LZI Hydrocodone Enzyme Immunoassay

300 ng/mL Cutoff

For Beckman Coulter, Inc.

IVD For In Vitro Diagnostic Use Only

REF C68823 (100/37.5 mL R_1/R_2 Kit)

2-8°C

Lin-Zhi International, Inc.

Intended Use

The Lin-Zhi International, Inc. (LZI) Hydrocodone Enzyme Immunoassay for Beckman Coulter, Inc. is intended for the qualitative and semi-quantitative determination of hydrocodone in human urine at a cutoff value of 300 ng/mL. The assay is designed for screening with the Beckman Coulter AU/DxC AU 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

Hydrocodone is an opioid compound derived from codeine. Hydrocodone acts on μ-opioid receptors (3). It is prescribed as a narcotic analgesic to treat moderate to severe pain and as an antitussive to treat cough (4). As an opioid compound, it is more potent than codeine but 1.5 times less potent than oxycodone (5). Hydrocodone can be addictive, causing physical and psychological dependence. Its risk of abuse is similar to morphine and lower than oxycodone's (6).

Hydrocodone is often administered in combination with paracetamol (acetaminophen) or ibuprofen. Combination with other medication is often used to increase efficacy and reduce adverse side effects (7, 8). Use of Hydrocodone in combination with alcohol, other opioids, antihistamines, antipsychotics, antianxiety medication, or other central nervous system (CNS) depressants can cause additive CNS depression (9). Hydrocodone may also interact with serotonergic medications (10).

The analgesic properties of hydrocodone begin 20-30 minutes after consumption and last between four to eight hours (3). Hydrocodone is metabolized in the liver by the cytochrome p450 enzyme CYP2D6 which converts it to hydromorphone, an even more potent opioid than hydrocodone itself (11).

In 72-hour urine, 26% of the hydrocodone dose is eliminated as unchanged drug (12%), norhydrocodone (5%), conjugated hydromorphone (4%), 6-hydrocodol (3%) and conjugated 6-hydromorphol (0.1%) (12, 13).

The hydrocodone metabolite, hydromorphone, is also a minor urinary metabolite of morphine. Initial studies suggest that hydromorphone may have advantages as an analgesic as compared to morphine and is seven to ten times more potent than morphine (14, 15). Hydromorphone is often prescribed by itself under the brand name Dilaudid.

In the 24-hour urine, an average of 6% of the dosage is eliminated as free hydromorphone and 30% as conjugated hydromorphone (16). The metabolite of hydromorphone, hydromorphone-3-glucuronide, has also been shown to have significant pharmacological activity (17).

Assay Principle

The LZI Hydrocodone Enzyme Immunoassay is a homogeneous enzyme immunoassay 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 (18). 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, hydrocodone-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 would bind to free drug; the unbound hydrocodone-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 a mouse monoclonal anti-hydrocodone 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 glucose-6-phosphate dehydrogenase (G6PDH) labeled with hydrocodone in buffer with sodium azide (0.09%) as a preservative.

Calibrators and Controls*

Materials required (but not provided)

**Calibrators and Controls are sold separately or as a semi-quantitative set and contain negative human urine with sodium azide as a preservative.*

Qualitative Calibration	REF
LZI Hydrocodone Qualitative Calibrator HYD Cutoff Calibrator (300 ng/mL)	C68830

Semi-Quantitative Calibration	REF
LZI Universal Negative Calibrator	C68807
LZI Hydrocodone Semi-Quantitative Calibrator Set HYD Low Calibrator (150 ng/mL) HYD Cutoff Calibrator (300 ng/mL) HYD Intermediate Calibrator (500 ng/mL) HYD High Calibrator (800 ng/mL)	C68831

Controls	REF
LZI Hydrocodone Level 1 Control HYD Level 1 Control (225 ng/mL)	C68828
LZI Hydrocodone Level 2 Control HYD Level 2 Control (375 ng/mL)	C68829

Others

WEDGE	REF
OSR Bottle kit, 20 x 60 mL	63093
OSR Bottle kit, 20 x 30 mL	63094

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 (19).*
- *Do not use the reagents beyond their expiration dates.*
- Rx ONLY *For USA: 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 2-8ºC when not in use. See the expiration date on individual bottle labels.

