ARK Diagnostics, Inc.

ARK™ *Gabapentin Assay*

This ARK Diagnostics, Inc. package insert for the ARK Gabapentin Assay must be read carefully prior to use. Package insert instructions must be followed accordingly. Reliability of the assay results cannot be guaranteed if there are any deviations from the instructions in this package insert.

Report any serious incident that has occurred in relation to the device to the manufacturer and the appropriate competent authority as applicable. A Summary of Safety and Performance is available through Eudamed (European database on medical devices), SRN: US-MF-000023925.

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Key to Symbols Used

LOT	Batch code	YYYY-MM-DD	Use by/Expiration date
REF	Catalog Number		Manufacturer
EC REP	Authorized Representative	CE 2797	CE Mark with notified body number
IVD	In Vitro Diagnostic Medical Device		Temperature limitation
	Consult Instructions for Use	R1 R2	Reagent 1/ Reagent 2
Rx Only	For Prescription Use Only		

1 Name

ARK™ ***Gabapentin Assay***

2 Intended Use

The ARK Gabapentin Assay is a homogeneous enzyme immunoassay intended for the quantitative determination of gabapentin in human serum or plasma on automated clinical chemistry analyzers. Gabapentin concentrations can be used as an aid in management of patients treated with gabapentin.

3 Summary and Explanation of the Test

Gabapentin [Neurontin®, 1-(aminomethyl)-cyclohexaneacetic acid] is indicated for use as adjunctive therapy in the treatment of partial seizures with and without secondary generalization in patients over 12 years of age with epilepsy and as adjunctive therapy in the treatment of partial seizures in pediatric patients age 3-12 years. Gabapentin is also indicated for the management of postherpetic neuralgia in adults. [1]

4 Principles of the Procedure

ARK Gabapentin Assay is a homogeneous immunoassay based on competition between drug in the specimen and gabapentin labeled with the enzyme glucose-6-phosphate dehydrogenase (G6PDH) for binding to the antibody reagent. As the latter binds antibody, enzyme activity decreases. In the presence of drug from the specimen, enzyme activity increases and is directly proportional to the drug concentration. Active enzyme converts the coenzyme nicotinamide adenine dinucleotide (NAD) to NADH that is measured spectrophotometrically as a rate of change in absorbance. Endogenous serum G6PDH does not interfere with the results because the coenyzme NAD functions only with the bacterial enzyme used in the assay.

5 Reagents

REF	Product Description	Quantity/Volume
5025-0001-00 **5025-0001-01**	**ARK Gabapentin Assay** **Reagent R1 – Antibody/Substrate** rabbit polyclonal antibodies to gabapentin, glucose-6-phosphate, nicotinamide adenine dinucleotide, bovine serum albumin, sodium azide, and stabilizers	1 X 28 mL
	Reagent R2 – Enzyme Gabapentin labeled with bacterial G6PDH, buffer, bovine serum albumin, sodium azide, and stabilizers	1 X 14 mL

Reagent Handling and Storage

ARK Gabapentin Assay reagents are provided liquid, ready to use and may be used directly from the refrigerator. When not in use, reagents must be stored at 2–8°C (36–46°F), upright and with screw caps tightly closed. If stored as directed, reagents are stable until the expiration date printed on the label. Do not freeze reagents. Avoid prolonged exposure to temperatures above 32°C (90°F). **Improper storage of reagents can affect assay performance.**

ARK Gabapentin products contain ≤0.09% sodium azide. As a precaution, affected plumbing including instrumentation should be flushed adequately with water to mitigate the potential accumulation of explosive metal azides. No special handling is required regarding other assay components.

6 Warnings and Precautions

- For **In Vitro Diagnostic** Use**.** For prescription use only.
- Reagents R1 and R2 are provided as a matched set and should not be interchanged with reagents from different lot numbers.
- Reagents contain ≤0.09% sodium azide.

