Alinity c Valproic Acid-25

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SUPERSEDES: Procedure titled _____

INTENDED USE

The Alinity c Valproic Acid assay is used for the quantitative *in vitro* measurement of valproic acid in human serum or plasma on the Alinity c analyzer.

SUMMARY AND EXPLANATION OF THE TEST

Valproic acid (2-propylpentanoic acid; Depakene) is a broad-spectrum anticonvulsant drug used solely or in combination with other anticonvulsant drugs for the treatment of absence seizures.[1], [2] It also has demonstrated effectiveness in the management of generalized tonic-clonic and myoclonic seizures, as well as atypical absence, simple and complex partial, and mixed grand mal and petit mal seizures.[1], [3], [4] The capability of treating many types of seizures with a single anticonvulsant has resulted in the widespread use of valproic acid,

particularly in children in whom tonic-clonic and myoclonic seizures are most prevalent.[5], [6], [7] Valproic acid has proven effective in the treatment of many patients otherwise refractory to other anticonvulsant treatments. Most patients receiving valproic acid do not develop a tolerance to its anticonvulsant effects.[8]

PRINCIPLES OF THE PROCEDURE

The Alinity c Valproic Acid assay is a homogeneous particle-enhanced turbidimetric inhibition immunoassay (PETINIA) used for the analysis of valproic acid in serum or plasma. The assay is based on competition between drug in the sample and drug coated onto a microparticle, for antibody binding sites of the valproic acid antibody reagent. The valproic acid-coated microparticle reagent is rapidly agglutinated in the presence of the anti-valproic acid antibody reagent and in the absence of any competing drug in the sample. The rate of absorbance change is measured photometrically, and is directly proportional to the rate of agglutination of the microparticles. When a sample containing valproic acid is added, the agglutination reaction is partially inhibited, slowing down the rate of absorbance change. A concentration-dependent classic agglutination inhibition curve can be obtained, with maximum rate of agglutination at the lowest valproic acid concentration and the lowest agglutination rate at the highest valproic acid concentration.

Methodology: Particle-enhanced turbidimetric inhibition immunoassay (PETINIA)

For additional information on system and assay technology, refer to the Alinity ci-series Operations Manual, Section 3.

REAGENTS

Kit Contents

Alinity c Valproic Acid Reagent Kit 09P92

Volumes (mL) listed in the table below indicate the volume per cartridge.

REF	**09P9220**
Tests per cartridge	100
Number of cartridges per kit	2
Tests per kit	200
R1	30.2 mL
R2	10.4 mL

R1 Active ingredients: anti-valproic acid monoclonal antibody (mouse) (< 2.0%). Inactive ingredients: bovine-, goat-, and mouse-sourced material and buffer, detergent, and anti-foaming agent. Preservative: sodium azide (< 0.1%).

R2 Active ingredients: valproic acid coated microparticles (< 0.5%). Preservative: sodium azide (< 0.1%).

Warnings and Precautions

- IVD
- For *In Vitro* Diagnostic Use
- Rx ONLY

Safety Precautions

CAUTION: This product requires the handling of human specimens. It is recommended that all human-sourced materials be considered potentially infectious and handled in accordance with the OSHA Standard on Bloodborne Pathogens. Biosafety Level 2 or other appropriate biosafety practices should be used for materials that contain or are suspected of containing infectious agents.[9], [10], [11], [12]

The following warnings and precautions apply to: R1	
WARNING	Contains bis-tris propane* and sodium azide.
H316*	Causes mild skin irritation.
EUH032	Contact with acids liberates very toxic gas.
Response	
P332+P313*	If skin irritation occurs: Get medical advice / attention.
Disposal	
P501	Dispose of contents / container in accordance with local regulations.

* Not applicable where regulation EC 1272/2008 (CLP) or OSHA Hazard Communication 29 CFR 1910.1200 (HCS) 2012 have been implemented.

The following warnings and precautions apply to: R2	
Contains sodium azide.	
EUH032	Contact with acids liberates very toxic gas.
P501	Dispose of contents / container in accordance with local regulations.

