Elecsys Estradiol III

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REF		Σ	SYSTEM
07027249190* 07027249214*	07027249500	300	**cobas e** 402 **cobas e** 801

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

English

System information

Short name	ACN (application code number)
E2 3	10100

Intended use

Immunoassay for the in vitro quantitative determination of estradiol 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

Estradiol measurements, performed with this assay, in human serum and plasma are used as an aid in diagnosing disorders of the hypothalamus-pituitary-gonad axis, assessment of ovarian function and monitoring of fertility therapy.

Estrogens are responsible for the development of the secondary female sex characteristics.[1] Estradiol is a C18 steroid hormone of the estrogen family[2] and constitutes the major gonadal steroid involved in the pubertal growth spurt in females.[3] Like other steroid hormones, estradiol is derived from cholesterol.[4]

Estrogens are secreted primarily in healthy women by the ovarian follicles and the corpus luteum and during pregnancy by the placenta. The adrenal glands and testes (in men) are also believed to secrete minute quantities of estrogens.[4]

Levels of estradiol in premenopausal women are highly variable throughout the menstrual cycle.

Estradiol concentrations decrease abruptly after ovulation but increase again as the corpus luteum is formed during the luteal phase. Together with the progesterone produced by the corpus luteum, estradiol exerts a negative effect on the hypothalamus and anterior lobe of the pituitary gland and LH and FSH secretion is suppressed again during the luteal phase. The decrease in negative feedback from estradiol on the anterior lobe of the pituitary gland triggers the FSH surge, which begins the development of an ovarian follicle for the next cycle.[4]

The major fraction of estradiol (about 97 %) circulates in blood bound with high affinity to sex-hormone binding globulin (SHBG) and with lower affinity to albumin. The unbound fraction (between 1–3 %) is considered to be the biologically active fraction.[2] Estradiol concentrations can span multiple orders of magnitude among different age groups, between males and females, and under different conditions (e.g. fertility treatments, pregnancy, use of aromatase inhibitors).[5]

The determination of estradiol is utilized clinically in the diagnosis of disorders of the hypothalamus-pituitary-gonad axis such as gynecomastia,[6] in case of estrogen-producing ovarian and testicular tumors,[7,8] in the context of fertility disorders such as polycystic ovary syndrome[9] and within the framework of in vitro fertilization (IVF).[10,11]

The Elecsys Estradiol III assay employs a competitive test principle using two monoclonal antibodies specifically directed against 17β-estradiol. Endogenous estradiol released from the sample by mesterolone competes with the added estradiol derivative labeled with a ruthenium complex[a)] for the binding sites on the biotinylated antibody.

a) Tris(2,2'-bipyridyl)ruthenium(II)-complex ($Ru(bpy)_3^{2+}$)

Test principle

Competition principle. Total duration of assay: 18 minutes.

- 1st incubation: By incubating the sample (15 µL) with two estradiol-specific biotinylated antibodies, immunocomplexes are formed, the amount of which is dependent upon the analyte concentration in the sample.
- 2nd incubation: After addition of streptavidin-coated microparticles and an estradiol derivative labeled with a ruthenium complex, the still-vacant sites of the biotinylated antibodies become occupied, with formation of an antibody-hapten complex. The entire 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.

Reagents - working solutions

The **cobas e** pack is labeled as E2 3.

M Streptavidin-coated microparticles, 1 bottle, 12.4 mL:
Streptavidin-coated microparticles 0.72 mg/mL; preservative.

R1 Anti-estradiol-Ab~biotin, 1 bottle, 19.7 mL:
Two biotinylated monoclonal anti-estradiol antibodies (rabbit) 2.5 ng/mL and 4.5 ng/mL; mesterolone 130 ng/mL; MES[b)] buffer 50 mmol/L, pH 6.0; preservative.

R2 Estradiol-peptide~$Ru(bpy)_3^{2+}$, 1 bottle, 18.8 mL:
Estradiol derivative, labeled with ruthenium complex 4.5 ng/mL; MES buffer 50 mmol/L, pH 6.0; preservative.

b) MES = 2-morpholino-ethane sulfonic acid

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:

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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.

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 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.

Li-heparin plasma tubes containing separating gel can be used.

