


ARK™ Zopiclone Assay

This ARK Diagnostics, Inc. package insert for the ARK Zopiclone Assay must be read prior to use. Package insert instructions must be followed accordingly. The assay provides a simple and rapid analytical screening procedure for detecting Zopiclone in urine. Reliability of the assay results cannot be guaranteed if there are any deviations from the instructions in this package insert.

Report any serious incident that has occurred in relation to the device to the manufacturer and the appropriate competent authority as applicable.

Customer Service





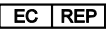



 **ARK Diagnostics, Inc.**
48089 Fremont Blvd

Fremont, CA 94538 USA
Tel: 1-877-869-2320
Fax: 1-510-270-6298
customersupport@ark-tdm.com
www.ark-tdm.com
SRN: US-MF-000023925

CE
2797

EC REP
Emergo Europe
Westervoortsedijk 60
6827 AT Arnhem
The Netherlands

Key to Symbols Used

	Batch code	 YYYY-MM-DD	Use by/Expiration date
	Catalog Number		Manufacturer
	Authorized Representative	CE 2797	CE Mark with notified body number
	In Vitro Diagnostic Medical Device	Rx Only	For Prescription Use Only
	Consult Instructions for Use	R1 R2	Reagent 1/ Reagent 2
	Temperature limitation		

1 Name

ARK Zopiclone Assay

2 Intended Use

The ARK Zopiclone Assay is intended for the qualitative and semi-quantitative determination of zopiclone in human urine at a cutoff concentration of 10 ng/mL. The assay is intended for use in laboratories with automated clinical chemistry analyzers.

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

The ARK Zopiclone Assay provides only a preliminary analytical test result. A more specific alternative chemical method must be used in order to obtain a confirmed positive analytical result. Gas Chromatography/Mass Spectrometry (GC/MS) or Liquid Chromatography/tandem Mass Spectrometry (LC-MS/MS) is the preferred confirmatory method. Clinical consideration and professional judgment should be exercised with any drug test result, particularly when the preliminary test result is positive.

3 Summary and Explanation of Test

Zopiclone is a sleep medication that is prescribed to treat insomnia.¹ The drug is available as a racemic mixture, under the brand name Imovane as well as the S isomer, Eszopiclone, under the brand name Lunesta. Zopiclone is a central nervous system depressant and schedule IV drug under the US Controlled Substance Act.

Zopiclone is of the “Z-drug” sedative-hypnotics and has been clinically available since the 1980’s.¹ Other Z-drugs include zaleplone, zolpidem, and eszopiclone. Chemically, zopiclone is a cyclopyrrolone, a class of nonbenzodiazepine drugs with similar pharmacological profiles to benzodiazepines. Like benzodiazepines, binding in the body occurs at the benzodiazepine receptor increasing the normal transmission of the neurotransmitter gamma-aminobutyric acid (GABA).² Zopiclone’s pharmacological properties are: hypnotic, sedative, anxiolytic, anti-convulsant, and muscle-relaxant. Impairment of activities requiring alertness can occur the following day after taking zopiclone.⁵ Prescribed doses range from 3.75 mg to 7.5 mg tablets.¹ The half-life of zopiclone is approximately 3.5 to 6.5 hours.⁴ Primary metabolism of zopiclone occurs in the liver via N-demethylation and N-oxidation to form the active demethylated metabolite (N-desmethylzopiclone) and inactive metabolite, zopiclone-N-oxide, respectively.⁴ About 4 to 5% of the drug is excreted unchanged in urine.³

4 Principles of the Procedure

The ARK Zopiclone Assay is a homogeneous enzyme immunoassay. The assay uses specific antibodies that can detect zopiclone in human urine. The assay is based on competition between a drug labeled with recombinant glucose-6-phosphate dehydrogenase (rG6PDH) and free drug from the urine sample, for a fixed amount of specific antibody binding sites. In the absence of free drug from the sample, rabbit polyclonal anti-zopiclone antibody binds to the drug labeled with rG6PDH and causes a decrease in enzyme activity. In the presence of zopiclone from the specimen, enzyme activity increases and is directly related to the zopiclone concentration. Endogenous G6PDH does not interfere because the coenzyme NAD functions only with the bacterial enzyme used in the assay. The enzyme activity is determined spectrophotometrically at 340 nm by measuring the conversion of nicotinamide adenine dinucleotide (NAD) to NADH.

