MPA

cobas®

Mycophenolic Acid

Order information

REF	CONTENT		Analyzer(s) on which **cobas c** pack(s) can be used
04357213 190	Mycophenolic Acid (100 tests)	System-ID 07 6823 5	Roche/Hitachi **cobas c** 311, **cobas c** 501/502
04357221 190	Total MPA Calibrators A-F (1 x 5 mL) Diluent (1 x 10 mL)	System-ID 07 6824 3 Codes 490-495	
04357230 190	Total MPA Controls Level I (2 x 5 mL) Level II (2 x 5 mL) Level III (2 x 5 mL)	 Code 107 Code 108 Code 109	

English

System information

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

TMPA: ACN 623

For **cobas c** 502 analyzer:

TMPA: ACN 8623

Intended use

In vitro test for the quantitative determination of total mycophenolic acid in serum or plasma as an aid in the management of mycophenolic acid therapy in renal and cardiac transplant patients on Roche/Hitachi **cobas c** systems.

Summary

Mycophenolic acid is prescribed as mycophenolate mofetil (MMF), a morpholino ester, or as mycophenolate sodium. The MMF prodrug is rapidly metabolized to the active compound, MPA, via cleavage of the ester linkage.[1] MPA inhibits de novo purine biosynthesis by the reversible, noncompetitive inhibition of inosine monophosphate dehydrogenase (IMPDH-II).[1,2] The inhibition of IMPDH-II in activated lymphocytes reduces intracellular guanine nucleotide pools, thus arresting lymphocyte proliferation.[3,4]

MPA is metabolized in the liver by glucuronidation at the phenolic hydroxyl group to the pharmacologically inactive mycophenolic acid glucuronide (MPAG). Plasma levels of MPAG are approximately 40-fold higher than those of the parent drug.[5,6] In addition to the primary metabolite, two additional metabolites of MPA have been identified, the acyl glucuronide (Ac-MPAG) and the phenolic glucoside of MPA. Of these two, only the acyl glucuronide is able to inhibit IMPDH-II in vitro.[1]

Growing clinical evidence indicates that therapeutic drug monitoring of MPA can maximize the therapeutic benefit of the drug and minimize its adverse effects.[7,8,9,10,11] It is generally co-administered with calcineurin inhibitors (cyclosporine or tacrolimus) and, more recently, other immunosuppressants including sirolimus.[7,12]

Peak levels of MPA in plasma occur approximately 1 to 2 hours after oral dosing. A secondary peak then occurs 6 to 12 hours after dosing due to enterohepatic recirculation of the drug. The pharmacokinetics of MPA exhibit wide between-patient variability and may be altered in specific patient populations due to concomitant disease states or interactions with other immunosuppressants.[13,14,15] Cyclosporine inhibits the transport of MPAG from hepatocytes into bile, resulting in decreased enterohepatic recirculation.[15] Thus, in comparison to tacrolimus coadministration, MPA plasma levels may be reduced with coadministration of cyclosporine. Due to the variability in patient plasma MPA levels, monitoring MPA levels may help to optimize outcomes in patients with high risks of organ rejection after transplantation.[12,16]

Test principle

The Roche Total MPA assay is a two-reagent system containing IMP (inosine monophosphate), NAD (nicotinamide adenine dinucleotide), and a mutant IMPDH II (inosine monophosphate dehydrogenase) enzyme. The reagents used to measure MPA concentrations in serum or plasma mimic the in vivo mechanism of the enzyme. In vivo, IMPDH II combines with IMP and NAD to form a complex. The NAD is reduced to form NADH, and IMP is converted to XMP. The NADH leaves the enzyme first. When MPA is present, the XMP is not released from the enzyme.

