BNZ2

cobas®

ONLINE DAT Benzodiazepines II

Order information

REF		CONTENT		Analyzer(s) on which **cobas c** pack(s) can be used
08056927190	08056927500	ONLINE DAT Benzodiazepines II (850 tests)	System-ID 2028 001	**cobas c** 303, **cobas c** 503, **cobas c** 703

Materials required (but not provided):

Serum/plasma		
03304671190	Preciset DAT Plus I CAL 5 (1 x 5 mL)	Code 20435
07978766190	Serum DAT Control Low (ACQ Partner Channel*)	
07978740190	Serum DAT Control High (ACQ Partner Channel*)	
08063494190	NaCl Diluent 9 % (123 mL)	System-ID 2906 001

*Roche does not hold the product registration for Partner Channels. The legal manufacturer indicated on the kit is solely responsible for all of the design, legal, and regulatory aspects of the product.

Urine		
03304671190	Preciset DAT Plus I CAL 1-6 (6 x 5 mL)	Codes 20431-20436
03304680190	Preciset DAT Plus II CAL 1-6 (6 x 5 mL)	Codes 20437-20442
03304698190	C.f.a.s. DAT Qualitative Plus (6 x 5 mL)	Code 20698
04590856190	C.f.a.s. DAT Qualitative Plus Clinical (3 x 5 mL)	Code 20699
03312950190	Control Set DAT I (for 300 ng/mL assay) PreciPos DAT Set I (2 x 10 mL) PreciNeg DAT Set I (2 x 10 mL)	
03312968190	Control Set DAT II (for 100 ng/mL assay) PreciPos DAT Set II (2 x 10 mL) PreciNeg DAT Set II (2 x 10 mL)	
04500873190	Control Set DAT Clinical (for 100 ng/mL assay) PreciPos DAT Clinical (2 x 10 mL) PreciNeg DAT Clinical (2 x 10 mL)	
03312976190	Control Set DAT III (for 200 ng/mL assay) PreciPos DAT Set III (2 x 10 mL) PreciNeg DAT Set III (2 x 10 mL)	

English

System information

BEQ2S: ACN 20287 (Serum/plasma): for qualitative assay, 200 ng/mL

BZ1Q2: ACN 20280 (Urine): for qualitative assay, 100 ng/mL

BZ2Q2: ACN 20281 (Urine): for qualitative assay, 200 ng/mL

BZ3Q2: ACN 20282 (Urine): for qualitative assay, 300 ng/mL

BZ1S2: ACN 20284 (Urine): for semiquantitative assay, 100 ng/mL

BZ2S2:ACN 20285 (Urine): for semiquantitative assay, 200 ng/mL

BZ3S2: ACN 20286 (Urine): for semiquantitative assay, 300 ng/mL

BZQ1C: ACN 20283 (Urine): for qualitative assay, 100 ng/mL; using C.f.a.s. DAT Qualitative Plus Clinical

BZ3-QP: ACN 20288 (Urine): for qualitative assay, 300 ng/mL; using C.f.a.s. DAT Qualitative Plus

Intended use

Application in urine

Benzodiazepines II (BNZ2) is an in vitro diagnostic test for the qualitative and semiquantitative detection of benzodiazepines in human urine on **cobas c** systems at cutoff concentrations of 100 ng/mL, 200 ng/mL, and 300 ng/mL. Semiquantitative test results may be obtained that permit laboratories to assess assay performance as part of a quality control program. Benzodiazepines 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. Gas chromatography/massspectrometry (GC-MS) or Liquid Chromatography coupled with Tandem Mass Spectrometry (LC-MS/MS) is the preferred confirmatory method.[1,2] Clinical consideration and professional judgment should be applied to any drug of abuse test result, particularly when preliminary positive results are used.

Application in serum and plasma*

**not available in all countries*

ONLINE DAT Benzodiazepines II (BNZ2) is an in vitro diagnostic test for the qualitative detection of benzodiazepines in human serum and plasma on **cobas c** systems at a cutoff concentration of 200 ng/mL.

Benzodiazepines 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. Gas chromatography/mass spectrometry (GC-MS) or Liquid Chromatography coupled with Tandem Mass Spectrometry (LC-MS/MS) is the preferred confirmatory method.[1,2] 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 benzodiazepines with this assay in human serum, plasma and urine is used as an aid in monitoring adherence to treatment in patients who are prescribed benzodiazepines and for presumptive testing of exposure to benzodiazepines in individuals with suspected exposure.

