VITROS Products Chemistry

INSTRUCTIONS FOR USE

VALP

VITROS Chemistry Products VALP Reagent

Valproic Acid

REF 680 1710

Rx ONLY

Intended Use

For *in vitro* diagnostic use only.

VITROS Chemistry Products VALP Reagent is used on the VITROS 5,1 FS Chemistry System, the VITROS 4600 Chemistry System and the VITROS 5600 Integrated System to quantitatively measure valproic acid (VALP) concentration in human serum and plasma.

Summary and Explanation of the Test

Valproic acid is used as sole or adjunctive therapy in the treatment of simple and complex absence seizures, and adjunctively in patients with multiple seizure types, which include absence seizures. [1] High concentrations of valproic acid may lead to central nervous system depression, tremor, and thrombocytopenia. Very high concentrations of valproic acid may also increase the risk of developing fatal hepatotoxicity, stupor, coma, or cerebral edema. [2] Valproic acid is extensively metabolized by the liver. Other coadministered drugs, including other antiepileptics, may induce or inhibit the drug metabolizing enzymes of the liver. When these drugs are added or removed from the therapeutic regimen of a patient, the clearance and concentration of valproic acid may be altered, requiring dosage adjustment. [2] Serum or plasma valproic acid measurements are used in the diagnosis and treatment of valproic acid overdose and in monitoring levels of valproic acid to ensure appropriate therapy.

Principles of the Procedure

The VITROS VALP assay is performed using the VITROS Chemistry Products VALP Reagent in conjunction with the VITROS Chemistry Products Calibrator Kit 12 on the VITROS 5,1 FS/4600 Chemistry Systems and the VITROS 5600 Integrated System.

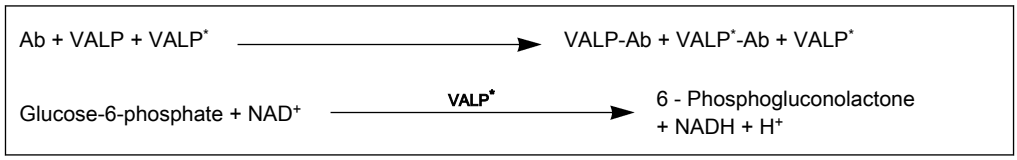
The VITROS VALP Reagent is a dual chambered package containing ready-to-use liquid reagents that are used in a two-step reaction to quantitatively measure valproic acid. Test sample is added to Reagent 1 containing antibody reactive to valproic acid, glucose-6-phosphate and nicotinamide adenine dinucleotide (NAD), followed by Reagent 2 containing valproic acid labeled with the enzyme glucose-6-phosphate dehydrogenase (G6P-DH). The assay is based on competition between valproic acid in the sample and valproic acid labeled with G6P-DH for antibody binding sites. G6P-DH activity decreases upon binding to the antibody, so valproic acid concentration in the sample can be measured in terms of G6P-DH activity. G6PDH converts NAD^+ to NADH, resulting in an absorbance change that is measured spectrophotometrically at 340 nm. Endogenous serum G6P-DH does not participate in the reaction since NAD^+ functions only with the bacterial (Leuconostoc mesenteroides) enzyme conjugate employed in the assay. Once a calibration has been performed for each reagent lot, the valproic acid concentration in each unknown sample can be determined using the stored calibration curve and the measured absorbance obtained in the assay of the sample.

Test Type and Conditions

Test Type	VITROS System	Approximate Incubation Time	Temperature	Wavelength	Reaction Sample Volume
Two-point Rate	5600, 4600, 5,1 FS	Incubation 1: 5 minutes Incubation 2: 4 minutes	37 °C (98.6 °F)	340 nm	3 µL

Not all products and systems are available in all countries.

Reaction Scheme



VALP* = Valproic acid/Glucose-6-Phosphate-dehydrogenase conjugate

Warnings and Precautions

For *in vitro* diagnostic use only.

