MPA

Mycophenolic Acid - Total Mycophenolic Acid Application

Therapeutic drug monitoring

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	COBAS INTEGRA 400 plus COBAS INTEGRA 800
04357221 190	Total MPA Calibrators Calibrators A-F (6 × 1 × 5 mL) Diluent (1 × 10 mL)	System-ID 07 6824 3	
04357230 190	Total MPA Controls Level I (2 × 5 mL) Level II (2 × 5 mL) Level III (2 × 5 mL)	System-ID 07 6935 5 System-ID 07 6936 3 System-ID 07 6937 7	

English

System information

Test TMPA, test ID 0-623

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 COBAS INTEGRA 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 1-2 hours after oral dosing. A secondary peak then occurs 6-12 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, 6-point calibration.

Reagents - working solutions

R1 Enzyme reagent
IMPDH-II in buffer: 15.7 U/L; IMP: 4.8 mmol/L; stabilizer; preservative

R2 Substrate reagent
NAD: 10 mmol/L in buffer; stabilizer; preservative

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

Precautions and warnings

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

Reagent handling

Ready for use

Storage and stability

Shelf life at 2-8 °C	See expiration date on **cobas c** pack label
COBAS INTEGRA 400 plus system	
On-board in use at 10-15 °C	12 weeks
COBAS INTEGRA 800 system	
On-board in use at 8 °C	12 weeks

The on-board in use stability period begins at the time of **cobas c** pack puncture.

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. Nonhemolyzed serum: Collect serum using standard sampling tubes. Nonhemolyzed 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 2-8 °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.

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 serum and plasma

COBAS INTEGRA 400 plus test definition

Measuring mode	Absorbance
Abs. calculation mode	Kinetic
Reaction mode	R1/R2-S
Reaction direction	Increase
Wavelength	340/409 nm
Reading cycle blank/test	52/65
Unit	µg/mL

Pipetting parameters

		Diluent (H_2O)
R1	185 µL	4 µL
R2	19 µL	4 µL
Sample	3 µL	7 µL
Total volume	222 µL	

COBAS INTEGRA 800 test definition

Measuring mode	Absorbance
Abs. calculation mode	Kinetic
Reaction mode	R1/R2-S
Reaction direction	Increase
Wavelength	340/409 nm
Reading cycle blank/test	175/197
Unit	µg/mL

Pipetting parameters

		Diluent (H_2O)
R1	185 µL	4 µL
R2	19 µL	4 µL
Sample	3 µL	7 µL
Total volume	222 µL	

Calibration

Calibrators	Total MPA Calibrators Bottles A-F
MPA conc.	0, 1, 3, 5, 10, 15 µg/mL
Calibration mode	Logit/log 4
Calibration replicate	Duplicate recommended
Calibration interval	Each lot, every 9 days and as required following quality control procedures

A calibration curve must be prepared using the Total MPA Calibrators. Calibrators must be placed from the highest concentration (F) first, to the lowest (A) last, on the CAL/QC rack. This curve is retained in memory by the COBAS INTEGRA systems and recalled for later use.

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

Quality control	Total MPA Controls
Control interval	24 hours recommended
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.

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

COBAS INTEGRA analyzers automatically calculate the analyte concentration of each sample. For more details, please refer to Data Analysis in the Online Help (COBAS INTEGRA 400 plus/800 analyzers).

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

Limitations - interference

See the Analytical specificity section of this method sheet 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 (3.12-15.6 µmol/L) and 8-12 µg/mL (25.0-37.5 µmol/L).

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:[18] 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 %.
No significant interference up to an intralipid level of 93 mg/dL. There is poor correlation between the L index (corresponds to turbidity) and triglycerides concentration. Avoid the use of lipemic specimens.

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

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 500 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.

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.

Limits and ranges

Measuring range

0.4-15 µg/mL (1.2-46.8 µmol/L)

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 organ 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.[7,8,19] 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 COBAS INTEGRA analyzers are given below. Results obtained in individual laboratories may differ.

Precision

Precision was determined using Roche Total MPA Controls and human plasma samples in accordance with the CLSI (Clinical and Laboratory Standards Institute)guidelines.

