JUL 18 2003

510(k) Summary

diaDexus PLAC™ Test

This summary of 510(k) safety and effectiveness information is being submitted in accordance with the requirements of SMDA 1990 and 21 CFR 807.92.

The assigned 510(k) number is: **K030477.**

General Information

Name and Address of Applicant:	diaDexus, Inc. 343 Oyster Point Blvd. South San Francisco, CA 94080 650-246-6400 Robert Wolfert, Ph.D.
Date Prepared	July 16, 2003
Device Trade Name:	diaDexus PLAC™ Test
Generic Name:	Enzyme Immunoassay for the Quantitative Determination of Lp-PLA2 (Lipoprotein-Associated Phospholipase A2) in Human Plasma

Identification of Legally Marketed Device

The Lp(a) Test - K013128
(N Latex Lp(a) Reagent, Dade Behring Inc., Newark, DE)

Intended Use

The diaDexus PLAC™ test is an enzyme immunoassay for the quantitative determination of Lp-PLA2 (lipoprotein-associated phospholipase A2) in human plasma, to be used in conjunction with clinical evaluation and patient risk assessment as an aid in predicting risk for coronary heart disease.

Device Description

The diaDexus PLAC™ test is based on the principle of a sandwich enzyme immunoassay using two specific monoclonal antibodies.

The assay system utilizes monoclonal anti-Lp-PLA2 antibody (2C10) for solid phase immobilization on the microtiter stripwells. The test sample is first diluted with the sample diluent and incubated at 2-8°C for 60 minutes. The diluted test sample is then allowed to react with the immobilized monoclonal antibody at 2-8°C for 90 minutes. The wells are washed with distilled water to remove any unbound antigen. A second monoclonal anti-Lp-PLA2 antibody (4B4) labeled with the enzyme horseradish peroxidase (HRP) is then added and reacted with the immobilized antigen at 2-8°C for 60 minutes, resulting in the Lp-PLA2 molecules being captured between the solid phase and the enzyme-labeled antibodies. The wells are washed with distilled water to remove unbound labeled antibodies. The substrate, tetramethylbenzidine (TMB), is then added and incubated at 2-8°C for 20 minutes resulting in the development of a blue color. Color development is stopped with the addition of Stop Solution (1N HCl), changing the color to yellow. The absorbance of the enzymatic turnover of the substrate is determined spectrophotometrically at 450 nm using a standard microplate reader and is directly proportional to the concentration of Lp-PLA2 present. A set of Lp-PLA2 calibrators is used to plot a standard curve of absorbance (y-axis) versus Lp-PLA2 concentration in ng/mL (x-axis) from which the Lp-PLA2 concentration in the test sample can be interpolated. The standard curve is constructed using a point-to-point curve fit manually or by using appropriate calibration curve fitting software.

Characterization of Rare Reagents

Antigen

The antigen used in the diaDexus enzyme immunoassay PLAC™ test is purified recombinant Lp-PLA2 (DDX-RA). Antigen preparations were characterized using SDS-polyacrylamide gels under reducing and non-reducing conditions and Western blot analysis using an anti-Lp-PLA2 antibody, to demonstrate consistency with the molecular weight of the antigen reported in the literature.

Antibodies

The monoclonal anti-Lp-PLA2 antibodies used in the preparation of the coated microtiter stripwells (2C10) and conjugate (4B4) were characterized for purity and reactivity in a series of procedures including Paragon gel electrophoresis, SDS-PAGE, size exclusion chromatography, isotyping and enzyme immunoassay. These results demonstrated that the monoclonal antibodies bind to the Lp-PLA2 antigen quantitatively and specifically.

Comparison of New Device to Predicate Device

The chart below identifies the similarities and differences between PLAC™ test and the predicate device, the Lp(a) test (N Latex Lp(a) Reagent, Dade Behring Inc., Newark, DE).

