VITROS Products Immunodiagnostic

INSTRUCTIONS FOR USE FSH

VITROS Immunodiagnostic Products FSH Reagent Pack

REF 193 1922

VITROS Immunodiagnostic ProductsFSH Calibrators

REF 190 1263

Rx ONLY

Intended Use

For *in vitro* diagnostic use only.

VITROS Immunodiagnostic Products FSH Reagent Pack

For the quantitative measurement of follicle stimulating hormone (FSH) concentration in human serum and plasma (EDTA or heparin) using the VITROS ECi/ECiQ/3600 Immunodiagnostic Systems and the VITROS 5600/XT 7600 Integrated Systems.

VITROS Immunodiagnostic Products FSH Calibrators

For use in the calibration of the VITROS ECi/ECiQ/3600 Immunodiagnostic Systems and the VITROS 5600/XT 7600 Integrated Systems for the quantitative measurement of follicle stimulating hormone (FSH) in human serum and plasma (EDTA or heparin).

Summary and Explanation of the Test

FSH is secreted by the anterior pituitary under the control of hypothalamic gonadotrophin releasing hormone. The function of FSH in both males and females is to facilitate the development and maintenance of the gonadal tissues. These tissues synthesize and secrete steroid hormones, which in turn control FSH concentrations by negative feedback. [1-3] At menopause, ovarian function and steroid secretion cease, causing FSH concentrations to rise due to a lack of negative feedback control. FSH concentrations are similarly raised in women of pre-menopausal age who suffer ovarian failure, [4] or whose ovaries failed to mature during puberty. [5] Elevated FSH concentrations are found in males when the testes have failed to develop to functional maturity, or, in cases of infertility due to primary testicular failure. [6-7]

Principles of the Procedure

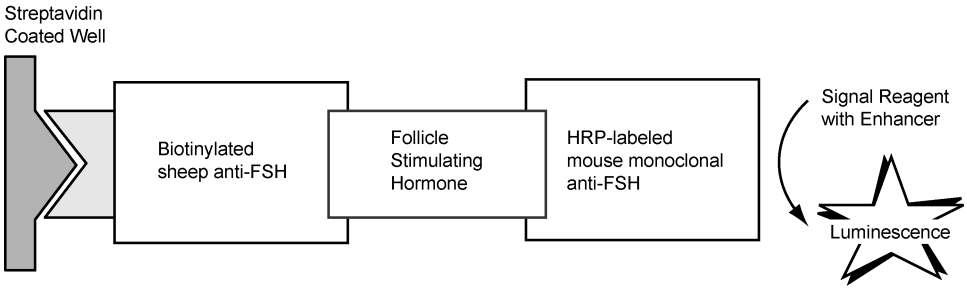
An immunometric immunoassay technique is used, which involves the simultaneous reaction of FSH present in the sample with a biotinylated antibody (sheep anti-FSH) and a horseradish peroxidase (HRP)-labeled antibody conjugate (mouse monoclonal anti-FSH). The antigen-antibody complex is captured by streptavidin on the wells. Unbound materials are removed by washing.

The bound HRP conjugate is measured by a luminescent reaction. [8] A reagent containing luminogenic substrates (a luminol derivative and a peracid salt) and an electron transfer agent, is added to the wells. The HRP in the bound conjugate catalyzes the oxidation of the luminol derivative, producing light. The electron transfer agent (a substituted acetanilide) increases the level of light produced and prolongs its emission. The light signals are read by the system. The amount of HRP conjugate bound is directly proportional to the concentration of FSH present.

Test Type	System *	Incubation Time	Time to first result	Test Temperature	Reaction Sample Volume
Immunometric immunoassay	ECi/ECiQ, 3600, 5600, XT 7600	16 minutes	24 minutes	37 °C	40 µL

* Not all products and systems are available in all countries.

