LZI Oral Fluid 6-Acetylmorphine Enzyme Immunoassay

IVD For In Vitro Diagnostic Use Only

REF S0290 (75/37.5 mL R_1/R_2 Kit)
S0291 (750/375 mL R_1/R_2 Kit)

2°C – 8°C

Rx ONLY

Lin-Zhi International, Inc.

Intended Use

The Lin-Zhi International, Inc. (LZI) Oral Fluid 6-Acetylmorphine Enzyme Immunoassay (EIA) is a homogeneous enzyme immunoassay intended for the qualitative and semi-quantitative determination of 6-Acetylmorphine in neat human oral fluid, collected into an LZI Oral Fluid Collector, at the cutoff value of 4 ng/mL. The assay is designed for prescription use with a number of automated clinical chemistry analyzers.

The assay provides a rapid screening procedure for determining the presence of 6-Acetylmorphine in human oral fluid. The assay provides only a preliminary analytical result. A more specific alternative analytical chemistry method must be used in order to obtain a confirmed analytical result. Gas or Liquid Chromatography/Mass Spectrometry (GC/MS or LC/MS) is the preferred confirmatory methods (1, 2). Clinical consideration and professional judgment should be exercised with any drug of abuse test result, particularly when the preliminary test result is positive.

Summary and Explanation of Test

6-Acetylmorphine (6AM), otherwise known as 6-monoacetylmorphine (6MAM), is a unique metabolite of heroin (3, 6-diacetylmorphine). Due to the fact that it is a unique metabolite of heroin and because 6AM cannot be synthesized in the human body from either codeine or morphine, its detection can be used as a specific assay for the use of heroin (3-5). The specificity of this assay is significant, as traditional immunoassays for heroin test for the presence of morphine, which is also a metabolite of a number of different opiates including codeine, morphine, and heroin (6, 7).

Within the body, heroin is rapidly metabolized via deacetylation into 6AM. 6AM is then further hydrolyzed into morphine then morphine glucuronides and finally excreted in urine (8, 9). Clearance rates for 6AM are dependent on factors such as frequency of drug use, amount of drug use, and metabolism rates. Previous studies have found detectable levels of 6AM within urine for up to 8 hours (4). Previous studies have also shown that following IV infusion of heroin, the urinary metabolites accumulated over a 40 hour period include morphine (4.2 %), conjugated morphine (38.3 %), 6AM (1.3 %), and unchanged heroin (0.1 %) (10).

Due to the short detection window of 6AM in urine, oral fluid testing may be a better alternative. 6-Acetylmorphine appears in oral fluid within minutes after intravenous heroin administration and is can be found in higher concentration in oral fluid than in plasma (11).

Studies by Presley et al. found 6AM present in 66.7 % of morphine-positive specimens. Their data indicate that the mean concentration of 6AM was approximately one-half that of morphine, but exceeded morphine concentrations in two instances. Based on controlled dose studies of heroin administration, it is suggested that ratios >1 for 6AM to morphine in oral fluid are consistent with heroin use within the hour prior to specimen collection. (12)

Assay Principle

The LZI Oral Fluid 6-Acetylmorphine Enzyme Immunoassay is a homogeneous enzyme immunoassay with ready-to-use liquid reagents. The assay is based on competition between drug in the sample and drug labeled with the enzyme glucose-6-phosphate dehydrogenase (G6PDH) for a fixed amount of antibody in the reagent (13). Enzyme activity decreases upon binding to the antibody, and the drug concentration in the sample is measured in terms of enzyme activity. In the absence of drug in the sample, 6-acetylmorphine-labeled G6PDH conjugate is bound to antibody, and the enzyme activity is inhibited. On the other hand, when drug is present in the sample, antibody will bind to free drug, and the unbound 6-acetylmorphine-labeled G6PDH then exhibits its maximal enzyme activity. Active enzyme converts nicotinamide adenine dinucleotide (NAD) to NADH, resulting in an absorbance change that can be measured spectrophotometrically at 340 nm.

