EUROIMMUN US

K132195

JUN 27 2014

**PREMARKET NOTIFICATION**
**510(K) SAFETY AND EFFECTIVENESS SUMMARY**
*(As required by 21 CFR § 807.92)*

**A. 510(k)Number:**
K132195

**B. Purpose for Submission:**
New Device

**C. Measurand:**
Anti-PLA2R Autoantibodies

**D. Type of Test:**
Qualitative or Semi-Quantitative Enzyme Immunoassay

**E. Applicant:**
EUROIMMUN US INC.

**F. Proprietary and Established Names:**
EUROIMMUN Anti-PLA2R ELISA (IgG)

**G. Regulatory Information:**

1. Regulation:
   21 CFR 866.5780 - Anti-phospholipase A2 receptor immunological test system
2. Classification:
   Class II
3. Product code:
   PGV- Anti-phospholipase A2 receptor
4. Panel:
   Immunology

**H. Intended Use:**

1. Intended Use(s):
   The EUROIMMUN Anti-PLA2R ELISA (IgG) test kit is intended for the qualitative or semi-quantitative determination of IgG class autoantibodies against phospholipase A2 receptor (PLA2R) in human serum. It is used as an aid in the diagnosis of primary membranous glomerulonephritis (pMGN), in conjunction with other laboratory and clinical findings.
2. Indication(s) for Use:
   Same as Intended Use.
3. Special Conditions for the Use Statement(s):
   *For Prescription Use Only.*
4. Special Instrument Requirements:
   Microwell plate reader capable of measuring OD at 450nm and at 620nm for dual wavelength readings.

## I. Device Description:

The EUROIMMUN Anti-PLA2R ELISA (IgG) consists of a microwell ELISA plate coated with PLA2R antigen, 5 calibrators, positive and negative control, peroxidase-labelled anti-human IgG conjugate, sample buffer, wash buffer concentrate, TMB chromogen/substrate solution and stop solution.

## J. Substantial Equivalence Information:

1. Predicate device name (s):
   EUROIMMUN Anti-PLA2R IFA (IgG)

2. Predicate 510(k) number(s):
   k132379

3. Comparison with predicate:

*Similarities*

| Item | New device | Predicate device |
|---|---|---|
| Manufacturer | EUROIMMUN AG | Same |
| Intended use | Detection of IgG antibodies against PLA2R | Same |
| Sample types | Serum | Same |
| Controls | 2 controls: 1 positive, 1 negative | Same |
| Reagent preparation | All reagents are ready to use, except for the wash buffer. | Same |

*Differences*

| Item | New device | Predicate device |
|---|---|---|
| Assay format | Qualitative or semi-quantitative (using either all calibrators or the cut-off calibrator only) | Qualitative |
| Antigen | Recombinant PLA2R (type M) | PLA2R transfected cells and control-transfected cells |
| Reagents | 96 well microplate, 5 Calibrators (2, 20, 100, 500 and 1500 RU/ml), Conjugate (anti-human IgG labeled with horseradish peroxidase), Sample buffer, Wash buffer (10x concentrate), Substrate solution (TMB), Stop solution (0.5 M sulphuric acid), 2 Controls, | BIOCHIP slides, Conjugate (fluorescein-labeled anti-human IgG), Salt for PBS pH 7.2, Tween 20, Embedding medium, Cover glasses, 2 Controls |
| Sample dilution | 1:101 | 1:10 |
| Procedure | ELISA: Sample incubation with micro-well antigen coated plate, followed by a wash step, incubation with conjugate, wash step, incubation with substrate, addition of stop solution, photometric reading | IFA: Sample incubation with tissues/cells, followed by a wash step, incubation with conjugate, wash step, embedding, fluorescence microscopy reading |
| Reported results | Qualitative, RU/ml or Ratio | Qualitative |
| Cut-off level | Qualitative: Ratio 1.0<br>Semi-quantitative: 20 RU/ml | 1:10 dilution |

## K. Standard/Guidance Document Referenced (if applicable):

*None Referenced.*

## L. Test Principle:

Patient samples are diluted 1:101 in sample buffer, 100 µl of each diluted patient sample and pre-diluted controls and calibrators are added to the antigen coated microtiter wells and incubated for 30 minutes at room temperature. After incubation the microtiter well strips are washed with wash buffer to remove unbound antibodies and 100 µl of the anti-human IgG enzyme conjugate reagent is added to each microtiter well. After an additional 30-minutes incubation at room temperature, the microtiter wells are again washed 3 times with 300 µl of wash buffer to remove any unbound enzyme conjugate and 100 µl of

the chromogen substrate is added. The strips are incubated for 15 minutes at room temperature and 100 µl stop solution is added. The microtiter plates are placed in an ELISA reader and read at a wavelength of 450 nm and a reference wavelength of between 620 nm and 650 nm within 30 minutes.

## M. Analytical Performance Characteristics (where applicable):

1. Reproducibility

*a. Intra- and Inter-Assay Reproducibility:*

Intra- and Inter-Assay coefficients of variation (CV) were determined using samples with values at different points on the calibration curve. The Intra-Assay CVs are based on 20 determinations and the Inter-Assay CVs on 30 determinations performed in 10 different runs on 5 different days (with 3 replicates per run). Tests were performed according to the package insert with the same lot and by the same technician. Acceptance criterium was that the CV's show results below 12% for positive and borderline samples. Acceptance criterium for negative samples was that all qualitative results be negative. Acceptance criterium for the ratio-based results was that all qualitative results (positive, borderline, negative) of the samples be in line with the expected result.