7 Specimen Collection and Preparation for Analysis

- Each laboratory is responsible for supplying a valid specimen for analysis according to their quality procedures.
- Serum or plasma is required. For consistency, using the same specimen matrix for individual patients is a good practice. A steady state, trough (pre-dose) sample is generally accepted as most consistent for therapeutic drug monitoring of gabapentin. Time of blood draw since last dose should be noted.
- Whole blood cannot be used. The following anticoagulants may be used with this assay.
    - Sodium heparin
    - Lithium heparin
    - Potassium EDTA

- Blood collection must be performed with collection tubes compatible for use with therapeutic drug monitoring (TDM).
- Follow the collection tube manufacturer's recommendations for collection, processing and centrifugation
- CLSI document GP44-A4 outlines procedures for minimizing artifacts due to specimen collection and handling for common laboratory tests.[25]

- Do not induce foaming and avoid repeated freezing and thawing to preserve the integrity of the specimen from the time it is collected until the time it is assayed.
- Fibrin, red blood cells, and other particulate matter may cause an erroneous result. Ensure adequate centrifugation.
- The presence of bubbles or foam on specimens may lead to short samples and erroneously low results.
- Each laboratory should consult available literature and internal data regarding specimen stability.
- Testing of fresh specimens is preferred. Clarified specimens may be stored up to one week at 2 to 8°C. If testing will be delayed more than one week, specimens may be stored frozen (≤ -10°C) up to four weeks prior to being tested (acceptance criterion ± 10%). Care should be taken to limit the number of freeze-thaw cycles. Specimens were shown to withstand 3 freeze-thaw cycles when stored at -20°C.
- **Handle all patient specimens as if they were potentially infectious.**

8 Procedure

Materials Provided
ARK Gabapentin Assay – **REF** 5025-0001-00
ARK Gabapentin Assay, Roche® cobas c pack – **REF** 5025-0001-01

Materials Required – Provided Separately
ARK Gabapentin Calibrator – **REF** 5025-0002-00
Quality Controls – ARK Gabapentin Control – **REF** 5025-0003-00

Instruments
Reagents R1 and R2 may need to be transferred to analyzer-specific reagent containers prior to use. Avoid cross-contamination of R1 and R2. Many automated clinical chemistry analyzers with photometric rate determination at 340 nm are suitable. Consult the analyzer-specific application sheet for programming the ARK Gabapentin Assay, available from your distributor or ARK Customer Service. Application Protocol Sheets which have been CLIA categorized or bear the CE Mark have been verified by the manufacturer. It is the responsibility of the laboratory to perform all appropriate validation for use of the assay with other settings or analyzers.

Refer to the instrument-specific operator's manual for daily maintenance.

Assay Sequence
To run or calibrate the assay, see the instrument-specific operator's manual.

Calibration
Perform a full calibration (6- point) procedure using the ARK Gabapentin Calibrators A, B, C, D, E, and F; run calibrators in duplicate. Calibration is required with each new reagent kit lot number. Verify the calibration curve with at least two levels of quality controls according to the established laboratory quality assurance plan.

When to Re-Calibrate
- Whenever a new lot number of reagents is used
- Whenever indicated by quality control results
- Whenever required by standard laboratory protocols

Quality Control (QC)
Laboratories should establish QC procedures for the ARK Gabapentin Assay. All quality control requirements and testing should be performed in conformance with local, state and/or federal regulations or accreditation requirements.

Good laboratory practice suggests that at least two levels (low and high medical decision points) of quality control be tested each day patient samples are assayed and each time a calibration is performed. Monitor the control values for any trends or shifts. If any trends or shifts are detected, or if the control does not recover within the specified range, review all operating parameters according to your clinical laboratory quality procedures. Contact Customer Service for further assistance.

Manual Dilution Protocol
To estimate drug levels in specimens exceeding the upper limit of quantitation, manually dilute the specimen with zero calibrator (CAL A). Multiply the assayed result by the dilution factor. A four-fold dilution factor is suggested.

$$\text{Manual Dilution Factor} = \frac{\text{(Volume of Specimen + Volume of CAL A)}}{\text{Specimen Volume}}$$

9 Results

Report result units as µg/mL or µmol/L. To convert results from µg/mL gabapentin to µmol/L gabapentin, multiply µg/mL by 5.84. The gabapentin value from this assay should be used in conjunction with other clinical information. Refer to the instrument specific operator's manual for any result error codes.

10 Limitations of Procedure

This assay is designed for use with serum or plasma only; refer to the sections **Specimen Collection and Preparation for Analysis**. It is generally good practice to use the same method (as well as matrix) consistently for individual patient care due to the potential for method-to-method variabilities. See the section **Expected Values** below.