Reagents Provided

Antibody/Substrate Reagent (R_1): Contains mouse monoclonal anti-6-acetylmorphine antibody, glucose-6-phosphate (G6P), nicotinamide adenine dinucleotide (NAD), stabilizers, and sodium azide (0.09 %) as a preservative.

Enzyme-drug Conjugate Reagent (R_2): Contains 6-acetylmorphine-labeled glucose-6-phosphate dehydrogenase (G6PDH) in buffer with sodium azide (0.09 %) as a preservative.

Calibrators and Controls*

** Calibrators and Controls are sold separately and contain a negative synthetic oral fluid matrix with sodium azide as a preservative.*

ORAL FLUID 6-ACETYLMORPHINE Calibrator/Control	REF #
Oral Fluid 6-Acetylmorphine Negative Calibrator	S0298
Low Calibrator/Level 1 Control: Contains 2 ng/mL 6-Acetylmorphine	S0292
Cutoff Calibrator: Contains 4 ng/mL 6-Acetylmorphine	S0293
Intermediate Calibrator: Contains 10 ng/mL 6-Acetylmorphine	S0294
High Calibrator: Contains 20 ng/mL 6-Acetylmorphine	S0295
Level 2 Control: Contains 6 ng/mL 6-Acetylmorphine	S0297

Collectors**

*** Collectors are sold separately.*

ORAL FLUID Collector	REF #
LZI Oral Fluid Collector: 50 mL Polypropylene Centrifuge Tube	S0000b

Precautions and Warning

- *This test is for in vitro diagnostic use only.*
- *Harmful if swallowed.*
- *Reagent contains sodium azide as a preservative, which may form explosive compounds in metal drain lines. When disposing such reagents or wastes, always flush with a large volume of water to prevent azide build-up. See National Institute for Occupational Safety and Health Bulletin: Explosive Azide Hazards (8/16/76).*
- *Do not use the reagents beyond their expiration dates.*

Reagent Preparation and Storage

The reagents are ready to use. No reagent preparation is required. All assay components should be refrigerated at 2-8ºC when not in use.

Specimen Storage and Shipping

Note: If oral fluid samples cannot be analyzed immediately, they may be stored in amber glass vials and refrigerated (2-8ºC) for up to seven days or frozen (-20ºC) for up to three months.

Samples should always be shipped cold (2-8ºC), packed in gel ice, and shipped for next day delivery (within 24 hours). Failure to store or ship samples under these conditions may result in a significant decrease in recovery of analyte.

Specimen Collection and Handling

Oral fluid samples should be collected into a device without an absorbing pad, such as the LZI Oral Fluid Collector (a 50 mL polypropylene centrifuge tube) (14). At least 2 mL's of oral fluid sample for both EIA and confirmatory testing should be collected into the LZI Oral Fluid Collector (polypropylene collection tubes).

Prior to testing, samples should be frozen overnight (at minimum) and then allowed to thaw at room temperature. Samples should then be spun for five minutes at 3000 rpm to remove particulates. Only the clear top layer should be assayed for EIA testing and/or confirmatory testing. Samples should be at room temperature (18-25ºC) for testing.

Samples do not require dilution or any additional correction factors.

Fresh and properly stored oral fluid samples should be within the normal pH range of 6-8; however, any sample with pH ranging from 3-10 can be tested without any pretreatment of the samples.

Handle all oral fluid specimens as if they are potentially infectious.

Instrument

Clinical chemistry analyzers capable of maintaining a constant temperature, pipetting sample, mixing reagents, measuring enzyme rates at 340 nm and timing the reaction accurately can be used to perform this homogeneous immunoassay. Performance characteristics presented in this package insert have been validated on the Beckman AU400e. If other instruments are used, performance will need to be validated by the laboratory (15, 16).