Safety Data Sheets are available at www.abbottdiagnostics.com or/and SDS folder.

For a detailed discussion of safety precautions during system operation, refer to the Alinity ci-series Operations Manual, Section 8.

Reagent Handling

- Reagents are shipped refrigerated or on wet ice/cold packs.
- Upon receipt, place reagent cartridges in an upright position for 1 hour before use to allow bubbles that may have formed to dissipate.
- If a reagent cartridge is dropped, place in an upright position for 8 hours before use to allow bubbles that may have formed to dissipate.
- Prior to running, gently invert cartridge 5 times.
- Reagents are susceptible to the formation of foam and bubbles. Bubbles may interfere with the detection of the reagent level in the cartridge and cause insufficient reagent aspiration that may adversely affect results.

For a detailed discussion of reagent handling precautions during system operation, refer to the Alinity ci-series Operations Manual, Section 7.

Reagent Storage

- Do not freeze.
- Do not expose reagents to temperatures above 32°C.

	Storage Temperature	Maximum Storage Time	Additional Storage Instructions
Unopened	2 to 8°C	Until expiration date	Store in upright position.
Onboard	System Temperature	54 days (1296 hours)	
Opened	2 to 8°C	Until expiration date	Store in upright position. Do not reuse original reagent caps or replacement caps due to the risk of contamination and the potential to compromise reagent performance.

Reagents may be stored on or off the system. If removed from the system, store reagents with new replacement caps in an upright position at 2 to 8°C. For reagents stored off the system, it is recommended that they be stored in their original trays or boxes to ensure they remain upright.

For information on unloading reagents, refer to the Alinity ci-series Operations Manual, Section 5.

Indications of Reagent Deterioration

Deterioration of the reagents may be indicated when:

- a calibration error occurs
- a control value is out of the specified range

Associated test results are invalid, and samples must be retested. Assay recalibration may be necessary.

For troubleshooting information, refer to the Alinity ci-series Operations Manual, Section 10.

INSTRUMENT PROCEDURE

The Alinity c Valproic Acid assay file must be installed on the Alinity c analyzer prior to performing the assay.

For detailed information on assay file installation and viewing and editing assay parameters, **refer to the Alinity ci-series Operations Manual, Section 2**.

For information on printing assay parameters, **refer to the Alinity ci-series Operations Manual, Section 5.**

For a detailed description of system procedures, **refer to the Alinity ci-series Operations Manual.**

Alternate Result Units

Edit assay parameter "Result Units" to select an alternate unit.

Conversion formula:

(Concentration in Default result unit) x (Conversion factor) = (Concentration in Alternate result unit)

Default Result Unit	Conversion Factor	Alternate Result Unit
µg/mL	6.93*13*	µmol/L

SPECIMEN COLLECTION AND PREPARATION FOR ANALYSIS

Specimen Types

The specimen types listed below were verified for use with this assay.

Other specimen types, collection tube types, and anticoagulants have not been verified with this assay.

Specimen Type	Collection Vessel	Special Conditions
Serum	Serum tubes (with or without gel barrier)	
Plasma	Collection tubes Acceptable anticoagulants are: Lithium heparin Sodium heparin Potassium EDTA Heparin gel plasma separator	Sodium citrate and sodium fluoride anticoagulants were tested and found to be unacceptable.

- To confirm that an adequate dose has been prescribed, specimens for the Alinity c Valproic Acid assay should be drawn at trough levels, just prior to a dose. The trough concentration is most indicative of the therapeutic value of valproic acid.*14*
- The instrument does not provide the capability to verify specimen types. It is the responsibility of the operator to verify that the correct specimen types are used in the assay.
- NOTE: Some gel separation tubes may not be suitable for use with therapeutic drug monitoring assays; refer to information provided by the tube manufacturer.*15*

Specimen Conditions

- Analyze fresh specimens if possible.
- For accurate results, serum and plasma specimens should be free of fibrin, red blood cells, and other particulate matter. Serum specimens from patients receiving anticoagulant or thrombolytic therapy may contain fibrin due to incomplete clot formation.
- For accurate results, plasma specimens should be free of platelets and other particulate matter. Ensure centrifugation is adequate to remove platelets.
- To prevent cross contamination, use of disposable pipettes or pipette tips is recommended.

