or reduced pancreatic synthesis (type II), circulating antibodies to insulin, delayed release of insulin or the absence (or inadequacy) of insulin receptors.¹²

Conversely, autonomous, non-regulated insulin secretion is generally the cause of hypoglycemia. This condition is brought about by inhibition of gluconeogenesis, e.g. as a result of severe hepatic or renal failure, islet cell adenoma, or carcinoma. Hypoglycemia can, however, also be facilitated intentionally or unintentionally (factitious hypoglycemia).^{10,13}

In certain individuals with reduced glucose tolerance, the metabolic state deteriorates towards diabetes mellitus over a period of time. Reduced glucose tolerance during pregnancy always requires treatment. The clearly elevated risk of mortality for the fetus necessitates intensive monitoring.¹²

The Elecsys Insulin assay employs two monoclonal antibodies which are specific for human insulin.

Test principle

Sandwich principle. Total duration of assay: 18 minutes.

- 1st incubation: Insulin from 20 μ L sample, a biotinylated monoclonal insulin-specific antibody, and a monoclonal insulin-specific antibody 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 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)₃²⁺)

Reagents - working solutions

The reagent rackpack is labeled as INSULIN.

- M Streptavidin-coated microparticles (transparent cap), 1 bottle, 6.5 mL:
Streptavidin-coated microparticles 0.72 mg/mL; preservative.
- R1 Anti-insulin-Ab~biotin (gray cap), 1 bottle, 10 mL:
Biotinylated monoclonal anti-insulin antibody (mouse) 1 mg/L; MES^{b)} buffer 50 mmol/L, pH 6.0; preservative.
- R2 Anti-insulin-Ab~Ru(bpy)₃²⁺ (black cap), 1 bottle, 10 mL:
Monoclonal anti-insulin antibody (mouse) labeled with ruthenium complex 1.75 mg/L; MES buffer 50 mmol/L, pH 6.0; preservative.

b) MES = 2-morpholino-ethane sulfonic acid

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.

For USA: Caution: Federal law restricts this device to sale by or on the order of a physician.

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 |

| | |
|------------------|---------|
| Stability: | |
| on the analyzers | 4 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, K₃-EDTA and sodium citrate plasma.

Hemolysis interferes, as insulin-degrading peptidases are released from erythrocytes.¹⁴

Criterion: Recovery within 90-110 % of serum value or slope 0.9-1.1 + intercept within $\pm 2 \times$ analytical sensitivity (LDL) + coefficient of correlation > 0.95 .

Stable for 24 hours at 2-8 °C, 6 months at -20 °C. Freeze only once.¹⁵

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] 12017504122, Insulin CalSet, for 4 x 1.0 mL
- [REF] 05341787190, PreciControl Multimarker, for 6 x 2.0 mL or [REF] 11731416190, PreciControl Universal, for 4 x 3.0 mL
- [REF] 11731416160, PreciControl Universal, for 4 x 3.0 mL (for USA) or [REF] 05341787160, PreciControl Multimarker, for 6 x 2.0 mL (for USA)

- General laboratory equipment
- MODULAR ANALYTICS E170 or **cobas e** analyzer

Accessories for **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

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] 12102137001, AssayTip/AssayCup, 48 magazines x 84 reaction cups or pipette tips, waste bags
- [REF] 03023150001, WasteLiner, waste bags
- [REF] 03027651001, SysClean Adapter M

Accessories for all analyzers:

- [REF] 11298500316, ISE Cleaning Solution/Elecsys SysClean, 5 x 100 mL system cleaning solution
- [REF] 11298500160, ISE Cleaning Solution/Elecsys SysClean, 5 x 100 mL system cleaning solution (for USA)

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 (except for the **cobas e** 602 analyzer).

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 using the 1st IRP WHO Reference Standard 66/304 (NIBSC).

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 Multimarker or 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.

Please note: Commercial controls may contain insulin of animal origin. When assessing results, the corresponding cross-reactivity of this test must be taken into account; see under "Analytical specificity".

Calculation

The analyzer automatically calculates the analyte concentration of each sample (either in $\mu\text{U/mL}$ or pmol/L).