WARNING: *Contains 5-chloro-2-methyl-3(2h)-isothiazolone mixt. with 2-methyl-3(2h)-isothiazolone (CAS 55965-84-9)*[3]

VITROS VALP Reagent 1 contains 5-chloro-2-methyl-3(2h)-isothiazolone mixt. with 2-methyl-3(2h)-isothiazolone. H317: May cause an allergic skin reaction. P280: Wear protective gloves/protective clothing/eye protection/face protection. P272: Contaminated work clothing should not be allowed out of the workplace. P302 + P352: IF ON SKIN: Wash with plenty of soap and water. P333 + P313: If skin irritation or rash occurs: Get medical advice/attention. P501: Dispose of contents/ container to an approved incineration plant.

Refer to www.orthoclinical.com for the Safety Data Sheets and for OCD contact information.

WARNING

WARNING: *This product contains bovine blood components and should be handled using the same precautions as with any other blood or blood-derived product.*

WARNING: *This product contains sodium azide. Disposal of product into sinks with copper or lead plumbing should be followed with plenty of water to prevent formation of potentially explosive metallic azides.*

WARNING: *Take care when handling materials and samples of human origin. Since no test method can offer complete assurance that infectious agents are absent, consider all clinical specimens, controls, and calibrators potentially infectious. Handle specimens, solid and liquid waste, and test components in accordance with local regulations and CLSI Guideline M29*[4] *or other published biohazard safety guidelines.*

For specific warnings and precautions for calibrators, quality control materials, and other components, refer to the Instructions for Use for the appropriate VITROS product, or to other manufacturer's product literature.

Reagents

Reactive Ingredients

Reagent 1 (R1): Mouse monoclonal antibodies reactive to valproic acid 30,125 pg/mL; nicotinamide adenine dinucleotide (NAD) 18 mM; glucose-6-phosphate (Na-G6P) 22 mM

Reagent 2 (R2): Valproic acid labeled with glucose-6-phosphate dehydrogenase (G6P-DH, EC 1.1.1.49, from Leuconostoc mesenteroides) 0.57 pg/mL

Other Ingredients

Reagent 1 (R1): Inorganic salt, organic salt, proteins, protease inhibitor, stabilizer, surfactant, preservative, displacing agent

Reagent 2 (R2): Buffers, inorganic salt, organic salt, proteins, protease inhibitor, biological material (mouse monoclonal antibody), preservatives

Reagent Handling

Caution: **Do not use reagent packs with damaged or incompletely sealed packaging.**

- Inspect the packaging for signs of damage.
- Be careful when opening the outer packaging with a sharp instrument so as to avoid damage to the individual product packaging.
- The reagents are liquid and ready for use.
- Avoid agitation, which may cause foaming or the formation of bubbles.

Reagent Preparation

1. Remove from refrigerated storage.
2. Immediately load into Supply 3.

IMPORTANT: *Do not loosen or remove caps prior to loading.*

Reagent Storage and Stability

VITROS Chemistry Products VALP Reagents are stable until the expiration date on the carton when it is stored and handled as specified. Do not use beyond the expiration date.

IMPORTANT: *Do not freeze.*

Reagent	Storage Condition		Stability
Unopened	Refrigerated	2–8 °C (36–46 °F)	Until expiration date
Opened	**5,1 FS:** On-analyzer	System turned on	≤ 7 days
	4600/5600: On-analyzer	System turned on	≤ 28 days
	On-analyzer	System turned off	≤ 30 minutes

IMPORTANT: *In order to ensure the established stability for open (in use) packs, VITROS Chemistry Products VALP Reagent packs must not be transferred from the VITROS 5,1 FS Chemistry System to either the VITROS 4600 Chemistry System or the VITROS 5600 Integrated System.*

Verify performance with quality control materials:

- If the system is turned off for more than 30 minutes.
- After reloading reagents that have been removed from Supply 3 and stored for later use.

Specimen Collection, Preparation and Storage

Specimens Recommended

- Serum
- Plasma:
  - Heparin
  - EDTA

IMPORTANT: *Certain collection devices have been reported to affect other analytes and tests*[5]*. 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.*

Specimens Not Recommended

Plasma:

- Fluoride oxalate
- Citrate

Serum and Plasma

Specimen Collection and Preparation

Collect specimens using standard laboratory procedures.[6, 7]

Note: For details on minimum fill volume requirements, refer to the operating instructions for your system.

