LZI Benzodiazepine Enzyme Immunoassay

IVD For In Vitro Diagnostic Use Only

REF 0130 (100/37.5 mL R_1/R_2 Kit)
0131 (1000/375 mL R_1/R_2 Kit)

2°C – 8°C

Lin-Zhi International, Inc.

Intended Use

The Lin-Zhi International, Inc. (LZI) Benzodiazepine (BZO) Enzyme Immunoassay is intended for the qualitative and semi-quantitative determination of benzodiazepines in human urine at a cutoff value of 200 ng/mL or 300 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

Benzodiazepines are a family of sedative-hypnotics (3, 4) that are structurally similar and include widely used drugs such as lorazepam, diazepam, chlordiazepoxide, triazolam, and oxazepam. The different benzodiazepines are absorbed at different rates, and the timing of their psychoactive effects varies with the absorption rate and varied half-lives (5).

Benzodiazepines are prescribed for various conditions including panic disorders (6), insomnia (7), seizures (8), alcohol withdrawal (9), and anxiety (10). However, chronic use of benzodiazepines may lead to tolerance and dependence (11, 12). Benzodiazepines are usually taken orally and are metabolized in the liver via cytochrome p450s (13) or glucuronidation (14). Detection of benzodiazepines or their metabolites in urine can be used as an indication for use of benzodiazepines (15).

Assay Principle

The LZI Benzodiazepine assay 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 (16). 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, benzodiazepine-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 benzodiazepine-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_1): Contains mouse monoclonal anti-benzodiazepine 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 benzodiazepine 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.*

BENZODIAZEPINE Calibrators/Controls	REF
Negative Calibrator	0001
Calibrator #2/Control 1: Contains 100 ng/mL oxazepam	0132
Calibrator #3/Cutoff A/ Control 2: Contains 200 ng/mL oxazepam	0133
Calibrator #4/Cutoff B/Control 3: Contains 300 ng/mL oxazepam	0134
Calibrator #5: Contains 1000 ng/mL oxazepam	0135
Control 4: Contains 400 ng/mL oxazepam	0136

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 (17).*
- *Do not use the reagents beyond their expiration dates.*
- Rx ONLY *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 2-8ºC when not in use.

Specimen Collection and Handling

Urine samples may be collected in plastic or glass containers. Some plastics may adsorb drugs. Use of plastics such as polyethylene is recommended (18). Use fresh urine specimens for the test. If a sample cannot be analyzed immediately, it may be refrigerated at 2-8ºC for up to seven days (19). For longer storage, keep sample frozen at -20ºC and then thaw before use. Studies have shown benzodiazepine analytes in urine are stable at -20ºC up to six months (19, 20). Samples should be at 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 forward both samples 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 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 200 ng/mL or 300 ng/mL as the cutoff calibrator. For semi-quantitative analysis, use all five 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 of each cutoff level: use the 100 ng/mL and 300 ng/mL controls for the 200 ng/mL cutoff, and use the 200 ng/mL and 400 ng/mL controls for the 300 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 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 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 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 200 ng/mL or 300 ng/mL of oxazepam, is used as a reference for distinguishing a preliminary positive from negative samples. A sample with a change in absorbance (ΔmA/min) equal to or greater than that obtained with the cutoff calibrator is considered a preliminary positive. A sample with a change in absorbance (ΔmA/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 five calibrators. The concentration of benzodiazepines in the sample may then be estimated from the calibration curve.

Limitations

1. *Certizine may cause false positive results at concentrations greater than 3,200 ng/mL at the 200 ng/mL cutoff and 5,500 ng/mL at the 300 ng/mL cutoff.*
2. *Fluoxetine may cause false positive results at concentrations greater than 15,000 ng/mL at 200 ng/mL cutoff and 21,000 ng/mL at the 300 ng/mL cutoff.*
3. *Hydroxyzine may cause false positive results at concentrations greater than 16,000 ng/mL at 200 ng/mL cutoff and 24,000 ng/mL at the 300 ng/mL cutoff.*
4. *Boric Acid may cause false negative results at concentrations greater than 1,000 mg/dL at the 200 ng/mL and 300 ng/mL cutoffs.*
5. *A preliminary positive result from the assay indicates only the presence of benzodiazepines. The test is not intended for quantifying these single analytes in samples.*
6. *A preliminary positive result does not necessarily indicate drug abuse.*
7. *A negative result does not necessarily mean a person did not take benzodiazepines.*
8. *Care should be taken when reporting results as numerous factors (e.g., fluid intake, endogenous or exogenous interferents) may influence the urine test result.*
9. *Preliminary positive results should be confirmed by other affirmative, analytical chemical methods (e.g., chromatography), preferably GC/MS or LC/MS.*
10. *The test is designed for use with human urine only.*
11. *The test is not for therapeutic drug monitoring.*
12. *Glucuronide metabolites of oxazepam, lorazepam, and temazepam do not cross-react with the antibodies in this immunoassay. The cross-reactivity of other glucuronide metabolites with this assay is not known.*