Characteristic	PLAC™ Test	N Latex Lp(a) Reagent (K013128)
Intended Use	The diaDexus PLAC™ test is an enzyme immunoassay for the quantitative determination of Lp-PLA2 (lipoprotein-associated phospholipase A2) in human plasma, to be used in conjunction with clinical evaluation and patient risk assessment as an aid in predicting risk for coronary heart disease.	Measurement of Lp(a) aids in the identification of individuals at risk from cardiovascular disease in specific populations when used in conjunction with clinical evaluation.
Analyte	Lp-PLA2 (lipoprotein-associated phospholipase A2)	Lipoprotein (a) [Lp(a)]
Sample	Human EDTA-plasma	Human serum and heparin-plasma
Methodology	Microplate enzyme immunoassay	Particle enhanced immunonephelometry
Detection Method	Spectrophotometer at 450 nm	BN Systems Nephelometer
Risk to Patients	Minimal risk	Minimal risk
Laboratory Environment	Professional laboratory	Professional laboratory

Performance Characteristics

Analytical Sensitivity (Detection Limit)

The minimum detection limit, as calculated by interpolation of the mean plus two standard deviations of 24 replicates of the 0 ng/mL Lp-PLA2 Calibrator is 1.2 ng/mL.

Linearity

Four EDTA-plasma samples containing different levels of endogenous Lp-PLA2 were diluted with Sample Diluent and assayed (dilution range: 1:5 to 1:20). Percent recovery was determined as the observed value divided by the expected value, multiplied by 100. The average recovery, demonstrating linearity of diluted samples over a range of 133 to 1310 ng/mL Lp-PLA2, was 104%.

Dilution Linearity

Six EDTA-plasma samples with known high Lp-PLA2 levels were intermixed with six plasma samples with known low Lp-PLA2 levels. Percent recovery was determined as the measured value divided by the expected value, multiplied by 100. The average recovery, demonstrating linearity of diluted samples over a range of 79 to 982 ng/mL Lp-PLA2, was 104%.

Antigen Recovery

Known amounts of recombinant Lp-PLA2 (80, 179, and 436 ng/mL) were added to 15 human plasma samples and fetal bovine serum (control). Recovery was determined as the observed spiked concentration in the plasma samples, calculated as a percent of the observed control concentration (with no endogenous Lp-PLA2). Results demonstrated a mean antigen recovery from 97-119% across the assay range, with an overall mean recovery of 109%.

Interfering Substances

Five endogenous substances found in blood were evaluated for interference in the assay. Five individual plasma samples with Lp-PLA2 values ranging from 92 to 664 ng/mL were spiked with potential interferents endogenous to blood. No appreciable interference was observed at spiked levels of 500 mg/dL hemoglobin, 3000 mg/dL triglycerides, 500 mg/dL cholesterol, 20 mg/dL bilirubin and up to 6.2 g/dL albumin.

Precision

Intra-assay and inter-assay variability were determined by testing three human plasma pools with Lp-PLA2 concentrations distributed throughout the calibration range of the assay. The three plasma pools were assayed, using a single lot of reagents, in duplicate, on two separate stripwells per day, for twenty days. The intra-assay precision (n = 80) was < 7% CV and the inter-assay precision (n = 20) was < 9% CV.

Reference Interval

EDTA-plasma samples obtained from apparently healthy males (n=251) and apparently healthy females (n=174), in the clinically relevant age range of 40-70 years, were evaluated with the diaDexus PLAC™ test. The reference interval calculated from the samples (central 90%) was determined to be 120-342 ng/mL for females and 131-376 ng/mL for males.

Summary of Clinical Study

To determine the efficacy of the diaDexus PLAC™ test as a predictor of risk for coronary heart disease (CHD), Lp-PLA2 levels were measured in 1348 banked EDTA-plasma samples from a large, multi-center, epidemiology study, the Atherosclerosis Risk In Communities (ARIC) Study, sponsored by the National Institutes of Health's, National Heart, Lung, and Blood Institute. In this case-cohort study, participants, age 47-69, free of CHD were enrolled and followed for the development of CHD for up to nine years. Of the 1348

samples selected for the Lp-PLA2 study, 608 were from CHD cases, and 740 were from participants who were free of CHD at the time of censor (controls).

Cox regression models were used to evaluate the association of Lp-PLA2 and CHD in a univariate analysis (Model 1), a univariate analysis adjusted for demographics (Model 2), and a multivariate model adjusted for demographics and other prognostics factors (Model 3). Using high and low cutpoints of Lp-PLA2, generated from the ARIC data set (420 and 310 ng/mL, the 67th and 33rd percentiles, respectively), the hazard ratios of the Cox regression analyses demonstrated that Lp-PLA2 is a significant predictor of risk for CHD, for the highest and intermediate levels when compared to the lowest level of Lp-PLA2, for all participants (see Table 1). It should be noted that different cutpoints may be appropriate for different clinical populations.