The following results were obtained on a COBAS INTEGRA 700 analyzer with repeatability (n = 63) and intermediate precision (3 aliquots per run, 1 run per day, 21 days):

Repeatability	*Mean µg/mL (µmol/L)*	*SD µg/mL (µmol/L)*	*CV %*
Level 1	0.93 (2.90)	0.01 (0.03)	1.1
Level 2	3.54 (11.05)	0.01 (0.03)	0.4
Level 3	12.37 (38.62)	0.06 (0.19)	0.5
HP 1*	1.61 (5.03)	0.01 (0.03)	0.8
HP 2*	6.36 (19.86)	0.04 (0.12)	0.7

Intermediate precision	*Mean µg/mL (µmol/L)*	*SD µg/mL (µmol/L)*	*CV %*
Level 1	0.93 (2.90)	0.04 (0.12)	4.5
Level 2	3.54 (11.05)	0.06 (0.19)	1.8
Level 3	12.37 (38.62)	0.16 (0.50)	1.3
HP 1*	1.61 (5.03)	0.04 (0.12)	2.2
HP 2*	6.36 (19.86)	0.11 (0.34)	1.8

*HP 1 and HP 2 are non-spiked pooled clinical samples.

The following results were obtained on a COBAS INTEGRA 400 analyzer with repeatability (n = 30) and intermediate precision (3 aliquots per run, 1 run per day, 10 days):

Repeatability	*Mean µg/mL (µmol/L)*	*SD µg/mL (µmol/L)*	*CV %*
Level 1	0.91 (2.84)	0.02 (0.06)	2.0
Level 2	3.48 (10.86)	0.04 (0.12)	1.1
Level 3	12.22 (38.15)	0.03 (0.09)	0.3
HP 1**	1.55 (4.84)	0.03 (0.09)	1.7
HP 2**	9.11 (28.44)	0.07 (0.21)	0.8

Intermediate precision	*Mean µg/mL (µmol/L)*	*SD µg/mL (µmol/L)*	*CV %*
Level 1	0.91 (2.84)	0.04 (0.12)	4.5
Level 2	3.48 (10.86)	0.06 (0.19)	1.8
Level 3	12.22 (38.15)	0.09 (0.28)	0.7
HP 1**	1.55 (4.84)	0.05 (0.16)	3.0
HP 2**	9.11 (28.44)	0.08 (0.25)	0.9

**HP 1 and HP 2 are spiked MPA plasma pools.

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
100.0	21.25	18.11	85.2
90.0	19.13	17.18	89.8
80.0	17.00	15.73	92.5
70.0	14.88	14.27	95.9
60.0	12.75	12.70	99.6
50.0	10.63	10.89	102.5
40.0	8.50	8.90	104.7
30.0	6.38	6.53	102.4
20.0	4.25	4.25	100.0
10.0	2.13	1.93	90.8
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
100.0	4.92	5.12	104.1
90.0	4.43	4.54	102.5
80.0	3.94	3.94	100.1

MPA

Mycophenolic Acid - Total Mycophenolic Acid Application

Therapeutic drug monitoring

% High sample	Theoretical Value (µg/mL)	Assayed Value (µg/mL)	% Recovery
70.0	3.44	3.44	99.9
60.0	2.95	2.90	98.3
50.0	2.45	2.38	96.8
40.0	1.97	1.88	95.5
30.0	1.48	1.45	98.3
20.0	0.98	1.02	103.7
10.0	0.49	0.56	113.8
0	0	0	—

Method comparison

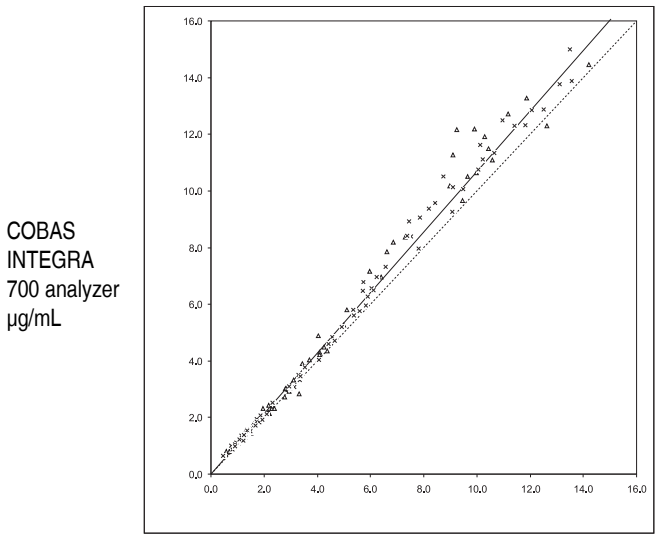
Mycophenolic acid values for human plasma samples obtained with the Roche Total Mycophenolic Acid assay were compared to those determined with three independent validated MPA HPLC methods. Samples from renal and cardiac transplant patients were tested with the Roche Total Mycophenolic Acid assay at two external clinical sites and also internally, with concurrent HPLC testing at each site.