Patient Preparation

- Pharmacokinetic factors including dosage form, mode of administration and biological variation can influence the appropriate time of sample collection following administration of valproic acid. [8]
- Valproic acid monitoring is most appropriate when the blood sample is drawn after steady-state conditions have been reached (after 4–5 half-lives on an unchanged dose regimen). [9]
- For patients receiving valproic acid orally the blood sample should be drawn immediately before the next dose because of its short half-life. [8]
- Valproic acid samples should be monitored at a consistent time of day because concentration is affected by circadian rhythm. [9]

Special Precautions

- For EDTA plasma, specimens must be collected in tubes that are at least half full. Smaller volumes can result in negative biases.
- Centrifuge specimens and remove the serum or plasma from the cellular material within 4 hours of collection. [10]
- Each lab should evaluate the suitability of serum separators or any blood collection device before use in therapeutic drug monitoring. [11]

Specimen Handling and Storage

- Handle and store specimens in stoppered containers to avoid contamination and evaporation.
- Mix samples by gentle inversion and bring to room temperature, 18–28 °C (64–82 °F), prior to analysis.

Specimen Storage and Stability

Storage	Temperature	Stability
Room Temperature	18–28 °C (64–82 °F)	≤ 1 Day
Refrigerated	2–8 °C (36–46 °F)	≤ 14 Days
Frozen	≤-20 °C (≤-4 °F)	≤ 14 Days

Testing Procedure

Materials Provided

VITROS Chemistry Products VALP Reagent

Materials Required but Not Provided

- VITROS Chemistry Products Calibrator Kit 12
- Quality control materials, such as VITROS Chemistry Products TDM Performance Verifiers I, II, and III
- VITROS Chemistry Products FS Diluent Pack 2 (BSA/Saline)

Operating Instructions

- Check reagent inventories at least daily to ensure that quantities are sufficient for the planned workload.
- For additional information, refer to the operating instructions for your system.

IMPORTANT: *Bring all fluids and samples to room temperature, 18–28 °C (64–82 °F), prior to analysis.*

Sample Dilution

If VALP concentrations exceed the system's measuring (reportable) range:

Manual Sample Dilution

1. Dilute sample with 7% Bovine Serum Albumin (BSA) using VITROS Chemistry Products FS Diluent Pack 2 (BSA/Saline). Samples may be diluted up to 1 part sample with 3 parts 7% BSA.
2. Multiply the results by the dilution factor to obtain an estimate of the original sample's VALP concentration.

IMPORTANT: *If using the system in On-Analyzer Dilution Mode, do not manually dilute samples for analysis. Refer to the operating instructions for your system for more information on the On-Analyzer Dilution Procedure.*

On-Analyzer Sample Dilution

Refer to the operating instructions for your system for more information on the On-Analyzer Dilution Procedure. Use VITROS Chemistry Products FS Diluent Pack 2 (BSA/Saline) for the dilution.

Calibration

Required Calibrators

VITROS Chemistry Products Calibrator Kit 12

Calibrator Preparation, Handling, and Storage

Refer to the Instructions for Use for VITROS Chemistry Products Calibrator Kit 12.

Calibration Procedure

Refer to the operating instructions for your system.

When to Calibrate

Calibrate:

- When the reagent lot number changes.
- When critical system parts are replaced due to service or maintenance.
- When government regulations require.
  For example, in the USA, CLIA regulations require calibration or calibration verification at least once every six months.

The VITROS VALP assay may also need to be calibrated:

- If quality control results are consistently outside acceptable range.
- After certain service procedures have been performed.

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

Calculations

Absorbance is measured at 340 nm after a fixed incubation time. Once a calibration has been performed for each reagent lot, valproic acid concentration in the unknown samples can be determined using the stored calibration curve and the measured absorbance obtained in the assay of each sample.

Validity of a Calibration

Calibration parameters are automatically assessed by the system against a set of quality parameters detailed in the Review Assay Data screen (found via Options → Review/Edit Calibrations → Review Assay Data). Failure to meet any of the pre-defined quality parameters results in a failed calibration. The calibration report should be used in conjunction with quality control results to determine the validity of a calibration.

Measuring (Reportable) Range

Conventional Units (µg/mL)	SI Units (µmol/L)
10.0–150.0	69.3–1039.5

For out-of-range samples, refer to “Sample Dilution.”

