VITROS Products Immunodiagnostic

INSTRUCTIONS FOR USE

Ferr

VITROS Immunodiagnostic Products Ferritin Reagent Pack

REF 835 6636

VITROS Immunodiagnostic ProductsFerritin Calibrators

REF 115 8864

Rx ONLY

Intended Use

For *in vitro* diagnostic use only.

VITROS Immunodiagnostic Products Ferritin Reagent Pack

For the quantitative measurement of ferritin in human serum and plasma (heparin) using the VITROS ECi/ECiQ/3600 Immunodiagnostic Systems and the VITROS 5600/XT 7600 Integrated Systems. Measurements of ferritin aid in the diagnosis of diseases affecting iron metabolism such as hemachromatosis (iron overload) and iron deficiency anemia.

VITROS Immunodiagnostic Products Ferritin 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 ferritin in human serum and plasma (heparin).

Summary and Explanation of the Test

Ferritin functions as an intracellular site of iron storage. Clinically significant concentrations are found in serum, and the concentration of serum ferritin is directly related to total body iron stores. [1] Serum ferritin concentrations are determined to evaluate iron stores in normal patients, patients with iron deficiency and iron overload, and to monitor the response to iron therapy. The clinical use of the ferritin measurements have been extensively reviewed. [1-6]

Principles of the Procedure

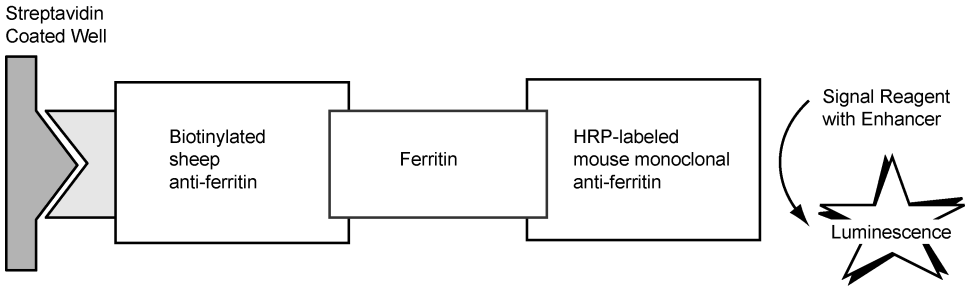
A two-step immunometric technique is used, which involves the reaction of ferritin present in the sample with a biotinylated antibody (sheep polyclonal anti-ferritin) in the first step. The antigen-antibody complex is captured by streptavidin coated on the well. Unbound materials are removed by washing. The second step involves the reaction of antigen-antibody complex with a horseradish peroxidase (HRP)-labeled antibody conjugate (mouse monoclonal anti-ferritin). Unbound materials are removed by washing.

The bound HRP conjugate is measured by a luminescent reaction. [7] 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 ferritin present.

Test Type	System *	Incubation Time	Time to first result	Test Temperature	Reaction Sample Volume
Immunometric	ECi/ECiQ, 3600, 5600, XT 7600	32 minutes	42 minutes	37 °C	15 µL

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

Reaction Scheme



Warnings and Precautions

WARNING: Potentially Infectious Material

Human blood products provided as components of the VITROS Ferritin Calibrators have been obtained from donors who were tested individually and who were found to be negative for hepatitis B surface antigen, and for antibodies to human immunodeficiency virus (HIV 1+2) and hepatitis C virus (HCV), using approved methods (enzyme immunoassays). Treat as if capable of transmitting infection.

Use caution when handling material of human origin. Consider all samples potentially infectious. No test method can offer complete assurance that hepatitis B virus, HCV, 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). [8]

WARNING: Contains ProClin 300 (CAS 55965-84-9) [9]

The VITROS Ferritin Reagent Pack contains 0.5% ProClin 300. H317: May cause an allergic skin reaction. P280: Wear protective gloves/protective clothing/eye protection/face protection. P302 + P352: IF ON SKIN: Wash with plenty of soap and water. P333 + P313: If skin irritation or rash occurs: Get medical advice/attention. P363: Wash contaminated clothing before reuse.