The benzodiazepines constitute a class of versatile and widely prescribed central nervous system (CNS) depressant drugs with medically useful anxiolytic, sedative, hypnotic, muscle relaxant, and anticonvulsant activities.[3] The absorption rates, distribution, metabolism, and elimination rates depend on the benzodiazepine derivatives.[4] The quantitative

differences in their potencies, pharmacodynamic spectra, and pharmacokinetic properties have led to various therapeutic applications.[5] Clinical distinction of short-acting versus long-acting benzodiazepines have been observed in their efficacy, side effect, withdrawal, and dependence potential.[3,6] Pain management centers may perform drug testing for benzodiazepines to aid in monitoring patient adherence to the treatment.[7,8] Benzodiazepines have an increased risk of abuse and dependence because of the development of tolerance, which leads many chronic users to require increasing dosages to achieve similar effects.[5] Benzodiazepine overdoses are frequently associated with co-administration of drugs of other classes. Acute or chronic alcohol ingestion and benzodiazepines co-administered may lead to various significant toxicological interactions. The net effect may be influenced by internal, external, and pharmacokinetic factors.[9] Abuse patterns or prescription use may involve relatively low benzodiazepine doses, as well as high-dose overuse; therefore, proper selection of a cutoff that suits the purpose of the drug testing program is required.[7,10] Benzodiazepines are predominantly excreted in the urine as glucuronides.[3,5,6] The enzymatic hydrolysis of glucuronidated benzodiazepines can increase their cross-reactivities to benzodiazepine immunoassays.[11,12] 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 drugs indicated by a positive screening result may need to be confirmed using a suitable confirmatory technique (e.g., GC-MS or LC-MS).[13,14,15,16]

Test principle

The assay is based on the kinetic interaction of microparticles in a solution (KIMS)[17,18] as measured by changes in light transmission. In the absence of sample drug, free antibody binds to drug-microparticle conjugates causing the formation of particle aggregates that are photometrically detected by turbidity measurements. 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 particle-bound drug derivative for free 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.

The presence of β-glucuronidase enzyme enhances the Benzodiazepines II assay cross-reactivity to some of the glucuronidated metabolites. Enzymatic cleavage makes the benzodiazepine part of the glucuronides more accessible for the antibody.

Reagents - working solutions

R1 Benzodiazepines antibody (sheep polyclonal); buffer; β-glucuronidase enzyme; bovine serum albumin (BSA); 0.09 % sodium azide

R2 Conjugated benzodiazepine derivative microparticles; buffer; 0.09 % sodium azide

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

Precautions and warnings

For in vitro diagnostic use for laboratory 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.

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:	26 weeks

Do not freeze.

Specimen collection and preparation

For specimen collection and preparation only use suitable tubes or collection containers.

Only the specimens listed below were tested and found acceptable.
Serum: Serum tubes with and without separating gel.
Plasma: K_2- or K_3-EDTA, lithium heparin plasma.

The sample types listed were tested with a selection of sample collection tubes that were commercially available at the time of testing, i.e. not all available tubes of all manufacturers were tested. Sample collection systems from various manufacturers may contain differing materials which could affect the test results in some cases. When processing samples in primary tubes (sample collection systems), follow the instructions of the tube manufacturer.

Stability in serum/plasma:

5 days capped at 15-25 °C

14 days capped at 2-8 °C

6 months capped at -20 °C (± 5 °C)

Specimens can be repeatedly frozen and thawed up to 3 times.

Invert thawed specimens several times prior to testing.

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.

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]

Centrifuge highly turbid specimens or samples containing precipitates before performing the assay.

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

CAUTION: Specimen dilutions should only be used to interpret results of Calc.? and Samp.? alarms, or when estimating concentration in preparation for GC-MS or LC-MS/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 serum and plasma

Test definition

	Qualitative
Reporting time	10 min
Wavelength (sub/main)	– /546 nm
Reagent pipetting	
R1	63 µL

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R2	28 µL
Sample volumes	*Sample*
200 ng/mL cutoff	
Normal	3.2 µL
Decreased	3.2 µL
Increased	3.2 µL

Application for urine

	Semiquantitative	Qualitative	
Reporting time	10 min	10 min	
Wavelength (sub/main)	– /546 nm	– /546 nm	
Reagent pipetting		Diluent (H_2O)	
R1	63 µL	–	
R2	28 µL	–	
Sample volumes	*Sample*	*Sample dilution*	
100 and 200 ng/mL cutoffs		*Sample*	*Diluent (NaCl)*
Normal	3.2 µL	–	–
Decreased	3.2 µL	–	–
Increased	3.2 µL	–	–
300 ng/mL cutoff			
Normal	1.4 µL	–	–
Decreased	1.4 µL	–	–
Increased	1.4 µL	–	–

For further information about the assay test definitions refer to the application parameters setting screen of the corresponding analyzer and assay.

Calibration

Serum/plasma

Qualitative application

Calibrator	*200 ng/mL cutoff assay*
	S1: Preciset DAT Plus I, CAL 5
	1000 ng/mL with automatic pre-dilution
Cutoff Calibrator	A value of "0" is encoded in the e-barcode in order to ensure flagging of positive samples with >Test and negative absorbance values for negative samples.
Calibration K factor	The K factor of -1000 is predefined in the application settings.
Calibration mode	Linear
Calibration frequency	Full calibration
	- after reagent lot change
	- as required following quality control procedures

Urine

Semiquantitative applications

Calibrators	*100 and 200 ng/mL cutoff assays*
	S1-6: Preciset DAT Plus II, CAL 1-6
	0, 50, 100, 200, 400, 1000 ng/mL
	300 ng/mL cutoff assay
	S1-6: Preciset DAT Plus I, CAL 1-6
	0, 150, 300, 600, 1000, 3000 ng/mL
Calibration mode	Non-linear
Calibration frequency	Full calibration
	- after reagent lot change
	- every 13 weeks on-board
	- as required following quality control procedures