Assay Procedure

Analyzers with the specifications indicated above are suitable for performing this homogeneous enzyme immunoassay. Refer to the specific parameter used for each analyzer before performing the assay. Typical Oral Fluid 6AM assay parameters used for the Beckman AU400e analyzer include a 36 µL sample, 90 µL of antibody reagent (R_1), and 45 µL of enzyme conjugate reagent (R_2) in 37ºC incubation temperature, 13-18 reading points, and 340 nm primary wavelength.

For qualitative analysis, use the 4 ng/mL as the cutoff calibrator. For semi-quantitative analysis, use all five calibrators to calibrate the assay. Recalibration should be performed after reagent bottle change or if there is a change in calibrators or reagent lot. Two levels of controls are also available for monitoring the cutoff level: 2 ng/mL and 6 ng/mL.

Calibration and Quality Control

Good laboratory practices recommend the use of at least two levels of control specimens (one positive and one negative control near the cutoff) to ensure proper assay performance. Controls should be run with each new calibration and after specific maintenance or troubleshooting procedures as detailed in the instrument system manual. Each laboratory should establish its own control frequency. If any trends or sudden change in control values are observed, review all operating parameters, or contact LZI technical support for further assistance. Laboratories should comply with all federal, state, and local laws, guidelines, and regulations.

Results

Note: A positive test result does not always mean a person took illegal drugs and a negative test result does not always mean a person did not take illegal drugs. There are a number of factors that influence the reliability of drug tests.

Qualitative: The cutoff calibrator, which contains 4 ng/mL of 6AM, is used as a reference for distinguishing positive from negative samples. A sample with a change in absorbance (ΔOD, mAu) equal to or greater than that obtained with the cutoff calibrator is considered positive. A sample with a change in absorbance (ΔOD, mAu) lower than that obtained with the cutoff calibrator is considered negative.

Semi-Quantitative: The semi-quantitative mode is for purposes of (1) enabling laboratories to determine an appropriate dilution of the specimen for verification by a confirmatory method such as GC/MS, or (2) permitting laboratories to establish quality control procedures. This mode requires a calibration curve that can be established with the five assay calibrators.

Limitations

1. *A positive result from the assay indicates only the presence of 6AM. The test is not intended for quantifying this single analyte in samples.*
2. *A positive result does not necessarily indicate drug abuse.*
3. *A negative result does not necessarily mean a person did not take heroin.*
4. *There is a possibility that other substances and/or factors not listed above may interfere with the test and cause incorrect results (e.g., technical or procedural error, fluid intake, endogeneous or exogeneous interferents).*
5. *Positive results should be confirmed by other affirmative, analytical chemistry methods (e.g., chromatography), preferably GC/MS or LC/MS.*
6. *The test is designed for use with human oral fluid only.*

Typical Performance Characteristics

The results shown below were performed with a Beckman AU400e automated chemistry analyzer.

Precision:

Semi-quantitative analysis: The following concentrations were determined with reference curves from five calibrators. Results (ng/mL) are as follows:

4 ng/mL Cutoff Result:		Total Precision		Within Run	
Sample [ ] (ng/mL)	% of Cutoff	# Samples	EIA Result	# Samples	EIA Result
0 ng/mL	0 %	80	80 Neg	20	20 Neg
1 ng/mL	25 %	80	80 Neg	20	20 Neg
2 ng/mL	50 %	80	80 Neg	20	20 Neg
3 ng/mL	75 %	80	80 Neg	20	20 Neg
4 ng/mL	100 %	80	32 Pos/ 48 Neg	20	8 Pos/ 12 Neg
5 ng/mL	125 %	80	80 Pos	20	20 Pos
6 ng/mL	150 %	80	80 Pos	20	20 Pos
7 ng/mL	175 %	80	80 Pos	20	20 Pos
8 ng/mL	200 %	80	80 Pos	20	20 Pos