In the Roche Total MPA assay, a fixed amount of mutant IMPDH in the reagent combines with fixed amounts of IMP and NAD in the reagents. The formation of NADH is measured at 340 nm. When MPA is present in the serum or plasma sample, the formation of NADH by the reagents is inhibited, as measured by a decrease in the signal at 340 nm. MPA concentration is inversely proportional to the rate of NADH formation. The reaction has been optimized for a non-linear, six-point calibration.

Reagents - working solutions

R1	IMPDH-II in buffer: 15.7 U/L; IMP: 4.8 mmol/L; stabilizer; preservative
R2	NAD: 10 mmol/L in buffer; stabilizer; preservative.

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

Precautions and warnings

For in vitro diagnostic use.
Exercise the normal precautions required for handling all laboratory reagents.
Disposal of all waste material should be in accordance with local guidelines.
Safety data sheet available for professional user on request.

For USA: For prescription use only.

Reagent handling

Ready for use

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:	12 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: Collect serum using standard sampling tubes.
Plasma: K_2- and K_3-EDTA 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.

Centrifuge samples containing precipitates before performing the assay.

Specimens should be tested within 8 hours of collection if kept at room temperature. If specimens must be stored for later testing, they should be kept at 2 to 8 °C for up to 96 hours or at -20 °C or below for up to 11 months.[15,17] Specimens should not be repeatedly frozen and thawed (do not exceed 5 freeze/thaw cycles).

Invert thawed specimens several times prior to testing.

Materials provided

See “Reagents – working solutions” section for reagents.

Materials required (but not provided)

See “Order information” section

General laboratory equipment

MPA

Mycophenolic Acid

cobas®

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

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

cobas c 311 **test definition**

Assay type	Rate-A		
Reaction time / Assay points	10 / 40-57		
Wavelength (sub/main)	415/340 nm		
Reaction direction	Increase		
Unit	µg/mL		
Reagent pipetting		Diluent (H_2O)	
R1	180 µL	–	
R2	19 µL	–	
Sample volumes	*Sample*	*Sample dilution*	
		Sample	*Diluent (NaCl)*
Normal	3.0 µL	–	–
Decreased	3.0 µL	–	–
Increased	3.0 µL	–	–

cobas c 501/502 **test definition**

Assay type	Rate-A		
Reaction time / Assay points	10 / 54-70		
Wavelength (sub/main)	415/340 nm		
Reaction direction	Increase		
Unit	µg/mL		
Reagent pipetting		Diluent (H_2O)	
R1	180 µL	–	
R2	19 µL	–	
Sample volumes	*Sample*	*Sample dilution*	
		Sample	*Diluent (NaCl)*
Normal	3.0 µL	–	–
Decreased	3.0 µL	–	–
Increased	3.0 µL	–	–

Calibration

Calibrators	S1-6: Total MPA Calibrators
Calibration mode	RCM
Calibration frequency	6-point calibration - after reagent lot change and every 2 weeks - as required following quality control procedures

Traceability: The Total MPA Calibrators are prepared to contain known quantities of mycophenolic acid in normal human serum and are traceable to a primary reference method (HPLC).

Quality control

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

In addition, other suitable control material can be used.

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.

Calculation

Roche/Hitachi **cobas c** systems automatically calculate the analyte concentration of each sample.

Conversion factor: µg/mL x 3.122 = µmol/L

Limitations - interference

See the Analytical specificity section of this insert for information on substances tested for cross-reactivity in 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). Specimens with assay values greater than the highest calibrator will be flagged by the system and must be repeated after appropriate dilution of the original sample with the zero calibrator or with the diluent from the Total MPA Calibrator kit.

Criterion: Recovery within ± 10 % of initial value at MPA concentrations of approximately 1-5 µg/mL (3.1-15.6 µmol/L) and 8-12 µg/mL (25.0-37.5 µmol/L).

Serum/Plasma

Icterus:[18] No significant interference up to an I index of 66 for conjugated bilirubin and 17 for unconjugated bilirubin (approximate conjugated bilirubin concentration: 1129 µmol/L or 66 mg/dL; approximate unconjugated bilirubin concentration: 291 µmol/L or 17 mg/dL).