Reaction Scheme



Warnings and Precautions

WARNING: ***Potentially Infectious Material***

Use caution when handling material of human origin. Consider all samples potentially infectious. No test method can offer complete assurance that hepatitis B virus, hepatitis C virus (HCV), human immunodeficiency virus (HIV 1+2) or other infectious agents are absent. Handle, use, store and dispose of solid and liquid waste from samples and test components, in accordance with procedures defined by appropriate national biohazard safety guideline or regulation (e.g. CLSI document M29). [9]

WARNING: ***Contains Kathon or ProClin 200 (CAS 55965-84-9)*** [10]

The VITROS FSH Reagent Pack contains 1% Kathon or ProClin 200. H317: May cause an allergic skin reaction. H319: Causes serious eye irritation. P280: Wear protective gloves, Eye Protection. P302 + P352: IF ON SKIN: Wash with plenty of soap and water. P305 + P351 + P338: IF IN EYES: Rinse cautiously with water for several minutes. Remove contact lenses, if present and easy to do. Continue rinsing. P333 + P313: If skin irritation or rash occurs: Get medical advice/attention. P337 + P313: If eye irritation persists: Get medical advice/attention. P362: Take off contaminated clothing and wash before reuse.

Refer to www.Orthoclinicaldiagnostics.com for the Safety Data Sheets and for Ortho contact information.

WARNING

Reagents

Reagent Pack Contents

1 reagent pack containing:

- 100 coated wells (streptavidin, bacterial; binds ≥3 ng biotin/well)
- 6.2 mL conjugate reagent (HRP-mouse monoclonal anti-FSH, binds ≥484 mIU FSH/mL) in buffer with bovine serum albumin and antimicrobial agent
- 13.3 mL biotinylated antibody reagent (biotin-sheep anti-FSH, binds ≥96.8 mIU FSH/mL) in buffer with bovine serum albumin, bovine serum, sheep serum and antimicrobial agent

Reagent Pack Handling

- The reagent pack is supplied ready for use.
- The reagent pack contains homogeneous liquid reagents that do not require shaking or mixing prior to loading on the system.

- As with all immunoassay protein-based solutions, inappropriate handling of the reagent pack can cause foam to occur on the surface of the reagent. Avoid agitation, which may cause foaming or the formation of bubbles.
  - If reagent packs are dropped or agitated, small levels of fine foam could be generated that may not be detected by the system.
  - Reagent packs containing fine foam that is not detected by the system, may show a negative bias.
- If you must use a dropped or agitated reagent pack before it has been allowed to settle, you should verify performance by running high and low quality control samples in duplicate after loading the pack on the system.

Reagent Pack Storage and Preparation

Reagent	Storage Condition		Stability
Unopened	Refrigerated	2–8 °C (36–46 °F)	expiration date
Opened	On system	System turned on	≤8 weeks
Opened	Refrigerated	2–8 °C (36–46 °F)	≤8 weeks

- The VITROS FSH Reagent Pack is suitable for use until the expiration date on the carton when stored and handled as specified. Do not use beyond the expiration date.
- Do not freeze unopened reagent packs.
- Load reagent packs directly from refrigerated storage to minimize condensation.
- Store opened refrigerated reagent packs in a sealed reagent pack storage box that contains dry desiccant.

Calibrator Contents

- 1 set of VITROS FSH Calibrators 1 and 2 (human pituitary FSH in bovine serum with antimicrobial agent, 2.0 mL); nominal values 2 and 40 mIU/mL (IU/L) (2nd IRP 78/549)
- Lot calibration card
- Protocol card
- 16 calibrator bar code labels (8 for each calibrator)

Calibrator Handling

- Use only with reagent packs of the same lot number. Mix thoroughly by inversion and bring to 15–30 °C (59–86 °F) before use. Each pack contains sufficient for a minimum of 6 determinations of each calibrator.
- Handle calibrators in stoppered containers to avoid contamination and evaporation. To avoid evaporation, limit the amount of time calibrators are on the system. Refer to the operating instructions for your system. Return to 2–8 °C (36–46 °F) as soon as possible after use, or load only sufficient for a single determination.

