

# LZI Buprenorphine Enzyme Immunoassay

REF 0270 (100/37.5 mL R<sub>1</sub>/R<sub>2</sub> Kit)  
0271 (1000/375 mL R<sub>1</sub>/R<sub>2</sub> Kit)



IVD For In Vitro Diagnostic Use Only



**Lin-Zhi International, Inc.**

## Intended Use

The Lin-Zhi International (LZI) Buprenorphine Enzyme Immunoassay is intended for the qualitative and semi-quantitative determination of norbuprenorphine (a buprenorphine metabolite) in human urine at a cutoff value of 5 ng/mL and 10 ng/mL. The assay is designed for prescription use with a number of automated clinical chemistry analyzers.

**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) are 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

Buprenorphine is a semi-synthetic opioid derived from thebaine, an alkaloid of the poppy plant, *Papaver somniferum*. It is an analgesic often used as a substitution treatment for heroin addiction or opiate dependence. Buprenorphine structurally resembles morphine but has both antagonist and agonist properties (3). As an opioid partial agonist, buprenorphine can produce typical opioid effects and side effects such as euphoria and respiratory depression. However, its maximal effects are less than those of full agonists like heroin and methadone. At low doses, buprenorphine produces sufficient agonist effects to enable opioid-addicted individuals to discontinue the misuse of opioids without experiencing withdrawal symptoms. The agonist effects of buprenorphine increase linearly with increasing doses of the drug until it reaches a plateau and no longer continues to increase with further increases in dosage. Buprenorphine also acts as an antagonist, blocking other opioids, while allowing for some opioid effect of its own to suppress withdrawal symptoms and cravings (4). Buprenorphine is metabolized in the human liver by N-dealkylation to the pharmacologically active norbuprenorphine, which, along with the parent compound, is conjugated with glucuronic acid (5), and excreted in urine. Clearance rates are dependent on many factors, such as frequency of drug use, the amount of drug taken, metabolism rates, and even body fat content. For typical opioid-dependent patients who received a stable daily sublingual dose of 16 mg of buprenorphine and 4 mg of Naloxone for at least two weeks, 24-hour urinary elimination is approximately 11 % of daily dose (6). Therapeutically, buprenorphine is as effective as methadone but exhibits a much lower level of physical dependence. However, studies have shown that buprenorphine has abuse potential and may itself cause dependency (7).

## Assay Principle

The LZI buprenorphine assay is a homogeneous enzyme immunoassay using a ready-to-use liquid reagent. 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 (8). 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, buprenorphine-labeled G6PDH conjugate is bound to antibody, and the enzyme activity is inhibited. On the other hand, when free drug is present in the sample, antibody binds to the free drug; the unbound buprenorphine-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 a 340 nm primary wavelength.

## Reagents Provided

**Antibody/Substrate Reagent (R<sub>1</sub>):** Contains mouse monoclonal anti-buprenorphine antibody, glucose-6-phosphate (G6P), nicotinamide adenine dinucleotide (NAD), stabilizers, and sodium azide (0.09 %) as a preservative.  
**Enzyme-drug Conjugate Reagent (R<sub>2</sub>):** Contains glucose-6-phosphate dehydrogenase (G6PDH) labeled with buprenorphine in buffer with sodium azide (0.09 %) as a preservative.

## Calibrators and Controls\*

\*Calibrators and controls are sold separately and contain negative human urine with sodium azide as a preservative.

| NORBUPRENORPHINE Calibrators/Controls                 | REF  |
|---|------|
| Negative Calibrator                                   | 0001 |
| Control: Contains 3 ng/mL norbuprenorphine            | 0272 |
| Cutoff/Calibrator: Contains 5 ng/mL norbuprenorphine  | 0273 |
| Control: Contains 7 ng/mL norbuprenorphine            | 0274 |
| Cutoff/Calibrator: Contains 10 ng/mL norbuprenorphine | 0275 |
| Control: Contains 13 ng/mL norbuprenorphine           | 0276 |
| Calibrator: Contains 20 ng/mL norbuprenorphine        | 0277 |
| Calibrator: Contains 40 ng/mL norbuprenorphine        | 0278 |
| Calibrator: Contains 75 ng/mL norbuprenorphine        | 0279 |

## Precautions and Warning

- This test is for in vitro diagnostic use only. Harmful if swallowed.
- Reagents used in the assay contain sodium azide as a preservative, which may react with lead or copper plumbing to form potentially explosive metal azide. 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 (9).
- Do not use the reagents beyond their expiration dates.
- For USA: Caution: Federal law restricts this device to sale by or on the order of a physician.

