06334482500V6.0

MDN2

cobas®

Methadone II

Order information

REF	[i]	CONTENT		Analyzer(s) on which **cobas c** pack(s) can be used
06334482190	06334482500	ONLINE DAT Methadone II (100 tests)	System‑ID 01 6948 7	**cobas c** 701/702

Materials required (but not provided):

03304671190	Preciset DAT Plus I CAL 1‑6 (6 x 5 mL)	Codes 431‑436
03304698190	C.f.a.s. DAT Qualitative Plus (6 x 5 mL)	
04590856190	C.f.a.s. DAT Qualitative Plus Clinical (3 x 5 mL)	Code 699
03312950190	Control Set DAT I PreciPos DAT Set I (2 x 10 mL) PreciNeg DAT Set I (2 x 10 mL)	
04500873190	Control Set DAT Clinical PreciPos DAT Clinical (2 x 10 mL) PreciNeg DAT Clinical (2 x 10 mL)	

English

System information

MD3Q0: ACN 8447: for qualitative assay

MD3S0: ACN 8448: for semiquantitative assay

MD3QC: ACN 8792: for qualitative assay; using C.f.a.s. DAT Qualitative Plus Clinical

Intended use

Methadone II (MDN2) is an in vitro diagnostic test for the qualitative and semiquantitative detection of methadone in human urine on **cobas c** systems at a cutoff concentration of 300 ng/mL. Semiquantitative test results may be obtained that permit laboratories to assess assay performance as part of a quality control program. Semiquantitative assays are intended to determine an appropriate dilution of the specimen for confirmation by a confirmatory method such as gas chromatography/mass spectrometry (GC‑MS).

Methadone II provides only a preliminary analytical test result. A more specific alternate chemical method must be used in order to obtain a confirmed analytical result. GC‑MS is the preferred confirmatory method.[1] Clinical consideration and professional judgment should be applied to any drug of abuse test result, particularly when preliminary positive results are used.

Summary

Detection of methadone in human urine with this assay is used as an aid in monitoring adherence to treatment in patients under addiction programs and/or under pain treatment and for presumptive testing of illicit use of methadone in individuals with suspected exposure.

Methadone belongs to the fully synthetic opioids. It can be administered orally or intravenously and is used for detoxification and temporary maintenance of opioid use disorder, as well as treatment of acute and chronic pain.[2,3] Methadone is also subject of abuse, in this context withdrawal syndrome is qualitatively similar to morphine, yet it differs in that it develops more slowly, is less intense, and is more prolonged.[2] Methadone has a high bioavailability, a half‑life of 28 h allowing a single dose daily.[4] Similar as morphine, methadone has affinity not only for the mu‑opioid receptor (MOR) but also for the delta‑opioid receptor (DOR). This might explain its utility in patients whose pain no longer responds to other opioids.[3] However, unlike morphine, repeated administration causes marked sedative effects due to drug accumulation in the body based on tissue protein binding.[5] It is distributed to the liver, lung, kidney, brain, gut, muscle, and urine.[6]

Methadone is metabolized largely by mono‑ and di‑N‑demethylation. Spontaneous cyclization of the resulting unstable compounds forms the major metabolites, 2‑ethylidene‑1,5‑dimethyl‑3,3‑diphenylpyrrolidine (EDDP) and 2‑ethyl‑5‑methyl‑3,3‑diphenylpyrroline (EMDP). Both are hydrolyzed to some extent, with subsequent glucuronidation.[7,8] In opioid dependent patients, excretion of unchanged methadone can account for 5‑50 % of the dose. Urinary pH affects the percentage of unchanged drug excreted, as does urinary volume, dose, and individual metabolism.[9,10]

Clinical urine opioid drug testing is done to monitor adherence to methadone treatment and methadone is detectable from 1.5 to 3 days after administration.[11,12] To confirm that the patient has taken methadone and is not simply adding it to a urine specimen, the test for the methadone metabolite, EDDP, can be ordered.[11] Because many drugs are cleared from the blood rapidly, testing of blood or its components (serum) has short periods of detection.[13] Measurement in serum or plasma is an acceptable alternative for the detection of methadone in pain management patients with end‑stage renal failure.[14]

In the context of drug screening, samples that test negative on initial screening tests can be reported as negative and disposed of as planned. Otherwise, depending on the situation, presence of the drug indicated by a positive screening result may need to be confirmed using a suitable confirmatory technique (e.g., GC‑MS or LC‑MS).[12,13,14,15]

Test principle

The assay is based on the kinetic interaction of microparticles in a solution (KIMS)[16,17] as measured by changes in light transmission. In the absence of sample drug, soluble drug conjugates bind to antibody‑bound microparticles, causing the formation of particle aggregates. As the aggregation reaction proceeds in the absence of sample drug, the absorbance increases.