11 Expected Values

A therapeutic range for gabapentin has not been well established. A reference range of 2 µg/mL to 20 µg/mL[2, 3] has been proposed. Studies have suggested that optimal responses to gabapentin in patients with difficult-to-treat partial seizures are achieved at concentrations >2 µg/mL[4] or in a range of 4 to 11 µg/mL[5], while others proposed a higher range of 6 to 21 µg/mL[2]. It has been reported that toxicity with gabapentin tends to occur with increasing frequency when serum concentrations exceed 25 µg/mL.[6] Interindividual variability may be influenced by dose-related saturable drug absorption, and hence, variable pharmacokinetic properties.[7]

Kidney impairment poses a significant risk for gabapentin accumulation and toxicity. As reported in the literature, [8-17] gabapentin toxicity in patients with impaired renal function can manifest as a coma, myoclonus, tremulousness, hearing loss, altered consciousness, altered mental status or rhabdomyolysis. Older patients without known renal disease may respond with higher gabapentin concentration-to-dose ratio than younger adults.[18]
Gabapentin drug concentrations should not be the only means of therapeutic drug management. The assay should be used in conjunction with information available from clinical evaluations and other diagnostic procedures. Clinicians should carefully monitor patients during therapy initiation and dosage adjustments. Multiple measurements of gabapentin may be needed.

The reference range of drug concentrations which is quoted should only imply a lower limit below which a therapeutic response is relatively unlikely to occur, and an upper limit above which toxicity is relatively likely to occur in the specific patient populations studied. Generally, clinicians using reference ranges such as these should be aware that, because of individual variation, patients may achieve therapeutic benefit with serum drug concentrations outside of these ranges and may experience toxicity with levels below the lower limit of the reference range. Because gabapentin has a relatively short half-life, sampling time in relation to dose ingestion is important for the interpretation of the drug concentration. Sampling time should be standardized such that trough serum concentrations are measured just before the next dosage, preferably in the morning.[3]

12 Specific Performance Characteristics

The following performance characteristics were obtained on the Roche/Hitachi 917 System. Each laboratory is responsible for verification of performance using instrument parameters established for their analyzer.

Sensitivity

Limit of Quantitation (LOQ)

The LOQ of the ARK Gabapentin Assay was determined according to CLSI EP17-A and is defined as the lowest concentration for which acceptable inter-assay precision and recovery is observed (≤20% CV with ±15% recovery). The LOQ was determined to be 0.75 µg/mL, and may depend on analyzer-specific performance.

Assay Range

The range of the assay is 0.75 to 40.0 µg/mL. Report results below this range as <0.75 µg/mL or below the analyzer-specific lower LOQ established in your laboratory. Report results above this range as >40.0 µg/mL or above the analyzer-specific upper LOQ established in your laboratory.

Recovery

Accuracy (analytical recovery) was performed by adding concentrated gabapentin drug into human serum negative for gabapentin. A stock concentrate of highly pure gabapentin was added volumetrically to human serum negative for gabapentin, representing drug concentrations across the assay range. Six replicates of each sample were assayed on an automated clinical chemistry analyzer. The results were averaged and compared to the target concentration and percent recovery calculated. Results are shown below.

$$\% \text{ Recovery} = 100 \times \frac{\text{Mean recovered concentration}}{\text{Theoretical concentration}}$$

Theoretical Concentration (µg/mL)	Mean Recovered Concentration (µg/mL)	Percent Recovery
1.0	0.99	98.5
2.0	2.07	103.3
3.5	3.55	101.3

9.0	8.98	99.7
16.0	16.03	100.2
22.0	22.00	100.0
28.0	27.85	99.5
35.0	35.59	101.7
40.0	41.49	103.7

Mean percent recovery: 100.9%

Linearity

Linearity studies were performed as suggested in CLSI/NCCLS Protocol EP6-A. A 48.0 µg/mL serum sample was prepared and dilutions were made proportionally with human serum negative for gabapentin. Gabapentin concentrations ranged from 0.75 to 48.0 µg/mL. Linearity at specific dilutions was considered acceptable if the percent difference was ±10% between the predicted 1st and 2nd order regressed values or ±15% ≤ 1.0 µg/mL. Results are shown below.

