510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
ASSAY ONLY

I Background Information:

A 510(k) Number

K221605

B Applicant

Siemens Healthcare Diagnostics, Inc.

C Proprietary and Established Names

Emit® II Plus Buprenorphine Assay

D Regulatory Information

Product Code(s)	Classification	Regulation Section	Panel
DJG	Class II	21 CFR 862.3650 - Opiate Test System	TX - Clinical Toxicology

II Submission/Device Overview:

A Purpose for Submission:

Modified device

B Measurand:

Buprenorphine

C Type of Test:

Qualitative and semiquantitative immunoassay

III Intended Use/Indications for Use:

A Intended Use(s):

See Indication(s) for Use below.

B Indication(s) for Use:

The Emit® II Plus Buprenorphine Assay is a homogeneous enzyme immunoassay with a 5 ng/mL cutoff. The assay is intended for use in laboratories for the qualitative and/or semiquantitative analyses of buprenorphine in human urine. Emit® II Plus assays are designed for use with a number of chemistry analyzers.

The semiquantitative mode is for the purpose of enabling laboratories to determine an appropriate dilution of the specimen for confirmation by a confirmatory method such as Liquid Chromatography/Mass Spectrometry (LC/MS) or permitting laboratories to establish quality control procedures.

The Emit® II Plus Buprenorphine Assay provides only a preliminary analytical test result. A more specific alternative chemical method(s) must be used to obtain a confirmed analytical result. Gas Chromatography/Mass Spectrometry (GC/MS) or LC/MS are the preferred confirmatory methods. Other chemical confirmation methods are available. Clinical consideration and professional judgment should be applied to any drug-of-abuse test result, particularly when preliminary positive results are used.

For Professional Use.

Caution: Federal (USA) law restricts this device to sale by or on the order of a licensed healthcare professional.

For in vitro diagnostic use.

C Special Conditions for Use Statement(s):

For Prescription Use Only.

D Special Instrument Requirements:

All performance studies were conducted on the DxC 500 AU Clinical Chemistry Analyzer.

IV Device/System Characteristics:

A Device Description:

The Emit® II Plus Buprenorphine Assay is a homogeneous enzyme immunoassay consisting of the following components:

Antibody/Substrate
Reagent 1
Mouse monoclonal antibodies to buprenorphine (0.53 µg/mL) NAD (6.9 mM), G6P (10.9 mM), bovine serum albumin, preservatives, and stabilizers.

Enzyme
Reagent 2
Norbuprenorphine labeled with bacterial rG6PDH (0.50 µg/mL), HEPES buffer, bovine serum albumin, preservatives, and stabilizers.

B Principle of Operation:

The Emit® II Plus Buprenorphine Assay is a homogenous enzyme immunoassay. The assay is based upon competition between drug in the specimen and drug labeled with the recombinant glucose-6-phosphate dehydrogenase (rG6PDH) for the antibody binding sites. Active enzyme converts nicotinamide adenine dinucleotide (NAD) to NADH in the presence of glucose-6-phosphate (G6P), resulting in an absorbance change that is measured spectrophotometrically.

V Substantial Equivalence Information:

A Predicate Device Name(s):

Emit® II Plus Buprenorphine Assay

B Predicate 510(k) Number(s):

K150606

C Comparison with Predicate(s):

Device & Predicate Device(s):	Emit® II Plus Buprenorphine Assay (K221605)	Emit® II Plus Buprenorphine Assay (K150606)
Device Trade Name	Emit® II Plus Buprenorphine Assay	Same
General Device Characteristic Similarities		
Intended Use/Indications For Use	A homogeneous enzyme immunoassay with a 5 ng/ml cutoff. The assay is intended for use in laboratories for the qualitative and/or semiquantitative analyses of buprenorphine in human urine.	Same
General Device Characteristic Differences		
Instrument	DxC 500 AU Clinical Chemistry Analyzer	Viva-E Analyzer

VI Standards/Guidance Documents Referenced:

CLSI Guideline EP09c, Measurement Procedure Comparison and Bias Estimation Using Patient Samples – Third Edition

CLSI Guideline EP12-A2, User Protocol for Evaluation of Qualitative Test Performance; Approved Guideline—Second Edition

CLSI EP05-A3, Evaluation of Precision of Quantitative Measurement Procedures: Approved Guideline -Third Edition.