5 Reagents

REF	Product Description	Quantity/Volume
5043-0001-00	ARK Zopiclone Assay Reagent [R1] – Antibody/Substrate Rabbit polyclonal antibodies to zopiclone, glucose-6-phosphate, nicotinamide adenine dinucleotide, bovine serum albumin, sodium azide, and stabilizers	1 X 28 mL
	Reagent [R2] – Enzyme Zopiclone derivative labeled with recombinant glucose-6-phosphate dehydrogenase (rG6PDH), bovine serum albumin, buffer, sodium azide and stabilizers	1 X 14 mL

Reagent Handling and Storage

ARK Zopiclone Assay reagents are provided liquid, ready to use and may be used directly from the refrigerator. When not in use, reagents must be stored at 2–8°C (36–46°F), upright and with screw caps tightly closed. If stored as directed, reagents are stable until the expiration date printed on the label. Do not freeze reagents. Avoid prolonged exposure to temperatures above 32°C (90°F). **Improper storage of reagents can affect assay performance.**

ARK Zopiclone products contain ≤0.09% sodium azide. As a precaution, affected plumbing including instrumentation should be flushed adequately with water to mitigate the potential accumulation of explosive metal azides. No special handling is required regarding other assay components.

6 Warnings and Precautions

- For *In Vitro* Diagnostic Use. Laboratory professional use only.
- For prescription use only. *Caution: US federal law restricts this device to sale by or on the order of a licensed practitioner.*
- Reagents [R1] and [R2] are provided as a matched set and should not be interchanged with reagents from different lot numbers.
- Do not use reagents after the expiration date.
- Reagents contain ≤0.09% sodium azide.

7 Specimen Collection and Preparation for Analysis

- Each laboratory is responsible for supplying a valid specimen for analysis according to their quality procedures.
- Human urine is required. Treat as potentially infectious material.
- Collect urine using standard sampling cups and procedures. Care should be taken to preserve the chemical and physical integrity of the urine sample from the time it is collected until the time it is assayed, including during transport. Fresh urine specimens are suggested.
- **Cap the urine sample immediately after collection, store refrigerated at 2-8°C (36–46°F) and assay within 1 day after collection. If the assay cannot be performed within 1 day, store the urine sample frozen at -20°C for up to 2 months prior to analysis⁶⁻⁹.**
- Do not induce foaming and avoid repeated freezing and thawing to preserve the integrity of the specimen from the time it is collected until the time it is assayed.
- The presence of bubbles or foam on the sample can lead to short sample delivery and erroneous results.
- Frozen specimens must be thawed and mixed thoroughly prior to analysis.
- Centrifuge specimens with high turbidity or visible particulate matter before testing.
- Each laboratory should consult available literature and internal data regarding specimen stability. The recommended pH range for urine specimens is 4.0 – 8.0^{6-7, 10}. **It is recommended any sample >7.0 pH be assayed or frozen immediately to minimize time at ambient temperature.**
- Obtain another sample for testing if adulteration of the sample is suspected. Adulteration of urine specimens can affect the test result.

8 Procedure

Materials Provided

ARK Zopiclone Assay – REF 5043-0001-00

Materials Required – Provided Separately

ARK Zopiclone Calibrator (Set) – REF 5043-0002-00

ARK Zopiclone Calibrator A (Negative) – REF 5043-0002-01

ARK Zopiclone Calibrator C (Cutoff) – REF 5043-0002-02

ARK Zopiclone Control (7.5 ng/mL and 12.5 ng/mL) – REF 5043-0003-00

Instruments

Reagents R1 and R2 may need to be transferred to analyzer-specific reagent containers prior to use. Avoid cross-contamination of R1 and R2.

Many automated clinical chemistry analyzers with photometric rate determination at 340 nm are suitable. Consult the analyzer-specific application sheet for programming the ARK Zopiclone Assay, available from your distributor or ARK Customer Service. Application Protocol Sheets bearing the CE Mark have been

verified by the manufacturer. It is the responsibility of the laboratory to perform all appropriate validation for use of the assay with other settings or analyzers.

Refer to the instrument-specific operator's manual for daily maintenance.

Assay Sequence

To run or calibrate the assay, see the instrument-specific operator's manual.

Qualitative Results

Use the 10 ng/mL Calibrator C as a Cutoff Calibrator to distinguish negative and positive samples. Run the Low and High Controls as Negative and Positive respectively. Report test results less than the rate (mA/min) value for the Cutoff Calibrator as Negative. Report results equal to or greater than the rate (mA/min) value for the Cutoff Calibrator as Positive.