Criterion: Slope 0.9-1.1 + intercept within ≤ ± 10 pg/mL + coefficient of correlation ≥ 0.95.

Stable for 24 hours at 20-25 °C, 2 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 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 06656048190, Estradiol III CalSet, for 4 x 1.0 mL
- REF 11731416190, PreciControl Universal, for 4 x 3.0 mL
- REF 07299010190, Diluent MultiAssay, 36 mL sample diluent
- 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 CRM 6004a via ID-GC/MS (isotope dilution-gas chromatography/mass spectrometry).[12]

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 pmol/L, pg/mL, ng/L or nmol/L).

Conversion factors: pmol/L x 0.272 = pg/mL (ng/L)

pg/mL x 3.67 = pmol/L

pg/mL x 0.00367 = nmol/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	≤ 1129 µmol/L or ≤ 66 mg/dL
Hemoglobin	≤ 0.621 mmol/L or ≤ 1000 mg/dL
Intralipid	≤ 1000 mg/dL
Biotin	≤ 147 nmol/L or ≤ 36 ng/mL

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Compound	Concentration tested
Rheumatoid factors	≤ 1200 IU/mL
IgG	≤ 70 g/L
IgA	≤ 0.4 g/dL
IgM	≤ 10 g/L
Albumin	≤ 5 g/dL

Criterion: Recovery within ± 10 % of initial value.

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.

Pharmaceutical substances
In vitro tests were performed on 16 commonly used pharmaceuticals. No interference with the assay was found.

Erroneous test results may be obtained from samples taken from patients who have been exposed to vaccines containing rabbit serum or when keeping rabbits as pet animals.

Due to the risk of cross reactivity, this assay should not be used when monitoring Estradiol levels in patients being treated with Fulvestrant.

Steroid drugs may interfere with this test.

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

18.4-11010 pmol/L (5-3000 pg/mL) (defined by the Limit of Detection and the maximum of the master curve). Values below the Limit of Detection are reported as < 18.4 pmol/L or < 5 pg/mL. Values above the measuring range are reported as > 11010 pmol/L or > 3000 pg/mL (or up to 110100 pmol/L or 30000 pg/mL for 10-fold diluted samples).

Lower limits of measurement

Limit of Blank, Limit of Detection and Limit of Quantitation

Limit of Blank = 11.0 pmol/L (3 pg/mL)

Limit of Detection = 18.4 pmol/L (5 pg/mL)

Limit of Quantitation = 91.8 pmol/L (25 pg/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 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 defined as the lowest amount of analyte in a sample that can be accurately quantitated with a total allowable relative error of ≤ 30 %.

Dilution

Samples with estradiol concentrations above the measuring range can be diluted with Diluent MultiAssay. The recommended dilution is 1:10 (either automatically by the analyzer or manually). The concentration of the diluted sample must be ≥ 881 pmol/L (≥ 240 pg/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.

The endogenous analyte concentration of the diluent (< 220 pmol/L or < 60.0 pg/mL) is not taken into account for dilutions above the measuring range.

Expected values

The expected ranges were determined by testing specimens drawn from 150 apparently healthy males, 142 apparently healthy, post-menopausal women over the age of 50, and from 412 apparently healthy pregnant women between the ages of 18 and 50 (136 in the first trimester, 140 in the second trimester, and 136 in the third trimester). The expected range for healthy women was determined by collecting blood at multiple time points of one menstrual cycle from 85 apparently healthy subjects with a natural menstrual cycle that were not taking any hormonal contraceptives. A menstrual cycle was defined as the phase between two subsequent menstrual bleedings. Cycle length (29 days) and day of ovulation (day 15) were standardized to account for variation in cycle length within the study population and to enable determination of expected values for further sub-phases. Only ovulatory menstrual cycles were used for value analysis. The following ranges were obtained:

Test subjects	N	2.5th percentile pmol/L (90 % CI*)	Median pmol/L (90 % CI)	97.5th percentile pmol/L (90 % CI)
Healthy men	150	41.4 (22.4-49.0)	90.9 (84.9-97.7)	159 (151-337)
Healthy postmenopausal women				
• Postmenopause	142	< 18.4 (< 18.4-< 18.4)	< 18.4 (< 18.4-19.2)	505 (189-1151)
Healthy pregnant women				
• 1st trimester	136	563 (467-636)	3133 (2703-4004)	11902 (9891-15271)
• 2nd trimester	140	5729 (4173-7457)	28402 (24207-32090)	78098 (69143-92227)
• 3rd trimester	136	31287 (27151-34175)	64684 (62353-68189)	> 110100 (107164-> 110100)

* CI = confidence interval

Healthy women Cycle Phase	N **	5th percentile pmol/L (90 % CI)	Median pmol/L (90 % CI)	95th percentile pmol/L (90 % CI)
Follicular	85	114 (19.1-135)	198 (188-208)	332 (322-637)
Ovulation	81	222 (98.5-283)	757 (667-944)	1959 (1598-3338)
Luteal	85	222 (159-280)	412 (390-488)	854 (760-1334)

**N = number of patients contributing to the data in this menstrual cycle phase (not number of samples); differences in N per phase are due to cycle standardization procedure

Healthy women Cycle Sub-Phase	N	5th percentile pmol/L (90 % CI)	Median pmol/L (90 % CI)	95th percentile pmol/L (90 % CI)
Early follicular	78	75.5 (< 18.4-78.5)	125 (120-135)	231 (192-283)
Intermediate follicular	83	95.6 (19.1-114)	172 (159-180)	294 (262-695)
Late follicular	84	182 (84-215)	464 (424-519)	858 (711-1337)
Ovulation	79	222 (98.5-283)	817 (724-974)	2212 (1598-3338)
Early luteal	85	188 (163-218)	390 (330-412)	658 (608-1394)

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Healthy women Cycle Sub-Phase	N	5th percentile pmol/L (90 % CI)	Median pmol/L (90 % CI)	95th percentile pmol/L (90 % CI)
Intermediate luteal	81	244 (157-334)	505 (445-568)	1123 (942-1538)
Late luteal	84	111 (74.4-163)	396 (373-422)	815 (703-908)

Test subjects	N	2.5th percentile pg/mL (90 % CI)	Median pg/mL (90 % CI)	97.5th percentile pg/mL (90 % CI)
Healthy men	150	11.3 (6.1-13.4)	24.8 (23.1-26.6)	43.2 (41.0-91.9)
Healthy postmenopausal women				
• Postmenopause	142	< 5 (< 5-< 5)	<5 (< 5-5.24)	138 (51.6-314)
Healthy pregnant women				
• 1st trimester	136	154 (127-173)	854 (737-1091)	3243 (2695-4161)
• 2nd trimester	140	1561 (1137-2032)	7739 (6596-8744)	21280 (18840-25130)
• 3rd trimester	136	8525 (7398-9312)	17625 (16990-18580)	> 30000 (29200-> 30000)

Healthy women Cycle Phase	N	5th percentile pg/mL (90 % CI)	Median pg/mL (90 % CI)	95th percentile pg/mL (90 % CI)
Follicular	85	30.9 (5.21-36.7)	53.9 (51.1-56.6)	90.4 (87.7-173)
Ovulation	81	60.4 (26.8-77)	206 (181-257)	533 (435-908)
Luteal	85	60.4 (43.2-76)	112 (106-133)	232 (207-363)

Healthy women Cycle Sub-Phase	N	5th percentile pg/mL (90 % CI)	Median pg/mL (90 % CI)	95th percentile pg/mL (90 % CI)
Early follicular	78	20.5 (< 5-21.4)	34 (32.6-36.7)	62.8 (52.1-77)
Intermediate follicular	83	26 (5.21-31)	46.9 (43.2-49)	79.8 (71.4-189)
Late follicular	84	49.5 (22.8-58.5)	126 (115-141)	233 (193-364)
Ovulation	79	60.4 (26.8-77)	222 (197-265)	602 (435-908)
Early luteal	85	51.1 (44.3-59.2)	106 (89.8-112)	179 (166-379)
Intermediate luteal	81	66.5 (42.7-90.7)	137 (121-155)	305 (256-418)
Late luteal	84	30.2 (20.2-44.3)	108 (101-115)	222 (191-247)

