CEDIA™ Heroin Metabolite (6-AM) Assay

thermo scientific

IVD **For In Vitro Diagnostic Use Only**

Rx Only

REF 100107 (3 x 17 mL)
100108 (65 mL Kit)
100186 (495 mL Kit)
10015213 (3 x 17 mL Indiko Kit)

Intended Use

The CEDIA™ Heroin Metabolite (6-Acetylmorphine, or 6-AM) Assay is a homogeneous enzyme immunoassay for the in vitro qualitative and/or semi-quantitative determination of the presence of heroin metabolite (6-AM) in human urine at a cut-off concentration of 10 ng/mL. The assay is intended to be used in laboratories and provides a rapid analytical screening procedure to detect 6-Acetylmorphine in human urine. The assay is designed for use with a number of clinical chemistry analyzers. This product is intended to be used by trained professionals only.

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

The assay provides only a preliminary analytical test result. A more specific alternative chemical method must be used to obtain a confirmed analytical result. Gas chromatography/ mass spectrometry (GC/MS) or Liquid chromatography/ mass spectrometry (LC-MS/MS) is the preferred confirmatory method.[1]

Clinical and professional judgment should be applied to any drug of abuse test result, particularly when preliminary results are used. For In Vitro Diagnostic Use Only.

Summary and Explanation of the Test

Heroin (3,6-diacetylmorphine) is produced by chemical modification of morphine, a naturally occurring alkaloid found in the unripe pods of the opium poppy Papaver somniferum.[2,3] Heroin is highly addictive, and is currently a Schedule I substance (no currently accepted medical use). Heroin is the most abused opiate drug,[4,5] and its use is associated with a wide variety of health problems. Heroin is administered by intravenous or subcutaneous injection or by nasal insufflation.[3] It is rapidly metabolized (half-life of 9 minutes) to 6-AM by esterases in the blood, and then to morphine by hydrolysis in the liver. The presence of 6-AM in urine is regarded as a specific marker for the illicit use of heroin.[6-8] It is likely that even for higher doses of heroin the detection time is limited to 24 hours after use.[6] 6-AM cannot be formed by acetylation of morphine in the body; thus the presence of 6-AM cannot be caused by injection of legal opiate analgesics or large quantities of poppy seeds. For this reason, the Department of Health and Human Services (DHHS) introduced revised guidelines for opiate testing which required testing of all opiate-positive urine specimens for 6-AM for confirmation of heroin abuse.[9] The half-life of 6-AM is approximately 35 minutes.

The CEDIA Heroin Metabolite Assay uses recombinant DNA technology (US Patent No. 4708929) to produce a unique homogeneous enzyme immunoassay system.10 This assay is based on the bacterial enzyme β-galactosidase, which has been genetically engineered into two inactive fragments. These fragments, termed Enzyme Acceptor (EA) and Enzyme Donor (ED) spontaneously re-associate to form fully active enzyme that, in the assay format, cleaves a substrate, generating a color change that can be measured spectrophotometrically. In the CEDIA Heroin Metabolite Assay, the sample competes with 6-AM conjugated to ED for antibody binding sites. If 6-AM is present in the sample, it binds to antibody, leaving the ED-6-AM conjugate free to re-associate with EA to form active β-galactosidase. If no 6-AM is present in the sample, antibody binds to the ED-6-AM conjugate, inhibiting the re-association of inactive β- galactosidase fragments, and thus reducing the amount of active enzyme formed. The amount of active enzyme formed and resultant absorbance change are proportional to the amount of 6-AM present in the sample.

Reagents

- **1 EA Reconstitution Buffer:** Contains 0.32 mg/L mouse monoclonal antibodies to 6-Acetylmorphine, buffer salts, stabilizer, detergent and preservative.
- **1a EA Reagent:** Contains 0.171 g/L Enzyme Acceptor, buffer salts, detergent and preservative.
- **2 ED Reconstitution Buffer:** Contains buffer salts, stabilizer, and preservative.
- **2a ED Reagent:** Contains 16.2 µg/L Enzyme Donor conjugated to 6-Acetylmorphine, 1.67 g/L chlorophenol red-β-D galactopyranoside, stabilizer, detergent, and preservative.

