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

A. 510(k) Number:

k102779

B. Purpose for Submission:

New device

C. Measurand:

6-Acetylmorphine

D. Type of Test:

Qualitative and semi-quantitative immunoassay

E. Applicant:

Siemens Healthcare Diagnostics Inc.

F. Proprietary and Established Names:

Emit® II Plus 6-Acetylmorphine Assay
Emit® II Plus 6-AM / Ecstasy Calibrators
Emit® II Plus 6-AM / Ecstasy Controls

G. Regulatory Information:

Product Code	Classification	Regulation Section	Panel
DJG	II	862.3650 - Opiate test system	91 - Toxicology
DKB	II	862.3200 - Clinical toxicology calibrator	91 - Toxicology
DIF	I, reserved	862.3280 - Clinical toxicology control material	91 - Toxicology

H. Intended Use:

1. Intended use(s):

See indications for use below

2. Indication(s) for use:

Emit® II Plus 6-Acetylmorphine Assay:

The Emit® II Plus 6-Acetylmorphine Assay is a homogeneous enzyme immunoassay with 10 ng/mL cutoff. The assay is intended for use in laboratories for the qualitative and/or semiquantitative analyses of 6-acetylmorphine (6-AM), a heroin metabolite, in human urine. Emit® II Plus assays are designed for use with a number of chemistry analyzers.

Semiquantitative test results may be used to assess assay performance as part of a quality control program and to estimate a dilution of the specimen for confirmation by GC/MS.

The Emit® II Plus 6-Acetylmorphine Assay provides only a preliminary analytical test result. A more specific alternative chemical method must be used to obtain a confirmed analytical result. Gas chromatography/mass spectroscopy (GC/MS) is the preferred confirmatory method. 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.

Emit® II Plus 6-AM/Ecstasy Calibrators/Controls:

When used as Calibrators, the materials are for the calibration of the Emit® II Plus 6-Acetylmorphine and Emit® II Plus Ecstasy Assays.

When used as Controls, the materials may be used as quality control materials based on the specific Emit® II Plus 6-Acetylmorphine and Emit® II Plus Ecstasy Assay cutoffs.

3. Special conditions for use statement(s):

For prescription use.

4. Special instrument requirements:

Analyzers capable of maintaining a constant temperature, pipetting samples, mixing reagents, measuring enzymatic rates at 340 nm and timing the reaction accurately can be used to perform this assay. All performance studies were conducted on the Viva-E® analyzer.

I. Device Description:

Assay:

Emit® II Plus 6-Acetylmorphine Assay:

The Emit® II Plus 6-Acetylmorphine Assay is a homogenous enzyme immunoassay with a 10 ng/mL cutoff. The assay, used for the detection of 6-acetylmorphine (a heroin metabolite) in human urine, utilizes a two-reagent system. The Antibody/Substrate Reagent 1 is a liquid ready-to-use product comprised of mouse monoclonal antibodies to 6-acetylmorphine (6-AM), glucose-6-phosphate (G6P), and nicotinamide adenine dinucleotide (NAD) in a diluent containing bovine serum albumin (BSA), preservatives and stabilizers. The Enzyme Reagent 2 is a lyophilized product containing 6-AM labeled bacterial recombinant glucose-6-phosphate dehydrogenase (rG6PDH) in a diluent containing bovine serum albumin (BSA), Hepes buffer, preservatives and stabilizers. Reagent 2 is reconstituted with either deionized or distilled water.

The assay kit consists of Reagent 1 and Reagent 2 in plastic containers (Reagent 2 is provided in a plastic bag with desiccant) and is available in two sizes. Emit® II Plus Assays are designed for use with a number of chemistry analyzers.

Emit® II Plus 6-AM / Ecstasy Calibrators / Controls Levels 1 – 4:

The Emit® II Plus 6-AM / Ecstasy Calibrators / Controls are in-vitro diagnostic products used in the calibration of the Emit® II Plus 6-Acetylmorphine Assay and the Emit® II Plus Ecstasy Assay. These materials may also be used as quality controls based on the specific 6-Acetylmorphine Assay or Ecstasy Assay cutoffs.

