

AccuSign® DOA 6

AMP/OPI/COC/ BZO/MTD/BUP

New One-Step Panel Assay for Drugs of Abuse

For *In Vitro* Use Only

Simple One-Step Immunoassay for the Qualitative Detection of Amphetamine, Opiates, Cocaine, Benzodiazepines, Methadone, Buprenorphine and/or their Metabolites in Human Urine

Catalog No.	DOA-263-35	35 Test Kit
	DOA-263-10	10 Test Kit

Intended Use

AccuSign® DOA 6 AMP/OPI/COC/BZO/MTD/BUP Panel Assay is a simple, one-step immunochromatographic test for the rapid, qualitative detection of amphetamine, opiates, cocaine, benzodiazepines, methadone, buprenorphine and/or their metabolites in human urine.

*The AccuSign® DOA 6 AMP/OPI/COC/BZO/MTD/BUP test provides only a preliminary analytical result. A more specific alternative chemical method must be used in order to obtain a confirmed analytical result. Gas chromatography, mass spectrometry (GC/MS) is the preferred confirmatory method. Other chemical confirmatory methods are available. Clinical consideration and professional judgment should be applied to any drug of abuse test result, particularly when preliminary positive results are used.*¹

Summary and Explanation

Amphetamine is a potent sympathomimetic agent with therapeutic applications. It is chemically related to the human body's natural catecholamines, epinephrine and norepinephrine. Acute higher doses lead to enhanced stimulation of the central nervous system and induce euphoria, alertness, reduced appetite, and a sense of increased energy and power. Cardiovascular responses to amphetamine include increased blood pressure and cardiac arrhythmias. More acute responses include anxiety, paranoia, hallucinations, and psychotic behavior. Amphetamine is largely inactivated during metabolism, being deaminated to phenylacetone which is subsequently oxidized to benzoic acid and excreted as conjugates. However, a small amount is converted by oxidation to norephedrine, and this compound and its parent are p-hydroxylated. Probably the entire dose of amphetamine is eliminated from the urine over a period of several days; normally about 30% is excreted unchanged in the 24-hour urine, but this may increase to as much as 74% in acid urine and may decrease to 1% in alkaline urine. Under normal conditions 0.9% is excreted as phenylacetone, 16-28% as hippuric acid, 4% as benzoylglucuronide, 2% as norephedrine, 0.3% as conjugated p-hydroxynorephedrine, and 2-4% as conjugated phydroxyamphetamine.²

Morphine, codeine, and semisynthetic derivatives of morphine belong to the class of drugs called opiates. An opiate exerts its effects on the central nervous system and can produce euphoria, respiratory depression and coma when it is abused. Morphine is the prototype compound of opiates. Morphine is excreted in the urine as morphine-3-glucuronide, unchanged morphine, and other minor metabolites. Heroin is metabolized to morphine and codeine and excreted in the urine with a small amount in unchanged form. Codeine is also excreted as morphine and in the form of conjugates. Although some opiate metabolites appear in the feces, urinary excretion is the primary route of elimination.^{1,2,4}

Cocaine, derived from the leaves of coca plant, is a potent central nervous system (CNS) stimulant and a local anesthetic. Cocaine induces euphoria, confidence and a sense of increased energy in the user; these psychological effects are accompanied by increased heart rate, dilation of the pupils, fever, tremors and sweating. Cocaine is used by smoking, intravenous, intranasal or oral administration, and excreted in the urine primarily as benzoylecgonine in a short time. Benzoylecgonine has a longer biological half-life (5-8 hours) than cocaine (0.5-1.5 hours) and can generally be detected for 24-60 hours after cocaine use or exposure.^{3,4}

Benzodiazepines are a class of widely prescribed central nervous system (CNS) depressants and include widely used drugs such as chlordiazepoxide, diazepam, and oxazepam. They have medically useful properties, including antianxiety, sedative, anticonvulsant, and hypnotic effects. They are taken orally or sometimes by injection, and have a low potential for physical or psychological dependence. Benzodiazepines induce drowsiness and muscle relaxation; however, their use can also result in

intoxication, similar to drunken behavior except without evidence of alcohol use, and the loss of inhibitions. Chronic abuse can result in addiction and tardive dyskinesia (involuntary muscle movements of the face, limbs, and trunk). Overdose can result in coma and possible death. Withdrawal syndrome includes anxiety, insomnia, tremors, delirium, and convulsions. The effects of benzodiazepine use last 4-8 hours. The different benzodiazepines are absorbed at different rates, and the timing of their psychoactive effects varies with the absorption rate. The drugs are excreted in the urine primarily as the parent compounds or as oxazepam glucuronide, an inactive metabolite, (in the case of chlordiazepoxide and diazepam) and are detectable for 1-2 days. Oxazepam may be detectable in the urine for up to 7 days.^{2,3}

