K041417

JUL 2 0 2004

SUMMARY OF SAFETY AND EFFECTIVENESS INFORMATION

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.

Submitter's Name:	Richard M. Vaught Dade Behring Inc. P.O. Box 6101 Newark, DE 19714-6101
Date of Preparation:	May 26, 2004
Name of Product(s):	Dimension® NT-proBNP (PBNP) Flex® reagent cartridge method, and Dimension® PBNP Calibrator
FDA Classification Name(s):	B-type natriuretic peptide test system and calibrator (both Class II)
FDA Guidance Documents:	"Class II Special Control Guidance Document for B-Type Natriuretic Peptide Premarket Notifications; Final Guidance for Industry and FDA Reviewers" - 11/30/2000
Predicate Device(s):	Roche Diagnostics Elecsys® proBNP immunoassay and CalSet calibrator (K032646/K022516)

Device Description(s):

Method

The Dade Behring Dimension® NT-proBNP (PBNP) Flex® reagent cartridge method is an *in vitro* diagnostic test that consists of prepackaged reagents in a flexible plastic cartridge for use only on the Dimension® clinical chemistry system. The PBNP method is a one step enzyme immunoassay based on the "sandwich" principle. Sample is incubated with chromium dioxide particles coated with polyclonal antibodies which recognize an epitope located in the N-terminal part of proBNP, and a conjugate reagent [alkaline phosphatase (ALP)] labeled polyclonal antibody specific for a second independent epitope on NT-proBNP, to form a particle/NT-proBNP/conjugate sandwich. Unbound conjugate is removed by magnetic separation and washing. After separation and washing, the particle/NT-proBNP/conjugate sandwich is transferred to the cuvette where the sandwich-bound ALP triggers an amplification cascade.* ALP dephosphorylates synthetic flavin adenine dinucleotide phosphate (FADP) to produce FAD. FAD binds to apo D-amino acid oxidase and converts it to active holo D-amino acid oxidase. Each molecule of holo D-amino acid oxidase produces multiple molecules of hydrogen peroxide (H_2O_2). H_2O_2 in the presence of horseradish peroxidase (HRP), converts 3,5-dichloro-2-hydroxybenzenesulfonic acid (DCHBS) and 4-aminoantipyrine (4-AAP) to a colored product that absorbs at 510 nm. The color change measured is directly proportional to the concentration of proBNP present in the patient sample.

*Technology licensed from London Biotechnology, Ltd., London, U.K.

Calibrator
The Dade Behring PBNP Calibrator is a frozen liquid product containing synthetic human NT-proBNP in a bovine albumin matrix with stabilizers and preservative. The kit consists of ten vials, two vials at each of five levels, 1.0 mL in each vial.

Intended Use:
Method
The Dimension® PBNP Flex® method is an *in vitro* diagnostic assay for the quantitative determination of N-terminal pro-brain natriuretic peptide (NT-proBNP) in human plasma. Measurements of NT-proBNP are used as an aid in the diagnosis of individuals suspected of having congestive heart failure (CHF).

Calibrator
The PBNP Calibrator is an *in vitro* diagnostic product intended to be used to calibrate the N-terminal pro-brain natriuretic peptide (PBNP) method for the Dade Behring Dimension® clinical chemistry system with the heterogeneous immunoassay module.

Comparison to Predicate Device:
A summary of the features of the Dade Behring Dimension® PBNP Flex® method and the predicate Roche Diagnostics Elecsys® proBNP immunoassay (K032646/K022516) is provided in the following chart. The Dade Behring Dimension® PBNP assay utilizes the same antibody/antigen set as the predicate, Roche Diagnostics Elecsys® proBNP immunoassay.