Calibrator Storage and Preparation

Calibrator	Storage Condition		Stability
Unopened	Refrigerated	2–8 °C (36–46 °F)	expiration date
Opened	Refrigerated	2–8 °C (36–46 °F)	≤13 weeks
Opened	Frozen	≤-20 °C (≤-4 °F)	≤13 weeks

- VITROS FSH Calibrators are supplied ready for use.
- VITROS FSH Calibrators are suitable for use until the expiration date on the carton when stored and handled as specified. Do not use beyond the expiration date.
- Opened calibrators may be stored frozen (with no more than 1 freeze-thaw cycle).
- The VITROS FSH test uses 40 µL of calibrator for each determination. The VITROS FSH Calibrators may be used directly on the VITROS Immunodiagnostic and VITROS Integrated Systems. Alternatively, transfer an aliquot of each calibrator into a sample container (taking account of the minimum fill volume of the container), which may be bar coded with the labels provided. For details on minimum fill volume of sample cups or containers, refer to the operating instructions for your system.

Specimen Collection, Preparation and Storage

Patient Preparation

No special patient preparation is necessary.

Specimens Recommended

- Serum
- EDTA plasma
- Heparin plasma

Specimens Not Recommended

Do not use turbid specimens. Turbidity in specimens may affect test results.

Special Precautions

IMPORTANT:	*Certain collection devices have been reported to affect other analytes and tests.* [11] *Owing to the variety of specimen collection devices available, Ortho Clinical Diagnostics is unable to provide a definitive statement on the performance of its products with these devices. Confirm that your collection devices are compatible with this test.*

Specimen Collection and Preparation

- Collect specimens using standard procedures. [12- 13]
- Thoroughly mix samples by inversion and bring to 15–30 °C (59–86 °F) before use.
- The VITROS FSH test uses 40 µL of sample for each determination. This does not take account of the minimum fill volume of the chosen sample container. For details on minimum fill volume of sample cups or containers, refer to the operating instructions for your system.

Handling and Storage Conditions

- Handle samples in stoppered containers to avoid contamination and evaporation.
- The amount of time samples are on the system prior to analysis should be limited to avoid evaporation. Refer to the operating instructions for your system.
- Return to 2–8 °C (36–46 °F) as soon as possible after use, or load sufficient volume for a single determination.
- Serum and plasma samples may be stored for up to 6 days at 2–8 °C (36–46 °F) or 4 weeks at -20 °C (-4 °F).
- Avoid repeated freeze-thaw cycles.

Testing Procedure

Materials Provided

- VITROS Immunodiagnostic Products FSH Reagent Pack
- VITROS Immunodiagnostic Products FSH Calibrators

Materials Required but Not Provided

- VITROS Immunodiagnostic Products Signal Reagent
- VITROS Immunodiagnostic Products Universal Wash Reagent
- Quality control materials such as VITROS Immunodiagnostic Products RE Controls
- VITROS Immunodiagnostic Products Reagent Pack Storage Box (optional) with desiccant

Operating Instructions

Check the inventory regularly to aid the management of reagents and ensure that sufficient VITROS Signal Reagent, VITROS Universal Wash Reagent and calibrated reagent lots are available for the work planned. When performing panels of tests on a single sample, ensure that the sample volume is sufficient for the tests ordered.

For detailed information refer to the operating instructions for your system.

Note:	Do not use visibly damaged product.

Sample Dilution

FSH concentrations above the measuring range should be reported as >200 mIU/mL (IU/L). The dilution of samples in the VITROS FSH test is not supported.

Default Test Name

The default test name which will appear on patient reports is FSH. The default short name that will appear on the test selection menus and laboratory reports is FSH. These defaults may be reconfigured, if required. For detailed information refer to the operating instructions for your system.

Calibration

Calibration Procedure

- Calibration is lot specific; reagent packs and calibrators are linked by lot number. Reagent packs from the same lot may use the same calibration.