Theoretical (µg/mL)	Results (µg/mL)	1st Order Predicted Results	2nd Order Predicted Results	% Difference
0.75	0.73	0.76	0.85	12.0
1.0	1.0	1.0	1.1	8.4
2.4	2.4	2.4	2.4	2.2
3.2	3.3	3.2	3.2	1.1
4.8	4.9	4.8	4.8	0.0
8.0	8.0	8.0	7.9	-0.7
12.0	11.9	12.0	11.9	-0.9
24.0	23.6	23.9	23.8	-0.6
32.0	31.8	31.9	31.8	-0.3
40.0	39.7	39.8	39.9	0.2
48.0*	48.1	47.8	48.1	0.6

*Concentration exceeds the reportable limit.

Method Comparison

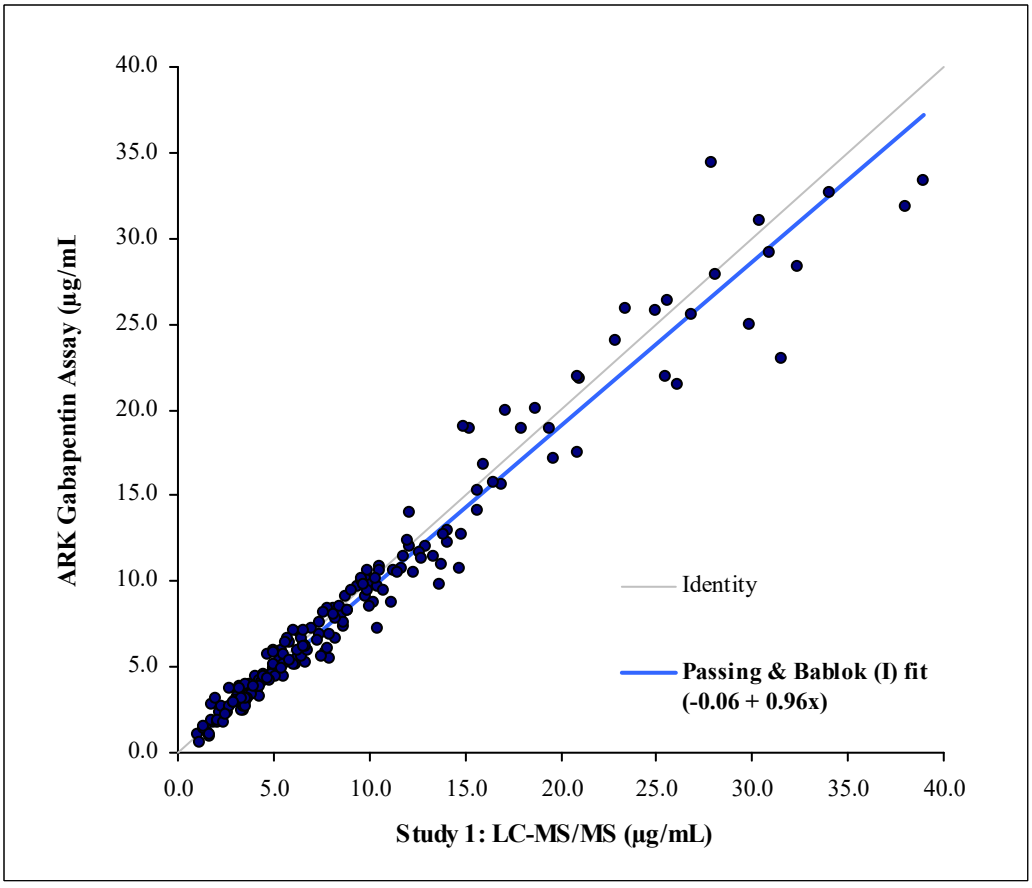
Correlation studies were performed using CLSI/NCCLS Protocol EP9-A2. Results from the ARK Gabapentin Assay were compared with results from three study sites using high performance liquid chromatography – mass

spectrometry methods (LC-MS/MS, Study 1), HPLC (Study 2) and LC-MS/MS (Study 3).

Study 1

Gabapentin concentrations by LC-MS/MS ranged 1.0 to 39.0 µg/mL. ARK gabapentin values ranged 0.6 to 34.4 µg/mL Results of the Passing-Bablok[19] regression analysis for the study are shown below (with 95% confidence limits).