Hemolysis:[18] No significant interference up to an H index of 1000 (approximate hemoglobin concentration: 621 µmol/L or 1000 mg/dL).

Lipemia (Intralipid):[18] No significant interference up to an L index of 93. There is poor correlation between the L index (corresponds to turbidity) and triglycerides concentration.

Avoid the use of lipemic specimens.

No significant interference up to a triglycerides level of 500 mg/dL (5.65 mmol/L) with a recovery specification of ± 10 % or 600 mg/dL (6.78 mmol/L) with a recovery specification of ± 15 %.

Total protein: No significant interference from 4-11 g/dL total protein.

Albumin: No significant interference up to 5.4 g/dL albumin.

Gamma globulin: No significant interference up to 6.2 g/dL gamma globulin.

Cholesterol: No significant interference up to 350 mg/dL cholesterol.

Creatinine: No significant interference up to 10 mg/dL creatinine.

Uric acid: No significant interference up to 20 mg/dL uric acid.

There is the possibility that other substances and/or factors may interfere with the test and cause unreliable results.

In very rare cases, gammopathy, in particular type IgM (Waldenström's macroglobulinemia), may cause unreliable results.[19]

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 not required.

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

Limits and ranges

Measuring range

0.4-15 µg/mL (1.2-46.8 µmol/L)

MPA

Mycophenolic Acid

Extended measuring range

Postdilution factor: 5 recommended

0.4-50 µg/mL (1.2-156.1 µmol/L)

Manually dilute samples above the measuring range with the diluent (equivalent to the 0 µg/mL calibrator) from the Roche Total MPA Calibrators (1 part sample + 4 parts diluent) and reassay. Multiply the result by 5 to obtain the specimen value.

Lower limits of measurement

Lower detection limit of the test

0.3 µg/mL (0.9 µmol/L)

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 0 µg/mL calibrator (standard A + 2 SD, repeatability, n = 21).

Functional sensitivity

0.4 µg/mL (1.2 µmol/L)

The functional sensitivity is calculated as the lowest concentration from clinical samples with a CV of ≤ 20 %, tested in triplicate over 10 days (n = 30).

Expected values

The therapeutic range of mycophenolic acid is not yet fully established and is dependent on transplant type and coadministered drugs. Optimal mycophenolic acid assay values to prevent rejection may vary based on the test system and therefore should be established for each test system. Laboratories should include identification of the assay or method used in order to aid in interpretation of the results.

Optimal ranges depend on the patient's clinical state, coadministration of other immunosuppressants, time post-transplant and a number of other factors. Therefore, individual MPA values cannot be used as the sole indicator for making changes in treatment regimen and each patient should be thoroughly evaluated clinically before changes in treatment regimens are made.

Decreased incidences of rejection in the early months post-transplantation have been reported in renal transplant patients with predose MPA concentrations (measured by HPLC) of ≥ 1.3 µg/mL with coadministration of cyclosporine and ≥ 1.9 µg/mL with coadministration of tacrolimus.[12,13] An upper therapeutic range based on development of toxicity has not been established. The clinical ramifications of MPA concentrations beyond the early post transplantation periods are not yet known.[12]

In cardiac transplant patients, predose MPA concentrations (measured by HPLC) of 1.2-3.5 µg/mL have been recommended to minimize incidences of rejection.[7,12] Higher pre-dose concentrations (≥ 2.5 µg/mL) in the early post-transplantation period (< 6 months) have also been suggested.[7,8,20] Pediatric cardiac transplant patients have been shown to require higher doses of MPA in comparison to adults due to differences in MPA metabolism.[7,8,9]

Each laboratory should investigate the transferability of the expected values to its own patient population and if necessary determine its own reference ranges.

