Elecsys Testosterone II

cobas®

REF		Σ	SYSTEM
08946370190	08946370501	300	**cobas e** 402 **cobas e** 801

English

For use in the USA only

System information

Short name	ACN (application code number)
TESTO 2	10020

Intended use

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

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

Measurements of testosterone are used in the diagnosis and treatment of disorders involving the male sex hormones (androgens), including primary and secondary hypogonadism, delayed or precocious puberty, impotence in males and, in females hirsutism (excessive hair) and virilization (masculinization) due to tumors, polycystic ovaries, and adrenogenital syndromes.

Summary

References[1,2,3,4,5,6]

The androgen testosterone (17β-hydroxyandrostenone) has a molecular weight of 288 daltons. In men, testosterone is synthesized almost exclusively by the Leydig cells of the testes. The secretion of testosterone is regulated by luteinizing hormone (LH), and is subject to negative feedback via the pituitary and hypothalamus.
Testosterone promotes the development of the secondary sex characteristics in men and serves to maintain the function of the prostate and seminal vesicles. Most of the circulating testosterone is bound to carrier proteins (SHBG = sex hormone-binding globulin).
In women, small quantities of testosterone are formed in the ovaries. In physiological concentrations, androgens have no specific effects in women. Increased production of testosterone in women can cause virilization (depending on the increase).
The Elecsys Testosterone II assay is based on a competitive test principle using a high affinity monoclonal antibody (sheep) specifically directed against testosterone. Endogenous testosterone released from the sample by 2-bromoestradiol competes with the added testosterone 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: 12 µL of sample are incubated with a biotinylated monoclonal testosterone-specific antibody. The binding sites of the labeled antibody become occupied by the sample analyte (depending on its concentration).
- 2nd incubation: After addition of streptavidin-coated microparticles and a testosterone derivate labeled with a ruthenium complex, 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.

Reagents - working solutions

The **cobas e** pack is labeled as TESTO 2.

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

R1 Anti-testosterone-Ab~biotin, 1 bottle, 21.0 mL:
Biotinylated monoclonal anti-testosterone antibody (sheep) 40 ng/mL; releasing reagent 2-bromoestradiol; MES[b)] buffer 50 mmol/L, pH 6.0; preservative.

R2 Testosterone-peptide~$Ru(bpy)_3^{2+}$, 1 bottle, 18.8 mL:
Testosterone derivative, labeled with ruthenium complex 1.5 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.

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

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 dust/fume/gas/mist/vapours/spray.

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: 1-800-428-2336

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.

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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 **cobas e** 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.

Criterion: Recovery within 80-120 % of serum value > 100 ng/dL, recovery of ± 20 ng/dL of serum value ≤ 100 ng/dL and slope 0.9-1.1 + bias at 50 ng/dL and 300 ng/dL ≤ 10 % + coefficient of correlation ≥ 0.95.

Stable for 14 days at 2-8 °C, 5 days at 20-25 °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.

Sample stability claims were established by experimental data by the manufacturer or based on reference literature and only for the temperatures/time frames as stated in the method sheet. It is the responsibility of the individual laboratory to use all available references and/or its own studies to determine specific stability criteria for its laboratory.

Materials provided

See "Reagents – working solutions" section for reagents.

Materials required (but not provided)

- REF 05202230190, Testosterone II CalSet II, for 4 x 1.0 mL
- REF 11731416160, PreciControl Universal, for 4 x 3.0 mL or
- REF 08740062160, PreciControl Maternal Care, for 6 x 3.0 mL
- General laboratory equipment
- **cobas e** analyzer

Additional materials for the **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 11298500160, 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 is traceable to highly purified testosterone by weight via ID-GC/MS ("Isotope Dilution - Gas Chromatography/Mass Spectrometry").[7]

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 or PreciControl Maternal Care.

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 ng/mL, ng/dL or nmol/L).