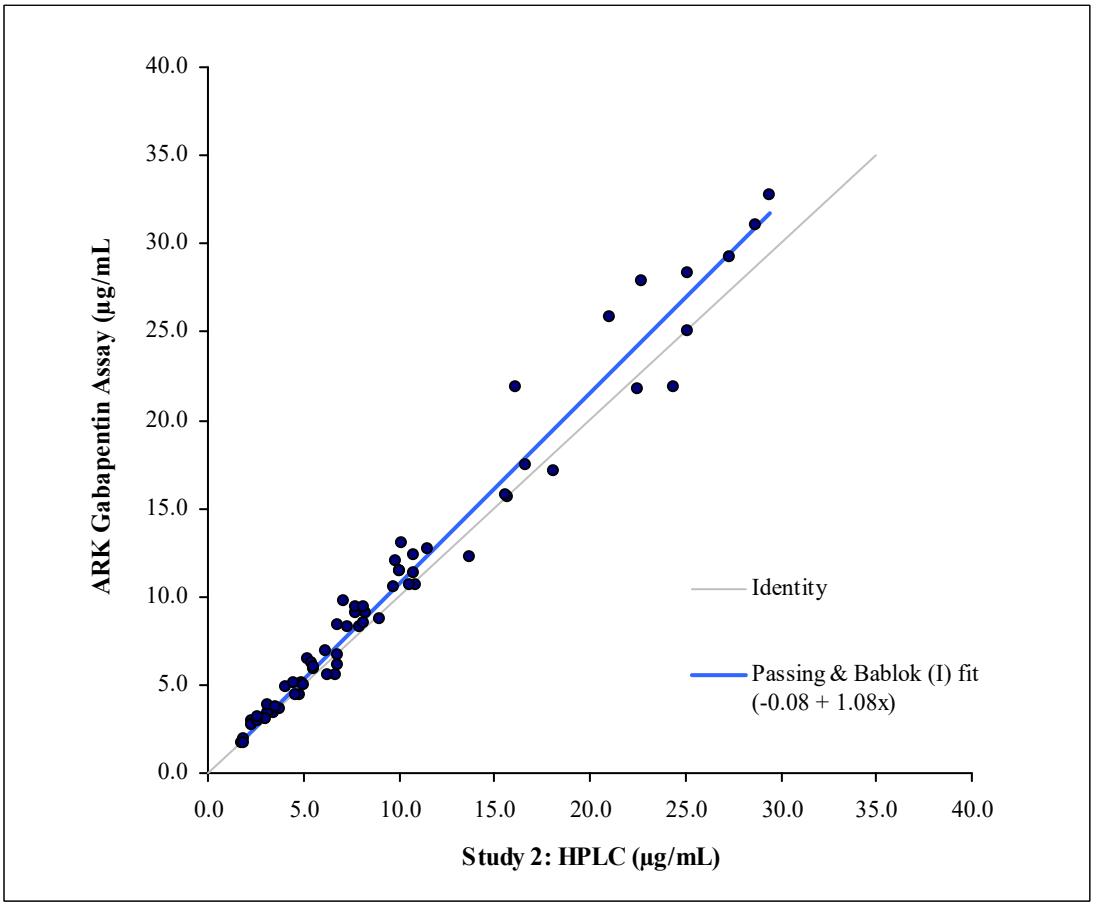
Slope	0.96	(0.92 to 0.99)
y-intercept	- 0.06	(- 0.28 to 0.18)
Correlation Coefficient (r^2)	0.96	(0.95 to 0.97)
Number of Samples	183	



Study 2

Gabapentin concentrations by HPLC ranged from 1.8 to 29.4 µg/mL. ARK gabapentin values ranged 1.6 to 32.6 µg/mL. Results of the Passing-Bablok[19] regression analysis for the study are shown below (with 95% confidence limits)..

