Elecsys IGFBP-3

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REF		Σ	SYSTEM
07574720190	07574720500	100	**cobas e** 402 **cobas e** 801

English

System information

Short name	ACN (application code number)
IGFBP-3	10117

Intended use

Immunoassay for the in vitro quantitative determination of insulin-like growth factor binding protein-3 (IGFBP-3) in human serum and plasma. The IGFBP-3 determination is intended to be used as an aid in the assessment of growth disorders in conjunction with other clinical and laboratory findings.

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

Summary

IGFBP-3 belongs to the family of 6 structurally similar proteins (IGFBP-1 to -6), which bind insulin-like growth factors (IGFs).[1] It has a molecular weight of 29 kDa (unglycosylated) and is the most abundant IGFBP in the circulation.[2] Around 80 % of IGFs in the circulation are bound to IGFBP-3 forming a ternary complex with a third component called ALS (acid-labile subunit),[2,3] increasing the half-life of IGF-1 significantly from 10 minutes to more than 12 hours.[1,4] While IGF-1 and ALS are regulated directly by growth hormone (GH) the IGFBP-3 may be regulated indirectly via IGF-1.[4,5]

In contrast to GH, which is secreted in pulses peaking every 60-90 minutes, diurnal IGFBP-3 serum levels are largely constant. The concentration of IGFBP-3 is mainly determined by age and gender. It constantly increases until adolescence/early adulthood and decreases slightly throughout adult life.[6,7]

Its role in the bioavailability of circulating IGF-1[2] makes IGFBP-3 another marker in the diagnosis of growth disorders, particularly during childhood and adolescence. Its concentration can be used as an additional value, instead or in addition to the IGF-1 concentration in the diagnosis of growth hormone disorders, particularly with some superiority over IGF-1 in young children.[2,8]

In case of suspicious growth hormone deficiency (GHD), a normal basal IGFBP-3 level of > -1 SD for the corresponding age of the patient is a strong argument against GHD, with high diagnostic specificity.[2,8] Additionally, very low basal levels of both serum IGFBP-3 and IGF-1 (< -3 SD for age and sex) and failure to raise serum IGFBP-3 and IGF-1 concentrations by exogenous growth hormone stimulation is an evidence for growth hormone insensitivity.[2,9] Similarly to IGF-1, IGFBP-3 can also be used in the diagnosis of excess of growth hormone, resulting in gigantism or acromegaly.[2]

The molar ratio of IGF-1/IGFBP-3 is used as an indicator of the bioavailability of IGF-1[6,10,11] and is another parameter in the diagnosis of growth hormone disorders.

Test principle

Sandwich principle. Total duration of assay: 18 minutes.

- 1st incubation: 6 µL of sample are automatically prediluted 1:20 with Diluent MultiAssay. The antigen (in 30 µL of prediluted sample), a biotinylated monoclonal IGFBP-3-specific antibody and a monoclonal IGFBP-3-specific antibody labeled with a ruthenium complex[a)] react to 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 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.

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

Reagents - working solutions

The **cobas e** pack is labeled as IGFBP-3.

M Streptavidin-coated microparticles, 1 bottle, 5.8 mL:
Streptavidin-coated microparticles 0.72 mg/mL; preservative.

R1 Anti-IGFBP-3-Ab~biotin, 1 bottle, 7.2 mL:
Biotinylated monoclonal anti-IGFBP-3 antibody (mouse) 2.5 µg/mL; phosphate buffer 100 mmol/L, pH 7.8, preservative.

R2 Anti-IGFBP-3-Ab~$Ru(bpy)_3^{2+}$, 1 bottle, 7.2 mL:
Monoclonal anti-IGFBP-3 antibody (mouse) labeled with ruthenium complex 5.5 µg/mL; phosphate buffer 100 mmol/L, pH 7.8; preservative.

Precautions and warnings

For in vitro diagnostic use for health care professionals. Exercise the normal precautions required for handling all laboratory reagents.

Infectious or microbial waste:
Warning: handle waste as potentially biohazardous material. Dispose of waste according to accepted laboratory instructions and procedures.

