SIEMENS Healthineers

Cyclosporine (CsA)

Current Revision and Date[a]	Rev. 05, 2020-08	
Product Name	Atellica IM Cyclosporine (CsA)	REF 10995548
Abbreviated Product Name	Atellica IM CsA	
Test Name/ID	CsA	
Systems	Atellica IM Analyzer	
Materials Required but Not Provided	Atellica IM CsA CAL	REF 10995549
	Atellica IM CsA PRE	REF 10995552
Optional Materials	Atellica IM Multi-Diluent 12	REF 10995550
	Atellica IM CsA MCM	REF 10995551
Specimen Types	EDTA whole blood	
Sample Volume	100 µL	
Measuring Interval	30.00–1500.00 ng/mL (24.95–1247.25 nmol/L)	

[a] A vertical bar in the page margin indicates technical content that differs from the previous version.

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Intended Use

The Atellica® IM Cyclosporine (CsA) assay is for *in vitro* diagnostic use in the quantitative determination of cyclosporine in human whole blood (EDTA) using the Atellica® IM Analyzer.

This assay is intended for use as an aid in the management of cyclosporine therapy in kidney, heart, and liver transplant patients.

Summary and Explanation

Cyclosporine is a hydrophobic cyclic oligopeptide of fungal origin that suppresses the immune system. Although the mechanism of action is not entirely understood, cyclosporine is thought to inhibit T-cell mediated responses, as well as the production and release of lymphokines. During the last 20 years, cyclosporine has substantially improved patient and graft survival in patients receiving heart, kidney, liver, pancreas, or lung transplants.[1-6]

Monitoring cyclosporine concentrations is recommended[7] in conjunction with other clinical tests and examinations to help optimize immunosuppression and reduce adverse events in organ transplant recipients. Whole blood is the recommended sample type since cyclosporine is rapidly distributed into the red blood cells.

Principles of the Procedure

The Atellica IM CsA assay is a competitive immunoassay using direct chemiluminescent technology. Cyclosporine in the patient sample competes with acridinium-ester-labeled cyclosporine in the Lite Reagent for a limited amount of biotin-labeled mouse monoclonal anti-cyclosporine antibody. Biotin-labeled anti-cyclosporine binds to streptavidin that is covalently coupled to paramagnetic particles in the Solid Phase. In the Atellica IM CsA assay, the sample is manually pretreated to lyse the cells and solubilize the cyclosporine.

An inverse relationship exists between the amount of cyclosporine present in the patient sample and the amount of relative light units (RLUs) detected by the system.

Reagents

Material Description	Storage	Stability[a]
Atellica IM CsA ReadyPack® primary reagent pack **Lite Reagent** 5.0 mL/reagent pack Cyclosporine (~6 ng/mL) labeled with acridinium ester in phosphate buffer; bovine serum albumin; surfactant; preservatives **Solid Phase** 12.5 mL/reagent pack Streptavidin coupled to paramagnetic particles (~160 µg/mL) in phosphate buffered saline; bovine serum albumin; mouse gamma globulin; surfactant; preservatives **Ancillary Well Reagent** 5.0 mL/reagent pack Biotinylated mouse monoclonal anti-cyclosporine antibody (100 ng/mL) in phosphate buffered saline; bovine serum albumin; mouse gamma globulin; surfactant; preservatives	Unopened at 2–8°C Onboard	Until expiration date on product 42 days
Atellica IM CsA PRE 26.0 mL/vial Detergents; glycerol; anti-foam; preservatives	Unopened at 2–8°C Opened	Until expiration date on product 21 weeks
Atellica IM Multi-Diluent 12[b] 20.0 mL/vial Human serum; detergents; glycerol; anti-foam; preservatives	At 2–8°C Opened	Until expiration date on product 21 weeks

[a] Refer to *Storage and Stability*.

[b] Refer to *Optional Materials*.

Warnings and Precautions

For *in vitro* diagnostic use.

For Professional Use.

CAUTION

Federal (USA) law restricts this device to sale by or on the order of a licensed healthcare professional.

Safety data sheets (SDS) available on siemens.com/healthineers.