CLSI Guideline EP17-A2, Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures; Approved Guideline – Second Edition

CLSI Guideline EP07, Interference Testing in Clinical Chemistry.- Third Edition

VII Performance Characteristics (if/when applicable):

1. Analytical Performance:

a. *Precision/Repeatability and Within-lab Precision:*

Repeatability and within lab precision studies were conducted using urine pools spiked with Buprenorphine into drug free human urine at 11 concentrations. For each level, samples were analyzed in duplicate twice a day, for 20 days (N=80). The precision study design was guided by recommendations in CLSI EP05-A3. The results are summarized below for the qualitative and semi-quantitative analyses.

Precision: Qualitative mode

Sample Conc. (ng/mL)	% of the Cutoff	# of Results	Repeatability Results (Pos/Neg)	Within-Lab (Pos/Neg)
0.00	-100%	80	80 Negative	80 Negative
1.25	-75%	80	80 Negative	80 Negative
2.5	-50%	80	80 Negative	80 Negative
3.0	-40%	80	80 Negative	80 Negative
3.75	-25%	80	80 Negative	80 Negative
5.0	0%	80	21 Negative 59 Positive	21 Negative 59 Positive
6.25	+25%	80	80 Negative	80 Negative
7.0	+40%	80	80 Negative	80 Negative
7.5	+50%	80	80 Negative	80 Negative
8.75	+75%	80	80 Negative	80 Negative
10.0	100%	80	80 Negative	80 Negative

Precision: Semi-quantitative mode

					Repeatability		Within-Lab Precision	
Sample Conc. (ng/mL)	% of the Cutoff	# of Results	Results (Pos/Neg)	Mean (ng/mL)	SD	%CV	SD	%CV
0.00	-100%	80	80 Negative	0.1	0.06	-	0.11	-
1.25	-75%	80	80 Negative	1.2	0.08	6.6	0.08	6.6
2.5	-50%	80	80 Negative	2.3	0.09	3.7	0.11	4.6
3.0	-40%	80	80 Negative	2.7	0.07	2.8	0.15	5.7
3.75	-25%	80	80 Negative	3.3	0.08	2.5	0.15	4.4
5.0	0%	80	21 Negative 59 Positive	5.1	0.08	1.6	0.18	3.5
6.25	+25%	80	80 Negative	6.1	0.11	1.3	0.21	3.4
7.0	+40%	80	80 Negative	6.8	0.08	1.7	0.24	3.5
7.5	+50%	80	80 Negative	7.3	0.10	1.1	0.21	2.9
8.75	+75%	80	80 Negative	8.8	0.10	1.1	0.24	2.8
10.0	100%	80	80 Negative	9.7	0.10	1.1	0.37	3.8

Reproducibility studies were conducted with urine samples at 3 concentration levels using the semi-quantitative mode. Samples were assayed in 5 replicates in 1 run for 5 days using 3 instruments and 3 reagent lots. The data were analyzed to calculate the following components of precision: repeatability, between-day, between-lot, between-instrument, and total reproducibility.

			Repeatability		Between-day		Between-lot	
Urine Conc. (ng/mL)	N	Mean (ng/mL)	SD	%CV	SD	%CV	SD	%CV
3	225	3.1	0.11	3.6	0.06	1.8	0.03	0.8
5	225	5.0	0.11	2.2	0.07	1.4	0.00	0.0
7	225	7.1	0.12	1.70	0.08	1.2	0.05	0.15

			Between-instrument		Total Reproducibility	
Urine Conc. (ng/mL)	N	Mean (ng/mL)	SD	%CV	SD	%CV
3	225	3.1	0.11	3.4	0.17	5.3
5	225	5.0	0.13	2.6	0.18	3.7
7	225	7.1	0.15	2.1	0.21	3.0

b. *Linearity/assay reportable range:*

Drug free urine pools were spiked with nine concentrations of buprenorphine at levels 2.2 - 25.6 ng/mL and analyzed semi-quantitatively in five replicates using the Emit® II Plus Buprenorphine Assay system. The mean observed buprenorphine concentration was compared to the expected Buprenorphine concentration and percent recovery results shown in the table below. Expected concentrations were confirmed by Liquid Chromatography/Tandem Mass Spectrometry.

Expected Buprenorphine Conc (ng/mL)	Mean Buprenorphine Conc. by Emit® II Plus Buprenorphine Assay (ng/mL)	% Recovery
2.2	1.9	86
3.2	2.9	91
4.4	4.1	93
5.1	4.9	96
8.8	7.6	86
13.1	11.6	89
18.1	18.1	100
22.9	22.9	100
25.6	24.7	96

c. *Analytical Specificity/Interference:*

The experimental design was one (1) reagent lot, one (1) calibrator lot, one (1) instrument, one (1) sample pool for each compound tested. The samples were assayed in five (5) replicates. The samples were evaluated on the DxC 500 AU Clinical Chemistry Analyzer.