Environmental hazards:
Apply all relevant local disposal regulations to determine the safe disposal.

Safety data sheet available for professional user on request.

This kit contains components classified as follows in accordance with the Regulation (EC) No. 1272/2008:

Warning

H317	May cause an allergic skin reaction.
Prevention:	
P261	Avoid breathing mist or vapours.
P272	Contaminated work clothing should not be allowed out of the workplace.
P280	Wear protective gloves.
Response:	
P333 + P313	If skin irritation or rash occurs: Get medical advice/attention.
P362 + P364	Take off contaminated clothing and wash it before reuse.
Disposal:	
P501	Dispose of contents/container to an approved waste disposal plant.

Product safety labeling follows EU GHS guidance.

Contact phone: all countries: +49-621-7590

Avoid foam formation in all reagents and sample types (specimens, calibrators and controls).

Reagent handling

The reagents in the kit have been assembled into a ready-for-use unit that cannot be separated.

All information required for correct operation is available via the **cobas** link.

Storage and stability

Store at 2-8 °C.

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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.

Plasma tubes containing separating gel can be used.

Criterion: Slope 0.9-1.1 + bias of ± 10 % at 3500 ng/mL + coefficient of correlation ≥ 0.95.

Stable for 8 hours at 15-25 °C, 48 hours at 2-8 °C, 8 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 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 07574762190, CalSet IGFBP-3, for 4 x 1.0 mL
- REF 07476108190, PreciControl Growth, for 4 x 3.0 mL
- REF 07299010190, Diluent MultiAssay, 45.2 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 IDS iSYS Insulin-Like Growth Factor Binding Protein-3 (IGFBP-3).

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

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

Controls for the various concentration ranges should be run individually at least once every 24 hours when the test is in use, once per **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, µg/mL or nmol/L).

Conversion factors: ng/mL x 0.001 = µg/mL

ng/mL x 0.036 = 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	≤ 0.62 mmol/L or ≤ 1000 mg/dL
Intralipid	≤ 2000 mg/dL
Biotin	≤ 2454 nmol/L or ≤ 600 ng/mL
Rheumatoid factors	≤ 1200 IU/mL
IgG	≤ 7.0 g/dL
IgA	≤ 1.6 g/dL
IgM	≤ 1.0 g/dL
Albumin	≤ 7.0 g/dL

Criterion: Recovery within ± 15 ng/mL for IGFBP-3 concentrations ≤ 150 ng/mL or ± 10 % for concentrations > 150 ng/mL 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.

There is no high-dose hook effect at IGFBP-3 concentrations up to 500000 ng/mL.

Pharmaceutical substances

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In vitro tests were performed on 17 commonly used pharmaceuticals. No interference with the assay was found.

In addition, the following special growth disorder drugs were tested. No interference with the assay was found.

Special growth disorder drugs

Drug	Concentration tested mg/L
Somatotropin	0.6
Octreotide	50
Pegvisomant	155
Lanreotide	2
Pasireotide	0.25
Vapreotide	0.01
Cabergoline	3
Bromocriptine	0.005
Pamidronate	25
Vitamin D	0.15

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

70-18000 ng/mL (defined by the Limit of Detection and the maximum of the master curve). Values below the Limit of Detection are reported as < 70 ng/mL. Values above the measuring range are reported as > 18000 ng/mL.

Lower limits of measurement

Limit of Blank, Limit of Detection and Limit of Quantitation

Limit of Blank = 35 ng/mL

Limit of Detection = 70 ng/mL

Limit of Quantitation = 70 ng/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 the lowest analyte concentration that can be reproducibly measured with an intermediate precision CV of ≤ 20 %.

Dilution

Use Diluent MultiAssay for automatic sample predilution.
Further dilution is not necessary due to the broad measuring range.

Expected values

Expected values were obtained in a clinical study (CIM RD002970) that enrolled over 3000 samples from femal subjects and over 3500 samples from male subjects, including over 1400 samples from subjects ≤ 17 years old.

See "Distribution of expected values" section for details.