Specific performance data

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

Precision

Precision was determined using human samples and controls in accordance with the CLSI (Clinical and Laboratory Standards Institute) EP5 requirements with repeatability (n = 63) and intermediate precision (3 aliquots per run, 1 run per day, 21 days). The following results were obtained on a Roche/Hitachi **cobas c** 501 analyzer.

Serum/Plasma

Repeatability	*Mean*	*SD*	*CV*
	µg/mL (µmol/L)	*µg/mL (µmol/L)*	*%*
Control 1	0.85 (2.65)	0.02 (0.06)	2.4
Control 2	3.46 (10.8)	0.03 (0.1)	0.8
Control 3	12.2 (38.1)	0.1 (0.3)	0.7
HP 1[a]	1.51 (4.71)	0.03 (0.09)	1.9
HP 2[a]	6.22 (19.4)	0.08 (0.3)	1.3
Intermediate precision	*Mean*	*SD*	*CV*
	µg/mL (µmol/L)	*µg/mL (µmol/L)*	*%*
Control 1	0.85 (2.65)	0.03 (0.09)	3.6
Control 2	3.46 (10.8)	0.06 (0.2)	1.6
Control 3	12.2 (38.1)	0.1 (0.4)	1.0
HP 1[a]	1.51 (4.71)	0.04 (0.12)	2.4
HP 2[a]	6.22 (19.4)	0.11 (0.3)	1.8

[a] HP 1 and HP 2 are non-spiked clinical samples

Linearity

To assess the linearity of the assay, an 11-level dilution series was prepared using a mycophenolic acid spiked human plasma pool diluted with a nonspiked pool. Results were calculated by linear regression.

% High sample	Theoretical Value (µg/mL)	Assayed Value (µg/mL)	% Recovery
100	20.4	18.0	88.1
90.0	18.4	16.8	91.2
80.0	16.3	15.3	93.4
70.0	14.3	13.7	95.9
60.0	12.3	12.3	100
50.0	10.2	10.4	102
40.0	8.17	8.29	102
30.0	6.13	6.19	101
20.0	4.08	4.08	99.9
10.0	2.04	1.87	91.6
0	0	0	—

To assess the low end linearity of the assay, an additional 11-level dilution series was prepared using a mycophenolic acid spiked human plasma pool diluted with a nonspiked pool. Results were calculated by linear regression.

% High sample	Theoretical Value (µg/mL)	Assayed Value (µg/mL)	% Recovery
100	5.10	5.11	100
90.0	4.59	4.49	97.8
80.0	4.08	3.94	96.6
70.0	3.57	3.49	97.8
60.0	3.06	2.93	95.8
50.0	2.55	2.41	94.5
40.0	2.04	1.93	94.6
30.0	1.53	1.47	96.1
20.0	1.02	1.02	100
10.0	0.51	0.59	116
0	0	0	—

Method comparison

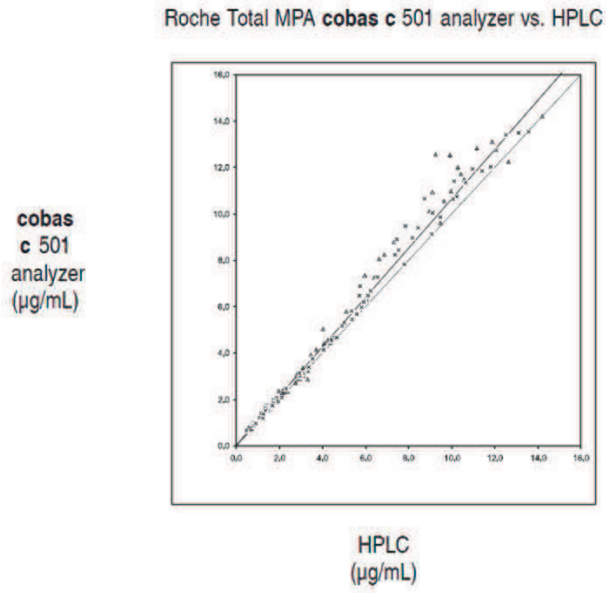
Serum/plasma

Mycophenolic acid values for human plasma samples from renal and cardiac transplant patients were obtained using the **cobas c** 501 analyzer compared to those determined with a validated MPA HPLC method. These same samples were also compared to values obtained on the COBAS INTEGRA 400/800 analyzers. The sample population for this internal study included 88 renal and 70 cardiac samples from post-transplant patients. Other demographics for this sample population are

