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**VALPROIC ACID**

**SERUM OR PLASMA**

**ABBOTT ARCHITECT**

**Intended Use**

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

**Clinical Significance**

Valproic acid (VPA; 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.

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. 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. 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.

**Principle**

The MULTIGENT 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)

**Specimen Collection and Handling**

Serum and plasma are acceptable specimens.

• **Serum:** Use serum collected by standard venipuncture techniques into glass or plastic tubes with or without gel barriers. Ensure complete clot formation has taken place prior to centrifugation.

Centrifuge according to tube manufacturer’s instructions to ensure proper separation of serum from blood cells.

Some specimens, especially those from patients receiving anticoagulant or thrombolytic therapy, may exhibit increased clotting time. If the specimen is centrifuged before a complete clot forms, the presence of fibrin may cause erroneous results.

• **Plasma:** Use plasma collected by standard venipuncture techniques into glass or plastic tubes. Acceptable anticoagulants are lithium heparin, sodium heparin, potassium EDTA, and heparin gel plasma separator. Sodium citrate and sodium fluoride anticoagulants were tested and found to be unacceptable. Ensure centrifugation is adequate to remove platelets. Centrifuge according to tube manufacturer’s instructions to ensure proper separation of plasma from blood cells.

**NOTE:** Some gel separation tubes may not be suitable for use with therapeutic drug monitoring assays; refer to information provided by the tube manufacturer.

**Specimen Storage**

**Serum and Plasma:** Analyze fresh specimens, if possible. If not, separated specimens may be stored for up to 48 hours at 2 to 8°C prior to being tested. If testing will be delayed more than 48 hours, separated specimens may be stored frozen at -20°C or colder for up to 7 days (168 hours).

**NOTE:** Stored specimens must be inspected for particulates. If present, mix and centrifuge the specimen to remove particulates prior to testing.

**Materials and Equipment Required**

**TEST INSTRUMENT**: Abbott ARCHITECT System

**MATERIALS PROVIDED**

1E13-20 MULTIGENT Valproic Acid

**MATERIALS REQUIRED BUT NOT PROVIDED**

• 5P04-01 TDM Multiconstituent Calibrator (TDM MCC)

• Control Material

• Saline (0.85% to 0.90% NaCl) for specimens that require dilution

**Reagent Handling and Storage:**

***CAUTION*:**

1. For in vitro diagnostic use.

2. Do not use components beyond the expiration date.

3. Do not mix materials from different kit lot numbers.

• Do not mix fresh reagents with in-use reagents.

**CAUTION:** This product requires the handling of human specimens.

It is recommended that all human sourced materials be considered

potentially infectious and be 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.

• The following warning and precaution apply to R1 and R2:

Contains sodium azide.

EUH032 Contact with acids liberates very toxic gas.

These materials and their containers must be disposed of in a safe way.

**Reagent Handling**

• R1 Ready for use. Before use, invert several times, avoiding the formation of bubbles.

• R2 Ready for use. Before use, invert several times, avoiding the formation of bubbles.

• Remove air bubbles, if present in the reagent cartridge, with a new applicator stick. Alternatively, allow the reagent to sit at the appropriate storage temperature to allow the bubbles to dissipate.

To minimize volume depletion, do not use a transfer pipette to remove the bubbles.

**CAUTION:** Reagent bubbles may interfere with proper detection of reagent level in the cartridge, causing insufficient reagent aspiration that could impact results.

• Do not mix materials from different kit lot numbers.

• When either the R1 or the R2 reagent cartridge becomes empty, replace both cartridges and verify with controls according to the established quality control requirements for your laboratory.

**Reagent Storage**

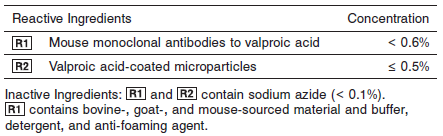
• Reagent stability is 54 (1296 Hours) days if the reagent is uncapped and onboard.