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, samples 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 ng/mL	SD ng/mL	CV %	SD ng/mL	CV %
Human serum 1	105	2.17	2.1	2.33	2.2
Human serum 2	3581	80.3	2.2	99.8	2.8
Human serum 3	4236	88.4	2.1	99.4	2.3
Human serum 4	17818	574	3.2	675	3.8
Human serum 5	8281	183	2.2	228	2.8
PC[b)] Growth 1	786	20.1	2.6	21.8	2.8
PC Growth 2	6951	130	1.9	145	2.1

b) PreciControl

Method comparison

a) A comparison of the Elecsys IGFBP-3 assay, REF 07574720190 (**cobas e** 801 analyzer; y) with the Elecsys IGFBP-3 assay, REF 07574690190 (**cobas e** 601 analyzer; x) using clinical samples gave the following correlations (ng/mL):

Number of samples measured: 153

Passing/Bablok[12]	Linear regression
y = 1.05x + 31.5	y = 1.04x + 68.8
τ = 0.955	r = 0.996

The sample concentrations were between 79.9 ng/mL and 17358 ng/mL.

b) A comparison of the Elecsys IGFBP-3 assay, REF 07574720190 (**cobas e** 402 analyzer; y), with the Elecsys IGFBP-3 assay, REF 07574720190 (**cobas e** 801 analyzer; x), gave the following correlations (ng/mL):

Number of samples measured: 144

Passing/Bablok[12]	Linear regression
y = 1.10x + 2.93	y = 1.11x - 51.4
τ = 0.937	r = 0.998

The sample concentrations were between 77.0 ng/mL and 15740 ng/mL.

Analytical specificity

No significant cross-reactivity was found for the following substances:

Substances	Concentration tested ng/mL
IGF-1	1000
IGFBP-1	150
IGFBP-5	2300

Distribution of expected values

The graphic below depicts the distribution of the expected values for male subjects:

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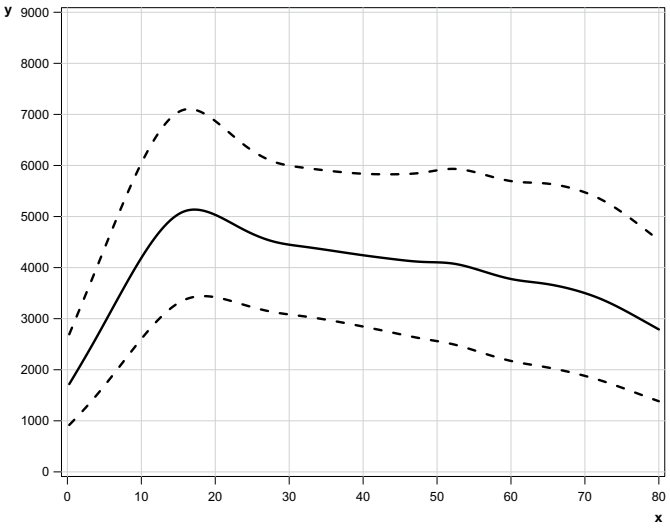

x-axis: age
y-axis: IGFBP-3 value in ng/mL
solid line: 50 % quantile
dashed line: 2.5 % and 97.5 % quantile

The table below is a representative read-out of the age depended expected values based on the graphic depicted above. The values represent the indicated quantiles (2.5 %, 50 % and 97.5 %) for each age.

Male subjects				
Age (years)	**N**	**Median (ng/mL)**	**2.5 % (ng/mL)**	**97.5 % (ng/mL)**
0.25	37	1719	919	2694
0.5	44	1779	955	2782
1	59	1900	1030	2957
2	38	2145	1183	3306
3	28	2394	1343	3658
4	28	2650	1511	4013
5	32	2911	1687	4371
6	51	3175	1868	4727
7	34	3438	2053	5077
8	58	3698	2239	5419
9	61	3950	2423	5741
10	52	4190	2603	6044
11	49	4413	2775	6321
12	47	4615	2935	6565
13	42	4791	3080	6771
14	37	4936	3205	6933
15	16	5044	3306	7044
16	13	5111	3379	7099
17	5	5136	3423	7098
18	1	5126	3441	7053
19	2	5090	3439	6973
20	3	5033	3420	6870
21	10	4964	3390	6753
22	10	4887	3352	6630
23	15	4808	3310	6508
24	19	4732	3267	6392