- A Master Calibration (a dose response curve covering the full calibration range) is established for each new reagent lot. Concentrations for the linked lot of calibrators are determined from the Master Calibration.
- Ensure that the Master Calibration for each new reagent lot is available on your system.
- Process calibrators in the same manner as samples. Calibration need not be programmed if bar code labels are used; load the calibrators in any order, calibration will be initiated automatically.
- When the calibrators are processed the signal expected for each calibrator is compared against the actual signal obtained. The Master Calibration is then rescaled to reflect the differences between the actual and expected signals. The validity of this calibration curve is assessed against a range of quality parameters, and if acceptable, it is stored for use with any reagent pack of that lot.
- The quality of calibration cannot be completely described by a single parameter. The calibration report should be used in conjunction with acceptable control values to determine the validity of the calibration.
- Recalibration is required after a pre-determined calibration interval, or when a different reagent lot is loaded.
- Calibration results are assessed against a range of quality parameters. Failure to meet any of the defined quality parameter ranges will be coded in the calibration report. For actions to be taken following a failed calibration refer to the operating instructions for your system.

Refer to the operating instructions for your system for detailed instructions on the calibration process.

When to Calibrate

- Calibrate when the reagent pack and calibrator lot changes.
- Calibrate every 28 days.
- After specified service procedures have been performed.
- If quality control results are consistently outside of your acceptable range.

For additional information on when to calibrate, refer to the operating instructions for your system.

Traceability of Calibration

Calibration of the VITROS FSH test is traceable to in-house reference calibrators, which have been calibrated against the 2nd International Reference Preparation 78/549.

Calibration Model

A modified four-parameter logistic curve fit function is used to construct the Master Calibration. The calibration process rescales the Master Calibration to establish a valid stored curve for the VITROS Immunodiagnostic and VITROS Integrated Systems.

Measuring (Reportable) Range

System	Measuring (Reportable) Range
3600 5600 XT 7600 ECi/ECiQ	0.66*–200 mIU/mL (IU/L)

* Lower limit of measuring range reported by the system software is based on the Limit of Detection.

The lower limit reported by the system can be reconfigured if desired. For details on how to reconfigure the lower limit refer to the operating instructions for your system.

Quality Control

Quality Control Material Selection

VITROS RE Controls are recommended for use with the VITROS Immunodiagnostic and VITROS Integrated Systems. The VITROS RE Controls contain 3 levels of FSH (low, medium and high). The performance of other commercial control fluids should be evaluated for compatibility with this test before they are used for quality control.

Control materials may show a difference when compared with other FSH methods if they contain high concentrations of preservatives, stabilizers, or other nonphysiological additives, or otherwise depart from a true human sample matrix.

Appropriate quality control value ranges must be established for all quality control materials used with the VITROS FSH test.

Quality Control Procedure Recommendations

- Good laboratory practice requires that controls be processed to verify the performance of the test.
- Choose control levels that check the clinically relevant concentrations.

- To verify system performance, analyze control materials:
  - After calibration
  - According to local regulations or at least once each day that the test is being performed
  - After specified service procedures are performed

If quality control procedures within your laboratory require more frequent use of controls, follow those procedures.

- Analyze quality control materials in the same manner as patient specimens.
- If control results fall outside your acceptable range, investigate the cause before deciding whether to report patient results.
- Refer to published guidelines for general quality control recommendations. [14]

For more detailed information, refer to the operating instructions for your system.

Quality Control Material Preparation and Storage

Refer to the manufacturer's product literature for preparation, storage, and stability information.

Results

Results are automatically calculated by the VITROS Immunodiagnostic and VITROS Integrated Systems.

Reporting Units and Unit Conversion

Analyte results are quoted in units of mIU/mL or IU/L. To configure the units, refer to the operating instructions for your system.

Conventional	Alternate
mIU/mL (IU/L× 1)	IU/L (mIU/mL× 1)

Note: LH and FSH results generated by the system may be used to automatically calculate the LH/FSH ratio (L/F). For additional information on programming derived tests, refer to the operating instructions for your system.