Qualitative applications

Calibrators	*100 ng/mL cutoff assay*
	S1: Preciset DAT Plus II, CAL 3, 100 ng/mL, S1: C.f.a.s. DAT Qualitative Plus Clinical, 100 ng/mL
	200 ng/mL cutoff assay
	S1: Preciset DAT Plus II, CAL 4, 200 ng/mL
	300 ng/mL cutoff assay
	S1: Preciset DAT Plus I, CAL 3, 300 ng/mL, S1: C.f.a.s. DAT Qualitative Plus, 300 ng/mL
Cutoff Calibrator	A value of "0" is encoded in the e-barcode in order to ensure flagging of positive samples with >Test and negative absorbance values for negative samples.
Calibration K factor	The K factor of -1000 is predefined in the application settings.
Calibration mode	Linear
Calibration frequency	Full calibration
	- after reagent lot change
	- every 13 weeks on-board
	- 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: 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 controls have been verified by GC-MS.

The control intervals and limits should be adapted to each laboratory’s individual requirements. It is recommended to perform quality control always after lot calibration and subsequently at least every 26 weeks.

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 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.

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.

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 or LC-MS/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.

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 benzodiazepines and/or their metabolites in serum or urine. It does not reflect the degree of intoxication.

Serum/plasma

Criterion: No cross-over at initial values of samples of 100 ng/mL and 300 ng/mL (control levels).

Icterus:[21] No significant interference up to an I index of 60 for conjugated and unconjugated bilirubin (approximate conjugated and unconjugated bilirubin concentration: 1026 µmol/L or 60 mg/dL).

Hemolysis:[21] No significant interference up to an H index of 1000 (approximate hemoglobin concentration: 622 µmol/L or 1000 mg/dL).

Lipemia (Intralipid):[21] No significant interference up to an L index of 2000. There is poor correlation between the L index (corresponds to turbidity) and triglycerides concentration.

Rheumatoid factors: No significant interference from rheumatoid factors up to a concentration of 1200 IU/mL.

Immunoglobulins: No significant interference from immunoglobulins up to a concentration of 16 g/L (simulated by human immunoglobulin A), up to a concentration of 70 g/L (simulated by human immunoglobulin G) and up to a concentration of 10 g/L (simulated by human immunoglobulin M).

Albumin: No significant interference from human serum albumin up to a concentration of 70 g/L.

Urine

Interfering substances were added to urine containing nordiazepam at -25 % and +25 % of the cutoff level at the concentration listed below. Samples were tested and the following results were obtained on a Roche/Hitachi 917 analyzer.

Semiquantitative (ng/mL)		**100 ng/mL cutoff**		**200 ng/mL cutoff**		**300 ng/mL cutoff**	
Compound	**Cmpd. conc.**	**Neg level**	**Pos level**	**Neg level**	**Pos level**	**Neg level**	**Pos level**
Acetone	1 %	77 (NEG)	134 (POS)	157 (NEG)	260 (POS)	231 (NEG)	402 (POS)
Ascorbic acid	1.5 %	78 (NEG)	132 (POS)	156 (NEG)	262 (POS)	233 (NEG)	399 (POS)
Conjugated bilirubin	0.25 mg/mL	82 (NEG)	129 (POS)	156 (NEG)	247 (POS)	229 (NEG)	392 (POS)
Creatinine	5 mg/mL	81 (NEG)	138 (POS)	158 (NEG)	259 (POS)	230 (NEG)	396 (POS)
Ethanol	1 %	78 (NEG)	136 (POS)	151 (NEG)	261 (POS)	228 (NEG)	395 (POS)
Glucose	20 mg/mL	81 (NEG)	138 (POS)	158 (NEG)	262 (POS)	236 (NEG)	403 (POS)
Hemoglobin	1 mg/mL	76 (NEG)	139 (POS)	159 (NEG)	261 (POS)	228 (NEG)	398 (POS)
Human serum albumin	5 mg/mL	83 (NEG)	140 (POS)	165 (NEG)	273 (POS)	243 (NEG)	422 (POS)
Oxalic acid	2 mg/mL	74 (NEG)	128 (POS)	151 (NEG)	254 (POS)	226 (NEG)	388 (POS)
Sodium chloride	0.5 M	79 (NEG)	139 (POS)	159 (NEG)	262 (POS)	234 (NEG)	389 (POS)
Urea	6 %	80 (NEG)	138 (POS)	157 (NEG)	261 (POS)	233 (NEG)	405 (POS)

The same experiment was performed in the qualitative mode for each cutoff. All negative and positive samples recovered properly in the presence of the interfering substance.

An additional protocol was executed in which samples containing nordiazepam at control levels (±25 % of cutoff) with specific gravities ranging from 1.006 to 1.034 were tested. As with the other interferences, there were no control cross-overs on any of the 3 assay cutoffs at either extreme specific gravity level.