Typical Performance Characteristics

The results shown below were performed with a single Hitachi 717 automated clinical chemistry analyzer.

Precision:

Qualitative analysis: The five calibrators were evaluated. Typical results (ΔmA/min) are as follows:

Concentration	Within Run (N=21)			Run-to-Run (N=12)		
	Mean	SD	% CV	Mean	SD	% CV
Negative	361.0	3.1	0.9 %	360.0	2.5	0.7 %
100 ng/mL	417.8	3.5	0.8 %	417.9	2.5	0.6 %
200 ng/mL	455.5	3.5	0.8 %	457.0	1.9	0.5 %
300 ng/mL	483.3	3.5	0.7 %	483.6	2.4	0.6 %
1000 ng/mL	559.7	4.9	0.7 %	561.8	3.3	0.6 %

Semi-quantitative analysis: The concentrations of the cutoff level and the two levels of controls were determined with reference curves from five calibrators. Typical results (ng/mL) are as follows:

Concentration	Within Run (N=21)			Run-to-Run (N=12)		
	Mean	SD	% CV	Mean	SD	% CV
100 ng/mL	105.7	7.6	7.2 %	95.8	6.4	6.7 %
200 ng/mL	203.6	5.9	2.9 %	192.0	6.5	3.4 %
300 ng/mL	281.8	11.1	3.9 %	294.8	15.5	5.3 %
400 ng/mL	373.9	15.3	4.1 %	398.6	15.4	3.9 %

Sensitivity: Sensitivity, defined as the lowest concentration that can be differentiated from negative urine with 95 % confidence, was tested to be 15 ng/mL.

Accuracy: The device as compared to GC/MS or HPLC analysis performed as follows:

200 ng/mL cutoff		GC/MS or HPLC	
		Positive	Negative
LZI Benzodiazepine EIA	Positive	64	2
	Negative	8	42

The following table summarizes the result for the discordant samples:

Discrepant Specimens – 200 ng/mL	
LZI BZO EIA	Reference Method
-	HPLC 518 ng/mL Lorazepam
-	HPLC 101 ng/mL Demoxepam, 68 ng/mL Oxazepam, 1889 ng/mL Temazepam
-	HPLC 280 ng/mL Lorazepam
-	HPLC 526 ng/mL Lorazepam
-	HPLC 1811 ng/mL Lorazepam
-	GC/MS 286 ng/mL Lorazepam
-	GC/MS 261 ng/mL Alprazolam
-	GC/MS 252 ng/mL Lorazepam
+	HPLC 114 ng/mL Oxazepam
+	GC/MS 185 ng/mL Oxazepam

300 ng/mL cutoff		GC/MS or HPLC	
		Positive	Negative
LZI Benzodiazepine EIA	Positive	61	2
	Negative	11	42

Accuracy, continued: The following table summarizes the result for the discordant samples:

Discrepant Specimens – 300 ng/mL	
LZI BZO EIA	Reference Method
-	HPLC 461 ng/mL Clonazepam
-	HPLC 518 ng/mL Lorazepam
-	HPLC 101 ng/mL Demoxepam, 68 ng/mL Oxazepam, 1889 ng/mL Temazepam
-	HPLC 280 ng/mL Lorazepam
-	HPLC 526 ng/mL Lorazepam
-	HPLC 1811 ng/mL Lorazepam
-	GC/MS 307 ng/mL Oxazepam
-	GC/MS 286 ng/mL Lorazepam
-	GC/MS 261 ng/mL Alprazolam
-	GC/MS 311 ng/mL Lorazepam
-	GC/MS 252 ng/mL Lorazepam
+	HPLC 114 ng/mL Oxazepam
+	GC/MS 185 ng/mL Oxazepam