Semi-quantitative Results

Perform a 5-point calibration procedure; run calibrators in duplicate. Verify the calibration curve with the ARK Zopiclone Assay Low and High quality controls according to the established laboratory quality assurance plan. Specimens with sample results above the highest ARK Zopiclone calibrator level (40 ng/mL) may be diluted in ARK Zopiclone Calibrator A (Negative urine) and retested.

When to Re-Calibrate

- Whenever a new lot number of reagents is used
- Whenever indicated by quality control results
- Whenever required by standard laboratory protocols

Quality Control (QC) and Calibration

Laboratories should establish QC procedures for the ARK Zopiclone Assay. All quality control requirements and testing should be performed in conformance with local, state and/or federal regulations or accreditation requirements.

Each laboratory should establish its own ranges for each new lot of controls. Control results should fall within established ranges as determined by laboratory procedures and guidelines. The ARK Zopiclone Control is intended for use in quality control of the ARK Zopiclone Assay.

In Qualitative Mode, the Low Control should be Negative and the High Control should be Positive relative to the 10 ng/mL Cutoff Calibrator.

9 Results and Expected Values

A more specific confirmatory method, such as LC-MS/MS or GC-MS, is required in order to obtain a confirmed positive result.

Qualitative Analysis – Negative Results

A specimen that gives a rate (mA/min) value less than the ARK Zopiclone Calibrator C Cutoff rate (mA/min) value is interpreted as negative; either the specimen does not contain Zopiclone or Zopiclone is present in a concentration below the cutoff level of this assay.

Qualitative Analysis – Positive Results

A specimen that gives a rate (mA/min) value equal to or greater than the ARK Zopiclone Calibrator C Cutoff rate (mA/min) value is interpreted as positive, indicating that Zopiclone is present.

Results of this test should always be interpreted in conjunction with the patient's medical history, clinical presentation, and other findings.

Semi-quantitative Analysis

The actual Zopiclone concentration cannot be determined with this assay. Semi-quantitative results for positive specimens enable the laboratory to determine an appropriate dilution of the specimen for the confirmatory method. Semi-quantitative results also permit the laboratory to establish quality control procedures and assess reproducibility. Specimens with sample results above the highest ARK Zopiclone calibrator level (40 ng/mL) may be diluted in ARK Zopiclone Calibrator A (Negative urine) and retested.

Results of this test should always be interpreted in conjunction with the patient's medical history, clinical presentation, and other findings, particularly when the preliminary result is positive.

10 Limitations

- The assay is designated for use with human urine only.
- ARK Zopiclone Assay reagents, ARK Zopiclone calibrators and ARK Zopiclone controls were developed as companion products. Performance with substituted products cannot be assured.
- A positive result using the ARK Zopiclone Assay indicates only the presence of Zopiclone and does not necessarily correlate with the extent of physiological and psychological effects.
- **Do not use Boric Acid as a preservative.**
- Interpretation of results must take into account that urine concentrations can vary extensively with fluid intake and other biological variables.
- It is possible that substances other than those tested in the specificity study may interfere with the test and cause false results.

11 Specific Performance Characteristics

The following performance characteristics were collected on the Beckman Coulter AU680® automated clinical chemistry analyzer using the ARK Zopiclone Assay.

Precision

Drug-free, negative human urine was supplemented with Zopiclone (0 to 20 ng/mL). Each level was assayed in quadruplicate twice a day for 20 days (N=160) and evaluated qualitatively and semi-quantitatively. Results are summarized in the tables below.

Qualitative Precision

Zopiclone (ng/mL)	Relative % Cutoff	# of Results	Results
0.0	-100	160	160 Negative

Zopiclone (ng/mL)	Relative % Cutoff	# of Results	Results
2.5	-75	160	160 Negative
5.0	-50	160	160 Negative
7.5	-25	160	160 Negative
10.0	Cutoff	160	115 Negative; 45 Positive
12.5	+25	160	160 Positive
15.0	+50	160	160 Positive
17.5	+75	160	160 Positive
20.0	+100	160	160 Positive

Semi-quantitative Precision

Zopiclone (ng/mL)	Relative % Cutoff	# of Results	Mean (ng/mL)	Results
0.0	-100	160	0.2	160 Negative
2.5	-75	160	2.6	160 Negative
5.0	-50	160	5.0	160 Negative
7.5	-25	160	7.3	160 Negative
10.0	Cutoff	160	9.8	123 Negative; 37 Positive
12.5	+25	160	12.4	160 Positive
15.0	+50	160	15.0	160 Positive
17.5	+75	160	17.7	160 Positive
20.0	+100	160	20.1	160 Positive

Analytical Recovery

Drug-free, negative human urine was spiked with Zopiclone across the assay range of the semi-quantitative calibration curve. Each sample was run in replicates of 5 in semi-quantitative mode and the average was used to determine percent recovery compared to the expected value.

