

## Order information

REF	CONTENT	Analizers on which <b>cobas c</b> pack can be used
<b>20737984</b> 122	Abuscreen OnLine Benzodiazepines (200 tests)	System-ID 07 3798 4 COBAS INTEGRA 400 plus COBAS INTEGRA 800
<b>03304671</b> 190	Preciset DAT Plus I CAL 1-6 (6 × 5 mL)	
<b>03304680</b> 190	Preciset DAT Plus II CAL 1-6 (6 × 5 mL)	
<b>03304698</b> 190	C.f.a.s. DAT Qualitative Plus (6 × 5 mL)	
<b>04590856</b> 190	C.f.a.s. DAT Qualitative Plus Clinical (3 × 5 mL)	
<b>03312968</b> 190	Control Set DAT II (for 100 ng/mL assay) PreciPos DAT Set II (2 × 10 mL) PreciNeg DAT Set II (2 × 10 mL)	
<b>04500873</b> 190	Control Set DAT Clinical (for 100 ng/mL assay) PreciPos DAT Clinical (2 × 10 mL) PreciNeg DAT Clinical (2 × 10 mL)	
<b>03312976</b> 190	Control Set DAT III (for 200 ng/mL assay) PreciPos DAT Set III (2 × 10 mL) PreciNeg DAT Set III (2 × 10 mL)	
<b>03312950</b> 190	Control Set DAT I (for 300 ng/mL assay) PreciPos DAT Set I (2 × 10 mL) PreciNeg DAT Set I (2 × 10 mL)	

## English

## System information

Test BENZS, test-ID 0-319 for semiquantitative assay, 100 ng/mL  
 Test BZ1QL, test-ID 0-320 for qualitative assay, 100 ng/mL  
 Test BZ2QL, test-ID 0-420 for qualitative assay, 200 ng/mL  
 Test BZ3QL, test-ID 0-520 for qualitative assay, 300 ng/mL  
 Test BZ1QC, test-ID 0-220 for qualitative assay, 100 ng/mL; using C.f.a.s. DAT Qualitative Plus Clinical

## Intended use

Benzodiazepines (BENZ) is an in vitro diagnostic test for the semiquantitative detection of benzodiazepines in human urine at a cutoff concentration of 100 ng/mL and the qualitative detection of benzodiazepines in human urine at cutoff concentrations of 100 ng/mL, 200 ng/mL, and 300 ng/mL on COBAS INTEGRA systems. 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).

**Benzodiazepines 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.<sup>1</sup> Clinical consideration and professional judgement should be applied to any drug of abuse test result, particularly when preliminary positive results are used.**

## Summary

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.<sup>1,2,3,4,5</sup> The absorption rates, distribution, metabolism, and elimination rates differ significantly among the benzodiazepine derivatives. The quantitative differences in their potencies, pharmacodynamic spectra, and pharmacokinetic properties have led to various therapeutic applications. Clinical distinction of short-acting versus long-acting benzodiazepines have been observed in their efficacy, side effect, withdrawal, and dependence potential.<sup>2,6,7</sup> The extensive and efficacious therapeutic use of the benzodiazepines over the last several decades has inadvertently led to their misuse. Benzodiazepine overdoses are frequently associated with co-administration of drugs of other classes.<sup>8,9</sup> 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. Abuse patterns may involve relatively low benzodiazepine doses, as well as high-dose overuse; therefore, urinary drug/metabolite detection requires the proper selection of a cutoff that suits the requirements of the drug testing program.

Following ingestion, the benzodiazepines of the 1,4-substituted class (including the triazolobenzodiazepine derivatives) are absorbed, metabolized, and excreted in the urine at different rates as a variety of structurally related metabolites. Metabolite diversity reflects the different physiochemical properties and metabolic pathways of the individual drugs. Overall metabolic similarities include removal of substituents from the β ring of the 1,4-substituted benzodiazepines, α-hydroxylation of the triazolobenzodiazepines, demethylation, hydroxylation of the three-position carbon of the β ring, and conjugation of hydroxylated metabolites followed by urinary excretion predominantly as glucuronides.<sup>1,2,3,4,5</sup>

## Test principle

Kinetic interaction of microparticles in a solution (KIMS)<sup>10,11</sup> 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. 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 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.

## Reagents - working solutions

Sample Diluent (SD)	Buffer containing stabilizer and 0.09 % sodium azide.
Antibody Reagent (AB)	Benzodiazepines antibody (sheep polyclonal) in buffer and 0.09 % sodium azide.
Microparticle Reagent (MP)	Conjugated benzodiazepine derivative microparticles in buffer and 0.09 % sodium azide.

