

**510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
ASSAY ONLY TEMPLATE**

A. 510(k) Number:

k060690

B. Purpose for Submission:

New device

C. Measurand:

Valproic acid

D. Type of Test:

Quantitative, homogeneous enzyme immunoassay

E. Applicant:

Roche Diagnostics Corporation

F. Proprietary and Established Names:

ONLINE TDM Valproic Acid

G. Regulatory Information:

Product Code	Classification	Regulation Section	Panel
<u>Enzyme Immunoassay, Valproic Acid (LEG)</u>	<u>Class II</u>	<u>21 CFR 862.3645, Neuroleptic drugs radioreceptor assay test system.</u>	<u>91 CLINICAL TOXICOLOGY (TX)</u>

H. Intended Use:

1. Intended use(s):

The ONLINE TDM Valproic Acid assay is for the quantitative determination of valproic acid in human serum or plasma on Roche automated clinical chemistry analyzers.

2. Indication(s) for use:

The ONLINE TDM Valproic Acid assay is for the quantitative determination of valproic acid in human serum or plasma on Roche automated clinical chemistry analyzers. Measurements obtained from this device are used in the diagnosis and treatment of valproic acid overdose and to help ensure appropriate therapy.

3. Special conditions for use statement(s):

For professional use only

4. Special instrument requirements:

Evaluations represented in the 510(k) were performed on the Hitachi 917. See manufacturer's application sheets for other instruments validated with this assay.

I. Device Description:

The device consists of 2 ready-to-use reagent mixes (R1 and R2). R1 contains anti-valproic antibody (mouse monoclonal), glucose-6-phosphate, NAD and bovine serum albumin in buffer. R2 contains valproic acid labeled with bacterial glucose-6-phosphate dehydrogenase in bovine serum albumin with buffer. Calibrators and controls to be used with the assay are sold separately

J. Substantial Equivalence Information:

Predicate	k951595, COBAS Integra Valproic Acid					
Describe the item being compared						
The Roche ONLINE TDM Valproic Acid assay is similar in intended use to the currently marketed Roche COBAS INTEGRA Valproic Acid assay (k951595).						
Similarities						
The ONLINE TDM Valproic Acid and the COBAS INTEGRA Valproic Acid assays are both indicated for the quantitative determination of valproic acid in human serum or plasma on automated clinical analyzers.						
Differences						
The predicate device uses fluorescence polarization immunoassay technology; the new device is a homogeneous enzyme immunoassay. The comparison of total precision for the 2 devices is shown below:						
	Roche Online TDM			Roche Cobas FP		
CLSI Total Precision						
Mean (ug/mL)	33.3	74.9	107.8	26.2	60.1	102.0
SD (ug/mL)	2.07	3.75	5.02	0.61	1.26	2.46
CV %	6.2	5.0	4.7	2.3	2.1	2.4

K. Standard/Guidance Document Referenced (if applicable):

Guidance for Industry and FDA Staff; Replacement Reagent and Instrument Family Policy

L. Test Principle:

The assay uses a homogeneous enzyme immunoassay technique based on competition between drug in the sample and drug labeled with the enzyme glucose-6-phosphate dehydrogenase (G6PDH) for antibody binding sites. Active enzyme converts oxidized nicotinamide adenine dinucleotide (NAD) to NADH, resulting in an absorbance change that is measured spectrophotometrically. Enzyme activity decreases upon binding to the antibody, so the drug concentration in the sample can be measured in terms of enzyme activity.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

a. *Precision/Reproducibility:*

Within-lab precision was evaluated at the manufacturer’s site on the Hitachi 911 and 917 analyzers. One run consisting of triplicates of each sample was performed each day over 21 days. The evaluation was performed by one operator using one lot of reagents and controls. Control material and spiked human serum pools were evaluated. Calculations were performed according to CLSI EP-5A, appendix C. Results are shown below.

Sample	TDM I	TDM II	TDM III	Low HSP	High HSP
Total mean	33.34	74.93	107.82	43.92	101.33
Within-run imprecision SD (ug/mL)	0.69	1.42	2.11	0.78	1.47
Within-run imprecision CV %	2.1%	1.9%	2.0%	1.8%	1.4%
Total imprecision SD (ug/mL)	6.2%	5.0%	4.7%	5.0%	4.6%
Total imprecision CV %					

b. *Linearity/assay reportable range:*

The linear range is 2.8 - 150.0 µg/mL. To determine the linearity of the assay, an evenly distributed dilution series was prepared using a valproic acid spiked human serum pool diluted with a non-spiked serum pool. Recoveries shown below represent the observed result (median value, n=3) divided by the expected result X 100%. The expected result is the starting concentration multiplied by the dilution factor.