Qualitative analysis: The following concentrations were evaluated. Results (ΔOD, mAu) are as follows:

4 ng/mL Cutoff Result:		Total Precision		Within Run	
Sample [ ] (ng/mL)	% of Cutoff	# Samples	EIA Result	# Samples	EIA Result
0 ng/mL	0 %	80	80 Neg	20	20 Neg
1 ng/mL	25 %	80	80 Neg	20	20 Neg
2 ng/mL	50 %	80	80 Neg	20	20 Neg
3 ng/mL	75 %	80	80 Neg	20	20 Neg
4 ng/mL	100 %	80	18 Pos/ 62 Neg	20	4 Pos/ 16 Neg
5 ng/mL	125 %	80	80 Pos	20	20 Pos
6 ng/mL	150 %	80	80 Pos	20	20 Pos
7 ng/mL	175 %	80	80 Pos	20	20 Pos
8 ng/mL	200 %	80	80 Pos	20	20 Pos

Accuracy: A total of 150 unaltered clinical specimens were tested with the Oral Fluid 6-Acetylmorphine Enzyme Immunoassay and confirmed by GC/MS. Specimens having a 6AM concentration greater than 4 ng/mL by GC/MS are defined as positive, and specimens with concentrations below 4 ng/mL by GC/MS are defined as negative in the table below. Near cutoff samples are defined as ± 50 % of the cutoff value. The correlation results are summarized as follows:

Semi-Quantitative Accuracy Study:

4 ng/mL Cutoff	Neg	<50 % of the cutoff	Near Cutoff Neg	Near Cutoff Pos	> 50 % above the cutoff	% Agree-ment
Positive	0	0	0	10	89	99.0 %
Negative	20	14	16	1*	0	100.0 %

The following table has the result for the discordant sample:

Cutoff Value 4 ng/mL	Assay Result		Sample Testing Method	
Sample	GC/MS Value (ng/mL)	Pos/Neg Result	LZI EIA (ng/mL)	Pos/Neg Result
51*	4.2	+	3.5	-

Qualitative Accuracy Study:

4 ng/mL Cutoff	Neg	<50 % of the cutoff	Near Cutoff Neg	Near Cutoff Pos	> 50 % above the cutoff	% Agree-ment
Positive	0	0	0	9	89	98.0 %
Negative	20	14	16	2*	0	100.0 %

The following table has the result for the discordant sample:

Cutoff Value 4 ng/mL	Assay Result		Sample Testing Method		
Sample	GC/MS Value (ng/mL)	Pos/Neg Result	LZI EIA (mAu)	EIA Cutoff Rate (mAu)	Pos/Neg Result
51*	4.2	+	662.9	678.6	-
52*	4.4	+	675.3	701.6	-

Analytical Recovery: To demonstrate linearity for purposes of sample dilution and quality control (see semi-quantitative results section), pooled human drug free oral fluid was spiked with 6AM and was serially diluted. Each sample was run in 10 replicates and the average was used to calculate the percent recovery.

Expected Value (ng/mL)	Observed Value (ng/mL)	% Recovery
1	1.2	120.0 %
2	2.2	110.0 %
4	4.3	107.5 %
6	5.8	96.7 %
8	8.1	101.3 %
10	10.1	101.0 %
12	12.1	100.8 %
14	15.0	107.1 %
16	16.8	105.0 %
18	18.8	104.4 %
20	20.6	103.0 %

Specificity: The cross reactivity of structurally related compounds were tested by spiking various concentrations of each substance into pooled human drug-free oral fluid, and then evaluated with the assay's calibrated dose-response curve. The following table summarizes the approximate quantity of each compound that is equivalent in assay reactivity (within ±25 %) to the 4 ng/mL 6AM cutoff.