WARNING

WARNING: Contains Kathon or ProClin 150 (CAS 55965-84-9) [9]

The VITROS Ferritin Calibrator contains 1.0% Kathon or ProClin 150. H317: May cause an allergic skin reaction. P280: Wear protective gloves/protective clothing/eye protection/face protection. P302 + P352: IF ON SKIN: Wash with plenty of soap and water. P333 + P313: If skin irritation or rash occurs: Get medical advice/attention. P363: Wash contaminated clothing 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)
- 19.4 mL biotinylated antibody reagent (biotin-sheep polyclonal anti-ferritin, binds ≥130 ng ferritin/mL) in buffer with bovine serum albumin, bovine gamma globulin and antimicrobial agent
- 19.4 mL conjugate reagent (HRP-mouse monoclonal anti-ferritin, 0.1 µg/mL) in buffer with bovine serum albumin 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 Ferritin 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

- 3 sets of VITROS Ferritin Calibrators 1, 2 and 3 (freeze-dried, human spleen ferritin in human plasma with antimicrobial agent, reconstitution volume 1.0 mL); nominal values 4.5; 90 and 800 ng/mL
- Lot calibration card
- Protocol card
- 24 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-reconstituted	Refrigerated	2–8 °C (36–46 °F)	≤13 weeks
Opened-reconstituted	Frozen	≤-20 °C (≤-4 °F)	≤13 weeks

- VITROS Ferritin Calibrators are supplied freeze-dried.
- VITROS Ferritin 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.

- Reconstitute with 1.0 mL distilled water.
- Opened, reconstituted calibrators may be stored frozen (with no more than 1 freeze-thaw cycle).
- The VITROS Ferritin test uses 15 µL of calibrator for each determination. 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
- Heparin plasma

Note:	Heparin plasma samples show approximately 15% negative bias when compared to matched serum samples.

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. [10] 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. [11- 12]
- Thoroughly mix samples by inversion and bring to 15–30 °C (59–86 °F) before use.
- The VITROS Ferritin test uses 15 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 samples may be stored for up to 5 days at 2–8 °C (36–46 °F) or 4 weeks at -20 °C (-4 °F).
- Avoid repeated freeze-thaw cycles of serum samples.
- Plasma (heparin) samples may be stored for up to 5 days at 2–8 °C (36–46 °F).
- Do not freeze plasma (heparin) samples.

Testing Procedure

Materials Provided

- VITROS Immunodiagnostic Products Ferritin Reagent Pack
- VITROS Immunodiagnostic Products Ferritin Calibrators

Materials Required but Not Provided

- VITROS Immunodiagnostic Products Signal Reagent
- VITROS Immunodiagnostic Products Universal Wash Reagent
- VITROS Immunodiagnostic Products High Sample Diluent B
- Quality control materials such as VITROS Immunodiagnostic Products Anemia Controls
- VITROS Immunodiagnostic Products Reagent Pack Storage Box (optional) with desiccant
- Calibrated pipette, distilled water and sample containers for reconstitution of VITROS Ferritin Calibrators

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

Serum samples with concentrations greater than the measuring range may be automatically diluted on the system up to 10-fold (1 part sample with 9 parts diluent) by the VITROS Immunodiagnostic and VITROS Integrated Systems with the VITROS High Sample Diluent B Reagent Pack prior to test. Refer to the VITROS High Sample Diluent B Reagent Pack instructions for use.

Default Test Name

The default test name which will appear on patient reports is Ferritin. The default short name that will appear on the test selection menus and laboratory reports is Ferr. 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 Ferritin test is traceable to in-house reference calibrators which have been value assigned to correlate to another commercially available test.

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	1.25*–1000 ng/mL

* 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 Anemia Controls are recommended for use with the VITROS Immunodiagnostic and VITROS Integrated Systems. The VITROS Anemia Controls contain 3 levels of ferritin (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 ferritin 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 Ferritin 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. [13]

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

Analyte results are quoted in units of ng/mL.

Limitations of the Procedure

Known Interferences

The VITROS Ferritin test was evaluated for interference consistent with CLSI document EP7. [14] Commonly encountered substances were tested on 2 lots of reagents. Of the compounds tested, none was found to cause a bias of >10%. Refer to "Specificity" for a list of compounds tested that did not show interference.

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.
- Certain drugs and clinical conditions are known to alter ferritin concentrations *in vivo*. For additional information, refer to one of the published summaries. [15-17]
- The VITROS Ferritin test has no high dose hook effect up to 93,093 ng/mL.

- Heterophilic antibodies in the serum or plasma of certain individuals are known to cause interference with immunoassays. [18] 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.
- Biotin levels in serum remain elevated for up to 24 hours after oral or intravenous biotin administration. [19]

Expected Values and Interpretation of Results

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

Category	Number of Subjects	Units = ng/mL	
		Range	Median
Normal male	310	17.9–464	96.2
Normal female <50 years of age	152	6.24–137	29.7
Normal female ≥50 years of age	98	11.1–264	48.7

Each of these reference intervals are the central 95% of results of a study of serum samples from the following populations; normal males, normal females less than 50 years of age, and normal females 50 years of age or over.

- An observed range of 2.83–30.7 ng/mL ferritin was obtained from 46 subjects with iron deficiency.
- A range of 382–6111 ng/mL ferritin was obtained from 43 subjects with iron overload.