*Intra-Assay Reproducibility*

| n = 20 | Anti-PLA2R ELISA (IgG); *RU/ml* | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **8** |
| Mean Value | 2 | 12 | 18 | 26 | 48 | 109 | 782 | 861 |
| StDev | 0.1 | 0.5 | 0.5 | 0.9 | 1.5 | 3.0 | 33.5 | 48.7 |
| %CV | 10.9 | 4.2 | 2.6 | 3.4 | 3.1 | 2.8 | 4.3 | 5.7 |

| n = 20 | Anti-PLA2R ELISA (IgG); *Ratio* | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **8** |
| Mean Value | 0.1 | 0.6 | 0.9 | 1.3 | 2.0 | 4.2 | 7.5 | 7.6 |
| Range | 0.1 – 0.1 | 0.5 – 0.6 | 0.9 – 0.9 | 1.2 – 1.4 | 1.9 – 2.1 | 4.0 – 4.3 | 7.4 – 7.6 | 7.5 – 7.7 |
| Expected | neg | neg | bl | pos | pos | pos | pos | pos |
| % Positive | 0% | 0% | 0% | 100% | 100% | 100% | 100% | 100% |
| % Borderline | 0% | 0% | 100% | 0% | 0% | 0% | 0% | 0% |
| % Negative | 100% | 100% | 0% | 0% | 0% | 0% | 0% | 0% |

*Inter-Assay Reproducibility*

| n = 30 | Anti-PLA2R ELISA (IgG); *RU/ml* | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **8** |
| Mean Value | 2 | 12 | 20 | 28 | 51 | 110 | 793 | 884 |
| StDev | 1.2 | 1.0 | 1.7 | 1.1 | 3.2 | 11.2 | 81.4 | 87.5 |
| %CV | --- | 7.9 | 8.6 | 4.2 | 6.2 | 10.2 | 10.3 | 9.9 |

| n = 30 | Anti-PLA2R ELISA (IgG); *Ratio* | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **8** |
| Mean Value | 0.1 | 0.6 | 1.0 | 1.3 | 2.2 | 3.7 | 7.8 | 7.9 |
| Range | 0.1 – 0.3 | 0.5 – 0.6 | 0.8 – 1.1 | 1.2 – 1.4 | 1.8 – 2.5 | 3.0 – 4.3 | 6.6 – 8.9 | 7.0 – 8.9 |
| Expected | neg | neg | pos | pos | pos | pos | pos | pos |
| % Positive | 0% | 0% | 27% | 100% | 100% | 100% | 100% | 100% |
| % Borderline | 0% | 0% | 73% | 0% | 0% | 0% | 0% | 0% |
| % Negative | 100% | 100% | 0% | 0% | 0% | 0% | 0% | 0% |

b. *Repeatability & Reproducibility (Total Imprecision)*

*Repeatability*

Investigated using samples with values at different points on the calibration curve. Within-run, between-run, between-day and total standard deviations (SD) and coefficients of variation (CV) were calculated based on 150 determinations per sample performed in 6 different runs on 3 different days (with 2 runs per day and 25 replicates per run) according to the package insert with the same lot and by the same technician. Acceptance criterium was that the CV's show results below 12% for positive and borderline samples. Acceptance criterium for negative samples was that all qualitative results be negative. Acceptance criterium for the ratio-based results was that all qualitative results (positive, borderline, negative) of the samples be in line with the expected result.

*Repeatability*

| n = 150 | | Anti-PLA2R ELISA (IgG); *RU/ml* | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Sample** | **Mean** | **Within-run** | | **Between-run** | | **Between-day** | | **Total** | |
| | | **SD** | **%CV** | **SD** | **%CV** | **SD** | **%CV** | **SD** | **%CV** |
| **1** | 3 | 0.28 | 9.2 | 0.38 | 12.9 | 0.64 | 22.4 | 0.43 | 14.8 |
| **2** | 17 | 0.57 | 3.3 | 1.04 | 6.4 | 1.25 | 7.5 | 0.95 | 5.7 |
| **3** | 22 | 0.87 | 3.9 | 1.56 | 7.3 | 1.08 | 5.1 | 1.17 | 5.4 |
| **4** | 24 | 0.75 | 3.2 | 1.60 | 6.7 | 1.51 | 6.4 | 1.28 | 5.4 |
| **5** | 884 | 69.95 | 7.9 | 72.49 | 8.3 | 66.51 | 7.6 | 69.65 | 7.9 |
| **6** | 1356 | 65.65 | 4.8 | 33.59 | 2.5 | 45.60 | 3.4 | 48.28 | 3.6 |

| n = 150 | Anti-PLA2R ELISA (IgG); *Ratio* | | | | | |
|---|---|---|---|---|---|---|
| | **1** | **2** | **3** | **4** | **5** | **6** |
| Mean Value | 0.20 | 0.74 | 0.91 | 1.00 | 7.57 | 8.20 |
| Range | 0.16 – 0.25 | 0.68 – 0.81 | 0.76 – 1.27 | 0.83 – 1.17 | 6.34 – 8.22 | 7.45 – 8.72 |
| Expected | neg | bl | bl | pos | pos | pos |
| % Positive | 0% | 0% | 1% | 52% | 100% | 100% |
| % Borderline | 0% | 97% | 99% | 48% | 0% | 0% |
| % Negative | 100% | 3% | 0% | 0% | 0% | 0% |

*Reproducibility (Lot-to-Lot)*

Investigated using samples with values at different points on the calibration curve. Within-run, between-run, between-lot and total SD's and %CV's were calculated based on 18 determinations per sample performed in 3 different runs on 3 different days (with 3 runs per lot and 2 replicates per run) according to the package insert by the same technician. Acceptance criterium was that the CV's show results below 12% for positive and borderline samples. Acceptance criterium for negative samples was that all qualitative results be negative. Acceptance criterium for the ratio-based results was that all qualitative results (positive, borderline, negative) of the samples be in line with the expected result.