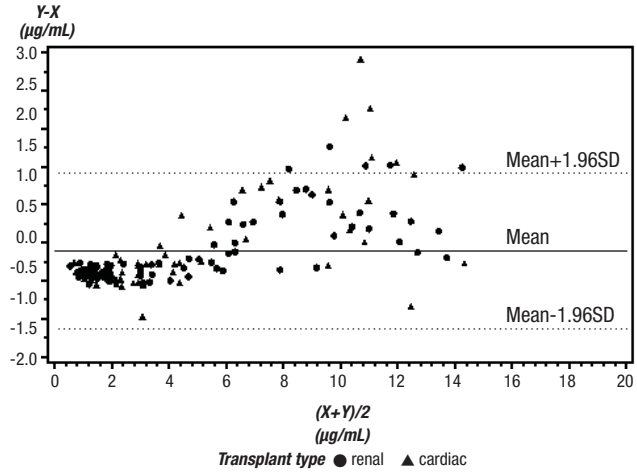
The trial included a total of 571 samples collected from post-transplant patients. The Passing-Bablok statistics of the correlations are shown in the table below.[20] Samples tested on the COBAS INTEGRA 800 analyzer were obtained from an international trial of renal transplant recipients (147 samples from 86 adult patients). Demographics for the other sites are subsequently described with the representative regression plots that follow the table.

Methodology vs. HPLC					
	Slope (95 % CI)	Intercept (95 % CI)	Correlation Coefficient	Sample Size	Sample Range (µg/mL)
COBAS INTEGRA 700 analyzer					
Renal	1.062 (1.044-1.079)	0.019 (-0.021-0.073)	0.997	89	0.46-13.6
Cardiac	1.088 (1.050-1.125)	-0.028 (-0.110-0.045)	0.993	70	0.57-14.2
Combined	1.068 (1.052-1.085)	0.005 (-0.029-0.050)	0.995	159	0.46-14.2
COBAS INTEGRA 400 plus analyzer					
Renal	1.010 (0.988-1.035)	0.068 (0.034-0.105)	0.995	148	0.4-14.8
Cardiac	1.014 (0.996-1.031)	0.057 (-0.004-0.103)	0.992	117	0.4-13.6
Combined	1.011 (1.000-1.025)	0.064 (0.038-0.090)	0.993	265	0.4-14.8
COBAS INTEGRA 800 analyzer					
Renal	1.100 (1.073-1.120)	-0.120 (-0.192-(-0.066))	0.994	147	0.5-14.7

The following graph shows the correlation testing of the Roche Total Mycophenolic Acid assay on the COBAS INTEGRA 700 analyzer vs HPLC. The same data sets are depicted in the Bland-Altman difference plot shown below the regression plot. The sample population for this internal study included 89 renal and 70 cardiac patients. Other demographics for this sample population are unknown. Passing-Bablok statistics for the correlation are included in the method comparison table above.

Roche Total Mycophenolic Acid
(COBAS INTEGRA 700 analyzer) vs HPLC

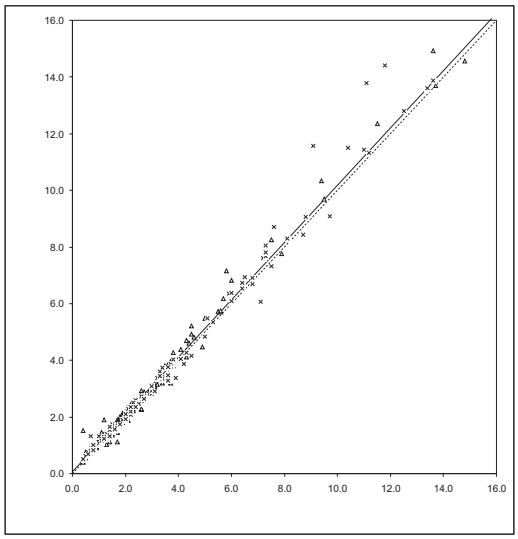




N = 159
Mean (Y-X) = 0.38
SD (Y-X) = 0.52
1.96 SD = 1.02
Mean + 1.96 SD = 1.41
Mean – 1.96 SD = -0.64