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 402 and **cobas e** 801 analyzers					
		Repeatability		**Intermediate precision**	
Sample	Mean pmol/L	SD pmol/L	CV %	SD pmol/L	CV %
Human serum 1	68.6	5.73	8.4	8.44	12.3
Human serum 2	5832	67.5	1.2	111	1.9
Human serum 3	701	9.84	1.4	12.9	1.8
Human serum 4	1718	20.8	1.2	34.7	2.0
Human serum 5	10129	244	2.4	276	2.7
PC[c)] Universal 1	307	6.24	2.0	7.96	2.6
PC Universal 2	1486	23.3	1.6	25.4	1.7

c) PC = PreciControl

cobas e 402 and **cobas e** 801 analyzers					
		Repeatability		**Intermediate precision**	
Sample	Mean pg/mL	SD pg/mL	CV %	SD pg/mL	CV %
Human serum 1	18.7	1.56	8.4	2.30	12.3
Human serum 2	1589	18.4	1.2	30.3	1.9
Human serum 3	191	2.68	1.4	3.51	1.8
Human serum 4	468	5.68	1.2	9.45	2.0
Human serum 5	2760	66.5	2.4	75.3	2.7
PC Universal 1	83.6	1.70	2.0	2.17	2.6
PC Universal 2	405	6.35	1.6	6.91	1.7

Method comparison

a) A comparison of the Elecsys Estradiol III assay, REF 07027249190 (**cobas e** 801 analyzer; y) with the Elecsys Estradiol III assay, REF 06656021190 (**cobas e** 601 analyzer; x) gave the following correlations (pg/mL):

Number of samples measured: 130

Passing/Bablok[13]	Linear regression
y = 1.008x + 0.381	y = 0.998x + 1.53
τ = 0.980	r = 1.000

The sample concentrations were between 7.26 and 2909 pg/mL.

b) A comparison of the Elecsys Estradiol III assay, REF 07027249190 (**cobas e** 402 analyzer; y) with the Elecsys Estradiol III assay, REF 07027249190 (**cobas e** 801 analyzer; x) gave the following correlations (pg/mL):

Number of serum samples measured: 190

Passing/Bablok[13]	Linear regression
y = 1.03x + 2.09	y = 1.03x + 1.83
τ = 0.988	r = 1.00

The sample concentrations were between 10.8 and 2861 pg/mL.

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Analytical specificity

For the Elecsys Estradiol III assay, the following cross-reactivities were found:

Substance	Cross-reactivity %	Additive concentration ng/mL
6-α-Hydroxy-Estradiol	102	1
4-Hydroxyestradiol	3.073	10
Aldosterone	n. d.[d)]	100
Androstenedione	0.005	100
Equiline	0.032	100
Estriol	0.325	100
Estrone	0.761	100
Estrone-3β-glucuronide	0.001	100
Estrone-3-sulfate	0.001	100
Ethisterone	0.006	100
Norethindrone acetate	n. d.	100
Pregnenolone	n. d.	100
Progesterone	n. d.	100
2-Methoxyestradiol	0.028	100
17β-Estradiol-3,17-sulfate	n. d.	100
17β-Estradiol-3-β-D-glucuronide	0.007	100
17β-Estradiol-17-β-D-glucuronide	n. d.	100
17β-Estradiol-3-glucuronide-17-sulfate	0.002	100
17β-Estradiol-3-sulfate-17-glucuronide	0.006	100
17β-Estradiol-3-sulfate	0.014	100
17β-Estradiol-17-valerate	0.059	100
17β-Estradiol-17-sulfate	0.016	100
2-Hydroxyestradiol	0.053	100
17-Hydroxyprogesterone	n. d.	100
17-α-Ethinylestradiol	0.279	200
Cortisol	0.004	200
Cortisone	0.002	200
Tamoxifen	n. d.	200
Chlomiphene	n. d.	250
Prednisolone	n. d.	1000
Danazol	n. d.	10000
DHEA-S	n. d.	10000
Mesterolone	n. d.	10000
Testosterone	n. d.	10000
5-α-Dihydrotestosterone (DHT)	n. d.	10000
5-Androstene-3β-,17β-diol	n. d.	10000

d) n. d. = not detectable

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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.

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

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CE 0123

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