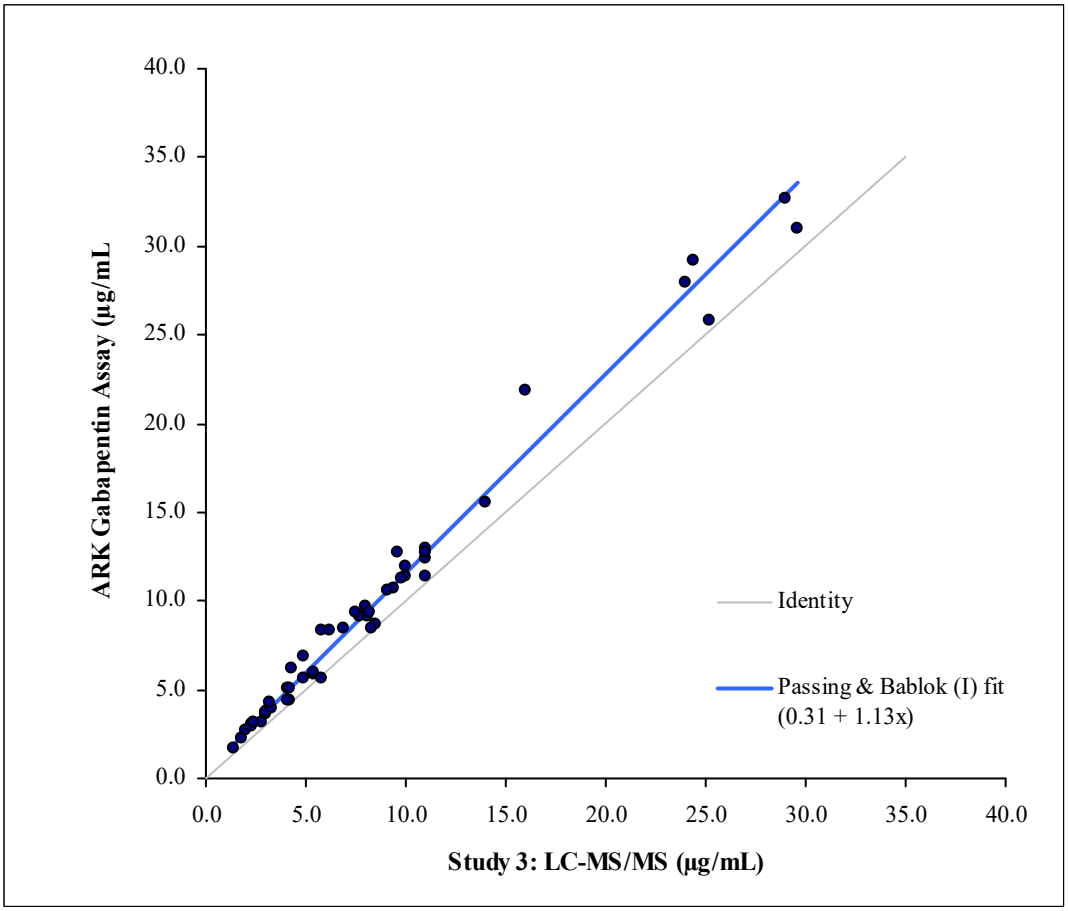
Slope	1.08	(1.03 to 1.13)
y-intercept	-0.08	(- 0.35 to 0.25)
Correlation Coefficient (r^2)	0.97	(0.95 to 0.98)
Number of Samples	64	



Study 3

Gabapentin concentrations by LC-MS/MS ranged 1.4 to 29.6 µg/mL. ARK gabapentin values ranged 1.6 to 32.6 µg/mL. Results of the Passing-Bablok[19] regression analysis for the study are shown below (with 95% confidence limits).

Slope	1.13	(1.08 to 1.17)
y-intercept	0.31	(0.06 to 0.52)
Correlation Coefficient (r^2)	0.98	(0.97 to 0.99)
Number of Samples	49	



Precision

Precision was determined as described in CLSI/NCCLS Protocol EP5-A2. Tri-level controls and three human serum pooled specimens containing gabapentin were used in the study. Each level was assayed in quadruplicate twice a day for 20 days. Each of the runs per day was separated by at least two hours. The within run, between day, total SD, and percent CVs were calculated. Results are shown below. Acceptance criteria: ≤10% total CV.

			Within Run		Between Day		Total	
Sample	**N**	**Mean (µg/mL)**	**SD**	**CV (%)**	**SD**	**CV (%)**	**SD**	**CV (%)**
ARK Gabapentin Control								
LOW	160	2.5	0.08	3.3	0.10	3.9	0.14	5.6
MID	160	7.9	0.21	2.6	0.26	3.3	0.35	4.4
HIGH	160	24.6	0.48	1.9	0.65	2.7	0.88	3.6
Human Serum								
LOW	160	2.2	0.11	4.7	0.11	4.8	0.17	7.7
MID	160	7.3	0.58	2.4	0.25	3.4	0.33	4.6
HIGH	160	24.9	0.54	2.2	0.97	3.9	1.17	4.7

Interfering Substances

Interference studies were conducted using CLSI/NCCLS Protocol EP7-A2 as a guideline. Clinically high concentrations of the following potentially interfering substances in serum with known levels of gabapentin (approximately 2 and 20 µg/mL) were evaluated. Each sample was assayed using the ARK Gabapentin Assay, along with a serum control of gabapentin. Measurement of gabapentin resulted in ≤10% error in the presence of interfering substances at the levels tested.