Methadone is a synthetic analogic drug which possesses many of the pharmacologic properties of morphine. Unlike morphine, however, methadone produces marked sedative effects with repeated administration as a result of drug accumulation. Overdosage with methadone is characterized by stupor, muscle flaccidity, respiratory depression, cold and clammy skin, pupillary constriction, hypotension, coma and circulatory collapse. Fatalities in adults from methadone overdosage have increased significantly in many urban areas as a result of widespread availability of the drug, both from licit and illicit sources.^{2,3}

Buprenorphine is a synthetic derivative of thebaine. Its structure is similar to morphine but has antagonist and agonist properties.^{2,3} Buprenorphine has been widely prescribed as a pain-killer since the early 1980s. It has also been used as a substitution treatment for opioid drug dependence as an alternative to methadone. In addition to therapeutic uses, buprenorphine is also abused either sublingually or intravenously. Buprenorphine is metabolized in the body to norbuprenorphine. Both buprenorphine and norbuprenorphine undergo extensive conjugation to buprenorphine-3-β-D-glucuronide and norbuprenorphine-3-β-D-glucuronide, respectively.³ These conjugates are subsequently excreted into urine during the course of several days.³ Concentrations of unconjugated buprenorphine and norbuprenorphine in urine may be less than 1 ng/mL after therapeutic administration, but can range up to 20 ng/mL in abuse situations.⁴ The presence of buprenorphine and its metabolites in urine can be detectable after 1-4 days.^{3,5}

Principle

The **AccuSign® DOA 6** test uses solid-phase chromatographic membrane immunoassay technology for the qualitative detection of amphetamine, opiates, cocaine, benzodiazepines, methadone and buprenorphine in urine. The test is based on the principle of the highly specific immunochemical reactions between antigens and antibodies which are used for the analysis of specific substances in biological fluids. The test relies on the competition between the drug conjugates and the drugs which may be present in the urine sample, for binding to antibodies. In the test procedure, a sample of urine is placed in the Sample well of the device and is allowed to migrate upward. If the drug is present in the urine sample, it competes with the drug conjugate bound to the dye, for the limited antibodies immobilized on the membrane. If the level of drug or drug metabolite is above the cutoff level, the drug will saturate the antibodies, thus inhibiting the binding of the dye coated with drug conjugates to the antibodies on the membrane. This prevents the formation of a line on the membrane. Therefore, a drug-positive urine sample will not generate a line at the specific drug position in the Result window, indicating a positive result. A negative urine sample will generate a line at the specific drug position in the Result window, indicating a negative result.

In addition to the Test line(s) that may appear in the Result window, a Control line is present to confirm the viability of the test. This Control line (validation line) should always appear if the test is conducted properly. Polyclonal sheep anti-mouse IgG antibody is immobilized on the control line. The monoclonal antibody-dye conjugates that pass the line will be captured and produce a colored line at the Control position (C). This works as a procedural control, confirming that proper sample volume was used and the reagent system at the Control line and the conjugate color indicator worked properly. If insufficient sample volume is used, there may not be a Control line, indicating the test is invalid.

Materials Provided

The **AccuSign® DOA 6** test kit contains all the reagents necessary to perform the assay.