Traceability of Calibration

The values assigned to the VITROS Chemistry Products Calibrator Kit 12 for valproic acid are traceable to the USP (U.S. Pharmacopoeia) valproic acid reference standard catalog #1708707 through gravimetric addition.

Quality Control

Quality Control Material Selection

IMPORTANT: *VITROS Chemistry Products TDM Performance Verifiers are recommended for use with the VITROS Chemistry and VITROS Integrated Systems. Evaluate the performance of other commercial control fluids for compatibility with this test before using for quality control.*

Control materials other than VITROS Chemistry Products TDM Performance Verifiers may show a difference when compared with other VALP methods if they:

- Depart from a true human matrix.
- Contain high concentrations of preservatives, stabilizers, or other non-physiological additives.

Quality Control Procedure Recommendations

- Choose control levels that check the clinically relevant range.

- Analyze quality control materials in the same manner as patient samples, before or during patient sample processing.
- To verify system performance, analyze control materials:
  - After calibration.
  - According to the appropriate local, state, federal or other government regulations or at least once each day that the test is being performed.
  - After specified service procedures are performed. Refer to the operating instructions for your system.
- If control results fall outside your acceptable range, investigate the cause before deciding whether to report patient results.
- For general quality control recommendations, refer to *Statistical Quality Control for Quantitative Measurements: Principles and Definitions; Approved Guideline–Third Edition*[12] or other published guidelines.
- For additional information, refer to the operating instructions for your system.

Quality Control Material Preparation, Handling, and Storage

Refer to the Instructions for Use for VITROS Chemistry Products TDM Performance Verifier I, II, and III or to other manufacturer's product literature.

Results

Reporting Units and Unit Conversion

The VITROS 5,1 FS/4600 Chemistry and VITROS Integrated Systems may be programmed to report VALP results in conventional, SI, or alternate units.

Conventional Units	SI Units	Alternate Units
µg/mL	µmol/L (µg/mL × 6.93)	mg/L (µg/mL × 1)

Limitations of the Procedure

Known Interferences

None identified.

Other Limitations

- Although the reagents contain a blocking agent for human anti-mouse antibody (HAMA), HAMA in some patient samples may interfere with the method.
- Under conditions where the combination of valproic acid concentration and sample turbidity yields an absorbance value that exceeds 3.0 AU, an analyzer condition code will be generated and the results suppressed. The sample should be diluted 1:2 (1 part 7% BSA and 1 part sample) and reanalyzed. Refer to the Sample Dilution section.
- Certain drugs and clinical conditions are known to alter valproic acid concentration *in vivo*. For additional information, refer to one of the published summaries.[13, 14]

Interpretation of Results and Expected Results

Interpretation of Results[2, 15, 16]

- Achieving and maintaining therapeutic concentrations of valproic acid is difficult due to inter- and intra-patient variability in pharmacokinetics.
- Valproic acid pharmacokinetics are affected by disease states or coadministered drugs that affect clearance or protein binding of valproic acid; age; alcohol and other central nervous system depressants; pregnancy; renal failure and liver disease or dysfunction.
- The concentration of valproic acid in serum or plasma depends on the time of the last drug dose and the time of sample collection.
- The therapeutic range concentrations depend on whether mono- or polytherapy is being used.
- The upper end of the therapeutic range for valproic acid is not well defined. The therapeutic endpoint is the abolition of seizures. The dose given to patients may continue to be increased in patients who do not experience side effects.
- The total measured serum or plasma concentration of valproic acid will increase linearly with dose up to the point of saturation of the protein binding sites. The unbound (free) concentration of valproic acid increases rapidly above this level. The free valproic acid fraction is metabolized rapidly so that total serum or plasma concentrations increase very little with increasing dose.

Expected Results

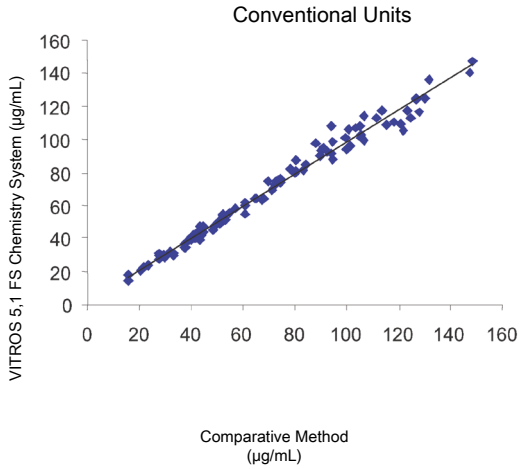
These guidelines represent a combination of the recommendations of the National Academy of Clinical Biochemistry and Jacobs, et al. [15, 16] Each laboratory should verify the validity of these recommendations for the population it serves.