H412	Harmful to aquatic life with long lasting effects.
P273, P501	Avoid release to the environment. Dispose of contents and container in accordance with all local, regional, and national regulations. **Contains:** 2-methyl-2H-isothiazol-3-one (in Atellica IM CsA ReadyPack and Atellica IM CsA PRE)

CAUTION POTENTIAL BIOHAZARD

Contains human source material. Each donation of human blood or blood component was tested by FDA-approved methods for the presence of antibodies to human immunodeficiency virus type 1 (HIV-1) and type 2 (HIV-2), as well as for hepatitis B surface antigen (HBsAg) and antibody to hepatitis C virus (HCV). The test results were negative (not repeatedly reactive). No test offers complete assurance that these or other infectious agents are absent; this material should be handled using good laboratory practices and universal precautions.[9–11]

CAUTION

This device contains material of animal origin and should be handled as a potential carrier and transmitter of disease.

Dispose of hazardous or biologically contaminated materials according to the practices of your institution. Discard all materials in a safe and acceptable manner and in compliance with prevailing regulatory requirements.

Note For information about reagent preparation, refer to *Preparing the Reagents* in the *Procedure* section.

Storage and Stability

Store reagents in an upright position. Protect the product from heat and light sources. Unopened reagents are stable until the expiration date on the product when stored at 2–8°C.

Store Atellica IM CsA PRE in an upright position. Unopened Atellica IM CsA PRE is stable until the expiration date on the product when stored at 2–8°C. Atellica IM CsA PRE is stable for 21 weeks after opening when stored at 2–8°C.

Store Atellica IM Multi-Diluent 12 in an upright position. Unopened Atellica IM Multi-Diluent 12 is stable until the expiration date on the product when stored at 2–8°C. Atellica IM Multi-Diluent 12 is stable for 21 weeks after opening when stored at 2–8°C.

Do not use products beyond the expiration date printed on the product labeling.

Onboard Stability

Reagents are stable onboard the system for 42 days. Discard reagents at the end of the onboard stability interval.

Do not use products beyond the expiration date printed on the product labeling.

Specimen Collection and Handling

Whole blood is the recommended sample type for this assay. EDTA is recommended as the anticoagulant of choice for assaying cyclosporine in whole blood samples. Heparinized samples are not recommended because they may form clots during storage.[8]

Collecting the Specimen

- Observe universal precautions when collecting specimens. Handle all specimens as if they are capable of transmitting disease.[11]
- Follow recommended procedures for collection of diagnostic blood specimens by venipuncture.[12]

- Follow the instructions provided with your specimen collection device for use and processing.[13]
- Keep tubes capped at all times.[10]
- Test samples as soon as possible after collecting.

Storing the Specimen

Whole Blood

- Do not use samples stored at room temperature for longer than 6 hours.
- Tightly cap and refrigerate specimens at 2–8°C if the assay is not completed within 6 hours. Samples can be stored at 2–8°C for up to 7 days.
- If longer storage is necessary, freeze samples at ≤ -20°C for up to 1 month. Do not store in a frost-free freezer.
- Freeze samples only 1 time and mix thoroughly after thawing.

Whole Blood Hemolysate

- Pretreated samples can be stored for up to 4 hours at room temperature or for up to 24 hours at 2–8°C.
- Do not freeze pretreated samples.

The handling and storage information provided here is based on data or references maintained by the manufacturer. It is the responsibility of the individual laboratory to use all available references and/or its own studies when establishing alternate stability criteria to meet specific needs.

Transporting the Specimen

Package and label specimens for shipment in compliance with applicable federal and international regulations covering the transport of clinical specimens and etiological agents.

Preparing the Samples

This assay requires 30 µL of whole blood hemolysate for a single determination. This volume does not include the unusable volume in the sample container or the additional volume required when performing duplicates or other tests on the same sample. For information about determining the minimum required volume, refer to the online help.

Note For a complete list of appropriate sample containers, refer to the online help.

Preparing the Whole Blood Hemolysate

Note Do not pretreat calibrators and master curve materials.

1. Dispense exactly 400 µL of the Atellica IM CsA PRE into a sample cup or test tube.
2. Thoroughly mix the capped sample by gentle inversion to ensure homogeneity of the sample.
3. Pipet exactly 100 µL of blood into the sample cup containing the Atellica IM CsA PRE. Use a new pipet tip for each sample, and carefully wipe the outside of the tip with a lint-free tissue before transfer to the sample cup. Avoid pipeting insoluble materials that may form when samples are frozen.
4. Cover the sample and vortex individually for 10 seconds. Examine each sample to ensure a homogeneous solution. Additional vortex may be required.
5. Place sample cup or test tube on the system.

