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β-CrossLaps/serum

cobas®

β-CrossLaps/serum (β-CTx in serum)

REF	Σ	SYSTEM
11972308 122	100	Elecsys 2010 MODULAR ANALYTICS E170 **cobas e** 411 **cobas e** 601 **cobas e** 602

English

Intended use

Immunoassay for the in vitro quantitative determination of degradation products of type I collagen in human serum and plasma as an aid in assessing bone resorption. The test may be used as an aid in monitoring antiresorptive therapies (e.g. bisphosphonates, hormone replacement therapy - HRT) in postmenopausal women and individuals diagnosed with osteopenia.

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

Summary

More than 90 % of organic bone matrix consists of type I collagen, which is preferentially synthesized in bone.[1] There is regulated anabolism and catabolism of the basic substance in bone. During normal bone metabolism, mature type I collagen is degraded and small fragments pass into the bloodstream and are excreted via the kidneys.

In physiologically or pathologically elevated bone resorption (e.g. in old age or as a result of osteoporosis), type I collagen is degraded to an increased extent, and there is a commensurate rise in the level of collagen fragments in the blood.

By determining these bone resorption markers, the activity of osteoclasts can be detected.

Especially relevant collagen type I fragments are the β-isomerized C-terminal telopeptides (β-CTx).[2,3] These isomerized telopeptides are highly specific for the degradation of type I collagen dominant in bone.

Elevated serum levels of isomerized C-terminal telopeptides of type I collagen have been reported for patients with increased bone resorption. The serum levels return to normal during anti-resorptive therapy.[4,5,6,7]

Determination of the C-terminal telopeptides in serum is recommended for monitoring the efficacy of antiresorptive therapy (e.g. bisphosphonates or hormone replacement therapy - HRT) in osteoporosis or other bone diseases. By these means, therapy-induced changes can be demonstrated after just a few weeks.[6,8]

The Elecsys β-CrossLaps/serum assay is specific for crosslinked isomerized type I collagen fragments, independent of the nature of the crosslink (e.g. pyrrole, pyridinolines etc.[9]). The assay specificity is guaranteed through the use of two monoclonal antibodies each recognizing linear β-8AA octapeptides (EKAHD-β-GGR). The Elecsys β-CrossLaps/serum assay therefore quantifies all type I collagen degradation fragments that contain the isomerized octapeptide β-8AA twice (β-CTx).[6,7]

Test principle

Sandwich principle. Total duration of assay: 18 minutes.

- 1st incubation: 50 µL of sample and a biotinylated monoclonal anti-β-CrossLaps antibody are incubated together; the antigen in the sample is liberated from the serum components.
- 2nd incubation: Following addition of streptavidin-coated microparticles and a monoclonal β-CrossLaps-specific antibody labeled with a ruthenium complex[a)], a sandwich complex is formed which 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.

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

Reagents - working solutions

The reagent rackpack is labeled as CROSSL.

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

R1 Anti-β-CrossLaps-Ab~biotin (gray cap), 1 bottle, 10 mL: Biotinylated monoclonal anti-β-CrossLaps antibody (mouse) 2.5 mg/L; phosphate buffer 100 mmol/L, pH 7.2; preservative.

R2 Anti-β-CrossLaps-Ab~$Ru(bpy)_3^{2+}$(black cap), 1 bottle, 8 mL: Monoclonal anti-β-CrossLaps antibody (mouse) labeled with ruthenium complex 2.4 mg/L; phosphate buffer 100 mmol/L, pH 7.2; preservative.

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.

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.

K_3-EDTA and sodium heparin plasma.

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

It is recommended to draw blood as fasting, morning samples. For long-term investigations, the samples should always be taken under same conditions as the baseline sample, as the serum β-CTx concentration is to some extent subject to a circadian rhythm.

Preference should be given to K_3-EDTA plasma, as it is stable longer than serum.

Stability of serum: 6 hours at 20-25 °C, 8 hours at 4-8 °C.

