ENGLISH

REAADS®

ANTI-PHOSPHATIDYLSERINE IgG/IgM
SEMI-QUANTITATIVE TEST KIT
For *In Vitro* Diagnostic Use

An enzyme-linked immunosorbent assay (ELISA) for the semi-quantitative determination of IgG and IgM anti-phosphatidylserine antibodies in human serum or citrated plasma (3.2% sodium citrate).

INTENDED USE

Detection and semi-quantitation of anti-phosphatidylserine antibodies in individuals with systemic lupus erythematosus (SLE) and lupus-like disorders (anti-phospholipid syndrome).

SUMMARY AND EXPLANATION OF THE ANTI-PHOSPHATIDYLSERINE TEST

Anti-phospholipid antibodies are a heterogeneous group of immunoglobulins that bind to several anionic phospholipids, including cardiolipin and phosphatidylserine.[1,2] High serum levels of anti-phospholipid antibodies are frequently detected in patients with autoimmune (i.e., SLE) and non-autoimmune diseases, as well as in apparently healthy individuals.[3,4] These antibodies have been associated with an increased risk for recurrent arterial and venous thrombotic events, thrombocytopenia and fetal loss. These manifestations are the main features of the anti-phospholipid syndrome.[5,6]

Anti-phospholipid antibodies are detected by either ELISAs using cardiolipin as the antigen (anti-cardiolipin antibodies)[7] or coagulation assays (lupus anticoagulants).[8] Unlike cardiolipin, phosphatidylserine is a more physiologically relevant phospholipid due to its presence in cell membranes of endothelial cells and platelets[9] and its role in the coagulation cascade.[10] The detection of anti-phosphatidylserine (aPS) antibodies by ELISA has been recommended for the serological diagnosis of anti-phospholipid syndrome.[8] Patients with positive reactions to both cardiolipin and phosphatidylserine were more likely to have clinical complications than those positive for only one.[11] Higher prevalence and mean serum levels of IgG anti-phosphatidylserine antibodies have been reported in autoimmune patients.[12] In addition, anti-phosphatidylserine antibodies in SLE patients correlated with clinical manifestations of anti-phospholipid syndrome[13] and their pathogenic role has been demonstrated in a murine model.[14]

Autoimmune anti-phospholipid antibodies require a serum cofactor (β_2-glycoprotein I) for optimal binding.[15,16] Antibodies to phosphatidylserine also require β_2-glycoprotein I.[17] Bovine serum is provided as the source of cofactor in this assay for increased detection of clinically relevant antibodies. The REAADS Anti-phosphatidylserine Test Kit uses the well known ELISA format to detect anti-phosphatidylserine antibodies in human serum and provides rapid, highly reproducible, accurate, and objective results. The values for IgG anti-phosphatidylserine antibodies and IgM anti-phosphatidylserine antibodies are reported separately.

PRINCIPLE OF THE TEST

The test is performed as an indirect ELISA. The concentration of IgG anti-phosphatidylserine antibodies and IgM anti-phosphatidylserine antibodies must be determined separately. Diluted serum or plasma samples, calibrator sera, and controls are incubated in phosphatidylserine coated microwells. β_2-glycoprotein I is provided in the sample diluent. Incubation allows the anti-phosphatidylserine (aPS) antibodies present in the samples to react with the immobilized antigen. After the removal of unbound serum or plasma proteins by washing, antibodies specific for human IgG or IgM, labeled with horseradish peroxidase (HRP), are added forming complexes with the phosphatidylserine bound antibodies. Two enzyme-conjugated antibody solutions are provided, one specific for human IgG antibodies and one specific for human IgM antibodies. Following another washing step, the bound enzyme-antibody conjugate is assayed by the addition of a single solution containing tetramethylbenzidine (TMB) and hydrogen peroxide (H_2O_2) as the chromogenic substrate. Color develops in the wells at an intensity proportional to the serum concentration of anti-phosphatidylserine (aPS) antibodies.