Before placing samples on the system, ensure that samples are free of:

- Bubbles or foam.
- Fibrin or other particulate matter.

Procedure

Materials Provided

The following materials are provided:

REF	Contents	Number of Tests
10995548	1 ReadyPack primary reagent pack containing Atellica IM CsA Lite Reagent, Solid Phase, and Ancillary Well Reagent Atellica IM CsA master curve and test definition MC TDEF	50

Materials Required but Not Provided

The following materials are required to perform this assay, but are not provided:

REF	Description	
	Atellica IM Analyzer[a]	
10995549	Atellica IM CsA CAL (calibrator)	2 x 2.0 mL low calibrator CAL L 2 x 2.0 mL high calibrator CAL H Calibrator lot-specific value sheet CAL LOT VAL
10995552	Atellica IM CsA PRE (pretreatment reagent)	2 x 26.0 mL/vial PRE

[a] Additional system fluids are required to operate the system: Atellica IM Wash, Atellica IM Acid, Atellica IM Base, and Atellica IM Cleaner. For system fluid instructions for use, refer to the Document Library.

Optional Materials

The following materials may be used to perform this assay, but are not provided:

REF	Description	
10995550	Atellica IM Multi-Diluent 12 (diluent)	20.0 mL/vial DIL
10995551	Atellica IM CsA MCM (master curve material)	5 x 1.0 mL levels of master curve material MCM

Assay Procedure

The system automatically performs the following steps:

1. Dispenses 30 µL of pretreated sample into a cuvette.
2. Dispenses 100 µL of Ancillary Well Reagent, then incubates for 3 minutes at 37°C.
3. Dispenses 100 µL of Lite Reagent, then incubates for 3 minutes at 37°C.
4. Dispenses 250 µL of Solid Phase, then incubates for 6 minutes at 37°C.
5. Separates, aspirates, then washes the cuvette with Atellica IM Wash.
6. Dispenses 300 µL each of Atellica IM Acid and Atellica IM Base to initiate the chemiluminescent reaction.
7. Reports results.

Preparing the Reagents

All reagents are liquid and ready to use. Before loading primary reagent packs onto the system, mix them by hand and visually inspect the bottom of the reagent pack to ensure that all particles are resuspended. For information about preparing the reagents for use, refer to the online help.

Preparing the System

Ensure that the system has sufficient reagent packs loaded in the reagent compartment. The system automatically mixes reagent packs to maintain homogeneous suspension of the reagents. For information about loading reagent packs, refer to the online help.

Master Curve Definition

Before initiating calibration on each new lot of reagent, load the assay master curve and test definition values by scanning the MC TDEF 2D barcodes. For loading instructions, refer to the online help.

Performing Calibration

For calibration of the Atellica IM CsA assay, use the Atellica IM CsA CAL. Use the calibrators in accordance with the calibrator instructions for use.

Calibration Frequency

Perform a calibration if one or more of the following conditions exist:

- When changing lot numbers of primary reagent packs.
- At the end of the lot calibration interval, for a specified lot of calibrated reagent on the system.
- At the end of the pack calibration interval, for calibrated reagent packs on the system.
- When indicated by quality control results.
- After major maintenance or service, if indicated by quality control results.

At the end of the onboard stability interval, replace the reagent pack on the system with a new reagent pack. Recalibration is not required, unless the lot calibration interval is exceeded.

Stability Interval	Days
Lot Calibration	32
Pack Calibration	28
Reagent Onboard Stability	42

For information about lot calibration and pack calibration intervals, refer to the online help.

Follow government regulations or accreditation requirements for calibration frequency. Individual laboratory quality control programs and procedures may require more frequent calibration.

Performing Quality Control

For quality control of the Atellica IM CsA assay, use an appropriate quality control material of known analyte concentration with at least 2 levels (low and high) at least once during each day that samples are analyzed. Use the quality control material in accordance with the quality control instructions for use.

A satisfactory level of performance is achieved when the analyte values obtained are within the expected control interval for the system or within your interval, as determined by an appropriate internal laboratory quality control scheme. Follow your laboratory's quality control procedures if the results obtained do not fall within the acceptable limits. For information about entering quality control definitions, refer to the online help.