When a sample contains the drug in question, this drug competes with the drug derivative conjugate for microparticle‑bound antibody. Antibody bound to sample drug is no longer available to promote particle aggregation, and subsequent particle lattice formation is inhibited. The presence of sample drug diminishes the increasing absorbance in proportion to the concentration of drug in the sample. Sample drug content is determined relative to the value obtained for a known cutoff concentration of drug.[18]

Reagents ‑ working solutions

R1 Conjugated methadone derivative; buffer; bovine serum albumin; 0.09 % sodium azide

R2 Microparticles attached to methadone antibody (mouse monoclonal); buffer; bovine serum albumin; 0.09 % sodium azide

R1 is in position B and R2 is in position C.

Precautions and warnings

For in vitro diagnostic use for health care professionals. Exercise the normal precautions required for handling all laboratory reagents.

Infectious or microbial waste:
Warning: handle waste as potentially biohazardous material. Dispose of waste according to accepted laboratory instructions and procedures.

Environmental hazards:
Apply all relevant local disposal regulations to determine the safe disposal.

Safety data sheet available for professional user on request.

Reagent handling

Ready for use

Carefully invert reagent container several times prior to use to ensure that the reagent components are mixed.

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Storage and stability

Shelf life at 2-8 °C:	See expiration date on **cobas c** pack label
On-board in use and refrigerated on the analyzer:	2 weeks
On-board on the Reagent Manager:	24 hours

Do not freeze.

Specimen collection and preparation

Only the specimens listed below were tested and found acceptable.

Urine: Collect urine samples in clean glass or plastic containers. Fresh urine specimens do not require any special handling or pretreatment, but an effort should be made to keep pipetted samples free of gross debris. Samples should be within the normal physiological pH range of 5-8. No additives or preservatives are required. It is recommended that urine specimens be stored at 2-8 °C and tested within 5 days of collection.[19]

For prolonged storage, freezing of the sample is recommended.[19]

Freeze only once.

Centrifuge highly turbid specimens before testing.

See the limitations and interferences section for details about possible sample interferences.

Adulteration or dilution of the sample can cause erroneous results. If adulteration is suspected, another sample should be collected. Specimen validity testing is required for specimens collected under the *Mandatory Guidelines for Federal Workplace Drug Testing Programs*[20].

CAUTION: Specimen dilutions should only be used to interpret results of Calc.? and Samp.? alarms, or when estimating concentration in preparation for GC-MS. Dilution results are not intended for patient values. Dilution procedures, when used, should be validated.

Materials provided

See “Reagents – working solutions” section for reagents.

Materials required (but not provided)

See “Order information” section

General laboratory equipment

Assay

For optimum performance of the assay follow the directions given in this document for the analyzer concerned. Refer to the appropriate operator’s manual for analyzer-specific assay instructions.

The performance of applications not validated by Roche is not warranted and must be defined by the user.

Application for urine

Deselect Automatic Rerun for these applications in the Utility menu, Application screen, Range tab.

cobas c 701/702 **test definition**

	Semiquantitative		Qualitative
Assay type	2-Point End		2-Point End
Reaction time / Assay points	10 / 10-30		10 / 10-30
Wavelength (sub/main)	– /546 nm		– /546 nm
Reaction direction	Increase		Increase
Unit	ng/mL		mAbs
Reagent pipetting			Diluent (H_2O)
R1	90 µL		–
R2	40 µL		–
Sample volumes	*Sample*	*Sample dilution*	
		Sample	Diluent (H_2O)
Normal	2.0 µL	–	–
Decreased	2.0 µL	–	–
Increased	2.0 µL	–	–

Calibration

Semiquantitative application

Calibrators	*300 ng/mL cutoff assay* S1-5: Preciset DAT Plus I, CAL 1-5 0, 150, 300, 600, 2000 ng/mL
Calibration mode	Result Calculation Mode (RCM) [a)]
Calibration frequency	Full calibration - after reagent lot change - as required following quality control procedures

a) See Result section.