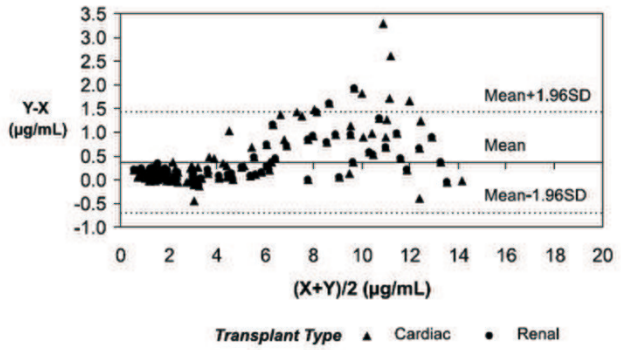
unknown. Passing-Bablok statistics for the correlation are included in the method comparison table below.[21]

Methodology	Slope (95 % CI)	Intercept (95 % CI)	Correlation Coefficient	Sample Size	Sample Range (µg/mL)
cobas c 501 analyzer vs. HPLC					
Renal	1.043 (1.025-1.060)	0.054 (0.010-0.093)	0.997	88	0.460-13.6
Cardiac	1.109 (1.077-1.141)	-0.077 (-0.147-0.005)	0.991	70	0.573-14.2
Combined	1.062 (1.043-1.084)	0.016 (-0.029-0.057)	0.994	158	0.460-14.2
cobas c 501 analyzer vs. COBAS INTEGRA 400 analyzer					
Combined	0.996 (0.990-1.00)	-0.032 (-0.040-(-0.014))	1.000	161	0.44-14.0
cobas c 501 analyzer vs. COBAS INTEGRA 800 analyzer					
Combined	0.977 (0.971-0.984)	0.000 (-0.018-0.014)	0.999	160	0.48-15.0

The following graph shows the correlation testing of the Roche Total MPA assay on the **cobas c** 501 analyzer vs HPLC with the combined renal and cardiac samples from the above table.



The same data set from the regression plot above is depicted in the Bland-Altman difference plot shown below.



N = 158

Mean (Y-X) = 0.36

SD (Y-X) = 0.54

1.96 SD = 1.07

Mean + 1.96 SD = 1.43

Mean – 1.96 SD = - 0.70

In a separate study, mycophenolic acid values for human plasma samples obtained with the Roche Total Mycophenolic Acid assay on COBAS INTEGRA analyzers were compared to those using independent validated MPA HPLC methods. Samples from renal and cardiac transplant patients were tested at two external clinical sites with concurrent HPLC testing at each site.

The external trial included a total of 412 samples collected from post-transplant patients. The sample population for the COBAS INTEGRA 400 plus analyzer study included 265 samples (148 renal and 117 cardiac) from a total of 209 "routine" adult transplant recipients. Samples tested on the COBAS INTEGRA 800 analyzer were obtained from an international trial of renal transplant recipients (147 samples from 86 adult patients). The Passing-Bablok statistics of the correlations are shown in the table below.