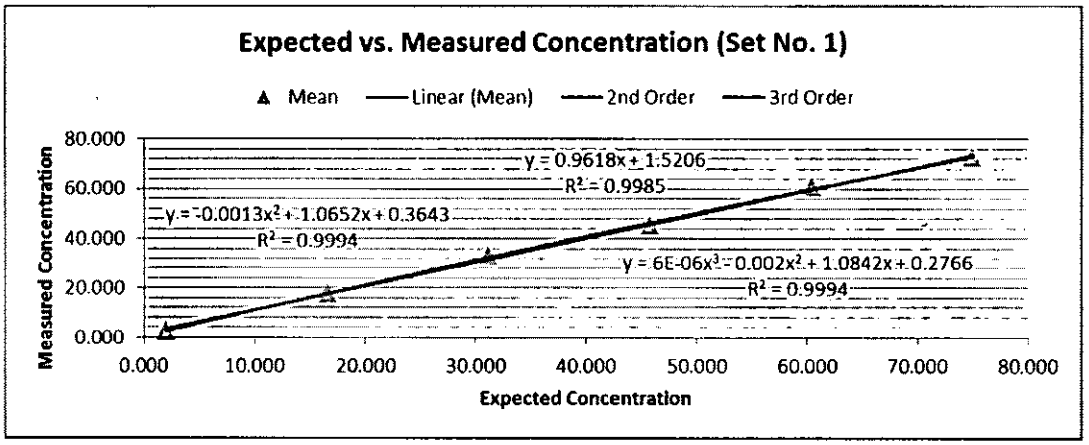
*Reproducibility*

| n = 18 | | Anti-PLA2R ELISA (IgG); *RU/ml* | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Sample** | **Mean** | **Within-run** | | **Between-run** | | **Between-Batch** | | **Total** | |
| | | **SD** | **%CV** | **SD** | **%CV** | **SD** | **%CV** | **SD** | **%CV** |
| **1** | 3 | 0.45 | 16.4 | 0.15 | 5.4 | 0.33 | 11.9 | 0.31 | 11.2 |
| **2** | 17 | 1.19 | 7.2 | 0.42 | 2.5 | 0.69 | 4.1 | 0.76 | 4.6 |
| **3** | 23 | 1.46 | 6.5 | 0.30 | 1.3 | 0.99 | 4.4 | 0.91 | 4.0 |
| **4** | 26 | 1.78 | 6.7 | 0.85 | 3.2 | 1.37 | 5.2 | 1.33 | 5.0 |
| **5** | 304 | 15.71 | 5.2 | 6.48 | 2.1 | 10.61 | 3.5 | 10.93 | 3.6 |
| **6** | 1260 | 127.19 | 10.1 | 35.80 | 2.8 | 33.53 | 2.7 | 65.51 | 5.2 |

| n = 18 | Anti-PLA2R ELISA (IgG); *Ratio* | | | | | |
|---|---|---|---|---|---|---|
| | **1** | **2** | **3** | **4** | **5** | **6** |
| Mean Value | 0.19 | 0.77 | 0.99 | 1.12 | 5.62 | 8.43 |
| Range | 0.16 – 0.21 | 0.68 – 0.83 | 0.91 – 1.12 | 1.06 – 1.20 | 5.29 – 6.12 | 7.71 – 9.04 |
| Expected | neg | neg | bl | pos | pos | pos |
| % Positive | 0% | 0% | 28% | 100% | 100% | 100% |
| % Borderline | 0% | 94% | 72% | 0% | 0% | 0% |
| % Negative | 100% | 6% | 0% | 0% | 0% | 0% |

c. *Linearity/Assay Reportable Range:*

Five sets of 11-step-wise dilutions were prepared by mixing low and high analyte samples. The concentrations ranged from a low concentration of 2 RU/mL to high concentrations of 75 RU/mL, 133 RU/mL, 790 RU/mL, 1100 RU/mL, or 1642 RU/mL. The assay was shown to be sufficiently linear from 2 to1500 RU/mL. Results from the two lowest ranges and the range throughout the AMR are shown below.