Limitations of the Procedure

Known Interferences

The VITROS FSH test was evaluated for interference consistent with CLSI document EP7. [15] Commonly encountered substances were tested on 2 lots of reagents. Of the compounds tested, Human Chorionic Gonadotrophin may interfere with the VITROS FSH test. Human Chorionic Gonadotrophin when tested caused the bias shown at the concentration indicated.

Refer to "Specificity" for a list of other compounds tested that did not show interference.

Interferent	Interferent Concentration		Units = mIU/mL (IU/L)	
			Analyte Conc*	Bias**
Human Chorionic Gonadotrophin (hCG)	125,000 mIU/mL	125,000 IU/L	5.16	-0.58

* Average test concentration of replicate determinations using 2 different lots of reagent.

** Estimate of the average difference observed.

Note: These results are representative. The degree of interference at concentrations other than those listed might not be predictable from these results. Other interfering substances may be encountered in the patient population.

Other Limitations

- The results from this or any other diagnostic test should be used and interpreted only in the context of the overall clinical picture.
- Heterophilic antibodies in the serum or plasma of certain individuals are known to cause interference with immunoassays. [16] These antibodies may be present in blood samples from individuals regularly exposed to animals or who have been treated with animal serum products. Results which are inconsistent with clinical observations indicate the need for additional testing.
- Certain drugs and clinical conditions are known to alter FSH concentrations *in vivo*. For additional information, refer to one of the published summaries. [17- 19]
- The VITROS FSH test has no high dose hook effect up to 1600 mIU/mL (IU/L).
- Biotin levels in serum remain elevated for up to 24 hours after oral or intravenous biotin administration. [20]

Expected Values and Interpretation of Results

It is recommended that each laboratory establish its own expected values for the population it serves.

Reference Interval

Phase	Units = mIU/mL (IU/L)		Number of Samples
	Range	Median	
Normal female follicular phase*	1.98–11.6	4.64	80
Normal female mid-cycle peak*	5.14–23.4	12.7	14
Normal female luteal phase*	1.38–9.58	3.54	188
Postmenopausal females	21.5–131	54.2	60
Normal males (Aged 19–65)	1.55–9.74	3.80	92

* The normal female cycles were separated into follicular phase (days up to peak minus 1 day) and luteal phase (days after peak plus 1 day). The positions of the mid-cycle peaks were confirmed using VITROS LH results.

Each of these reference intervals, with the exception of the mid-cycle peak, are the central 95% of results from studies of the following populations; female patients during the normal follicular and luteal phases, postmenopausal females, and normal males. The mid-cycle peak reference interval represents the observed range of data from 14 normal female cycles.

Interpretation of Results

For patient sample values outside of your established reference interval, the system may be configured to display a flag 'LO' or 'HI'. Refer to the operating instructions for your system.

Performance Characteristics

Limit of Detection

The Limit of Detection (LoD) for VITROS FSH is 0.66 mIU/mL (IU/L), determined consistent with NCCLS document EP17 [21] and with proportions of false positives (α) less than 5% and false negatives (β) less than 1%; based on 695 determinations, with 1 blank and 5 low-level samples. The Limit of Blank (LoB) is 0.20 mIU/mL (IU/L).

Limit of Blank and Limit of Detection

LoB*	LoD**
mIU/mL (IU/L)	mIU/mL (IU/L)
0.20	0.66

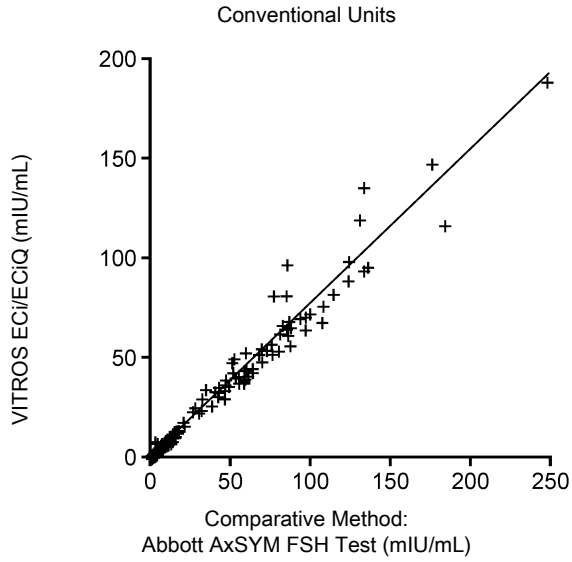
* Limit of Blank, or the highest value likely to be observed with a sample containing no analyte, replaces the term "analytical sensitivity."

