MDN2

cobas®

ONLINE DAT Methadone II

Order information

REF	CONTENT		Analyzer(s) on which **cobas c** pack(s) can be used
04490851 190	ONLINE DAT Methadone II (200 tests)	System-ID 07 6948 7	Roche/Hitachi **cobas c** 311, **cobas c** 501/502

Materials required (but not provided):

03304671 190	Preciset DAT Plus I calibrators CAL 1-6 (6 x 5 mL)	Codes 431-436	
03304698 190	C.f.a.s. DAT Qualitative Plus (6 x 5 mL)		
04590856 190	C.f.a.s. DAT Qualitative Plus Clinical (3 x 5 mL)	Code 699	
03312950 190	Control Set DAT I PreciPos DAT Set I (2 x 10 mL) PreciNeg DAT Set I (2 x 10 mL)		
04500873 190	Control Set DAT Clinical PreciPos DAT Clinical (2 x 10 mL) PreciNeg DAT Clinical (2 x 10 mL)		

English

System information

For **cobas c** 311/501 analyzers:

MD3Q0: ACN 447 (Urine): for qualitative assay

MD3S0: ACN 448 (Urine): for semiquantitative assay

MD3QC: ACN 792 (Urine): for qualitative assay; using C.f.a.s. DAT Qualitative Plus Clinical

For **cobas c** 502 analyzer:

MD3Q0: ACN 8447 (Urine): for qualitative assay

MD3S0: ACN 8448 (Urine): for semiquantitative assay

MD3QC: ACN 8792 (Urine): 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 Roche/Hitachi **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

Methadone is a synthetic diphenylpropylamine used for detoxification and temporary maintenance of narcotic addiction, as well as treatment of acute and chronic pain. Methadone has many of the pharmacologic properties of morphine, and its analgesic potency is similar. Unlike morphine, repeated administration causes marked sedative effects due to drug accumulation in the body. Methadone withdrawal syndrome is qualitatively similar to morphine, yet it differs in that it develops more slowly, is less intense, and is more prolonged.[2] For these reasons, methadone is used in the management of narcotic dependence, hopefully eliminating the need for illicit opiate drugs. Overdoses of methadone are characterized by stupor, respiratory depression, cold and clammy skin, hypotension, coma, and circulatory collapse.[3]

Methadone is given intramuscularly for analgesic purposes and orally for methadone maintenance therapy. Following ingestion, the drug is well absorbed from the gastrointestinal tract and is widely distributed to the liver, lung, kidney, spleen, blood, and urine. The fact that methadone is highly bound to tissue protein may explain its cumulative effects.[4] 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.[5,6] In maintenance 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.[7,8]

Test principle

The assay is based on the kinetic interaction of microparticles in a solution (KIMS)[9,10] 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 urine 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.[11]

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.

For USA: Caution: Federal law restricts this device to sale by or on the order of a physician.

Reagent handling

Ready for use

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

Storage and stability

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

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.[12]

For prolonged storage, freezing of the sample is recommended.

Centrifuge highly turbid specimens before testing.

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

Sample stability claims were established by experimental data by the manufacturer or based on reference literature and only for the temperatures/time frames as stated in the method sheet. It is the responsibility of the individual laboratory to use all available references and/or its own studies to determine specific stability criteria for its laboratory.

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*.[13]

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 311 **test definition**

	Semiquantitative		Qualitative
Assay type	2-Point End		2-Point End
Reaction time / Assay points	10 / 9-35		10 / 9-35
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 (NaCl)
Normal	2.0 µL	–	–
Decreased	2.0 µL	–	–
Increased	2.0 µL	–	–

cobas c 501/502 **test definition**

	Semiquantitative		Qualitative
Assay type	2-Point End		2-Point End
Reaction time / Assay points	10 / 17-44		10 / 17-44
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 (NaCl)
Normal	3.5 µL	–	–
Decreased	3.5 µL	–	–
Increased	3.5 µL	–	–

Calibration

Calibrators	*Semiquantitative application* S1-5: Preciset DAT Plus I calibrators, CAL 1-5 0, 150, 300, 600, 2000 ng/mL *Qualitative application* S1: C.f.a.s. DAT Qualitative Plus, C.f.a.s. DAT Qualitative Plus Clinical, or Preciset DAT Plus I calibrator - CAL 3 300 ng/mL The drug concentrations of the calibrators have been verified by GC-MS.
Calibration K Factor	For the qualitative application, enter the K Factor as -1000 into the Calibration menu, Status screen, Calibration Result window.
Calibration mode	*Semiquantitative application* Result Calculation Mode (RCM)[a)] *Qualitative application* Linear
Calibration frequency	Full (semiquantitative) or blank (qualitative) calibration • after reagent lot change • as required following quality control procedures

a) See Results section.