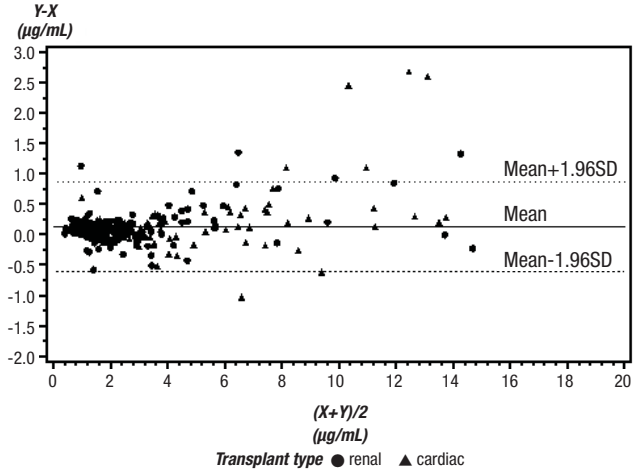
The following graph shows the correlation testing of the Roche Total Mycophenolic Acid assay on the COBAS INTEGRA 400 plus analyzer vs HPLC. The same data sets are depicted in the Bland-Altman difference plot shown below the regression plot. The sample population for this external study included 265 samples (148 renal and 117 cardiac) from a total of 209 "routine" adult transplant recipients. Passing-Bablok statistics for the correlation are included in the method comparison table above.

Roche Total Mycophenolic Acid
(COBAS INTEGRA 400 plus analyzer) vs HPLC



COBAS INTEGRA 400 plus analyzer µg/mL

HPLC µg/mL



N = 265
Mean (Y-X) = 0.13
SD (Y-X) = 0.38
1.96 SD = 0.75
Mean + 1.96 SD = 0.881
Mean – 1.96 SD = -0.62

Analytical specificity

The following cross-reactive substances were evaluated on the COBAS INTEGRA systems 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.

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

Drug	Level tested µg/mL	Cross-reactivity %
Mycophenolic acid glucuronide (MPAG)	1000	ND
Mycophenolic acid acyl glucuronide (AcMPAG)	10	5.6

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	Acyclovir	45
Albuterol	1.2	Allopurinol	120
Alprazolam	6	Amikacin	105
Amphotericin B	240	Ascorbic Acid	120
Atenolol	30	Azathioprene	9
Bromocriptine	0.75	Caffeine	180
Captopril	15	Carbamazepine	90
Cefaclor	225	Ceftriaxone	2430
Cephalosporine	0.3	Chloramphenicol	150
Chloroquine	2.5	Cimetidine	60
Ciprofloxacin	30	Clonidine	0.03
Colchicine	0.033	Cyclophosphamide	1125
Cyclosporine A	1.2	Digitoxin	0.075
Digoxin	0.015	Diltiazem	0.12
Dipyridamole	7.5	Disopyramide	30
Erythromycin	180	Ethanol	12000
Everolimus	0.12	Fluconazole	225
Flucytosine	240	Folic Acid	0.060
Furosemide	180	Ganciclovir	48
Gentamicin	36	Glipzide	6
Glyburide	6	Heparin	8000 U/L
Hydralazine	1.62	Hydrochlorothiazide	18
Ibuprofen	500	Insulin	1320 mU/L
Isoniazid	120	Isoproterenol	0.18
Itraconazole	6	Kanamycin	180
Ketoconazole	10.5	Labetalol	0.573
Lidocaine	36	Lovastatin	0.0357
Methylprednisolone	36	Metoclopramide	1.35
Minoxidil	0.921	Misoprostol	0.018
Morphine sulfate	1.5	N-Acetylprocainamide	120
Nadolol	3.6	Naproxen	500
Niacin	2400	Nicardipine	0.564
Nifedipine	1.2	Omeprazole	18
Penicillin G	36	Phenobarbital	300
Phenytoin	150	Piperacillin	120
Prazosin	0.057	Prednisolone	1.173
Prednisone	0.9	Primidone	120
Probucol	2400	Procainamide	72
Promethazine	3.6	Propanolol	6
Quinidine	36	Ranitidine	18
Rifampicin	192	Salicylic Acid	1800

Compound	µg/mL	Compound	µg/mL
Sirolimus	0.084	Spectinomycin	480
Sulfamethoxazole	1200	Tacrolimus	0.12
Theophylline	120	Ticlopidine	4.26
Tobramycin	36	Triamterene	18
Trimethoprim	120	Valproic Acid	1500
Vancomycin	300	Verapamil	6

In addition, tests were performed on 9 drugs. No significant interference with the assay was found.