The calibrator / control products have the same formulation as the existing Emit® II Plus Ecstasy Calibrators / Controls; cleared under k043028. The matrix is pooled, drug-free, human urine based product containing 6- acetylmorphine (6-AM), methylenedioxymethamphetamine (MDMA) and preservatives. The four levels of product are packaged separately in 15 mL plastic vials with a 10 mL fill per vial. The multi-analyte Calibrators / Controls Levels 1 through 4 contain 6-AM and MDMA at the following concentrations:

Calibrator / Control	Targeted 6-AM Concentration (ng/mL)	Targeted MDMA Concentration (ng/mL)
Level 1	5	150
Level 2	10	300
Level 3	15	500
Level 4	20	1000

The Emit® Calibrator / Control Level 0, which contains no drug and was cleared under k993755 will also be used with the Emit® II Plus 6-Acetylmorphine Assay. There was no change to the Calibrator Level 0 product.

J. Substantial Equivalence Information:

1. Predicate device name:

Microgenics CEDIA® DAU 6-Acetylmorphine Assay
Siemens Healthcare Diagnostics Inc. Emit® II Plus Ecstasy Calibrators / Controls Levels 1 – 4

2. Predicate 510(k) number:

k001178
k043028

3. Comparison with predicate:

Feature	Proposed Device Emit® II Plus 6-Acetylmorphine Assay	Predicate CEDIA® DAU 6-Acetylmorphine Assay (k001178)
Intended Use	The Emit® II Plus 6-Acetylmorphine Assay is a homogeneous enzyme immunoassay with 10 ng/mL cutoff. The assay is intended for use in laboratories for the qualitative and semiquantitative analyses of 6-acetylmorphine (6-AM), a heroin metabolite, in human urine. Emit® II Plus assays are designed for use with a number of chemistry analyzers.	Same
Assay Methodology	Homogeneous enzyme immunoassay using Emit® technology	Homogeneous enzyme immunoassay using CEDIA® technology
Antibody	Mouse monoclonal antibodies to 6-AM	Monoclonal antibodies to 6-AM
Reference Methodology	GC / MS	Same
Cutoff	10 ng/mL	Same
Sample Type	Human urine	Same
Reagents:	R1: Liquid – Ready to Use R2: Lyophilized (Reconstitution required)	R1 & R2: Lyophilized (Reconstitution required)
Stability (Reconstituted)	R1: Until expiration date on vial R2: 30 days	R1 & R2: 60 days
Instrument	Chemistry analyzers capable of maintaining constant reaction temperature, pipetting specimens/reagents and measuring enzyme rates at 340 nm, timing reaction accurately and mixing reagent thoroughly	Clinical chemistry analyzers capable of maintaining constant temperature, pipetting sample, mixing reagents, measuring enzyme rates at 570 nm and timing reaction accurately

Comparison of Calibrator Features:

Feature	Proposed Device Emit® II Plus 6-AM / Ecstasy Calibrators / Controls	Predicate Emit® II Plus Ecstasy Calibrators / Controls (k043028)
Indications for Use	Calibrators are used in the calibration of the Emit® II Plus 6-Acetylmorphine and Emit® II Plus Ecstasy Assays.	Same
Matrix	Human urine based	Same
Analyte	Contains 6-AM and MDMA	Contains MDMA
Target Concentrations for 6-AM	Level 1: 5 ng/mL Level 2: 10 ng/mL Level 3: 15 ng/mL Level 4: 20 ng/mL	None
Preparation	Liquid – Ready to Use	Liquid – Ready to Use
Storage	2 – 8°C	2 – 8°C

Comparison of Control Features:

Feature	Proposed Device Emit® II Plus 6-AM / Ecstasy Calibrators / Controls	Predicate Emit® II Plus Ecstasy Calibrators / Controls (k043028)
Indications for Use	Controls may be used as quality control materials based on the specific Emit® II Plus 6-Acetylmorphine and Emit® II Plus Ecstasy Assay cutoffs.	Same
Analyte	Contains 6-AM and MDMA	Contains MDMA
Positive Quality Control Level for Qualitative Analysis	Level 4	Level 4