**SET 1**

**Linear (1st Order)**

| $R^2$ | 0.998 | | SE | 1.152 | | |
|---|---|---|---|---|---|---|
| | *Coeff* | *SE* | *t* | *P* | ↓95% | ↑95% |
| Intercept | 1.521 | 0.865 | 1.758 | 0.154 | -0.881 | 3.922 |
| X Var 1 | 0.962 | 0.019 | 51.011 | 0.000 | 0.909 | 1.014 |

**2nd Order**

| $R^2$ | 0.999 | | SE | 0.864 | | |
|---|---|---|---|---|---|---|
| | *Coeff* | *SE* | *t* | *P* | ↓95% | ↑95% |
| Intercept | 0.364 | 0.865 | 0.421 | 0.702 | -2.387 | 3.116 |
| X Var 1 | 1.065 | 0.053 | 20.089 | 0.000 | 0.896 | 1.234 |
| X Var 2 | -0.001 | 0.001 | -2.025 | 0.136 | -0.003 | 0.001 |

**3rd Order**

| $R^2$ | 0.999 | | SE | 1.054 | | |
|---|---|---|---|---|---|---|
| | *Coeff* | *SE* | *t* | *P* | ↓95% | ↑95% |
| Intercept | 0.277 | 1.242 | 0.223 | 0.845 | -5.069 | 5.622 |
| X Var 1 | 1.084 | 0.156 | 6.957 | 0.020 | 0.414 | 1.755 |
| X Var 2 | -0.002 | 0.005 | -0.404 | 0.725 | -0.023 | 0.019 |
| X Var 3 | 0.000 | 0.000 | 0.134 | 0.906 | 0.000 | 0.000 |

**SET 2**

**Linear (1st Order)**

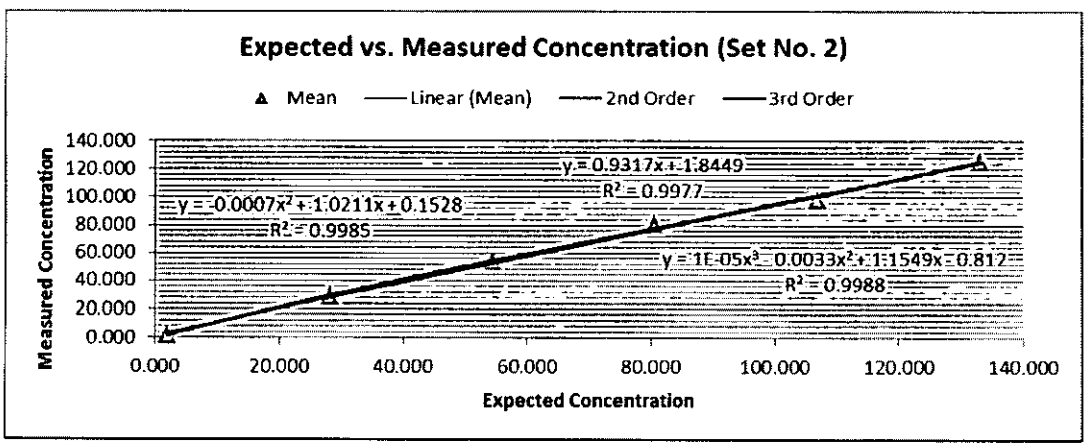
| $R^2$ | 0.998 | | SE | 2.445 | | |
|---|---|---|---|---|---|---|
| | *Coeff* | *SE* | *t* | *P* | ↓95% | ↑95% |
| Intercept | 1.845 | 1.806 | 1.021 | 0.365 | -3.170 | 6.861 |
| X Var 1 | 0.932 | 0.022 | 41.768 | 0.000 | 0.870 | 0.994 |

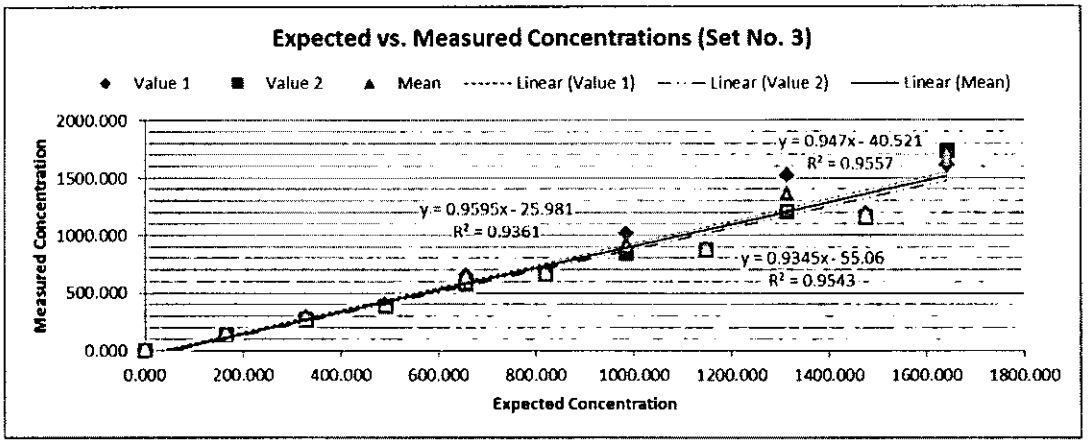
**2nd Order**

| $R^2$ | 0.998 | | SE | 2.323 | | |
|---|---|---|---|---|---|---|
| | *Coeff* | *SE* | *t* | *P* | ↓95% | ↑95% |
| Intercept | 0.153 | 2.224 | 0.069 | 0.949 | -6.925 | 7.231 |
| X Var 1 | 1.021 | 0.078 | 13.140 | 0.001 | 0.774 | 1.268 |
| X Var 2 | -0.001 | 0.001 | -1.196 | 0.318 | -0.002 | 0.001 |

**3rd Order**

| $R^2$ | 0.999 | | SE | 2.508 | | |
|---|---|---|---|---|---|---|
| | *Coeff* | *SE* | *t* | *P* | ↓95% | ↑95% |
| Intercept | -0.812 | 2.719 | -0.299 | 0.793 | -12.510 | 10.886 |
| X Var 1 | 1.155 | 0.196 | 5.903 | 0.028 | 0.313 | 1.997 |
| X Var 2 | -0.003 | 0.004 | -0.932 | 0.450 | -0.019 | 0.012 |
| X Var 3 | 0.000 | 0.000 | 0.757 | 0.528 | 0.000 | 0.000 |






d. *Traceability, Stability, Expected Values (Controls, Calibrators or Methods):*
A recognized standard or reference material for anti-PLA2R antibodies is not available. The assay is calibrated in relative arbitrary units (RU/ml). Alternatively, results may be given in ratios.