Qualitative application

Calibrators	*300 ng/mL cutoff assay* S1: C.f.a.s. DAT Qualitative Plus, C.f.a.s. DAT Qualitative Plus Clinical, or Preciset DAT Plus I, CAL 3 300 ng/mL
Cutoff Calibrator	Enter the value “0” without decimal place for the Std (1) concentration into the Calibration menu, Install screen, Edit Calibrator window
Calibration K factor	Enter the K factor as -1000 into the Calibration menu, Status screen, Calibration Result window.
Calibration mode	Linear
Calibration frequency	Blank calibration - after reagent lot change - as required following quality control procedures

The drug concentrations of the calibrators have been verified by GC-MS.

Calibration interval may be extended based on acceptable verification of calibration by the laboratory.

Traceability: These methods have been standardized against a primary reference method (GC-MS).

Quality control

For quality control, use control materials as listed in the "Order information" section.

In addition, other suitable control material can be used.

Drug concentrations of Control Set DAT I and Clinical have been verified by GC-MS.

The control intervals and limits should be adapted to each laboratory’s individual requirements. Values obtained should fall within the defined limits. Each laboratory should establish corrective measures to be taken if values fall outside the defined limits.

Follow the applicable government regulations and local guidelines for quality control.

Results

For the qualitative assay, the cutoff calibrator is used as a reference in distinguishing between preliminary positive and negative samples. Samples producing a positive or “0” absorbance value are considered preliminary positive. Preliminary positive samples are flagged with >Test. Samples producing a negative absorbance value are considered negative. Negative samples are preceded by a minus sign.

For the semiquantitative assay, the analyzer computer constructs a calibration curve from absorbance measurements of the standards using a 4 parameter logit-log fitting function (RCM). The logit-log function fits a smooth line through the data points. The analyzer computer uses absorbance measurements of samples to calculate drug or drug metabolite concentration by interpolation of the logit-log fitting function.

NOTE: If a result of Calc.? or Samp.? alarm is obtained, review the Reaction Monitor data for the sample and compare with the Reaction Monitor data for the highest calibrator. The most likely cause is a high

concentration of the analyte in the sample, in which case the absorbance value for the sample will be less than that of the highest calibrator. Make an appropriate dilution of the sample using the 0 ng/mL calibrator and rerun the sample. A normal drug-free urine may be substituted for the 0 ng/mL calibrator if the urine and procedure have been validated by the laboratory. To ensure that the sample was not over-diluted, the diluted result, prior to multiplying by the dilution factor, must be at least half the analyte cutoff value. If the diluted result falls below half the analyte cutoff value, repeat the sample with a smaller dilution. A dilution that produces a result closest to the analyte cutoff is the most accurate estimation. To estimate the preliminary positive sample's concentration, multiply the result by the appropriate dilution factor. Dilutions should only be used to interpret results of Calc.? and Samp.? alarms, or when estimating concentration in preparation for GC-MS.

Use caution when reporting results as there are various factors that influence a urine test result, such as fluid intake and other biological factors.

As with any sensitive test for drugs of abuse on automated clinical chemistry analyzers, the possibility exists for analyte carry-over from a sample with an extremely high concentration to a normal (negative) sample which immediately follows it.

Preliminary positive results should be confirmed by another method.

For the semiquantitative applications **cobas c** systems automatically calculate the drug or metabolite concentration of each sample in the unit ng/mL. Results equal to or greater than the respective cutoff value are considered preliminary positive. Concentration values below the respective cutoff indicate a negative result.

Limitations - interference

See the "Specific performance data" section of this document for information on substances tested with this assay. There is the possibility that other substances and/or factors may interfere with the test and cause erroneous results (e.g., technical or procedural errors).

A preliminary positive result with this assay indicates the presence of methadone and/or its metabolites in urine. It does not measure the level of intoxication.

For diagnostic purposes, the results should always be assessed in conjunction with the patient's medical history, clinical examination and other findings.

Interfering substances were added to drug free urine at the concentration listed below. These samples were then spiked to 300 ng/mL using a methadone stock solution. Samples were tested on a Roche/Hitachi 917 analyzer and the following results were obtained:

Substance	Concentration Tested	% Methadone Recovery
Acetone	1 %	111
Ascorbic acid	1.5 %	104
Bilirubin	0.25 mg/mL	92
Creatinine	5 mg/mL	104
Ethanol	1 %	108
Glucose	2 %	108
Hemoglobin	7.5 g/L	112
Human albumin	0.5 %	109
Oxalic acid	2 mg/mL	104
Sodium chloride	0.5 M	100
Sodium chloride	1 M	98
Urea	6 %	107

In very rare cases, gammopathy, in particular type IgM (Waldenström's macroglobulinemia), may cause unreliable results.[21]

ACTION REQUIRED

Special Wash Programming: The use of special wash steps is mandatory when certain test combinations are run together on **cobas c** systems. All special wash programming necessary for avoiding carry-over is available via the **cobas** link, manual input is required in certain cases. The latest version of the carry-over evasion list can be found with the NaOHD/SMS/SmpCln1+2/SCCS Method Sheet and for further instructions refer to the operator's manual.