Acetyl Cysteine	Ampicillin-Na
Ca-Dobesilate	Cefoxitin
Doxycycline (Tetracycline)	Levodopa
Methyldopa+1,5 H_2O	Metronidazole
Phenylbutazone	

References

1 Weber LT, Shipkova M, Armstrong VW, et al. The pharmacokinetic-pharmacodynamic relationship for total and free mycophenolic acid in pediatric renal transplant recipients: A report of the German study group on mycophenolate mofetil therapy. J Am Soc Nephrol 2002;13:759-768.

2 Shaw LM, Nichols A, Hale M, et al. Therapeutic monitoring of mycophenolic acid: A consensus panel report. Clin Biochem 1998;31(5):317-322.

3 Wu JC. Mycophenolate mofetil: molecular mechanism of action. Perspect Drug Discovery Design 1994;2:185-204.

4 Ransom JT. The mechanism of action of mycophenolate mofetil. Ther Drug Monit 1995;17:681-684.

5 Schutz E, Shikova M, Armstrong VW, et al. Therapeutic drug monitoring of mycophenolic acid: comparison of HPLC and immunoassay reveals new metabolites. Transplant Proc 1998;30:1185-1187.

6 Indjova D, Kassabova L, Svinarov D. J Chromatog B 2005;817:327-330.

7 Meiser BM. Therapeutic drug monitoring of mycophenolic acid in cardiac tranplant recipients: does it make sense? Curr Opin Organ Transplant 2005;10:350-354.

8 Gajarski RJ, Crowley DC, Zamberlan MC, et al. Lack of correlation between MMF dose and MPA level in pediatric and young adult cardiac transplant patients: Does the MPA level matter? Am J Transplant 2004;4:1495-1500.

9 Dipchand AI, Pietra B, McCrindle BW, et al. Mycophenolic acid levels in pediatric heart transplant recipients receiving mycophenolate mofetil. J Heart Lung Transplant 2001;20(10):1035-1043.

10 Kuypers DRJ. Immunosuppressive drug monitoring- What to use in clinical practice today to improve renal graft outcome? Transplant International 2005;18:140-150.

11 Hessilink DA, van Gelder T. The influence of cyclosporine on mycophenolic acid plasma concentrations: A review. Transplant Rev 2003;17(3):158-163.

12 Van Gelder T, Meur YL, Shaw LM, et al. Therapeutic drug monitoring of mycophenolate mofetil in transplantation. Ther Drug Monit 2006;28(2):145-154.

13 Cox VC, Ensom MHH. Mycophenolate mofetil for solid organ transplantation: Does the evidence support the need for clinical pharmacokinetic monitoring? Ther Drug Monit 2003;25(2):137-157.

14 Shaw LM, Korecka M, Venkataramanan R, et al. Mycophenolic acid pharmacodynamics and pharmacokinetics provide a basis for rational monitoring strategies. Am J Transplant 2003;3:534-542.

15 Shaw LM, Holt DW, Oellerich M, et al. Current issues in therapeutic drug monitoring of mycophenolic acid: Report of a roundtable discussion. Ther Drug Monit 2001;23(4):305-315.

16 Meiser BM, Pfeiffer M, Schmidt D, et al. Combination therapy with tacrolimus and mycophenolate mofetil following cardiac transplantation:importance of mycophenolic acid therapeutic drug monitoring. J Heart Lung Transplant 1999;18(2):143-149.

17 Shipkova M, Armstrong VM, Schneider T, et al. Stability of mycophenolic acid glucuronide in human plasma. Clin Chem 1999;45(1):127-129.

18 Glick MR, Ryder KW, Jackson SA. Graphical Comparisons of Interferences in Clinical Chemistry Instrumentation. Clin Chem 1986;32:470-475.

19 Meiser BM, Reichart B. New agents and new strategies in immunosuppression after heart transplantation. Curr Opin Organ Transplant 2002;7:226-232.

20 Bablok W, Passing H, Bender R, et al. A general regression procedure for method transformation. Application of linear regression procedures for method comparison studies in clinical chemistry, Part III. J Clin Chem Clin Biochem 1988 Nov;26(11):783-790.

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

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.

Significant additions or changes are indicated by a change bar in the margin.

CE

Roche Diagnostics GmbH, Sandhofer Strasse 116, D-68305 Mannheim
www.roche.com

Distribution in USA by:
Roche Diagnostics, Indianapolis, IN
US Customer Technical Support 1-800-428-2336

Roche