• Unopened reagents are stable until the expiration date when stored at 2 to 8°C.

• **Do not freeze reagents or expose reagents to temperatures above 32°C.**

Reagent Preparation:

1E13-20 MULTIGENT Valproic Acid is supplied as a liquid, ready-to-use, two-reagent kit which contains: **R1 & R2**



**Calibrator:** 5P04-01 TDM Multiconstituent Calibrator (TDM MCC)

**Quality Control:** Minimum 2 levels of ChemistryControl (Normal and Abnormal)

**Calibration**

**Frequency:**

Calibration is stable for 27 days (648 hours) for any one lot.

**A new calibration is required:**

1. If quality control results do not meet acceptance criteria defined by your laboratory, patient values may be suspect. Follow the established quality control procedures for your laboratory. Recalibration may be necessary.
2. Review quality control results and acceptance criteria following a change of reagent or calibrator lot.

**Calibrator Required:** 5P04-01 TDM Multiconstituent Calibrator (TDM MCC)

**Reagents:**

**NOTE:** TDM MCC CAL 1 is the calibration blank for this assay. TDM MCC is prepared from a bovine serum matrix and contains the following analytes: amikacin, carbamazepine, digoxin, gentamicin, phenobarbital, phenytoin, quinidine, theophylline, valproic acid, and vancomycin. Sodium azide and ProClin are present as preservatives.

**Calibrator Preparation:**

TDM MCC requires no preparation prior to use.

**Calibration Procedure:**

1. Verify that the lot number listed on each calibrator carton agrees with the lot number printed on the value sheet.

2. Verify that the correct calibrator values have been entered into the calibration file.

3. Mix several times by gentle inversion to ensure homogeneity of the solution. Avoid the formation of foam.

4. Place an appropriate amount of calibrator in a sample cup, and place in the assigned position.

5. Cap bottle tightly and return to refrigerated storage immediately after use.

6. Perform calibration as indicated in *Section 6* of the **ARCHITECT System Operations Manual**.

**Troubleshooting and Overall Acceptance Criteria Failure**

See ARCHITECT Operations Manual for further calibration troubleshooting.

**Quality Control:**

Abbott recommends, refer to your laboratory standard operating procedure(s) and/or quality assurance plan for additional quality control requirements and potential corrective actions:

• Two levels of controls (normal and abnormal) are to be run every 24 hours.

• If more frequent control monitoring is required, follow the established quality control procedures for your laboratory.

• If quality control results do not meet the acceptance criteria defined by your laboratory, patient values may be suspect. Follow the established quality control procedures for your laboratory.

Recalibration may be necessary.

• Review quality control results and acceptance criteria following a change of reagent or calibrator lot.

**Procedure**

For a detailed description of how to run an assay, refer to *Section 5* of the **ARCHITECT System Operations Manual**.

**Calculations**

Refer to *Appendix C* of the **ARCHITECT System Operations Manual** for information on results calculations.

**Reporting Results**

Results for the MULTIGENT Valproic Acid assay can be reported as μg/mL or μmol/L.

**Specific Performance Characteristics**

**Reference Ranges**

It is recommended that each laboratory determine its own reference range based upon its particular locale and population characteristics.

**Serum/Plasma:** 50 – 100 μg/mL

***Serum and Plasma***

There is no precise relationship between serum valproic acid levels and control of seizures,16 although most patients require at least a serum level of 50 μg/mL (346.5 μmol/L) for effective therapy. A therapeutic range of 50 to 100 μg/mL (346.5 to 693 μmol/L) has been suggested for valproic acid. Due to great individual differences in dosage requirements to achieve efficacious therapy, determination of valproic acid serum concentrations is required to direct effective therapy. 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.

**Critical Values: >120** μg/mL

**Performance Characteristics**

**Assay Range**

The linear range of the assay is 12.5 to 150.0 μg/mL (86.6 to 1,039.5 μmol/L).