K. **Standard/Guidance Document Referenced (if applicable):**
CLSI EP5-A2: Evaluation of Precision Performance of Quantitative Measurement Methods
CLSI EP7-A2: Interference Testing in Clinical Chemistry

L. Test Principle:

The Emit® II Plus 6-Acetylmorphine Assay is a homogeneous enzyme immunoassay technique used for the analysis of a specific compound in human urine. The assay is

based on competition between drug in the specimen and drug labeled with the recombinant glucose-6-phosphate dehydrogenase (rG6PDH) for antibody binding sites. Enzyme activity decreases upon binding to the antibody, so the drug concentration in the specimen can be measured in terms of enzyme activity. 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. Endogenous serum G6PDH does not interfere because the coenzyme NAD functions only with the bacterial (*Leuconostoc mesenteroides*) enzyme employed in the assay.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

   a. Precision/Reproducibility:

   Precision was determined by assaying urine pools spiked with 6-AM for 20 days, 2 runs per day in duplicate (N=80). Precision data were calculated according to the Clinical and Laboratory Standards Institute (CLSI) Guidelines EP5-A2. Results are summarized in tables below:

Qualitative Analysis

Urine Pool (ng/mL)	% of cutoff	# of Determinations	Result
Repeatability			
0	-100%	40	40 Negative
2.5	-75%	40	40 Negative
5.0	-50%	40	40 Negative
7.5	-25%	40	40 Negative
10.0	cutoff	40	40 Positive
12.5	+25%	40	40 Positive
15.0	+50%	40	40 Positive
17.5	+75%	40	40 Positive
20.0	100%	40	40 Positive
Within-Lab			
0	-100%	80	80 Negative
2.5	-75%	80	80 Negative
5.0	-50%	80	80 Negative
7.5	-25%	80	80 Negative
10.0	cutoff	80	80 Positive
12.5	+25%	80	80 Positive
15.0	+50%	80	80 Positive
17.5	+75%	80	80 Positive

Urine Pool (ng/mL)	% of cutoff	# of Determinations	Result
20.0	100%	80	80 Positive

Semiquantitative Analysis

Urine Pool (ng/mL)	% of cutoff	# of Determinations	Result	Mean (ng/mL)	SD	CV (%)
Repeatability						
0	-100%	40	40 Negative	0.9	0.10	N/A
2.5	-75%	40	40 Negative	3.6	0.10	2.9
5.0	-50%	40	40 Negative	6.0	0.12	2.0
7.5	-25%	40	40 Negative	8.7	0.12	1.4
10.0	cutoff	40	40 Positive	11.3	0.14	1.3
12.5	+25%	40	40 Positive	14.2	0.16	1.1
15.0	+50%	40	40 Positive	17.0	0.15	0.9
17.5	+75%	40	40 Positive	19.6	0.20	1.0
20.0	100%	40	40 Positive	21.8	0.25	1.2
Within-Lab						
0	-100%	80	80 Negative	0.9	0.62	N/A
2.5	-75%	80	80 Negative	3.6	0.47	13.3
5.0	-50%	80	80 Negative	6.0	0.43	7.1
7.5	-25%	80	80 Negative	8.7	0.43	5.1
10.0	cutoff	80	80 Positive	11.3	0.48	4.2
12.5	+25%	80	80 Positive	14.2	0.50	3.5
15.0	+50%	80	80 Positive	17.0	0.54	3.2
17.5	+75%	80	80 Positive	19.6	0.73	3.7
20.0	100%	80	80 Positive	21.8	0.89	4.1

b. Linearity/assay reportable range:

Semiquantitative Results: Drug-free human urine was spiked with concentrations of 6-acetylmorphine at levels across the range of 0 to 20 ng/mL. For each known concentration, drug recovery was calculated using the mean concentration obtained by the Emit® II Plus 6-Acetylmorphine Assay. Semiquantitative results are shown below:

Expected 6-AM Concentration (ng/mL)	Mean 6-AM Concentration by Emit® II Plus 6-Acetylmorphine Assay (ng/mL)	Recovery (%)
0	0.3	N/A
2.5	2.8	112.2
5	5.7	114.7

7.5	8.2	109.8
10	10.8	108.4
12.5	13.5	108.2
15	16.1	107.6
17.5	19.0	108.7
20	22.7	113.5

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

A commercially available 6-Acetylmorphine standard solution from Cerilliant Analytical Reference Standards is used and traceable to NIST standard. This standard solution is made into a secondary (lower concentration) stock solution. The secondary stock solution is then spiked into the calibrators and controls to the desired concentration. The concentrations are confirmed by GC/MS.

Stability Studies:

Real time stability studies for both controls and calibrators were conducted. Protocols and acceptance criteria were described and found to be acceptable. The manufacturer claims the following expiration date for both controls and calibrators:

Real-time stability studies show that when stored at 2-8 ºC, open and unopened product is stable for nine months. Real time stability studies are on-going to support a 12 month stability claim.

d. *Detection limit:*

Performance at low drug concentrations in the semi-quantitative assay was characterized by determination of recovery (see section b above).

e. *Analytical specificity:*

Cross-reactivity was established by spiking various concentrations of structurally related compounds into drug-free urine. Results are expressed as a minimum concentration of metabolite or compound required to produce a response approximately equivalent to the cutoff concentration of the assay. The percent cross-reactivity of those compounds are presented below:

Structurally Related Compounds

Compound	Concentration Tested (ng/mL)	Cross-reactivity (%)
Buprenorphine	1,000,000	0.00
Codeine	500,000	0.00

Dextromethorphan	100,000	0.00
Dihydrocodeine	500,000	0.00
Heroin HCl	80	1.25
Hydrocodone	300,000	0.00
Hydromorphone	100,000	0.00
Imipramine	200,000	0.00
Levorphanol	100,000	0.00
Meperidine	800,000	0.00
Morphine	100,000	0.01
Morphine-3-Glucuronide	600,000	0.00
Morphine-6-Glucuronide	600,000	0.00
Nalorphine	100,000	0.01
Naloxone	300,000	0.00
Naltrexone	300,000	0.00
Norcodeine	600,000	0.00
Normorphine	100,000	0.00
Oxycodone	400,000	0.00
Oxymorphone	80,000	0.00

Structurally Unrelated Compounds

The following structurally unrelated compounds were added into drug-free urine spiked into two levels of controls at ± 25% of the cutoff concentration. The substances listed in the table below do not yield a false response relative to the cutoff in both qualitative and semiquantitative mode.

Compound	Concentration Tested (µg/mL)	Sample Mean (-25% Control) (ng/mL)		Sample Mean (+25% Control) (ng/mL)	
		Qualitative	Semi-Quantitative	Qualitative	Semi-Quantitative
10,11-Dihydrocarbamazepine	85	Negative	Negative	Positive	Positive
Acetaminophen	1000	Negative	Negative	Positive	Positive
Acetylsalicylic Acid	1500	Negative	Negative	Positive	Positive
Amitriptyline	100	Negative	Negative	Positive	Positive
Amoxicillin	500	Negative	Negative	Positive	Positive
AZT (Zipovudine)	2000	Negative	Negative	Positive	Positive
Benzoylecgonine	1000	Negative	Negative	Positive	Positive
Brompheniramine	75	Negative	Negative	Positive	Positive
Caffeine	1000	Negative	Negative	Positive	Positive
Captopril	500	Negative	Negative	Positive	Positive
Chlordiazepoxide	100	Negative	Negative	Positive	Positive
Chlorpromazine	10	Negative	Negative	Positive	Positive
Cimetidine	1000	Negative	Negative	Positive	Positive
Clomipramine	2.5	Negative	Negative	Positive	Positive

