LZI Buprenorphine Enzyme Immunoassay

For Beckman Coulter® Synchron Systems

REF A53684 (2 x 100 tests) 2ºC 8ºC

IVD For In Vitro Diagnostic Use Only

Lin-Zhi International, Inc.

Intended Use

The Lin-Zhi International (LZI) Buprenorphine Enzyme Immunoassay, when used in conjunction with Beckman Coulter UniCel DxC automated clinical system analyzers, is intended for the qualitative and semi-quantitative determination of norbuprenorphine (a buprenorphine metabolite) in human urine, at a cutoff value of 10 ng/mL. The assay is designed for prescription use in clinics and clinical chemistry laboratories 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 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_1): 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_2): Contains buprenorphine-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 negative human urine with sodium azide as a preservative.*

* Materials Needed But Not Supplied With Reagent Kit:

NORBUPRENORPHINE Calibrator/Control	REF
Negative Calibrator (0 ng/mL)	A53687
Low Calibrator (5 ng/mL)	A68826
Cutoff Calibrator (10 ng/mL)	A68827
Intermediate Calibrator #1 (20 ng/mL)	A68828
Intermediate Calibrator #2 (40 ng/mL)	A68829
High Calibrator (100 ng/mL)	A68830
Level 1 Negative Control (7 ng/mL)	A68824
Level 2 Positive Control (13 ng/mL)	A68825
User-Defined Reagent Cartridge (pkg. of 12)	442835

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

1. Transfer the entire contents of 1 bottle of Antibody/Substrate (R_1) to Compartment A (largest) of an empty reagent cartridge.
2. Transfer the entire contents of Enzyme-drug Conjugate Reagent (R_2) to Compartment B (middle) of the reagent cartridge.

Use care to avoid foaming when filling the cartridge. All assay components should be stored refrigerated when not in use.

The reagents are ready to use. No reagent preparation is required. All assay components should be stored 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 (10). Use fresh urine specimens for the test. If a sample cannot be analyzed immediately, it may be refrigerated at 2-8ºC for up to three days. For longer storage, keep sample frozen at -20ºC and then thaw before use. Studies have shown buprenorphine analytes in urine are stable at -20ºC up to 85 days (6). Samples should be at a room temperature of 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 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 Beckman Coulter UniCel DxC automated clinical system analyzer. If other instruments are used, performance will need to be validated by the laboratory (11, 12).

Assay Procedure

Assay parameters used for the Beckman Coulter UniCel DxC automated clinical analyzer include a 200 µL of antibody reagent (R_1), and 50 µL of enzyme conjugate reagent (R_2). A 35 µL sample size is used for the DxC. Refer to the application sheet for detailed information.

Calibration*

(*Calibrators and Controls are sold separately)
Recalibration should be performed after reagent bottle change or calibrator/reagent lot change. Two levels of controls are also available for monitoring of calibration: Level 1 Negative Control (7 ng/mL) and Level 2 Positive Control (13 ng/mL).
For qualitative calibration, use negative, cutoff, and high calibrators on the DxC. For semi-quantitative analysis, use all six calibrators consisting of negative, low, cutoff, intermediate I, intermediate II, and the high calibrators (0 ng/mL, 5 ng/mL, 10 ng/mL, 20 ng/mL, 40 ng/mL, and 100 ng/mL) on the DxC.

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.

On-board Stability: In qualitative and semi-quantitative mode, the stability of reagents on board the analyzer (at 2-8ºC) is 24 hours. It is recommended that the reagent be removed from the instrument, capped, and stored at 2-8ºC when not in use.

Calibration Stability: The stability of the calibration is 24 hours in both qualitative and semi-quantitative mode.

Results

Note: A 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 10 ng/mL of norbuprenorphine is used as a reference for distinguishing 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 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 confirmation by a confirmatory method such as GC/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 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 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. *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.*
8. *There is a possibility that metabolites of other opiate drugs may interfere with the test.*

Typical Performance Characteristics

Precision: Precision studies were conducted on a DxC600 analyzer. Typical results are as follows:

Semi-quantitative analysis:

DxC600 Analyzer: Results in concentration, ng/mL

	Within Run (n=21)			Run-to-Run (n=20) (taken in 2 weeks)		
	Mean	SD	%CV	Mean	SD	%CV
0 ng/mL	0.0	0.0	0.0 %	0.2	0.4	200.0 %
2.5 ng/mL	3.2	0.5	15.6 %	3.2	0.3	9.4 %
5.0 ng/mL	6.1	0.3	4.9 %	6.0	0.3	5.0 %
7.5 ng/mL	7.9	0.2	2.5 %	7.7	0.3	3.9 %
10.0 ng/mL	10.4	0.4	3.8 %	10.0	0.3	3.0 %
12.5 ng/mL	12.6	0.4	3.2 %	12.1	0.3	2.5 %
15.0 ng/mL	14.9	0.4	2.7 %	14.6	0.4	2.7 %
17.5 ng/mL	17.6	0.5	2.8 %	17.3	0.5	2.9 %
20.0 ng/mL	20.2	0.5	2.5 %	20.0	0.4	2.0 %

Qualitative analysis:

DxC600 Analyzer: Results in absorbance, mA/min

	Within Run (n=21)			Run-to-Run (n=20) (taken in 2 weeks)		
	Mean	SD	%CV	Mean	SD	%CV
0 ng/mL	378.7	2.4	0.6 %	384.9	3.3	0.9 %
2.5 ng/mL	395.1	2.9	0.7 %	397.6	2.5	0.6 %
5.0 ng/mL	414.6	2.4	0.6 %	415.4	2.4	0.6 %
7.5 ng/mL	428.4	1.6	0.4 %	428.5	2.4	0.6 %
10.0 ng/mL	449.1	3.6	0.8 %	446.6	2.0	0.4 %
12.5 ng/mL	467.5	3.4	0.7 %	463.6	1.5	0.3 %
15.0 ng/mL	484.9	2.6	0.5 %	481.4	2.4	0.5 %
17.5 ng/mL	503.3	3.2	0.6 %	499.9	2.2	0.4 %
20.0 ng/mL	518.7	2.9	0.6 %	515.6	2.2	0.4 %

Additional Qualitative analysis:

The following tables summarize the interpretation of the absorbance (mA/min) as being positive or negative results:

DxC600 Analyzer		Within Run		Run to Run	
Sample [ ] ng/mL	**% of Cutoff**	**# of Samples**	**Result**	**# of Samples**	**Result**
0 ng/mL	- 100 %	21	21 Neg	20	20 Neg
2.5 ng/mL	- 75 %	21	21 Neg	20	20 Neg
5.0 ng/mL	- 50 %	21	21 Neg	20	20 Neg
7.5 ng/mL	- 25 %	21	21 Neg	20	20 Neg
10.0 ng/mL	100 %	21	3 Neg/ 18 Pos	20	7 Neg/ 13 Pos
12.5 ng/mL	+ 25 %	21	21 Pos	20	20 Pos
15.0 ng/mL	+ 50 %	21	21 Pos	20	20 Pos
17.5 ng/mL	+ 175 %	21	21 Pos	20	20 Pos
20.0 ng/mL	+ 200 %	21	21 Pos	20	20 Pos

Limit of Detection: The lowest concentration that can be differentiated from the negative urine with 95 % confidence is determined as 3 ng/mL.

Accuracy: Eight-two (82) clinical urine specimens were collected and tested with LZI Buprenorphine Enzyme Immunoassay and confirmed with GC/MS on the DxC600. All specimens having a norbuprenorphine concentration greater than or equal to 10 ng/mL were defined as positive, while samples with concentration of 9.9 ng/mL or lower were defined as negative. The correlation results are summarized as follows: (near cutoff samples are defined as ± 50 % of the cutoff value of 10 ng/mL)

DxC600

	Neg	**< 50% of the cutoff**	**Near Cutoff Neg**	**Near Cutoff Pos**	**High Pos**	**% Agreement**
Pos	0	0	1*	6	32	97.4 %
Neg	10	18	13	2**	0	95.3 %

The following table summarizes the result for the three discordant samples:

Cutoff Value	**EIA Assay Result:**	**Sample Composition:**	
		NBUP (GC/MS)	**BUP (GC/MS)**
10 ng/mL	Positive*	8.5 ng/mL	3.2 ng/mL
10 ng/mL	Negative**	10.2 ng/mL	0.0 ng/mL
10 ng/mL	Negative**	10.7 ng/mL	0.0 ng/mL

Linearity: A linearity study was performed by serially diluting a spiked urine pool containing 100 ng/mL of norbuprenorphine in 10 % increments. 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 follow:

DxC600: $y = 1.0936x-0.2831$, $r^2 = 0.9941$

	DxC600	
Target [ ] (ng/mL)	**Observed [ ] (ng/mL)**	**% Recovery**
5	5.5	109.2 %
10	10.2	102.0 %
20	19.9	99.6 %
30	31.3	104.3 %
40	46.6	116.5 %
50	56.1	112.2 %
60	66.5	110.9 %
70	73.3	104.7 %
80	*	*
90	*	*