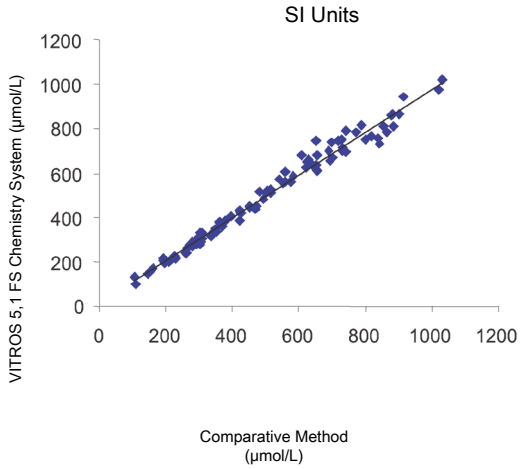
Classification	Conventional Units (µg/mL)	SI Units (µmol/L)	Alternate Units (mg/L)
Minimal	50.0	346.5	50.0
Therapeutic	50.0–120.0	346.5–831.6	50.0–120.0
Possible Toxic	> 100.0	693.0	> 100.0
Serious Toxic	> 200.0	1386.0	> 200.0

Performance Characteristics

Method Comparison

The plots and data below show the results of a method comparison study with serum samples analyzed on the VITROS 5,1 FS Chemistry System and a commercially available system, based on NCCLS Protocol EP9. [17]
In addition, the table shows the results of comparisons with serum and plasma samples on the VITROS 5600 Integrated System and the VITROS 5,1 FS Chemistry System. The testing followed NCCLS Protocol EP9. [17]





	n	Slope	Correlation Coefficient	Conventional Units (µg/mL) Range of Sample Conc.	Intercept	Sy.x	SI Units (µmol/L) Range of Sample Conc.	Intercept	Sy.x
5,1 FS† vs. comparative method*	96	0.969	0.992	14.3–147.1	1.3	4.24	99.2–1019.2	9.3	29.36
5600 vs. 5,1 FS†	110	0.98	0.994	14.0–142.5	0.7	3.37	97.0–987.5	4.9	23.35

* Syva® Emit® 2000 Valproic Acid Assay

† Analytical processing hardware and software algorithms on the VITROS 4600 Chemistry System are designed to the same specifications as those applied to the VITROS 5,1 FS Chemistry System. Assay performance on the VITROS 4600 System has been demonstrated to be comparable to that on the VITROS 5,1 FS System. All performance characteristics for VITROS 5,1 FS System are therefore applicable to the VITROS 4600 System.

Precision

Precision was evaluated with quality control materials on the VITROS 5,1 FS Chemistry System following NCCLS Protocol EP5. [18] Precision was also evaluated with quality control materials on the VITROS 5600 Integrated System following NCCLS Protocol EP5. [19]
These results are guidelines. Variables such as instrument maintenance, environment, reagent storage/handling, control material reconstitution, and sample handling can affect the reproducibility of test results.

	Conventional Units (µg/mL)			SI Units (µmol/L)					
	Mean Conc.	Within Day SD*	Within Lab SD**	Mean Conc.	Within Day SD*	Within Lab SD**	Within Lab CV%**	No. Observ.	No. Days
5,1 FS†	22.6	0.71	1.31	156.3	4.93	9.09	5.8	88	22
	61.3	1.62	2.83	424.4	11.26	19.61	4.6	88	22
	103.4	2.30	3.80	716.6	15.91	26.32	3.7	88	22
5600	18.9	0.78	1.16	131.0	5.41	8.04	6.1	92	23
	62.0	1.76	2.62	429.7	12.20	18.16	4.2	92	23
	105.4	2.29	2.98	730.4	15.87	20.65	2.8	92	23

* Within Day precision was determined using two runs per day with two replications per run.

