CEDIA™ Buprenorphine Assay

thermo scientific

IVD **For In Vitro Diagnostic Use**

Rx Only

REF 10015658 (3 x 17 mL Indiko Kit)
100190 (3 x 17 mL Kit)
100240 (65 mL Kit)

Intended Use

The CEDIA™ Buprenorphine Assay is a homogenous enzyme immunoassay for qualitative or semi-quantitative determination of the presence of buprenorphine in human urine at cutoff concentration of 5 ng/mL. The assay provides a simple and rapid analytical screening procedure to detect buprenorphine in human urine.

The 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 spectrometry (GC/MS) is the preferred confirmatory method.[1] Clinical and professional judgment should be applied to any drug of abuse test result, particularly when preliminary results are used.

Summary and Explanation of The Test

Buprenorphine is a semi-synthetic opioid analgesic derived from thebaine, a component of opium. Buprenorphine resembles morphine structurally but has both antagonist and agonist properties.[2] Buprenorphine has a longer duration of action than morphine and can be administered sublingually as an analgesic. Subutex®, a higher dose buprenorphine formulation, is widely used in Europe and elsewhere as a substitution treatment for opiate addiction.[3-5] Recently, the FDA has approved the use of Subutex and Suboxone® containing buprenorphine as active drug, for the treatment of opiate dependence in the US. The antagonist potency was reported as equivalent to naltrexone. Subutex and Suboxone are the first narcotic drugs available under the US Drug Abuse Treatment Act (DATA) of 2003 for the treatment of opiate dependence that can be prescribed in the US in a physician's work place.[6] It has also been shown that buprenorphine has abuse potential and may itself cause dependency. In addition, a number of deaths have been recorded as a result of overdose with intravenously injected buprenorphine in conjunction with other psychotropic drugs such as benzodiazepines.[7] Buprenorphine is metabolized primarily by N-dealkylation to form norbuprenorphine and by conjugation to form glucuronide-buprenorphine and glucuronide-norbuprenorphine.[8]

The CEDIA Buprenorphine Assay uses recombinant DNA technology (US Patent No. 4708929) to produce a unique homogeneous enzyme immunoassay system.[9] The assay is based on the bacterial enzyme β-galactosidase, which has been genetically engineered into two inactive fragments. These fragments spontaneously re-associate to form fully active enzymes that, in the assay format, cleave a substrate, generating a color change that can be measured spectrophotometrically.

In the assay, analyte in the sample competes with analyte conjugated to one inactive fragment (enzyme donor) of β-galactosidase for a limited number of antibody binding sites. If analyte is present in the sample, it binds to antibody, leaving the inactive enzyme fragment free to form active enzyme. If the analyte is not present in the sample, antibody binds to analyte conjugated on the inactive fragment, inhibiting the re-association of inactive β-galactosidase fragments, and no active enzyme is formed. The amount of active enzyme formed and resultant absorbance change are directly proportional to the amount of analyte present in the sample.

Reagents

- **1 EA Reconstitution Buffer:** Buffer salts, 0.35 mg/L mouse monoclonal anti-buprenorphine antibody, stabilizer, and preservative.
- **1a EA Reagent:** 0.171 g/L Enzyme Acceptor (microbial), buffer salts, and preservative.
- **2 ED Reconstitution Buffer:** Buffer salts, stabilizers, and preservative.
- **2a ED Reagent:** 25 µg/L Enzyme Donor (microbial) conjugated to buprenorphine, 1.67 g/L chlorophenol red-β-D-galactopyranoside, stabilizers, and preservative.

