

INSTRUCTIONS FOR USE

CA199

VITROS Immunodiagnostic Products
CA 19-9™ Reagent Pack

REF 680 0040

VITROS Immunodiagnostic Products
CA 19-9™ Calibrators

REF 680 0035

Intended Use

For *in vitro* diagnostic use only.

VITROS Immunodiagnostic Products CA 19-9 Reagent Pack

For the quantitative measurement of 1116-NS-19-9 defined antigen 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 CA 19-9 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 1116-NS-19-9 defined antigen in human serum and plasma (EDTA or heparin).

Summary and Explanation of the Test

The 1116-NS-19-9 antibody defines an epitope on a glycolipid, sialo-lacto-N fucopentaose II ganglioside expressed by a wide variety of malignant tumor tissues. In serum, the antigen appears associated with a mucin. Although certain bodily secretions provide high CA 19-9 test levels, the concentration in the blood of normal subjects or patients with benign disorders is very low. ¹ Elevated CA 19-9 levels in blood, however, are seen in most patients with pancreatic cancer or other gastrointestinal malignancies. ²⁻⁵

Using a cutoff value of 37–40 U/mL the CA 19-9 test provides a sensitivity of 82% and a specificity of 90% for the early detection of pancreatic cancer. As with other tumor marker tests, the clinical sensitivity decreases and the specificity increases when higher cutoff values are used. For a cutoff value of 100 U/mL, the sensitivity and specificity for pancreatic cancer is 68% and 98%, respectively. ⁶ The combination of CA 19-9 test results with computed tomography (CT) or ultrasound imaging increases the effectiveness in the early detection of malignancies even further. ⁷ After surgery, CA 19-9 levels can help prognosticate survival and, when used serially, help predicting recurrence of disease prior to radiographic or clinical findings. ⁶

Principles of the Procedure

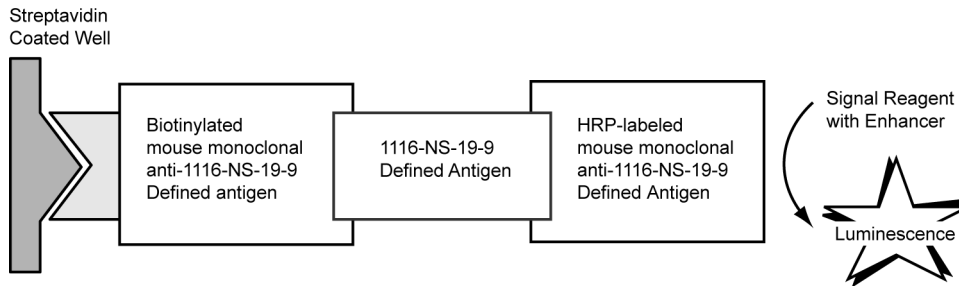
An immunometric technique is used, 1116-NS-19-9 defined antigen present in the sample reacts with a biotinylated antibody (mouse monoclonal anti-1116-NS-19-9 defined antigen). The antigen-antibody complex is captured by streptavidin on the wells. Unbound materials are removed by washing. In a second incubation a horseradish peroxidase (HRP)-labeled antibody conjugate (mouse monoclonal anti-1116-NS-19-9 defined antigen) binds to the immobilized 1116-NS-19-9 defined antigen. 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 1116-NS-19-9 defined antigen present.

Test Type	System *	Incubation Time	Time to first result	Test Temperature	Reaction Sample Volume
Immunometric immunoassay	ECi/ECiQ, 3600, 5600, XT 7600	32 minutes	42 minutes	37 °C	35 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 ProClin 300 (CAS 55965-84-9)¹⁰

The VITROS CA 19-9 Reagent Pack contains 1% 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.

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)
 - 20.0 mL conjugate reagent (HRP-mouse monoclonal anti-1116-NS-19-9 defined antigen, binds ≥ 336 U 1116-NS-19-9 defined antigen/mL) in buffer with bovine serum albumin, bovine gamma globulin and antimicrobial agent
 - 13.4 mL biotinylated antibody reagent (biotin-mouse monoclonal anti-1116-NS-19-9 defined antigen, binds ≥ 559 U 1116-NS-19-9 defined antigen/mL) in buffer with bovine serum, bovine gamma globulin 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 onto the system.
- Handle the reagent pack with care. Avoid the following:
 - allowing condensation to form on the pack
 - causing reagents to foam
 - agitation of the pack

INSTRUCTIONS FOR USE

Specimen Collection, Preparation and Storage

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 CA 19-9 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 CA 19-9 Calibrators 1, 2, and 3 (1116-NS-19-9 defined antigen in buffer with bovine serum albumin and antimicrobial agent, 1.75 mL); nominal values 15; 60 and 700 U 1116-NS-19-9 defined antigen/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	Refrigerated	2–8 °C (36–46 °F)	≤13 weeks
Opened	Frozen	≤-20 °C (≤-4 °F)	≤13 weeks