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

In very rare cases, gammopathy, in particular type IgM (Waldenström's macroglobulinemia), may cause unreliable results.[22]

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. The latest version of the carry-over evasion list can be found with the NaOHD/SMS/SCCS Method Sheet. For further instructions, refer to the operator's manual.

Expected values

Serum/plasma

Qualitative assay

Results of this assay distinguish preliminary positive (≥ 200 ng/mL) from negative samples only. The amount of drug detected in a preliminary positive sample cannot be estimated.

Urine

Qualitative assay

Results of this assay distinguish preliminary positive (≥ 100 ng/mL, ≥ 200 ng/mL, or ≥ 300 ng/mL depending on the cutoff) 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

Serum/plasma

Precision was determined using human samples and controls in accordance with the CLSI (Clinical and Laboratory Standards Institute) EP05-A3 requirements with repeatability (n = 84) and intermediate precision

(2 aliquots per run, 2 runs per day, 21 days). Results for repeatability and intermediate precision were obtained on the **cobas c** 503 analyzer.

Cutoff (200)	Number tested	Correct results	Confidence level
Serum -75 %	84	84	> 95 % negative reading
ACQ-L	84	84	> 95 % negative reading
Cutoff serum	84	n.a.**	n.a.**
ACQ-H	84	84	> 95 % positive reading
Serum +75 %	84	84	> 95 % positive reading

**n.a. = not applicable

The data obtained on **cobas c** 503 analyzer(s) are representative for **cobas c** 303 analyzer(s) and **cobas c** 703 analyzer(s).

Urine

Precision was determined using human samples and controls in accordance with the CLSI (Clinical and Laboratory Standards Institute) EP05-A3 requirements with repeatability (n = 84) and intermediate precision (2 aliquots per run, 2 runs per day, 21 days). Results for repeatability and intermediate precision were obtained on the **cobas c** 503 analyzer.

Semiquantitative precision - 100 ng/mL cutoff

Repeatability	*Mean ng/mL*	*SD ng/mL*	*CV %*
Urine -50 %	49.5	3.30	6.7
DATCN	79.5	3.10	3.9
DAT2N	80.0	3.51	4.4
Cutoff urine	105	3.68	3.5
DAT2P	129	3.38	2.6
DATCP	128	3.51	2.7
Urine +50 %	153	2.98	1.9

Intermediate precision	*Mean ng/mL*	*SD ng/mL*	*CV %*
Urine -50 %	49.5	4.00	8.1
DATCN	79.5	4.09	5.1
DAT2N	80.0	4.28	5.4
Cutoff urine	105	4.82	4.6
DAT2P	129	4.37	3.4
DATCP	128	4.31	3.4
Urine +50 %	153	4.58	3.0

Qualitative precision - 100 ng/mL cutoff

Cutoff (100)	Number tested	Correct results	Confidence level
Urine -50 %	84	84	> 95 % negative reading
DATCN	84	84	> 95 % negative reading
DAT2N	84	84	> 95 % negative reading
Cutoff urine	84	n.a.*	n.a.*
DAT2P	84	84	> 95 % positive reading
DATCP	84	84	> 95 % positive reading
Urine +50 %	84	84	> 95 % positive reading

*n.a. = not applicable

Semiquantitative precision - 200 ng/mL cutoff

Repeatability	*Mean ng/mL*	*SD ng/mL*	*CV %*
Urine -50 %	104	2.49	2.4
DAT3N	152	3.78	2.5
Cutoff urine	200	2.94	1.5
DAT3P	249	3.61	1.4
Urine +50 %	308	2.52	0.8

Intermediate precision	*Mean ng/mL*	*SD ng/mL*	*CV %*
Urine -50 %	104	4.20	4.0
DAT3N	152	4.31	2.8
Cutoff urine	200	5.85	2.9
DAT3P	249	3.94	1.6
Urine +50 %	308	3.71	1.2

Qualitative precision - 200 ng/mL cutoff

Cutoff (200)	Number tested	Correct results	Confidence level
Urine -50 %	84	84	> 95 % negative reading
DAT3N	84	84	> 95 % negative reading
Cutoff urine	84	n.a.*	n.a.*
DAT3P	84	84	> 95 % positive reading
Urine +50 %	84	84	> 95 % positive reading

*n.a. = not applicable

Semiquantitative precision - 300 ng/mL cutoff

Repeatability	*Mean ng/mL*	*SD ng/mL*	*CV %*
Urine -50 %	150	7.03	4.7
DAT1N	231	8.04	3.5
Cutoff urine	345	7.59	2.2
DAT1P	375	7.66	2.0
Urine +50 %	435	8.89	2.0

Intermediate precision	*Mean ng/mL*	*SD ng/mL*	*CV %*
Urine -50 %	150	10.5	7.0
DAT1N	231	10.0	4.3
Cutoff urine	345	10.6	3.1
DAT1P	375	9.26	2.5
Urine +50 %	435	11.7	2.7

Qualitative precision - 300 ng/mL cutoff

Cutoff (300)	Number tested	Correct results	Confidence level
Urine -50 %	84	84	> 95 % negative reading
DAT1N	84	84	> 95 % negative reading
Cutoff urine	84	n.a.*	n.a.*
DAT1P	84	84	> 95 % positive reading
Urine +50 %	84	84	> 95 % positive reading

*n.a. = not applicable

The data obtained on **cobas c** 503 analyzer(s) are representative for **cobas c** 303 analyzer(s) and **cobas c** 703 analyzer(s).