Male subjects				
Age (years)	**N**	**Median (ng/mL)**	**2.5 % (ng/mL)**	**97.5 % (ng/mL)**
25	25	4662	3225	6290
26	15	4601	3188	6201
27	19	4549	3154	6127
28	16	4506	3125	6069
29	18	4474	3102	6027
30	18	4449	3082	5996
31	16	4428	3064	5974
32	16	4409	3046	5955
33	15	4390	3026	5937
34	21	4369	3004	5919
35	14	4348	2981	5902
36	16	4327	2956	5886
37	16	4305	2930	5871
38	19	4284	2903	5858
39	18	4263	2875	5848
40	39	4242	2846	5839
41	90	4222	2817	5832
42	92	4203	2787	5828
43	101	4185	2757	5826
44	99	4167	2726	5827
45	75	4150	2696	5829
46	100	4135	2666	5835
47	98	4122	2637	5845
48	79	4113	2609	5860
49	88	4107	2584	5881
50	97	4103	2560	5904
51	61	4096	2534	5923
52	78	4082	2504	5933
53	75	4057	2468	5927
54	53	4023	2427	5906
55	62	3983	2382	5874
56	44	3938	2336	5836
57	63	3893	2291	5795
58	69	3850	2248	5756
59	69	3811	2208	5722
60	61	3777	2172	5694
61	58	3751	2142	5677
62	85	3731	2116	5668
63	62	3714	2093	5663
64	64	3697	2069	5657
65	45	3676	2044	5645
66	57	3650	2016	5625
67	53	3619	1985	5597
68	58	3584	1952	5562
69	68	3544	1917	5521
70	68	3500	1879	5472

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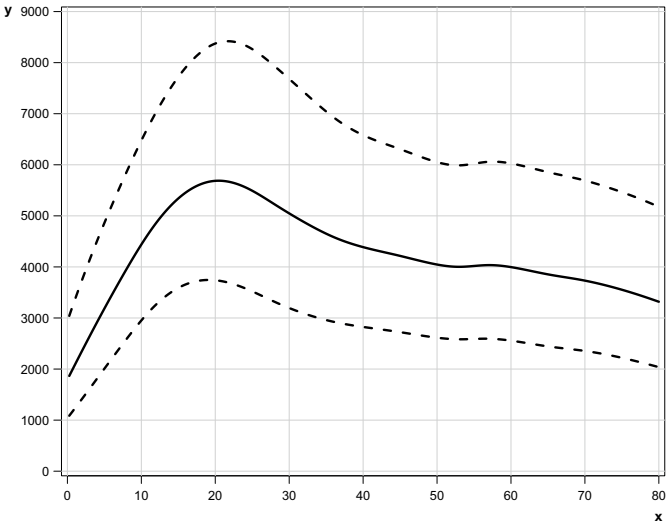
Male subjects				
Age (years)	**N**	**Median (ng/mL)**	**2.5 % (ng/mL)**	**97.5 % (ng/mL)**
71	68	3451	1839	5416
72	64	3396	1796	5349
73	72	3333	1750	5272
74	40	3264	1701	5182
75	39	3190	1649	5084
76	32	3112	1595	4979
77	27	3032	1542	4871
78	19	2952	1489	4761
79	14	2871	1436	4651
80	0	-	-	-

The graphic below depicts the distribution of the expected values for female subjects:



x-axis: age
y-axis: IGFBP-3 value in ng/mL
solid line: 50 %
quantile dashed line: 2.5 % and 97.5 % quantile

The table below is a representative read-out of the age depended expected values based on the graphic depicted above. The values represent the indicated quantiles (2.5 %, 50 % and 97.5 %) for each age.