	Observed result (median value, n=3)	Expected result	Recovery
1	0.0	0.0	N/A
2	16.0	17.1	93.6%
3	32.3	34.2	94.4%
4	51.6	51.3	100.6%
5	67.0	68.4	98.0%
6	85.5	85.5	100.0%
7	97.5	102.6	95.0%
8	112.9	119.7	94.3%
9	137.1	136.8	100.2%
10	153.7	153.9	99.9%
11	171.0	180.0	95.0%

An additional series was evaluated to include the low end of the assay range. Samples from patients treated with valproic acid were diluted with negative serum samples. Results are shown below:

Patient Sample	Observed result, median value (n=3)	Expected result	Recovery
1	2.8	3.1	90.6%
	3.0	3.7	80.9%
	4.6	4.9	93.0%
	8.0	7.7	103.6%
	13.6	13.7	99.0%
2	30.9	N/A	N/A
	3.1	3.7	84.0%
	4.0	4.4	90.3%
	5.9	5.9	99.9%
	8.9	9.2	96.5%
3	18.2	18.5	98.6%
	36.9	N/A	N/A
	3.9	4.7	82.8%
	4.4	5.7	77.8%
	6.9	7.5	91.6%
4	10.8	11.8	91.7%
	24.0	23.6	101.9%
	47.1	N/A	N/A
	4.1	4.9	83.7%
	5.4	5.9	91.8%
5	7.2	7.8	91.8%
	13.1	12.3	106.9%
	26.1	24.5	106.5%
	49.0	N/A	N/A

Dilution of high samples:

The package insert instructs customers to manually dilute (1:1) samples with Preciset TDM I Diluent when results exceed the reportable range. Validation of this procedure resulted in percent differences between expected and observed values within +/-3%.

c. *Traceability, Stability, Expected values (controls, calibrators, or methods):*

Calibrators were cleared under k031856. Controls were cleared under k060429.

d. *Detection limit:*

The manufacturer defines the detection limit as the mean plus 2 standard deviations of the 0 calibrator. For this evaluation, the assay was calibrated as in the normal procedure. The 0 Calibrator was measured in 21 replicates and Calibrator B in 5 replicates in a single run and absorbance values were recorded. Results support the detection limit of 2.8 ug/mL.

e. *Analytical specificity:*

The assay was evaluated on the Hitachi 917 for interference from drugs, and endogenous compounds.

Cross-reactivity:

The following compounds were tested for cross-reactivity in serum samples containing approximately 60 ug/mL valproic acid. Results were compared to those of control samples without cross-reactant.

Compound	Maximum concentration tested (ug/mL)	Percent cross reactivity
2-Propyl glutaric acid	400	1.6
Carbamazepine	1000	ND
Clonazepam	100	ND
Diazepam	100	ND
Ethosuximide	1000	ND
Phenobarbital	750	ND
Phenytoin	1000	ND
Primidone	1000	ND
2-n-Propyl-3-hydroxy-pentanoic acid (Rac-erythro-3-hydroxy	100	ND

valproic acid)	100	4.1
2-n-Propyl-3-hydroxy-pentanoic acid (Rac-threo-3-hydroxy valproic acid)	100	4.5
2-n-Propyl-4-hydroxy-pentanoic acid	50	ND
2-n-Propyl-5-hydroxy-pentanoic acid	20	ND
2-Propyl-2-pentenoic acid	10	35
20	100	ND
2-Propyl-4-pentenoic acid		
2-n-Propyl-3-oxo-pentanoic acid	500	ND
2-Propyl succinic acid		

Other drugs:

The drugs listed below were spiked into normal human serum pools containing valproic acid at 50 µg/mL and the drug levels shown below. The manufacturer indicated that the drug levels evaluated were at a concentration greater than what would be expected for a maximum daily dose. Control samples were serum spiked with valproic acid, without any additional added drug. The drugs and concentrations tested are shown below. Less than 10% interference was observed.