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 (20). Use fresh urine specimens for the test. If the sample cannot be analyzed immediately, it may be refrigerated at 2-8ºC for up to seven days (21, 22). For longer storage, keep sample frozen at -20ºC and then thaw before use. Studies have shown hydrocodone samples in urine are stable at -20ºC for up to three years (23). Samples should be equilibrated to room temperature (18-25ºC) 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 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 Coulter AU480, AU680, AU5800, DxC500 AU, DxC500i, and DxC700 AU automated clinical analyzers.

Assay Procedure

Analyzers with the specifications indicated above are suitable for performing this homogeneous enzyme immunoassay. Refer to the specific parameters used for each analyzer before performing the assay.

For qualitative analysis use the 300 ng/mL as the cutoff calibrator. The cutoff is normalized to 100. Positive samples are ≥ 100 and are flagged with a (P).

For semi-quantitative analysis, use all five calibrators including the universal negative calibrator. Recalibration should be performed after reagent bottle change or there is a change in calibrators or reagent lot. Two levels of controls are also available for monitoring the cutoff level: 225 ng/mL and 375 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 value are observed, review all operating parameters, or contact your local Beckman Coulter Representative 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 300 ng/mL of hydrocodone is used as a reference for distinguishing preliminary 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 preliminary 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, 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 5 calibrators. The concentration of hydrocodone 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 hydrocodone. 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 illegal drugs.*
4. *Care should be taken when reporting results as numerous factors (e.g., fluid intake, endogenous or exogenous interferents) may influence the urine test result.*
5. *Preliminary 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 urine only.*
7. *The test is not for therapeutic drug monitoring.*

Typical Performance Characteristics

The results shown below were performed with a single Beckman Coulter AU480 automated chemistry analyzer.

Precision:

Semi-quantitative analysis: The following concentrations were determined with reference curves from five calibrators. Typical results were measured in ng/mL. Positive/Negative results are as follows:

300 ng/mL Cutoff		Within Run (N=22)		Run-to-Run (N=88)	
Concentration	**% of Cutoff**	**# Samples**	**EIA Result**	**# Samples**	**EIA Result**
0 ng/mL	-100.0%	22	22 Neg	88	88 Neg
75 ng/mL	-75.0%	22	22 Neg	88	88 Neg
150 ng/mL	-50.0%	22	22 Neg	88	88 Neg
225 ng/mL	-25.0%	22	22 Neg	88	88 Neg
300 ng/mL	0%	22	8 Neg/ 14 Pos	88	41 Neg/ 47 Pos
375 ng/mL	+25.0%	22	22 Pos	88	88 Pos
450 ng/mL	+50.0%	22	22 Pos	88	88 Pos
525 ng/mL	+75.0%	22	22 Pos	88	88 Pos
600 ng/mL	+100.0%	22	22 Pos	88	88 Pos

Qualitative analysis: The following concentrations were evaluated. Typical qualitative results were measured by (ΔOD, mAU). Positive/Negative results are as follows:

300 ng/mL Cutoff		Within Run (N=22)		Run-to-Run (N=88)	
Concentration	**% of Cutoff**	**# Samples**	**EIA Result**	**# Samples**	**EIA Result**
0 ng/mL	-100.0%	22	22 Neg	88	88 Neg
75 ng/mL	-75.0%	22	22 Neg	88	88 Neg
150 ng/mL	-50.0%	22	22 Neg	88	88 Neg
225 ng/mL	-25.0%	22	22 Neg	88	88 Neg
300 ng/mL	0%	22	11 Neg/ 11 Pos	88	37 Neg/ 51 Pos
375 ng/mL	+25.0%	22	22 Pos	88	88 Pos
450 ng/mL	+50.0%	22	22 Pos	88	88 Pos
525 ng/mL	+75.0%	22	22 Pos	88	88 Pos
600 ng/mL	+100.0%	22	22 Pos	88	88 Pos