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

Traceability: This method has 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 the 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.

The semiquantitation of preliminary positive results should only be used by laboratories to determine an appropriate dilution of the specimen for confirmation by a confirmatory method such as GC-MS. It also permits the laboratory to establish quality control procedures and assess control performance.

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.? or 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.

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.

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

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

ACTION REQUIRED

Special Wash Programming: The use of special wash steps is mandatory when certain test combinations are run together on Roche/Hitachi **cobas c** systems. The latest version of the carry-over evasion list can be found with the NaOHD-SMS-SmpCln1+2-SCCS Method Sheets. For further instructions refer to the operator’s manual. **cobas c** 502 analyzer: All special wash programming necessary for avoiding carry-over is available via the **cobas** link, manual input is required in certain cases.

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 a Roche/Hitachi analyzer are given below. Results obtained in individual laboratories may differ.

Precision

Precision was determined in an internal protocol by running a series of calibrator and controls with repeatability (n = 20) and intermediate precision (n = 100). The following results were obtained on a Roche/Hitachi **cobas c** 501 analyzer.

Semiquantitative precision

Repeatability	*Mean* *ng/mL*	*SD* *ng/mL*	*CV* *%*
Level 1	240	5	2.2
Level 2	314	6	1.9
Level 3	388	6	1.5

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	100	100	> 95 % negative reading
1.25x	100	100	> 95 % positive reading

The data obtained on **cobas c** 501 analyzer(s) are representative for **cobas c** 311 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 Roche/Hitachi **cobas c** 501 analyzer and a Roche/Hitachi 917 analyzer. 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 the Roche/Hitachi 917 analyzer. 59 urine 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 the samples were positive on both the Roche/Hitachi **cobas c** 501 analyzer and the Roche/Hitachi 917 analyzer.

Methadone II Correlation (Cutoff = 300 ng/mL)			
		Roche/Hitachi 917 analyzer	
		+	-
cobas c 501 analyzer	+	59	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 a 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
Lu AA34443	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	EMDP (2-ethyl-5-methyl-3,3-diphenylpyrroline)
Benzphetamine	Fluoxetine
Carbamazepine	Imipramine
Chlorpheniramine	Maprotiline
Cyclobenzaprine	Meperidine
Cyproheptadine	Mianserin
Desipramine	Nordoxepin
Dextromethorphan	Nortriptyline
Diphenhydramine	Orphenadrine
Disopyramide	Perphenazine
Doxepin	*d*-Propoxyphene
Doxylamine	Protriptyline
EDDP (2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine)	*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).

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

Ecgonine methyl ester	Phenobarbital
d-Ephedrine	Phenothiazine
d,l-Ephedrine	Phentermine
l-Ephedrine	Phenylbutazone
Epinephrine	Phenylpropanolamine
Erythromycin	*d*-Phenylpropanolamine
Estriol	Procaine
Fenoprofen	*d*-Pseudoephedrine
Furosemide	*l*-Pseudoephedrine
Gentisic acid	Quinidine
Glutethimide	Quinine
Guaiacol glycerol ether	Secobarbital
Haloperidol	Sulindac
Hydrochlorothiazide	Tetracycline
Ibuprofen	Δ^9 THC-9-carboxylic acid
Isoproterenol	Tetrahydrozoline
Ketamine	Trifluoperazine
	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 %.

References

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9 Armbruster DA, Schwarzhoff RH, Pierce BL, et al. Method comparison of EMIT II and ONLINE with RIA for drug screening. J Forensic Sci 1993;38:1326-1341.
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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 (for USA: see dialog.roche.com for definition of symbols used):

CONTENT	Contents of kit
→	Volume after reconstitution or mixing
GTIN	Global Trade Item Number

FOR US CUSTOMERS ONLY: LIMITED WARRANTY

Roche Diagnostics warrants that this product will meet the specifications stated in the labeling when used in accordance with such labeling and will be free from defects in material and workmanship until the expiration date printed on the label. THIS LIMITED WARRANTY IS IN LIEU OF ANY OTHER WARRANTY, EXPRESS OR IMPLIED, INCLUDING ANY IMPLIED WARRANTY OF MERCHANTABILITY OR FITNESS FOR PARTICULAR PURPOSE. IN NO EVENT SHALL ROCHE DIAGNOSTICS BE LIABLE FOR INCIDENTAL, INDIRECT, SPECIAL OR CONSEQUENTIAL DAMAGES.

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