

For Export Only – Not For Sale in USA

ARK™ Meperidine Assay

This ARK Diagnostics, Inc. package insert for the ARK Meperidine 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 meperidine in urine. Reliability of the assay results cannot be guaranteed if there are any deviations from the instructions in this package insert.

CUSTOMER SERVICE

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KEY TO SYMBOLS USED

	Batch code	 YYYY-MM-DD	Use by/Expiration date
	Catalog Number		Manufacturer
	Authorized Representative		CE Mark
	Consult Instructions for Use		Reagent 1/ Reagent 2
	Temperature limitation		<i>In Vitro</i> Diagnostic Medical Device
Rx Only	For Prescription Use Only		

1 NAME

ARK™ Meperidine Assay

2 INTENDED USE

The ARK Meperidine Assay is an immunoassay intended for the qualitative and/or semiquantitative determination of meperidine in human urine at a cutoff concentration of 100 ng/mL. The assay is intended for use in laboratories with automated clinical chemistry analyzers. This *in vitro* diagnostic device is for prescription use only.

The semiquantitative 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 Meperidine 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 THE TEST

Meperidine (DEMEROL®) is a synthetic narcotic analgesic that is indicated for the management of pain, severe enough to require an opioid analgesic and for which alternative treatments are inadequate. Meperidine has multiple actions qualitatively similar to those of morphine, producing clinical effects such as analgesia, sedation, euphoria and respiratory depression.¹

Meperidine is a Schedule II narcotic substance under the United States Controlled Substances Act for its potential for abuse and risk of dependence.²

Meperidine is metabolized extensively in the human liver by *N*-demethylation (mainly by CYP3A4 and CYP2B6 enzymes) to normeperidine and by hydrolysis to meperidinic acid.³ Normeperidine, an active metabolite that possesses significant pharmacological activity, has half the analgesic potency of meperidine but two to three times the potency as a central nervous system excitatory agent.⁴ Following intravenous administration of meperidine, 48-hour urinary recoveries of meperidine and normeperidine in six healthy subjects were about 7% and 12%, respectively.⁵ However, in cirrhotic patients, urinary levels of normeperidine were found to be lower than meperidine due to impaired metabolism of meperidine.⁶

4 PRINCIPLES OF THE PROCEDURE

The ARK Meperidine Assay is a homogeneous enzyme immunoassay method used for the analysis of meperidine in human urine. The assay is based on competition between drug in the specimen and drug labeled with recombinant glucose-6-phosphate dehydrogenase (rG6PDH) for antibody binding sites. As the latter binds antibody, enzyme activity decreases. In the presence of drug from the specimen, enzyme activity increases and is directly related to the drug concentration. Active enzyme converts nicotinamide adenine dinucleotide (NAD) to NADH in the presence of glucose-6-phosphate (G6P), resulting in an absorbance change that is measured spectrophotometrically. Endogenous G6PDH does not interfere because the coenzyme NAD functions only with the bacterial enzyme used in the assay.

5 REAGENTS

REF	Product Description	QTY/ VOL
5039-0001-00	ARK Meperidine Assay Reagent [R1] – Antibody/Substrate rabbit polyclonal antibodies to meperidine, glucose-6-phosphate, nicotinamide adenine dinucleotide, bovine serum albumin, sodium azide, and stabilizers	1 X 28 mL
	Reagent [R2] – Enzyme Meperidine derivative labeled with recombinant glucose-6-phosphate dehydrogenase (rG6PDH), bovine serum albumin, buffer, sodium azide and stabilizers	1 X 14 mL

REF	Product Description	QTY/ VOL
5039-0001-01	ARK Meperidine Assay Reagent [R1] – Antibody/Substrate rabbit polyclonal antibodies to meperidine, glucose-6-phosphate, nicotinamide adenine dinucleotide, bovine serum albumin, sodium azide, and stabilizers	1 X 115 mL
	Reagent [R2] – Enzyme Meperidine derivative labeled with recombinant glucose-6-phosphate dehydrogenase (rG6PDH), bovine serum albumin, buffer, sodium azide and stabilizers	1 X 58 mL

Reagent Kit  5039-0001-00

Reagent Kit  5039-0001-01

Reagent Handling and Storage

ARK Meperidine 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 Meperidine 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. For prescription use only.
- 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

- 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 7 days after collection. If the assay cannot be performed within 7 days, store the urine sample frozen at -20°C.^{7,8}
- To protect the integrity of the sample, do not induce foaming and avoid repeated freezing and thawing.
- Frozen specimens must be thawed and mixed thoroughly prior to analysis.
- Centrifuge specimens with high turbidity or visible particulate matter before testing.
- The recommended pH range for urine specimens is 4.0 – 11.0.⁹
- Obtain another sample for testing if adulteration of the sample is suspected. Adulteration of urine specimens can affect the test result.
- Boric acid interferes with results from this device. Do not use boric acid as a preservative.