Preparation for Analysis

- Follow the tube manufacturer's processing instructions for collection tubes. Gravity separation is not sufficient for specimen preparation.
- Specimens should be free of bubbles. Remove bubbles with an applicator stick before analysis. Use a new applicator stick for each specimen to prevent cross contamination.

To ensure consistency in results, recentrifuge specimens prior to testing if

- they contain fibrin, red blood cells, or other particulate matter.

NOTE: If fibrin, red blood cells, or other particulate matter are observed, mix by low speed vortex or by inverting 10 times prior to recentrifugation.

Recentrifugation of Specimens

- Transfer specimens to a centrifuge tube and centrifuge at 80 000 to 100 000 g-minutes.
- Examples of acceptable time and force ranges that meet this criterion are listed in the table below.

  Centrifugation time using alternate RCF values can be calculated using the following formula:

$$\text{Centrifugation time (minutes)} = \frac{80\,000 \text{ g-minutes}}{\text{RCF}}$$

Recentrifugation Time (Minutes)	RCF (x g)	g-Minutes
10	8000 - 10 000	80 000 - 100 000
16	5000	80 000
32	2500	80 000

$RCF = 1.12 \times r_{max} (rpm/1000)^2$

RCF - The relative centrifugal force generated during centrifugation.

rpm - The revolutions per minute of the rotor on which the specimens are being spun (usually the digital readout on the centrifuge will indicate the rpm).

Centrifugation Time - The time should be measured from the time the rotor reaches the required RCF or rpm to the time it begins decelerating.

r_{max} - Radius of the rotor in millimeters. NOTE: If custom tube adapters (i.e., adapters not defined by the centrifuge manufacturer) are used, then the radius (r_{max}) should be manually measured in millimeters and the RCF calculated.

g-minutes - The unit of measure for the product of RCF (× g) and centrifugation time (minutes).

Specimen Storage

Analyze fresh specimens if possible.

Specimen Type	Temperature	Maximum Storage Time	Special Instructions
Serum/Plasma	2 to 8°C	48 hours	Remove serum or plasma from the clot, red blood cells, or separator gel.
	-20°C or colder	7 days (168 hours)	Remove serum or plasma from the clot, red blood cells, or separator gel.

Avoid multiple freeze/thaw cycles.

Stored specimens must be inspected for particulates. If present, mix with a low speed vortex or by inversion and centrifuge the specimen to remove particulates prior to testing.

Specimen Shipping

Package and label specimens in compliance with applicable state, federal, and international regulations covering the transport of clinical specimens and infectious substances.

PROCEDURE

Materials Provided

09P92 Alinity c Valproic Acid Reagent Kit

Materials Required but not Provided

- Alinity c Valproic Acid assay file
- 08P7403 Alinity c TDM Multiconstituent Calibrator Kit
- Commercially available control material containing valproic acid
- Saline (0.85% to 0.90% NaCl) for specimen dilution

For information on materials required for operation of the instrument, refer to the Alinity ci-series Operations Manual, Section 1.

For information on materials required for maintenance procedures, refer to the Alinity ci-series Operations Manual, Section 9.

Assay Procedure

For a detailed description of how to run an assay, refer to the Alinity ci-series Operations Manual, Section 5.

- If using primary or aliquot tubes, refer to the Alinity ci-series Operations Manual, Section 4 to ensure sufficient specimen is present.
- To minimize the effects of evaporation, verify adequate sample cup volume is present prior to running the test.
- Minimum sample volume requirements:
  - Sample volume for single test: 4.0 µL.