Additional Materials Required (sold separately):

REF	Kit Description
1557416	CEDIA Negative Calibrator, 5 mL
1661388	CEDIA Negative Calibrator, 15 mL
100031	CEDIA Heroin Metabolite (6-AM) Cutoff Calibrator, 5 mL
100034	CEDIA Heroin Metabolite (6-AM) High Calibrator, 5 mL
100202	MGC Select Control Set, 3 x 5 mL

⚠ Warnings and Precautions

The reagents are harmful if swallowed.

DANGER:

Powder reagents contain ≤55% w/w Bovine Serum Albumin (BSA) fragments and ≤1% w/w Sodium Azide.
Liquid reagents contain ≤0.5% Bovine Serum, ≤0.15% Sodium Azide, and ≤0.1% Drug-Specific Antibody (Mouse).

H317 - May cause allergic skin reaction.
H334 - May cause allergy or asthma symptoms or breathing difficulties if inhaled.
EUH032 - Contact with acids liberates very toxic gas.

Avoid breathing dust/mist/vapors/spray. Contaminated work clothing should not be allowed out of the workplace. Wear protective gloves/eye protection/face protection. In case of inadequate ventilation wear respiratory protection. If on skin: Wash with plenty of soap and water. IF INHALED: If breathing is difficult, remove victim to fresh air and keep at rest in a position comfortable for breathing. If skin irritation or rash occurs: Get medical advice/attention. If experiencing respiratory symptoms: Call a POISON CENTER or doctor/physician. Wash contaminated clothing before reuse. Dispose of contents/ container to location in accordance with local/regional/national/international regulations.

In the case of accidental spill, clean and dispose of material according to your laboratory's Standard Operating Procedure (SOP), and state regulations.

In the case of damage package on arrival contact your technical support representative (refer to last page of this Package Insert).

Reagent Preparation and Storage

For reparation of the solution, refer to the section below. Remove the kit from refrigerated storage (2-8°C) immediately prior to preparation of the solutions.

Prepare the solutions in the following order to minimize the risk of possible contamination:

R2 Enzyme donor solution:

Connect Bottle 2a (ED Reagent) to Bottle 2 (ED Reconstitution Buffer) using one of the enclosed adapters. Mix by gentle inversion, ensuring that all the lyophilized material from Bottle 2a is transferred into Bottle 2. Avoid the formation of foam. Detach Bottle 2a and adapter from Bottle 2 and discard. Cap Bottle 2 and let stand approximately 5 minutes at room temperature (21-25°C). Mix again. Record the reconstitution date on the bottle label. Place the bottle directly into the reagent compartment of the analyzer or into refrigerated storage (2-8°C) and let stand 30 minutes before use.

R1 Enzyme acceptor solution:

Connect Bottle 1a (EA Reagent) to Bottle 1 (EA Reconstitution Buffer) using one of the enclosed adapters. Mix by gentle inversion, ensuring that all the lyophilized material from bottle 1a is transferred into Bottle 1. Avoid the formation of foam. Detach Bottle 1a and adapter from Bottle 1 and discard. Cap Bottle 1 and let stand approximately 5 minutes at room temperature (21-25°C). Mix again. Record the reconstitution date on the bottle label. Place the bottle directly into the reagent compartment of the analyzer or into refrigerated storage (2-8°C) and let stand 30 minutes before use.

⚠ **NOTE 1:** The components supplied in this kit are intended for use as an integral unit. Do not mix components from different lots.

⚠ **NOTE 2:** Avoid cross-contamination of reagents by matching reagent stoppers to the proper reagent bottle. The R2 Solution (Enzyme Donor) should be yellow-orange in color. A dark red or purple-red color indicates that the reagent has been contaminated and must be discarded. Discard Reagent 1 or 2 if turbidity or precipitates are observed.

⚠ **NOTE 3:** The R1 and R2 Solutions must be at the reagent compartment storage temperature of the analyzer before performing the assay. Refer to the analyzer specific sheet for additional information.

Store reagents at 2-8°C. **DO NOT FREEZE.**

For stability of the unopened components, refer to the box or bottle labels for the expiration date.