Results are obtained by reading the O.D. (optical density or absorbance) of each well in a spectrophotometer. Calibrator sera are provided with the IgG and IgM anti-phosphatidyl-serine antibody concentrations expressed in GPS (IgG anti-phosphatidylserine) or MPS (IgM anti-phosphatidylserine) units, respectively. The user has the option of running either a single point calibrator or a four-point calibration curve. For single point calibration, dividing the concentration value of the calibrator sera by the O.D. value of the calibrator provides a conversion factor (one for IgG and one for IgM). The O.D. values of the other samples are multiplied by the conversion factor to obtain IgG and IgM anti-phosphatidylserine antibody concentrations in GPS or MPS units. For multipoint calibration, perform a linear regression analysis with calibrator values against calibrator O.D.s. Control and patient results are determined from the calibration curve. These units are traceable to the reference preparations of the Louisville Antiphospholipid Laboratory.

REAGENTS

Store at 2 - 8°C. Do Not Freeze.

Each REAADS Anti-phosphatidylserine 96-microwell Test Kit contains the following reagents **(volumes may vary depending on the kit size and configuration)**:

- 12x8 Phosphatidylserine (from porcine brain) coated microwells, with frame.
- 60 mL Sample Diluent I (green solution); contains bovine calf serum.*
- 0.250 mL IgG Calibrator Sera* (1-high, 2-moderate, 3-low) (human); see vial label for antibody concentration in GPS units. Calibrator 3 should be used when performing single point calibration.
- 0.250 mL IgM Calibrator Sera* (1-high, 2-moderate, 3-low) (human); see vial label for antibody concentration in MPS units. Calibrator 3 should be used when performing single point calibration.
- 0.250 mL IgG Positive Control Serum* (human); see vial label for expected GPS range.
- 0.250 mL IgM Positive Control Serum* (human); see vial label for expected MPS range.
- 0.250 mL Normal Control Serum* (human); see vial label for expected GPS and MPS ranges.
- 15 mL anti-human IgG (goat) HRP-Conjugated Antibody Solution (blue solution); contains 0.01% thimerosal and gentamycin sulfate as preservatives
- 15 mL anti-human IgM (goat) HRP-Conjugated Antibody Solution (red solution); contains 0.01% thimerosal and gentamycin sulfate as preservatives
- 15 mL One Component Substrate (TMB/ H_2O_2); ready to use.
- 15 mL Stopping Solution (0.36 N sulfuric acid).
- 2 bottles (30 mL) Wash Concentrate (33X PBS).

***CAUTION: Contains sodium azide**

WARNINGS AND PRECAUTIONS

For *In Vitro* Diagnostic Use

1. Human source material used to prepare the calibrators and controls included in this kit has been tested and shown to be negative for antibodies to HBsAg, HCV, and HIV 1 & 2 by FDA required tests. However, all human blood derivatives, including patient samples, should be handled as potentially infectious material.
2. Do not pipette by mouth.
3. Do not smoke, eat, or drink in areas where specimens or kit reagents are handled.
4. Wear disposable gloves while handling kit reagents and wash hands thoroughly afterwards.
5. Certain components of this product contain sodium azide as a preservative. Sodium azide has been reported to form lead and copper azides when left in contact with these metals. These metal azides are explosive. Any solutions containing azide must be thoroughly flushed with copious amounts of water to prevent the build-up of explosive metal azides in the plumbing system.
6. One component substrate can cause irritation to the eyes and skin. Absorption through the skin is possible. Use gloves when handling substrate and wash thoroughly after handling. Keep reagent away from ignition sources. Avoid contact with oxidizing agents.
7. Certain components are labeled with one or more of the following: Harmful if swallowed (R22). Avoid contact with skin and eyes (S24/25). In case of contact with eyes, rinse immediately with plenty of water and seek medical advice (S26). Wear suitable protective clothing and gloves (S36/37). Keep away from sources of ignition–no smoking (S16).

SPECIMEN COLLECTION AND PREPARATION

Serum is the preferred sample matrix. Blood should be collected by venipuncture and the serum separated from the cells by centrifugation after clot formation. If not tested immediately, specimens should be stored at 2 to 8°C. If specimens are to be stored for more than 72 hours, they should be frozen at -20°C or below. Avoid repeated freezing and thawing. Do not use hemolyzed, icteric, or lipemic serum or plasma as these conditions may cause aberrant results. Specimens containing visible particulate matter should be clarified by centrifugation before testing.