- VITROS CA 19-9 Calibrators are supplied ready for use.
- The VITROS CA 19-9 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 CA 19-9 test uses 35 µL of calibrator for each determination. The VITROS CA 19-9 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
- Heparin plasma
- EDTA plasma

Specimens Not Recommended

- Do not use turbid specimens. Turbidity in specimens may affect test results.
- Do not use hemolyzed specimens as hemolysis 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 CA 19-9 test uses 35 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 7 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 CA 19-9 Reagent Pack
- VITROS Immunodiagnostic Products CA 19-9 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
- 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

Serum or plasma (EDTA or heparin) samples with concentrations greater than the measuring range may be automatically diluted on the system up to 20-fold (1 part sample with 19 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 CA 19-9. The default short name that will appear on the test selection menus and laboratory reports is CA199. 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 CA 19-9 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	1.4 [*] –1000 U/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

Controls containing suitable levels of 1116-NS-19-9 defined antigen are recommended for use with the VITROS Immunodiagnostic and VITROS Integrated Systems. The performance of commercial controls 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 CA 19-9 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 CA 19-9 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 per 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 U/mL.

Limitations of the Procedure

Known Interferences

The VITROS CA 19-9 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, hemoglobin may interfere with the VITROS CA 19-9 test. At a CA 19-9 concentration of 17.4 U/mL*, hemoglobin at 1.7, 3.4 and 6.8 g/L caused a positive bias of <1%, 14% and 35%***, respectively.

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

** Estimate of the average difference observed.

Refer to "Specificity" for a list of other compounds tested that did not show interference (Bias <10%).

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.
- Because of the close relationship between the 1116-NS-19-9 defined antigen and the Lewis blood group antigen system, it appears that the Lewis antigen gene is required for the expression of the 1116-NS-19-9 defined antigen.
- Different test methods cannot be used interchangeably. 1116-NS-19-9 defined antigen in a given patient sample determined with different tests and from different manufacturers can vary due to differences in test methods and reagent specificity. A change to the test used during serial monitoring of a patient should be accompanied by additional sequential testing to confirm baseline values. The results reported by the laboratory to the physician must include the identity of the CA 19-9 test used.
- Serial test results obtained with the VITROS CA 19-9 test, in patients who are clinically free of disease, should be used in conjunction with all relevant information derived from diagnostic tests, physical examination, and full medical history in accordance with appropriate patient management procedures used for early detection of recurrence.
- Heterophilic antibodies in serum or plasma samples may cause interference in 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.
- Biotin levels in serum remain elevated for up to 24 hours after oral or intravenous biotin administration.
- The VITROS CA 19-9 test has no high dose hook effect up to 965,000 U/mL.
- Certain drugs and clinical conditions are known to alter CA 19-9 concentrations *in vivo*. For additional information, refer to one of the published summaries. ¹⁷⁻¹⁹

Expected Values and Interpretation of Result

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

As a guide, 97% of the VITROS CA 19-9 test values in a study of 200 samples from normal subjects were found to be 37 U/mL or less. Of 50 samples from patients with pancreatic cancer, 35 samples had VITROS CA 19-9 test values above 37 U/mL.

Distribution of VITROS CA 19-9 test values

	N	≤37	37.1–70	>70
Normal Subjects	200	194	6	0
Non-Malignant Conditions				
Colorectal	30	27	2	1
Cirrhosis	67	59	2	6
Non-GI	40	36	4	0
H. Pylori	50	46	4	0
Malignant Disease				
Pancreatic	50	15	2	33
Colorectal	100	49	8	43
Stomach	30	19	1	10
Lung	50	31	7	12

Units = U/mL

Interpretation of Results

For patient sample values outside the reference range a flag 'HI' will be displayed. Control values will be flagged when ≥ 2 SDs from the defined baseline mean.

Performance Characteristics

Limit of Detection

The Limit of Detection (LoD) for VITROS CA 19-9 is 1.4 U/mL, determined consistent with NCCLS document EP17²⁰ and with proportions of false positives (α) less than 5% and false negatives (β) less than 5%; based on 270 determinations, with 2 blank and 5 low-level samples. The Limit of Blank (LoB) is 1.05 U/mL.