Analytical Recovery: In qualitative analysis, the assay correctly identified spiked samples containing more than 200 ng/mL of oxazepam (n=25, spiked levels or higher than the cutoff calibrator) as positive, and those containing less than 200 ng/mL of oxazepam (n=20, spiked levels less than the cutoff calibrator) as negative. For semi-quantitative analysis, the average recovery for samples spiked with 20 ng/mL to 800 ng/mL (five samples at each level) of oxazepam is summarized in the following table:

Expected Value (ng/mL)	Observed Value (ng/mL)	% Recovery
20	18.9	94.4 %
50	52.1	104.3 %
100	108.2	108.2 %
180	173.4	96.3 %
225	218.8	97.3 %
375	379.8	101.3 %
450	468.1	104.0 %
600	575.1	95.9 %
800	791.2	98.9 %

Specificity: Various potentially interfering substances were tested for cross-reactivity with the assay. Test compounds were spiked into the drug-free urine to various concentrations and 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 to the 200 ng/mL and 300 ng/mL benzodiazepine cutoffs or the maximal concentration of the compound tested that gave a response with cross-reactivity below the response of the cutoff calibrators.

Benzodiazepine Compound:

Compound	Concentration (ng/mL) at 200 ng/mL	Concentration (ng/mL) at 300 ng/mL
Oxazepam	200	300

Structurally Related Benzodiazepine Compounds:

Compound	Concentration (ng/mL) at 200 ng/mL	Concentration (ng/mL) at 300 ng/mL
7-aminoflunitrazepam	67000	1000
α-hydroxyalprazolam	275	425
Alprazolam	75	100
Bromazepam	2100	5000
Clorazepate	65	125
Chlordiazepoxide	750	1300
Clobazam	169	247
Clonazepam	80	200
Diazepam	50	70
Efavirenz	500,000	500,000
Flunitrazepam	90	135
Flurazepam	50	75
Lorazepam	43	54
Lormetazepam	23	70
Medazepam	23	70
Midazolam	330	450
Nitrazepam	150	220
Nordiazepam	290	450
Norfludiazepam	15	25
Prazepam	75	105

Structurally Related Benzodiazepine Compounds, Continued:

Compound	Concentration (ng/mL) at 200 ng/mL	Concentration (ng/mL) at 300 ng/mL
Temzaepam	80	115
Triazolam	45	105
Oxazepam-Glucuronide	>10,000	>10,000
Lorazepam-Glucuronide	>10,000	>10,000
Quetiapine	100,000	100,000

Structurally Unrelated Pharmacological Compounds:

Compound	Concentration (ng/mL) at 200 ng/mL	Concentration (ng/mL) at 300 ng/mL
Acetaminophen	1,000,000	1,000,000
Acetylsalicylic Acid	1,000,000	1,000,000
Amitriptyline	180,000	400,000
Amobarbital	1,000,000	1,000,000
Amphetamine	1,000,000	1,000,000
Benzoylecgonine	1,000,000	1,000,000
Caffeine	1,000,000	1,000,000
Cetirizine	3500	6000
Chlorpromazine	200,000	500,000
Cocaine	400,000	700,000
Codeine	1,000,000	1,000,000
Cyclobenzaprine	42,000	63,000
Dextromethorphan	1,000,000	1,000,000
Emtricitabine	500,000	500,000
Ephedrine	1,000,000	1,000,000
Escitalopram	100,000	100,000
Hydroxyzine	16,000	24,000
Imipramine	300,000	500,000
Meperidine	600,000	1,000,000
Methadone	1,000,000	1,000,000
Methamphetamine	1,000,000	1,000,000
Methaqualone	1,000,000	1,000,000
Morphine	1,000,000	1,000,000
Norsertraline	10,000	10,000
Nortriptyline	600,000	1,000,000
Olanzapine	100,000	100,000
Paroxetine	4800	7100
Phenobarbital	1,000,000	1,000,000
Promethazine	1,000,000	1,000,000
Propoxyphene	1,000,000	1,000,000
Risperidone	100	100
Secobarbital	1,000,000	1,000,000
Sertraline	54,000	81,000
Tenofovir disoproxil fumarate	500,000	500,000
Valproic Acid	1,000,000	1,000,000
Lidocaine	1,000,000	1,000,000
Chlorpheniramine	100,000	150,000
Ecgonine	1,000,000	1,000,000
Bupropion	1,000,000	1,000,000
Ranitidine	1,000,000	1,000,000
Zolpidem	100,000	100,000

