

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

**A. 510(k) Number:**

k120761

**B. Purpose for Submission:**

New Device

**C. Measurand:**

Opiates

**D. Type of Test:**

Qualitative and semi-quantitative enzyme immunoassay

**E. Applicant:**

Lin-Zhi International, Inc.

**F. Proprietary and Established Names:**

LZI Opiate 2000 Enzyme Immunoassay  
LZI Opiate 2000 Enzyme Calibrators  
LZI Opiate 2000 Enzyme Controls

**G. Regulatory Information:**

<b>Product Code</b>	<b>Classification</b>	<b>Regulation Section</b>	<b>Panel</b>
DJG	Class II	21CFR 862.3650 Opiate Test System	Toxicology (91)
DLJ	Class II	21CFR 862.3200 Clinical Toxicology Calibrator	Toxicology (91)
LAS	Class I, Reserved	21CFR 862.3280 Clinical Toxicology Control Material	Toxicology (91)

## H. Intended Use:

1. Intended use(s):

Please see indications for use below.

2. Indication(s) for use:

The LZI Opiate 2000 Immunoassay is intended for the qualitative and semi-quantitative determination of morphine in human urine at a cutoff value of 2000 ng/mL. The assay is designated for professional use with a number of automated clinical chemistry analyzers.

The semi-quantitative mode is for purpose of (1) enabling laboratories to determine an appropriate dilution for the specimen for confirmation by a confirmatory method such as GC/MS and LC/MS or (2) permitting laboratories to establish quality control procedures.

LZI Opiate 2000 Enzyme Calibrators are for use as calibrators in the qualitative and semi-quantitative calibrations of the LZI Opiate 2000 Immunoassay at a cut off value of 2000 ng/mL.

LZI Opiate 2000 Enzyme Controls are for use as assayed quality control material to monitor the precision of the LZI Opiate 2000 Immunoassay at a cut off value of 2000 ng/mL.

The assay provides only preliminary analytical result. A more specific alternative chemical method must be used in order to obtain a confirmed analytical result. Gas or liquid chromatography/mass spectroscopy (GC/MS or LC/MS) is the preferred confirmatory method. Clinical consideration and professional judgment should be exercised with any drug of abuse test result, particularly when the preliminary test result is positive.

3. Special conditions for use statement(s):

For prescription use.

The assay provides only preliminary analytical test results.

A more specific alternative chemical method must be used in order to obtain a confirmed analytical result. Gas or liquid chromatography/mass spectroscopy (GC/MS or LC/MS) is the preferred confirmatory method. Clinical consideration and professional judgment should be exercised with any drug of abuse test result, particularly when the preliminary test result is positive.

4. Special instrument requirements:

Testing was performed on the Hitachi 717 automatic analyzer.

**I. Device Description:**

The LZI Opiate 2000 assay is a homogeneous enzyme immunoassay with two ready-to-use liquid reagents, and R1 and R2. These reagents are bottled separately but sold together within a kit.

R1 solution contains mouse monoclonal anti-morphine antibody, glucose-6-phosphate (G6P) nicotinamide adenine dinucleotide (NAD), stabilizers and sodium azide (0.09%) as a preservative.

R2 solution contains glucose-6-dehydrogenase (G6PDH) labeled with morphine in buffer with sodium azide (0.09%) as a preservative.

The LZI Opiate 2000 Immunoassay calibrators designated for use with the 2000ng/mL cutoff contains 5 levels, 0, 1000, 2000, 4000 and 6000 ng/mL of morphine in human urine with sodium azide (0.09%) as a preservative. These are sold as individual bottles.

The LZI Opiate 2000 Immunoassay controls designated for use with the 2000ng/mL cutoff contains 2 levels, 1500 and 2500 ng/mL of morphine in human urine with sodium azide (0.09%) as a preservative. These are sold as individual bottles.