Limit of Blank and Limit of Detection

LoB*	LoD**
U/mL	U/mL
1.05	1.4

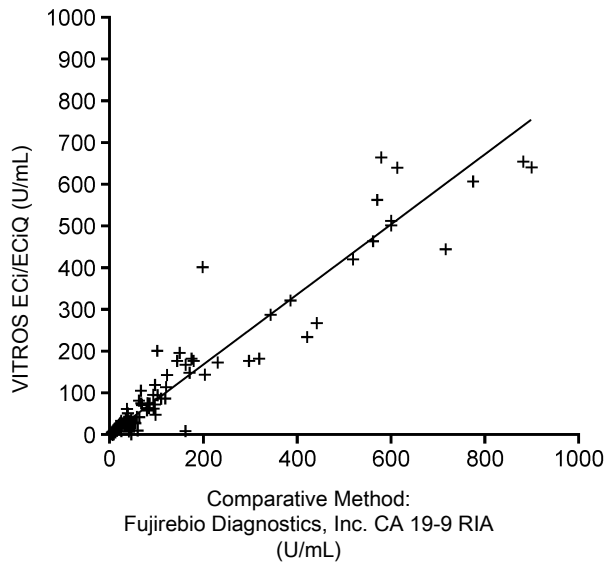
* Limit of Blank, or the highest value likely to be observed with a sample containing no analyte, replaces the term "analytical sensitivity."

** Proportions of false positives (α) and false negatives (β) were less than 5%; based on 270 determinations, with 2 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 serum samples from a variety of clinical categories analyzed on the VITROS ECi/ECiQ Immunodiagnostic System compared with those analyzed using the Fujirebio Diagnostics, Inc. CA 19-9 RIA test. The relationship between the 2 methods was determined by Passing and Bablok regression.²²

The table also shows the results of method comparison studies²³ 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.²²



System	n	Slope	Correlation Coefficient	Conventional Units (U/mL)	
				Range of Samples	Intercept
ECi/ECiQ vs. Comparative Method	292	0.991	0.931	0.0–970	-3.01
3600 vs. ECi/ECiQ	109	1.00	1.00	3.75–994	-0.500
5600* vs. ECi/ECiQ	106	1.01	1.00	3.75–994	-0.612

* 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 EP5.²⁴ Two replicates each of 3 pools of patient serum 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 EP5.²⁵ 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 1 reagent lot on each system. The data presented are a representation of the product performance.

System	Units = U/mL							No. Observ.	No. Days
	Mean CA 19-9 Conc.	Within-run*		Within-calibration**		Within-lab***			
		SD	CV (%)	SD	CV (%)	SD	CV (%)		
ECi/ECiQ system 1	30.9	0.383	1.2	0.970	3.1	1.06	3.4	80	20
	98.0	0.884	0.9	2.55	2.6	2.54	2.6	80	20
	236	1.97	0.8	6.87	2.9	6.75	2.9	80	20
ECi/ECiQ system 2	28.9	0.309	1.1	1.23	4.3	1.50	5.2	80	20
	90.2	1.18	1.3	3.50	3.9	4.41	4.9	80	20
	238	2.94	1.2	9.85	4.1	11.3	4.7	80	20
3600	20.0	0.277	1.4	1.06	5.3	0.805	4.0	88	22
	67.9	0.712	1.0	3.04	4.5	2.52	3.7	88	22
	283	3.17	1.1	13.7	4.8	10.1	3.6	88	22
5600****	19.5	0.174	0.9	0.986	5.1	1.11	5.7	88	22
	67.7	0.795	1.2	2.89	4.3	3.29	4.9	88	22
	282	2.70	1.0	12.2	4.3	13.2	4.7	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 CA 19-9 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 CA 19-9 concentrations of 23.3–26.1 U/mL.

Compound	Concentration	
Bilirubin	20 mg/dL	0.342 mmol/L
Biotin	1 µg/dL	40.9 nmol/L
Triolein	2000 mg/dL	22.6 mmol/L

References

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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
	Batch Code or Lot Number		Temperature Limitation		Midpoint
	Serial Number		Consult Instructions for Use		Revised
	Catalog Number or Product Code		Attention: The Instructions for Use (IFU) has been updated		Supersedes
	Caution		For use in Slide Supply 1		Contains Sufficient for "n" Tests
	Keep Dry (Protect from Moisture/Humidity)		For use in Slide Supply 2		<i>in vitro</i> Diagnostic Medical Device
	Manufacturer		SI Units		Der Grüne Punkt (the Green Dot). Manufacturer follows certain packaging material waste disposal management regulations
	Date of Manufacture		Conventional Units		Estimated within-lab SD
	Authorized Representative in the European Community		Value		Serious Health Hazards
	Corrosive		Flammable		Environmental or Aquatic Toxicity
	Health Hazards		Acute Toxicity		

Revision History

Date of Revision	Version	Description of Technical Changes*
2019-09-06	8.1	<ul style="list-style-type: none"> Glossary of Symbols: updated Added EC Representative address
2017-09-27	8.0	<ul style="list-style-type: none"> Added information for the VITROS XT 7600 Integrated System 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.

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