Plasma collected with 3.2% sodium citrate may be used. Blood should be collected by venipuncture and the plasma immediately separated from the cells by centrifugation at 1500g for 10 minutes. The supernatant must be carefully removed after centrifugation to avoid contamination with platelets. Repeating the centrifugation and separation steps may be advisable to minimize platelet contamination. Lysed or aged platelets can react with anti-phospholipid antibodies leading to aberrant results. If not tested immediately, plasma samples should be stored as described for serum.

INSTRUCTIONS FOR USE

Materials Provided

REAADS Anti-phosphatidylserine Test Kit; see “Reagents” for a complete list.

Materials Required but not Supplied

- Reagent grade water to prepare PBS wash solution and to zero or blank the plate reader during the final assay step
- Graduated cylinders
- Precision pipettors capable of delivering between 5 µL and 1000 µL, with appropriate tips
- Miscellaneous glassware appropriate for small volume handling
- Flask or bottle, 1 liter
- Wash bottles, preferably with the tip partially cut back to provide a wide stream, or an automated or semi-automated washing system
- Disposable gloves
- Plate reading spectrophotometer capable of reading absorbance at 450 nm (with a 650 nm reference if available)
- Multichannel pipettors capable of delivering to 8 wells simultaneously

Procedural Notes

1. Bring serum samples and kit reagents to room temperature (18-26°C) and mix well before using; **avoid foaming**. Return all unused samples and reagents to refrigerated storage as soon as possible.
2. All dilutions of calibrators, controls, and test sera must be made just prior to use in the assay.
3. A single water blank well can be set up on each plate with each run. No sample or kit reagents are to be added to this well. Instead, add 200 µL of reagent grade water to the well immediately prior to reading the plate in the spectrophotometer. The plate reader should be programmed to zero or blank against air or a water well.
4. Good washing technique is critical for optimal performance of the assay. Adequate washing is best accomplished by directing a forceful stream of wash solution into the bottom of the microwells from a plastic squeeze bottle with a wide tip. Wash solution in the water blank well will not interfere with the procedure. An automated microtiter plate washing system can also be used.
5. IMPORTANT: Failure to adequately remove residual PBS can cause inconsistent color development of the Substrate Solution.
6. Use a multichannel pipettor capable of delivering to 8 wells simultaneously when possible. This speeds the process and provides more uniform incubation and reaction times for all wells.
7. Careful controlled timing of all steps is critical. All calibrators, controls, and samples must be added within a five minute period. Batch size of samples should not be larger than the amount that can be added within this time period.
8. For all incubations, the start of the incubation period begins with the completion of reagent or sample addition.
9. Addition of all samples and reagents should be performed at the same rate and in the same sequence.
10. Incubation temperatures above or below normal room temperature (18-26°C) may contribute to inaccurate results.
11. Avoid contamination of reagents when opening and removing aliquots from the primary vials.
12. Do not use Tween 20 or other detergents in this assay.
13. Do not use kit components beyond expiration date.
14. Do not use kit components from different kit lot numbers.

REAGENT PREPARATION

Wash Solution (PBS): Measure 30 mL of Wash Concentrate (33X PBS) and dilute to 1 liter with reagent grade water. The pH of the final solution should be 7.35 ± 0.1. Store unused PBS solution in the refrigerator at 2-8°C. Discard if the solution shows signs of microbial or cross contamination.

Assay Procedure

1. The assay can be performed with a single point calibration (Calibrator 3) or a four-point calibration curve (Calibrators 1, 2, and 3 plus sample diluent/reagent blank as Calibrator 4 equal to 0 GPS or 0 MPS units). A reagent blank control should also be run for each conjugate, IgG and IgM, with the single point and multipoint calibration method; Sample Diluent without serum is added to the well. This well will be treated the same as sample wells in subsequent assay steps.
2. Remove any microwell strips that will not be used from the frame and store them in the bag provided.
3. Prepare a 1:50 dilution of the calibrators, controls, and patient samples in sample diluent (green solution); e.g. 10 µL sample added to 490 µL Sample Diluent I equals a 1:50 sample dilution.
4. Add 100 µL of diluted calibrators (including the reagent blank/Calibrator 4), controls, and patient sample(s) to the appropriate microwells.
5. Incubate 15 minutes at room temperature. After the incubation is complete, carefully invert the microwells and empty the sample fluid. Do not allow samples to contaminate other microwells.
6. Wash 4 times with PBS. Each well should be filled with PBS per wash. Invert microwells between each wash to empty fluid. Use a snapping motion of the wrist to shake the liquid from the wells. The frame must be squeezed at the center on the top and bottom to retain microwell modules during washing. Blot on absorbent paper to remove residual wash fluid. Do not allow wells to dry out between steps.