Stability of Li-heparin plasma: 4 hours at 20-25 °C, 8 hours at 4-8 °C.

Stability of EDTA plasma: 24 hours at 20-25 °C, 8 days at 4-8 °C.

Serum, heparinized and EDTA plasma are stable for 3 months at -20 °C. For longer periods, store at -70 °C. Freeze only once.

Hemolyzed samples (Hb > 0.5 g/dL) elicit a decrease in the β-CTx concentration.

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 11972316122, β-CrossLaps CalSet, for 4 x 1 mL
- REF 05618860190, PreciControl Varia, for 2 x 3 mL each of PreciControl Varia 1 and 2
- General laboratory equipment
- Elecsys 2010, MODULAR ANALYTICS E170 or **cobas e** analyzer

Accessories for Elecsys 2010 and **cobas e** 411 analyzers:

- 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, Elecsys 2010 AssayCup, 60 x 60 reaction vessels
- REF 11706799001, Elecsys 2010 AssayTip, 30 x 120 pipette tips

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 Combimagazine M, 48 magazines x 84 reaction vessels or pipette tips, waste bags
- REF 03023150001, WasteLiner, waste bags
- REF 03027651001, SysClean Adapter M

Accessories for all analyzers:

- REF 11298500316, 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 approx. 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 reference standards precisely defined by weighing out synthetic peptide.

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). Renewed calibration is recommended as follows:

- after 8 weeks 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 Varia.

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.

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 or pg/mL).

Limitations - interference

The assay is unaffected by icterus (bilirubin < 1112 µmol/L or < 65 mg/dL), hemolysis (Hb < 0.3 mmol/L or < 0.5 g/dL), lipemia (Intralipid < 1500 mg/dL) and biotin (< 123 nmol/L or < 30 ng/mL).

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.

No interference was observed from rheumatoid factors up to a concentration of 1500 IU/mL.

There is no high-dose hook effect at β-CTx concentrations up to 150 ng/mL (150000 pg/mL).

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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.

Results may be confounded by clinical conditions known to affect bone resorption, e.g. hyperparathyroidism or hyperthyroidism.

Caution should be exercised when measuring serum β-CTx levels in patients with reduced renal function as this may lead to reduced excretion of serum β-CTx and a consequent increase in the apparent serum CTx levels is seen.[10]

There is evidence that β-CTx can predict loss of bone density.[11] However, a correlation with increased fracture risk was not yet demonstrated. The properties of β-CTx in case of hyperparathyroidism or hyperthyroidism have not yet been unequivocally described.

For diagnostic purposes, the results should always be assessed in conjunction with the patient's medical history, clinical examination and other findings.

They should not be used as a sole determinant for executing or modifying an existing treatment regimen.

Limits and ranges

Measuring range

0.010-6.00 ng/mL or 10-6000 pg/mL (defined by the lower detection limit and the maximum of the master curve). Values below the lower detection limit are reported as < 0.010 ng/mL (< 10 pg/mL). Values above the measuring range are reported as > 6.00 ng/mL (> 6000 pg/mL).

Lower limits of measurement

Lower detection limit of the test

Lower detection limit: 0.01 ng/mL (10 pg/mL).

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

1. Healthy subjects

The following values have been obtained from studies with the Elecsys β-CrossLaps/serum assay in healthy test subjects:

	N	Mean		SD		Mean + 2 SD	
		ng/mL	pg/mL	ng/mL	pg/mL	ng/mL	pg/mL
Men							
• 30-50 years	165	0.300	300	0.142	142	0.584	584
• > 50-70 years	109	0.304	304	0.200	200	0.704	704
• > 70 years	365	0.394	394	0.230	230	0.854	854
Women							
• premenopausal	254	0.299	299	0.137	137	0.573	573
• postmenopausal	429	0.556	556	0.226	226	1.008	1008

Studies: Men, MCE study, 2/2000 (Data on file at Roche Diagnostics) Women, follow-up measurements of samples from the OFELY study.11,12

Intra-individual variance of serum β-CTx by monitoring in a placebo control group

Intra-individual variance was determined in a placebo control group (11 post-menopausal woman, 500 mg calcium) by measuring the Elecsys β-CrossLaps/serum concentration (β-CTx in ng/mL) over a period of 36 months. The intra-individual variance over this period resulted in a median CV of 17.9 % (see table).