**J. Substantial Equivalence Information:**

1. Predicate device name(s):

LZI Opiate Enzyme Immunoassay

Opiate Calibrators and Control

2. Predicate 510(k) number(s):

k020368 and k020769

3. Comparison with predicate:

Item	LZI Opiate 2000 Immunoassay (Candidate Device)	LZI Opiate Enzyme Immunoassay (Predicate - k020368)
Indication for Use	The LZI Opiate 2000 Immunoassay is intended for the qualitative and semi-quantitative determination of morphine in human urine at a cutoff value of 2000 ng/mL. The assay is designated for professional use with a number of automated clinical chemistry analyzers.	Same
Test System	Hitachi 717 automatic analyzer	Same

Analyte	Morphine	Same
Cutoff Concentration	2000 ng/mL	300 ng/mL
Test Principle	Enzyme Immunoassay (EIA)	Same
Matrix	Urine	Same
Confirmation Method	LC/MS/MS	Same
Storage	2-8 °C until expiration date	Same

Item	LZI Opiate 2000 Enzyme Calibrators (Candidate Device)	LZI Opiate Enzyme Calibrators (Predicate- <b>k020769</b> )
Indication for Use	LZI Opiate 2000 Enzyme Calibrators are for use as calibrators in the qualitative and semi-quantitative calibrations of the LZI Opiate 2000 Immunoassay at a cut off value of 2000 ng/mL.	Same
Levels	0, 1000, 2000, 4000 and 6000 ng/mL	0, 150, 300, 600 and 1000 ng/mL

Item	LZI Opiate 2000 Enzyme Controls (Candidate Device)	LZI Opiate Enzyme Controls (Predicate- <b>k020769</b> )
Indication for Use	LZI Opiate 2000 Enzyme Control are for use as assayed quality control material to monitor the precision of the LZI Opiate 2000 Immunoassay at a cut off value of 2000 ng/mL.	Same
Levels	1500 and 2500 ng/mL	225 and 375 ng/mL

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

CLSI Evaluation Protocols: EP5-A Evaluation of precision performance of clinical chemistry devices.

**L. Test Principle:**

The LZI Opiate 2000 Immunoassay is based on competition between drug in the sample and the drug labeled with the enzyme glucose-6-phosphate dehydrogenase (G6PDH) for a fixed amount of antibody in the reagent. 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 the drug in the sample, morphine-labeled G6PDH conjugate is bound to the antibody, and the enzyme activity is inhibited. When free drug is present in the sample, the antibody binds to the free drug; the unbound morphine-labeled G6PDH then exhibits maximal enzyme activity. Active enzyme converts nicotinamide adenine dinucleotide (NAD) to NADH, resulting in an absorbance change that can be measured spectrophotometrically at 340nm.

**M. Performance Characteristics (if/when applicable):**

1. Analytical performance:

a. *Precision/Reproducibility:*

1. Intra-assay precision around the cutoff

Urine samples containing morphine at concentrations 0, 500, 1000, 1500, 2000, 2500, 3000, 3500 and 4000 ng/mL were tested using two replicates per run, two runs per day for 22 days on the Hitachi 717 automatic analyzer. One experienced technician performed the analyses. The data is presented below.

Qualitative:

Sample concentration (ng/mL)	Within Run		Between Run	
	No. Observations	Immunoassay Results	No. Observations	Immunoassay Results
0	22	22 Negative	88	88 Negatives
500	22	22 Negative	88	88 Negatives
1000	22	22 Negative	88	88 Negatives
1500	22	22 Negative	88	88 Negatives
2000 (cutoff)	22	9 Positives / 13 Negatives	88	33 Positives / 55 Negatives
2500	22	22 Positives	88	88Positives
3000	22	22 Positives	88	88Positives
3500	22	22 Positives	88	88Positives
4000	22	22 Positives	88	88Positives

Semi-Quantitative:

Sample concentration (ng/mL)	Within Run		Between Run	
	No. Observations	Immunoassay Results	No. Observations	Immunoassay Results
0	22	22 Negative	88	88 Negatives
500	22	22 Negative	88	88 Negatives
1000	22	22 Negative	88	88 Negatives
1500	22	22 Negative	88	88 Negatives
2000 (cutoff)	22	18 Positives / 4 Negatives	88	59 Positives / 29 Negatives
2500	22	22 Positives	88	88Positives
3000	22	22 Positives	88	88Positives
3500	22	22 Positives	88	88Positives
4000	22	22 Positives	88	88Positives

b. *Linearity/assay reportable range:*

Linearity across the range was confirmed by using a morphine standard obtained from a commercial vendor and diluted several times using a pool of processed negative urine to create a stock solution with a concentration 6000 ng/mL of morphine. This stock was then diluted into twelve levels as presented in the table below. Each sample was tested in replicates of 10 on the Hitachi 717 analyzer.