## Reagent Preparation and Storage

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

## Specimen Collection and Handling

Urine samples may be collected in plastic or glass containers. Some plastics may absorb drugs. Use of plastics such as polyethylene is recommended (10). Use fresh urine specimens for the test. If a sample cannot be analyzed immediately, it may be refrigerated at 2-8°C for up to seven days (11, 12). For longer storage, keep sample frozen at -20°C and then thaw before use. Studies have shown buprenorphine analytes in urine are stable at -20°C up to 85 days (6). Samples should be at a room temperature of 18-25°C for testing. Samples with high turbidity should be centrifuged before analysis. Adulteration may cause erroneous results. If sample adulteration is suspected, obtain a new sample and both samples should be forwarded to the laboratory for testing.

Handle all urine specimens as if they are potentially infectious.

## Instrument

Clinical chemistry analyzers capable of maintaining a constant temperature, pipetting samples, mixing reagents, measuring enzyme rates at a 340 nm primary wavelength 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 Hitachi 717, Beckman Coulter® AU680, and the Synermed IR500 clinical analyzers.

## Assay Procedure

Refer to the specific parameters used for each analyzer before performing the assay. For qualitative analysis, use the 5 ng/mL or 10 ng/mL as the cutoff calibrator. For semi-quantitative analysis, use all six calibrators. 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 each cutoff level: use the 3 ng/mL and 7 ng/mL controls for the 5 ng/mL cutoff, and use the 7 ng/mL and 13 ng/mL controls for the 10 ng/mL cutoff level.

## 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 manual. Each laboratory should establish its own control frequency. If any trends or sudden change in control value are observed, review all operating parameters, or contact LZI technical support for further assistance. Laboratories should comply with all federal, state, and local laws, as well as all guidelines and regulations.

## Results

**Note:** A preliminary positive test result does not necessarily mean a person took illegal drugs and a negative test result does not necessarily 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 5 ng/mL or 10 ng/mL of norbuprenorphine, is used as a reference for distinguishing a preliminary positive from negative samples. A sample with a change in absorbance ( $\Delta A/\text{min}$ ) equal to or greater than that obtained with the cutoff calibrator is considered a preliminary positive. A sample with a change in absorbance ( $\Delta A/\text{min}$ ) 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 LC/MS, or (2) permitting laboratories to establish quality control procedures.

When an approximation of concentration is required, a calibration curve can be established with six calibrators. The concentration of norbuprenorphine in the sample may then be estimated from the calibration curve.

## Limitations

1. A preliminary positive result from the assay indicates only the presence of buprenorphine and/or norbuprenorphine. The test is not intended for quantifying this single analyte in samples.
2. A preliminary positive result does not necessarily indicate drug abuse.
3. A negative result does not necessarily mean a person did not take buprenorphine and/or norbuprenorphine.
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, endogenous or exogenous interferents).
5. Preliminary positive results should be confirmed by other affirmative, analytical chemical methods (e.g., chromatography), preferably GC/MS or LC/MS.
6. The test is designed for use with human urine only.
7. The test is not for therapeutic drug monitoring.
8. There is a possibility that metabolites of other opiate drugs may interfere with the test.

## Typical Performance Characteristics

The assay's range from 0 ng/mL to 20 ng/mL was tested in qualitative (mA/min) and semi-quantitative (ng/mL) modes using a modified NCCLS protocol. Results shown below were obtained by testing all samples in replicates of two, two runs per day for 22 days on the Hitachi 717 analyzer.