***** *Out of linearity range.*

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 10 ng/mL norbuprenorphine cutoff: (result listed in ng/mL)

Buprenorphine Compounds:

Compound	Quantity equivalent to 10 ng/mL	Approx. % Cross-reactivity
Buprenorphine	10.6	94.3 %
Buprenorphine-Glucuronide	33,333	0.03 %
Norbuprenorphine-Glucuronide	1,036	0.97 %

Structurally Related Opiate Compounds:

Compound	Quantity equivalent to 10 ng/mL	Approx. % Cross-reactivity
6-acetylcodeine	5,000,000	0.0002 %
Codeine	>100,000	0 %
Dextromethorphan	>100,000	0 %
Dihydrocodeine	>100,000	0 %
Heroin	625,000	0.0016 %
Hydrocodone	>100,000	0 %
Hydromorphone	>100,000	0 %
6-Monoacetylmorphine	>100,000	0 %
Morphine	>100,000	0 %
M3G	>100,000	0 %
M6G	>100,000	0 %
Nalorphine	>100,000	0 %
Naloxone	1,052,631	0.00095 %
Naltrexone	>100,000	0 %
Norcodeine	>100,000	0 %
Noroxycodone HCl	>100,000	0 %
Noroxymorphone HCl	>100,000	0 %
Oxycodone	>100,000	0 %
Oxymorphone	>100,000	0 %

Structurally Unrelated Pharmacological Compounds:

Compound	Quantity equivalent to 10 ng/mL	Approx. % Cross-reactivity
alpha-methadol	>100,000	0 %
Citalopram	>100,000	0 %
EDDP	>100,000	0 %
EMDP	>100,000	0 %
Fluoxetine	>100,000	0 %
Gabapentin	>100,000	0 %
Imipramine	>100,000	0 %
LAAM	>100,000	0 %
Levorphanol	108,108	0.00925 %
Meperidine	>100,000	0 %
Methadone	>100,000	0 %
Norpropoxyphene	>100,000	0 %
Paroxetine	>100,000	0 %
Sertraline	>100,000	0 %

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 substances were tested for interference with the LZI Buprenorphine Assay and found to have no observed significant interference.

Substance	Final [ ] mg/dL	Spiked sample containing 0 ng/mL of norbuprenorphine		Spiked sample containing 13 ng/mL of norbuprenorphine	
		ng/mL	Result	ng/mL	Result
Acetone	1000	0.0	Neg	11.7	Pos
Ascorbic Acid	400	0.0	Neg	11.6	Pos
Creatinine	500	0.2	Neg	11.7	Pos
Galactose	10	0.0	Neg	11.5	Pos
γ-Globulin	500	0.0	Neg	12.1	Pos
Glucose	1500	0.0	Neg	12.3	Pos
Hemoglobin	300	0.0	Neg	12.6	Pos
NaCl	6000	1.0	Neg	13.4	Pos
Oxalic Acid	100	0.0	Neg	11.5	Pos
HSA*	500	0.0	Neg	12.0	Pos
Urea	2000	0.0	Neg	11.6	Pos
Ethanol	1000	0.0	Neg	11.6	Pos
pH 3	N/A	0.0	Neg	12.5	Pos
pH 11	N/A	0.1	Neg	13.5	Pos

**Human Serum Albumin*

Specific Gravity: Samples ranging in specific gravity from 1.001 to 1.027 were tested with the assay and no interference was observed.

Additional Information: For more detailed information on Synchron Systems or UniCel 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.

Qualitative Mode UDR Parameters:

INSTRUMENT PARAMETERS:	**DxC**
Chemistry Name	
Test Name	BUPX
Reaction Type:	Rate 1
Units	mA/min
Decimal Precision/Precision:	X.XXX
Reaction Direction:	Positive
Calculation Factor:	1
Math Model:	DAT
Cal. Time Limit:	24
Number of Calibrators:	3
#1	0.0
#2	10.0
#3	100.0
Primary Wavelength:	340 nm
Secondary Wavelength:	650 nm
Sample Volume:	35 µL
REAGENTS:	
Primary Inject (first)/First Inject	
Compartment/Component:	A
Volume/Dispense Volume:	200 µL
Add Time/Inject Time:	N/A[a]
Primary Inject (first)/Second Inject	
Compartment/Component:	None
Volume/Dispense Volume:	N/A[a]
Add Time/Inject Time:	-180 [a & b]
Second Inject/Third Inject	
Compartment/Component:	B
Volume/Dispense Volume:	50 µL
Add Time/Inject Time:	48 sec
Blank	
Start Read:	-64 sec
End Read:	-16 sec
Initial (DxC only)	
Start Read:	49 sec
End Read:	64 sec
Reaction 1	
Start Read:	96 sec
End Read:	144 sec
Reaction 2	
Start Read:	N/A[a]
End Read:	N/A[a]
USABLE RESULT RANGE:	
Lower Limit:	0.000 [b]
Upper Limit:	99999.99 [b]
ERROR DETECTION LIMITS:	