    NOTE: This amount does not include the dead volume plus the additional over-aspiration volume. For total sample volume requirements, refer to the Alinity ci-series Operations Manual, Section 4.
- Refer to the Alinity c TDM Multiconstituent Calibrator Kit package insert and commercially available control material package insert for preparation and usage.
- For general operating procedures, refer to the Alinity ci-series Operations Manual, Section 5.
- For optimal performance, it is important to perform routine maintenance as described in the Alinity ci-series Operations Manual, Section 9. Perform maintenance more frequently when required by laboratory procedures.

Sample Dilution Procedures

Samples with a valproic acid value exceeding 150.0 µg/mL (1039.5 µmol/L) or the highest calibrator are flagged with the code "> 150.0 µg/mL" (">1039.5 µmol/L") and may be diluted with either the Automated Dilution Protocol or the Manual Dilution Procedure.

Automated Dilution Protocol

The system performs a 1:4 or a 1:8 dilution of the sample and automatically calculates the concentration by multiplying the result by the dilution factor.

Manual Dilution Procedure

Dilute the sample with saline (0.85% to 0.90% NaCl).

Do not use 08P7403 Alinity c TDM Multiconstituent CAL 1 to dilute patient samples.

The operator must enter the dilution factor in the Specimen or Control tab of the Create Order screen. The system will use this dilution factor to automatically calculate the concentration of the sample and report the result.

If the operator does not enter the dilution factor, the result must be manually multiplied by the appropriate dilution factor before reporting the result. If a diluted sample result is less than the lower value of the measuring interval of 12.5 µg/mL (86.6 µmol/L), do not report the result. Rerun using an appropriate dilution.

For detailed information on ordering dilutions, refer to the Alinity ci-series Operations Manual, Section 5.

Calibration

For instructions on performing a calibration, refer to the Alinity ci-series Operations Manual, Section 5.

Calibration is stable for approximately **27 days (648 hours),** but is required with each change in reagent lot. Verify calibration with at least 2 levels of controls according to the established quality control requirements for your laboratory. If control results fall outside acceptable ranges, recalibration may be necessary.

This assay may require recalibration after maintenance to critical parts or subsystems or after service procedures have been performed.

Quality Control Procedures

- At least two levels of controls (NORMAL, ABNORMAL) are to be run every day testing performed..
- If quality control results do not meet the acceptance criteria defined by laboratory quality controls procedure, sample results may be suspect. Follow the established quality control procedures to troubleshoot. Recalibration may be necessary. For troubleshooting information, refer to the Alinity ci-series Operations Manual, Section 10.
- Review quality control results and acceptance criteria following a change of reagent or calibrator lot.

Commercial controls should be used according to the guidelines and recommendations of the control manufacturer. Concentration ranges provided in the control package insert should be used only for guidance.

For any control material in use, the laboratory should ensure that the matrix of the control material is suitable for use in the assay per the assay package insert.

Quality Control Guidance

Refer to “Basic QC Practices” by James O Westgard, Ph.D. for guidance on laboratory quality control practices.*16*

Verification of Assay Claims

For protocols to verify package insert claims, refer to Verification of Assay Claims in the Alinity ci-series Operations Manual.

RESULTS

Calculation

The Alinity c Valproic Acid assay utilizes the Spline data reduction method to generate a calibration and results.

For information on alternate result units, refer to the INSTRUMENT PROCEDURE, Alternate Result Units section of this package insert.

Interpretation of Results

IMPORTANT: In very rare cases, patient samples may contain heterophile antibodies, which may produce low results with the Alinity c Valproic Acid assay. Refer to the LIMITATIONS OF THE PROCEDURE section of this package insert.

As with all analyte determinations, the valproic acid value should be used in conjunction with information available from clinical evaluation and other diagnostic procedures.

Flags

Some results may contain information in the Flags field. For a description of the flags that may appear in this field, refer to the Alinity ci-series Operations Manual, Section 5.

Measuring Interval

Measuring interval is defined as the range of values in µg/mL (µmol/L) which meets the limits of acceptable performance for linearity, imprecision, and bias.

The measuring interval of the Alinity c Valproic Acid assay is **12.5 to 150.0 µg/mL** (86.6 to 1039.5 µmol/L).