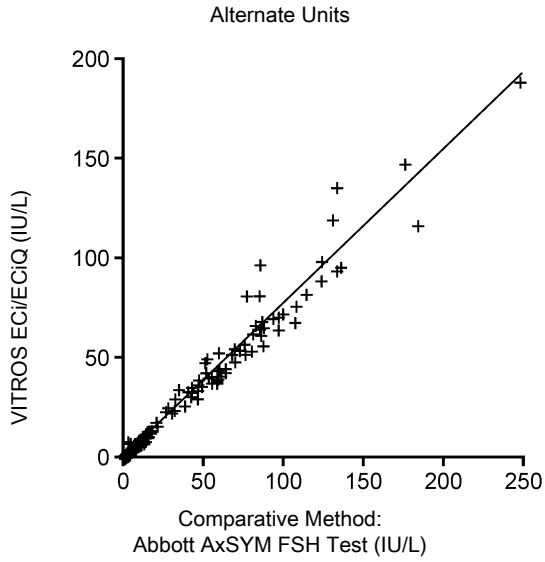
** Proportions of false positives (α) and false negatives (β) were less than 5% and 1% respectively; based on 695 determinations, with 1 blank and 5 low-level samples.

Accuracy (Method Comparison)

Accuracy was evaluated consistent with NCCLS document EP9. [22] The plot and table show the results of a method comparison study using patient samples from a variety of clinical categories analyzed on the VITROS ECi/ECiQ Immunodiagnostic System compared with those analyzed using the Abbott AxSYM FSH test. The relationship between the 2 methods was determined by Deming regression. [23]

The table also shows the results of method comparison studies [24] using patient serum and plasma samples analyzed on the VITROS ECi/ECiQ Immunodiagnostic System compared with those analyzed using the VITROS 3600 Immunodiagnostic System and the VITROS 5600 Integrated System. The relationship between the 2 methods was determined by Passing and Bablok regression. [25]





System	n	Slope	Correlation Coefficient	Conventional Units (mIU/mL) Range of Sample	Conventional Units (mIU/mL) Intercept	Alternate Units (IU/L) Range of Sample	Alternate Units (IU/L) Intercept
ECi/ECiQ vs. Comparative Method	204	0.774	0.985	0.82–189	0.103	0.82–189	0.103
3600 vs. ECi/ECiQ	107	0.998	0.999	2.67–186	-0.064	2.67–186	-0.064
5600* vs. ECi/ECiQ	109	1.005	0.999	2.67–186	-0.027	2.67–186	-0.027

* Performance characteristics for the VITROS 5600 System are applicable to the VITROS XT 7600 System.

Precision

VITROS ECi/ECiQ Immunodiagnostic System

Precision was evaluated consistent with NCCLS document EP5. [26] Two replicates each of 3 freeze-dried control samples were tested on 2 separate occasions per day on at least 20 different days. The experiment was performed using 2 reagent lots on 2 different systems. The data presented are a representation of the product performance.

VITROS 3600 Immunodiagnostic System and VITROS 5600 Integrated System

Precision was evaluated consistent with NCCLS document EP5. [27] Two replicates each of 3 freeze-dried control samples were tested on 2 separate occasions per day on at least 20 different days. The experiment was performed using 1 reagent lot on each system. The data presented are a representation of the product performance.