Buprenorphine Metabolite Recovery:
Buprenorphine and the buprenorphine metabolites: norbuprenorphine, buprenorphine glucuronide, and norbuprenorphine glucuronide were spiked into aliquots of drug free urine

at the levels shown and run in replicates of 5. The samples were assayed, and the mean recovery results were determined and shown in the table below.

Buprenorphine and Buprenorphine Metabolites Recovery

Compound	Conc. tested (ng/mL)	Mean (ng/mL)	Cutoff (ng/mL)	% Cross-reactivity
Buprenorphine	5	4.9	5.0	98%
Norbuprenorphine	5	5.3	5.0	106%
Buprenorphine Glucuronide	1000	1.4	5.0	0.10%
Norbuprenorphine Glucuronide	1000	1.4	5.0	0.10%

Structurally Related Compounds:

Samples were prepared by spiking drug-free human urine with individual cross-reactants to the targeted level. The samples were evaluated on the DxC 500 AU analyzer. All samples were tested in replicates of 5.

Cross-Reactivity with the Structurally Related Drugs

Compound	Conc. Tested (ng/mL)	Qual. Result (Pos/Neg)	Semi-quant. Result (Pos/Neg)	% Cross-reactivity
6-acetylcodeine	100000	Neg	Neg	<0.01
6-acetylmorphine	100000	Neg	Neg	<0.01
Codeine	100000	Neg	Neg	<0.01
Dextromethorphan	100000	Neg	Neg	<0.01
Dihydrocodeine	100000	Neg	Neg	<0.01
Ethyl Morphine	100000	Neg	Neg	<0.01
Heroin	100000	Neg	Neg	<0.01
Hydrocodone	100000	Neg	Neg	<0.01
Hydromorphone	100000	Neg	Neg	<0.01
Levorphanol	100000	Neg	Neg	<0.01
Morphine	100000	Neg	Neg	<0.01
Morphine 3-glucuronide	100000	Neg	Neg	<0.01
Morphine 6-glucuronide	100000	Neg	Neg	<0.01
Nalorphine	100000	Neg	Neg	<0.01
Naloxone	100000	Neg	Neg	<0.01
Naltrexone	100000	Neg	Neg	<0.01
Norcodeine	100000	Neg	Neg	<0.01
Normorphine	100000	Neg	Neg	<0.01
Noroxycodone	100000	Neg	Neg	<0.01
Noroxymorphone	100000	Neg	Neg	<0.01
Oxycodone	100000	Neg	Neg	<0.01

Oxymorphone	100000	Neg	Neg	<0.01

Structurally Unrelated Compounds:
The following structurally unrelated compounds were added into drug-free urine spiked with the measurand to form two concentration levels, ±40% (3ng/mL and 7 ng/mL, respectively) of the cutoff concentration. All samples were tested in 5 replicates. The substances listed in the table below do not yield a false response relative to the cutoff in both qualitative and semi-quantitative mode.

Interference (Structurally Unrelated Compounds)	Conc. Tested (µg/mL)	-40% Cutoff (3 ng/mL)		+40% Cutoff (7 ng/mL)	
		Qualit. Result Pos/Neg	Semi-quant. Result Pos/Neg	Qualit. Result Pos/Neg	Semi-quant. Result Pos/Neg
10, 11-dihydrocarbamazepine	85	Neg	Neg	Pos	Pos
Acetaminophen	1000	Neg	Neg	Pos	Pos
Acetylsalicylic Acid	1500	Neg	Neg	Pos	Pos
Amitriptyline	100	Neg	Neg	Pos	Pos
Amoxicillin	500	Neg	Neg	Pos	Pos
ZT (Zidovudine)	2000	Neg	Neg	Pos	Pos
Benzoylecgonine	1000	Neg	Neg	Pos	Pos
Brompheniramine	75	Neg	Neg	Pos	Pos
Caffeine	1000	Neg	Neg	Pos	Pos
Captopril	500	Neg	Neg	Pos	Pos
Chlordiazepoxide	100	Neg	Neg	Pos	Pos
Chlorpromazine	10	Neg	Neg	Pos	Pos
Cimetidine	1000	Neg	Neg	Pos	Pos
Clomipramine	2.5	Neg	Neg	Pos	Pos
Clonidine	1000	Neg	Neg	Pos	Pos
Cyclobenzaprine	125	Neg	Neg	Pos	Pos
d-amphetamine	700	Neg	Neg	Pos	Pos
Desipramine	800	Neg	Neg	Pos	Pos
Diazepam	100	Neg	Neg	Pos	Pos
Digoxin	0.01	Neg	Neg	Pos	Pos
Diphenhydramine	1000	Neg	Neg	Pos	Pos
d-methamphetamine	500	Neg	Neg	Pos	Pos
Doxepin	100	Neg	Neg	Pos	Pos
EDDP	1000	Neg	Neg	Pos	Pos
EMDP	100	Neg	Neg	Pos	Pos
Enalapril	500	Neg	Neg	Pos	Pos
Fluoxetine	500	Neg	Neg	Pos	Pos
Glutethimide	500	Neg	Neg	Pos	Pos