Methodology	Slope (95 % CI)	Intercept (95 % CI)	Correlation Coefficient	Sample Size	Sample Range (µg/mL)
COBAS INTEGRA 400 plus analyzer vs. HPLC	1.011 (1.000-1.025)	0.064 (0.038-0.090)	0.993	265	0.4-14.8
COBAS INTEGRA 800 analyzer vs. HPLC	1.100 (1.073-1.120)	-0.120 (-0.192-(-0.066))	0.994	147	0.5-14.7

Analytical specificity

The following cross-reactive substances were evaluated on the **cobas c** 501 analyzer in normal human serum spiked with mycophenolic acid at 1.7 µg/mL (5.3 µmol/L) and 8.0 µg/mL (25.0 µmol/L). Cross-reactivity was designated as "not detectable" (ND) if the obtained value was less than the sensitivity of the assay.

$$\text{Cross-reactivity (\%)} = \frac{100 \times (\text{analytical result} - \text{analyte concentration})}{\text{concentration of interferent}}$$

Drug	Level tested (µg/mL)	Cross-reactivity %
Mycophenolic acid glucuronide (MPAG)	1000	ND

Mycophenolic acid acyl glucuronide (AcMPAG)	10	6.5

The following compounds were tested at the concentrations listed for interference in normal human serum spiked with mycophenolic acid at approximately 1.5 µg/mL (4.7 µmol/L) and 9.0 µg/mL (28.1 µmol/L). No significant interference with the assay was found.

Compound	µg/mL	Compound	µg/mL
Acetaminophen	60	Isoproterenol	0.18
Acyclovir	45	Itraconazole	6
Albuterol	1.2	Kanamycin	180
Allopurinol	120	Ketoconazole	10.5
Alprazolam	6	Labetalol	0.573
Amikacin	105	Lidocaine	36
Amphotericin B	240	Lovastatin	0.036
Ascorbic Acid	120	Methylprednisolone	36
Atenolol	30	Metoclopramide	1.35
Azathioprene	9	Minoxidil	0.921
Bromocriptine	0.75	Misoprostol	0.018
Caffeine	180	Morphine sulfate	1.5
Captopril	15	N-Acetylprocainamide	120
Carbamazepine	90	Nadolol	3.6
Cefaclor	225	Naproxen	500
Ceftriaxone	2430	Niacin	2400
Cephalosporine	0.3	Nicardipine	0.564
Chloramphenicol	150	Nifedipine	1.2
Chloroquine	2.5	Omeprazole	18
Cimetidine	60	Penicillin G	36
Ciprofloxacin	30	Phenobarbital	300
Clonidine	0.03	Phenytoin	150
Colchicine	0.033	Piperacillin	120
Cyclophosphamide	1125	Prazosin	0.057
Cyclosporine A	1.2	Prednisolone	1.17
Digitoxin	0.075	Prednisone	0.9
Digoxin	0.015	Primidone	120
Diltiazem	0.12	Probucol	2400
Dipyridamole	7.5	Procainamide	72
Disopyramide	30	Promethazine	3.6
Erythromycin	180	Propanolol	6
Ethanol	12000	Quinidine	36
Everolimus	0.12	Ranitidine	18
Fluconazole	225	Rifampicin	192
Flucytosine	240	Salicylic Acid	1800
Folic Acid	0.060	Sirolimus	0.084
Furosemide	180	Spectinomycin	480
Ganciclovir	48	Sulfamethoxazole	1200
Gentamicin	36	Tacrolimus	0.12
Glipzide	6	Theophylline	120
Glyburide	6	Ticlopidine	4.26
Heparin	8000 U/L	Tobramycin	36
Hydralazine	1.62	Triamterene	18
Hydrochlorothiazide	18	Trimethoprim	120
Ibuprofen	500	Valproic Acid	1500
Insulin	1320 mU/L	Vancomycin	300
Isoniazid	120	Verapamil	6

In addition, tests were performed on the following drugs, and no significant interference with the assay was found.

Acetylcysteine	Levodopa
Ampicillin-Na	Methyldopa + 1.5 H_2O
Ca-Dobesilate	Metronidazole
Cefoxitin	Phenylbutazone
Doxycycline (Tetracycline)	

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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.

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 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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