Expected Value (ng/mL)	Observed Value (ng/mL)	Recovery (%)
2.5	2.7	107.6
4.5	4.6	102.7
9	8.8	97.5
18	18.1	100.3
24	24.6	102.4
32	32.6	101.9
40	39.6	99.0

Analytical Specificity

All compounds tested were added to drug-free, negative human urine and tested with the ARK Zopiclone Assay in both qualitative and semi-quantitative modes.

The cross-reactivity of Zopiclone and its metabolites was evaluated by spiking these compounds into drug-free, negative human urine and evaluated by dose-response to determine the approximate equivalence to the 10 ng/mL Zopiclone cutoff. These concentrations were used to determine the percent cross-reactivity according to the formula:

$$\% \text{ Cross-reactivity} = (\text{Cutoff concentration} / \text{Concentration approximately equivalent to the 10 ng/mL cutoff}) \times 100$$

For compounds that did not produce a positive result, the highest concentration tested was used to calculate percent cross-reactivity.

Cross-reactivity of zopiclone metabolites and z-drugs

Compound	Concentration Approximately Equivalent to the Cutoff (ng/mL)	Cross-reactivity (%)
Eszopiclone-N-oxide	4.3	232.6
Eszopiclone	4.7	212.8
N-Desmethyleszopiclone	9.5	105.3
N-Desmethylzopiclone	11.1	90.1
Zopiclone-N-Oxide	11.1	90.1
(R) – Zopiclone	106.1	9.4
ACP (2-amino-5-chloropyridine)	>100,000	<0.01
Zaleplon	>100,000	<0.01
Zolpidem	>100,000	<0.01

The following benzodiazepine compounds tested negative at the concentrations tested with the ARK Zopiclone Assay.

Cross-reactivity of benzodiazepine compounds

Compound	Concentration Tested (ng/mL)	Compound	Concentration Tested (ng/mL)
Alpha-Hydroxyalprazolam	100,000	Flunitrazepam	100,000
Alpha-Hydroxymidazolam	100,000	Flurazepam	100,000
Alpha-Hydroxytriazolam	100,000	Halazepam	100,000
2-Hydroxyethylflurazepam	100,000	Ketazolam	100,000
3-Hydroxyflunitrazepam	100,000	Loprazolam	100,000
3-Hydroxyphenazepam	100,000	Lorazepam	100,000
4-Hydroxyalprazolam	100,000	Lorazepam glucuronide	100,000
7-Aminoclonazepam	100,000	Lormetazepam	100,000
7-Aminoflunitrazepam	100,000	Meclonazepam	100,000
7-Aminonimetazepam	100,000	Medazepam	100,000
7-Aminonitrazepam	100,000	Midazolam	100,000

Alprazolam	100,000	N-Desmethyloclobazam	100,000
Bromazepam	100,000	N-Desmethylflunitrazepam	100,000
Chlordiazepoxide	100,000	Nimetazepam	100,000
Clobazam	100,000	Nitrazepam	100,000
Clonazepam	100,000	Norchlordiazepoxide	100,000
Clonazolam	100,000	Nordiazepam	100,000
Clorazepate	100,000	Oxazepam	100,000
Delorazepam	100,000	Oxazepam glucuronide	50,000*
Demoxepam	100,000	Phenazepam	100,000
Desalkylflurazepam	100,000	Prazepam	100,000
Deschloroetizolam	100,000	Pyrazolam	100,000
Diazepam	100,000	Temazepam	100,000
Diclazepam	100,000	Temazepam glucuronide	50,000*
Estazolam	100,000	Tetrazepam	100,000
Flubromazepam	100,000	Triazolam	100,000
Flubromazolam	100,000		

*High drug concentration was commercially unavailable

The following structurally unrelated compounds tested negative at the concentrations tested with the ARK Zopiclone Assay.