** Within Lab precision was determined using a single lot of reagents and at least four calibrations for each system.

† Analytical processing hardware and software algorithms on the VITROS 4600 Chemistry System are designed to the same specifications as those applied to the VITROS 5,1 FS Chemistry System. Assay performance on the VITROS 4600 System has been demonstrated to be comparable to that on the VITROS 5,1 FS System. All performance characteristics for VITROS 5,1 FS System are therefore applicable to the VITROS 4600 System.

Specificity

Substances that Do Not Interfere

The substances listed in this table, at the concentrations shown, were tested according to NCCLS Protocol EP7 [20] with VITROS VALP Reagent and a serum pool at a valproic acid concentration of 70 µg/mL (485 µmol/L), and found not to interfere [bias <6.6 µg/mL (46 µmol/L)]. Bilirubin, hemoglobin and Intralipid were also tested with a serum pool at a valproic acid concentration of 135 µg/mL (936 µmol/L), and found not to interfere [bias < 11.2 µg/mL (77.4 µmol/L)].

Compound	Concentration	
Bilirubin	60 mg/dL	1026 µmol/L
Carbamazepine	1000 µg/mL	4.2 mmol/L
Clonazepam	100 µg/mL	317 µmol/L
Diazepam	100 µg/mL	351 µmol/L
Ethosuximide	1000 µg/mL	7.1 mmol/L
Hemoglobin	1000 mg/dL	10 g/L
Intralipid	1000 mg/dL	10 g/L
2-n-Propyl-3-hydroxy-pentanoic acid	100 µg/mL	624 µmol/L
2-n-Propyl-4-hydroxy-pentanoic acid	100 µg/mL	624 µmol/L
2-n-Propyl-5-hydroxy-pentanoic acid	50 µg/mL	312 µmol/L
2-n-Propyl-3-oxo-pentanoic acid	100 µg/mL	633 µmol/L
Phenobarbital	750 µg/mL	3.2 mmol/L
Phenytoin	1000 µg/mL	4.0 mmol/L
Primidone	1000 µg/mL	4.6 mmol/L
2-Propyl glutaric acid	400 µg/mL	1.6 mmol/L
2-Propyl-2-pentenoic acid	20 µg/mL	141 µmol/L
2-Propyl-4-pentenoic acid	10 µg/mL	70 µmol/L
2-Propyl succinic acid	500 µg/mL	3.1 mmol/L