Conversion factors:
ng/mL x 3.47 = nmol/L
ng/mL x 100 = ng/dL
nmol/L x 0.288 = ng/mL

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	≤ 0.373 mmol/L or ≤ 600 mg/dL
Intralipid	≤ 800 mg/dL
Biotin	≤ 4912 nmol/L or ≤ 1200 ng/mL
Rheumatoid factors	≤ 1000 IU/mL

Biotin interference

This assay has no biotin interference in serum concentrations up to 1200 ng/mL. Pharmacokinetic studies have shown that serum concentrations of biotin can reach up to 355 ng/mL within the first hour after biotin ingestion for subjects consuming supplements of 20 mg biotin per

day[8] and up to 1160 ng/mL for subjects after a single dose of 300 mg biotin[9].

Criterion: Recovery within ± 10 % of initial value (concentration range > 100-1500 ng/dL), recovery within ± 15 % of initial value (concentration range 50-100 ng/dL) and recovery of ± 7.50 ng/dL (concentration range of 2.50-50.0 ng/dL).

Pharmaceutical substances
In vitro tests were performed on 17 commonly used pharmaceuticals and 2 special pharmaceuticals. Of these, only phenylbutazone at therapeutic dosage levels showed interference with the assay (testosterone values increased).

Drug tested	No interference up to
Acetylcysteine	150 mg/L
Acetylsalicylic acid	30 mg/L
Ampicillin - Na	75 mg/L
Ascorbic acid	52.5 mg/L
Cefoxitin	750 mg/L
Doxycycline	18 mg/L
Heparin	3300 IU/L
Levodopa	7.5 mg/L
Methyldopa + 1.5	22.5 mg/L
Metronidazole	123 mg/L
Rifampicin	48 mg/L
Acetaminophen	156 mg/L
Cyclosporine	1.8 mg/L
Ibuprofen	73 mg/L
Theophylline	60 mg/L
Phenylbutazone	107 mg/L
Itraconazole	10 mg/L

Special pharmaceuticals

Drug	Concentration tested
Testosterone Undecanoate	32 mg/L
Nandrolone	11.4 mg/L

Criterion: Recovery within ± 10 % of initial value.

A strong interaction with Nandrolone (INN international nonproprietary name) was found. Do not use samples from patients under Nandrolone treatment.

Testosterone undecanoate (INN international nonproprietary name, WHO) is metabolized to testosterone after administration. The Elecsys Testosterone II assay does not differentiate between endogenous testosterone and exogenous testosterone resulting from metabolized testosterone under testosterone supplementation therapy.

In isolated cases, elevated testosterone levels can be seen in samples from female patients with end stage renal disease (ESRD).

Implausible elevated testosterone values in women should be verified by an extraction method or a validated LC-MS/MS tandem method.[5]

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

2.50-1500 ng/dL or 0.087-52.0 nmol/L (defined by the Limit of Detection and the maximum of the master curve). Values below the Limit of Detection are reported as < 2.50 ng/dL or < 0.087 nmol/L. Values above the measuring range are reported as > 1500 ng/dL or > 52.0 nmol/L.

Lower limits of measurement

Limit of Blank, Limit of Detection and Limit of Quantitation

Limit of Blank = 1.50 ng/dL or 0.052 nmol/L

Limit of Detection = 2.50 ng/dL or 0.087 nmol/L

Limit of Quantitation = 12.0 ng/dL or 0.416 nmol/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 (functional sensitivity) is the lowest analyte concentration that can be reproducibly measured with an intermediate precision CV of ≤ 20 %. It has been determined using low concentration testosterone samples.

Note: When reporting values < 12.0 ng/dL, the client report should be annotated with the following information: "Values < 12.0 ng/dL are not reliable as the intermediate precision coefficient of variation is > 20 %".

Dilution

Not necessary due to the broad measuring range.

Expected values

The following tables show the results obtained using the Elecsys Testosterone II assay in a reference population of 95 males (7-18 years) and 100 females (8-18 years), who were in good endocrinological health. Subjects were clinically characterized according to their age as well as Tanner Stage. Tanner Stage was characterized according to the method of Marshall and Tanner.[10,11]

Reference values for males (7-18 years) characterized by age			
Age	N	Range, ng/dL	
		Minimum	Maximum
7	3	< 2.50	< 2.50
8	6	< 2.50	< 2.50
9	8	< 2.50	< 2.50
10	2	< 2.50	< 2.50
11	13	< 2.50	237
12	6	29.4	278
13	8	< 2.50	432
14	9	40.1	778
15	23	78.7	763
16	14	238	1048
17	1	506	506
18	2	557	685