7. Add 100 µL anti-human IgG Conjugate (blue) to the wells corresponding to the IgG calibrator, controls, reagent blank, and patient samples. Add 100 µL anti-human IgM Conjugate (red) to the wells corresponding to the IgM calibrator, controls, reagent blank, and patient samples.
8. Incubate for 15 minutes at room temperature. After the incubation is complete, carefully invert the microwells and empty the conjugate solutions. Take care to prevent cross-contamination of IgG and IgM Antibody Conjugate Solutions.
9. Wash 4 times with PBS as in step 7. Use a snapping motion to drain the liquid and blot on absorbent paper after the final wash. Do not allow the wells to dry out.
10. Add 100 µL Substrate to each well and incubate for 10 minutes at room temperature. Add the substrate to the wells at a steady rate. Blue color will develop in wells with positive samples.
11. Add 100 µL Stopping Solution (0.36 sulfuric acid) to each well to stop the enzyme reaction. Add the Stopping Solution to the wells in the same order and at the same rate as the Substrate was added. Blue Substrate will turn yellow and colorless solution will remain colorless. Blank or zero the plate reader against air or a water blank well. Read the O.D. of each well at 450 nm (and 650 nm reference if dual beam). The O.D. values should be measured within 30 minutes after the addition of Stopping Solution.

Results

Single Point Calibration

1. Calculate the mean O.D. values if duplicates of Calibrator 3, controls and patient samples were performed.
2. Divide the concentration value of Calibrator 3 (printed on the vial label) by the O.D. or mean O.D. value of the calibrator serum to obtain the conversion factor.
3. Multiply the O.D. or mean O.D. values for each of the controls and patient samples by the appropriate conversion factor to obtain a concentration value in GPS or MPS units.

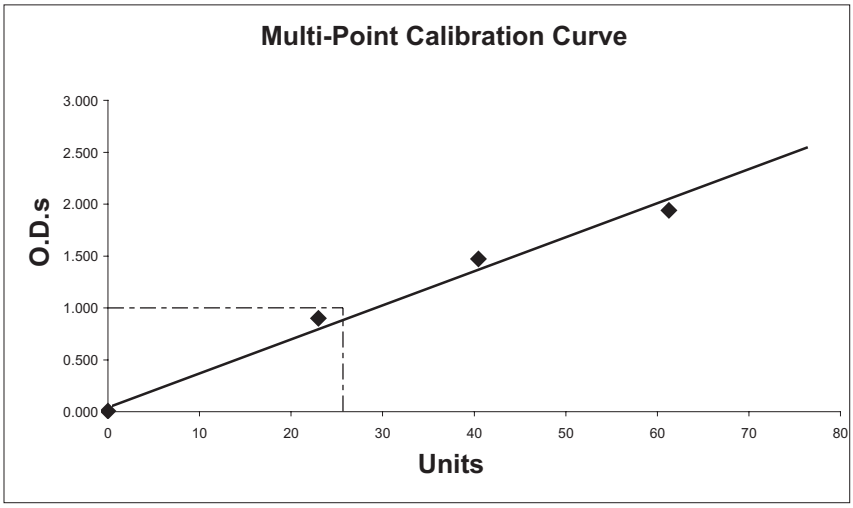
$$\text{Conversion Factor} = \frac{\text{Anti-phosphatidylserine concentration of Calibrator 3(GPS or MPS)}}{\text{Absorbance value of the Calibrator 3 (O.D. – G or M)}}$$

$$\text{Anti-phosphatidylserine concentration of sample} = \text{Conversion Factor X Absorbance of the Sample (O.D.)}$$

4. The conversion factor must be calculated for both calibrators for each assay run. Using a conversion factor from another assay or interchanging GPS and MPS Conversion Factors will invalidate the results.