8 PROCEDURE

Materials Provided

ARK Meperidine Assay – **REF** 5039-0001-00 or 5039-0001-01

Materials Required – Provided Separately

ARK Meperidine Calibrator – **REF** 5039-0002-00

ARK Meperidine Calibrator A (Negative) – **REF** 5039-0002-01

ARK Meperidine Calibrator B (Cutoff) – **REF** 5039-0002-02

Quality Controls – ARK Meperidine Control – **REF** 5039-0003-00

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**. Refer to the instrument-specific operator's manual for daily maintenance. Consult the analyzer-specific application sheet for programming the ARK Meperidine Assay or contact Customer Support.

Assay Sequence

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

Qualitative Results

Use the 100 ng/mL Calibrator B as a Cutoff Calibrator to distinguish negative and positive samples. Run the ARK Meperidine Low (75 ng/mL) and High (125 ng/mL) Controls as Negative and Positive respectively. Report test results less than the response value for the Cutoff Calibrator as Negative. Report test results equal to or greater than the response value for the Cutoff Calibrator as Positive.

Semiquantitative Results

Perform a 5-point calibration procedure; test calibrators in duplicate. Verify the calibration curve with the ARK Meperidine Low (75 ng/mL) and High (125 ng/mL) quality controls according to the established laboratory quality assurance plan. Specimens with sample results above the highest ARK Meperidine calibrator level (1000 ng/mL) may be diluted in ARK Meperidine 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
- A stored calibration curve was effective up to at least 32 days based on supporting data

Quality Control (QC) and Calibration

Laboratories should establish QC procedures for the ARK Meperidine 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 Meperidine Control is intended for use in quality control of the ARK Meperidine Assay. In Qualitative Mode, the Low Control should be Negative and the High Control should be Positive relative to the 100 ng/mL Cutoff Calibrator.

9 RESULTS AND EXPECTED VALUES

The actual meperidine concentration cannot be determined. A confirmatory method is required.

Qualitative Analysis - Negative Results

A specimen that gives a response value less than the ARK Meperidine Calibrator B Cutoff response value is interpreted as negative; either the specimen does not contain meperidine or meperidine is present in a concentration below the cutoff level of this assay.

Qualitative Analysis - Positive Results

A specimen that gives a response value equal to or greater than the ARK Meperidine Calibrator B Cutoff response value is interpreted as positive, indicating that meperidine is present.

Semiquantitative Analysis

Semiquantitative results for positive specimens enable the laboratory to determine an appropriate dilution of the specimen for the confirmatory method. Semiquantitative results also permit the laboratory to establish quality control procedures and assess reproducibility. Specimens with sample results above the highest ARK Meperidine calibrator level (1000 ng/mL) may be diluted in ARK Meperidine 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.

10 LIMITATIONS

- The assay is designated for use with human urine only.
- ARK Meperidine Assay reagents, calibrators and controls were developed as companion products. Performance with substituted products cannot be assured.
- A positive result using the ARK Meperidine Assay indicates only the presence of meperidine and does not necessarily correlate with the extent of physiological and psychological effects.
- Boric acid interferes with results from this device. Do not test samples that have 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 investigated 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 Meperidine Assay.

Precision

Drug-free, negative human urine was supplemented with meperidine (0.0 to 200.0 ng/mL). Each level was assayed in quadruplicate twice a day for 20 days (N=160) and evaluated both qualitatively and semiquantitatively. Results are summarized in the tables below.