R1 Solution: 60 days refrigerated on analyzer or at 2-8°C.
R2 Solution: 60 days refrigerated on analyzer or at 2-8°C.

Specimen Collection and Handling

Collect urine specimens in plastic or glass containers. Care should be taken to preserve the chemical integrity of the urine sample from the time it is collected until the time it is assayed.

Specimens kept at room temperature that do not receive initial test within 7 days[11] of arrival at the laboratory may be placed into a secure refrigeration unit at 2 to 8°C for two months.[12] For longer storage prior to analysis or for sample retention after analysis, urine specimens may be stored at -20°C.[12, 13]

Laboratories following the SAMHSA mandatory guidelines should refer to SAMHSA "Short-Term Refrigerated Storage" and "Long-Term Storage" requirements.[9]

To protect the integrity of the sample, do not induce foaming and avoid repeated freezing and thawing. An effort should be made to keep pipetted samples free of gross debris. It is recommended that grossly turbid specimens be centrifuged before analysis. Frozen samples should be thawed and mixed prior to analysis. Adulteration of the urine sample may cause erroneous results. If adulteration is suspected, obtain another sample and forward both specimens to the laboratory for testing.

Handle all urine specimens as if they were potentially infectious.

Assay Procedure

The CEDIA Heroin Metabolite (6-AM) Assay is intended for use on automated clinical analyzers capable of maintaining a constant temperature, pipetting, mixing reagents, measuring enzymatic rates at 570 nm and timing the reaction accurately can be used to perform this immunoassay. Refer to specific application instructions for each analyzer for chemistry parameters before performing the assay.

Qualitative analysis

For analysis of samples, use the CEDIA Heroin Metabolite (6-AM) Cutoff Calibrator.

Semi-quantitative analysis

For semi-quantitative analysis of samples, use the CEDIA Negative Calibrator, the CEDIA Heroin Metabolite (6-AM) Cutoff Calibrator and CEDIA Heroin Metabolite (6-AM) High Calibrator to analyze results.

Quality Control and Calibration

Good laboratory practice suggests that controls be tested each day patient samples are tested and each time calibration is performed. It is recommended that two controls be run; a positive control and a negative control. Base assessment of quality control on the values obtained for the controls, which should fall within specified limits. If any trends or sudden shifts in values are detected, review all operating parameters. Contact Customer Technical Support for further assistance. All quality control requirements should be performed in conformance with local, state and/or federal regulations or accreditation requirements. Each laboratory should establish its own quality control testing frequency.

Results and Expected Values

Qualitative

The CEDIA Heroin Metabolite (6-AM) Cutoff calibrator (10 ng/mL) is used as a reference in distinguishing between 'positive' and 'negative' samples. Samples producing a response value that is equal to or greater than the response value of the cutoff calibrator are considered positive. Samples producing a response value less than the response value of the cutoff calibrator are considered negative.

Semi-quantitative

The CEDIA Heroin Metabolite (6-AM) Cutoff Calibrator and High Calibrator used in conjunction with the CEDIA DAU Negative Calibrator, can be used to estimate relative concentration of 6-Acetylmorphine. Refer to the analyzer specific application sheet for detailed information. Concentrations of drug values only can be used for making controls and dilutions for confirmatory testing.

Limitations

1. A positive test result indicates the presence of 6-AM; it does not indicate or measure intoxication and does not necessarily correlate with the extent of physiological and psychological effects. It is possible that substances other than those investigated in the specificity study may interfere with the test and cause false results. This is a screening test. All positive results must be confirmed via GC/MS or LC-MS/MS.
2. There is a possibility that other substances and/or factors (e.g., technical or procedural errors) may interfere with the test and cause false results.
3. Performance characteristics for the CEDIA Heroin Metabolite (6-AM) assay performance have not been established with body fluids other than human urine.

Specific Performance Characteristics

Typical performance results obtained on a Beckman Coulter AU680 analyzer are shown below. The results obtained in your laboratory may differ from these data.

Precision

Samples were prepared by spiking 6-Acetylmorphine into drug free urine at the cutoff (100%), 25%, 50% & 75% above and below the cutoff and tested in both qualitative and semi-quantitative modes using a Clinical Laboratory and Standards Institute (CLSI) protocol. Results presented below were generated by testing all samples in replicates of 2, twice per day for 20 days, total n=80.