SD is in position A, AB is in position B and MP is in position C.

## Pipetting Sequence

COBAS INTEGRA 400 plus analyzer	R1 = AB R2 = SD R3 (SR) = MP
COBAS INTEGRA 800 analyzer	R1 = SD

R2 = AB

R3 (SR) = MP

 Postdilution factor 10 recommended<sup>a)</sup> No  
 Calc. first/last 49/69 49/69

Unit ng/mL

a) For use when estimating concentration in preparation for GC/MS analysis.

**Precautions and warnings**

Pay attention to all precautions and warnings listed in Section 1 / Introduction of this Method Manual.

For USA: For prescription use only.

**Reagent handling**

COBAS INTEGRA 400 plus analyzer

Mix all new (non-punctured) **cobas c** packs for 1 minute on a cassette mixer before loading on the analyzer. All in-use **cobas c** packs must also be mixed in the same manner at the beginning of each week (once a week).

COBAS INTEGRA 800 analyzer

Ready for use. After **cobas c** pack puncture, the analyzer automatically mixes the reagent for 1 minute and for half a minute during Begin of Day.

**Storage and stability**

Shelf life at 2-8 °C:

 See expiration date on  
**cobas c** pack label

COBAS INTEGRA 400 plus analyzer

On-board in use at 10-15 °C

28 days

COBAS INTEGRA 800 analyzer

On-board in use at 8 °C

59 days

Do not freeze reagents. Reagents that have been frozen should be discarded.

**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.<sup>12</sup>

For prolonged storage, freezing of the sample is recommended.

Centrifuge highly turbid specimens before testing.

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*.<sup>13</sup>

**Caution:** Specimen dilutions should only be used as an estimation for GC/MS and are not intended for patient values. Dilution procedures, when used, should be validated.

**Materials provided**

See "Reagents – working solutions" section for reagents.

**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.

**Application for urine****COBAS INTEGRA 400 plus test definition**

	<i>Semiquantitative</i>	<i>Qualitative</i>
Measuring mode	Absorbance	Absorbance
Abs. calculation mode	Endpoint	Endpoint
Reaction mode	R1-R2-S-SR	R1-R2-S-SR
Reaction direction	Increase	Increase
Reaction start	SR	SR
Wavelength A	520 nm	520 nm
Test range	0-200 ng/mL	0-2000
with postdilution	0-2000 ng/mL	

**Pipetting parameters***BENZS, BZ1QL, BZ1QC (100 ng/mL cutoff)*

		Diluent (H <sub>2</sub> O)
R1	52 µL	9 µL
R2	46 µL	11 µL
Sample	9.5 µL	15 µL
SR	15 µL	8 µL
Total volume	165.5 µL	

*BZ2QL (200 ng/mL cutoff)*

		Diluent (H <sub>2</sub> O)
R1	53 µL	10 µL
R2	47 µL	11 µL
Sample	5.5 µL	15 µL
SR	15 µL	8 µL
Total volume	164.5 µL	

*BZ3QL (300 ng/mL cutoff)*

		Diluent (H <sub>2</sub> O)
R1	53 µL	10 µL
R2	47 µL	11 µL
Sample	4.0 µL	15 µL
SR	15 µL	10 µL
Total volume	165.0 µL	

**COBAS INTEGRA 800 test definition**

	<i>Semiquantitative</i>	<i>Qualitative</i>
Measuring mode	Absorbance	Absorbance
Abs. calculation mode	Endpoint	Endpoint
Reaction mode	R1-R2-S-SR	R1-R2-S-SR
Reaction direction	Increase	Increase
Reaction start	SR	SR
Wavelength A	520 nm	520 nm
Test range	0-200 ng/mL	0-2000
with postdilution	0-2000 ng/mL	
Postdilution factor	10 recommended <sup>b)</sup>	No
Calc. first/last	44/78	44/78
Unit	ng/mL	

b) For use when estimating concentration in preparation for GC/MS analysis.