Multi-Point Curve Calibration

1. Calculate the mean O.D. values if duplicates of the calibrators, controls and patient samples were performed.
2. Perform linear regression analysis with the four calibrator values (See vial labels for GPS or MPS units. Calibrator 4 [sample diluent] is equal to 0 GPS or 0 MPS units) against the mean O.D.s for each calibrator.
3. The calibrator curve can be plotted either automatically using a validated software program or manually with graph paper. It is recommended to use a zero intercept when generating the regression line to avoid negative values. If this option is not available, any negative values should be reported as zero units. When generating the curve manually, draw a best fit line through the plotted points using a zero incercept.
4. Determine the control and patient sample values from the calibrator curve.
5. Example of a multi-point curve calibration.



Using the example calibration curve provided, a specimen O.D. of 1.000 at 450 nm would correspond to a calculated value of 26.2 units. The calibration curve provided is an example only and should not be used to calculate patient results. A new calibration curve should be performed with every test run.

Quality Control

1. The O.D. value of Calibrator 3 should be at least 0.400 to assure that the kit is functioning properly. Calibrator 3 O.D. readings of less than 0.400 may indicate that the kit is no longer suitable for use.
2. The O.D. of Calibrator 4 or reagent blank should be less than 0.100 when the spectrophotometer has been blanked against air or a water well. Readings greater than 0.100 may indicate possible reagent contamination or inadequate plate washing.
3. The anti-phosphatidylserine values obtained for the control sera should be within the ranges indicated on the container labels. Occasional small deviations outside these ranges are acceptable.
4. O.D. values for duplicates (if performed) of the controls or patient samples should be within 20% of the mean O.D. value for samples with absorbance readings greater than 0.200.
5. Each laboratory should periodically determine its own normal cut-off values for the appropriate population of patients. See Performance Characteristics, Clinical Specificity, as an example.
6. Samples with anti-phosphatidylserine values greater than 100 GPS or 80 MPS may be reported as “greater than 100 GPS or 80 MPS”.
7. Assure that all quality control parameters have been met (see Quality Control section) before reporting test results.

NORMAL RANGE

Serum samples from 130 healthy blood donors were tested for IgG anti-phosphatidylserine and 128 for IgM anti-phosphatidylserine (aPS) antibodies; the following normal ranges were established (mean + 3 SD):

- Less than 16 GPS
- Less than 22 MPS

EXPECTED PREVALENCE

SLE:

Serum samples from 53 individuals with SLE were tested with the kit. Seventeen of the samples (32%) were positive for IgG anti-phosphatidylserine antibodies. Four of the samples (8%) were positive for IgM anti-phosphatidylserine antibodies. A good correlation (r = 0.87) was found between anti-phosphatidylserine and anti-cardiolipin antibody levels in this group.

Other Disease States:

Twenty-seven serum samples from patients with rheumatoid arthritis (RA) were tested in the assay. Only one sample was positive for IgG anti-phosphatidylserine antibodies. None were positive for IgM anti-phosphatidylserine antibodies.

The clinical significance of positive results in disease states, other than SLE, is still under investigation.

PERFORMANCE CHARACTERISTICS

Clinical Specificity

Normal Samples:

Multiple healthy blood donor populations were evaluated against an IgG cut-off of 16 GPS and IgM cut-off of 22 MPS. When the results were averaged, the assay was shown to be 96% specific for IgG aPS antibodies, and 96% specific for IgM aPS antibodies.

Disease Controls:

Serum samples from 10 patients with SLE or a lupus-like disorder who were known not to have had thrombotic episodes, nor any other feature of the anti-phospholipid syndrome, were tested in the assay. None of the samples were positive for IgG anti-phosphatidylserine antibodies (100%). One sample was weakly positive for IgM anti-phosphatidylserine antibodies (90%).