Reagent Blank/Blank	
ABS Low Limit:	-1.5 [b]
ABS High Limit:	2.2 [b]
Rate Low Limit:	-1.5 [b]
Rate High Limit:	2.2 [b]
Mean Deviation:	2.2 [b]
Reaction/Reaction 1	
ABS Low Limit:	-1.5 [b]
ABS High Limit:	2.2 [b]
Rate Low Limit:	-1.5 [b]
Rate High Limit:	2.2 [b]
Mean Deviation:	2.2 [b]
Reaction 2	
ABS Low Limit:	-1.5 [b]
ABS High Limit:	2.2 [b]
Rate Low Limit:	-1.5 [b]
Rate High Limit:	2.2 [b]
Mean Deviation:	2.2 [b]
SUBSTRATE DEPLETION	
Initial Rate:	99.999 [b]
Delta ABS:	2.2 [b]
MULTI POINT SPAN:	0.000 [b]

Semi-Quantitative UDR Parameters:

INSTRUMENT PARAMETERS:	**DxC**
Chemistry Name	
Test Name	BUPX
Reaction Type:	Rate 1
Units	ng/mL
Decimal Precision/Precision:	X.X
Reaction Direction:	Positive
Calculation Factor:	1
Math Model:	1
Cal. Time Limit:	24
Number of Calibrators:	6
#1	0.0
#2	5.0
#3	10.0
#4	20.0
#5	40.0
#6	100.0
Primary Wavelength:	340 nm
Secondary Wavelength:	650 nm
Sample Volume:	35 µL
REAGENTS:	
Primary Inject (first)/First Inject	
Compartment/Component:	A
Volume/Dispense Volume:	200 µL
Add Time/Inject Time:	N/A [a]
Primary Inject (first)/Second Inject	
Compartment/Component:	None
Volume/Dispense Volume:	N/A [a]
Add Time/Inject Time:	-180 [a & b]
Second Inject/Third Inject	
Compartment/Component:	B
Volume/Dispense Volume:	50 µL
Add Time/Inject Time:	48 sec
Blank	
Start Read:	-64 sec
End Read:	-16 sec
Initial (DxC only)	
Start Read:	49 sec
End Read:	64 sec
Reaction 1	
Start Read:	96 sec
End Read:	144 sec
Reaction 2	
Start Read:	N/A [a]
End Read:	N/A [a]
USABLE RESULT RANGE:	
Lower Limit:	3.00
Upper Limit:	70.0
ERROR DETECTION LIMITS:	
Reagent Blank/Blank	
ABS Low Limit:	-1.5 [b]
ABS High Limit:	2.2 [b]
Rate Low Limit:	-1.5 [b]
Rate High Limit:	2.2 [b]
Mean Deviation:	2.2 [b]
Reaction/Reaction 1	
ABS Low Limit:	-1.5 [b]
ABS High Limit:	2.2 [b]
Rate Low Limit:	-1.5 [b]
Rate High Limit:	2.2 [b]
Mean Deviation:	2.2 [b]
Reaction 2	
ABS Low Limit:	-1.5 [b]
ABS High Limit:	2.2 [b]
Rate Low Limit:	-1.5 [b]
Rate High Limit:	2.200 [b]
Mean Deviation:	2.200 [b]
SUBSTRATE DEPLETION	
Initial Rate:	99.999 [b]
Delta ABS:	2.2 [b]
MULTI POINT SPAN:	
(1 –2)	0.001
(2 –3)	0.001
(3 –4)	0.001
(4 –5)	0.001
(5 –6)	0.001
(6 –1)	0.001

a N/A = Not Applicable
b Denotes Default Value

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

For technical assistance please call: (408) 970-8811

Manufacturer:
Lin-Zhi International, Inc.
2945 Oakmead Village Court
Santa Clara, CA 95051
USA
Tel: (408) 970-8811
Fax: (408) 970-9030
www.lin-zhi.com

Authorized European Rep. within the EU:
CEpartner4U
Esdoornlaan 13
3951 DB Maarn
The Netherlands
www.cepartner4u.eu

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