Haloperidol	100	Neg	Neg	Pos	Pos
Hydroxyzine	500	Neg	Neg	Pos	Pos
Ibuprofen	1000	Neg	Neg	Pos	Pos
Imipramine	200	Neg	Neg	Pos	Pos
Ketamine	100	Neg	Neg	Pos	Pos
Ketorolac Tromethamine	400	Neg	Neg	Pos	Pos
LAAM (L-a-acetylmethadol)	25	Neg	Neg	Pos	Pos
L-Cotinine	100	Neg	Neg	Pos	Pos
Levofloxacin	100	Neg	Neg	Pos	Pos
Levothyroxine (L-Thyroxine)	50	Neg	Neg	Pos	Pos
Lidocaine	1000	Neg	Neg	Pos	Pos
Lormetazepam	1	Neg	Neg	Pos	Pos
LSD	10	Neg	Neg	Pos	Pos
MDMA (Ecstasy)	1000	Neg	Neg	Pos	Pos
Meperidine	800	Neg	Neg	Pos	Pos
Methadone	500	Neg	Neg	Pos	Pos
Methaqualone	600	Neg	Neg	Pos	Pos
NAPA	400	Neg	Neg	Pos	Pos
Naproxen	1000	Neg	Neg	Pos	Pos
Nicotinic Acid	500	Neg	Neg	Pos	Pos
Nifedipine	500	Neg	Neg	Pos	Pos
Nordiazepam	100	Neg	Neg	Pos	Pos
Nortriptyline	250	Neg	Neg	Pos	Pos
Oxazepam	300	Neg	Neg	Pos	Pos
Perphenazine	150	Neg	Neg	Pos	Pos
Phencyclidine	900	Neg	Neg	Pos	Pos
Phenobarbital	500	Neg	Neg	Pos	Pos
Phenelzine	100	Neg	Neg	Pos	Pos
Phenytoin	1000	Neg	Neg	Pos	Pos
Procainamide	1000	Neg	Neg	Pos	Pos
Procyclidine	800	Neg	Neg	Pos	Pos
Promethazine	100	Neg	Neg	Pos	Pos
Propoxyphene	1000	Neg	Neg	Pos	Pos
Protriptyline	200	Neg	Neg	Pos	Pos
Pseudoephedrine	1000	Neg	Neg	Pos	Pos
Quinacrine	900	Neg	Neg	Pos	Pos
Ranitidine	1000	Neg	Neg	Pos	Pos
Ritalin	1000	Neg	Neg	Pos	Pos
Salicylic Acid	500	Neg	Neg	Pos	Pos
Scopolamine	500	Neg	Neg	Pos	Pos
Secobarbital	1000	Neg	Neg	Pos	Pos
Tapetal	100	Neg	Neg	Pos	Pos
THC	100	Neg	Neg	Pos	Pos
Thioridazine	100	Neg	Neg	Pos	Pos

Tramadol	1000	Neg	Neg	Pos	Pos
Trazodone	5	Neg	Neg	Pos	Pos
Trimethoprim	1000	Neg	Neg	Pos	Pos
Triprolidine (zymine)	50	Neg	Neg	Pos	Pos
Tyramine	100	Neg	Neg	Pos	Pos
Verapamil	500	Neg	Neg	Pos	Pos
Zolpidem	100	Neg	Neg	Pos	Pos

Endogenous Substances Interference:

Each compound was spiked into samples with -40% cutoff and +40% cutoff concentration pools which were prepared by spiking buprenorphine to aliquots of drug-free human urine. The results show that the tested endogenous substances at the levels tested caused no interference relative to the 5 ng/mL cutoff. Testing was conducted using both the qualitative and semi-quantitative modes. Results are provided in the table below.