Accuracy: Eighty (80) unaltered clinical urine specimens were tested with the LZI Hydrocodone Enzyme Immunoassay and confirmed with GC/MS or LC/MS. Specimens having a hydrocodone and hydromorphone total concentration greater than 300 ng/mL by GC/MS or LC/MS are defined as positive, and specimens with total concentrations below 300 ng/mL by GC/MS or LC/MS are defined as negative in the table below. The correlation results are summarized as follows: (near cutoff samples are defined as ±50% of the cutoff value). Adjusted GC/MS or LC/MS values have been corrected for cross-reactivity (12, 13).

Semi-Quantitative Accuracy Study:

300 ng/mL Cutoff	Neg	< 50% below the cutoff	Near Cutoff Neg	Near Cutoff Pos	> 50% above the cutoff	% Agree-ment
Positive	0	0	2*	6	32	95.0%
Negative	20	12	6	2**	0	95.0%

* Discrepant below 50% of the cutoff concentration
** Discrepant between -50% of the cutoff concentration and the cutoff concentration

The following table summarizes the result for the discrepant samples:

300 ng/mL Cutoff	GC/MS or LC/MS	LZI EIA	Adjusted Total Hydrocodone + Hydromorphone GC/MS or LC/MS (ng/mL)	LZI EIA (ng/mL)
36*	-	+	206.9	375.5
39*	-	+	246.0	323.1
41**	+	-	301.0	252.8
43**	+	-	306.2	254.1

Qualitative Accuracy Study:

300 ng/mL Cutoff	Neg	< 50% below the cutoff	Near Cutoff Neg	Near Cutoff Pos	> 50% above the cutoff	%Agree-ment
Positive	0	0	2*	6	32	95.0%
Negative	20	12	6	2**	0	95.0%

* Discrepant below 50% of the cutoff concentration
** Discrepant between -50% of the cutoff concentration and the cutoff concentration

Analytical Recovery: To demonstrate linearity for purposes of sample dilution and quality control (see semi-quantitative results section) of the entire assay range, a drug-free urine pool spiked with hydrocodone at 800 ng/mL was serially diluted. Each sample was run in 10 replicates and the average was used to determine percent recovery compared to the expected target value. When comparing the result (y) and target (x) value, using the least squares regression technique, the regression equation and correlation are as follow:

$y = 1.0316x + 1.1461$, $r^2 = 0.9988$

Expected Value (ng/mL)	Observed Value (ng/mL)	% Recovery
800	806.3	100.8%
700	736.9	105.3%
600	634.2	105.7%
500	510.1	102.0%
425	445.5	104.8%
375	393.2	104.9%
300	304.4	101.5%
225	230.7	102.5%
150	152.9	101.9%
100	104.0	104.0%
10	12.5	124.6%
0	0.5	N/A

Specificity: Various potentially interfering substances were tested for cross-reactivity with the assay. Test compounds were spiked into the drug-free urine calibrator matrix to various concentrations and evaluated against the cutoff calibrator.

The table below lists the concentration of each test compound that gave a response approximately equivalent to that of the cutoff calibrator (as preliminary positive) or the maximal concentration of the compound tested that gave a response below the response of the cutoff calibrator (as negative).