### Precision:

**Qualitative analysis:** Typical results (mA/min) are as follows:

| Concentration | Within Run (N=22) |     |       | Total Precision (N=88) |     |       |
|---------------|-------------------|-----|-------|------------------------|-----|-------|
|               | Mean              | SD  | % CV  | Mean                   | SD  | % CV  |
| 0 ng/mL       | 400.9             | 3.2 | 0.8 % | 400.9                  | 5.1 | 1.3 % |
| 2.5 ng/mL     | 419.6             | 2.7 | 0.6 % | 419.6                  | 4.0 | 0.9 % |
| 5.0 ng/mL     | 439.2             | 3.2 | 0.7 % | 439.2                  | 5.0 | 1.1 % |
| 7.5 ng/mL     | 461.2             | 3.3 | 0.7 % | 461.2                  | 4.7 | 1.0 % |
| 10 ng/mL      | 479.2             | 3.2 | 0.7 % | 479.2                  | 4.5 | 0.9 % |
| 12.5 ng/mL    | 495.4             | 3.3 | 0.7 % | 495.4                  | 4.8 | 1.0 % |
| 15 ng/mL      | 511.7             | 3.3 | 0.6 % | 511.7                  | 4.6 | 0.9 % |
| 17.5 ng/mL    | 526.8             | 3.2 | 0.6 % | 526.8                  | 4.5 | 0.9 % |
| 20 ng/mL      | 540.3             | 3.5 | 0.6 % | 540.3                  | 4.5 | 0.8 % |

| 5 ng/mL Cutoff |             | Within Run (N=22) |                  | Total Precision (N=88) |                   |
|----------------|-------------|-------------------|------------------|------------------------|-------------------|
| Concentration  | % of Cutoff | # Samples         | EIA Result       | # Samples              | EIA Result        |
| 0 ng/mL        | 0 %         | 22                | 22 Neg           | 88                     | 88 Neg            |
| 2.5 ng/mL      | 50 %        | 22                | 22 Neg           | 88                     | 88 Neg            |
| 5 ng/mL        | 100 %       | 22                | 13 Neg/<br>9 Pos | 88                     | 45 Neg/<br>43 Pos |
| 7.5 ng/mL      | 150 %       | 22                | 22 Pos           | 88                     | 88 Pos            |
| 10 ng/mL       | 200 %       | 22                | 22 Pos           | 88                     | 88 Pos            |

| 10 ng/mL Cutoff |             | Within Run (N=22) |                  | Total Precision (N=88) |                   |
|-----------------|-------------|-------------------|------------------|------------------------|-------------------|
| Concentration   | % of Cutoff | # Samples         | EIA Result       | # Samples              | EIA Result        |
| 0 ng/mL         | 0 %         | 22                | 22 Neg           | 88                     | 88 Neg            |
| 2.5 ng/mL       | 25 %        | 22                | 22 Neg           | 88                     | 88 Neg            |
| 5 ng/mL         | 50 %        | 22                | 22 Neg           | 88                     | 88 Neg            |
| 7.5 ng/mL       | 75 %        | 22                | 22 Neg           | 88                     | 88 Neg            |
| 10 ng/mL        | 100 %       | 22                | 4 Neg/<br>18 Pos | 88                     | 29 Neg/<br>59 Pos |
| 12.5 ng/mL      | 125 %       | 22                | 22 Pos           | 88                     | 88 Pos            |
| 15 ng/mL        | 150 %       | 22                | 22 Pos           | 88                     | 88 Pos            |
| 17.5 ng/mL      | 175 %       | 22                | 22 Pos           | 88                     | 88 Pos            |
| 20 ng/mL        | 200 %       | 22                | 22 Pos           | 88                     | 88 Pos            |