Reference values for females (8-18 years) characterized by age			
Age	N	Range, ng/dL	
		Minimum	Maximum
7	0	-	-
8	11	< 2.50	6.14
9	16	< 2.50	7.49
10	7	< 2.50	5.45
11	13	< 2.50	17.1

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Reference values for females (8-18 years) characterized by age			
Age	N	Range, ng/dL	
		Minimum	Maximum
12	10	< 2.50	26.2
13	7	< 2.50	23.7
14	4	11.2	28.8
15	21	7.64	39.8
16	8	< 2.50	29.4
17	0	-	-
18	3	15.3	31.1

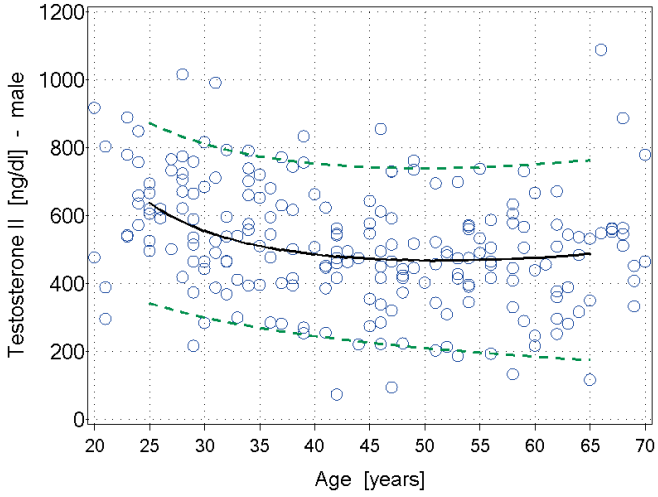
Reference values for males (7-18 years) characterized by Tanner Stage			
		Percentiles, ng/dL	
Tanner Stage	N	Median	5-95th
1	26	< 2.50	< 2.50
2	18	59.7	< 2.50-432
3	15	245	64.9-778
4	16	344	180-763
5	20	446	188-882

Reference values for females (8-18 years) characterized by Tanner Stage			
		Percentiles, ng/dL	
Tanner Stage	N	Median	5-95th
1	37	< 2.50	< 2.50-6.12
2	12	< 2.50	< 2.50-10.4
3	12	7.90	< 2.50-23.7
4	12	12.2	< 2.50-26.8
5	27	19.7	4.60-38.3

The following table shows the results obtained with the Elecsys Testosterone II assay in an apparently healthy group of 214 males and 160 females without intake of contraceptives and prescription drugs (study number CIM 000669).

Test subjects	N	Percentiles			
		Median	5-95th	Median	5-95th
		ng/dL		nmol/L	
Males 20-49 years	136	536	249-836	18.6	8.64-29.0
Males ≥ 50 years	78	476	193-740	16.5	6.68-25.7
Females 20-49 years	89	27.1	8.40-48.1	0.941	0.290-1.67
Females ≥ 50 years	71	16.2	2.90-40.8	0.563	0.101-1.42

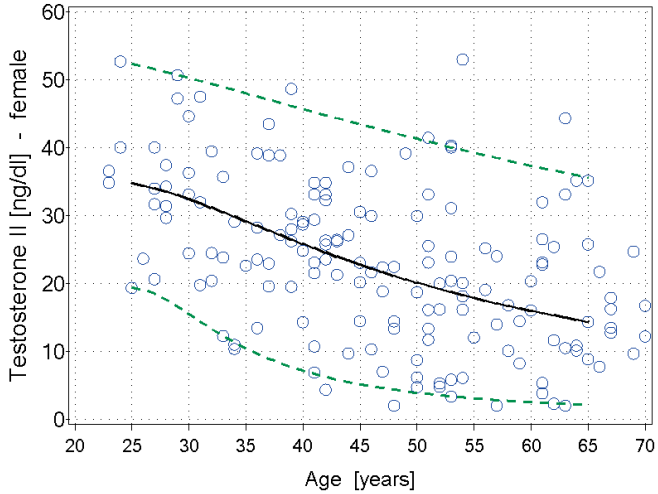
Distribution of testosterone values in the apparently healthy male group based on age (n = 214). Solid line: 50th percentile, upper line: 95th percentile, lower line: 5th percentile.