**Pipetting parameters***BENZS, BZ1QL, BZ1QC (100 ng/mL cutoff)*

		Diluent (H <sub>2</sub> O)
R1	40 µL	6 µL
R2	53 µL	6 µL
Sample	9.5 µL	10 µL
SR	15 µL	8 µL
Total volume	147.5 µL	

**BZ2QL (200 ng/mL cutoff)**

		Diluent (H <sub>2</sub> O)
R1	40 µL	6 µL
R2	53 µL	6 µL
Sample	5.5 µL	10 µL
SR	15 µL	8 µL
Total volume	143.5 µL	

**BZ3QL (300 ng/mL cutoff)**

		Diluent (H <sub>2</sub> O)
R1	40 µL	6 µL
R2	53 µL	6 µL
Sample	4.0 µL	10 µL
SR	15 µL	8 µL
Total volume	142.0 µL	

**Calibration**

Calibrators	<i>Semiquantitative application</i>
<b>BENZS, 0-319</b>	Preciset DAT Plus II calibrators, CAL 1-4 0, 50, 100, 200 ng/mL nordiazepam (100 cutoff, DATS7, system-ID 07 6795 6)
	<i>Qualitative applications</i>
<b>BZ1QL, 0-320</b>	Preciset DAT Plus II calibrators, CAL 1 0 ng/mL or deionized water and Preciset DAT Plus II calibrators, CAL 3 100 ng/mL (100 cutoff, DATQ3, system-ID 07 6770 0) For qualitative applications, the cutoff of 100 ng/mL is assigned a value of 1000.
<b>BZ2QL, 0-420</b>	Preciset DAT Plus II calibrators, CAL 1 0 ng/mL or deionized water and Preciset DAT Plus II calibrators, CAL 4 200 ng/mL (200 cutoff, DATQ4, system-ID 07 6794 8) For qualitative applications, the cutoff of 200 ng/mL is assigned a value of 1000.
<b>BZ3QL, 0-520</b>	Preciset DAT Plus I calibrators, CAL 1 0 ng/mL or deionized water and C.f.a.s. DAT Qualitative Plus 300 ng/mL (300 cutoff, DATQ1, system-ID 07 6744 1) For qualitative applications, the cutoff of 300 ng/mL is assigned a value of 1000.
<b>BZ1QC, 0-220</b>	Preciset DAT Plus I or II calibrators, CAL 1 0 ng/mL or deionized water and C.f.a.s. DAT Qualitative Plus Clinical 100 ng/mL (100 cutoff, DATQ5, system-ID 07 6880 4) For qualitative applications, the cutoff of 100 ng/mL is assigned a value of 1000.

**Calibration mode***Semiquantitative application*

Linear interpolation

*Qualitative applications*

Linear regression

**Calibration replicate**

Duplicate recommended

**Calibration interval**COBAS INTEGRA 400 plus analyzer:  
Each lot, every 84 days, and as required  
following quality control proceduresCOBAS INTEGRA 800 analyzer:  
Each lot, every 30 days, and as required  
following quality control procedures

A calibration curve is generated using the calibrators. Calibrators must be placed from the highest concentration first to the lowest last on the CAL/QC rack. This curve is retained in memory by the COBAS INTEGRA system and recalled for later use.

Traceability: This method has been standardized against a primary reference method (GC/MS).

**Quality control****Quality control****100 ng/mL cutoff**

Control Set DAT II

PreciPos DAT Set II

(DAT2P, system-ID 07 6771 9)

PreciNeg DAT Set II

(DAT2N, system-ID 07 6772 7)

or

Control Set DAT Clinical

PreciPos DAT Clinical

(DATCP, system-ID 07 6879 0)

PreciNeg DAT Clinical

(DATCN, system-ID 07 6878 2)

**200 ng/mL cutoff**

Control Set DAT III

PreciPos DAT Set III

(DAT3P, system-ID 07 6773 5)

PreciNeg DAT Set III

(DAT3N, system-ID 07 6774 3)

**300 ng/mL cutoff**

Control Set DAT I

PreciPos DAT Set I

(DAT1P, system-ID 07 6753 0)

PreciNeg DAT Set I

(DAT1N, system-ID 07 6754 9)

**Control sequence**

User defined

**Control after calibration**

Recommended

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, II, III, 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**

COBAS INTEGRA systems report results with the following test flags:

**Semiquantitative result reporting****BENZS (100 ng/mL cutoff)**

Flag	COBAS INTEGRA	Value range
No flag	Negative	< 100 ng/mL
<TEST RNG	Negative	< 0 ng/mL
>TEST RNG	Positive	> 200 ng/mL
POS 100	Positive	≥ 100 ng/mL

Value ranges listed above are based on a cutoff value of 100 ng/mL.

**Qualitative result reporting****BZ1QL, BZ1QC (100 ng/mL cutoff)**

Flag	COBAS INTEGRA	Value range
No flag	Negative	< 1000
<TEST RNG	Negative	< 0
>TEST RNG	Positive	> 2000
POS 1000	Positive	≥ 1000

Value ranges above are based on assigning the cutoff of 100 ng/mL a value of 1000.