Compound	Concentration Tested (µg/mL)	Sample Mean (-25% Control) (ng/mL)		Sample Mean (+25% Control) (ng/mL)	
		Qualitative	Semi-Quantitative	Qualitative	Semi-Quantitative
Clonidine	1000	Negative	Negative	Positive	Positive
Cyclobenzaprine	125	Negative	Negative	Positive	Positive
d-Amphetamine	700	Negative	Negative	Positive	Positive
Desipramine	800	Negative	Negative	Positive	Positive
Diazepam	100	Negative	Negative	Positive	Positive
Digoxin	0.01	Negative	Negative	Positive	Positive
Diphenhydramine	1000	Negative	Negative	Positive	Positive
d-Methamphetamine	500	Negative	Negative	Positive	Positive
Doxepine	100	Negative	Negative	Positive	Positive
EDDP	1000	Negative	Negative	Positive	Positive
Enalapril	500	Negative	Negative	Positive	Positive
Fluoxetine	500	Negative	Negative	Positive	Positive
Glutethimide	500	Negative	Negative	Positive	Positive
Haloperidol	100	Negative	Negative	Positive	Positive
Hydroxyzine	500	Negative	Negative	Positive	Positive
Ibuprophen	1000	Negative	Negative	Positive	Positive
Ketamine	100	Negative	Negative	Positive	Positive
Ketorolac Tromethamine	400	Negative	Negative	Positive	Positive
LAAM (L-α-Acetylmethadol)	25	Negative	Negative	Positive	Positive
L-Cotinine	100	Negative	Negative	Positive	Positive
Levofloxacin	100	Negative	Negative	Positive	Positive
Levothyroxine	50	Negative	Negative	Positive	Positive
Lidocaine	1000	Negative	Negative	Positive	Positive
Lormetazepam	1	Negative	Negative	Positive	Positive
LSD	10	Negative	Negative	Positive	Positive
MDMA (Ecstasy)	1000	Negative	Negative	Positive	Positive
Methadone	500	Negative	Negative	Positive	Positive
Methaqualone	600	Negative	Negative	Positive	Positive
NAPA (N-Acetylprocainamide)	400	Negative	Negative	Positive	Positive
Naproxen	1000	Negative	Negative	Positive	Positive
Nicotinic Acid	500	Negative	Negative	Positive	Positive
Nifedipine	500	Negative	Negative	Positive	Positive
Nordiazepam	100	Negative	Negative	Positive	Positive
Nortryptiline	250	Negative	Negative	Positive	Positive
Oxazepam	300	Negative	Negative	Positive	Positive
Perphenazine	150	Negative	Negative	Positive	Positive
Phencyclidine	1000	Negative	Negative	Positive	Positive
Phenobarbital	500	Negative	Negative	Positive	Positive
Phenelzine	100	Negative	Negative	Positive	Positive

Compound	Concentration Tested (µg/mL)	Sample Mean (-25% Control) (ng/mL)		Sample Mean (+25% Control) (ng/mL)	
		Qualitative	Semi-Quantitative	Qualitative	Semi-Quantitative
Phenytoin	1000	Negative	Negative	Positive	Positive
Procainamide	1000	Negative	Negative	Positive	Positive
Procyclidine	800	Negative	Negative	Positive	Positive
Promethazine	100	Negative	Negative	Positive	Positive
Propoxyphene	1000	Negative	Negative	Positive	Positive
Protriptyline	200	Negative	Negative	Positive	Positive
Pseudoephedrine	1000	Negative	Negative	Positive	Positive
Quinacrine	1000	Negative	Negative	Positive	Positive
Ranitidine	1000	Negative	Negative	Positive	Positive
Ritalin	1000	Negative	Negative	Positive	Positive
Salicylic Acid	500	Negative	Negative	Positive	Positive
Scopolamine	500	Negative	Negative	Positive	Positive
Secobarbital	1000	Negative	Negative	Positive	Positive
THC (11-nor-Δ9-THC-9-COOH)	100	Negative	Negative	Positive	Positive
Thioridazine	100	Negative	Negative	Positive	Positive
Tramadol	1000	Negative	Negative	Positive	Positive
Trazodone	5	Negative	Negative	Positive	Positive
Trimethoprim	1000	Negative	Negative	Positive	Positive
Triprolidine	50	Negative	Negative	Positive	Positive
Tyramine	100	Negative	Negative	Positive	Positive
Verapamil	500	Negative	Negative	Positive	Positive
Zolpidem	100	Negative	Negative	Positive	Positive

The following endogenous compounds were added into drug-free urine spiked into two levels of controls at ± 25% of the cutoff concentration. The substances listed in the table below do not yield a false response relative to the cutoff in both qualitative and semiquantitative mode.