% Dilution	Expected Concentration (ng/mL)	Observed Concentration (ng/mL)	% Recovery
100	6000	6811.48	113.5
90	5400	5837.71	108.1
80	4800	4881.50	101.7
70	4200	4239.37	100.9
60	3600	3622.10	100.6
50	3000	3007.99	100.3
40	2400	2380.17	99.2
30	1800	1842.90	102.4
20	1200	1252.90	104.4
10	600	596.78	99.5
3.33	200	214.43	107.2
0	0	80.72	not applicable

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

Five levels of calibrators (0, 1000, 2000, 4000 and 6000 ng/mL) and two levels of control material (1500 and 2500 ng/mL) are available for use with the LZI Opiate 2000 Immunoassay. A commercially available morphine standard solution 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:**

Accelerated and long term studies for both controls and calibrators have been conducted. Protocols and acceptance criteria were described and found to be acceptable. The manufacturer claims the following expiration date for both controls and calibrators:

When stored at 2-8 °C unopened or opened product is stable until expiration date which is 18 months.

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 for the qualitative and semi-quantitative mode by spiking various concentrations of each substance into drug-free urine and then calibrated with the assay's calibrated dose-response curve. 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 is presented below:

Structurally related compounds

Compound	Target Concentration (ng/mL)	% Cross-reactivity
6-Monoacetyl Morphine	2,000	111.74
Codeine	1,900	113.92
Dihydrocodeine	7,000	31.81
Heroin	2,600	79.97
Hydrocodone	15,000	15.64
Hydromorphone	12,500	18.83
Levorphanol	56,000	3.88
Morphine	2,000	101.84
Morphine-3-Glucuronide (M3G)	5,000	40.06
Morphine-6-Glucuronide (M6G)	2,500	83.93
Norcodeine	305,000	0.66
Oxycodone	600,000	0.37
Oxymorphone	1,020,000	0.20
Thebaine	15,000	13.49
Codeine-6-B-Glucuronide	2,000	107.95
Norhydrocodone	1,000,000	0.15
JHydromorphone-3B-D-Glucuronide	50,000	4.14

## Structurally unrelated

Compound	Target Concentration (ng/mL)	-25% Morphine Cutoff	+25% Morphine Cutoff
Acetaminophen	3,000,000	Negative	Positive
Acetylsalicylic Acid	2,000,000	Negative	Positive
Albuterol	70,000	Negative	Positive
Amitriptyline	25,000	Negative	Positive
Amobarbital	300,000	Negative	Positive
d-Amphetamine	3,000,000	Negative	Positive
Benzoyllecgonine	3,000,000	Negative	Positive
Bupropion	3,000,000	Negative	Positive
Caffeine	1,500,000	Negative	Positive
Carbamazepine	3,000,000	Negative	Positive
Chlorpomazine	5,000	Negative	Positive
Clomipramine	500,000	Negative	Positive
Desipramine	1,000	Negative	Positive
Dextromethorphan	400,000	Negative	Positive
Doxepine	50,000	Negative	Positive
Ecgonine	3,000,000	Negative	Positive
Ephedrine	3,000,000	Negative	Positive
Fentanyl	300	Negative	Positive
Fluoxetine	60,000	Negative	Positive
Fluphenazine	750,000	Negative	Positive
Ibuprofen	3,000,000	Negative	Positive
Imipramine	200,000	Negative	Positive
Lidocaine	60,000	Negative	Positive
Maprotiline	75,000	Negative	Positive
Meperidine	30,000	Negative	Positive
Methadone	400,000	Negative	Positive
Methapyrilene	600,000	Negative	Positive
Methaqualone	51,000	Negative	Positive
Metronidazole	700,000	Negative	Positive
Nalbuphine	30,000	Negative	Positive
Naloxone	9,000	Negative	Positive
Naltrexone	1,200,000	Negative	Positive
Nicotine	10,000	Negative	Positive
Normorphine	30,000	Negative	Positive
Nortriptyline	360,000	Negative	Positive
Oxazepam	3,000,000	Negative	Positive
Phencyclidine	360,000	Negative	Positive
Phenobarbital	120,000	Negative	Positive
Propoxyphene	110,000	Negative	Positive
Ranitidine	318,000	Negative	Positive
Secobarbital	100,000	Negative	Positive