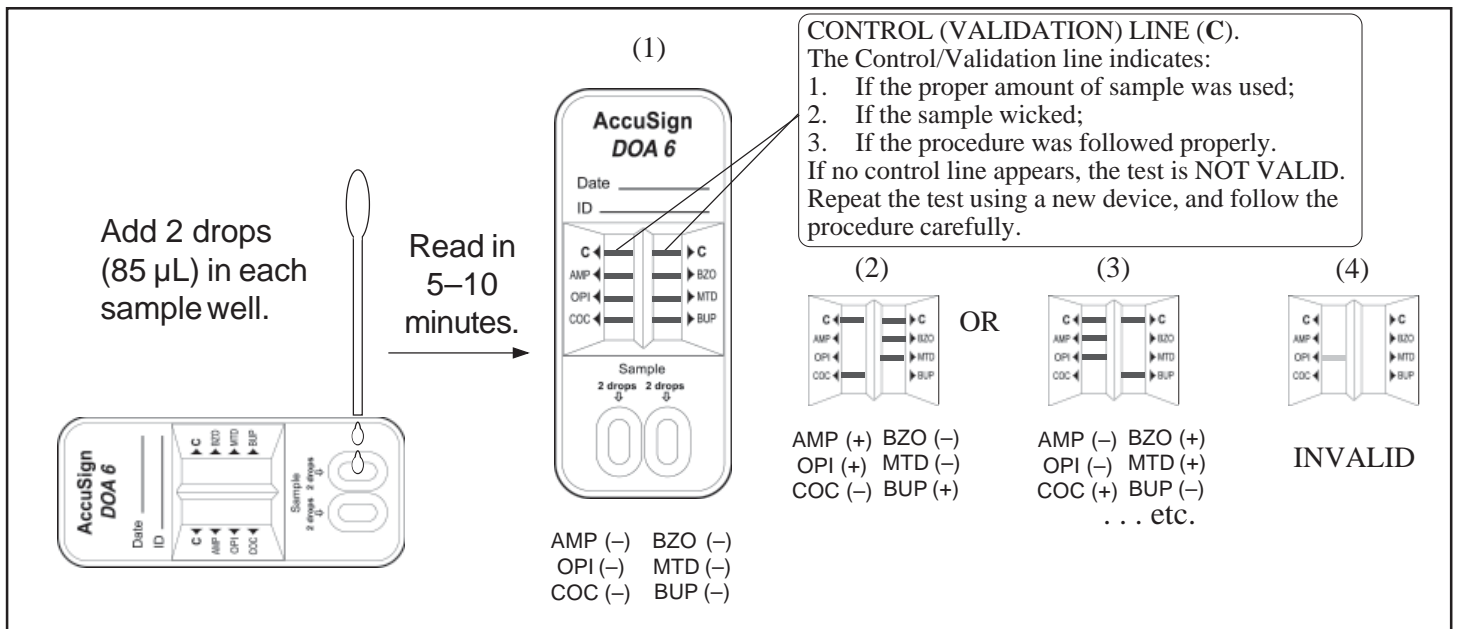
- **AccuSign® DOA 6** device. The test device contains a membrane strip and a dye pad. Membrane strips are coated with monoclonal anti-amphetamine, anti-morphine, antibenzoylecgonine, anti-methadone antibodies as well as polyclonal anti-benzodiazepine antibody. Sheep anti-mouse antibody is coated for the control band. Dye pads contain colloidal gold coated with conjugates of amphetamine, morphine, benzoylecgonine, oxazepam, methadone and buprenorphine (each drug is conjugated with a purified bovine protein).
- Disposable sample dispenser.
- Instructions for use.

Precautions

- For *in vitro* diagnostic use only.
- Avoid cross contamination of urine samples by using a new urine specimen container and dropper for each urine sample.
- The test kit does not contain any HIV or hepatitis infective components.
- Urine specimens are potentially infectious. Proper handling and disposal methods should be established according to good laboratory practices.
- The **AccuSign® DOA 6** device should remain in its original sealed pouch until ready for use. Do not use the test if the pouch is damaged or the seal is broken.
- Do not use the test kit after the expiration date.

Storage and Stability

The **AccuSign® DOA 6** test kit should be stored at 2-30°C (35-86°F) in the original sealed pouch. The expiration dating was established under these storage conditions.



Specimen Collection and Preparation

Approximately 85 μ L of urine sample is required for each test sample well. Fresh urine specimens do not require any special handling or pretreatment. Specimens should be collected in a clean glass or plastic container. If testing will not be performed immediately, specimens should be refrigerated (2–8°C) or frozen. Frozen specimens must be completely thawed, and thoroughly mixed before using.

Specimens containing a large amount of particulate matter may give inconsistent test results. Such specimens should be clarified by centrifuging or allowing to settle before testing.

Test Procedure

The test procedure consists of adding the urine sample to each of two Sample wells of the device and watching for the appearance of colored lines in both result windows.

Test Protocol

1. For each test, open one **AccuSign® DOA 6** pouch and label the device with the patient ID.
2. Holding the dropper vertically, dispense 2 drops (85 μ L) of the urine sample into each Sample well.
3. Read the result after 5 minutes, but within 10 minutes.