Additional Materials Required but not Provided:

REF	Kit Description
100241	CEDIA Buprenorphine S1 Calibrator (0 ng/mL)
100242	CEDIA Buprenorphine S2 Calibrator (5 ng/mL)
100243	CEDIA Buprenorphine S3 Calibrator (20 ng/mL)
100244	CEDIA Buprenorphine S4 Calibrator (50 ng/mL)
100245	CEDIA Buprenorphine S5 Calibrator (75 ng/mL)
100246	CEDIA Buprenorphine Low and High Controls:

⚠ Precautions and Warnings

DANGER: Powder reagent contains ≤56% w/w bovine serum albumin (BSA) and ≤2% w/w sodium azide. Liquid reagent contains ≤1.0% bovine serum, ≤0.3% sodium azide and ≤0.1% Drug-specific antibody (Mouse).

H317 - May cause allergic skin reaction.
H334 - May cause allergy or asthma symptoms or breathing difficulties if inhaled.
EUH032 - Contact with acids liberates very toxic gas.

Avoid breathing dust/mist/vapors/spray. Contaminated work clothing should not be allowed out of the workplace. Wear protective gloves/eye protection/face protection. In case of inadequate ventilation wear respiratory protection. If on skin: Wash with plenty of soap and water. IF INHALED: If breathing is difficult, remove victim to fresh air and keep at rest in a position comfortable for breathing. If skin irritation or rash occurs: Get medical advice/ attention. If experiencing respiratory symptoms: Call a POISON CENTER or doctor/physician. Wash contaminated clothing before reuse. Dispose of contents/container to location in accordance with local/regional/national/international regulations.

Reagent Preparation and Storage

For preparation of the solutions for Hitachi analyzers, refer to the section below. For all other analyzers, refer to the analyzer specific application sheet

Remove the kit from refrigerated storage (2-8°C) immediately prior to preparation of the solutions. Prepare the solutions in the following order to minimize possible contamination.

R2 Enzyme Donor solution: Connect Bottle 2a (ED Reagent) to Bottle 2 (ED Reconstitution Buffer) using one of the enclosed adapters. Mix by gentle inversion, ensuring that all the lyophilized material from Bottle 2a is transferred into Bottle 2. Avoid the formation of foam. Detach Bottle 2a and adapter from Bottle 2 and discard. Cap Bottle 2 and let stand approximately 5 minutes at room temperature (15-25°C). Mix again. Record the reconstitution date on the bottle label. Place the bottle directly into the reagent compartment of the analyzer or into refrigerated storage (2-8°C) and let stand 30 minutes before use.
R1 Enzyme acceptor solution: Connect Bottle 1a (EA Reagent) to Bottle 1 (EA Reconstitution Buffer) using one of the enclosed adapters. Mix by gentle inversion, ensuring that all the lyophilized material from Bottle 1a is transferred into Bottle 1. Avoid the formation of foam. Detach Bottle 1a and adapter from Bottle 1 and discard. Cap Bottle 1 and let stand approximately 5 minutes at room temperature (15-25°C). Mix again. Record the reconstitution date on the bottle label. Place the bottle directly into the reagent compartment of the analyzer or into refrigerated storage (2-8°C) and let stand 30 minutes before use.

NOTE 1: The components supplied in this kit are intended for use as an integral unit. Do not mix components from different lots.
NOTE 2: Avoid cross-contamination of reagents by matching reagent caps to the proper reagent bottle. The R2 solution (Enzyme Donor) should be yellow-orange in color. A red or red-purple color indicates that the reagent has been contaminated and must be discarded.
NOTE 3: The R1 and R2 solutions must be at the reagent compartment storage temperature of the analyzer before performing the assay. Refer to the analyzer specific application sheet for additional information.
NOTE 4: Hitachi 911 and 917 analyzers
If the analyzer cannot read the bar code, the numerical sequence on the bar code label can be entered via the keyboard.

Storage Conditions

Store CEDIA Buprenorphine reagents at 2-8°C. **DO NOT FREEZE.**

For stability of the unopened components, refer to the box or bottle labels for the expiration date.

To ensure reconstituted EA reagent stability, protect it from prolonged continuous exposure to bright light.

R1 Solution: 60 days refrigerated on analyzer or at 2-8°C.
R2 Solution: 60 days refrigerated on analyzer or at 2-8°C.