Accuracy

Serum/plasma

109 serum samples, partly obtained from a clinical laboratory where they screened negative in a drug test panel, were evaluated with the Benzodiazepines II assay. 100 % of these normal serum samples were negative relative to the 200 ng/mL cutoff.

55 samples obtained from a clinical laboratory, where they screened preliminary positive with a commercially available immunoassay, were evaluated with the Benzodiazepines II assay. 100 % of these samples were positive relative to the 200 ng/mL cutoff.

The following results were obtained with the Benzodiazepines II assay on the **cobas c** 501 analyzer relative to the **cobas c** 503 analyzer.

Benzodiazepines II correlation (cutoff = 200 ng/mL)			
		cobas c 501 analyzer	
		+	-
cobas c 503 analyzer	+	55	0
	-	0	109

110 serum samples, partly obtained from a clinical laboratory where they screened negative in a drug test panel, were evaluated with the Benzodiazepines II assay. 100 % of these normal serum samples were negative relative to the 200 ng/mL cutoff.

54 samples obtained from a clinical laboratory, where they screened preliminary positive with a commercially available immunoassay, were evaluated with the Benzodiazepines II assay. 100 % of these samples were positive relative to the 200 ng/mL cutoff.

The following results were obtained with the Benzodiazepines II assay on the **cobas c** 501 analyzer relative to the **cobas c** 303 analyzer.

Benzodiazepines II correlation (cutoff = 200 ng/mL)			
		cobas c 501 analyzer	
		+	-
cobas c 303 analyzer	+	54	0
	-	0	110

110 serum samples, partly obtained from a clinical laboratory where they screened negative in a drug test panel, were evaluated with the Benzodiazepines II assay. 100 % of these normal serum samples were negative relative to the 200 ng/mL cutoff.

55 samples obtained from a clinical laboratory, where they screened preliminary positive with a commercially available immunoassay, were evaluated with the Benzodiazepines II assay. 100 % of these samples were positive relative to the 200 ng/mL cutoff.

The following results were obtained with the Benzodiazepines II assay on the **cobas c** 503 analyzer relative to the **cobas c** 703 analyzer.

Benzodiazepines II correlation (cutoff = 200 ng/mL)			
		cobas c 503 analyzer	
		+	-
cobas c 703 analyzer	+	55	0
	-	0	110

Urine

Additional clinical samples were evaluated with this assay on a **cobas c** 503 analyzer and on a **cobas c** 501 analyzer. 104 urine samples screened negative in a drug test panel, were evaluated with the Benzodiazepines II assay. 100 % of these normal urines were negative for all cutoffs relative to the **cobas c** 503 analyzer. 76 urine samples for the 100 ng/mL cutoff, 68 urine samples for the 200 ng/mL cutoff and 51 urine samples for the 300 ng/mL cutoff, screened preliminary positive with a commercially available immunoassay and subsequently confirmed by GC-MS, were evaluated with the Benzodiazepines II assay. At the 100 ng/mL, 200 ng/mL and 300 ng/mL cutoffs, 100 % of the samples were positive on both the **cobas c** 501 analyzer and the **cobas c** 503 analyzer.

Benzodiazepines II correlation (cutoff = 100 ng/mL)			
		cobas c 501 analyzer	
		+	-
cobas c 503 analyzer	+	76	0
	-	0	104

Benzodiazepines II correlation (cutoff = 200 ng/mL)			
		cobas c 501 analyzer	
		+	-
cobas c 503 analyzer	+	68	0
	-	0	104

Benzodiazepines II correlation (cutoff = 300 ng/mL)			
		cobas c 501 analyzer	
		+	-
cobas c 503 analyzer	+	51	0
	-	0	104

Additional clinical samples were evaluated with this assay on a **cobas c** 303 analyzer and on a **cobas c** 501 analyzer. 110 urine samples screened negative in a drug test panel, were evaluated with the Benzodiazepines II assay. 100 % of these normal urines were negative for all cutoffs relative to the **cobas c** 303 analyzer. 55 urine samples for the 100 ng/mL cutoff, 55 urine samples for the 200 ng/mL cutoff and 55 urine samples for the 300 ng/mL cutoff, screened preliminary positive with a commercially available immunoassay and subsequently confirmed by GC-MS, were evaluated with the Benzodiazepines II assay. At the 100 ng/mL, 200 ng/mL and 300 ng/mL cutoffs, 100 % of the samples were positive on both the **cobas c** 501 analyzer and the **cobas c** 303 analyzer.