Feature	Dimension® PBNP	Roche Elecsys® proBNP
Intended Use	For the *in vitro* quantitative determination of N-terminal pro-brain natriuretic peptide in human plasma as an aid in the diagnosis of individuals suspected of having congestive heart failure.	For the *in vitro* quantitative determination of N-terminal pro-brain natriuretic peptide in human serum and plasma as an aid in the diagnosis of individuals suspected of having congestive heart failure. The test is further indicated for the risk stratification of patients with acute coronary syndrome and congestive heart failure.
Assay Type (detection)	immunoassay (photometric)	immunoassay (electrochemiluminescent)
Reportable Range	10 - 30,000 pg/mL	5 - 35,000 pg/mL
Antibody	Roche Diagnostics' polyclonal (sheep) antibody	polyclonal (sheep) antibody

Cut-off	125 pg/mL for patients < 75 years; 450 pg/mL for patients ≥ 75 years	125 pg/mL for patients < 75 years; 450 pg/mL for patients ≥ 75 years
Analytical Sensitivity	≤ 10 pg/mL	5 pg/mL
Functional Sensitivity	≤ 30 pg/mL	< 50 pg/mL
Analytical Specificity	The pharmaceutical Natrecor® shows no significant cross reactivity at 0 and 125 pg/mL NT-proBNP; sixteen other substances show no significant cross reactivity	The pharmaceutical Natrecor® shows no significant cross reactivity at 300 pg/mL and 3000 pg/mL NT-proBNP; sixteen other substances show no significant cross reactivity
Interferences	No significant interference from: bilirubin, conj. up to 60 mg/dL bilirubin, unconj. up to 20 mg/dL hemoglobin up to 1000 mg/dL triglycerides up to 3000 mg/dL rheumatoid factors up to 500 IU/mL	No significant interference from: bilirubin up to 35 mg/dL hemoglobin up to 1.4 g/dL triglycerides up to 4000 mg/dL rheumatoid factors up to 1500 IU/mL
Reference	Roche purified synthetic NT-proBNP (1-76)	Roche purified synthetic NT-proBNP (1-76)
Hook Effect	No high dose effect (up to 300,000 pg/mL)	No high dose effect (up to 300,000 pg/mL)
Calibration Interval	30 days - same reagent lot	30 days - same reagent lot
Sample Volume	50 uL	20 uL

Method Performance Summary

CLINICAL

For the Reference Study Group, NT-proBNP concentrations were determined in 308 individuals without congestive heart failure (163 women and 145 men); this population included apparently health individuals and individuals with diabetes, hypertension, and pulmonary disease. For the Disease Study Group, blood

samples were obtained from 227 patients diagnosed with congestive heart failure (CHF); this population included 69 women and 158 men.

The high level of equivalence on clinical performance measures justifies using the cutoffs recommended for the predicate device, as shown below:

Patients < 75 years: 125 pg/mL [14.8 pmol/L]
Patients ≥75 years: 450 pg/mL [53.2 pmol/L]

The clinical performance of the Dade Behring assay was substantially equivalent to that of the predicate device. Data used to calculate the values are from the method comparison and reference interval data sets generated at the University of Maryland Medical Center.

Clinical Performance of Dade Behring NT-proBNP assay vs. predicate device on Male patients.

Males		<75 yrs (95% CI)	≥75 yrs (95% CI)
Sensitivity (%)	Dimension® PBNP	84 (77 – 91)	91 (84 – 99)
	Elecsys® proBNP	90 (85 – 96)	91 (84 – 99)
Specificity (%)	Dimension® PBNP	94 (90- 99)	77 (67 – 88)
	Elecsys® proBNP	92 (87 – 98)	73 (61 – 84)
NPV	Dimension® PBNP	82	92
	Elecsys® proBNP	88	92

Clinical Performance of Dade Behring NT-proBNP assay vs. predicate device on Female patients.

Females		<75 yrs (95% CI)	≥75 yrs (95% CI)
Sensitivity (%)	Dimension® PBNP	77 (64 – 89)	91 (79 – 100)
	Elecsys® proBNP	81 (70 – 92)	95 (87 – 104)
Specificity (%)	Dimension® PBNP	93 (89 – 98)	88 (80 – 96)
	Elecsys® proBNP	91 (85 – 96)	87 (78 – 95)
NPV	Dimension® PBNP	91	96
	Elecsys® proBNP	92	98

ANALYTICAL

Comparison using split patient heparinized plasma samples between the Dade Behring Dimension® PBNP Flex® method and the predicate Roche Elecsys® proBNP immunoassay demonstrated good agreement between the methods as summarized below:

Method Correlation

Comparative Method	Slope	Intercept (pg/mL)	Correlation Coefficient	n
Roche Elecsys® proBNP	0.90	-15.4	0.985	352

Model equation by Passing-Bablok linear regression statistics is: [results for Dimension® system] = slope x [comparative method results] + intercept. The range of NT-proBNP values in the correlation study was: 16.1 to 29,893.1 pg/mL.