*Stability*
Stability studies are conducted following the international standard EN 13640:2002: Stability testing of in vitro diagnostic reagents. Three production lots of all kit reagents are tested. Real-time testing at 2-8°C and accelerated testing at 37°C are conducted. The shelf-life stability is 12 months at 2-8°C. Open-vial stability of the kit is 6 months when stored at 2-8°C. The wash buffer was found to be stable for at least 28 days when diluted to working strength.
*Controls & Calibrators*
The calibrators and controls are derived from human materials. Human originated material is tested and found negative for HBsAg, anti-HCV, anti-HIV-1 and anti-HIV-2, diluted to the appropriate concentration, stabilized and colored.

Calibrators are adjusted to match the required performance criteria in use with the corresponding microtiter strip lot and the corresponding kit controls.

Negative and Positive Controls are included. The positive control is *Ready for Use* with a 3-4+ fluorescence. Negative control is *Ready for Use* and is autoantibody negative. EUROIMMUN US INC. recommends using the positive and negative controls undiluted for the screening protocol.

e. *Limit of Blank, Limit of Detection and Limit of Quantitation/Functional Sensitivity:*
Limit of blank (LoB) and limit of detection (LoD) and limit of quantitation (LoQ)/functional sensitivity (FS) were investigated following CLSI standard EP17-A. The LoB was found to be 1.8 RU/ml & LoD of the Anti-PLA2R ELISA (IgG) was found to be 2.2 RU/ml.

The LoQ was estimated from the functional sensitivity which is defined as the lowest concentration at which the CV is 20%. From the same data LoB and LoD were calculated, the mean concentrations (X-axis) vs. % CVs (Y-axis) were plotted. The functional sensitivity was read from the potential regression line crossing the 20% CV line and was found to be approx. 1.4 RU/ml, which is in the range of the LoD and the lower limit of the measurement range of 2 RU/ml. Following CLSI standard EP17-A , "If this estimate is less than the defined goal for total error, then: LoQ = LoD"; 2.2 RU/ml.

f. *Analytical Specificity:*
Cross-reactivity: Cross reactivity was investigated using a panel of 65 clinically characterized sera positive for thyreoiditis, systemic lupus erythematosus (SLE), Sjögren's syndrome (SS),

systemic sclerosis (SSc), rheumatoid arthritis (RA), cANCA, pANCA, GBM and Hepatitis B surface antigen (HBsAg). All 65 sera were negative in the Anti-PLA2R ELISA (IgG), so no cross reactivity was found.

Interference: To investigate the influence from hemoglobin, triglycerides and bilirubin, sera at anti-PLA2R concentrations were spiked with potential interfering substances and incubated with the test system according to the package insert. The recovery in relation to the unspiked sample without interferent was calculated. Acceptance criterium was that the individual recovery be within the range of 70 – 130 % and the mean of recoveries for each interferent be within the range of 85 – 115 %. No significant interference was observed for concentrations of up to 1000 mg/dl for hemoglobin, 2000 mg/dl for triglyceride and 40 mg/dl for bilirubin.

g. *Assay Cut-Off:*
Qualitative evaluation: Ratio 1.0; <0.7: negative; ≥0.7 to <1.0: borderline; ≥1.0: positive
OD of the control or patient sample = Ratio
OD of calibrator 2
Semi-quantitative evaluation: 20 RU/ml; <14 RU/mL: negative; ≥14-<20 RU/mL borderline; ≥20 RU/mL positive

1. Comparison Study(s):

a. *Method comparison with predicate device:*
The samples from the clinical studies, in total 560 (275 from pMGN patients, 285 from control groups) were investigated for anti-PLA2R antibodies (IgG) using the two test systems EUROIMMUN Anti-PLA2R IFA and EUROIMMUN Anti-PLA2R ELISA (IgG). The discrepant samples were all from pMGN patients. Of the 25 discrepant samples positive with the EUROIMMUN Anti-PLA2R IFA and negative/borderline with the EUROIMMUN Anti-PLA2R ELISA (IgG), 19 samples exhibited a low IFA titer (1:10 to 1:32) and/or the ELISA result(s) was near cut-off (+/- 30%).