Female subjects				
Age (years)	**N**	**Median (ng/mL)**	**2.5 % (ng/mL)**	**97.5 % (ng/mL)**
0.25	26	1865	1086	3041
0.5	35	1937	1133	3146
1	37	2080	1228	3352
2	34	2362	1420	3752
3	48	2641	1614	4136
4	42	2915	1810	4505
5	51	3184	2007	4860
6	49	3447	2203	5202
7	37	3705	2397	5535
8	48	3958	2588	5858
9	41	4203	2774	6172

Female subjects				
Age (years)	**N**	**Median (ng/mL)**	**2.5 % (ng/mL)**	**97.5 % (ng/mL)**
10	42	4438	2951	6474
11	51	4658	3116	6761
12	54	4860	3264	7031
13	38	5042	3392	7282
14	39	5202	3501	7512
15	22	5340	3589	7720
16	11	5456	3658	7905
17	13	5549	3705	8065
18	6	5618	3734	8198
19	3	5664	3745	8302
20	13	5686	3739	8374
21	7	5685	3718	8413
22	7	5663	3684	8418
23	15	5622	3638	8394
24	16	5564	3583	8342
25	15	5492	3521	8265
26	18	5409	3454	8167
27	13	5320	3386	8055
28	13	5228	3319	7934
29	14	5137	3255	7808
30	10	5048	3195	7681
31	12	4962	3140	7552
32	10	4879	3088	7422
33	7	4799	3041	7292
34	10	4722	2998	7165
35	11	4651	2960	7043
36	9	4585	2925	6929
37	14	4526	2895	6826
38	15	4475	2869	6734
39	6	4429	2846	6652
40	51	4388	2825	6580
41	74	4350	2804	6517
42	87	4316	2785	6460
43	79	4283	2765	6408
44	71	4250	2744	6358
45	72	4216	2723	6306
46	53	4180	2700	6252
47	70	4144	2677	6198
48	69	4109	2654	6145
49	94	4076	2633	6096
50	57	4047	2614	6052
51	47	4023	2598	6017
52	52	4007	2588	5994
53	47	4002	2583	5989
54	44	4007	2585	6000
55	67	4018	2590	6021

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Female subjects				
Age (years)	N	Median (ng/mL)	2.5 % (ng/mL)	97.5 % (ng/mL)
56	46	4030	2594	6044
57	53	4035	2594	6059
58	51	4031	2587	6061
59	36	4017	2574	6049
60	59	3997	2556	6026
61	60	3971	2535	5997
62	55	3942	2512	5963
63	57	3912	2488	5927
64	47	3882	2465	5891
65	40	3854	2444	5855
66	50	3829	2425	5822
67	41	3805	2408	5791
68	71	3782	2391	5761
69	45	3758	2374	5728
70	48	3732	2355	5692
71	59	3701	2333	5652
72	47	3668	2308	5608
73	44	3632	2281	5562
74	33	3594	2252	5514
75	24	3553	2220	5464
76	24	3510	2187	5412
77	20	3465	2151	5357
78	25	3418	2114	5300
79	10	3368	2076	5239
80	3	3318	2038	5177

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For further information, please refer to the appropriate user guide or operator's manual for the analyzer concerned, the respective application sheets and the Method Sheets of all necessary components (if available in your country).

A point (period/stop) is always used in this Method Sheet as the decimal separator to mark the border between the integral and the fractional parts of a decimal numeral. Separators for thousands are not used.

Any serious incident that has occurred in relation to the device shall be reported to the manufacturer and the competent authority of the Member State in which the user and/or the patient is established.

Symbols

Roche Diagnostics uses the following symbols and signs in addition to those listed in the ISO 15223-1 standard (for USA: see navifyportal.roche.com for definition of symbols used):

CONTENT	Contents of kit
SYSTEM	Analyzers/Instruments on which reagents can be used
REAGENT	Reagent
CALIBRATOR	Calibrator
→	Volume for reconstitution
GTIN	Global Trade Item Number
Rx only	For USA: Caution: Federal law restricts this device to sale by or on the order of a physician.

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Additions, deletions or changes are indicated by a change bar in the margin.

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