		Percentage Recovery	
Interfering Substance	**Interferent Concentration**	**2 µg/mL Gabapentin**	**20 µg/mL Gabapentin**
Albumin	12 g/dL	102.1	98.2
Bilirubin - conjugated	70 mg/dL	95.2	98.3
Bilirubin - unconjugated	70 mg/dL	106.6	98.4
Cholesterol	623 mg/dL	101.6	98.0
Gamma-Globulin	12 g/dL	103.2	99.7
Hemoglobin	1000 mg/dL	102.5	101.6
Intralipid®	1500 mg/dL	97.0	99.2

Rheumatoid Factor	1100 IU/mL	97.0	97.1
Triglycerides	1220 mg/dL	105.6	99.6
Uric Acid	30 mg/dL	106.6	97.9

Specificity

Gabapentin is eliminated from the systemic circulation solely by renal excretion as unchanged drug and is not appreciably metabolized in humans.[1] Therefore, no metabolites are known to result that could interfere in the measurement of gabapentin.

Medications that may be routinely co-administered with gabapentin, anti-epileptic drugs or L-amino acids were tested to determine whether these compounds affect the quantitation of gabapentin concentrations using the ARK Gabapentin Assay. High levels of these compounds were spiked into serum pools containing low (2 µg/mL) and high (20 µg/mL) therapeutic levels of gabapentin. The samples were analyzed and the gabapentin concentrations of samples containing co-administered with gabapentin, anti-epileptic drugs or L-amino acids were compared to the serum control.

Drug that Interferes - Pregabalin

Pregabalin was analyzed from 15 to 100 µg/mL in the presence of either Low (2 µg/mL) or High (20 µg/mL) gabapentin. High concentrations of pregabalin may interfere by elevating the measurement of gabapentin. Pregabalin plasma levels in patients under therapy have been reported to range from approximately 0.2 to 14.2 µg/mL.[20-23] Excessive pregabalin levels up to 60 µg/mL in combination with lamotrigine in a self-poisoning incident have been reported.[24] The results of interference testing are shown below.

Pregabalin (µg/mL)	Percent Crossreactivity		Percent Recovery	
	Gabapentin (2 µg/mL)	Gabapentin (20 µg/mL)	Gabapentin (2 µg/mL)	Gabapentin (20 µg/mL)
100	1.10	1.95	156.9	109.7
50	1.18	2.06	130.6	105.1
15	1.13	- 1.47	108.9	98.9

Care should be taken when interpreting ARK Gabapentin results if pregabalin is also being administered to the patient.

Drug Interference

Gabapentin-selective antibody did not crossreact with most other anti-epileptic or coadministered drugs tested. Due to structural similarities with

gabapentin, high pregabalin levels may interfere. A high concentration of each compound was spiked into normal human serum with known levels of gabapentin (approximately 2 and 20 µg/mL) and assayed along with a serum control of gabapentin. Measurement of gabapentin resulted in ≤10% error in the presence of drug compounds at the levels tested.