Specimen Collection and Handling

Collect urine specimens in plastic or glass containers. Testing of fresh urine specimens is suggested. Care should be taken to preserve the chemical integrity of the urine sample from the time it is collected until the time it is assayed.

Specimens kept at room temperature that do not receive initial test within 8 days[10] of arrival at the laboratory should be placed into a secure refrigeration unit at 2 to 8°C for up to 30 days.[11,12] For longer storage prior to analysis or for sample retention after analysis, urine specimens may be stored at -20°C.[13] Studies have shown buprenorphine analytes in urine are stable at -20°C up to 85 days.[13]

Laboratories following the SAMHSA mandatory guidelines should refer to SAMHSA "Short-Term Refrigerated Storage" and "Long-Term Storage" requirements.[14]

To protect the integrity of the sample, do not induce foaming and avoid repeated freezing and thawing. An effort should be made to keep pipetted samples free of gross debris. It is recommended that grossly turbid specimens be centrifuged before analysis. Frozen samples should be thawed and mixed prior to analysis. Adulteration of the urine sample may cause erroneous results. If adulteration is suspected, obtain another sample and forward both specimens to the laboratory for testing.

Handle all urine specimens as if they were potentially infectious.

Assay Procedure

The CEDIA Buprenorphine Assay is intended for use on automated clinical analyzers capable of maintaining a constant temperature, pipetting, mixing reagents, measuring enzymatic rates at an absorbance of 660 nm, and timing the reaction can be used to perform this assay. Specific application performance data are on file at Microgenics Corporation, a part of Thermo Fisher Scientific. For application parameter settings on your analyzer, refer to the applicable application diskette, barcode transfer sheet or instrument specific application sheet available at Microgenics Corporation. The performance of applications not obtained from Microgenics Corporation is not warranted and must be defined by the user.

Calibrators and Controls

The approximate concentration of buprenorphine for each of the five calibrators and two controls used in the CEDIA Buprenorphine Assay are as follows:

S1: CEDIA Buprenorphine Calibrator (0 ng/mL)
S2: CEDIA Buprenorphine Calibrator (5 ng/mL)
S3: CEDIA Buprenorphine Calibrator (20 ng/mL)
S4: CEDIA Buprenorphine Calibrator (50 ng/mL)
S5: CEDIA Buprenorphine Calibrator (75 ng/mL)
C1: CEDIA Buprenorphine Low Control (3 ng/mL)
C2: CEDIA Buprenorphine High Control (7 ng/mL)

Calibration Frequency

Recalibration is recommended

- After reagent bottle change
- After calibrator or reagent lot change
- After instrument maintenance is performed
- As required following quality control procedures

See below for calibration frequency recommendations for Hitachi analyzers. For other analyzers, refer to the instrument-specific application sheet.

Reportable Range

The CEDIA Buprenorphine Assay is designed for semi-quantitative use in the range between 5 ng/mL, the lowest calibrator of the assay containing buprenorphine, and the value of the S5 calibrator.

The minimum detectable concentration on the Buprenorphine Assay is 1.25 ng/mL.

Out of Range Samples

Specimens giving concentration greater than the S5 calibrator can be reported as greater than the value of the high calibrator or diluted one part sample with one part of negative calibrator and re-assayed for dilutions up to 1:100.

The value obtained on re-assay should be derived as follows:
Actual Value = (dilution factors x diluted value) - concentration of negative calibrator

Specimens giving values below the cutoff concentration should be reported as negative.

Quality Control

Each laboratory should establish its own control frequency.

Good laboratory practice suggests that at least two levels of quality controls (one below and one above the cutoff of the assay) 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 doses not recover within the specified range, review all operating parameters. Contact Customer Technical Support for further assistance and recommendations on suitable control material. All QC requirements should be performed in conformance with local, state and /or federal regulations or accreditation requirements.

NOTE: Reassess control targets and ranges following a change of reagent lot.

Calculation

Refer to the appropriate operator's manual or analyzer-specific application protocol for detailed calculation information.