Follow government regulations or accreditation requirements for quality control frequency. Individual laboratory quality control programs and procedures may require more frequent quality control testing.

Test quality control samples after a successful calibration.

Taking Corrective Action

If the quality control results do not fall within the assigned values, do not report results. Perform corrective actions in accordance with established laboratory protocol. For suggested protocol, refer to the online help.

Results

Calculation of Results

The system determines the result using the calculation scheme described in the online help. The system reports results in ng/mL (common units) or nmol/L (SI units), depending on the units defined when setting up the assay.

Conversion formula: 1 ng/mL = 0.8315 nmol/L

For information about results outside the specified measuring interval, refer to *Measuring Interval*.

Dilutions

The assay measuring interval for whole blood hemolysate is 30.00–1500.00 ng/mL (24.95–1247.25 nmol/L).

For manual dilutions, perform the following actions:

- Manually dilute the pretreated patient samples 1:5 when cyclosporine levels are > 1500.00 ng/mL (1247.25 nmol/L), or when laboratory protocol requires manual dilution.
- Use Atellica IM Multi-Diluent 12 to prepare a manual dilution.
- For information about ordering tests for manually diluted samples, refer to the online help.
- Ensure that results are mathematically corrected for dilution. If a dilution factor is entered when scheduling the test, the system automatically calculates the result.

Interpretation of Results

Results of this assay should always be interpreted in conjunction with the patient's medical history, clinical presentation, and other findings.

Limitations

The following information pertains to limitations of the assay:

- This assay has not been evaluated in a pediatric population.
- Always use measurements of cyclosporin in conjunction with other diagnostic procedures, including information from the patient's clinical evaluation.

- Patients with impaired liver function, elevated bilirubin levels, unexpectedly high drug values, or increased time post-therapy can show falsely increased values in cyclosporine immunoassays because of accumulation of CsA metabolites. For these patients, results of cyclosporine immunoassays may be supported by an HPLC-MS method which is highly specific for the parent drug.[14]
- High levels of triglycerides and cholesterol may result in low quantitation in lipemic samples.
- Patient samples may contain heterophilic antibodies that could react in immunoassays to give falsely elevated or depressed results. This assay is designed to minimize interference from heterophilic antibodies.[15,16] Additional information may be required for diagnosis.
- Do not use in patients taking biotin supplements.
- Clearance of biotin could be different in patients that are not apparently healthy, for example patients with impaired renal function may have higher concentrations of biotin in whole blood.

Expected Values

No firm therapeutic range exists for cyclosporine in whole blood. The complexity of the clinical state, individual differences in sensitivity to immunosuppressive and nephrotoxic effects of cyclosporine, co-administration of other immunosuppressants, type of transplant, time post-transplant, and a number of other factors, will cause different requirements for optimal blood levels of cyclosporine. Each clinician should establish a range based on clinical experience and evaluate each patient before treatment adjustments are made. In addition, ranges will vary according to the commercial *in vitro* diagnostic test used. Do not use conversion factors between commercial assays to predict values for individual patients. Consistent use of one assay for an individual patient is recommended because of varying patterns of cross-reactivity with metabolites.[14]

Measurements of CsA should be used in conjunction with other diagnostic procedures and clinical evaluation. Do not base changes in the cyclosporine treatment regimen on individual cyclosporine values.

Performance Characteristics

The reagent formulations used on the Atellica IM Analyzer are the same as those used on the ADVIA Centaur® system. Some performance characteristics for the Atellica IM assay were established using the ADVIA Centaur system.

Measuring Interval

The Atellica IM CsA assay provides results from 30.00–1500.00 ng/mL (24.95–1247.25 nmol/L). The lower end of the measuring interval is defined by the design requirement for functional sensitivity. Report results below the measuring interval as < 30.00 ng/mL (24.95 nmol/L). When sample results exceed the measuring interval, refer to *Dilutions*.

Specificity

Whole blood samples containing 200 ng/mL of cyclosporine were spiked with 1000 ng/mL of metabolites AM1, AM1c, AM4N, AM9, and AM19. The calculated cross-reactivity is shown below:

Metabolite	Tested Concentration (ng/mL)	Cross-Reactivity (%)
AM1	1000	< 5%
AM1c	1000	< 5%

Metabolite	Tested Concentration (ng/mL)	Cross-Reactivity (%)
AM4N	1000	< 5%
AM19	1000	< 5%
AM9	1000	15.0

Results were established using the ADVIA Centaur system. Assay results obtained at individual laboratories may vary from the data presented.