Compound	Concentration (µg/mL)	Percentage Recovery	
		Gabapentin (2 µg/mL)	Gabapentin (20 µg/mL)
γ-Aminobutyric Acid	100	97.8	99.2
L-2-Aminobutyric Acid	100	98.6	99.2
Acetaminophen	200	98.7	98.1
Acetazolamide	100	99.2	98.6
Acetylsalicylic acid	1000	100.6	100.4
Amikacin	100	100.2	98.7
Amitriptyline	20	98.2	97.9
Amoxapine	40	98.9	99.6
Amphotericin B	100	98.2	98.2
Ampicillin	100	100.8	100.0
Ascorbic Acid	100	97.3	98.3
Baclofen	100	103.3	100.6
Bupropion	40	106.9	100.6
Caffeine	100	99.8	99.8
Carbamazepine	120	99.4	98.9
Carbamazepine- 10, 11 epoxide	120	98.9	98.9
10-Hydroxy carbamazepine	100	102.8	100.4
Chloramphenicol	250	101.4	96.7
Chlorpromazine	20	103.1	100.8
Citalopram	20	102.8	100.8
Clobazam	100	96.3	108.0
Clonazepam	20	101.2	101.4
Cyclosporin A	40	95.1	97.2
Diazepam	20	102.6	100.5
Digoxin	80	103.0	101.8
Doxepin	20	103.9	101.2
Erythromycin	200	97.9	98.9
Ethanol	4000 (0.4%)	105.2	99.3
Ethotoin	100	97.1	97.5
Ethosuximide	250	95.8	99.6
Felbamate	250	98.2	99.1
Fluoxetine	20	103.8	101.2
Furosemide	100	95.2	98.0
Gentamicin	100	100.0	100.4
Haloperidol	20	102.5	101.7
Heparin	200 U/mL	94.8	96.2
Ibuprofen	500	96.5	96.9

Compound	Concentration (µg/mL)	Percentage Recovery	
		Gabapentin (2 µg/mL)	Gabapentin (20 µg/mL)
Imipramine	20	101.2	101.1
Kanamycin B	200	96.7	101.3
Lamotrigine	250	102.9	95.9
Levetiracetam	400	97.4	96.0
Lidocaine	100	97.7	98.7
Lincomycin	1000	102.4	100.4
Mephenytoin	100	100.6	99.6
Mesoridazine	40	106.2	96.2
Methicillin	250	101.5	98.0
Naproxen	600	100.2	97.3
Neomycin	1000	97.8	102.1
Niacin	100	98.9	100.3
Nitrazepam	20	96.5	97.5
Nortriptyline	20	101.6	97.1
Olanzapine	20	99.9	98.5
Oxcarbazepine	200	100.9	100.8
Paroxetine	40	102.4	96.0
2-phenyl-ethyl--malonamide (PEMA)	1000	105.8	98.7
Penicillin V	100	95.8	99.0
Perphenazine	100	102.4	99.0
Phenobarbital	200	100.3	98.3
Phenytoin	200	96.9	93.6
Primidone	100	93.0	99.1
Procainamide	100	95.9	95.9
Prochlorperazine	40	97.8	98.7
Ranitidine	100	97.2	98.3
Rifampin	100	95.3	102.4
Risperidone	20	101.8	103.2
Sertraline	100	98.5	97.5
Spectinomycin	100	98.3	102.1
Stiripentol	100	95.9	96.7
Sulfamethoxazole	400	97.5	98.0
Theophylline	200	103.0	100.5
Thioridazine	20	102.6	102.5
Tobramycin	100	94.6	100.3
Tiagabine	200	91.6	97.9
Topiramate	250	96.9	96.9
Trimethoprim	40	96.7	99.0
Valproic Acid	600	96.7	96.9
Vancomycin	250	100.3	99.8
Vigabatrin	150	101.3	99.9
Zonisamide	400	98.6	104.1

L-Amino Acid Interference

The L-amino acids listed below resulted in <10% error in detecting gabapentin at the concentrations tested.

Compound	Concentration (µg/mL)	Percentage Recovery	
		Gabapentin (2 µg/mL)	Gabapentin (20 µg/mL)
L-Arginine	100	96.9	104.4
L-Asparagine	100	95.1	101.8
L-Aspartic Acid	25	93.9	102.0
L-Cysteine	25	92.6	101.9
L-Glutamic Acid	100	95.7	101.4
L-Glycine	100	98.0	100.8
L-Histidine	100	92.2	102.5
L-Isoleucine	100	92.2	101.9
L-Leucine	100	96.3	101.5
L-Methionine	25	93.3	100.9
L-Phenylalanine	50	94.4	99.6
L-Serine	50	95.1	99.3
L-Threonine	100	95.6	100.7
L-Tyrosine	100	93.9	99.0
L-Alanine	150	98.9	97.0
L-Lysine	150	97.8	98.2
L-Proline	150	96.0	98.3
L-Valine	150	97.5	97.7
L-Tryptophan	150	98.0	99.1
L-Glutamine	350	97.3	96.9

13 References

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14 Trademarks

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