**RU/mL:**

| | | EUROIMMUN Anti-PLA2R IFA (Predicate) | | | |
|---|---|---|---|---|---|
| | | **Positive** | **Borderline*** | **Negative** | |
| **EUROIMMUN Anti-PLA2R ELISA (IgG)** | **Positive** | 184 | 0 | 1 | 185 |
| | **Borderline*** | 6 | 0 | 0 | 6 |
| | **Negative** | 22 | 0 | 347 | 369 |
| | | 212 | 0 | 348 | 560 |

**Borderline defined as ≥14 to <20 RU/mL in the Instructions for Use. Borderline samples should be considered as potentially positive and retested.*

**Borderline samples counted as NEGATIVE:**

| | | EUROIMMUN Anti-PLA2R IFA (Predicate) | | |
|---|---|---|---|---|
| | | **Positive** | **Negative** | |
| **EUROIMMUN Anti-PLA2R ELISA (IgG)** | **Positive** | 184 | 1 | 185 |
| | **Negative** | 28 | 347 | 375 |
| | | 212 | 348 | 560 |

| | | | | |
|---|---|---|---|---|
| **Positive Agreement:** | 184 / 212 | = 86.79% | **95% C.I.:** | 81.5% - 91.0% |
| **Negative Agreement:** | 347 / 348 | = 99.71% | **95% C.I.:** | 98.4% - 100.0% |

**Borderline samples counted as POSITIVE:**

| | EUROIMMUN Anti-PLA2R IFA (Predicate) | | |
|---|---|---|---|
| | **Positive** | **Negative** | |

| EUROIMMUN Anti-PLA2R ELISA (IgG) | | | | |
|---|---|---|---|---|
| | **Positive** | 190 | 1 | 191 |
| | **Negative** | 22 | 347 | 369 |
| | | 212 | 348 | 560 |

**Positive Agreement:** 190 / 212 = 89.62% **95% C.I.:** 84.7% - 93.4%

**Negative Agreement:** 347 / 348 = 99.71% **95% C.I.:** 98.4% - 100.0%

**Ratio:**

| | | EUROIMMUN Anti-PLA2R IFA (Predicate) | | | |
|---|---|---|---|---|---|
| | | **Positive** | **Borderline*** | **Negative** | |
| **EUROIMMUN Anti-PLA2R ELISA (IgG)** | **Positive** | 184 | 0 | 1 | 185 |
| | **Borderline*** | 12 | 0 | 1 | 13 |
| | **Negative** | 16 | 0 | 346 | 362 |
| | | 212 | 0 | 348 | 560 |

**Borderline defined as ≥14 to <20 RU/mL in the Instructions for Use. Borderline samples should be considered as potentially positive and retested.*

**Borderline samples counted as NEGATIVE:**

| | | EUROIMMUN Anti-PLA2R IFA (Predicate) | | |
|---|---|---|---|---|
| | | **Positive** | **Negative** | |
| **EUROIMMUN Anti-PLA2R ELISA (IgG)** | **Positive** | 184 | 1 | 185 |
| | **Negative** | 28 | 347 | 375 |
| | | 212 | 348 | 560 |

| | | | | | |
|---|---|---|---|---|---|
| **Positive Agreement:** | 184 / 212 | = 86.79% | **95% C.I.:** | 81.5% | - 91.0% |
| **Negative Agreement:** | 347 / 348 | = 99.71% | **95% C.I.:** | 98.4% | - 100.0% |

**Borderline samples counted as POSITIVE:**

| | | EUROIMMUN Anti-PLA2R IFA (Predicate) | | |
|---|---|---|---|---|
| | | **Positive** | **Negative** | |
| **EUROIMMUN Anti-PLA2R ELISA (IgG)** | **Positive** | 196 | 2 | 198 |
| | **Negative** | 16 | 346 | 362 |
| | | 212 | 348 | 560 |

| | | | | | |
|---|---|---|---|---|---|
| **Positive Agreement:** | 196 / 212 | = 92.45% | **95% C.I.:** | 88.0% | - 95.6% |
| **Negative Agreement:** | 347 / 348 | = 99.71% | **95% C.I.:** | 98.4% | - 100.0% |

*b. Matrix comparison:*
Not Applicable

2. Clinical Study(s):

Clinical studies were performed in cooperation with different sites (see below). In total 560 clinically characterized samples (275 from pMGN patients, 285 from control groups) were investigated for anti-PLA2R antibodies (IgG). pMGN diagnosis was based on renal biopsy and was considered to be idiopathic/primary when no secondary cause of MN was suspected on the basis of clinical and laboratory criteria. The samples were drawn within 8 weeks after biopsy, before treatment; excluding patients who had been or were currently being treated with immunosuppressive drugs. With the EUROIMMUN Anti-PLA2R ELISA (IgG) using the 5-point calibrated analysis and a cut-off of 20 RU/ml, a sensitivity of 66.9% (95% C.I.: 61.0 – 72.4%) was found in pMGN, which is within the expected range of approximately 70% of anti-PLA2R as reported in the scientific literature. Specificity was 99.6% (95% C.I.: 98.1 – 100.0%).