Detection Capability

Detection capability was determined in accordance with CLSI Document EP17-A2.[17] The assay is designed to have a limit of blank (LoB) ≤ 25.00 ng/mL (20.79 nmol/L), a limit of detection (LoD) ≤ 25.00 ng/mL (20.79 nmol/L), and functional sensitivity < 30.00 ng/mL (24.95 nmol/L). The functional sensitivity is defined as the cyclosporine concentration at which the within-laboratory CV is ≤ 20%.

Representative detection capability data are shown below. Assay results obtained at individual laboratories may vary from the data presented.

The LoB corresponds to the highest measurement result that is likely to be observed for a blank sample. The LoB of the Atellica IM CsA assay is 8.60 ng/mL (7.15 nmol/L).

The LoD corresponds to the lowest concentration of cyclosporine that can be detected with a probability of 95%. The LoD for the Atellica IM CsA assay is 13.50 ng/mL (11.23 nmol/L) and was determined using 352 determinations, with 160 blank and 192 low-level replicates, and an LoB of 8.60 ng/mL (7.15 nmol/L).

Functional sensitivity corresponds to the lowest amount of cyclosporine in a sample at which the within-laboratory CV is ≤ 20%. The functional sensitivity of the Atellica IM CsA assay is 29.40 ng/mL (24.45 nmol/L), and was determined using multiple patient samples in the interval 7.12–33.36 ng/mL (5.92–27.74 nmol/L). All samples were assayed in duplicate in each of 2 runs per day using 2 reagent lots, over a period of 20 days.

Precision

Precision was determined in accordance with CLSI Document EP05-A3.[18] Samples were assayed on an Atellica IM Analyzer in duplicate in 2 runs per day for 20 days. The assay was designed to have within-laboratory precision of ≤ 9.00 ng/mL (7.48 nmol/L) SD for samples ≤ 99.00 ng/mL (82.32 nmol/L) and ≤ 9%CV for samples from 100.00–1500.00 ng/mL (83.15–1247.25 nmol/L).

		Mean		Repeatability			Within-Laboratory Precision		
				SD[b]		CV[c]	SD		CV
Sample Type	N[a]	(ng/mL)	(nmol/L)	(ng/mL)	(nmol/L)	(%)	(ng/mL)	(nmol/L)	(%)
Whole Blood Sample A	80	127.97	106.41	2.68	2.23	2.1	8.85	7.36	6.9
Whole Blood Sample B	80	466.74	388.09	8.14	6.77	1.7	23.09	19.20	4.9
Whole Blood Sample C	80	946.03	786.62	18.54	15.42	2	53.03	44.09	5.6
Whole Blood Sample D	80	1300.71	1081.54	36.43	30.29	2.8	91.89	76.41	7.1
Control 1	80	55.67	46.29	1.73	1.44	N/A[d]	5.42	4.51	N/A

		Mean		Repeatability			Within-Laboratory Precision		
				SD[b]		CV[c]	SD		CV
Sample Type	N[a]	(ng/mL)	(nmol/L)	(ng/mL)	(nmol/L)	(%)	(ng/mL)	(nmol/L)	(%)
Control 2	80	127.14	105.72	3.01	2.50	2.4	9.67	8.04	7.6
Control 3	80	284.55	236.60	9.52	7.92	3.3	15.93	13.25	5.6
Control 4	80	640.89	532.90	17.18	14.29	2.7	41.79	34.75	6.5
Control 5	80	1106.89	920.38	31.13	25.88	2.8	91.25	75.87	8.2

[a] Number of samples tested.
[b] Standard deviation.
[c] Coefficient of variation.
[d] Not applicable.

Assay results obtained at individual laboratories may vary from the data presented.

Assay Comparison

The Atellica IM CsA assay is designed to have a correlation coefficient of ≥ 0.95 and a slope of 1.0 ±0.1 compared to the ADVIA Centaur CsA assay. Assay comparison was determined using the Deming linear regression model in accordance with CLSI Document EP09-A3.[19] The following results were obtained:

Specimen	Comparative Assay (x)	Regression Equation	Sample Interval	N[a]	r[b]
Whole blood	ADVIA Centaur CsA	y = 0.97x - 4.23 ng/mL (y = 0.97x - 3.52 nmol/L)	34.77–1461.94 ng/mL (28.91–1215.60 nmol/L)	127	0.99

[a] Number of samples tested.
[b] Correlation coefficient.