Where required, special wash/carry-over evasion programming must be implemented prior to reporting results with this test.

Expected values

Qualitative assay

Results of this assay distinguish preliminary positive (≥ 300 ng/mL) from negative samples only. The amount of drug detected in a preliminary positive sample cannot be estimated.

Semiquantitative assay

Results of this assay yield only approximate cumulative concentrations of the drug and its metabolites (see Analytical specificity section).

Specific performance data

Representative performance data on the analyzers are given below. These data represent the performance of the analytical procedure itself. Results obtained in individual laboratories may differ due to heterogenous sample materials, aging of analyzer components and mixture of reagents running on the analyzer.

Precision

Precision was determined in an internal protocol by running a series of calibrator and controls (repeatability n = 21, intermediate precision n = 100). The following results were obtained on the **cobas c** 701 analyzer:

Semiquantitative precision

Repeatability	*Mean ng/mL*	*SD ng/mL*	*CV %*
Level 1	230	8	3.3
Level 2	322	7	2.0
Level 3	410	9	2.2
Intermediate precision	*Mean ng/mL*	*SD ng/mL*	*CV %*
Level 1	236	7	2.9
Level 2	308	11	3.5
Level 3	395	10	2.5

Qualitative precision

Cutoff (300)	Number tested	Correct results	Confidence level
0.75x	105	105	> 95 % negative reading
1.25x	105	105	> 95 % positive reading

Results for intermediate precision were obtained on the **cobas c** 501 analyzer.

The data obtained on **cobas c** 501 analyzer(s) are representative for **cobas c** 701 analyzer(s).

Accuracy

100 urine samples, obtained from a clinical laboratory where they screened negative in a drug test panel, were evaluated with the Methadone II assay. 100 % of these normal urines were negative relative to a 300 ng/mL cutoff. 55 samples obtained from a clinical laboratory, where they screened preliminary positive with a commercially available immunoassay and were subsequently confirmed by GC-MS, were evaluated with the Methadone II assay. 100 % of these samples were positive relative to a 300 ng/mL cutoff. In addition, 10 samples were diluted to a methadone concentration of 75-100 % of the cutoff concentration; and 10 samples were diluted to a methadone concentration of 100-125 % of the cutoff concentration. Data from the accuracy studies described above that fell within the near cutoff value ranges were combined with data generated from the diluted positive urine samples. The following results were obtained with the Methadone II assay on the Roche/Hitachi 917 analyzer relative to the GC-MS values.

Methadone II Clinical Correlation (Cutoff = 300 ng/mL)					
		Negative Samples	GC-MS values (ng/mL)		
			Near Cutoff		470-10410
			225-241	310-375	
Roche/Hitachi 917 analyzer	+	0	0	10	55
	-	100	10	0	0

Additional clinical samples were evaluated with this assay on a **cobas c** 701 analyzer and a **cobas c** 501 analyzer. 100 urine samples that screened negative were evaluated with the Methadone II assay. 100 % of these normal urines were negative relative to the **cobas c** 501 analyzer. 50 urine samples that screened preliminary positive were evaluated with the Methadone II assay. 100 % of the samples were positive on both the **cobas c** 701 analyzer and the **cobas c** 501 analyzer.

Methadone II Correlation (Cutoff = 300 ng/mL)			
		cobas c 501 analyzer	
		+	-
cobas c 701 analyzer	+	50	0
	-	0	100

Analytical specificity

The specificity of this assay for structurally similar compounds was determined by generating inhibition curves for each of the compounds listed and determining the approximate quantity of each compound that is equivalent in assay reactivity to a 300 ng/mL assay cutoff. Caution should be taken when interpreting results of patient samples containing structurally related compounds having greater than 0.5 % cross-reactivity. The following results were obtained on Roche/Hitachi 917 and **cobas c** analyzers.