Qualitative Precision

Human Urine (ng/mL)	% Cutoff	# of Determinations	Qualitative Precision Results
0.0	-100	160	160 Negative
25.0	-75	160	160 Negative
50.0	-50	160	160 Negative
75.0	-25	160	160 Negative
100.0	Cutoff	160	38 Negative/122 Positive
125.0	+25	160	160 Positive
150.0	+50	160	160 Positive
175.0	+75	160	160 Positive
200.0	+100	160	160 Positive

Semiquantitative Precision

Human Urine (ng/mL)	Relative % Cutoff	# of Results	Mean (ng/mL)	Semiquantitative Precision Results
0.0	-100	160	1.0	160 Negative
25.0	-75	160	26.8	160 Negative
50.0	-50	160	50.0	160 Negative
75.0	-25	160	74.5	160 Negative
100.0	Cutoff	160	101.0	47 Negative/113 Positive
125.0	+25	160	124.0	160 Positive
150.0	+50	160	148.0	160 Positive
175.0	+75	160	172.5	160 Positive
200.0	+100	160	195.8	160 Positive

Analytical Recovery

Recovery across the assay range was assessed using the semiquantitative mode. Drug-free, negative human urine was supplemented with meperidine (1250.0 ng/mL) and dilutions were made proportionally with drug-free human urine. Meperidine concentrations ranged from 50.0 to 1000.0 ng/mL. At each level, percentage recovery was calculated based on the mean concentration (N=6) compared to the expected concentration. Results are summarized in the table below.

Theoretical Concentration (ng/mL)	Mean Concentration (ng/mL)	Recovery (%)
50.0	51.9	103.8
100.0	99.4	99.4
200.0	203.4	101.7
300.0	304.9	101.6
400.0	399.2	99.8
500.0	497.6	99.5
600.0	581.4	96.9
700.0	667.1	95.3
800.0	767.6	96.0
900.0	847.5	94.2
1000.0	965.4	96.5

Analytical Specificity

Normeperidine (Major Metabolite)

The cross-reactivity of the major metabolite normeperidine was evaluated by spiking the compound into drug-free, negative human urine to determine the minimum concentration that would give a positive result approximately equivalent to the 100 ng/mL meperidine cutoff. This concentration was used to determine the percent cross-reactivity according to the formula:

% Cross-reactivity = (Cutoff concentration / Lowest concentration of cross-reactant causing a positive result) X 100

Compound	Lowest Concentration Tested That Produced a Response Approximately Equivalent to the Cutoff (ng/mL)	Percent Cross-reactivity (%)
Normeperidine	300	33.33%

Structurally Related Compounds

The following structurally related compounds were added to drug-free, negative human urine and tested with the ARK Meperidine Assay. The results were evaluated both qualitatively and semiquantitatively. The compounds at the concentrations listed below were negative when tested with the ARK Meperidine Assay.

Compound	Concentration Tested (ng/mL)
Buprenorphine	100,000
Buprenorphine Glucuronide	100,000
Codeine	1,000,000
Dihydrocodeine	1,000,000
Hydromorphone	1,000,000
Hydrocodone	1,000,000
Morphine	1,000,000
Morphine 3-Glucuronide	100,000

Compound	Concentration Tested (ng/mL)
Norbuprenorphine	100,000
Norcodeine	100,000
Normorphine	100,000
Naloxone	100,000
Naltrexone	100,000
Oxycodone	100,000
Oxymorphone	100,000
Propoxyphene	1,000,000

Structurally Unrelated Compounds

The following structurally unrelated compounds were added to drug-free, negative human urine and tested with the ARK Meperidine Assay. The results were evaluated both qualitatively and semiquantitatively. The compounds at the concentrations listed below were negative when tested with the ARK Meperidine Assay.

Compound	Concentration Tested (ng/mL)
Acetaminophen	100,000
6-Acetylmorphine	100,000
Acetylsalicylic Acid	100,000
Alprazolam	100,000
Amphetamine	100,000
Aminopyrine	100,000
Amitriptyline	100,000
Ampicillin	100,000
Amobarbital	100,000
Ascorbic Acid	100,000
Atropine	100,000
Barbital	100,000
Benzoylcegonine	100,000
Benzylpiperazine	100,000
Bromazepam	100,000
Butabarbital	100,000
Caffeine	100,000
Clonazepam	100,000
Carbamazepine	100,000
Chloroquine	100,000
Chlorpromazine	100,000
Cocaine	100,000
Desipramine	100,000
Dextromethorphan	100,000
Diacetyl Morphine	100,000
Diazepam	100,000
Diphenhydramine	100,000
5,5-Diphenylhydantoin (Phenytoin)	100,000
Doxepin	100,000
EDDP	100,000
(1R,2S)-(-)-Ephedrine	100,000
(1S,2R)-(+)-Ephedrine	100,000
Ethosuximide	100,000
Ethyl Morphine	100,000
Ethotoin	100,000
Flunitrazepam	100,000
Flurazepam	100,000
Glutethimide	100,000
Hexobarbital	100,000
Ibuprofen	100,000
Imipramine	100,000
Ketamine	100,000
Levorphanol	100,000
Lidocaine	100,000
LSD	100,000
Lorazepam	100,000