Conversion factors: $\mu\text{U/mL} \times 6.945 = \text{pmol/L}$
 $\text{pmol/L} \times 0.144 = \mu\text{U/mL}$

Limitations - interference

The assay is unaffected by icterus (bilirubin $< 1539 \mu\text{mol/L}$ or $< 90 \text{ mg/dL}$), lipemia (Intralipid $< 1800 \text{ mg/dL}$) and biotin ($< 246 \text{ nmol/L}$ or $< 60 \text{ ng/mL}$).

Criterion: Recovery within $\pm 10 \%$ of initial value. Hemolysis interferes.

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

No interference was observed from rheumatoid factors up to a concentration of 18900 IU/mL.

There is no high-dose hook effect at insulin concentrations up to 20000 $\mu\text{U/mL}$ or 138900 pmol/L .

Insulin

In vitro tests were performed on 20 commonly used pharmaceuticals. No interference with the assay was found.

Samples from patients treated with bovine, porcine or human insulin sometimes contain anti-insulin antibodies which can affect the test results.^{16,17}

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

0.2-1000 µU/mL or 1.39-6945 pmol/L (defined by the lower detection limit and the maximum of the master curve). Values below the lower detection limit are reported as < 0.2 µU/mL (< 1.39 pmol/L). Values above the measuring range are reported as > 1000 µU/mL (> 6945 pmol/L).

Lower limits of measurement

Lower detection limit of the test

Lower detection limit: 0.2 µU/mL (1.39 pmol/L)

The lower detection limit represents the lowest measurable 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

Not necessary due to the broad measuring range.

Expected values

Studies with the Elecsys Insulin assay conducted in a clinical center in Germany with samples from 57 healthy, fasting individuals gave the following results (5th-95th percentile range):

2.6-24.9 µU/mL (17.8-173 pmol/L)

Status: Elecsys Insulin MCE, study No.: B99P027 of 29 March 2001.

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 and pooled human sera in a modified protocol (EP5-A) of the CLSI (Clinical and Laboratory Standards Institute): 6 times daily for 10 days (n = 60); repeatability on MODULAR ANALYTICS E170 analyzer, n = 21. The following results were obtained:

| cobas e 411 analyzer | | | | | |
|----------------------|-------|--------|---------------|--------|-----|
| | | | Repeatability | | |
| Sample | Mean | | SD | | CV |
| | µU/mL | pmol/L | µU/mL | pmol/L | % |
| Human serum 1 | 6.36 | 44.2 | 0.122 | 0.847 | 1.9 |
| Human serum 2 | 20.9 | 145 | 0.391 | 2.71 | 1.9 |
| Human serum 3 | 747 | 5188 | 15.1 | 105 | 2.0 |

| cobas e 411 analyzer | | | | | |
|----------------------|-------|--------|------------------------|--------|-----|
| | | | Intermediate precision | | |
| Sample | Mean | | SD | | CV |
| | µU/mL | pmol/L | µU/mL | pmol/L | % |
| Human serum 1 | 6.36 | 44.2 | 0.163 | 1.11 | 2.6 |
| Human serum 2 | 20.9 | 145 | 0.593 | 4.10 | 2.8 |
| Human serum 3 | 747 | 5188 | 18.6 | 129 | 2.5 |

| MODULAR ANALYTICS E170, cobas e 601 and cobas e 602 analyzers | | | | | |
|---|---------------|--------|-------|--------|-----|
| | Repeatability | | | | |
| Sample | Mean | | SD | | CV |
| | µU/mL | pmol/L | µU/mL | pmol/L | % |
| Human serum 1 | 5.93 | 41.2 | 0.09 | 0.62 | 1.5 |
| Human serum 2 | 14.5 | 101 | 0.13 | 0.92 | 0.9 |
| Human serum 3 | 49.9 | 346 | 0.58 | 4.05 | 1.2 |
| Human serum 4 | 399 | 2768 | 3.32 | 23.1 | 0.8 |

| MODULAR ANALYTICS E170, cobas e 601 and cobas e 602 analyzers | | | | | |
|---|------------------------|--------|-------|--------|-----|
| | Intermediate precision | | | | |
| Sample | Mean | | SD | | CV |
| | µU/mL | pmol/L | µU/mL | pmol/L | % |
| Human serum 1 | 6.85 | 47.6 | 0.336 | 2.33 | 4.9 |
| Human serum 2 | 16.7 | 116 | 0.616 | 4.28 | 3.7 |
| Human serum 3 | 55.1 | 383 | 1.86 | 12.9 | 3.4 |
| Human serum 4 | 425 | 2949 | 10.0 | 69.6 | 2.4 |