Limitations

1. It is possible that other substances or factors other than those investigated in the specificity study may interfere with the test and cause false results.
2. A positive result using the CEDIA Buprenorphine Assay indicates only the presence of buprenorphine or cross-reactant and does not necessarily correlate with the extent of physiological and psychological effects. An assay result may not be able to distinguish between therapeutic use and abuse of buprenorphine.
3. Performance characteristics for the CEDIA Buprenorphine Assay performance have not been established with body fluids other than human urine.
4. Care should be taken when reporting results since there are many factors, e.g., fluid intake and other biologic factors, that may influence a urine test result.
5. This CEDIA Buprenorphine Assay was validated on analyzers utilizing an integral cell wash. If your analyzer does not have an integral cell wash, contact your local Thermo Fisher Scientific representative.

Results and Expected Values

The published data may be used as a reference for therapeutic and toxic values until a laboratory has established its own ranges. The results obtained in your laboratory may differ from these data.

Qualitative results

The CEDIA Buprenorphine Assay cutoff calibrator, containing 5 ng buprenorphine/mL, is used as a reference for distinguishing between positive and negative samples. A sample having an observed absorbance value (A) equal to or greater than that obtained with cutoff calibrator is considered positive. Conversely, a sample having an observed absorbance less than the cutoff calibrator is considered negative. Refer to the analyzer specific application sheet for additional information.

Semiquantitative Results

Use of all the CEDIA Buprenorphine Assay Calibrators enables estimation of a relative concentration of buprenorphine in urine. The approximate concentration of buprenorphine in a specimen can be obtained by comparing the absorbance observed for the specimen, comparing it to the standard calibration curve, and interpolating its estimated concentration. When the estimated sample concentration is greater than the highest calibrator, the sample can be diluted with negative calibrator and retested as previously described. Care should be taken when reporting results since there are many factors, e.g., fluid intake and other biologic factors, that may influence a urine test result. The assay may be run in semi-quantitative mode for estimating dilutions for GC/MS confirmation or for quality control purposes.

Specific Performance Characteristics

Typical performance data obtained on the Hitachi 717 analyzer are shown below.[11] The results obtained in your laboratory may differ from these data. For additional analyzer specific performance data, refer to the analyzer specific application protocol.

Sensitivity

The minimum detectable concentration of the CEDIA Buprenorphine Assay on the Hitachi 717 is 1.25 ng/mL.

Limit of Detection

The limit of detection (average+ 3SD of 21 buprenorphine free urine specimens) for the CEDIA Buprenorphine Assay is 1.25 ng/mL.

Precision

Precision studies conducted using a modified NCCLS protocol with packaged reagents and controls on the Hitachi 717 gave the following results in ng/mL.

	Within-Run Precision			Between-Run Precision		
	Low	Med	High	Low	Med	High
n	120	120	120	120	120	120
$\bar{x}$ (ng/mL)	4.4	6.8	36.5	4.4	6.8	36.5
SD (ng/mL)	0.3	0.3	1.0	0.2	0.3	1.4
% CV	5.7	3.9	2.6	5.0	3.8	4.0

Linearity

A urine pool containing a known high concentration of buprenorphine was serially diluted in 10% increments (successive 1:10 dilutions) with a human urine pool free of buprenorphine. Buprenorphine concentration for each of the resulting 10 dilutions was determined and the percent recovery was calculated as the quotient of the observed to expected value. Results shown below demonstrate that the observed buprenorphine concentrations for serially diluted specimens are within ±10% of expected values. When comparing observed (y) and expected (x) values using least squares fitting techniques, the observed regression equation (y=1.025x-0.021) and correlation (r=0.9986) support the linearity of the assay with successively diluted specimens originating from a single high pool.