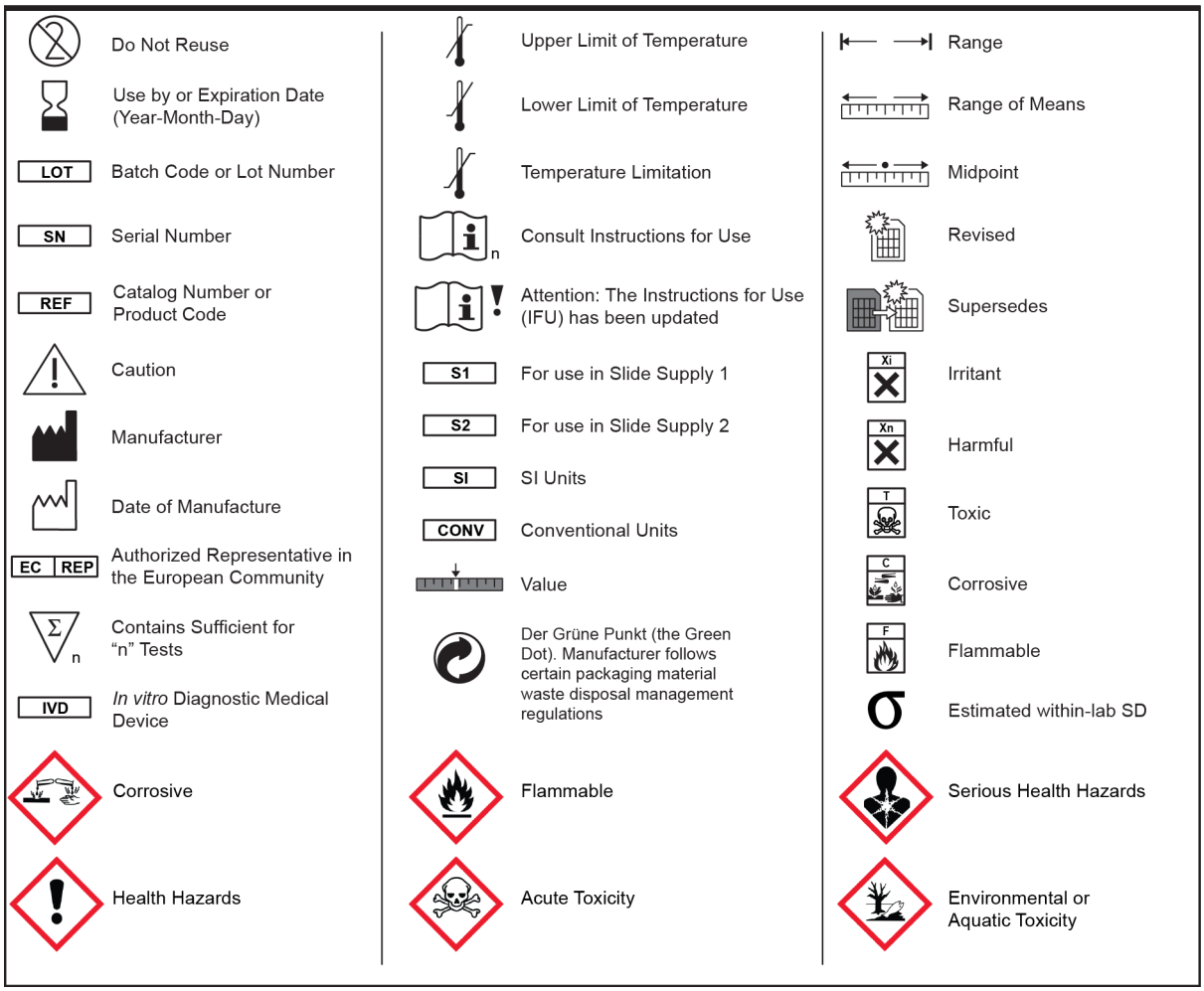
References

1. Depakene (Valproic Acid), In: *Physicians Desk Reference*, 54th ed. Montvale, NJ: Medical Economics Company, 426-427; 2000.
2. Garnett WR. Antiepileptics, in Schumacher GE (ed). *Therapeutic Drug Monitoring*. Norwalk, CT: Appleton & Lange; 1995:345–362.
3. Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008 on classification, labelling and packaging of substances and mixtures, amending and repealing Directives 67/548/EEC and 1999/45/EC, and amending Regulation (EC) No 1907/2006.
4. CLSI. *Protection of Laboratory Workers from Occupationally Acquired Infections; Approved Guideline – Fourth Edition.* CLSI document M29-A4. Wayne, PA: Clinical and Laboratory Standards Institute; 2014.
5. Calam RR. Specimen Processing Separator Gels: An Update. *J Clin Immunoassay*. 11:86–90; 1988.
6. NCCLS. *Procedures for the Collection of Diagnostic Blood Specimens by Venipuncture; Approved Standard – Sixth Edition.* NCCLS document H3-A6 (ISBN 1-56238-650-6). CLSI, 940 West Valley Road, Suite 1400, Wayne, PA 19087-1898 USA; 2007.