a. *Sensitivity:*

| No. | Panel | n | Anti-PLA2R ELISA (IgG) | | |
|---|---|---|---|---|---|
| | | | positive | % | 95% C.I. |
| 1 | Primary membranous glomerulonephritis (pMGN) | 275 | 184<br>5 borderline | 66.9% | 61.0 – 72.4% |

b. *Specificity:*

| No. | Panel | n | Anti-PLA2R ELISA (IgG) | | |
|---|---|---|---|---|---|
| | | | negative | % | 95% C.I. |
| 2 | Secondary membranous glomerulonephritis (sMGN) | 68 | 67 | 98.5% | 92.1 – 100.0% |
| 3 | Non-membranous gromerulonephritides (GN) | 63 | 63 | 100.0% | 94.3 – 100.0% |
| 4 | Systemic lupus erythematosus (SLE) | 30 | 30 | 100.0% | 88.4 – 100.0% |
| 5 | Systemic sclerosis (SSc) | 30 | 30 | 100.0% | 88.4 – 100.0% |
| 6 | Psoriasis arthritis (PSA) | 30 | 30 | 100.0% | 88.4 – 100.0% |
| 7 | Rheumatoid arthritis (RA) | 14 | 14 | 100.0% | 76.8 – 100.0% |
| 8 | Thyreoiditis | 50 | 50 | 100.0% | 92.9 – 100.0% |
| | Total | 285 | 284 | 99.6% | 98.1 – 100.0% |

c. *Summary of Sensitivity & Specificity:*

| Clinical Samples (N = 560) | | Clinical Diagnosis | | |
|---|---|---|---|---|
| | | positive | negative | Total |
| EUROIMMUN Anti-PLA2R ELISA (IgG) (RU/ml) | positive | 184 | 1 | 185 |
| | borderline | 5 | 0 | 5 |
| | negative | 86 | 284 | 370 |
| | Total | 275 | 285 | 560 |

Borderline samples counted as negative:

Prevalence 184 / 275 = 66.9% 95% C.I.: 61.0% - 72.4%

Specificity 284 / 285 = 99.6% 95% C.I.: 98.1% - 100.0%

Borderline samples counted as positive:

Prevalence 189 / 275 = 68.7% 95% C.I.: 62.9% - 74.2%

Specificity 284 / 285 = 99.6% 95% C.I.: 98.1% - 100.0%

| Clinical Samples (N = 560) | | Clinical Diagnosis | | |
|---|---|---|---|---|
| | | positive | negative | Total |
| EUROIMMUN Anti-PLA2R ELISA (IgG) (Ratio) | positive | 181 | 1 | 182 |
| | borderline | 9 | 1 | 10 |
| | negative | 85 | 283 | 288 |
| | Total | 275 | 285 | 560 |

Borderline samples counted as negative:

Prevalence 181 / 275 = 65.8% 95% C.I.: 59.9% - 71.4%

Specificity 283 / 285 = 99.3% 95% C.I.: 97.5% - 99.9%

Borderline samples counted as positive:

Prevalence 190 / 275 = 69.1% 95% C.I.: 63.3% - 74.5%

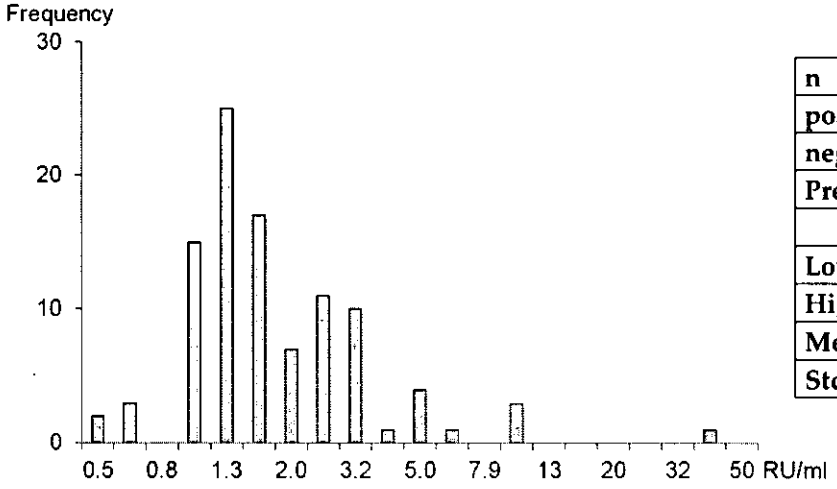
Specificity 283 / 285 = 99.3% 95% C.I.: 97.5% - 99.9%

d. *Other clinical supportive data (when a. and b. are not applicable):*

3. Clinical Cut-off:
   See Assay Cut-off.

4. Expected Values/Reference Range:
   **European Donors:** The levels of anti-PLA2R antibodies (IgG) were analyzed in a panel of 100 samples from apparently healthy blood donors (83 men and 17 women with an average age of 38 y; age range: 18 – 68 y).

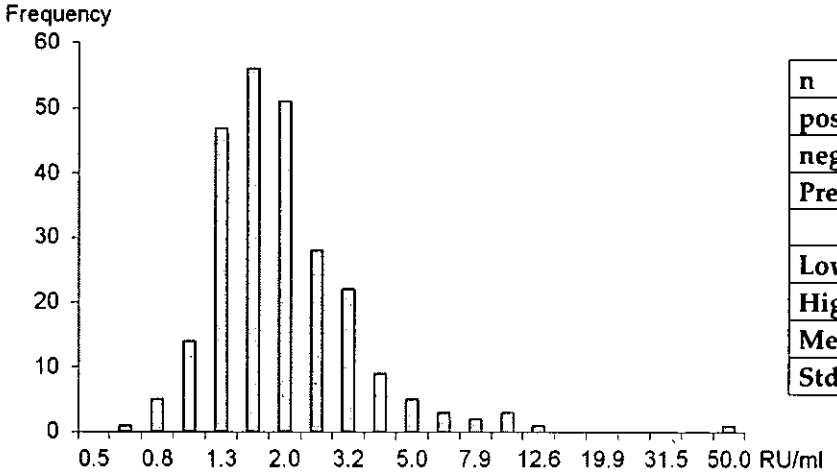
Diagram & Table Expected Values/Reference Range (Europe)




| n | | 100 |
|---|---|---|
| positives | | 1 |
| negatives | | 99 |
| Prevalence | | 1.0 % |
| | RU/ml | Ratio |
| Lowest Value | 0 | 0.0 |
| Highest Value | 32 | 1.6 |
| Mean Value | 2 | 0.1 |
| Std Deviation | 3.4 | 0.18 |

**US Donors:** The levels of anti-PLA2R antibodies (IgG) were analyzed in a panel of 248 samples from apparently healthy blood donors (151 men, 97 women, mean age 36 y, age range 17 – 50 y). The results are shown in the table below.