Qualitative Study Analysis

6-Acetylmorphine Spiked Concentration (ng/mL)	% of Cutoff (10 ng/mL)	GC/MS (ng/mL)	Total Precision (n=80)	
			Number of Determinations	Immunoassay Results (Negative/Positive)
0	-100%	0.00	80	80/0
2.5	-75%	2.67	80	80/0
5	-50%	5.17	80	80/0
7.5	-25%	7.82	80	80/0
10	100%	10.2	80	56/24
12.5	+25%	12.8	80	0/80
15	+50%	15.2	80	0/80
17.5	+75%	18.0	80	0/80
20	+100%	21.5	80	0/80

Semi-Quantitative Study Analysis

6-Acetylmorphine Spiked Concentration (ng/mL)	% of Cutoff (10 ng/mL)	GC/MS (ng/mL)	Total Precision (n=80)	
			Number of Determinations	Immunoassay Results (Negative/Positive)
0	-100%	0.00	80	80/0
2.5	-75%	2.67	80	80/0
5	-50%	5.17	80	80/0
7.5	-25%	7.82	80	80/0
10	100%	10.2	80	42/38
12.5	+25%	12.8	80	0/80
15	+50%	15.2	80	0/80
17.5	+75%	18.0	80	0/80
20	+100%	21.5	80	0/80

Accuracy

One hundred patient samples were analyzed by the CEDIA Heroin Metabolite (6-AM) 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 CEDIA Heroin Metabolite (6-AM) Assay was 99%.

Qualitative Accuracy study with LC-MS/MS as reference method

Candidate Device Results	Negative	<50% of Cutoff concentration by LC-MS/MS (<5 ng/mL)	Near Cutoff Negative (Between 50% below the cutoff and the cutoff concentration as determined by LC-MS/MS) (5 – 9.9 ng/mL)	Near Cutoff Positive (Between the cutoff and 50% above the cutoff concentration as determined by LC-MS/MS) (10 – 15.0 ng/mL)	High Positives (Greater than 50% above cutoff concentration (>15.0 ng/mL)
Positive	0	0	1*	5	45
Negative	43	2	4	0	0

Semi-Quantitative Accuracy study with LC-MS/MS as reference method

Candidate Device Results	Negative	<50% of Cutoff concentration by LC-MS/MS (<5 ng/mL)	Near Cutoff Negative (Between 50% below the cutoff and the cutoff concentration as determined by LC-MS/MS) (5 – 9.9 ng/mL)	Near Cutoff Positive (Between the cutoff and 50% above the cutoff concentration as determined by LC-MS/MS) (10 – 14.9 ng/mL)	High Positives (Greater than 50% above cutoff concentration (>15.0 ng/mL)
Positive	0	0	1*	5	45
Negative	43	2	4	0	0

*** Discordant Result Table for Discrepant Sample near cutoff**

Sample ID	EIA		LC-MS/MS (ng/mL)
	Qualitative mode	SQ (ng/mL)	6-Acetylmorphine
CA170418-025	Positive	Positive	9.61

Sample showed 13.8 ng/mL in semi-quantitative mode, and is discordant due to cross reactivity to morphine present in the sample at a concentration of 4449 ng/mL as measured by LC-MS/MS.

Analytical Recovery and Dilution Linearity

To demonstrate the dilution linearity for purposes of sample dilution and quality control of the entire assay range, drug free urine was spiked to the high calibrator level of 6-Acetylmorphine (20 ng/mL) and diluted with drug free urine to generate 10 intermediate levels. 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 target value.

Target 6-Acetylmorphine Value (ng/mL)	Observed Value (ng/mL)	Recovery (%)
0	0.18	N/A
2	2.26	113.0%
4	4.02	100.5%
6	6.10	101.7%
8	7.86	98.3%
10	9.88	98.8%
12	11.90	99.2%
14	13.72	98.0%
16	15.52	97.0%
18	18.04	100.2%
20	19.64	98.2%

Specificity

The cross-reactivity of 6-Acetylmorphine was evaluated by adding known amounts of each analyte to drug free urine. As indicated by the results in the table below, 6-Acetylmprhine exhibited 100% cross-reactivity.