Dilution (%)	Expected Value (ng/mL)	Observed Value (ng/mL)	Recovery (%)
0	0.0	0.8	-
10	7.7	8.1	105.1
20	15.3	15.1	98.6
30	23.0	22.0	95.5
40	30.6	30.3	98.7
50	38.3	38.6	100.8
60	46.0	48.7	105.9
70	53.6	57.6	107.4
80	61.3	63.7	103.9
90	68.9	70.2	101.8
100	76.6	76.6	100.0

Cutoff Characterization

A human urine pool free of buprenorphine was spiked with a stock solution having a high buprenorphine concentration to produce two sets of 21 specimens each, one set with a buprenorphine concentration 25% greater (6.25 ng/mL) and the other 25% less (3.75 ng/mL) than the assay cutoff of 5 ng buprenorphine/mL. Each set of 21 aliquots was assayed using the CEDIA Buprenorphine Assay. Cutoff characterization was deemed acceptable if the observed buprenorphine concentration for 95% of the 21 specimens from each of the two sets assayed set were greater or lesser than the concentration observed for the 5 ng/mL cutoff calibrator. As is shown in the table below, the buprenorphine concentration observed for all specimens were appropriately greater or lesser than the concentration of 5.4 ng buprenorphine/mL observed for the 5 ng/mL cutoff calibrator.

	Low-Aliquot	High-Aliquot
Sample	3.75 ng/mL (-25%)	6.25 ng/mL (+25%)
Mean Dose	3.7	6.6
SD	0.2	0.2
% C.V.	6.6	2.5
Cut off dose	5.4	5.4

Specificity

Interference with Endogenous Substances

The potential interference of endogenous physiologic substances on recovery of buprenorphine using the CEDIA Buprenorphine Assay was assessed by spiking known amounts of potentially interfering substances to into urine specimens having a known buprenorphine concentration. Buprenorphine concentration for each specimen (substance and final concentration noted in the table below) was determined and the percent recovery calculated as the quotient of the spiked to control value. Results shown below demonstrate that the observed buprenorphine concentrations for spiked specimens are within ±10% of the values for the control specimens.

Interfering Substance	Final Concentration	Control Dose (ng/mL)	Spike Dose (ng/mL)	% of Control
Acetone	1000 mg/dL	5.2	5.1	98.1
Ascorbate	1500 mg/dL	5.3	4.9	91.2
Creatinine	500 mg/dL	5.5	5.6	101.8
Galactose	10 mg/dL	4.9	5.3	108.2
γ-Globulin*	500 mg/dL	5.5	5.2	93.4
Glucose	1500 mg/dL	5.3	4.9	93.0
Hemoglobin	300 mg/dL	5.6	5.7	101.2
NaCl	6000 mg/dL	5.7	5.7	100.0
Oxalic Acid	100 mg/dL	5.6	5.8	103.0
HSA*	500 mg/dL	5.9	5.7	97.2
Urea	2000 mg/dL	5.4	5.1	93.5
Riboflavin	7.5 mg/dL	5.6	5.1	91.7
Ethanol	1000 mg/dL	5.8	6.3	108.0

* γ - Globulin = Gamma Globulin; HSA = Human Serum Albumin

Buprenorphine Degradation Products

Potential cross-reactants evaluated included buprenorphine-3-β-D glucuronide, norbuprenorphine, and norbuprenorphine-3-β-D glucuronide. Potential cross-reactivity was determined by adding known amounts of each cross-reactant to buprenorphine-free urine specimens. A metabolite was determined to cross react with native buprenorphine if recovery observed for the metabolite spiked specimen was greater than 1% of the estimated target concentration. As indicated by the results provided, when prepared specimens are assayed using the CEDIA Buprenorphine Assay, buprenorphine 3-β-D-glucuronide exhibits nearly 100% cross-reactivity with buprenorphine while norbuprenorphine and its conjugated glucuronide show no evidence of significant cross-reactivity.