Precision was determined using Elecsys reagents and controls in a protocol (EP5-A2) 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 | | |
| Sample | Mean | | SD | | CV |
| | µU/mL | pmol/L | µU/mL | pmol/L | % |
| PreciControl MM ^{c)} 1 | 23.7 | 165 | 0.270 | 1.88 | 1.1 |
| PreciControl MM2 | 81.7 | 567 | 1.14 | 7.92 | 1.4 |

c) MM = Multimarker

| cobas e 411 analyzer | | | | | |
|----------------------|-------|--------|------------------------|--------|-----|
| | | | Intermediate precision | | |
| Sample | Mean | | SD | | CV |
| | µU/mL | pmol/L | µU/mL | pmol/L | % |
| PreciControl MM1 | 23.7 | 165 | 0.834 | 5.79 | 3.5 |
| PreciControl MM2 | 81.7 | 567 | 3.04 | 21.1 | 3.7 |

| MODULAR ANALYTICS E170, cobas e 601 and cobas e 602 analyzers | | | | | |
|---|-------|--------|---------------|--------|-----|
| | | | Repeatability | | |
| Sample | Mean | | SD | | CV |
| | µU/mL | pmol/L | µU/mL | pmol/L | % |
| PreciControl MM1 | 21.9 | 152 | 0.712 | 4.94 | 3.2 |
| PreciControl MM2 | 74.3 | 516 | 2.72 | 18.9 | 3.7 |

| MODULAR ANALYTICS E170, cobas e 601 and cobas e 602 analyzers | | | | | |
|---|-------|--------|------------------------|--------|-----|
| | | | Intermediate precision | | |
| Sample | Mean | | SD | | CV |
| | μU/mL | pmol/L | μU/mL | pmol/L | % |
| PreciControl MM1 | 21.9 | 152 | 0.926 | 6.43 | 4.2 |
| PreciControl MM2 | 74.3 | 516 | 3.42 | 23.8 | 4.6 |

Method comparison

a) A comparison of the Elecsys Insulin assay (y) with the Enzymun-Test Insulin method (x) using clinical samples gave the following correlations (µU/mL):

Insulin

Number of samples measured: 99

Passing/Bablok¹⁸ Linear regression

$$y = 1.00x - 1.16$$

$$y = 0.92x + 0.59$$

$$r = 0.844$$

$$r = 0.958$$

The sample concentrations were between approximately 3.9 and 80 µU/mL (approximately 27 and 550 pmol/L).

b) A comparison of the Elecsys Insulin assay (y) with a commercially available Insulin test (x) using clinical samples gave the following correlations (µU/mL):

Number of samples measured: 99

Passing/Bablok¹⁸ Linear regression

$$y = 0.89x - 0.62$$

$$y = 0.93x - 1.02$$

$$r = 0.935$$

$$r = 0.981$$

The sample concentrations were between approximately 1 and 118 µU/mL (approximately 7 and 820 pmol/L).

Analytical specificity

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

| | Concentration tested | Cross-reactivity % |
|------------------------------|----------------------|--------------------|
| Bovine insulin | 17360 pmol/L | 25.0 |
| Porcine insulin | 8334 pmol/L | 19.2 |
| Human proinsulin | 1000 ng/mL | 0.05 |
| C-peptide | 100 ng/mL | n.d. ^{d)} |
| Glucagon | 1000 pg/mL | n.d. |
| Somatostatin | 100 pg/mL | n.d. |
| Insulin-like growth factor I | 6579 pmol/L | 0.04 |

d) n.d. = not detectable

Results for cross-reactivity with recombinant insulin analogs in a number of insulin methods have been published for example by two groups in France and the USA.^{17,19,20} The following results were published by Owen et al.¹⁹ for the Elecsys Insulin assay:

Insulin lispro, insulin aspart, and insulin glargine were each tested in concentrations of 30, 100, 300, and 1000 mIU/L in the absence of insulin. The results obtained were below the detection limit of the Elecsys Insulin assay (< 0.2 µU/mL or < 1.39 pmol/L) at all the concentrations tested.

Moreover, these results also correlate with those published earlier by Sapin et al. for insulin lispro.¹⁷

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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 (for USA: see <https://usdiagnostics.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 after reconstitution or mixing |
| GTIN | Global Trade Item Number |

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