Interpretation of Results

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

Performance Characteristics

Limit of Detection

The Limit of Detection (LoD) for VITROS Ferritin is 1.25 ng/mL, determined consistent with NCCLS document EP17 [20] and with proportions of false positives (α) less than 5% and false negatives (β) less than 1%; based on 794 determinations, with 4 blank and 4 low-level samples. The Limit of Blank (LoB) is 0.00 ng/mL.

Limit of Blank and Limit of Detection

LoB*	LoD**
ng/mL	ng/mL
0.00	1.25

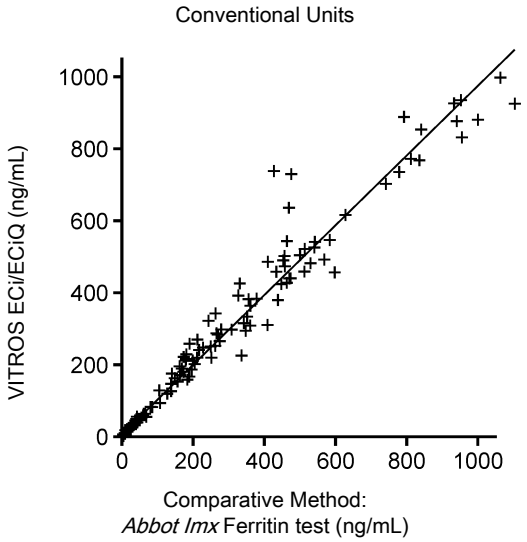
* Limit of Blank, or the highest value likely to be observed with a sample containing no analyte, replaces the term "analytical sensitivity."

** Proportions of false positives (α) and false negatives (β) were less than 5% and 1% respectively; based on 700 determinations, with 1 blank and 5 low-level samples.

Accuracy (Method Comparison)

Accuracy was evaluated consistent with NCCLS document EP9. [21] 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 *Abbot Imx* Ferritin test. The relationship between the 2 methods was determined by Deming regression. [22]

The table also shows the results of method comparison studies [23] 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. [24]



System	n	Slope	Correlation Coefficient	Conventional Units (ng/mL) Range of Samples	Conventional Units (ng/mL) Intercept
ECi/ECiQ vs. Comparative Method	130	0.974	0.979	2–997	10.7
3600 vs. ECi/ECiQ	109	0.972	0.995	6.58–977	2.11
5600* vs. ECi/ECiQ	109	0.977	0.996	6.58–977	2.63

* 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 Protocol EP5. [25] 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. [26] Two replicates each of 3 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 = ng/mL							No. Observ.	No. Days
	Mean ferritin Result	Within-run*		Within-calibration**		Within-lab***			
		SD	CV (%)	SD	CV (%)	SD	CV (%)		
ECi/ECiQ system 1	10.7	0.132	1.2	0.476	4.4	0.507	4.7	80	20
	160	2.29	1.4	8.49	5.3	8.40	5.3	80	20
	474	10.0	2.1	24.5	5.2	25.1	5.3	80	20
ECi/ECiQ system 2	10.6	0.205	1.9	0.484	4.6	0.467	4.4	80	20
	166	3.43	2.1	7.64	4.6	11.4	6.9	80	20
	507	9.00	1.8	24.5	4.8	52.5	10.4	80	20
3600	9.49	0.330	3.5	0.364	3.8	0.414	4.4	88	22
	149	4.62	3.1	6.05	4.1	6.83	4.6	88	22
	454	15.8	3.5	17.6	3.9	19.7	4.4	88	22
5600****	9.78	0.242	2.5	0.273	2.8	0.348	3.6	88	22
	149	4.46	3.0	5.41	3.6	6.06	4.1	88	22
	445	16.6	3.7	18.6	4.2	17.5	3.9	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 Ferritin test was evaluated for interference consistent with CLSI document EP7. [14] Of the compounds tested, none was found to cause a bias of >10% with the test at the concentrations indicated at ferritin concentrations of 10.4–11.9 ng/mL.

Compound	Concentration	
Bilirubin	0.342 mmol/L	20 mg/dL
Biotin	40.9 nmol/L	1.0 µg/dL
Hemoglobin*	0.31 mmol/L	500 mg/dL
Triolein	33.9 mmol/L	3000 mg/dL

* Hemolysate was added to a series of specimens with VITROS Ferritin concentrations of 11.9– 75.4 ng/mL.

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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	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	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*
2019-09-06	10.1	• Glossary of Symbols: updated • Added EC Representative address
2018-03-20	10.0	• Added information for the VITROS XT 7600 Integrated System • Updated data: – Measuring (Reportable) Range – Limit of Detection • Minor formatting and wording updates • References: updated • Glossary of Symbols: updated

* 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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