	Target (ng/mL)	Observed Value (ng/mL)	% Cross-Reactivity
BG	5 20	4.9 19.3	98 97
Norbuprenorphine	1000	0.6	< 0.015
NG	1000	0.1	< 0.015

BG = Buprenorphine-3-β-D Glucuronide;
NG = Norbuprenorphine-3-β-D Glucuronide

Cross Reactivity with Pharmacologic Substances

The potential cross-reactivity posed by drugs commonly co-administered with buprenorphine was evaluated by adding a final concentration of 100000 ng/mL of each substance to buprenorphine free urine. The observed difference in quantitation between a control and the sample with the added drug was then used to calculate cross-reactivity. All of the pharmacologic compounds evaluated are included in the following table and were < 0.015% cross-reactive in the CEDIA Buprenorphine Assay.

Compound	Target Concentration	Observed Value (ng/mL)	% Cross-Reactivity
Codeine	100000	14.80*	0.01
Codeine 6-glucuronide	100000	0.00	0.00
Dextromethorphan	100000	1.20	0.00
Dihydrocodeine	100000	11.40*	0.01
EDDP	100000	0.00	0.00
EMDP	100000	0.00	0.00
Heroin	100000	2.60	0.00
Hydrocodone	100000	8.90*	0.01
Hydromorphone	100000	4.70	0.00
Imipramine	100000	0.00	0.00
LAAM	100000	0.30	0.00
Levorphanol	100000	2.60	0.00
Methadol	100000	0.50	0.00
alpha-methadol	100000	0.00	0.00
alpha-levo-acetylmethadol	100000	0.00	0.00
alpha-levo-noracetylmethadol	100000	0.00	0.00
alpha-levo-dinoracetylmethadol	100000	0.00	0.00
Meriperidine	100000	2.30	0.00
Methadone	100000	2.60	0.00
6-Monoacetylmorphine	100000	3.80	0.00
Morphine	100000	3.40	0.00
Morphine 3-glucuronide	100000	3.20	0.00
Morphine 6-glucuronide	100000	0.00	0.00
Nalorphine	100000	86.70*	0.09
Naloxone	100000	3.50	0.00
Naltrexone	100000	6.70*	0.01
Noroxycodeine	100000	1.80	0.00
Noroxymorphine	100000	1.50	0.00
Norpropoxyphene	100000	5.50*	0.01
Oxymorphone	100000	1.40	0.00
Oxycodone	100000	0.00	0.00

* Concentrations of 100,000 ng/mL or greater will result in recovery above the cut-off.

Accuracy

Method Comparison - Semi-quantitative

The relationship between buprenorphine concentrations assayed using both the CEDIA Buprenorphine and gas chromatography/mass spectrometry methods was evaluated using linear regression techniques for 96 urine specimens representing the dynamic range of the assay (from 1.25 to 75.0 ng buprenorphine/mL). The correlation coefficient (r) of 0.988 as well as Deming and least squares regression parameters, shown in the following table and associated figure demonstrate overall excellent, unbiased agreement between the CEDIA Buprenorphine (y) and GC/MS (x) assay results.

	Deming's	Least Squares
n	96	96
Equation	y = 0.993x + 0.10	y = 0.981x + 0.27
S.E.E.	3.08	3.07
r	0.988	0.988

Method Comparison - Qualitative

The same 96 urine specimens described in the previous section were also qualitatively evaluated using a threshold of 5 ng buprenorphine/mL as the cutoff discriminating a negative or positive test result. In this analysis all specimens having a buprenorphine concentration greater than or equal to 5 ng/mL (≥ 5 ng/mL) were defined as positive for both methods while samples with concentrations of 4.99 ng/mL or lower (< 5 ng/mL) were defined as negative. The results shown in Table VII-9 demonstrate excellent overall concordance of 99.0% (95/96=98.95%, Yates-corrected χ^2=89.17, p < 0.0001) between GC/MS and the CEDIA Buprenorphine Assay.

	GC/MS Positive	GC/MS Negative	
CEDIA Positive	45	1	**46**
CEDIA Negative	0	50	**50**
	45	**51**	**96**

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Glossary:

http://www.thermofisher.com/symbols-glossary

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