Hydrocodone and Metabolites:

Compound	Target [ ] (ng/mL)	% Cross-Reactivity
Hydrocodone	300	99.70%
Hydromorphone	375	82.19%
Hydromorphone Glucuronide	625	49.15%
Dihydrocodeine	8750	3.32%
Norhydrocodone	30000	0.51%

Structurally Related Compounds:

Compound	Target [ ] (ng/mL)	% Cross-Reactivity
6-Mono Acetylmorphine	30000	1.00%
Codeine	13400	2.16%
Codeine-6-glucuronide	80000	0.37%
Dextromethorphan	100000	0.00%
Levorphanol	100000	0.32%
Morphine	22000	1.30%
Morphine-3-glucuronide	37000	0.73%
Morphine-6-glucuronide	100000	0.17%
Nalbuphine	100000	0.00%
Naloxone	100000	0.03%
Naltrexone	100000	0.01%
Norbuprenorphine	100000	0.00%
Norcodeine	100000	0.02%
Noroxycodone	100000	0.02%
Noroxymorphone	100000	0.27%
Oxycodone	20000	0.08%
Oxymorphone	35000	0.90%
Thebaine	25000	0.75%

Structurally Unrelated Compounds:

Compound	Spiked [ ] (ng/mL)	Spiked Hydrocodone Concentration		
		0 ng/mL (ng/mL)	225 ng/mL Control (ng/mL)	375 ng/mL Control (ng/mL)
d-Amphetamine	250000	Neg	Neg	Pos
Benzoylecgonine	100000	Neg	Neg	Pos
MDA (3,4-Methylenedioxy-Amphetamine)	100000	Neg	Neg	Pos
MDMA (3,4-Methylenedioxy-Methamphetamine)	100000	Neg	Neg	Pos
d-Methamphetamine	250000	Neg	Neg	Pos
Phencyclidine	250000	Neg	Neg	Pos
THC-COOH (11-Nor-Delta-9-THC-9-Carboxylic Acid)	1000	Neg	Neg	Pos
Acetaminophen	500000	Neg	Neg	Pos
Acetylsalicylic Acid	500000	Neg	Neg	Pos
Albuterol (Salbutamol)	500000	Neg	Neg	Pos
Amitriptyline	500000	Neg	Neg	Pos
Amobarbital	500000	Neg	Neg	Pos
Bupropion	500000	Neg	Neg	Pos
Caffeine	500000	Neg	Neg	Pos
Carbamazepine	500000	Neg	Neg	Pos
Chlorpheniramine	500000	Neg	Neg	Pos
Chlorpromazine	500000	Neg	Neg	Pos
Clomipramine	500000	Neg	Neg	Pos
Desipramine	500000	Neg	Neg	Pos
Ephedrine	500000	Neg	Neg	Pos
Fentanyl	10000	Neg	Neg	Pos
Fluoxetine	100000	Neg	Neg	Pos
Fluphenazine	500000	Neg	Neg	Pos
Ibuprofen	500000	Neg	Neg	Pos
Imipramine	50000	Neg	Neg	Pos
Lidocaine	500000	Neg	Neg	Pos
Maprotiline	500000	Neg	Neg	Pos
Meperidine	50000	Neg	Neg	Pos
Methadone	100000	Neg	Neg	Pos
Methapyrilene	500000	Neg	Neg	Pos
Methaqualone	500000	Neg	Neg	Pos
Metronidazole	500000	Neg	Neg	Pos
Nicotine	500000	Neg	Neg	Pos
Nortriptyline	500000	Neg	Neg	Pos
Oxazepam	100000	Neg	Neg	Pos
Phenobarbital	500000	Neg	Neg	Pos
d-Propoxyphene	100000	Neg	Neg	Pos
Propranolol	100000	Neg	Neg	Pos
Ranitidine	500000	Neg	Neg	Pos
Secobarbital	100000	Neg	Neg	Pos
Sertraline	100000	Neg	Neg	Pos
Pentazocine	20000	Neg	Neg	Pos
Thioridazine	100000	Neg	Neg	Pos
Tramadol	100000	Neg	Neg	Pos
Valproic Acid	500000	Neg	Neg	Pos

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

Endogenous Compound Interference Study:

Endogenous Substance	Spiked [ ] (mg/dL)	Spiked Hydrocodone Concentration		
		0 ng/mL (ng/mL)	225 ng/mL Control (ng/mL)	375 ng/mL Control (ng/mL)
Acetone	1000	Neg	Neg	Pos
Ascorbic Acid	500	Neg	Neg	Pos
Creatinine	500	Neg	Neg	Pos
Ethanol	1000	Neg	Neg	Pos
Galactose	10	Neg	Neg	Pos
γ-Globulin	500	Neg	Neg	Pos
Glucose	3000	Neg	Neg	Pos
Hemoglobin	300	Neg	Neg	Pos
Human Serum Albumin	500	Neg	Neg	Pos
Oxalic Acid	100	Neg	Neg	Pos
Riboflavin	0.3	Neg	Neg	Pos
Urea	6000	Neg	Neg	Pos
Sodium Chloride	1000	Neg	Neg	Pos

pH Interference Study:

pH	Spiked Hydrocodone Concentration		
	0 ng/mL (ng/mL)	225 ng/mL Control (ng/mL)	375 ng/mL Control (ng/mL)
pH 3	Neg	Neg	Pos
pH 4	Neg	Neg	Pos
pH 5	Neg	Neg	Pos
pH 6	Neg	Neg	Pos
pH 7	Neg	Neg	Pos
pH 8	Neg	Neg	Pos
pH 9	Neg	Neg	Pos
pH 10	Neg	Neg	Pos
pH 11	Neg	Neg	Pos

Specific Gravity: Samples ranging in specific gravity from 1.000 to 1.030, were split into three portions each and either left unspiked or further spiked to a final hydrocodone concentration of either 225 ng/mL or 375 ng/mL (the negative and positive control concentrations, respectively). These samples were then evaluated in semi-quantitative and qualitative modes. No interference was observed.

Open-Vial Calibrator/Control Stability: Real-time data for open-vial calibrator/control stability studies at cold temperature (2-8ºC) have been carried out and support stability up to 18 months. Open-vial calibrators/controls should be stored at 2-8ºC for maximum shelf life.

Closed-Vial Calibrator/Control Stability: Real-time data for closed-vial calibrator/control stability studies at cold temperature (2-8ºC) have been carried out and support stability up to 18 Months. Closed-vial calibrators/controls should be stored at 2-8ºC for maximum shelf life.

Additional Information

For more detailed information on AU 8 series and DxC AU Systems, refer to the appropriate system manual.

Since Beckman Coulter does not manufacture the reagent or perform quality control or other tests on individual lots, Beckman Coulter cannot be responsible for the quality of the data obtained which is caused by performance of the reagent, any variation between lots of reagent, or protocol changes by the manufacturer.

Shipping Damage

Please notify your Beckman Coulter Clinical Support Center if this product is received damaged.

Bibliography:

1. Urine Testing for Drug of Abuse, National Institute on Drug Abuse (NIDA) Research Monograph 73, (1986).
2. Mandatory Guidelines for Federal Workplace Drug Testing Program, National Institute on Drug Abuse, Federal Register, **23**(82):7920-7970 (2017).
3. Vallejo, R., Barkin, R. L., and Wang, V.C. Pharmacology of opioids in the treatment of chronic pain syndromes. *Pain physician* **14**(4): E343–E360. (2011)
4. Karch, S.B. Pharmacokinetics and pharmacodynamics of abused drugs. CRC Press, Boca Raton; 55–56 (2008).
5. Zacny, J. P., and Gutierrez, S. Within-subject comparison of the psychopharmacological profiles of oral hydrocodone and oxycodone combination products in non-drug-abusing volunteers. *Drug and Alcohol Dependence* **101**(1–2): 107–114 (2009).