Structurally unrelated compounds

Compound	Concentration Tested (ng/mL)	Compound	Concentration Tested (ng/mL)
4-Bromo-2,5-Dimethoxyphenethylamine	100,000	(+)-MDA	100,000
6-Acetylcodeine	100,000	MDEA	100,000
6-Acetylmorphine	100,000	MDMA	100,000
Acetaminophen	500,000	Meperidine	100,000
Acetylsalicylic Acid	500,000	Meprobamate	100,000
Amitriptyline	100,000	Methadone	100,000
Amobarbital	100,000	S (+)-Methamphetamine	100,000
S -(+)Amphetamine	100,000	Methaqualone	100,000
Benzoylcegonine	100,000	Methylphenidate	100,000
Benzylpiperazine	100,000	Mirtazapine	100,000
Buprenorphine	100,000	Morphine	100,000
Bupropion	100,000	Morphine-3-glucuronide	100,000
Butobarbital	100,000	Morphine-6-glucuronide	100,000
Caffeine	100,000	Nalorphine	100,000
Carbamazepine	100,000	Naloxone	100,000
Chlorpromazine	100,000	Naltrexone	100,000
cis-Tramadol	100,000	Naproxen	100,000
Citalopram	100,000	Norbuprenorphine	100,000
Clomipramine	100,000	Norcodeine	100,000
Cannabidiol	100,000	Normorphine	100,000

Cannabinol	100,000	Norpropoxyphene	100,000
Carisoprodol	100,000	Norpseudoephedrine	100,000
Cocaine	100,000	Nortriptyline	100,000
Codeine	100,000	Olanzapine	100,000
Cotinine	100,000	Opipramol	100,000
Cyclobenzaprine	100,000	Oxycodone	100,000
Delta-9-THC	100,000	Oxymorphone	100,000
Desipramine	100,000	Paraxanthine	100,000
N-desmethyltapentadol	100,000	Paroxetine	100,000
Dextromethorphan	100,000	PCP	100,000
Dihydrocodeine	100,000	Pentazocine	100,000
Diphenhydramine	100,000	Pentobarbital	100,000
Doxepin	100,000	Phentermine	100,000
Ecgonine	100,000	Phenobarbital	100,000
Ecgonine methyl ester	100,000	Phenylephedrine	100,000
EDDP	100,000	Phenylpropanolamine	100,000
1R,2S (-)-Ephedrine	100,000	Phenytoin	100,000
1S,2R (+)-Ephedrine	100,000	PMA	100,000
Escitalopram	100,000	Propoxyphene	100,000
Ethyl β -D-glucuronide	100,000	Propranolol	100,000
Ethylmorphine	100,000	Prothipendyl	100,000
Fenfluramine	100,000	Protriptyline	100,000
Fentanyl	50,000	R, R (-)-Pseudoephedrine	100,000
Fluoxetine	100,000	S, S (+)-Pseudoephedrine	100,000
Fluvoxamine	100,000	Quetiapine	100,000
Heroin	100,000	Ranitidine	100,000
Hexobarbital	100,000	Ritalinic Acid	100,000
Hydrocodone	100,000	Salicylic Acid	100,000
Hydromorphone	100,000	Secobarbital	100,000
11-hydroxy-delta-9-THC	100,000	Sertraline	100,000
Ibuprofen	100,000	Sufentanil Citrate	100,000
Imipramine	100,000	11-nor-9-carboxy-THC	100,000
Indometacin	100,000	Theophylline	100,000
Ketamine	100,000	Thioridazine	100,000
Lamotrigine	100,000	Trifluoromethylphenylpiperazine	100,000
Levorphanol Tartrate	100,000	Trimipramine	100,000
Lidocaine	100,000	Trazodone	100,000
LSD	100,000	Venlafaxine	100,000
Maprotiline	100,000	Vortioxetine	100,000

Interference – Endogenous Substances

High concentrations of the following endogenous substances were added into Zopiclone-spiked urine (\pm 25% of the cutoff concentration). No interference was observed when tested with the ARK Zopiclone Assay.

Compound	Concentration Tested (mg/dL)	7.5 ng/mL (-25% Cutoff)	12.5 ng/mL (+25% Cutoff)
Acetone	1000	Negative	Positive
Ascorbic acid	1500	Negative	Positive
Bilirubin	2	Negative	Positive
Boric Acid	1 % w/v	Negative	Positive
Creatinine	500	Negative	Positive
Ethanol	1000	Negative	Positive
Galactose	10	Negative	Positive
Glucose	2000	Negative	Positive
Hemoglobin	500	Negative	Positive
Human Albumin	500	Negative	Positive
Oxalic Acid	100	Negative	Positive
Human γ - Globulin	500	Negative	Positive
Riboflavin	7.5	Negative	Positive
NaCl	6000	Negative	Positive
Sodium Fluoride	1% w/v	Negative	Positive
Urea	6000	Negative	Positive

Interference – Specific Gravity and pH

Urine samples with specific gravity values from 1.002 to 1.024 and pH values ranging from 3.0 to 11.0 were tested in the presence of the two levels of Zopiclone at \pm 25% of the cutoff concentration. No interference was observed with the specific gravity samples and pH values ranging from 3.0 to 9.0 when tested with the ARK Zopiclone Assay. Interference was observed in samples with pH values ranging from 10.0 to 11.0 due to the rapid degradation of zopiclone in alkaline conditions.