Diagram & Table Expected Values/Reference Range (USA)




| n | | 248 |
|---|---|---|
| positives | | 1 |
| negatives | | 247 |
| Prevalence | | 0.4 % |
| | RU/ml | Ratio |
| Lowest Value | 1 | 0.0 |
| Highest Value | 40 | 1.6 |
| Mean Value | 2 | 0.1 |
| Std Deviation | 2.8 | 2.8 |

**N. Proposed Labeling:**

The labeling is sufficient and it satisfies the requirements of 21 CFR Part 809.10.

**O. Conclusion:**

The submitted information in this premarket notification is complete and supports a substantial equivalence decision.

| Michael Locke | Michael Locke/Dir. of Regulatory | 6/27/14 |
|---|---|---|
| *Signature* | *Printed Name/Title* | *Date* |

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
10903 New Hampshire Avenue
Document Control Center – WO66-G609
Silver Spring, MD 20993-0002

June 27, 2014

EUROIMMUN US Inc.
Michael Locke
Director, Regulatory Affairs
1100 The American Road
Morris Plains NJ 07950

Re: k132195
Trade/Device Name: EUROIMMUN Anti-PLA2R ELISA (IgG)
Regulation Number: 21 CFR 866.5780
Regulation Name: Anti-phospholipid A2 receptor immunological test system
Regulatory Class: II
Product Code: PGV
Dated: June 9, 2014
Received: June 11, 2014

Dear Mr. Locke:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration. Please note: CDRH does not evaluate information related to contract liability warranties. We remind you, however, that device labeling must be truthful and not misleading.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 898. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Parts 801 and 809); medical device reporting (reporting of medical device-related adverse events) (21 CFR 803); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820); and if applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR 1000-1050.

If you desire specific advice for your device on our labeling regulations (21 CFR Parts 801 and 809), please contact the Division of Industry and Consumer Education at its toll-free number (800) 638 2041 or (301) 796-7100 or at its Internet address http://www.fda.gov/MedicalDevices/ResourcesforYou/Industry/default.htm. Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21 CFR Part 807.97). For questions regarding the reporting of adverse events under the MDR regulation (21 CFR Part 803), please go to http://www.fda.gov/MedicalDevices/Safety/ReportaProblem/default.htm for the CDRH's Office of Surveillance and Biometrics/Division of Postmarket Surveillance.

You may obtain other general information on your responsibilities under the Act from the Division of Industry and Consumer Education at its toll-free number (800) 638-2041 or (301) 796-7100 or at its Internet address http://www.fda.gov/MedicalDevices/ResourcesforYou/Industry/default.htm.

Sincerely yours,

Elizabeth A. Stafford -S

for Maria M. Chan, Ph.D.
Director
Division of Immunology and Hematology Devices
Office of In Vitro Diagnostics
and Radiological Health
Center for Devices and Radiological Health

Enclosure

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

# Indications for Use

Form Approved: OMB No. 0910-0120
Expiration Date: January 31, 2017
*See PRA Statement below.*

510(k) Number *(if known)*
K132195

Device Name
EUROIMMUN Anti-PLA2R ELISA (IgG)

Indications for Use *(Describe)*
The EUROIMMUN Anti-PLA2R ELISA (IgG) test kit is intended for the qualitative or semi-quantitative determination of IgG class autoantibodies against phospholipase A2 receptor (PLA2R) in human serum. It is used as an aid in the diagnosis of primary membranous glomerulonephritis (pMGN), in conjunction with other laboratory and clinical findings.

Type of Use *(Select one or both, as applicable)*

☒ Prescription Use (Part 21 CFR 801 Subpart D) ☐ Over-The-Counter Use (21 CFR 801 Subpart C)

**PLEASE DO NOT WRITE BELOW THIS LINE – CONTINUE ON A SEPARATE PAGE IF NEEDED.**

**FOR FDA USE ONLY**

Concurrence of Center for Devices and Radiological Health (CDRH) *(Signature)*

Elizabeth A. Stafford -S

This section applies only to requirements of the Paperwork Reduction Act of 1995.

***DO NOT SEND YOUR COMPLETED FORM TO THE PRA STAFF EMAIL ADDRESS BELOW.***

The burden time for this collection of information is estimated to average 79 hours per response, including the time to review instructions, search existing data sources, gather and maintain the data needed and complete and review the collection of information. Send comments regarding this burden estimate or any other aspect of this information collection, including suggestions for reducing this burden, to:

Department of Health and Human Services
Food and Drug Administration
Office of Chief Information Officer
Paperwork Reduction Act (PRA) Staff
*PRAStaff@fda.hhs.gov*

*"An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB number."*