Table 1. Risk Ratios of CHD for Subjects Across All LDL Levels

	Lp-PLA2 Risk Ratio (95% CI, p value)*		
Lp-PLA2 (ng/mL)	**<310**	**310-420**	**>420**
Model 1	**1.0**	**1.49** (1.11-1.99, p=0.008)	**2.50** (1.89-3.31, p<0.001)
Model 2	**1.0**	**1.24** (0.92-1.66, p=0.154)	**1.76** (1.32=2.36, p<0.001)
Model 3	**1.0**	**1.71** (1.06-2.75, p=0.029)	**2.12** (1.29-3.48, p=0.003)

*The lowest tertile with Lp-PLA2 values <310 ng/mL is used as the reference group

Model 1: univariate analysis
Model 2: adjusted for age, race, gender
Model 3: adjusted for age, race, gender, current smoking status, blood pressure, diabetes, HDL, LDL, CRP and Lp-PLA2 - LDL interaction

Conclusions

The PLAC™ test demonstrated acceptable analytical performance, i.e., the test is reproducible, linear and accurate, and is not subject to appreciable crossreactivity or interference. The detection limit of 1.2 ng/mL is acceptable for the intended use of this assay. Results were consistent across several manufactured reagent lots evaluated over a period of time. Therefore, this assay should provide reliable and reproducible results when used by clinical laboratories.

Clinical data were collected from a large, multi-center epidemiology study sponsored by the National Institutes of Health, following a well-designed protocol conducted by qualified experts in a CLIA-certified laboratory. The results of this clinical study and performance testing demonstrate that the levels of Lp-PLA2 are associated with the risk of CHD, and support the safety and effectiveness of the PLAC™ test for use as a predictor of risk for coronary heart disease.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
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Rockville MD 20850

JUL 18 2003

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diaDexus, Inc.
343 Oyster Point Blvd.
South San Francisco, CA 94080

Re: k030477
Trade/Device Name: diaDexus PLAC™ Test
Regulation Number: 21 CFR 866.5600
Regulation Name: Low-density lipoprotein immunological test system
Regulatory Class: Class II
Product Code: NOE; JJX
Dated: May 21, 2003
Received: May 22, 2003

Dear Dr. Wolfert:

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.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to such additional controls. Existing major regulations affecting your device can be found in Title 21, Code of Federal Regulations (CFR), Parts 800 to 895. 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); and good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820).

This letter will allow you to begin marketing your device as described in your Section 510(k) premarket notification. The FDA finding of substantial equivalence of your device to a legally marketed predicate device results in a classification for your device and thus, permits your device to proceed to the market.

If you desire specific information about the application of labeling requirements to your device, or questions on the promotion and advertising of your device, please contact the Office of In Vitro Diagnostic Device Evaluation and Safety at (301) 594-3084. Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21CFR Part 807.97). You may obtain other general information on your responsibilities under the Act from the Division of Small Manufacturers, International and Consumer Assistance at its toll-free number (800) 638-2041 or (301) 443-6597 or at its Internet address http://www.fda.gov/cdrh/dsma/dsmamain.html.

Sincerely yours,

Steven Gutman

Steven I. Gutman, M.D., M.B.A.
Director
Office of *In Vitro* Diagnostic Device
Evaluation and Safety
Center for Devices and
Radiological Health

Enclosure

INTENDED USE

510(k) Number: K030477

Device Name: diaDexus PLAC™ test

Indications for Use:

The diaDexus PLAC™ test is an enzyme immunoassay for the quantitative determination of Lp-PLA2 (lipoprotein-associated phospholipase A2) in human plasma, to be used in conjunction with clinical evaluation and patient risk assessment as an aid in predicting risk for coronary heart disease.

Division Sign-Off

Office of In Vitro Diagnostic Device Evaluation and Safety

510(k) K030477

(PLEASE DO NOT WRITE BELOW THIS LINE- CONTINUE ON ANOTHER PAGE AS NEEDED)

Concurrence of CDRH, Office of Device Evaluation (ODE)

Prescription Use X OR Over-the-Counter Use ___