The relationship between the ADVIA Centaur CsA assay and Tandem mass spectrometry (Tandem-MS) was established by testing whole blood samples from transplant patients on cyclosporine therapy at 3 clinical trial sites. Testing was also performed at 3 sites with the Abbott TDx assay and at 1 site with the Abbott AxSYM assay. These relationships, as determined by Deming regression, are described in the following tables:

Specimen	Comparative Assay (x)	Regression Equation	N[a]	r[b]
Kidney	Tandem MS	y = 1.11x - 8 ng/mL (y = 1.11x - 6.65 nmol/L)	108	0.96
Liver	Tandem MS	y = 1.04x - 5 ng/mL (y = 1.04x - 4.16 nmol/L)	75	0.97
Heart	Tandem MS	y = 0.89x + 20 ng/mL (y = 0.89x + 16.63 nmol/L)	67	0.97
All	Tandem MS	y = 1.03x - 1 ng/mL (y = 1.03x - 0.83 nmol/L)	250	0.96

[a] Number of samples tested.
[b] Correlation coefficient.

Specimen	Comparative Assay (x)	Regression Equation	N[a]	r[b]
Site 1	Tandem MS	y = 0.88x + 14 ng/mL (y = 0.88x + 11.64 nmol/L)	97	0.96
Site 2	Tandem MS	y = 1.05x - 15 ng/mL (y = 1.05x - 12.47 nmol/L)	105	0.98
Site 3	Tandem MS	y = 1.14x + 35 ng/mL (y = 1.14x + 29.10 nmol/L)	48	0.96
All	Tandem MS	y = 1.03x - 1 ng/mL (y = 1.03x - 0.83 nmol/L)	250	0.96

[a] Number of samples tested.
[b] Correlation coefficient.

Specimen	Comparative Assay (x)	Regression Equation	N[a]	r[b]
Site 1	Abbott TDx	y = 0.76x + 10 ng/mL (y = 0.76x + 8.32 nmol/L)	97	0.97
Site 2	Abbott TDx	y = 0.67x - 2 ng/mL (y = 0.67x - 1.66 nmol/L)	97	0.99
Site 3	Abbott TDx	y = 0.73x + 9 ng/mL (y = 0.73x + 7.48 nmol/L)	48	0.97
All	Abbott TDx	y = 0.72x +4 ng/mL (y = 0.72x + 3.33 nmol/L)	242	0.97
Site 1	Abbott AxSYM	y = 0.68x +18 ng/mL (y = 0.68x + 14.97 nmol/L)	219	0.96

[a] Number of samples tested.
[b] Correlation coefficient.

Specimen	Comparative Assay (x)	Regression Equation	N[a]	r[b]
Trough	Tandem MS	y = 1.02x + 8 ng/mL (y = 1.02x + 6.65 nmol/L)	182	0.91
Peak	Tandem MS	y = 1.15x - 104 ng/mL (y = 1.15x - 86.48 nmol/L)	68	0.90
All	Tandem MS	y = 1.03x - 1 ng/mL (y = 1.03x - 0.83 nmol/L)	250	0.96

[a] Number of samples tested.
[b] Correlation coefficient.

Agreement of the assays may vary depending on the study design, comparative assay, and sample population used. Assay results obtained at individual laboratories may vary from the data presented.

Interferences

Interference testing was performed in accordance with CLSI Document EP7-A2.[20]

Whole blood specimens that are or that contain . . .	Demonstrate ≤ 10% change in results . . .
icteric	up to 60 mg/dL conjugated bilirubin
icteric	up to 40 mg/dL unconjugated bilirubin

Whole blood specimens that are or that contain . . .	Demonstrate ≤ 10% change in results . . .
lipemic	up to 900 mg/dL triglycerides
lipemic	up to 300 mg/dL cholesterol
uremic	up to 20 mg/dL uric acid
hypoproteinemic	as low as 8 g/dL albumin
hyperproteinemic	up to 12 g/dL gamma globulin
hematocrit range	between 12.3%–58.6%

Analyte Concentration (ng/mL)	Biotin Test Level (ng/mL)					
	9	19	38	75	150	600
	% Bias					
595	-3	2	6	33	491	> MI[a]
736	7	-4	5	31	125	> MI

[a] Measuring interval

Specimens that contain biotin at a concentration of 38 ng/mL demonstrate a less than or equal to 10% change in results. Biotin concentrations greater than this may lead to falsely elevated results for patient samples.