**Semi-quantitative analysis:** Typical results (ng/mL) are as follows:

| Concentration | Within Run (N=22) |     |       | Total Precision (N=88) |     |        |
|---------------|-------------------|-----|-------|------------------------|-----|--------|
|               | Mean              | SD  | % CV  | Mean                   | SD  | % CV   |
| 0 ng/mL       | 0.5               | 0.6 | N/A   | 0.5                    | 0.6 | N/A    |
| 2.5 ng/mL     | 3.1               | 0.3 | 9.5 % | 3.1                    | 0.4 | 14.4 % |
| 5.0 ng/mL     | 5.2               | 0.3 | 6.5 % | 5.2                    | 0.5 | 9.4 %  |
| 7.5 ng/mL     | 7.7               | 0.3 | 4.3 % | 7.7                    | 0.5 | 6.0 %  |
| 10 ng/mL      | 10.0              | 0.4 | 4.0 % | 10.0                   | 0.5 | 5.3 %  |
| 12.5 ng/mL    | 12.1              | 0.4 | 3.4 % | 12.1                   | 0.5 | 4.4 %  |
| 15 ng/mL      | 14.5              | 0.6 | 4.4 % | 14.5                   | 0.8 | 5.5 %  |
| 17.5 ng/mL    | 17.0              | 0.5 | 3.0 % | 17.0                   | 0.6 | 3.7 %  |
| 20 ng/mL      | 19.9              | 0.7 | 3.4 % | 19.9                   | 0.8 | 4.0 %  |

**Sensitivity:** Sensitivity, defined as the lowest concentration that can be differentiated from negative urine with 95 % confidence, was tested to be 2 ng/mL for both the 5 ng/mL and 10 ng/mL cutoffs.

**Accuracy:** Ninety (90) unaltered clinical urine specimens were tested with LZI Buprenorphine Enzyme Immunoassay and confirmed with GC/MS. Specimens having a norbuprenorphine concentration greater than 5 ng/mL or 10 ng/mL by GC/MS are defined as positive, and specimens with lower concentrations by GC/MS are defined as negative in the table below. Near cutoff samples are defined as  $\pm 50$  % of the cutoff value. The correlation results are summarized as follows:

| 5 ng/mL Cutoff | Neg | < 50 % below the cutoff | Near Cutoff Neg | Near Cutoff Pos | > 50 % above the cutoff | % Agreement |
|----------------|-----|-------------------------|-----------------|-----------------|-------------------------|-------------|
| Positive       | 0   | 0                       | 2*              | 7               | 47                      | 96.4 %      |
| Negative       | 16  | 6                       | 12              | 0               | 0                       | 100.0 %     |

| 10 ng/mL Cutoff | Neg | < 50 % below the cutoff | Near Cutoff Neg | Near Cutoff Pos | > 50 % above the cutoff | % Agreement |
|-----------------|-----|-------------------------|-----------------|-----------------|-------------------------|-------------|
| Positive        | 0   | 0                       | 2**             | 8               | 31                      | 95.1 %      |
| Negative        | 16  | 20                      | 12              | 1***            | 0                       | 98.0 %      |

The following table summarizes the results for the five discordant samples:

| Cutoff Value | Assay Result | Sample Composition: |             |
|--------------|--------------|---------------------|-------------|
|              |              | NBUP (GC/MS)        | BUP (GC/MS) |
| 5 ng/mL      | Positive*    | 4.1 ng/mL           | 0.0 ng/mL   |
| 5 ng/mL      | Positive*    | 4.4 ng/mL           | 0.0 ng/mL   |
| 10 ng/mL     | Positive**   | 8.5 ng/mL           | 3.2 ng/mL   |
| 10 ng/mL     | Positive**   | 9.5 ng/mL           | 0.0 ng/mL   |
| 10 ng/mL     | Negative***  | 10.2 ng/mL          | 0.0 ng/mL   |

**Linearity:** To demonstrate linearity for purposes of sample dilution and quality control (see semi-quantitative results section), a drug-free urine pool spiked with pure norbuprenorphine was serially diluted. Each sample was run in 10 replicates and the average was used to determine the functional linearity range of the assay. When comparing the result (y) and target (x) value, using the least squares regression technique, the regression equation and correlation are as follows:

$$y = 1.0026x + 0.9053, r^2 = 0.991$$

| Expected Value (ng/mL) | Observed Value (ng/mL) | % Recovery |
|------------------------|------------------------|------------|
| 2                      | 2.3                    | 115.0 %    |
| 5                      | 5.0                    | 99.6 %     |
| 10                     | 9.9                    | 99.4 %     |
| 20                     | 20.7                   | 103.7 %    |
| 30                     | 33.2                   | 110.8 %    |
| 40                     | 44.4                   | 111.1 %    |
| 50                     | 52.7                   | 105.3 %    |
| 60                     | 56.3                   | 93.8 %     |
| 70                     | 71.4                   | 102.1 %    |