**Limit of Quantitation (LOQ)**

The LOQ for the MULTIGENT Valproic Acid assay was calculated to be 6.0 μg/mL (41.6 μmol/L).

**Dilution:**

Specimens with valproic acid values exceeding 150 μg/mL (1,039.5 μmol/L) or the highest calibrator are flagged and may be diluted by following either the Automated Dilution Protocol or the Manual Dilution Procedure. For additional information regarding configuration of automated onboard specimen dilution, refer to *Section 2* of the **ARCHITECT System Operations Manual**.

***Automated Dilution Protocol***

If using the Automated Dilution Protocol, the system performs a 1:4 or a 1:8 dilution of the specimen and automatically corrects the concentration by multiplying the result by the appropriate dilution factor.

***Manual Dilution Procedure***

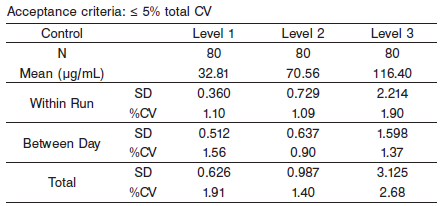
A manual dilution can be performed on patient samples with valproic acid concentrations reported as greater than 150.0 μg/mL (1,039.5 μmol/L) or the highest calibrator. Make a dilution of the specimen with 1E13-02 MULTIGENT Valproic Acid (0 μg/mL) or saline before pipetting the sample into the sample cup. Do not use 5P04-01 TDM MCC to dilute patient samples. The dilution must be performed so the diluted test results are greater than the linear low limit of 12.5 μg/mL (86.6 μmol/L).



The operator must enter the manual dilution factor in the patient or control order screen. The system uses this dilution factor to automatically correct the concentration by multiplying the result by the entered factor. The printed result is the reportable result if no errors are present.

**NOTE:** If the operator does not enter the manual dilution factor, the printed result must be multiplied by the manual dilution factor before reporting the result.

**Precision:**

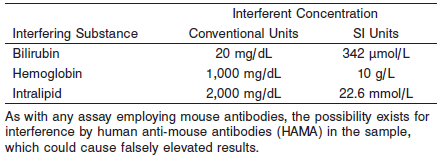


#### Limitations of Procedure

In very rare cases, patient samples may contain heterophile antibodies, which may produce low results with the MULTIGENT 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.

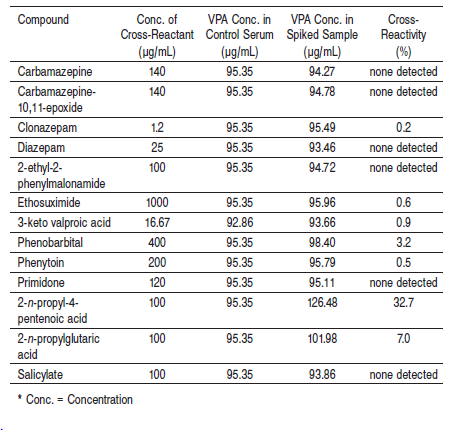
**Interfering Substances**

Potential interference in the MULTIGENT Valproic Acid assay from bilirubin, hemoglobin, and Intralipid is ≤ 10% at the interferent levels indicated below.



**Specificity**

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 MULTIGENT Valproic Acid assay. High concentrations of these compounds were spiked into a serum pool (control) containing a therapeutic level of valproic acid.



**References:**

1. ABBOTT ARCHITECT Valproic Acid package insert

Abbott Laboratories

Diagnostics Division

Abbott Park, IL 60064

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1. ABBOTT ARCHITECT TDM Multiconstituent Calibrator package insert

Abbott Laboratories

Diagnostics Division

Abbott Park, IL 60064

1. Abbott ARCHITECT Operator’s Guide

**Related Documents:**

**Attachments:**