Endogenous Substances

Substance	Level Tested	Sample Mean (-25% Control) (ng/mL)		Sample Mean (+25% Control) (ng/mL)	
		Qualitative	Semi-quantitative	Qualitative	Semi-quantitative
Acetone	1.0 g/dL	Negative	Negative	Positive	Positive
Ascorbic Acid	1.5 g/dL	Negative	Negative	Positive	Positive
Bilirubin, Conjugated	2.0 mg/dL	Negative	Negative	Positive	Positive
Bilirubin,	2.0 mg/dL	Negative	Negative	Positive	Positive

Unconjugated					
Creatinine	0.5 g/dL	Negative	Negative	Positive	Positive
Ethanol	1.0 g/dL	Negative	Negative	Positive	Positive
Galactose	10 mg/dL	Negative	Negative	Positive	Positive
γ-Globulin	500 mg/dL	Negative	Negative	Positive	Positive
Glucose	2.0 g/dL	Negative	Negative	Positive	Positive
Hemoglobin	115 mg/dL	Negative	Negative	Positive	Positive
Human Serum Albumin	0.5 g/dL	Negative	Negative	Positive	Positive
Oxalic Acid	0.1 g/dL	Negative	Negative	Positive	Positive
Riboflavin	7.5 mg/dL	Negative	Negative	Positive	Positive
Sodium Chloride	6.0 g/dL	Negative	Negative	Positive	Positive
Urea	6.0 g/dL	Negative	Negative	Positive	Positive

Specific Gravity and pH

Urine samples with specific gravity values ranging from 1.002 to 1.030 and pH values ranging from 4.0 to 10.0 were tested in the presence of 7.5 and 12.5 ng/mL of 6-AM. No interference was observed.

f. Assay cut-off:

Analytical performance of the device around the claimed cutoff is described in precision section (1 a.) above.

2. Comparison studies:

a. Method comparison:

One hundred five (105) samples were analyzed by the Emit® II Plus 6-Acetylmorphine Assay and by GC/MS. Both methods used a cutoff of 10 ng/mL. 22 samples were within +/- 50% of the cutoff by GC/MS.

Forty nine (49) samples showed positive results by both methods, while fifty five (55) samples showed negative results by both methods. One specimen showed a negative result by GC/MS and a positive result by the Emit® II Plus 6-Acetylmorphine Assay.

Qualitative and Semiquantitative Accuracy Summary

	GC/MS				
	LOW NEG Less than 50% below the cutoff (<5 ng/mL)	NEG Within 50% below the cutoff (5.0 ~ 9.9 ng/mL)	POS Within 50% above the cutoff (10.0 ~ 15 ng/mL)	HIGH POS Greater than 50% above the cutoff (>15 ng/mL)	% Agreement
Qualitative Summary					

Emit®	POS	0	1	15	34	98%
	NEG	49	6	0	0	100%
Semiquantitative Summary						
Emit®	POS	0	1	15	34	98%
	NEG	49	6	0	0	100%

Discordant Result Summary

Cutoff Value (10 ng/mL)	Qualitative Result		Semiquantitative Result	
	Emit® Assay	GC/MS	Emit® Assay	GC/MS
Sample # 55	Positive	7.8 ng/mL	Positive	7.8 ng/mL

b. Matrix comparison: Test is for urine samples only.

3. Clinical studies:

a. Clinical Sensitivity: Not applicable

b. Clinical specificity: Not applicable

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

Not applicable

4. Clinical cut-off**:** Not applicable

5. Expected values/Reference range: Not applicable

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.