Benzodiazepines II correlation (cutoff = 100 ng/mL)			
		cobas c 501 analyzer	
		+	-
cobas c 303 analyzer	+	55	0
	-	0	110

Benzodiazepines II correlation (cutoff = 200 ng/mL)			
		cobas c 501 analyzer	
		+	-
cobas c 303 analyzer	+	55	0
	-	0	110

Benzodiazepines II correlation (cutoff = 300 ng/mL)			
		cobas c 501 analyzer	
		+	-
cobas c 303 analyzer	+	55	0
	-	0	110

Additional clinical samples were evaluated with this assay on a **cobas c** 703 analyzer and on a **cobas c** 503 analyzer. 110 urine samples screened negative in a drug test panel, were evaluated with the Benzodiazepines II assay. 100 % of these normal urines were negative for all cutoffs relative to the **cobas c** 703 analyzer. 73 urine samples for the 100 ng/mL cutoff, 66 urine samples for the 200 ng/mL cutoff and 63 urine samples for the 300 ng/mL cutoff, screened preliminary positive with a commercially available immunoassay and subsequently confirmed by GC-MS, were evaluated with the Benzodiazepines II assay. At the 100 ng/mL, 200 ng/mL and 300 ng/mL cutoffs, 100 % of the samples were positive on both the **cobas c** 503 analyzer and the **cobas c** 703 analyzer.

Benzodiazepines II correlation (cutoff = 100 ng/mL)		
	cobas c 503 analyzer	
	+	-

cobas c 703 analyzer	+	73	0
	-	0	110

Benzodiazepines II correlation (cutoff = 200 ng/mL)			
		cobas c 503 analyzer	
		+	-
cobas c 703 analyzer	+	66	0
	-	0	110

Benzodiazepines II correlation (cutoff = 300 ng/mL)			
		cobas c 503 analyzer	
		+	-
cobas c 703 analyzer	+	63	0
	-	0	110

Analytical specificity

Serum/plasma

The specificity of the Benzodiazepines II assay for various benzodiazepines and benzodiazepine metabolites 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 200 ng/mL nordiazepam assay cutoff. The following results were obtained on a **cobas c** 501 analyzer.

Compound[a)]	**ng/mL Equivalent to 200 ng/mL nordiazepam**	**Approximate % cross-reactivity**
Alprazolam	154	130
α-OH-Alprazolam	196	102
4-OH-Alprazolam	259	77
Bromazepam	140	143
Buspirone	> 100000	n.d.
Chlordiazepoxide hydrochloride	336	60
Norchlordiazepoxide	415	48
Clobazam	170	118
Clonazepam	211	95
7-Aminoclonazepam	220	91
Clorazepate dipotassium	302	66
Delorazepam	200	100
Demoxepam	154	130
Diazepam	144	139
Estazolam	177	113
Flunitrazepam	184	109
3-OH-Desmethylflunitrazepam	367	55
3-OH-Flunitrazepam	241	83
Desmethylflunitrazepam	191	105
7-Acetamido-3OH-desmethyl-flunitrazepam	> 100000	n.d.
7-Acetamido-3OH-flunitrazepam	> 100000	n.d.
7-Acetamidoflunitrazepam	39684	0.5
7-Amino-3OH-desmethylflunitrazepam	872	23
7-Amino-3OH-flunitrazepam	211	95
7-Aminodesmethylflunitrazepam	161	124
7-Aminoflunitrazepam	156	128
Flurazepam dihydrochloride	209	96
Desalkylflurazepam	162	123
Didesethylflurazepam hydrochloride	125	160
2-Hydroxyethylflurazepam	173	116
Halazepam	194	103
Lorazepam	194	103
Lormetazepam	209	96
Medazepam hydrochloride	184	109
Desmethylmedazepam	287	70
Midazolam	165	121
α-OH-Midazolam	195	103
Nitrazepam	153	131
7-Aminonitrazepam	184	109
Oxaprozin	10610	1.89
Oxazepam	173	116
Phenazepam	222	90
Pinazepam	150	133
Prazepam	168	119
Temazepam	157	127
Tetrazepam	177	113
Triazolam	180	111
α-OH-Triazolam	208	96
4-OH-Triazolam	193	104
Zopiclone	> 100000	n.d.

n.d. = not detectable

a) Indented compounds are metabolites of the preceding drug.

Urine

The specificity of the Benzodiazepines II assay for various benzodiazepines and benzodiazepine metabolites 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 100 ng/mL, 200 ng/mL, and 300 ng/mL nordiazepam assay cutoff. The following results were obtained on Roche/Hitachi and **cobas c** analyzers.