6-Acetylmorphine and Heroin	Tested Concentration (ng/mL)	Pos/Neg	Cross-reactivity (%)
6-Acetylmorphine	10	Pos	100
Heroin	160	Pos	6

Cross reactivity of structurally related or unrelated opiate compounds

Structurally related compounds and other opiates	Tested Concentration (ng/mL)	Pos/Neg	Cross-reactivity (%)
6-Acetylcodeine	100,000	Pos	0.01
Buprenorphine	100,000	Neg	<0.01
Buprenorphine-3β-D-glucuronide	100,000	Neg	<0.01
Codeine	100,000	Neg	<0.01
Dextromethorphan	100,000	Neg	<0.01
Dihydrocodeine	100,000	Neg	<0.01
EDDP	100,000	Neg	<0.01
EMDP	100,000	Neg	<0.01
Ethylmorphine	100,000	Neg	<0.01
Fentanyl	100,000	Neg	<0.01
Hydrocodone	100,000	Neg	<0.01
Hydromorphone	20,000	Pos	0.05
Hydromorphone-3β-D-glucuronide	100,000	Neg	<0.01
LAAM	100,000	Neg	<0.01
Levorphanol	20,000	Pos	0.05
Methadone	100,000	Neg	<0.01
Meperidine	100,000	Neg	<0.01
Mitragynine	100,000	Neg	<0.01
7-Hydroxymitragynine	100,000	Neg	<0.01
Morphine	13,500	Pos	0.07
Morphine-3β-D-Glucuronide	100,000	Neg	<0.01
Morphine-6β-D-Glucuronide	100,000	Neg	<0.01
Nalorphine	10,500	Pos	0.1
Naloxone	100,000	Neg	<0.01
Naltrexone	100,000	Neg	<0.01
Norbuprenorphine	100,000	Neg	<0.01
Norbuprenorphine glucuronide	100,000	Neg	<0.01
Norcodeine	100,000	Neg	<0.01
Norhydrocodone	100,000	Neg	<0.01
Normorphine	50,000	Pos	0.02
Norpropoxyphene	100,000	Neg	<0.01
Noroxycodone	100,000	Neg	<0.01
Noroxymorphone	100,000	Neg	<0.01
Oxycodone	100,000	Neg	<0.01
Oxymorphone	100,000	Neg	<0.01
Oxymorphone-3β-D-glucuronide	100,000	Neg	<0.01
Tapentadol HCl	100,000	Neg	<0.01
Tramadol	100,000	Neg	<0.01

Structurally unrelated compounds were evaluated by adding each substance to 6-Acetylmorphine spiked at low (7.5 ng/mL) and high (12.5 ng/mL) controls at the concentrations indicated. A drug was considered to cross-react if the observed 6-Acetylmorphine concentrations result exceeded 10 ng/mL. As shown in the tables below, all the pharmacologic compounds evaluated, including a number of opiate compounds, exhibited minimal cross reactivity at the concentrations tested.

Structurally unrelated compounds spiked at the concentration listed below into Low and High controls

Cross reactants	Spiked Concentration (ng/mL)	Spiked 6-Acetylmorphine Level	
		Low Control	High Control
10,11 Dihydrocarbamazepine	85,000	Neg	Pos
11-nor-Δ9-THC-COOH	10,000	Neg	Pos
Acetaminophen	500,000	Neg	Pos
Acetylsalicylic Acid	500,000	Neg	Pos
Amitriptyline	125,000	Neg	Pos
Amoxicillin	500,000	Neg	Pos
Amphetamine	100,000	Neg	Pos
Amisulpride	100,000	Neg	Pos
Benzotropine Mesylate	125,000	Neg	Pos
Benzoylecgonine	100,000	Neg	Pos
Brompheniramine	75,000	Neg	Pos
Caffeine	500,000	Neg	Pos
Captopril	500,000	Neg	Pos
Chlordiazepoxide	100,000	Neg	Pos
Chlorpromazine	10,000	Neg	Pos
Clomipramine	250,000	Neg	Pos
Chloroquine	500,000	Neg	Pos
Cimetidine	500,000	Neg	Pos
Desipramine	125,000	Neg	Pos
Diazepam	100,000	Neg	Pos
Digoxin	100,000	Neg	Pos
Diphenhydramine	50,000	Neg	Pos
Doxepine HCl	50,000	Neg	Pos
Enalapril	500,000	Neg	Pos
Fluoxetine	500,000	Neg	Pos
Fluophenazine	500,000	Neg	Pos
Haloperidol	50,000	Neg	Pos
Hydroxychlroquine	100,000	Neg	Pos
Hydroxyzine	250,000	Neg	Pos
Ibuprofen	500,000	Neg	Pos
Imipramine	50,000	Neg	Pos
Levothyroxine	50,000	Neg	Pos
Methamphentamine	100,000	Neg	Pos
Maprotiline	500,000	Neg	Pos
Nalbuphine	100,000	Neg	Pos
Naproxen	500,000	Neg	Pos
Nortryptiline	250,000	Neg	Pos
Nifedipine	500,000	Neg	Pos
Nordiazepam	100,000	Neg	Pos