**BZ2QL (200 ng/mL cutoff)**

Flag	COBAS INTEGRA	Value range
No flag	Negative	< 1000
<TEST RNG	Negative	< 0
>TEST RNG	Positive	> 2000
POS 1000	Positive	≥ 1000

Value ranges above are based on assigning the cutoff of 200 ng/mL a value of 1000.

**BZ3QL (300 ng/mL cutoff)**

Flag	COBAS INTEGRA	Value range
No flag	Negative	< 1000
<TEST RNG	Negative	< 0
>TEST RNG	Positive	> 2000
POS 1000	Positive	≥ 1000

Value ranges above are based on assigning the cutoff of 300 ng/mL a value of 1000.

**Semiquantitative result reporting**

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:** When using the post-dilution function (1:10 dilution), to ensure the sample was not over-diluted, the diluted result must be at least half the analyte cutoff value times 10. If the diluted result falls below half the analyte cutoff value times 10, 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 as an estimation for GC/MS.

**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 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.

**ACTION REQUIRED**

**Special Wash Programming:** The use of special wash steps is mandatory when certain test combinations are run together on COBAS INTEGRA analyzers. Refer to the CLEAN Method Sheet for further instructions and for the latest version of the Extra wash cycle list.

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

**Specific performance data**

Representative performance data on the COBAS INTEGRA analyzers are given below. Results obtained in individual laboratories may differ.

**Precision**

Precision was determined in an internal protocol by using a series of nordiazepam controls in replicates of 40, once a day, for 5 days. The following results were obtained on a COBAS INTEGRA 700 analyzer.

**Semiquantitative precision (100 ng/mL cutoff)**

Repeatability	Mean ng/mL	SD ng/mL	CV %
Level 1	49	3.4	7.1
Level 2	80	3.4	4.3
Level 3	101	4.4	4.4
Level 4	126	5.6	4.4

Intermediate precision	Mean ng/mL	SD ng/mL	CV %
Level 1	49	3.7	7.6
Level 2	80	4.1	5.1
Level 3	101	5.7	5.6
Level 4	126	6.9	5.5

**Qualitative precision****100 ng/mL cutoff; 200 ng/mL cutoff; 300 ng/mL cutoff**

Cutoff (x)	Number tested	Correct results	Confidence level
0.8x	200	200	> 95 % negative reading
1.2x	200	200	> 95 % positive reading

**Lower detection limit of the test**

5.0 ng/mL

The lower detection limit represents the lowest measurable analyte level that can be distinguished from zero. It is calculated as the value lying 2 standard deviations above that of the zero calibrator (zero calibrator + 2 SD, repeatability, n = 40).

**Accuracy**

100 urine samples, obtained from a clinical laboratory where they screened negative in a drug test panel by another technology, were evaluated for benzodiazepines on the COBAS INTEGRA systems. All 100 clinical samples were negative relative to the 100 ng/mL cutoff.

50 urine samples, obtained from clinical laboratories where they screened preliminary positive by a commercially available enzyme immunoassay and confirmed positive for benzodiazepines by GC/MS, were also evaluated on a COBAS INTEGRA 700 analyzer. All 50 samples were positive with the COBAS INTEGRA Benzodiazepines assay relative to the 100 ng/mL cutoff, 49 samples were positive relative to the 200 ng/mL cutoff, and 46 samples were positive relative to the 300 ng/mL cutoff.

**100 ng/mL cutoff**

		GC/MS	
		+	-
COBAS INTEGRA 700 analyzer	+	50	0
	-	0	0

## 200 ng/mL cutoff

		GC/MS	
		+	-
COBAS INTEGRA 700 analyzer	+	49	0
	-	1	0

## 300 ng/mL cutoff

		GC/MS	
		+	-
COBAS INTEGRA 700 analyzer	+	46	0
	-	4	0

**Analytical specificity**

The specificity of the COBAS INTEGRA Benzodiazepines assay 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 the 100 ng/mL nordiazepam assay cutoff.

Compound <sup>c)</sup>	Approximate ng/mL equivalent to 100 ng/mL of nordiazepam	Approximate percent cross-reactivity
Flubromazepam	72	139
3-OH-Flubromazepam	130	77
Deschloroetizolam	73	136
Clonazepam	88	114
Flubromazolam	97	103
Diclazepam	99	101
Pyrazolam	101	99
Etizolam	121	83
Bentazepam	253	39
Meclonazepam	847	12
Nifoxipam	536	19
Alprazolam	74	135
α-Hydroxyalprazolam	101	99
4-Hydroxyalprazolam	123	81
Diazepam	79	127
N-Methyloxazepam	172	58
Oxazepam	188	53
Triazolam	113	88
α-Hydroxytriazolam	120	84
Pinazepam	115	87
Flurazepam	116	86
Hydroxyethylflurazepam	108	93
Didesethylflurazepam	147	68
Desalkylflurazepam	192	52
Midazolam	124	81
Clorazepate K <sup>+</sup> salt	127	79
Bromazepam	129	78
Prazepam	145	69
Nitrazepam	149	67
7-Aminonitrazepam	282	35