Compound[b])	**ng/mL Equivalent to 300 ng/mL Methadone**	**Approximate % Cross-reactivity**
Hydroxymethadone	3289	9.1
Vortioxetine	7339	4.1
LuAA34443	2622	11
Cyamemazine	8477	3.5
Methotrimeprazine (Levomepromazine)	8939	3.4
Chlorpromazine	26071	1.2
Thiothixene	39267	0.8
Clomipramine	135747	0.2
Promazine	142857	0.2
Thioridazine	146341	0.2
Chlorprothixene	186335	0.2
l-α-methadol	220588	0.1
Promethazine	288462	0.1
l-α-acetylmethadol (LAAM)	370370	0.1
Trimipramine	422535	0.1

b) Indented compounds are metabolites of the preceding drug.

Additionally, the following compounds were tested at a concentration of 100000 ng/mL in pooled normal human urine and shown to have cross-reactivity values of less than 0.05 %.

Amitriptyline
Benzphetamine
Carbamazepine
Chlorpheniramine
Cyclobenzaprine
Cyproheptadine
Desipramine
Dextromethorphan
Diphenhydramine
Disopyramide
Doxepin
Doxylamine
EDDP (2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine)
EMDP (2-ethyl-5-methyl-3,3-diphenylpyrroline)
Fluoxetine
Imipramine
Maprotiline
Meperidine
Mianserin
Nordoxepin
Nortriptyline
Orphenadrine
Perphenazine
d-Propoxyphene
Protriptyline
d,l-Verapamil

The cross-reactivity for Disopyramide at a concentration of 1 mg/mL was tested with the Methadone II assay.The result obtained was < 0.01 %.Specimens from Seroquel (quetiapine fumarate) users have screened positive for methadone.

Drug interference

The following compounds were added to aliquots of pooled normal human urine at a concentration of 100000 ng/mL. None of these compounds gave values in the assay that were equal to or greater than 0.2 % cross-reactivity, and no results were greater than the assay cutoff (300 ng/mL). The following results were obtained on a Roche/Hitachi 917 analyzer.

Acetaminophen
Acetylsalicylic acid
Aminopyrine
Amobarbital
d-Amphetamine
l-Amphetamine
Ampicillin
Ascorbic acid
Aspartame
Atropine
Benzocaine
Benzoylecgonine
(cocaine metabolite)
Butabarbital
Caffeine
Calcium hypochlorite
Chlordiazepoxide
Chloroquine
Cocaine
Codeine
Cotinine
Diazepam
Diphenylhydantoin
Dopamine
Ecgonine
Ecgonine methyl ester
d-Ephedrine
d,l-Ephedrine
l-Ephedrine
Epinephrine
Erythromycin
Lidocaine
LSD
MDA
MDMA
Melanin
d-Methamphetamine
l-Methamphetamine
Methaqualone
Methylphenidate
Methyprylon
Morphine sulfate
Naloxone
Naltrexone
Naproxen
Niacinamide
Nicotine
Nordiazepam
Norethindrone
l-Norpseudoephedrine
Oxazepam
Penicillin G
Pentobarbital
Phencyclidine
β-Phenethylamine
Phenobarbital
Phenothiazine
Phentermine
Phenylbutazone
Phenylpropanolamine
d-Phenylpropanolamine
Procaine

Estriol	*d*-Pseudoephedrine
Fenoprofen	*l*-Pseudoephedrine
Furosemide	Quinidine
Gentisic acid	Quinine
Glutethimide	Secobarbital
Guaiacol glycerol ether	Sulindac
Haloperidol	Tetracycline
Hydrochlorothiazide	Δ^9 THC-9-carboxylic acid
Ibuprofen	Tetrahydrozoline
Isoproterenol	Trifluoperazine
Ketamine	Tyramine

The cross-reactivity for Tramadol, at a concentration of 102465 ng/mL, is 0.3 %.
The cross-reactivity for Ofloxacin, at a concentration of 220000 ng/mL, is 0.1 %.

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A point (period/stop) is always used in this Method Sheet as the decimal separator to mark the border between the integral and the fractional parts of a decimal numeral. Separators for thousands are not used.

Any serious incident that has occurred in relation to the device shall be reported to the manufacturer and the competent authority of the Member State in which the user and/or the patient is established.

Symbols

Roche Diagnostics uses the following symbols and signs in addition to those listed in the ISO 15223-1 standard:

	Contents of kit
	Volume for reconstitution
	Global Trade Item Number
Rx only	For USA: Caution: Federal law restricts this device to sale by or on the order of a physician.

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