Interpretation of Results

Negative: The appearance of a reddish-purple Control line (C) and a line for a specific drug indicates a negative test result; i.e., no drug above the cutoff level has been detected. The color intensities of the Control line and a specific drug line may not be equal. *Any faint line at a specific drug name in the Result window, visible in 10 minutes, should be interpreted as negative. A negative test result does not indicate the absence of drug in the sample; it only indicates the sample does not contain drug above the cutoff level in qualitative terms.*

Positive: The appearance of only a reddish-purple Control line and no distinct line next to T indicates the test result is positive for BUP (i.e., the specimen contains BUP at a concentration above the cutoff level). *A positive test result does not provide any indication of the level of intoxication or urinary concentration of the drug in the sample; it only indicates the sample contains drug above the cutoff level in qualitative terms.*

Invalid: A distinct Control line (C) should always appear. The test is invalid if no Control line forms at the C position. Such tests should be repeated with a new **AccuSign® DOA 6** test device.

Examples of possible results are shown in the diagram in page 2.

- (1) **Amphetamine (-), Opiates (-), Cocaine (-), Benzodiazepines (-), Methadone (-), Buprenorphine (-):** Eight reddish-purple lines—one line each at the C positions and one each at the AMP, OPI, COC, BZO, MTD and BUP positions.
- (2) **Amphetamine (+), Opiates (+), Cocaine (-), Benzodiazepines (-), Methadone (-), Buprenorphine (+):** Five reddish-purple lines—one line each at the C positions and one line each at the COC, BZO and MTD positions; no line at the AMP, OPI, and BUP positions.
- (3) **Amphetamine (-), Opiates (-), Cocaine (+), Benzodiazepines (+), Methadone (+), Buprenorphine (-):** Five reddish-purple lines—one line each at the C positions and one line each at the AMP, OPI, and BUP positions; no line at the COC, BZO and MTD positions.
- (4) **Invalid:** No line at the C position.

There are other possible results, depending on the combinations of drugs present in the urine sample.

Limitations

- The test is designed for use with unadulterated urine only.
- There is a possibility that factors such as technical or procedural errors, as well as other substances in the urine sample than those listed in Table 10 below, may interfere with the test and cause erroneous results.
- Adulterants, such as bleach and/or alum, in urine specimens may produce erroneous results regardless of the method of analysis. If adulteration is suspected, the test should be repeated with a new sample.
- The test result read after 10 minutes may not be consistent with the original reading obtained within the 10 minute reading period. The test result must be read within 10 minutes of sample application.
- Certain medications containing opiates or derivatives of opiate or amphetamine may produce a positive result. Additionally, foods and tea containing poppy products and/or coca leaves may produce a positive result.

User Quality Control

Internal Control: Each **AccuSign® DOA 6** test device has built-in controls. The Control line is an internal positive procedural control. A distinct reddish-purple Control line should always appear in the C position, if the test procedure is performed properly, an adequate sample volume is used, the sample and reagent are wicking on the membrane, and the test reagents at the control line and the conjugate-color indicator are reactive. In addition, if the test has been performed correctly and the device is working properly, the background in the result window will become clear and provide a distinct result. This may be considered an internal negative procedural control.

The positive and negative procedural controls contained in each **AccuSign® DOA 6** test device satisfy the requirements of testing a positive control and a negative control on a daily basis. If the Control line does not appear in the Control position, the test is invalid and a new test should be performed. If the problem persists, contact PBM for technical assistance.

External Control: External controls may also be used to assure that the reagents are working properly and that the assay procedure is followed correctly. It is recommended that a control be tested at regular intervals as good laboratory testing process. For information on how to obtain controls, contact PBM's Technical Services.

Expected Values

AccuSign® DOA 6 AMP/OPI/COC/BZO/MTD/BUP is a qualitative test. The amount of amphetamine, opiates, cocaine, benzodiazepines, methadone, buprenorphine and/or their metabolites present in the urine cannot be estimated by the test. The test results distinguish positive from negative samples. Positive results indicate the samples contain amphetamine, opiates, cocaine, benzodiazepines, methadone, buprenorphine and/or their metabolites above the cutoff concentration. The **AccuSign® DOA 6** test has been shown to detect following cutoff level for each drug: 1,000 ng/mL of amphetamine, 300 ng/mL of morphine, 300 ng/mL of benzoylecgonine, 300 ng/mL of oxazepam, 300 ng/mL of methadone, and 8 ng/mL for buprenorphine in urine.