Compound[a)]	**ng/mL Equivalent to 100 ng/mL nordiazepam**	**Approx. % cross-reactivity**
Deschloroetizolam	80	125
Flubromazepam	94	107
3-OH-Flubromazepam	126	79
Clonazolam	96	104
Pyrazolam	105	95
Diclazepam	118	85
Flubromazolam	119	84
Etizolam	122	82
Meclonazepam	132	76
Nifoxipam	157	64
Bentazepam	173	58
Estazolam	93	107
Bromazepam	101	99
Nitrazepam	104	96
7-Aminonitrazepam	71	141

7-Acetamidonitrazepam	16909	0.59
Oxazepam	105	95
Oxazepam glucuronide	234	43
Phenazepam	112	89
Alprazolam	113	89
α-Hydroxyalprazolam	115	87
4-Hydroxyalprazolam	117	86
Demoxepam	114	88
Clorazepate	115	87
Clobazam	122	82
Diazepam	128	78
Nordiazepam	101	99
Delorazepam	131	76
Temazepam	133	75
Temazepam glucuronide	302	33
Triazolam	136	74
α-Hydroxytriazolam	145	69
Flunitrazepam	136	73
7-Aminoflunitrazepam	109	92
Desmethylflunitrazepam	114	88
Lormetazepam	138	73
Brotiazolam	144	70
Clonazepam	152	66
7-Aminoclonazepam	107	94
Lorazepam	153	65
Lorazepam glucuronide	275	36
Chlordiazepoxide	156	64
Desmethylchlordiazepoxide	138	73
Norchlordiazepoxide	150	67
Pinazepam	160	63
Flurazepam	164	61
Desalkylflurazepam	106	95
Hydroxyethylflurazepam	127	79
Didesethylflurazepam	144	70
Desmethylmedazepam	168	59
Halazepam	187	53
Midazolam	190	53
α-Hydroxymidazolam	125	80
Prazepam	194	51
Nimetazepam	1045	10
Oxaprozin	2283	4
Zolpidem	106383	0.09

a) Indented compounds are metabolites of the preceding drug.

Compound[a)]	**ng/mL Equivalent to 200 ng/mL nordiazepam**	**Approx. % cross-reactivity**
Deschloroetizolam	159	126
Flubromazepam	180	111
3-OH-Flubromazepam	246	81
Clonazolam	185	108
Pyrazolam	188	106
Flubromazolam	221	91
Diclazepam	225	89
Etizolam	234	86
Meclonazepam	329	61
Bentazepam	376	53
Nifoxipam	391	51
Estazolam	197	101
Bromazepam	208	96
Oxazepam	224	89
Oxazepam glucuronide	506	40
Clorazepate	227	88
Phenazepam	230	87
Alprazolam	236	85
α-Hydroxyalprazolam	241	83
4-Hydroxyalprazolam	246	81
Nitrazepam	243	82
7-Aminonitrazepam	159	126
7-Acetamidonitrazepam	55488	0.36
Demoxepam	253	79
Clobazam	256	78
Diazepam	258	78
Nordiazepam	204	98
Delorazepam	258	77
Triazolam	279	72
α-Hydroxytriazolam	287	70
Temazepam	282	71
Temazepam glucuronide	647	31
Flunitrazepam	284	70
7-Aminoflunitrazepam	244	82
Desmethylflunitrazepam	248	81
Lormetazepam	284	70
Brotiazolam	292	68
Clonazepam	318	63
7-Aminoclonazepam	232	86
Flurazepam	333	60
Desalkylflurazepam	225	89
Hydroxyethylflurazepam	259	77
Didesethylflurazepam	297	67
Lorazepam	335	60
Lorazepam glucuronide	584	34
Midazolam	343	58
α-Hydroxymidazolam	253	79
Halazepam	354	56
Pinazepam	364	55
Chlordiazepoxide	371	54
Desmethylchlordiazepoxide	313	64

Norchlordiazepoxide	360	56
Prazepam	408	49
Desmethylmedazepam	422	47
Nimetazepam	2191	9
Oxaprozin	7500	3
Zolpidem	206186	0.10

a) Indented compounds are metabolites of the preceding drug.

Compound[a)]	ng/mL Equivalent to 300 ng/mL nordiazepam	Approx. % cross-reactivity
Deschloroetizolam	242	124
Flubromazepam	274	110
3-OH-Flubromazepam	358	84
Pyrazolam	279	107
Clonazolam	290	103
Diclazepam	346	87
Etizolam	343	88
Flubromazolam	351	85
Meclonazepam	424	71
Bentazepam	504	60
Nifoxipam	552	54
Bromazepam	299	100
Estazolam	303	99
Oxazepam	325	92
Oxazepam glucuronide	684	44
Phenazepam	346	87
Demoxepam	352	85
Nitrazepam	354	85
7-Aminonitrazepam	218	138
7-Acetamidonitrazepam	55328	0.54
Alprazolam	372	81
4-Hydroxyalprazolam	342	88
α-Hydroxyalprazolam	347	86
Clorazepate	374	80
Clobazam	386	78
Delorazepam	389	77
Diazepam	400	75
Nordiazepam	316	95
Lormetazepam	410	73
Temazepam	416	72
Temazepam glucuronide	923	33
Triazolam	425	71
α-Hydroxytriazolam	440	68
Flunitrazepam	439	68
Desmethylflunitrazepam	338	89
7-Aminoflunitrazepam	368	82
Brotiazolam	464	65
Clonazepam	483	62
7-Aminoclonazepam	334	90
Chlordiazepoxide	499	60
Desmethylchlordiazepoxide	452	66
Norchlordiazepoxide	483	62
Lorazepam	506	59
Lorazepam glucuronide	825	36
Flurazepam	511	59
Desalkylflurazepam	336	89
Hydroxyethylflurazepam	394	76
Didesethylflurazepam	458	65
Desmethylmedazepam	539	56
Midazolam	564	53
α-Hydroxymidazolam	428	70
Pinazepam	572	52
Halazepam	595	50
Prazepam	637	47
Nimetazepam	3247	9
Oxaprozin	7507	4
Zolpidem	200000	0.15

a) Indented compounds are metabolites of the preceding drug.