Table Continued

Cross reactants	Spiked Concentration (ng/mL)	Spiked 6-Acetylmorphine Level	
		Low Control	High Control
Oxazepam	100,000	Neg	Pos
Perphenazine	150,000	Neg	Pos
Phencyclidine	7,500	Neg	Pos
Phenobarbital	100,000	Neg	Pos
Procyclidine	400,000	Neg	Pos
Propoxyphene	25,000	Neg	Pos
Protriptyline	50,000	Neg	Pos
Ranitidine	500,000	Neg	Pos
Salicyluric Acid	500,000	Neg	Pos
Secobarbital	100,000	Neg	Pos
Sulpiride	500,000	Neg	Pos
Thioridazine	250,000	Neg	Pos
Triprolidine	125,000	Neg	Pos
Verapamil	500,000	Neg	Pos

Interference

The potential interference of pH and endogenous physiologic substances on recovery of 6-Acetylmorphine using CEDIA Heroin Metabolite (6-AM) Assay was assessed by spiking known compounds of potentially interfering substances into the low (7.5 ng/mL) and high (12.5 ng/mL) controls for 10 ng/mL cutoff. In the presence of the compounds listed below, the controls were detected accurately, indicating that these compounds did not show interference in the assay.

Compound	Tested Concentration (mg/dL)	Spiked 6-Acetylmorphine Level	
		Low Control	High Control
Acetone	1000	Neg	Pos
Ascorbic acid	1500	Neg	Pos
Creatinine	500	Neg	Pos
Ethanol	1000	Neg	Pos
Galactose	10	Neg	Pos
ϒ-globulin	500	Neg	Pos
Glucose	1000	Neg	Pos
Hemoglobin	300	Neg	Pos
Human serum albumin	500	Neg	Pos
Oxalic acid	100	Neg	Pos
Riboflavin	7.5	Neg	Pos
Sodium Chloride	6000	Neg	Pos
Urea	2000	Neg	Pos
pH	3.0	Neg	Pos
pH	4.0	Neg	Pos
pH	5.0	Neg	Pos
pH	6.0	Neg	Pos
pH	7.0	Neg	Pos
pH	8.0	Neg	Pos
pH	9.0	Neg	Pos
pH	10.0	Neg	Pos
pH	11.0*	Neg	Neg*

*pH 11 urine interferes in CEDIA 6-AM urine assay.

Specific Gravity

Drug free urine samples with specific gravity ranging in value from 1.004 to 1.029 were split and spiked to a final concentration of either 7.5 ng/mL or 12.5 ng/mL (the low and high control concentrations, respectively). These samples were then evaluated in qualitative and semi-quantitative modes. No interference was observed.

Specific Gravity: 10 ng/mL Cutoff

Spiked 6-Acetylmorphine Concentration		
Specific Gravity	**Low Control**	**High Control**
1.004	Neg	Pos
1.005	Neg	Pos
1.007	Neg	Pos
1.010	Neg	Pos
1.011	Neg	Pos
1.013	Neg	Pos
1.019	Neg	Pos
1.023	Neg	Pos
1.025	Neg	Pos
1.029	Neg	Pos

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Glossary:

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