Performance Characteristics

The accuracy of **AccuSign® DOA 6 AMP/OPI/COC/BZO/MTD/BUP** test was evaluated in comparison to commercially available immunoassays **AccuSign® AMP**, **AccuSign® OPI**, **AccuSign® COC**, **AccuSign® BZO**, and **AccuSign® MTD**, which are proven to be substantially equivalent to Syva's Emit® II and Microgenics' CEDIA® Buprenorphine assays. The results are shown in Tables 1, 2, 3, 4, 5 and 6. A complete agreement (100%) was observed.

Table 1. Amphetamine Accuracy: Comparison of **AccuSign® DOA 6** with **AccuSign® AMP**

		AccuSign® AMP		
		Positive	Negative	Total
AccuSign® DOA 6 (AMP)	Positive	98	0	98
	Negative	0	200	200
Total		98	200	298

Table 2. Opiates Accuracy: Comparison of **AccuSign® DOA 6** with **AccuSign® OPI**

		AccuSign® OPI		
		Positive	Negative	Total
AccuSign® DOA 6 (OPI)	Positive	150	0	150
	Negative	0	200	200
Total		150	200	350

Table 3. Cocaine Accuracy: Comparison of **AccuSign® DOA 6** with **AccuSign® COC**

		AccuSign® COC		
		Positive	Negative	Total
AccuSign® DOA 6 (COC)	Positive	150	0	150
	Negative	0	200	200
Total		150	200	350

Table 4. Benzodiazepine Accuracy: Comparison of **AccuSign® DOA 6** with **AccuSign® BZO**

		AccuSign® BZO		
		Positive	Negative	Total
AccuSign® DOA 6 (BZO)	Positive	174	0	174
	Negative	0	200	200
Total		174	200	374

Table 5. Methadone Accuracy: Comparison of **AccuSign® DOA 6** with **AccuSign® MTD**

		AccuSign® MTD		
		Positive	Negative	Total
AccuSign® DOA 6 (MTD)	Positive	100	0	100
	Negative	0	153	153
Total		100	153	253

Table 6. Accuracy: Comparison of **AccuSign® DOA 6** with **CEDIA® Buprenorphine Assay**

		CEDIA® Buprenorphine Assay		
		Positive	Negative	Total
AccuSign® DOA 6	Positive	34	1*	35
BUP	Negative	2**	49	51
Total		36	50	86

*The concentration of BUP in this sample was 9.6 ng/mL by GC/MS.

**The concentrations of BUP in these two samples were zero and 0.9 ng/mL by GC/MS.

Specificity

The following table lists compounds that are detected by the **AccuSign® DOA 6** test. The specificity of the **AccuSign® DOA 6** test was determined by adding various drugs and drug metabolites to drug-negative urine specimens and testing with the **AccuSign® DOA 6** test. The results are expressed in terms of the minimum concentration required to produce a positive result (Table 7).

Table 7. Specificity

Concentration	Compound (ng/mL)
AMP	
D-Amphetamine	1,000
D,L-Amphetamine	1,500
L-Amphetamine	60,000
Benzphetamine	>100,000

d-Methamphetamine	>100,000
p-OH-Methamphetamine	>100,000
Methylenedioxyamphetamine	700
Methylenedioxyamphetamine	>100,000
β-Phenethylamine	60,000
l-Phenylpropanolamine	>100,000
Phentermine	350
Tryptamine	50,000
Tyramine	70,000
3-OH-Tyramine	>100,000

OPI

Codeine	300
Hydrocodone	500
Hydromorphone	600
Levophanol	5,000
Meperidine	80,000
Morphine	300
Morphine-3-β-D-glucuronide	500
Nalorphine	1,000
Naloxane	100,000
Norcodeine	60,000
Oxycodone	20,000
Oxymorphone	60,000
Procaine HCl	100,000
Thebaine	5,000

COC

Benzoylcegonine	300
Cocaine HCl	300
Ecgonine HCl	>100,000

BZO

Alprazolam	10,000
Bromazepam	2,500
Chlordiazepoxide	1,000
Clobazam	10,000
Clonazepam	10,000
Clorazepate dipotassium	250
Delorazepam	1,000
N-Desalkylflurazepam	1,250
Diazepam	2,000
Estazolam	500
Flunitrazepam	>10,000
7-amino flunitrazepam	4,000
a-Hydroxyalprazolam	250
a-Hydroxytriazolam	2,500
Lorazepam	750
Lormetazepam	8,000
Medazepam	2,500
Midazolam	4,000
Nitrazepam	2,500
Nordiazepam (N-Desmethyl diazepam)	500
Oxazepam	300
Prazepam	9,000
Temazepam	800
Triazolam	>10,000