Structurally Related 6-Acetylmorphine Compounds:

Cross-reactant	Spiked Concentration (ng/mL)	Dose (ng/mL)	% Cross Reactivity
Codeine	100,000	0.5	0.00 %
Dextromethorphan	100,000	0.4	0.00 %
Dihydrocodeine	100,000	0.0	0.00 %
Heroin	200	5.6	2.78 %
Hydrocodone Bitartrate	100,000	0.2	0.00 %
Hydromorphone	100,000	1.1	0.00 %
Imipramine	100,000	0.4	0.00 %
Levorphanol	100,000	0.4	0.00 %
Meperidine	100,000	0.6	0.00 %
Morphine	100,000	0.2	0.00 %
M3G	100,000	0.4	0.00 %
M6G	100,000	0.2	0.00 %
Nalophine	100,000	1.4	0.00 %
Naloxone	100,000	0.0	0.00 %
Naltrexone	100,000	0.5	0.00 %
Norcodeine	100,000	0.2	0.00 %
Normorphine	100,000	2.0	0.00 %
Oxycodone	100,000	0.4	0.00 %
Oxymorphone	100,000	-1.1	0.00 %

There is a possibility that metabolites of the compounds listed above may interfere with the 6-Acetylmorphine immunoassay and cause false results.

Structurally Unrelated Pharmacological Compounds:
The following structurally unrelated compounds were spiked into into pooled human drug-free oral fluid to the desired concentrations, split into portions, and then spiked with 6AM to a final concentration of 0 ng/mL, the negative control concentration of 2 ng/mL, or the positive control concentration of 6 ng/mL. The spiked solutions were evaluated against the assay's calibration curve. Results indicate there is no major interference with these compounds. Results are summarized in the following table:

Cross-reactant	Spiked [ ] (ng/mL)	Spiked 6AM Concentration (ng/mL)			
		0 ng/mL	% Cross	2 ng/mL Control	6 ng/mL Control
11-nor-Δ9-THC-COOH	100,000	0.1	0.00 %	1.6	6.3
Acetaminophen	100,000	0.0	0.00 %	2.1	5.3
Acetylsalicylic Acid	100,000	0.3	0.00 %	3.0	7.3
Amitriptyline	100,000	-0.1	0.00 %	2.6	7.5
Benzoylecgonine	100,000	0.1	0.00 %	2.3	6.5
Brompheniramine	100,000	0.0	0.00 %	2.1	6.2
Caffeine	100,000	0.3	0.00 %	2.6	7.0
Chlorpomazine	100,000	-0.2	0.00 %	2.3	6.7
Desipramine	100,000	-0.2	0.00 %	2.7	7.3
Diazepam	100,000	-0.1	0.00 %	2.0	7.1
Digoxin	100,000	-0.1	0.00 %	2.7	7.0
Diphenhydramine	100,000	0.0	0.00 %	2.6	6.6
Doxepin	100,000	-0.1	0.00 %	1.7	6.8
Fluoxetine	100,000	-0.2	0.00 %	2.0	6.9
Hydroxyzine Pamoate	100,000	-0.1	0.00 %	2.5	6.5
Ibuprofen	100,000	-0.2	0.00 %	3.0	7.0
Methadone	100,000	0.0	0.00 %	2.0	8.1
Methamphetamine	100,000	-0.1	0.00 %	2.4	6.2
Oxazepam	100,000	-0.1	0.00 %	2.2	6.9
Phencyclidine	100,000	-0.6	0.00 %	1.7	6.6
Phenobarbital	100,000	0.3	0.00 %	2.5	6.8
Propoxyphene	100,000	0.3	0.00 %	2.8	6.5
Ranitidine	100,000	-0.1	0.00 %	2.2	6.5
Secobarbital	100,000	-0.2	0.00 %	1.8	6.7
Triprolidine	100,000	0.0	0.00 %	2.6	6.9

It is possible that other substances and/or factors not listed above may interfere with the test and cause false results.