Compound <sup>c)</sup>	Approximate ng/mL equivalent to 100 ng/mL of nordiazepam	Approximate percent cross-reactivity
7-Acetamidonitrazepam	115740	0.1
Demoxepam	168	59
Flunitrazepam	170	59
Desmethyflunitrazepam	188	53
3-Hydroxyflunitrazepam	819	12
Clonazepam	178	56
Chlordiazepoxide	221	45
Desmethylchlordiazepoxide	338	30
Lorazepam	228	44
Medazepam	292	34
Desmethylmedazepam	427	23

c) Indented compounds are metabolites of the preceding drug.

Many benzodiazepines appear in the urine largely as the glucuronidated conjugate. Glucuronidated metabolites may have more or less cross-reactivity than the parent compound.

**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 0.5 % cross reactivity.

Acetaminophen	Isoproterenol
Acetylsalicylic acid	Ketamine
Aminopyrine	Lidocaine
Amitriptyline	LSD
Amobarbital	MDA
d-Amphetamine	MDMA
l-Amphetamine	Melanin
Ampicillin	Meperidine
Ascorbic acid	Methadone
Aspartame	d-Methamphetamine
Atropine	l-Methamphetamine
Benzocaine	Methaqualone
Benzoyllecgonine	Methylphenidate
(cocaine metabolite)	Methypylon
Benzphetamine	Morphine
Butabarbital	Naloxone
Caffeine	Naltrexone
Calcium hypochlorite	Naproxen
Chloroquine	Niacinamide
Chlorpheniramine	Norethindrone
Chlorpromazine	l-Norpseudoephedrine
Cocaine	Penicillin G
Codeine	Pentazocine
Dextromethorphan	Pentobarbital
Dextropropoxyphene	Phencyclidine
Diphenhydramine	β-Phenethylamine
Diphenylhydantoin	Phenobarbital
Dopamine	Phenothiazine

Ecgonine	Phenylbutazone
Ecgonine methyl ester	Phenylpropanolamine
<i>d</i> -Ephedrine	Procaine
<i>l</i> -Ephedrine	Promethazine
Erythromycin	Pseudoephedrine
Estriol	Quinidine
Fenoprofen	Quinine
Flumazenil	Secobarbital
Furosemide	Sulindac
Gentisic acid	Tetracycline
Glutethimide	$\Delta^9$ THC-9-carboxylic acid
Guaiacol glycerol ether	Tetrahydrozoline
Hydrochlorothiazide	Trifluoperazine
<i>p</i> -Hydroxyamphetamine	Tyramine
Ibuprofen	Verapamil
Imipramine	Zopiclone

Any modification of the instrument as set force in this labeling requires validation by the laboratory.

#### References

- 1 Karch SB, ed. Drug Abuse Handbook. Boca Raton, FL: CRC Press LLC 1998.
- 2 Hardman JG, Limbird LE, Gilman A, eds. Goodman and Gilman's The Pharmacological Basis of Therapeutics. 10th ed. New York, NY: McGraw Hill Pub Co. 2001.
- 3 Baselt RC. Disposition of Toxic Drugs and Chemicals in Man. 7th ed. Foster City, CA: Biomedical Publications 2004.
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- 8 Abernethy DR, Greenblatt DJ, Ochs HR, et al. Benzodiazepine drug-drug interactions commonly occurring in clinical practice. Curr Med Res Opin 1984;8:80-93.
- 9 Tanaka E. Toxicological interactions between alcohol and benzodiazepines. J Toxicol Clin Toxicol 2002;40:69-75.
- 10 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.
- 11 Beck O, Lin Z, Brodin K, et al. The online screening technique for urinary benzodiazepines: comparison with EMIT, FPIA, and GC-MS. J Anal Toxicology 1997;21(7):554-557.
- 12 Toxicology and Drug Testing in the Clinical Laboratory; Approved Guideline. 2nd ed. (C52-A2). Clinical and Laboratory Standards Institute 2007;27:33.
- 13 Mandatory Guidelines for Federal Workplace Drug Testing Programs. Fed Regist 2008 Nov 25;73:71858-71907.

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.

#### Symbols

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

CONTENT



GTIN

Contents of kit

Volume after reconstitution or mixing

Global Trade Item Number

#### FOR US CUSTOMERS ONLY: LIMITED WARRANTY

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