MTD

Diphenhydramine	100,000
Doxylamine	>100,000
EDDP	>100,000
EMDP	>100,000
Imipramine	>100,000
LAAM	2,000
Meperidine	>100,000
Methadone	300
Nor-LAAM	10,000

BUP

Buprenorphine	8
Buprenorphine-3-β-D-glucuronide	10
Codeine	70,000
Dextromethorphan	>200,000
Dihydrocodeine	200,000
EDDP	>200,000
EMDP	>200,000
Heroin	>50,000
Hydrocodone	>200,000
Hydromorphone	>200,000
Imipramine	>200,000
LAAM	>200,000
Meperidine	>200,000
Methadone	>200,000
Morphine	>200,000
Morphine-3-D-glucuronide	>200,000

Morphine-6-D-glucuronide	>50,000
Nalorphine	5,000
Naloxone	>200,000
Naltrexone	>200,000
Norbuprenorphine	>50,000
Norbuprenorphine-3-β-D-glucuronide	>50,000
Noroxycodone	>200,000
Noroxymorphone	>50,000
(+)Norpropoxyphene	>200,000
Oxycodone	>200,000
Oxymorphone	>200,000

Interfering Substances

The following compounds showed no cross-reactivity when tested with the **AccuSign® DOA 6 AMP/OPI/COC/BZO/MTD/BUP** at a concentration of 100 µg/mL (Table 8).

Table 8. Non Cross-Reacting Compounds

4-Acetamidophenol	Estrone-3-sulfate	Papaverine
Acetophenetidin (Phenacetin)	Ethyl-p-aminobenzoate	Penicillin-G
N-Acetylprocainamide	Fenoprofen	Pentazocaine
Acetylsalicylic acid	Furoxime	Phendimetrazine
Aminopyrine	Gentisic acid	Phenelzine
Amoxapine	Glutethimide	Prednisolone
Amoxicillin	(-) Isoproterenol	Prednisone
Apomorphine	Isoxsuprine	Promethazine
Aspartame	Ketoprofen	D,L-Propranolol
Atropine	Labetalol	Propiomazine
Benzilic acid	Lidocaine	D-Propoxyphene
Benzoic acid	Loperamide	Quinidine
Benzphetamine	Loxapine succinate	Rantidine
Chloralhydrate	Meprobamate	Salicylic acid
Chloramphenicol	Methaqualone	Serotonin
Chlorothiazide	Methoxyphenamine	Sulfamethazine
Chlorquine	Methylphenidate	Sulindac
Cholesterol	Methyprylon	Tetracycline
Clonidine	Nalidixic acid	Tetrahydrocortisone
Cortisone	Naproxen	Tetrahydrozoline
(-) Cotinine	Niacinamide	Thiamine
Deoxycorticosterone	Nifedipine	Thioridazine
Diclofenac	Norethindrone	D,L-Thyroxine
Diethylpropion	Noroxymorphone	Tolbutamide
Diflunisal	D-Norpropoxyphene	Triamterene
Digoxin	(-) Norpseudoephedrine	Trifluoperazine
Domperidone	Noscapine	Trimethoprim
Doxylamine	Nylidrin	D,L-Tryptophan
Erythromycin	D,L-Octopamine	D,L-Tyrosine
Guaifenesin	Oxalic acid	Uric acid
Hippuric acid	Oxolinic acid	Verapamil
Hydralazine	Oxymetazoline	Zomepirac
Hydrochlorothiazide		
Hydrocortisone		
O-Hydroxyhippuric acid		
Iproniazid		
β-Estradiol		

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Symbols Key

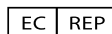
	Manufactured by
	CE Mark
	Authorized Representative
	In Vitro Diagnostic Medical Device
	Catalog Number
	Consult Instructions for Use
	Batch Code
	“Use By” date in year-month-day format
	Temperature Limitation
	Contains sufficient for <n> tests
	Do not reuse
	Contents
	Test Device
	Transfer Pipette
	Instructions for Use
	One-step immunochromatographic Assay for the Detection of Drugs of Abuse in Urine
	Amphetamine/Opiates/Cocaine/Benzodiazepines/ Methadone/Buprenorphine Test

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Patent No.: 5,559,041



© 2006 PBM
Printed in U.S.A.
Revised Nov 2006
T-58061 1107BL



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Manufactured by
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