Interference: Endogenous Substances
The following endogenous compounds were spiked into pooled human drug-free oral fluid to the desired concentrations, split into portions, and then spiked with 6AM to a final concentration of 0 ng/mL, the negative control concentration of 2 ng/mL, or the positive control concentration of 6 ng/mL. The spiked solutions were evaluated against the assay's calibration curve. Results indicate there is no major interference with these compounds at physiological relevant concentrations as all spiked samples gave correct responding positive/negative results against the cutoff value of 4 ng/mL. Results are summarized in the following table:

Interference: Endogenous Substances, continued:

Interfering Substances	Spiked [ ] (mg/mL)	Spiked 6AM Concentration (ng/mL)		
		0 ng/mL	2 ng/mL Control	6 ng/mL Control
Albumin	15	-1.1	1.1	4.7
Ascorbic Acid	3	-0.5	1.3	4.4
Bilirubin	0.15	0.2	1.7	6
hemoglobin	3	0.2	1.7	5.7
IgA	1	-0.3	1.2	5.4
Salivary-α-Amylase	1000 U/mL	-0.4	1.3	4.9
Cholesterol	0.45	0.2	2.2	6.9
Continine	0.01	-0.1	2	6.3
Y-globulin	0.8	0.2	2.3	7.3
Nicotine	0.03	0.1	2.4	7.1

Ascorbic acid concentrations above 3 mg/mL cause false-negative results.

Interference: Exogenous Substances
The following potentially interfering compounds were spiked into pooled human drug-free oral fluid to the desired concentrations, split into portions, and then spiked with 6AM to a final concentration of 0 ng/mL, the negative control concentration of 2 ng/mL, or the positive control concentration of 6 ng/mL. The spiked solutions were evaluated against the assay's calibration curve. Results indicate there is no major interference with these compounds at physiologically relevant concentrations as all spiked samples gave correct corresponding positive/negative results against the cutoff value of 4 ng/mL. Results are summarized in the following table:

Interfering Substances	Spiked [ ] (%V/V)	Spiked 6AM Concentration (ng/mL)		
		0 ng/mL	2 ng/mL Control	6 ng/mL Control
Alcohol (Ethanol)	5	0.5	2.4	6.3
Cough (Mucinex)	5	0.1	2.0	6.2
Cranberry juice	5	0.3	2.3	5.8
Hydogen Peroxide	2	-1.0	2.2	6.0
Mouthwash	5	0.3	2.7	6.2
Soft drink (Sprite)	5	0.3	2.3	6.9
Sodium Chloride	18 ng/mL	0.4	2.5	7.2
Sugar	50 mg/mL	0.2	2.1	7.5
Toothpaste (Crest)	2.5	-0.3	2.4	6.6
Coffee	5	0.1	2	6.2
Milk	5	-0.1	2	7
Orange juice	5	-0.2	1.8	6.2
Cola (Coke)	5	0.1	2.2	7.4
Tea	5	0.0	2.0	6.4

Interference: pH
Pooled human drug-free oral fluid was adjusted to various pH ranges and then spiked with 6AM to a final concentration of 0 ng/mL, the negative control concentration of 2 ng/mL, or the positive control concentration of 6 ng/mL. The spiked solutions were evaluated against the assay's calibration curve. Results indicate that there is no major interference at various pH ranges and all spiked samples gave correct responding positive/negative results against the cutoff value of 4 ng/mL. Results are summarized in the following table:

pH Interference	Spiked [ ]	Spiked 6AM Concentration (ng/mL)		
		0 ng/mL	2 ng/mL Control	6 ng/mL Control
pH 3	N/A	-0.3	1.5	5.1
pH 4	N/A	-0.3	1.5	5.8
pH 5	N/A	-0.2	1.8	5.5
pH 6	N/A	-0.3	1.7	5.7
pH 7	N/A	0.1	1.7	6.6
pH 8	N/A	1.0	2.5	7.2
pH 9	N/A	0.0	2.3	7.0
pH 10	N/A	-0.1	2.1	7.1

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