N[b)]	Months									
	0	6	12	18	24	30	36	Mean	SD	CV%
1	0.33	0.28	0.25	0.22	0.31	0.40	0.29	0.30	0.057	19.3
2	0.52	0.37	0.43	0.41	0.50	0.44	0.52	0.45	0.059	13.0
3	0.34	0.25	0.36	0.22	0.23	0.29	0.27	0.28	0.055	19.7
4	0.45	0.38	0.43	0.38	0.48	0.49	0.40	0.43	0.044	10.3
5	0.25	0.23	0.28	0.27	0.21	0.19	0.24	0.24	0.032	13.3
6	0.17	0.15	0.18	0.10	0.14	0.15	0.19	0.15	0.030	19.5
7	0.35	0.43	0.37	0.27	0.34	0.34	0.48	0.37	0.066	17.9
8	0.35	–	0.26	0.19	0.21	0.24	0.31	0.26	0.059	22.8
9	0.40	0.33	0.29	0.26	0.27	0.31	0.35	0.32	0.049	15.4
10	0.11	–	0.15	–	0.15	0.13	0.16	0.14	0.020	14.1
11	0.22	0.35	0.12	0.33	0.22	0.17	0.15	0.22	0.088	39.2
								Median CV 17.9 %		

b) N = Subject number

2. Monitoring during antiresorptive therapy

The response of β-CTx concentrations to antiresorptive therapies has been assessed in clinical studies on postmenopausal women undergoing bisphosphonate therapy or hormone replacement therapy (HRT).

a) Bisphosphonate therapy (Ibandronate)

DIVA (**D**osing **I**ntra**V**enous **A**dministration) study[13] in a total of 1395 women (aged 55-80 years, ≥ 5 years postmenopausal, mean lumbar spine [L2-L4] T-score < -2.5 and ≥ -5). Each participant received daily 500 mg calcium and 400 IU vitamin D. The dosing scheme for intravenous (IV) ibandronate is provided in the table below.

The table below shows the median (%) change from baseline in serum levels of β-CrossLaps after 2, 3, 4, 6 and 12 months.

	Oral ibandronate 2.5 mg daily		**IV ibandronate 2 mg every 2 months**		**IV ibandronate 3 mg every 3 months**	
Month	Median (95 % CI)[c)]	N	Median (95 % CI)	N	Median (95 % CI)	N
2	-45.0 (-48.7, -40.5)	181	-47.1 (-51.0, -43.8)	348	-	-
3	-54.1 (-57.8, -48.7)	192	-	-	-43.2 (-45.9, -40.8)	356
4	-57.6 (-66.7, -50.0)	180	-61.4 (-63.2, -58.4)	349	-	-
6	-62.5 (-65.3, -60.0)	372	-65.1 (-67.4, -62.5)	346	-58.4 (-61.5, -55.2)	353
12	-62.6 (-66.0, -58.9)	368	-64.6 (-67.2, -62.5)	345	-58.6 (-61.5, -55.4)	352

c) 95 % CI = 95 % confidence intervall

The table below shows the median (%) change from baseline in serum levels of β-CrossLaps from the same DIVA study after 1 and 2 years compared with BMD (bone mineral density) measurements.[14]