Compound	Concentration Tested (ng/mL)
Methadone	100,000
Methaqualone	100,000
Methamphetamine	100,000
Mephenytoin	100,000
Meprobamate	100,000
Mephobarbital	100,000
Methsuximide	100,000
Nalorphine	100,000
Niacinamide	100,000
Nitrazepam	100,000
Nordiazepam	100,000
Nordoxepin	100,000
N-normethsuximide	100,000
Norpropoxyphene	100,000
Nortriptyline	100,000
Oxazepam	100,000
Pentazocine	100,000
Pentobarbital	100,000
Phenobarbital	100,000
Phensuximide	100,000
PEMA	100,000
Phencyclidine (PCP)	100,000
Phentermine	100,000
Phenothiazine	100,000
Phenylpropanolamine	100,000
Primidone	100,000
Procaine	100,000
Protriptyline	100,000
Quinine	100,000
Secobarbital	100,000
Temazepam	100,000
Tetracycline	100,000
Tetrahydrozoline	100,000
THCCOOH	100,000
Theophylline	100,000
Triamterene	100,000
Trimipramine	100,000

Interference – Endogenous Substances

High concentrations of the following endogenous substances were added into urine spiked with meperidine (\pm 25% of the cutoff concentration). The results were evaluated both qualitatively and semiquantitatively. No interference was observed when tested with the ARK Meperidine Assay.

Compound	Concentration Tested (mg/dL)	75 ng/mL (-25% Cutoff)	125 ng/mL (+25% Cutoff)
Acetone	1000	Negative	Positive
Ascorbic Acid	200	Negative	Positive
Bilirubin – Conjugated	2	Negative	Positive
Bilirubin – Unconjugated	2	Negative	Positive
Creatinine	400	Negative	Positive
Ethanol	1000	Negative	Positive
Galactose	10	Negative	Positive
Gamma Globulin	500	Negative	Positive
Glucose	2000	Negative	Positive
Hemoglobin	300	Negative	Positive
Human Albumin	500	Negative	Positive
Oxalic Acid	30	Negative	Positive
Riboflavin	3.75	Negative	Positive
Sodium Chloride	900	Negative	Positive
Urea	1000	Negative	Positive

Interference – Boric Acid

One percent (1%) w/v of boric acid was added into urine spiked with meperidine (\pm 25% of the cutoff concentration) and tested with the ARK Meperidine Assay. The results were evaluated both qualitatively and semiquantitatively. Results are provided in the table below.

Compound	Concentration Tested	75 ng/mL (-25% Cutoff)	125 ng/mL (+25% Cutoff)
Boric Acid	1% w/v	Negative	Negative

Boric acid interferes with results from this device. Do not test samples that have boric acid as a preservative.

Interference – Specific Gravity and pH

Urine samples with specific gravity values from 1.004 to 1.028 and pH values ranging from 3.0 to 11.0 were tested in the presence of the two levels of meperidine at \pm 25% of the cutoff concentration. The results were evaluated both qualitatively and semiquantitatively. No interference was observed when tested with the ARK Meperidine Assay.

Method Comparison

A total of one hundred (100) unaltered clinical human urine specimens that are not individually identifiable were analyzed for meperidine with the ARK Meperidine Assay in both qualitative and semiquantitative modes and the results were compared to a confirmatory method, such as LC-MS/MS or GC/MS. Results are summarized in the table below.

Confirmatory Method			
ARK Meperidine Assay (100 ng/mL Cutoff)		(+)	(-)
	(+)	50	0
	(-)	0	50

12 REFERENCES

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8. Gonzales, E. et al. 2013. Stability of pain-related medications, metabolites, and illicit substances in urine. *Clinica Chimica Acta* **416**:80-85.
9. 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.

13 TRADEMARKS

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