LIMITATIONS OF THE PROCEDURE

Refer to the SPECIMEN COLLECTION AND PREPARATION FOR ANALYSIS and SPECIFIC PERFORMANCE CHARACTERISTICS sections of this package insert.

- In very rare cases, patient samples may contain heterophile antibodies, which may produce low results with the Alinity c Valproic Acid assay. Interfering heterophile antibodies occur at a low frequency in the general population. These antibodies can cause autoagglutination of the microparticle reagent leading to undetected erroneously low results.
- For diagnostic purposes, the test findings should always be assessed in conjunction with the patient's medical history, clinical examinations, and other findings.

EXPECTED VALUES

There is no precise relationship between serum valproic acid levels and control of seizures,[17] although **most patients require at least a serum level of 50 µg/mL (346.5 µmol/L) for effective therapy.**[3, 4] A therapeutic range of **50 to 100 µg/mL** (346.5 to 693 µmol/L) has been suggested for valproic acid.[1, 2, 3] Due to great individual differences in dosage requirements to achieve efficacious therapy, determination of valproic acid serum concentrations is required to direct effective therapy.[3, 7, 18] Refer to the drug manufacturer's package insert or the Physicians' Desk Reference (PDR) for proper drug dosage and for valproic acid measurement sampling times.

Valproic acid modulates the action of various other common anti-epileptic drugs. It inhibits the non-renal clearance of phenobarbital, resulting in elevated phenobarbital levels. It competes with phenytoin for protein-binding sites. The free phenytoin concentration remains approximately the same, but the total phenytoin in the plasma decreases. Because the free phenytoin concentration remains unchanged, the pharmacological effect is retained. Other common anti-epileptic drugs that induce hepatic oxidative enzymes result in increased valproic acid clearance; this increased clearance rate requires a higher dose to maintain effective therapeutic levels.[14]

SPECIFIC PERFORMANCE CHARACTERISTICS

Representative performance data are provided in this section. Results obtained in individual laboratories may vary.

The Alinity c analyzer and the ARCHITECT c System and AEROSET System utilize the same reagents and sample/reagent ratios.

Unless otherwise specified, all studies were performed on the Alinity c analyzer.

Precision

Within-Laboratory Precision

A study was performed based on guidance from CLSI EP05-A2.[19] Testing was conducted using 1 lot of the Alinity c Valproic Acid Reagent Kit, 1 lot of the Alinity c TDM Multiconstituent Calibrator Kit, and 1 lot of commercially available controls and 1 instrument. Three controls and one human serum panel were assayed in a minimum of 2 replicates at 2 separate times per day on 20 different days.

Sample	n	Mean (µg/mL)	Within-Run (Repeatability)		Within-Laboratory (Total)[a]	
			SD	%CV	SD	%CV
Control 1	120	36.1	0.55	1.5	0.66	1.8
Control 2	120	52.7	0.58	1.1	0.76	1.4
Control 3	120	84.9	1.31	1.5	1.37	1.6
Panel	120	133.3	3.36	2.5	3.36	2.5

[a]Includes within-run, between-run, and between-day variability.

Sample	n	Mean (µmol/L)	Within-Run (Repeatability)	Within-Laboratory (Total)[a]

			SD	%CV	SD	%CV
Control 1	120	250.4	3.84	1.5	4.60	1.8
Control 2	120	365.2	4.02	1.1	5.24	1.4
Control 3	120	588.6	9.08	1.5	9.50	1.6
Panel	120	923.6	23.25	2.5	23.25	2.5

[a]Includes within-run, between-run, and between-day variability.

Lower Limits of Measurement

A study was performed based on guidance from CLSI EP17-A2. Testing was conducted using 3 lots of the Alinity c Valproic Acid Reagent Kit on each of 2 instruments over a minimum of 3 days. The Limit of Blank (LoB), Limit of Detection (LoD), and Limit of Quantitation (LoQ) values are summarized below. These representative data support the lower limit of the measuring interval.*20*

	µg/mL	µmol/L
LoB[a]	0.5	3.5
LoD[b]	0.8	5.5
LoQ[c, d]	6.0	41.6

[a]The LoB represents the 95th percentile from n ≥ 60 replicates of zero-analyte samples.