Bibliography, continued:

6. Wightman, R., Perrone, J., Portelli, I., and Nelson, L. Likeability and Abuse Liability of Commonly Prescribed Opioids. *J Med Tox* **8**(4): 335–340 (2012).
7. Beaver, W. T., and McMillan, D. Methodological considerations in the evaluation of analgesic combinations: Acetaminophen (paracetamol) and hydrocodone in postpartum pain". *British journal of clinical pharmacology*. **10**(Suppl 2): 215S–223S (1980).
8. Raffa, R. B. Pharmacology of oral combination analgesics: Rational therapy for pain. *J Clin Pharm andTher* **26**(4): 257–264 (2001).
9. "REPREXAIN(hydrocodone bitartrate, ibuprofen) tablet, film coated". *http://dailymed.nlm.nih.gov*. (2013).
10. Gnanadesigan, N., Espinoza, R.T., and Smith, R.L. The serotonin syndrome. *N Engl J Med* **352**(23): 2454–6 (2005).
11. Gardiner, S. J., and Begg, E. J., Pharmacogenetics, Drug-Metabolizing Enzymes, and Clinical Practice. *Pharmacological Reviews* **58** (3): 521–590 (2006).
12. Cone, E.J. and Darwin, W.D., Simultaneous determination of hydromorphone, hydrocodone and their 6α- and 6β-hydroxy metabolites in urine using selected ion recording with methane chemical ionization., *Biomed. Mass Spect.* **5**:291-295 (1978).
13. Valtier, S. and Bebarta, V.S., Excretion profile of hydrocodone, hydromorphone, and norhydrocodone in urine following single dose administration of hydrocodone to healthy volunteers. *J. Anal. Toxicol.* **36**(7):507-14 (2012).
14. Felden, L., Walter, C., Harder, S., Treede, R.-D., Kayser, H., Drover, D., Geisslinger, G., and J. Lötsch. Comparative Clinical Effects of Hydromorphone and Morphine. *British Journal of Anaesthesia* **107**(3): 319–328 (2011).
15. Baselt, R.C., Disposition of Toxic Drugs and Chemicals in Man. 9th edition. Biomedical Publications, Seal Beach, CA. 818-820 (2011).
16. Cone, E.J., Phelps, B.A., and C.W. Gorodetzky. Urinary excretion of hydromorphone and metabolites in humans, rats, dogs, guinea pigs, and rabbits. *J. Pharm. Sci.* **66**:1709-1713 (1977).
17. Wright, A.W., Nocente, M.L., and M.T. Smith. Hydromorphone-3-glucuronide: biochemical synthesis and preliminary pharmacological evaluation. *Life Sci.* **63**:401-411 (1998)
18. Rubenstein, K.E., R.S. Schneider, and E.F. Ullman, Homogeneous Enzyme Immunoassay: A New Immunochemical Technique, *Biochem Biophys Res Commun*, **47**: 846 (1972).
19. Sodium Azide. National Institute for Occupational Safety (NIOSH). Pocket Guide to Chemical Hazards. Third Printing, September 2007. Available online at: https://www.cdc.gov/niosh/npg/default.html
20. Yahya, A.M., McElnay, J.C., and P.F. D'Arcy. Drug sorption to glass and plastics. *Drug Metabol Drug Interact*. **6**(1):1-45 (1988).
21. Gonzales, E.G., Ng, G., Pesce, A.J., West, C., West, R., Mikel, C., Latyshev, S., and Almazan, P. Stability of Commonly Prescribed Opioids and Other Pain Medications in Urine. 2012 AAPM Annual Meeting Presentation.
22. Dixon, R. B., Stability study of opioids and benzodiazepines in urine samples by liquid chromatography tandem mass spectrometry, Journal of Analytical Science and Technology, **6**:17 (2015).
23. ARUP Consult Physician's Guide. http://www.aruplab.com/guides/ug/tests/0090364.jsp

Symbols

LZI uses the symbols and signs listed on the symbol glossary on the website. Visit www.lin-zhi.com/symbol-glossary for detailed information.

Additions, deletions, or changes are indicated by a change bar in the margin.
For technical assistance please call (408) 970-8811

For instructions for use (including translations) please visit:
https://www.lin-zhi.com/bci_applications/

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