Method Comparison

One hundred and ten (110) unaltered clinical urine specimens that are not individually identifiable were analyzed by ARK Zopiclone Assay in both qualitative and semi-quantitative modes and the results were compared to LC-MS/MS. The overall concordance between LC-MS/MS and the ARK Zopiclone Assay was 99.1%.

Qualitative method comparison with LC-MS/MS as reference method

		LC-MS/MS	
		(+)	(-)
ARK Zopiclone Assay	(+)	49	0
	(-)	1*	60

Semi-quantitative method comparison with LC-MS/MS as reference method

		LC-MS/MS	
		(+)	(-)
ARK Zopiclone Assay	(+)	49	0
	(-)	1*	60

**Discordant Result Summary*

Sample ID	ARK Zopiclone Assay (Negative/Positive)	LC-MS/MS Zopiclone Positive/Negative	LC-MS/MS N-desmethylzopiclone Positive/Negative
2004332496	Negative	Negative	Positive

*One (1) sample was negative for zopiclone and positive for N-desmethylzopiclone by LC-MS/MS (1.4 ng/mL N-desmethylzopiclone LOQ) and 6.3 ng/mL (negative) by the ARK Zopiclone Assay relative to the 10 ng/mL Cutoff.

12 References

1. Nevio Cimolai, Zopiclone: Is it a pharmacologic agent for abuse? Canadian Family Physician. Dec 2007, 53 (12) 2124-2129.
2. S. Ueki, Behavioral Pharmacology of Zopiclone, Sleep, Volume 10, Issue suppl_1, April 1987, Pages 1–6
3. Gaillot J, Heusse D, Houghton G, W, Marc Aurele J, Dreyfus J, F: Pharmacokinetics and Metabolism of Zopiclone. Pharmacology 1983;27(suppl 2):76-91. doi: 10.1159/000137914
4. Fernandez, C., Martin, C., Gimenez, F. et al. Clinical Pharmacokinetics of Zopiclone. Clin. Pharmacokinet. 29, 431–441 (1995).
5. Gunja, Naren. “The clinical and forensic toxicology of Z-drugs.” Journal of medical toxicology : official journal of the American College of Medical Toxicology vol. 9,2 (2013): 155-62. doi:10.1007/s13181-013-0292-0
6. Nilsson GH, Kugelberg FC, Ahlner J, Kronstrand R. Quantitative analysis of zopiclone, N-desmethylzopiclone, zopiclone N-oxide and 2-amino-5-chloropyridine in urine using LC-MS-MS. J Anal Toxicol. 2014 Jul-Aug;38(6):327-34.
7. Mata DC. Stability of 26 Sedative Hypnotics in Six Toxicological Matrices at Different Storage Conditions. J Anal Toxicol. 2016 Oct;40(8):663-668.
8. Gonzales, E. et al. 2012. Stability of pain-related medications, metabolites, and illicit substances in urine. *Clinica Chimica Acta* **416**:80 – 85.
9. Dixon, R. B. et al. 2015. Stability of opioids and benzodiazepines in urine samples by liquid chromatography tandem mass spectrometry. *Journal of Analytical Science and Technology* **6**:17.
10. Department of Health and Human Services (DHHS), Substance Abuse and Mental Health Services Administration. Mandatory Guidelines for Federal Workplace Drug Testing Programs. Federal Register / Vol. 82, No. 13 / Monday, January 23, 2017 (Effective Date: October 1, 2017) / Notices.
11. Pesce, A., et al. 2011. Determination of medication cutoff values in a pain patient population. J. Opioid Management **7**(2):117-122.

13 Trademarks

ARKTM is a trademark of ARK Diagnostics, Inc.

Other brand or product names are trademarks of their respective holders.



ARK Diagnostics, Inc.
Fremont, CA 94538 USA

Revised February 2026
1600-1348-00 Rev 03