Clinical Sensitivity

Serum samples from 18 female SLE patients with a clinical history of thrombosis, thrombocytopenia or recurrent fetal loss were evaluated for anti-phosphatidylserine antibodies. Nine of the samples were positive for IgG anti-phosphatidylserine antibodies, for a sensitivity of 50% in this sample population. Two of the samples were positive for IgM anti-phosphatidylserine antibodies. Seven of the samples had elevated levels of IgG anti-phosphatidylserine antibodies only, two samples had elevated levels of both IgG and IgM anti-phosphatidylserine antibodies, and none were positive for IgM anti-phosphatidylserine antibodies only. As described above, serum samples from 10 SLE patients with no clinical history of thrombosis, thrombocytopenia or recurrent fetal loss were used as controls. None of these samples tested positive for IgG anti-phosphatidylserine antibodies. One sample tested positive for IgM anti-phosphatidylserine antibodies.

Precision

Three samples with known GPS values (two low and one high), and three samples with known MPS values (two low and one high) were assayed in 23 replicates on three different occasions. The mean intraassay and interassay coefficients of

variation (CVs) are presented in the following table. The reported intraassay coefficient of variation is the mean of the three separate intraassay CVs. Interassay CV is the coefficient of variation obtained from three plates from one lot.

Sample Value	Intraassay CV	Mean Interassay CV
Low (<10 GPS)	14.9%	8.3%
Low (<10 MPS)	10.7%	7.0%
Low (15 GPS)	9.3%	9.3%
Low (15 MPS)	9.4%	4.8%
High (40 GPS)	14.2%	6.9%
High (40 MPS)	10.3%	5.0%

Recovery

Three samples with known GPS concentration values were mixed in various proportions. The calculated value was compared to the observed value. The observed value divided by the calculated value is given as a percent recovery and is presented in the following table.

Sample Value	Recovery Value (%)
< 10 GPS	78%
~ 30 GPS	91%
~ 40 GPS	98%

Three samples with known MPS concentration values were mixed in various proportions. The calculated value was compared to the observed value. The observed value divided by the calculated value is given as a percent recovery and is presented in the following table.

Sample Value	Recovery Value (%)
< 10 MPS	103%
~ 30 MPS	107%
~ 45 MPS	96%

LIMITATIONS OF THE TEST

The anti-phosphatidylserine antibody concentration values obtained from this assay are an aid to diagnosis only. Each physician must interpret these results in light of the patient's history, physical findings and other diagnostic procedures. If clinical findings suggest the presence of anti-phospholipid antibodies and the patient is negative for anti-phosphatidyl-serine antibodies, some investigators recommend testing for anti-cardiolipin antibodies and the lupus anticoagulant to confirm the negative result. A patient is considered positive for anti-phospholipid antibodies if one or all of the tests give positive results.

Anti-phosphatidylserine antibodies can appear transiently at low levels during many infections.[18,19] If a patient first tests positive while there are clinical signs of infection, the test should be repeated after an interval of six to eight weeks.

WARRANTY

This product is warranted to perform as described in this package insert. Corgenix, Inc. disclaims any implied warranty of merchantability or fitness for a particular use, and in no event shall Corgenix, Inc. be liable for consequential damage.

For Technical or Customer Service in the United States, phone 1-800-729-5661. Outside the United States phone (303)-457-4345, fax (303)-457-4519 or contact a Corgenix authorized distributor.

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EC REP Authorized Representative
(Bevollmächtigter)
(Représentant autorisé)
(Representante autorizado)
(Rappresentante autorizzato)

IVD In vitro diagnostic medical device
(In-vitro-Diagnostikum)
(Dispositif de diagnostic in vitro)
(Dispositivo médico para diagnóstico in vitro)
(Dispositivo medico-diagnostico in vitro)

LOT Batch
(Charge)
(Lot)
(Lote)
(Lotto)

Expiry date
(Verfallsdatum)
(Date de péremption)
(Fecha de caducidad)
(Data di scadenza)

Storage conditions
(Lagerbedingungen)
(Conditions de stockage)
(Condiciones de almacenamiento)
(Condizioni di conservazione)

Xn Harmful
(Gesundheitsschädlich)
(Nocif)
(Perjudicial)
(Nocivo)

Xi Irritant
(Reizend)
(Irritant)
(Irritante)
(Irritante)

Biological Risk
(Biologisches Risiko)
(Risque biologique)
(Riesgo biológico)
(Rischio biologico)

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