System	Units = mIU/mL (IU/L)							No. Observ.	No. Days
	Mean FSH Conc.	Within-run*		Within-calibration**		Within-lab***			
		SD	CV (%)	SD	CV (%)	SD	CV (%)		
ECi/ECiQ system 1	6.13	0.169	2.8	0.621	10.1	0.650	10.6	80	20
	20.6	0.532	2.6	1.28	6.2	1.55	7.5	80	20
	59.2	1.02	1.7	4.09	6.9	4.69	7.9	80	20
ECi/ECiQ system 2	6.39	0.140	2.2	0.230	3.6	0.238	3.7	80	20
	21.3	0.397	1.9	0.794	3.7	0.965	4.5	80	20
	59.5	1.11	1.9	2.32	3.9	2.72	4.6	80	20
3600	6.96	0.0588	0.8	0.159	2.3	0.194	2.7	84	21
	22.0	0.268	1.2	0.443	2.0	0.556	2.5	84	21
	44.6	0.407	0.9	0.846	1.9	1.12	2.5	84	21
5600****	6.76	0.0836	1.2	0.167	2.5	0.180	2.5	88	22
	21.6	0.205	1.0	0.507	2.4	0.503	2.2	88	22
	43.4	0.407	0.9	0.924	2.1	0.871	1.9	88	22

* Within-run (repeatability). Between Duplicate precision averaged over all runs

** Within-calibration. Total precision with weighted components of within-run, between–run and between-day variation

*** Within-lab. A measure of the effect of recalibration on total precision, calculated within reagent lot, using data from at least 4 calibrations

**** Performance characteristics for the VITROS 5600 System are applicable to the VITROS XT 7600 System.

Specificity

Substances that do not Interfere

The VITROS FSH test was evaluated for interference consistent with CLSI document EP7. [15] Of the compounds tested, none was found to cause a bias of >10% with the test at the concentrations indicated at FSH concentrations of 5.16–5.97 mIU/mL (IU/L).

Compound	Concentration	
Bilirubin	0.684 mmol/L	40 mg/dL
Biotin	40.9 nmol/L	1.0 µg/dL
Hemoglobin*	0.31 mmol/L	500 mg/dL
Luteinizing Hormone (LH)	400 mIU/mL	400 IU/L
Thyroid Stimulating Hormone (TSH)	250 µIU/mL	250 mIU/L
Triolein	33.9 mmol/L	3000 mg/dL

* Hemolysate was added to a series of specimens with a VITROS FSH concentration of 7.85–68.5 mIU/mL (IU/L).

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Glossary of Symbols

The following symbols may have been used in the labeling of this product.

Do Not Reuse	Upper Limit of Temperature	Range
Use by or Expiration Date (Year-Month-Day)	Lower Limit of Temperature	Range of Means
LOT Batch Code or Lot Number	Temperature Limitation	Midpoint
SN Serial Number	Consult Instructions for Use	Revised
REF Catalog Number or Product Code	Attention: The Instructions for Use (IFU) has been updated	Supersedes
Caution	S1 For use in Slide Supply 1	Σ Contains Sufficient for "n" Tests
Keep Dry (Protect from Moisture/Humidity)	S2 For use in Slide Supply 2	IVD *in vitro* Diagnostic Medical Device
Manufacturer	SI SI Units	Der Grüne Punkt (the Green Dot). Manufacturer follows certain packaging material waste disposal management regulations
Date of Manufacture	CONV Conventional Units	σ Estimated within-lab SD
EC REP Authorized Representative in the European Community	Value	
Corrosive	Flammable	Serious Health Hazards
Health Hazards	Acute Toxicity	Environmental or Aquatic Toxicity

Revision History

Date of Revision	Version	Description of Technical Changes*
2020-04-10	10.0	• Warnings and Precautions: updated Hazard and Precaution Statements to align with the new Safety Data Sheets

* The change bars indicate the position of a technical amendment to the text with respect to the previous version of the document.

When this Instructions For Use is replaced, sign and date below and retain as specified by local regulations or laboratory policies, as appropriate.

Signature

Obsolete Date

Conditions of supply: all supplies are made subject to the standard terms and conditions of Ortho Clinical Diagnostics or its distributors. Copies of these are available on request.

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