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

Interference: Endogenous Substances: 200 ng/mL Cutoff

The following endogenous compounds were spiked into negative urine and the two levels of controls (100 ng/mL and 300 ng/mL) for the assay. The spiked solution is 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 200 ng/mL. Results are summarized in the following table:

Interfering Substances	Spiked [ ] (mg/dL)	Oxazepam Concentration		
		0 ng/mL	100 ng/mL Control	300 ng/mL Control
Acetone	1000	Neg	Neg	Pos
Ascorbic Acid	1500	Neg	Neg	Pos
Bilirubin	2	Neg	Neg	Pos
Boric Acid	1000	Neg	Neg	Neg
Calcium Chloride ($CaCl_2$)	300	Neg	Neg	Pos
Citric Acid (pH 3)	800	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
β-hydroxybutyric Acid	100	Neg	Neg	Pos

Interference: Endogenous Substances, Continued: 200 ng/mL Cutoff

Interfering Substances	Spiked [ ] (mg/dL)	Oxazepam Concentration		
		0 ng/mL	100 ng/mL Control	300 ng/mL Control
Human Serum Albumin	500	Neg	Neg	Pos
Oxalic Acid	100	Neg	Neg	Pos
Potassium Chloride	6000	Neg	Neg	Pos
Riboflavin	7.5	Neg	Neg	Pos
Sodium Azide	1000	Neg	Neg	Pos
Sodium Chloride	6000	Neg	Neg	Pos
Sodium Fluoride	1000	Neg	Neg	Pos
Sodium Phosphate	300	Neg	Neg	Pos
Urea	6000	Neg	Neg	Pos
Uric Acid	10	Neg	Neg	Pos

pH Interference Study: Negative urine and urine spiked with analyte to the two levels of controls (100 ng/mL and 300 ng/mL) were adjusted to the following pH levels and tested by the assay. The pH adjusted solutions were evaluated against the cutoff calibrator. No major interference with these pH levels was observed as all pH adjusted levels gave correct corresponding preliminary positive/negative results against the cutoff value of 200 ng/mL. Results are summarized in the following table:

pH	Spiked Oxazepam Concentration		
	0 ng/mL	100 ng/mL Control	300 ng/mL Control
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

Interference: Endogenous Substances: 300 ng/mL Cutoff

The following endogenous compounds were spiked into negative urine and the two levels of controls (200 ng/mL and 400 ng/mL) for the assay. The spiked solution is 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 300 ng/mL. Results are summarized in the following table:

Interfering Substances	Spiked [ ] (mg/dL)	Oxazepam Concentration		
		0 ng/mL	200 ng/mL Control	400 ng/mL Control
Acetone	1000	Neg	Neg	Pos
Ascorbic Acid	1500	Neg	Neg	Pos
Bilirubin	2	Neg	Neg	Pos
Boric Acid	1000	Neg	Neg	Neg
Calcium Chloride ($CaCl_2$)	300	Neg	Neg	Pos
Citric Acid (pH 3)	800	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
β-hydroxybutyric Acid	100	Neg	Neg	Pos
Human Serum Albumin	500	Neg	Neg	Pos
Oxalic Acid	100	Neg	Neg	Pos
Potassium Chloride	6000	Neg	Neg	Pos
Riboflavin	7.5	Neg	Neg	Pos
Sodium Azide	1000	Neg	Neg	Pos
Sodium Chloride	6000	Neg	Neg	Pos
Sodium Fluoride	1000	Neg	Neg	Pos
Sodium Phosphate	300	Neg	Neg	Pos
Urea	6000	Neg	Neg	Pos
Uric Acid	10	Neg	Neg	Pos

pH Interference Study: Negative urine and urine spiked with analyte to the two levels of controls (200 ng/mL and 400 ng/mL) were adjusted to the following pH levels and tested by the assay. The pH adjusted solutions were evaluated against the cutoff calibrator. No major interference with these pH levels was observed as all pH adjusted levels gave correct corresponding preliminary positive/negative results against the cutoff value of 300 ng/mL. Results are summarized in the following table:

pH Interference Study, Continued:

pH	Spiked Oxazepam Concentration		
	0 ng/mL	200 ng/mL Control	400 ng/mL Control
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

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Additions, deletions, or changes are indicated by a change bar in the margin.
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