Drug (maximum concentration tested)
Acetyl cysteine (150 ug/mL)
Ampicillin-Na (1000 ug/mL)
Ascorbic acid (300 ug/mL)
K-Dobesilate (200 ug/mL)
Cyclosporine (5000 ng/mL)
Cefoxitin-Na (2500 ug/mL)
Heparin (5 ug/mL)
Levodopa (20 ug/mL)
Methyldopa + 1,5 (20 ug/mL)
Metronidazole (200 ug/mL)
Phenylbutazone (400 ug/mL)
Doxycycline HCl (50 ug/mL)
Acetylsalicylic acid (1 mg/mL)
Rifampicin (60 ug/mL)
Acetaminophen (200 ug/mL)

Ibuprofen (500 ug/mL)
Theophylline (100 ug/mL)

Endogenous substances:

The effect of endogenous substances on assay recovery was evaluated using spiked serum pools containing 50 and 100µg/mL valproic acid. Dilution series of the endogenous compounds listed were prepared and each level was evaluated in triplicate. The following concentrations showed less than 10% interference.

I index of 1-30 (approximate conjugated and unconjugated bilirubin concentration: 30 mg/dL)

H index of 0-300 (approximate hemoglobin concentration: 300 mg/dL)

Lipemic index of 0-500 (0-500 mg/dL intralipid).

HAMA 1 and HAMA 2 samples

Rheumatoid factors up to 100 IU/mL.

Total protein 2-12 g/dL.

Triglycerides up to 1000 mg/dL

f. Assay cut-off:

Not applicable. This is a quantitative assay.

2. Comparison studies:

a. Method comparison with predicate device:

A comparison of the ONLINE TDM Valproic Acid assay on the Roche/Hitachi 917 analyzer (y) with a commercially available method (CEDIA Valproic Acid II) on a Roche/Hitachi 911 analyzer (x) was performed at the manufacturer's site. Fifty four non-pooled human samples were assayed in singlicate in 1 run. Sample concentrations ranged between 15 and 132 µg/mL. Results of analysis are shown:

Passing/Bablok:

$$y = 0.939 x + 0.973$$

$$r=0.997$$

$$SD (md 95) = 3.365$$

Another evaluation compared the same samples on the ONLINE TDM Valproic Acid assay on a Roche/Hitachi 917 analyzer (y) with a commercially

available method (COBAS FP Valproic Acid). Results of analysis are shown:

Passing/Bablok:

$$1.017x - 0.053$$

$$r = 0.995$$

$$SD(md\ 95) = 4.801$$

The patient sample data listed in the linearity section above (concentration range 3-50) was evaluated by comparing observations from the Roche FP to those from the INTEGRA 700. Results of analysis are:

$$y = 1.026x - 0.8, r = 0.99$$

b. *Matrix comparison:*

A series of serum samples were tested and compared to concentration equivalent plasma samples. No significant matrix effects were observed. Results are shown below:

Sample type	Min x	Max x	Slope	Inter cept	r
X: Serum, Y: Li Heparin	27.4	129.1	0.988	0.112	0.99
X: Serum Y: 1/2 fill Li Heparin	27.9	129.1	1.017	2.175	0.99
X: Serum Y: Na Heparin	28.4	115.3	1.012	0.141	0.98
X: Serum Y: 1/2 fill Na Heparin	28.4	111.9	1.063	3.552	0.99
X: Serum Y: K2 EDTA	27.4	129.1	0.997	2.197	0.99
X: Serum Y: 1/2 fill K2 EDTA	27.4	129.1	0.966	0.844	0.99
X: Serum Y: K3 EDTA	28.4	115.3	1.046	3.064	0.99
X: Serum Y: 1/2 fill K3 EDTA	29.0	115.3	0.994	0.653	0.99

3. Clinical studies:

a. *Clinical Sensitivity:*

Not typically submitted for this device type

b. Clinical specificity:

Not typically submitted for this device type

c. Other clinical supportive data (when a. and b. are not applicable):

4. Clinical cut-off:

Not applicable

5. Expected values/Reference range:

Ranges based on the literature are presented in the package insert.

N. Proposed Labeling:

The labeling is sufficient and it satisfies the requirements of 21 CFR Part 809.10.

O. Conclusion:

The submitted information in this premarket notification is complete and supports a substantial equivalence decision.