**Specificity:** Cross-reactivity of various potentially interfering drugs was tested by spiking a final concentration of 100,000 ng/mL of each substance into drug-free urine, and then evaluated with the assay's calibrated dose-response curve. Cross-reactivity of the parent drug buprenorphine and its glucuronic acid metabolite is listed below as well. The assay detects the parent drug buprenorphine equally to norbuprenorphine, but has only minimal cross reactivity to either of the glucuronides.

The following table summarizes the approximate quantity of each compound that is equivalent in assay reactivity to the 5 ng/mL and 10 ng/mL norbuprenorphine cutoff. For compounds tested at 100,000 ng/mL and which gave an immunoassay result below 2 ng/mL, which is the assay's limit of detection, equivalent concentration and percent cross reactivity are listed as "not detected" ("ND").

### Structurally Related Buprenorphine Compounds:

| Compound                     | Equivalent [ ] to 5 ng/mL | Equivalent [ ] to 10 ng/mL | % Cross-Reactivity |
|------------------------------|---------------------------|----------------------------|--------------------|
| Buprenorphine                | 4.9                       | 9.9                        | 101 %              |
| Buprenorphine-Glucuronide    | 3846                      | 7692                       | 0.1 %              |
| Norbuprenorphine-Glucuronide | 556                       | 1111                       | 0.9 %              |

### Structurally Related Opiate Compounds\*:

| Compound               | Equivalent [ ] to 5 ng/mL | Equivalent [ ] to 10 ng/mL | % Cross-Reactivity |
|------------------------|---------------------------|----------------------------|--------------------|
| 6-Acetylcodeine        | ND                        | ND                         | ND                 |
| Codeine                | ND                        | ND                         | ND                 |
| Dextromethorphan       | ND                        | ND                         | ND                 |
| Dihydrocodeine         | ND                        | ND                         | ND                 |
| Heroin                 | 192308                    | 384615                     | 0.003 %            |
| Hydrocodone            | ND                        | ND                         | ND                 |
| Hydromorphone          | ND                        | ND                         | ND                 |
| Levorphanol            | 70423                     | 140845                     | 0.007 %            |
| 6-Monoacetylmorphine   | ND                        | ND                         | ND                 |
| Morphine               | ND                        | ND                         | ND                 |
| Morphine-3-Glucuronide | ND                        | ND                         | ND                 |
| Morphine-6-Glucuronide | ND                        | ND                         | ND                 |
| Nalorphine             | ND                        | ND                         | ND                 |
| Naloxone               | ND                        | ND                         | ND                 |
| Naltrexone             | ND                        | ND                         | ND                 |
| Norcodeine             | ND                        | ND                         | ND                 |
| Noroxycodone HCl       | ND                        | ND                         | ND                 |
| Noroxymorphone HCl     | ND                        | ND                         | ND                 |
| Oxycodone              | ND                        | ND                         | ND                 |
| Oxymorphone            | ND                        | ND                         | ND                 |

\*There is a possibility that metabolites of the compounds listed above may interfere with buprenorphine immunoassays and cause false results.

### Structurally Unrelated Pharmacological Compounds\*\*:

| Compound           | Equivalent [ ] to 5 ng/mL | Equivalent [ ] to 10 ng/mL | % Cross-Reactivity |
|--------------------|---------------------------|----------------------------|--------------------|
| $\alpha$ -Methadol | ND                        | ND                         | ND                 |
| Citalopram         | ND                        | ND                         | ND                 |
| EDDP               | ND                        | ND                         | ND                 |
| EMDP               | 185185                    | 370370                     | 0.003 %            |
| Fluoxetine         | ND                        | ND                         | ND                 |
| Gabapentin         | ND                        | ND                         | ND                 |
| Imipramine         | ND                        | ND                         | ND                 |
| LAAM               | ND                        | ND                         | ND                 |
| Meperidine         | ND                        | ND                         | ND                 |
| Methadone          | ND                        | ND                         | ND                 |
| Norpropoxyphene    | ND                        | ND                         | ND                 |
| Paroxetine         | ND                        | ND                         | ND                 |
| Sertraline         | ND                        | ND                         | ND                 |
| Tramadol           | ND                        | ND                         | ND                 |

\*\* It is possible that other substances and/or factors not listed above may interfere with the test and cause false results, e.g., technical or procedure errors.