	Oral ibandronate 2.5 mg daily		**IV ibandronate 2 mg every 2 months**		**IV ibandronate 3 mg every 3 months**	
	after 1 year	after 2 years	after 1 year	after 2 years	after 1 year	after 2 years
Lumbar spine BMD	3.6 (n = 436)	4.6 (n = 422)	4.8 (n = 414)	6 (n = 389)	4.6 (n = 433)	5.8 (n = 413)
Total hip BMD	1.6 (n = 432)	1.9 (n = 418)	2.4 (n = 407)	3.1 (n = 385)	2.2 (n = 430)	2.8 (n = 410)
Femoral neck BMD	1.6 (n = 432)	2.1 (n = 418)	1.96 (n = 407)	2.7 (n = 385)	2.2 (n = 430)	2.4 (n = 410)
Trochanter BMDd)	2.8 (n = 432)	3.1 (n = 418)	3.9 (n = 407)	4.6 (n = 385)	3.6 (n = 430)	4.5 (n = 410)
Serum β-CTxe)	**-62.3 (n = 414)**	**-58.6 (n = 386)**	**-64.3 (n = 385)**	**-56.1 (n = 363)**	**-58 (n = 399)**	**-51.7 (n = 373)**

d) BMD results reported as mean percent change from baseline

e) Serum β-CTx results reported as median percent change from baseline

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β-CrossLaps/serum (β-CTx in serum)

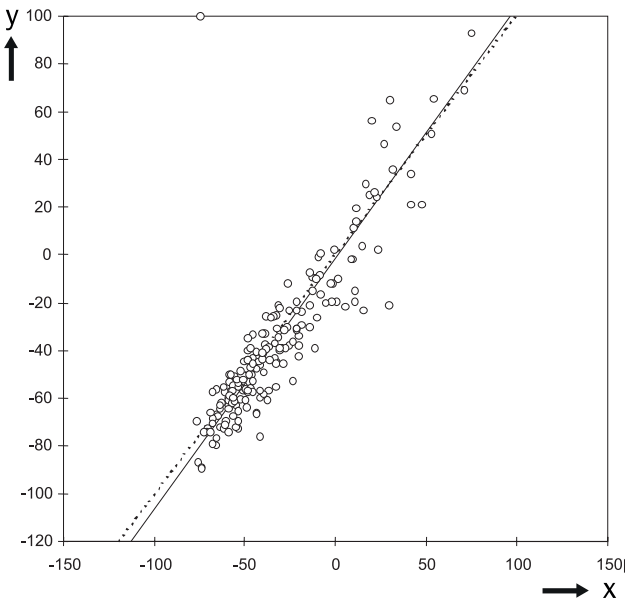
Study results: Substantial decreases in serum β-CTx values were observed in all treatment arms after 1 year compared to values normally seen in premenopausal women. There was a rapid and pronounced decrease in median serum β-CTx values during the first 6 months of treatment compared to values ≥ 50 % below baseline. After 6 months, the values approached steady state and remained at ≥ 50 % below baseline values. The median reductions in serum β-CTx values after 1 year ranged from 58 to 64.2 %.

Serum β-CTx levels decreased with similar magnitude after 2 years regardless of whether the treatment was given oral or intravenous.

Similar results have been reported in a previous study.[15]

b) Hormone replacement therapy (HRT)

Correlation (Passing/Bablok[16]) of relative changes in Elecsys β-CrossLaps/serum concentrations to those of CrossLaps™ One Step ELISA test. Data from 24 women (< 75 years, more than 10 years since menopause); monitored over a period of 24 months.



x: Serum CrossLaps™ One Step ELISA, % change

y: Elecsys β-CrossLaps/serum assay, % change

Slope: 1.05 (95 % confidence range: 0.99-1.11)

Intercept: -1.52 (95 % confidence range: -3.72-0.89)

Correlation coefficient: 0.862

SD (y-x residuals): 17.59

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 (EP5-A2) of the CLSI (Clinical and Laboratory Standards Institute): 2 runs per day in duplication each for 21 days (n = 84). The following results were obtained:

Elecsys 2010 and **cobas e** 411 analyzers					
		Repeatability		**Intermediate precision**	
Sample	Mean ng/mL	SD ng/mL	CV %	SD ng/mL	CV %
Human serum 1	0.051	0.002	3.5	0.004	8.4
Human serum 2	0.488	0.010	2.1	0.018	3.8
Human serum 3	2.35	0.048	2.0	0.066	2.8
Human serum 4	4.48	0.124	2.8	0.186	4.2
Human serum 5	4.62	0.104	2.2	0.176	3.8
PreciControl Varia 1	0.259	0.006	2.2	0.009	3.5
PreciControl Varia 2	0.687	0.018	2.6	0.022	3.2

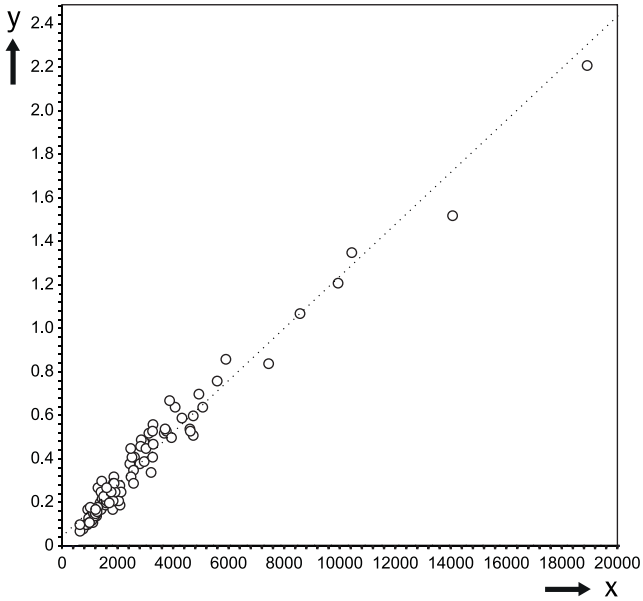
MODULAR ANALYTICS E170, **cobas e** 601 and **cobas e** 602 analyzers					
	Repeatability			**Intermediate precision**	
Sample	Mean ng/mL	SD ng/mL	CV %	SD ng/mL	CV %
Human serum 1	0.058	0.003	4.7	0.003	5.7
Human serum 2	0.502	0.007	1.5	0.009	1.8
Human serum 3	2.37	0.028	1.2	0.041	1.7
Human serum 4	4.47	0.073	1.6	0.099	2.2
Human serum 5	4.64	0.092	2.0	0.113	2.4
PreciControl Varia 1	0.272	0.004	1.6	0.006	2.2
PreciControl Varia 2	0.697	0.010	1.4	0.011	1.5

Method comparison

A comparison of the Elecsys β-CrossLaps/serum assay (y) - ng/mL - with the Serum CrossLaps™ One Step ELISA test from Osteometer (x) - pmol/L - using human serum is shown in the diagram below (linear regression):

Number of samples measured: 96

The sample concentrations were between approximately 0.07 and 2.2 ng/mL for the Elecsys β-CrossLaps/serum assay and between approximately 620 and 18900 pmol/L for the comparison test.



x: CrossLaps comparison test (pmol/L)

y: Elecsys β-CrossLaps/serum assay (ng/mL)

y = 0.0001x + 0.048

r = 0.983

The differing magnitudes of the concentrations is mainly due to the different forms of standardization used. Recalculation of the units is not possible.

Analytical specificity

The monoclonal antibodies used in the Elecsys β-CrossLaps/serum assay recognize all fragments of type I collagen containing the β-8AA octapeptide twice. No cross-reactivity detectable with osteocalcin, PTH or bone ALP.

Functional sensitivity

0.07 ng/mL (70 pg/mL)

The functional sensitivity is the lowest analyte concentration that can be reproducibly measured with an intermediate precision CV of < 20 %.

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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.

CONTENT	Contents of kit
SYSTEM	Analyzers/Instruments on which reagents can be used
REAGENT	Reagent
CALIBRATOR	Calibrator
→	Volume after reconstitution or mixing

CE

Roche Diagnostics GmbH, Sandhofer Strasse 116, D-68305 Mannheim
www.roche.com

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