Compound	Target Concentration (ng/mL)	-25% Morphine Cutoff	+25% Morphine Cutoff
Talwin	100,000	Negative	Positive
Thioridazine	6,000	Negative	Positive
Tramadol	330,000	Negative	Positive
Valproic Acid	2,000,000	Negative	Positive

### Endogenous Compounds

The following endogenous compounds were added into drug-free urine, urine sample spiked to -25% of morphine and spiked to +25% of Morphine at various concentrations. The substances listed in the table below were determined not to interfere at the concentration shown:

Interfering Substance	Concentration Tested ng/mL	-25% Morphine Cutoff	+25% Morphine Cutoff
Acetone	1000	Negative	Positive
Ascorbic Acid	1500	Negative	Positive
Creatinine	500	Negative	Positive
Ethanol	1000	Negative	Positive
Galactose	10	Negative	Positive
$\gamma$ -Globulin	500	Negative	Positive
Glucose	3000	Negative	Positive
Hemoglobin	300	Negative	Positive
Human Serum Albumin	500	Negative	Positive
Oxalic Acid	100	Negative	Positive
Riboflavin	0.3	Negative	Positive
Sodium Chloride	6000	Negative	Positive
Urea	6000	Negative	Positive

There is the possibility that other substances and/or factors not listed above may interfere with the test and cause false results, e.g., technical or procedural errors.

### pH and Specific Gravity

To test for possible positive and/or negative interference from pH urine samples having pH from 3, 4, 5, 6, 7, 8, 9, 10 and 11 were used. Each of these samples were spiked with commercially available standard to -25% of the cutoff and +25% of the cutoff and evaluated against the assay's calibration curve. No positive or negative interference due to pH was observed.

To test for possible positive and/or negative interference from specific gravity urine

samples having specific gravity from 1.000, 1.002, 1.005, 1.007, 1.010, 1.012, 1.015, 1.017, 1.020 and 1.022 were used. The samples were spiked to -25% of the cutoff and 125% of the cutoff. No positive or negative interference due to specific gravity 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 with predicate device:*

One hundred and fifty unaltered clinical urine samples were evaluated by the Lin-Zhi Opiate 2000 Enzyme Immunoassay on the Hitachi 717 analyzer and compared to LC/MS. Results from the study are presented below:

Semi-Quantitative:

Candidate Device Results	Negative	< 50% of cutoff concentration by LC/MS analysis	Near Cutoff Negative (Between 50% below the cutoff and the cutoff concentration)	Near Cutoff Positive (Between the cutoff and 50% above the cutoff concentration)	High Positive (greater than 50% above the cutoff concentration)
Positive	0	0	8	19	33
Negative	20	43	27	0	0

% Agreement among positives is 100.00%

% Agreement among negatives is 91.67%

Discordant

Cutoff Value (ng/mL)	LZI Opiate Assay (POS/NEG)	Drug/Metabolite LC/MS value (ng/mL)
2000	Positive	1160
2000	Positive	1708
2000	Positive	1715
2000	Positive	1726
2000	Positive	1745
2000	Positive	1854
2000	Positive	1853
2000	Positive	1869

Qualitative

Candidate Device Results 2000 ng/mL Cutoff	Negative	< 50% of cutoff concentration by LC/MS analysis	Near Cutoff Negative (Between 50% below the cutoff and the cutoff concentration)	Near Cutoff Positive (Between the cutoff and 50% above the cutoff concentration)	High Positive (greater than 50% above the cutoff concentration)
Positive	0	0	4	19	33
Negative	20	43	31	0	0

% Agreement among positives is 100.00%

% Agreement among negatives is 95.83%

Discordant

Cutoff Value (ng/mL)	LZI Opiate Assay (POS/NEG)	Drug/Metabolite LC/MS value (ng/mL)
2000	Positive	1708
2000	Positive	1726
2000	Positive	1853
2000	Positive	1869

b. *Matrix comparison:*

Not applicable.

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.