[b]The LoD represents the lowest concentration at which the analyte can be detected with 95% probability based on n ≥ 60 replicates of low-analyte level samples.

[c]The LoQ is defined as the lowest concentration at which a maximum allowable precision of 20 %CV and a maximum allowable bias of 10% were independently met.

[d]This value represents the observed LoQ on the ARCHITECT System. The LoQ observed on the Alinity c analyzer supports this LoQ.

Linearity

A study was performed based on guidance from CLSI EP06-A.*21*

This assay is linear across the measuring interval **of 12.5 to 150.0 µg/mL** (86.6 to 1039.5 µmol/L).

Analytical Specificity

This study was performed on the AEROSET System.

Cross reactivity was tested for the major metabolite of valproic acid (3-keto valproic acid), the minor metabolites (2-n-propylglutaric acid, 2-n-propyl-4-pentenoic acid, and 2-ethyl-2-phenylmalonamide), and other medications routinely administered with valproic acid to determine whether these compounds affect the quantitation of valproic acid concentrations on the Valproic Acid assay. High concentrations of these compounds were spiked into a serum pool (control) containing a therapeutic level of valproic acid. The samples were assayed and the valproic acid concentrations of the spiked samples were compared to the control serum. Cross-reactivity was calculated using the following equation:

$$\% \text{ Cross-Reactivity} = \frac{(\text{Valproic Acid Conc.* in Spiked Sample} - \text{Valproic Acid Conc. in Control})}{\text{Valproic Acid Conc. in Control}} \times 100$$

Compound	Conc. of Cross-Reactant (µg/mL)	Valproic Acid Conc. in Control Serum (µg/mL)	Valproic Acid Conc. in Spiked Sample (µg/mL)	Cross-Reactivity (%)
Carbamazepine	140	95.35	94.27	none detected
Carbamazepine-10,11-epoxide	140	95.35	94.78	none detected
Clonazepam	1.2	95.35	95.49	0.2
Diazepam	25	95.35	93.46	none detected
2-ethyl-2-phenylmalonamide	100	95.35	94.72	none detected
Ethosuximide	1000	95.35	95.96	0.6
3-keto valproic acid	16.67	92.86	93.66	0.9
Phenobarbital	400	95.35	98.40	3.2
Phenytoin	200	95.35	95.79	0.5
Primidone	120	95.35	95.11	none detected
2-n-propyl-4-pentenoic acid	100	95.35	126.48	32.7
2-n-propylglutaric acid	100	95.35	101.98	7.0
Salicylate	100	95.35	93.86	none detected

* Conc. = Concentration

Interference

This study was performed on the AEROSET System.

Potentially Interfering Substances

A study was performed based on guidance from NCCLS EP7-P.[22]

Potential interference in the Valproic Acid assay from bilirubin, hemoglobin, and Intralipid is ≤ 10% at the interferent levels indicated below. Specimens with approximately 90.0 µg/mL (623.7 µmol/L) valproic acid were supplemented with the potentially interfering compounds.

Potentially Interfering Substance	Interferent Level	
	Default Units	Alternate Units
Bilirubin	20 mg/dL	342 µmol/L
Hemoglobin	1000 mg/dL	10 g/L
Intralipid	2000 mg/dL	22.6 mmol/L

As with any assay employing mouse antibodies, the possibility exists for interference by human anti-mouse antibodies (HAMA) in the sample, which could cause falsely elevated results.

Method Comparison

A study was performed based on guidance from CLSI EP09-A3[23] using the Passing-Bablok regression method.

		Units	n	Correlation Coefficient	Intercept	Slope	Concentration Range
Alinity c Valproic Acid vs ARCHITECT Valproic Acid	Serum	µg/mL	122	1.00	-0.78	1.00	14.7 - 137.8
		µmol/L	122	1.00	-5.35	1.00	101.6 - 954.7

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