In addition, comparison of lithium heparin versus sodium heparin and EDTA plasma samples on the Dimension® system showed very good agreement. Lithium heparin samples ranging from 13 to 29,221 pg/mL when compared to sodium heparin and EDTA samples gave slopes of 0.95 and 0.96, correlation coefficients of 0.998 and 0.998, and intercepts of 0.9 and 10.9 respectively, using Passing-Bablok regression statistics.

Reproducibility

Typical precision observed for the Dimension® PBNP Flex® method is summarized below:

		Within-Run Precision		Total Precision	
	Mean (pg/mL)	**SD (pg/mL)**	**%CV**	**SD (pg/mL)**	**%CV**
Human Plasma Pool					
Pool 1	159.0	3.4	2.2	9.1	5.7
Internal QC Pools					
Pool 1	449.5	8.1	1.8	16.6	3.7
Pool 2	956.7	15.3	1.6	34.9	3.6
Audit™ MicroFD™ BNP Control *					
Level 1	175.5	2.0	1.1	6.8	3.8
Level 2	3733.8	71.8	1.9	115.9	3.1

The reproducibility testing was done in accordance with the NCCLS Approved Guideline for User Evaluation of Precision Performance of Clinical Chemistry Devices EP5-A, 1999. Specimens at each level were analyzed in duplicate once per day for 20 days. The within-run and total standard deviations were calculated by the analysis of variance method.

* Audit™ and MicroFD™ are registered trademarks of Audit™ MicroControls, Inc., Las Vegas, NV

Comments on Substantial Equivalence:
Both the Dade Behring Dimension® PBNP and the Roche Elecsys® proBNP immunoassays are intended for the quantitative determination of NT-proBNP. Comparative data for human plasma samples demonstrate good analytical and clinical agreement between the methods.

Conclusion:
The Dade Behring Dimension® PBNP Flex® method and the predicate Roche Elecsys® proBNP immunoassay (K032646/K022516) are substantially equivalent based on their intended use and performance characteristics as described above. The calibrator products are also equivalent in their design and intended use with their respective assay systems.

Richard M. Vaught
Regulatory Affairs and Compliance Manager
May 26, 2004

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
2098 Gaither Road
Rockville MD 20850

Mr. Richard M. Vaught
Regulatory Affairs and Compliance Manager
Dade Behring Inc.
P.O. Box 6101
Newark, DE 19714

JUL 2 0 2004

Re: k041417
Trade/Device Name: Dimension® NT-proBNP (PBNP) Flex® reagent cartridge method
Dimension® PBNP Calibrator
Regulation Number: 21 CFR 862.1117
Regulation Name: B-type natriuretic peptide test system
Regulatory Class: Class II
Product Code: NBC, JIT
Dated: May 26, 2004
Received: May 27, 2004

Dear Mr. Vaught:

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,

Jean M. Cooper MS, DVM.

Jean M. Cooper, MS, D.V.M.
Director
Division of Chemistry and Toxicology
Office of *In Vitro* Diagnostic Device
Evaluation and Safety
Center for Devices and
Radiological Health

Enclosure

INDICATIONS FOR USE STATEMENT

Device(s) Name(s):

Dimension® NT-proBNP (PBNP) Flex® reagent cartridge method, and
Dimension® PBNP Calibrator

Indications for Use:

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The Dade Behring Dimension® PBNP Calibrator is intended to be used to calibrate the N-terminal pro-brain natriuretic peptide (PBNP) method for the Dade Behring Dimension® clinical chemistry system.

RM Vaught

Richard M. Vaught
Regulatory Affairs and Compliance Manager

May 26, 2004

Prescription Use ✓ AND/OR Over-The-Counter Use _____
(Part 21 CFR 801 Subpart D) (21 CFR 807 Subpart C)

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

Concurrence of CDRH, Office of In Vitro Diagnostic Devices (OIVD)

Division Sign-Off

Office of In Vitro Diagnostic Device Evaluation and Safety

510(k) K041417