The recommended adult daily dietary intake for biotin is 30 µg/day. Over the counter dietary supplements promoted for use in hair, skin and nail health may contain 5–100 mg of biotin, with recommendations to take multiple pills per day. Pharmacokinetic studies in healthy adults have shown that, in subjects ingesting 5 mg, 10 mg, and 20 mg of biotin, serum concentrations of biotin can reach up to 73 ng/mL, 141 ng/mL, and 355 ng/mL, respectively.[21] Subjects who take up to 300 mg of biotin per day may have plasma biotin levels as high as 1160 ng/mL.[22]

Whole blood samples containing 200 ng/mL of cyclosporine were spiked with the compounds listed below to the concentrations shown. Results from the spiked samples were compared with those of unspiked control samples. These compounds caused < 10% bias in cyclosporine measurements.

Compound	Amount Added (µg/mL)	Compound	Amount Added (µg/mL)
Tacrolimus (FK506)	100	Lidocaine	100
Mycophenolic acid	100	Lincomycin	100
Mycophenolic acid glucuronide	1000	Methotrexate	100
Rapamycin (Sirolimus)	5	Methylprednisolone	100
N-acetylprocainamide	100	Neomycin sulfate	100
Acetaminophen	200	Oxytocin	100
Amikacin	100	Penicillin-G (sodium salt)	100
Amikacin sulfate	100	Penicillin V	100
Ampicillin	100	Phenobarbital	150

Compound	Amount Added (µg/mL)	Compound	Amount Added (µg/mL)
Apresoline	100	Phenytoin	100
Azathioprine	100	Prazosin	100
Carbamazepine	120	Prednisolone	100
Cefaclor (Cephalosporin)	230	Prednisone	100
Chloramphenicol	250	Primidone	100
Cimetidine	100	Procainamide	100
Digitoxin	100	Propranolol	100
Digoxin	100	Quinidine sulfate	100
Dipyridamole	100	Rifampicin	100
Disopyramide	100	Salicylic acid	500
EDTA	2924	Spectinomycin	100
Erythromycin	200	Theophylline	250
Ethosuximide	100	Tobramycin	100
Furosemide	100	Triamterene	100
Gentamicin	120	Valproic acid	500
Kanamycin	100	Vancomycin	630
Kanamycin sulfate B	100	Verapamil	100
Ketoconazole	100		

Results were established using the ADVIA Centaur system, except for biotin which were established using an Atellica IM Analyzer. Assay results obtained at individual laboratories may vary from the data presented.

Dilution Recovery

Three human whole blood samples in the range of 1164.24–1321.28 ng/mL (968.07–1098.64 nmol/L) of cyclosporine were diluted 1:2, 1:4, and 1:8 with Atellica IM Multi-Diluent 12 and assayed for recovery. The recoveries ranged from 100.0%–114.7% with a mean recovery of 105.4%.

Sample	Dilution	Expected (ng/mL)	Observed (ng/mL)	Expected (nmol/L)	Observed (nmol/L)	Recovery (%)
Serum 1	—	1321.28	1321.28	1098.64	1098.64	100.0
	1:2	660.64	708.36	549.32	589.00	107.2
	1:4	330.32	341.40	274.66	283.87	103.4
	1:8	165.16	172.13	137.33	143.13	104.2
	Mean					103.7
Serum 2	—	1164.24	1164.24	968.07	968.07	100.0
	1:2	582.12	609.58	484.03	506.87	104.7

Sample	Dilution	Expected (ng/mL)	Observed (ng/mL)	Expected (nmol/L)	Observed (nmol/L)	Recovery (%)
	1:4	291.06	319.92	242.02	266.01	109.9
	1:8	145.53	152.48	121.01	126.79	104.8
	Mean					104.9
Serum 3	—	1201.69	1201.69	999.21	999.21	100.0
	1:2	600.85	628.96	499.61	522.98	104.7
	1:4	300.42	344.54	249.80	286.49	114.7
	1:8	150.21	167.63	124.90	139.38	111.6
	Mean					107.7
Mean						105.4

Results were established using the Atellica IM Analyzer. Assay results obtained at individual laboratories may vary from the data presented.