### Interference: Endogenous Substances

The following endogenous compounds were spiked into negative urine and the three levels of controls (3 ng/mL, 7 ng/mL, and 13 ng/mL) for the assay. The spiked solution was 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 responding preliminary positive/negative results against the cutoff value of 5 ng/mL or 10 ng/mL. Results are summarized in the following table:

| Interfering Substances | Spiked [ ] (mg/dL) | 0 ng/mL Control (ng/mL) | 3 ng/mL Control (ng/mL) | 7 ng/mL Control (ng/mL) | 13 ng/mL Control (ng/mL) |
|------------------------|--------------------|-------------------------|-------------------------|-------------------------|--------------------------|
| Acetone                | 1000               | 0.0                     | 3.2                     | 6.5                     | 12.2                     |
| Ascorbic Acid          | 400                | 0.4                     | 3.3                     | 6.5                     | 13.2                     |
| Creatinine             | 500                | 0.9                     | 3.8                     | 7.1                     | 13.0                     |
| Galactose              | 10                 | 0.4                     | 3.5                     | 6.4                     | 11.7                     |
| $\gamma$ -Globulin     | 500                | 0.0                     | 3.0                     | 8.1                     | 11.2                     |
| Glucose                | 1500               | 0.0                     | 3.1                     | 7.1                     | 11.5                     |
| Hemoglobin             | 300                | 0.4                     | 4.0                     | 8.2                     | 13.0                     |
| NaCl                   | 6000               | 0.9                     | 3.9                     | 7.8                     | 13.0                     |
| Oxalic Acid            | 100                | 0.5                     | 3.3                     | 6.7                     | 11.8                     |
| Human Serum Albumin    | 500                | 0.0                     | 3.2                     | 7.1                     | 11.8                     |
| Riboflavin             | 7.5                | 0.0                     | 3.0                     | 7.9                     | 12.5                     |
| Urea                   | 2000               | 0.0                     | 3.3                     | 7.2                     | 11.6                     |
| Ethanol                | 1000               | 0.0                     | 3.0                     | 8.1                     | 11.9                     |
| pH 3                   | N/A                | 0.0                     | 3.3                     | 5.9                     | 13.6                     |
| pH 11                  | N/A                | 0.0                     | 3.7                     | 8.0                     | 12.7                     |

**Specific Gravity:** Samples ranging in specific gravity from 1.001 to 1.027 were tested with the assay in the presence of 0 ng/mL, 3 ng/mL, 7 ng/mL, and 13 ng/mL of norbuprenorphine, and no interference was observed.

**Note:** All endogenous substances listed above, including specific gravity, were also tested in qualitative mode. No interference is observed. The results were identical to the semi-quantitative mode as all samples gave correct positive/negative results corresponding to the cutoff value of 5 ng/mL or 10 ng/mL.

### Symbols Used

|  |                                    |      |  |
|--|------------------------------------|------|--|
|  | Authorized Representative          |      | Medical Prescription Only                      |
|  | Biological Risks                   |      | R <sub>1</sub> , Antibody/Substrate Reagent    |
|  | CE Mark                            |      | R <sub>2</sub> , Enzyme-Drug Conjugate Reagent |
|  | Consult Instructions for Use       |      | Reference Number                               |
|  | Contents                           |      | Safety Data Sheet                              |
|  | Global Trade Item Number           |      | Temperature Limits                             |
|  | In Vitro Diagnostic medical device | T.K. | Test Kit Number                                |
|  | Lot Number                         |      | Use-by Date                                    |
|  | Manufacturer                       |      |  |

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A point (period/stop) is always used in this instruction for use document as the decimal separator to mark the border between the integral and the fractional parts of a decimal numeral. Separators for thousands are not used.

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