x: Age (years)

y: Testosterone (ng/dL) - male group

Distribution of testosterone values in the apparently healthy female group based on age (n = 160). Solid line: 50th percentile, upper line: 95th percentile, lower line: 5th percentile.



x: Age (years)

y: Testosterone (ng/dL) - female group

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		
Sample	Mean		SD		CV
	ng/dL	nmol/L	ng/dL	nmol/L	%
Human serum 1	10	0.347	0.57	0.020	5.7
Human serum 2	31.5	1.09	0.93	0.032	3.0

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cobas e 402 and **cobas e** 801 analyzers					
			Repeatability		
Sample	Mean		SD		CV
	ng/dL	nmol/L	ng/dL	nmol/L	%
Human serum 3	76.5	2.66	1.23	0.043	1.6
Human serum 4	209	7.26	3.19	0.111	1.5
Human serum 5	1392	48.33	23.5	0.816	1.7
PreciControl U[c)]1	558	19.38	7.10	0.247	1.3
PreciControl U2	257	8.92	3.45	0.120	1.3

c) U = Universal

cobas e 402 and **cobas e** 801 analyzers					
			Intermediate precision		
Sample	Mean		SD		CV
	ng/dL	nmol/L	ng/dL	nmol/L	%
Human serum 1	10	0.347	1.15	0.040	11.5
Human serum 2	31.5	1.09	1.48	0.051	4.7
Human serum 3	76.5	2.66	2.47	0.086	3.2
Human serum 4	209	7.26	4.64	0.161	2.2
Human serum 5	1392	48.33	30.6	1.06	2.2
PreciControl U1	558	19.38	11.2	0.389	2.0
PreciControl U2	257	8.92	5.09	0.177	2.0

Method comparison

A comparison of the Elecsys Testosterone II assay, REF 08946370190, on the **cobas e** 801 analyer (y) with the Elecsys Testosterone II assay, REF 07027915190, on the **cobas e** 801 analyzer (x) gave the following correlations (ng/dL):

Number of samples measured: 169

Passing/Bablok[12]	Linear regression
y = 1.02x - 2.71	y = 1.02x - 6.04
τ = 0.980	r = 0.999

The sample concentrations were between 4.61 and 1400 ng/dL.

Analytical specificity

For the antibody derivative used, the following cross-reactivities were found (in %):

	Concentration ng/mL	**Cross-reactivity %**
Androstenedione	100	≤ 3.15
Cortisol	5000	n.d.[d)]
Cortisone	5000	n.d.
Danazol	1000	≤ 0.504
Dexamethasone	5000	n.d.
DHEA	5000	≤ 0.014
DHEA-S	50000	≤ 0.003
D-5-Androstene-3β,17β-diol	1000	≤ 0.289
Estradiol	5000	≤ 0.211
Estrone	5000	n.d.
Ethisterone	300	≤ 3.57
Norgestrel	1000	≤ 0.539
Testosterone propionate	100	≤ 0.718
5-α-Androstane-3β,17β-diol	500	≤ 2.15
5-α-Dihydro-testosterone	500	≤ 1.30
11-β-Hydroxy-testosterone	50	≤ 20.6
11-Keto-testosterone	200	≤ 4.87
19-Norethisterone	40	≤ 5.51
Prednisone	5000	n.d.
Prednisolone	5000	n.d.
Progesterone	5000	≤ 0.009

d) n.d. = not detectable

References

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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).

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

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→ Volume for reconstitution

GTIN Global Trade Item Number

FOR US CUSTOMERS ONLY: LIMITED WARRANTY

Roche Diagnostics warrants that this product will meet the specifications stated in the labeling when used in accordance with such labeling and will be free from defects in material and workmanship until the expiration date printed on the label. THIS LIMITED WARRANTY IS IN LIEU OF ANY OTHER WARRANTY, EXPRESS OR IMPLIED, INCLUDING ANY IMPLIED WARRANTY OF MERCHANTABILITY OR FITNESS FOR PARTICULAR PURPOSE. IN NO EVENT SHALL ROCHE DIAGNOSTICS BE LIABLE FOR INCIDENTAL, INDIRECT, SPECIAL OR CONSEQUENTIAL DAMAGES.

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