Spiking Recovery

Varying amounts of cyclosporine were added to 2 cyclosporine-free normal whole blood samples and 2 samples from patients taking cyclosporine. The recoveries ranged from 91.1%–108.2% with a mean of 96.5%.

Sample	Amount Added (ng/mL)	Expected (ng/mL)	Observed (ng/mL)	Amount Added (nmol/L)	Expected (nmol/L)	Observed (nmol/L)	Recovery (%)
1	100	100	97	83	83	81	97.0
	400	400	400	333	333	332	99.9
	800	800	787	665	665	654	98.3
	1500	1500	1624	1247	1247	1350	108.2
	Mean						100.9
2	100	100	96	83	83	80	95.8
	400	400	389	333	333	324	97.3
	800	800	739	665	665	614	92.3
	1500	1500	1367	1247	1247	1136	91.1
	Mean						94.1
3	—	175.1	175	—	145.6	145.5	—
	400	575.1	526	333	478	437	91.4
	800	975.1	938	665	811	780	96.2
	Mean						93.8
4	—	318.4	318	—	264.7	264.4	—
	400	718.4	667	333	597	554	92.8
	800	1118.4	1098	665	930	913	98.2

Sample	Amount Added (ng/mL)	Expected (ng/mL)	Observed (ng/mL)	Amount Added (nmol/L)	Expected (nmol/L)	Observed (nmol/L)	Recovery (%)
	Mean						95.5
Mean							96.5

Results were established using the ADVIA Centaur system. Assay results obtained at individual laboratories may vary from the data presented.

Standardization

The Atellica IM CsA assay is traceable to an internal standard manufactured using highly purified cyclosporine (USP grade). Assigned values for calibrators are traceable to this standardization.

Technical Assistance

For customer support, contact your local technical support provider or distributor.

siemens.com/healthineers

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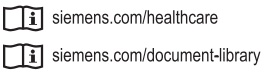
Definition of Symbols

The following symbols may appear on the product labeling:

Symbol	Symbol Title and Description
	Consult instructions for use
 Rev. 01	Version of instructions for use
 siemens.com/healthcare siemens.com/document-library	Internet URL address to access the electronic instructions for use
Rev. REVISION	Revision

Symbol	Symbol Title and Description
	Caution Consult instructions for use or accompanying documents for cautionary information such as warnings and precautions that cannot, for a variety of reasons, be presented on the medical device.
	Biological risks Potential biological risks are associated with the medical device.
	Corrosive
	Dangerous to environment
	Irritant Oral, dermal, or inhalation hazard
	Inhalation hazard Respiratory or internal health
	Flammable Flammable to extremely flammable
	Oxidizing
	Explosive
	Toxic
	Compressed gas
	Keep away from sunlight Prevent exposure to sunlight and heat.
	Up Store in an upright position.
	Do not freeze
	Temperature limit Upper and lower limits of temperature indicators are adjacent to the upper and lower horizontal lines.
	Handheld barcode scanner

Symbol	Symbol Title and Description
IVD	*In vitro* diagnostic medical device
Σ (n)	Contains sufficient for <n> tests Total number of IVD tests the system can perform with the IVD kit reagents appears adjacent to the symbol.
RxOnly	Prescription device (US only) Applies only to United States-registered IVD assays. CAUTION: Federal (USA) law restricts this device to sale by or on the order of a licensed healthcare professional.
	Mixing of substances Mix product before use.
	Reconstitute and mix lyophilized product before use.
	Target
	Interval
	Legal Manufacturer
EC REP	Authorized Representative in the European Community
	Use-by date Use by the designated date.
LOT	Batch code
REF	Catalog number
	Recycle
PRINTED WITH SOY INK	Printed with soy ink
CE	CE Mark
CE 0088	CE Mark with notified body ID number Notified body ID number can vary.
YYYY-MM-DD	Date format (year-month-day)
CHECKSUM	Variable hexadecimal number that ensures the Master Curve and Calibrator definition values entered are valid.
UNITS C	Common Units
UNITS SI	International System of Units

Symbol	Symbol Title and Description
MATERIAL	Material
MATERIAL ID	Unique material identification number
CONTROL NAME	Name of control
CONTROL TYPE	Type of control

Legal Information

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