7. NCCLS. *Procedures and Devices for the Collection of Diagnostic Capillary Blood Specimens; Approved Standard—Fifth Edition.* NCCLS document H4-A5 [ISBN 1-56238-538-0]. CLSI, 940 West Valley Road, Suite 1400, Wayne, PA 19087-1898 USA; 2004.
8. Antiepileptics. W.R. Garnett in G.E. Schumacher GE (ed) . *Therapeutic Drug Monitoring*. Norwalk, CT.: Appleton and Lange. 1995. 345-362.
9. Standards of laboratory practice: antiepileptic drug monitoring. Ann Warner, Michael Privitera, and David Bates. *Clinical Chemistry*. 1998. 44:5. 1085-1095.
10. *Clinical Laboratory Handbook for Patient Preparation & Specimen Handling.* Fascicle IV. Therapeutic Drug Monitoring and Toxicology. Prepared by the Committee on Patient Preparation and Specimen Handling". College of American Pathologists. March, 1985.
11. Dasgupta A, Dean R, Saldana S, Kinnaman G, McLawhon RW. Absorption of Therapeutic Drugs by Barrier Gels in Serum Separator Blood Collection tubes. *Am J Clin Pathology* 101:456-461; 1994
12. CLSI. *Statistical Quality Control for Quantitative Measurements: Principles and Definitions; Approved Guideline – Third Edition.* CLSI document C24-A3 (ISBN 1-56238-613-1). CLSI, 940 West Valley Road, Suite 1400, Wayne, PA 19087-1898 USA; 2006.
13. Young DS. *Effects of Drugs on Clinical Laboratory Tests*. ed. 5. Washington, D.C.: AACC Press 2000.
14. Friedman RB, Young DS. *Effects of Disease on Clinical Laboratory Tests*. Washington, D.C.: AACC Press; 1990.
15. National Academy of Clinical Biochemistry Symposium. Standards of laboratory practice: antiepileptic drug monitoring. Ann Warner, Michael Privitera, and David Bates. *Clinical Chemistry* 44:5 1085
16. Jacobs, DS, DeMott WR, Grady HJ, Horvat RT, Kasten BL, Jr. *Laboratory Test Handbook*. 4th ed. Hudson, Ohio: Lex – Comp Inc; 1996: 577
17. NCCLS. *Method Comparison and Bias Estimation Using Patient Samples; Approved Guideline- Second Edition*. NCCLS document EP9-A2 [ISBN 1-56238-472-4]. NCCLS, 940 West Valley Road, Suite 1400, Wayne, Pennsylvania 19087-1898 USA; 2002.
18. NCCLS. *Evaluation of Precision Performance of Clinical Chemistry Devices; Approved Guideline*. NCCLS document EP5-A [ISBN 1-56238-368-x]. NCCLS, 940 West Valley Road, Suite 1400, Wayne, PA 19087-1898 USA; 1999.
19. NCCLS. *Evaluation of Precision Performance of Quantitative Measurement Methods; Approved Guideline – Second Edition*. NCCLS document EP5-A2 [ISBN 1-56238-542-9]. CLSI, 940 West Valley Road, Suite 1400, Wayne, PA 19087-1898 USA; 2004.
20. NCCLS. *Interference Testing In Clinical Chemistry*; Approved Guideline. NCCLS document EP7-A [ISBN 1-56238-480-5]. NCCLS, 940 West Valley Road, Suite 1400, Wayne, PA 19087-1898, USA; 2002.

Glossary of Symbols

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



Revision History

Date of Revision	Version	Description of Technical Changes*
2015-04-28	9.0	• Prescription Use Statement added • Warnings and Precautions: – added reference – updated Hazard and Precaution Statements to align with the new Safety Data Sheets – added Globally Harmonized Symbol to comply with the Classification, Labelling and Packaging (CLP) Regulations • References: – added reference – updated M29 • Glossary of Symbols: added Globally Harmonized Symbols to comply with the Classification, Labelling and Packaging (CLP) Regulations
2014-09-05	8.0	Glossary of Symbols: added Date of Manufacture
2012-02-28	7.0	Glossary of Symbols: updated
2010-11-01	6.0	• Added information for the VITROS 4600 Chemistry System • Reagent Storage and Stability – Opened: updated; added statement

Date of Revision	Version	Description of Technical Changes*
2008-10-29	5.0	• Added information for the VITROS 5600 Integrated System • Test Type and Conditions – Added statement • Method Comparison – Added information on sample types, corrected data for 5,1 FS • References – Updated • Glossary of Symbols– Updated data • Minor wording and formatting changes
2005-06-02	4.0	Updated ADD DRV version
2005-04-25	3.0	Updated ADD DRV version
2005-02-08	2.0	• Added “Requires Software Version 1.2.1 or Above and ADD DRV 5398 or Above” • Revised: – Reagent Handling – Reagent Storage and Stability – Quality Control – Specificity
2004-09-09	1.0	First release of document

* 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

CE

EC REP
Ortho-Clinical Diagnostics
50-100 Holmers Farm Way
High Wycombe
Buckinghamshire
HP12 4DP
United Kingdom

Ortho-Clinical Diagnostics, Inc.
100 Indigo Creek Drive
Rochester, NY 14626

Ortho Clinical Diagnostics