Many benzodiazepines appear in the urine and serum largely as the glucuronidated conjugate. Glucuronidated metabolites may have more or less cross-reactivity than the parent compound. The presence of β-glucuronidase enzyme enhances the Benzodiazepines II assay cross-reactivity to some of the glucuronidated metabolites.

Drug interference

Serum/plasma

Interfering substances were added to serum containing nordiazepam at -50 % and +50 % of the cutoff level at the concentration listed below. Samples were tested and the following results were obtained on a **cobas c** 501 analyzer.

Compound	Compd. conc. mg/L	Neg. level	Pos. level
Acetaminophen	200	neg	pos
Acetylcysteine	1660	neg	pos
Acetylsalicylic acid	1000	neg	pos
Amitriptyline	1.00	neg	pos
Ampicillin-Na	1000	neg	pos
Ascorbic acid	300	neg	pos
Caffeine	59.8	neg	pos
Cefoxitin	2500	neg	pos
Cyclosporine	5.00	neg	pos
d-Amphetamine	1.36	neg	pos
Doxycycline	50.0	neg	pos
d-Pseudoephedrine	9.98	neg	pos
Erythromycin	59.9	neg	pos
Fenoprofen	195	neg	pos
Furosemide	59.9	neg	pos
Gentisic acid	18.0	neg	pos
Heparin	5000 U/L	neg	pos
Hydrochlorothiazide	6.02	neg	pos
Ibuprofen	500	neg	pos

Imipramine	0.70	neg	pos
Ketamine	10.0	neg	pos
l-Amphetamine	1.00	neg	pos
Levodopa	20.0	neg	pos
Lidocaine	12.0	neg	pos
Methyldopa + 1.5 H_2O	20.0	neg	pos
Metronidazole	200	neg	pos
Naproxen	499	neg	pos
Phenylbutazone	400	neg	pos
Procaine	39.9	neg	pos
Promethazine	1.20	neg	pos
Quinidine	12.0	neg	pos
Quinine	48.0	neg	pos
Rifampicin	60.0	neg	pos
Tetracycline	15.1	neg	pos
Theophylline	100	neg	pos
Trifluoperazine hydrochloride	1.00	neg	pos

Urine

The following compounds were prepared in aliquots of pooled normal human urine to yield a final concentration of 100000 ng/mL. None of these compounds gave values in the assay that were greater than 0.08 % cross-reactivity for the 100 ng/mL and 200 ng/mL cutoffs and 0.13 % cross-reactivity for the 300 ng/mL cutoff.

Acetaminophen	Imipramine
Acetylsalicylic acid	Isoproterenol
Amitriptyline	Ketamine
Amobarbital	Lidocaine
d-Amphetamine	LSD
l-Amphetamine	MDA
Ampicillin	MDMA
Ascorbic acid	Melanin
Aspartame	Meperidine
Atropine	Methadone
Benzocaine	*d*-Methamphetamine
Benzoylecgonine (cocaine metabolite)	*l*-Methamphetamine
Benzphetamine	Methaqualone
Buspirone	Methylphenidate
Butabarbital	Methyprylon
Caffeine	Morphine sulfate
Calcium hypochlorite	Naloxone
Cannabidiol	Naltrexone
Captopril	Naproxen
Chloroquine	Niacinamide
Chlorpheniramine	Nicotine
Chlorpromazine	Norethindrone
Cocaine	*l*-Norpseudoephedrine
Codeine	Omeprazole
Desipramine HCl	Penicillin G
Dextromethorphan	Pentazocine
Dextropropoxyphene	Pentobarbital
Digoxin	Phencyclidine
Diphenhydramine	Phenobarbital
Diphenylhydantoin	Phenothiazine
Doxepin	Phenylbutazone
Ecgonine	*d,l*-Phenylpropanolamine
Ecgonine methyl ester	Procaine
Enalapril	Promethazine
d-Ephedrine	*d*-Pseudoephedrine
l-Ephedrine	Quinidine
Epinephrine	Quinine
Erythromycin	Secobarbital
Estriol	Sulindac
Fenoprofen	Tetracycline
Flumazenil	Δ^9 THC-9-carboxylic acid
Furosemide	Tetrahydrozoline
Gentisic acid	Thioridazine
Glutethimide	Tolmetin
Guaiacol glycerol ether	Trifluoperazine
Hydrochlorothiazide	Trimipramine
Hydroxyindole acetic acid	Tyramine
Hydroxyindole carboxylic acid	Verapamil
Ibuprofen	Zomepirac

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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:

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

CE 0123

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