Interference (Endogenous Substances)	Conc. Tested (µg/mL)	-40% Cutoff (3 ng/mL)		+40% Cutoff (7 ng/mL)	
		Qualit. Result Pos/Neg	Semi-quant. Result Pos/Neg	Qualit. Result Pos/Neg	Semi-quant. Result Pos/Neg
Acetone	1.0 g/dL	Neg	Neg	Pos	Pos
Ascorbic Acid	1.5 g/dL	Neg	Neg	Pos	Pos
Conjugated Bilirubin	2.0 mg/dL	Neg	Neg	Pos	Pos
Unconjugated Bilirubin	2.0 mg/dL	Neg	Neg	Pos	Pos
Creatinine	0.5 g/dL	Neg	Neg	Pos	Pos
Ethanol	1.0 g/dL	Neg	Neg	Pos	Pos
IgG	0.5 g/dL	Neg	Neg	Pos	Pos
Glucose	2.0 g/dL	Neg	Neg	Pos	Pos
Hemoglobin	115 mg/dL	Neg	Neg	Pos	Pos
Human Serum Albumin	0.5 g/dL	Neg	Neg	Pos	Pos
Oxalic Acid	0.1 g/dL	Neg	Neg	Pos	Pos
Riboflavin	7.5 mg/dL	Neg	Neg	Pos	Pos
Sodium Chloride	6.0 g/dL	Neg	Neg	Pos	Pos
Urea	6.0 g/dL	Neg	Neg	Pos	Pos
Sodium Azide	1% w/v	Neg	Neg	Pos	Pos
Sodium Fluoride	1% w/v	Neg	Neg	Pos	Pos
Galactose	1.0 g/dL	Neg	Neg	Pos	Pos

Specific Gravity and pH:
Negative urine pools with specific gravity values ranging from 1.002–1.035 and pH values ranging from 3.0–11.0 were tested in the presence of two levels of controls at +/- 40% (3 and 7 ng/mL) of the cutoff concentration. All samples were tested in triplicates and no interference was observed.

d. *Assay Reportable Range:*

See linearity section (1 b.) above.

e. *Traceability, Stability, Expected Values (Controls, Calibrators, or Methods):*

Emit® II Plus Specialty Drug Calibrator/Control is traceable to a commercially available standard.

f. *Detection Limit:*

Not applicable.

g. *Assay Cut-Off:*

Analytical performance of the device around the claimed cutoff is described in the precision section (section VII, A1) above.

2. Comparison Studies:

a. *Method comparison*
One-hundred twenty (120) unaltered human urine samples were qualitatively and semi-quantitatively evaluated using the Emit® II Plus Buprenorphine Assay system and compared with the results obtained by the reference method LC/MS/MS. The results are presented below:

Emit® II Plus Buprenorphine Assay vs. LC/MS/MS
Comparison Table for Qualitative and Semi-quantitative Assay Performance

	LC/MS/MS			
	Negative (<2.5 ng/mL)	Negative Within 50% below the cutoff (2.5 – 4.9 ng/mL)	Positive Within 50% above the cutoff (5.0-7.5 ng/mL)	Positive (>7.5 ng/mL)
Qualitative				
Emit® Positive	0	9	23	40
Emit® Negative	32	16	0	0
Semiquantitative				
Emit® Positive	0	9	23	40

Emit® Negative	32	16	0	0

Discordant Samples LC/MS/MS Analysis Results

Sample ID	DxC 500 AU (ng/mL)	LC/MS/MS		Emit +/-	LC/MS/MS +/-
		Bup (ng/mL)	NorBup (ng/mL)		
BUP35	6.1	0	4.2	+	-
BUP45	6.0	0	4.6	+	-
BUP51	6.1	0	4.3	+	-
BUP60	5.6	0	3.8	+	-
BUP62	6.1	0	3.9	+	-
BUP87	5.5	0	4.3	+	-
BUP95	5.6	0	4.5	+	-
BUP101	6.3	0	4.8	+	-
BUP109	5.0	0	4.3	+	-

Bup = Buprenorphine; NorBup = Norbuprenorphine

b. *Matrix Comparison*:

Not Applicable. The device is only intended to be used with urine samples.

3. Clinical Studies:

1. Clinical Sensitivity:

Not applicable.

2. Clinical Specificity:

Not applicable.

3. Other Clinical Supportive Data (When 1. and 2. Are Not Applicable):

Not applicable.

B Clinical Cut-Off:

Not applicable.

C Expected Values/Reference Range:

Not applicable.

VIII Proposed Labeling:

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

IX Conclusion:

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