510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
ASSAY ONLY TEMPLATE

A. 510(k) Number:

k071767

B. Purpose for Submission:

Addition of serum as a sample type and change in antibodies from polyclonal to monoclonal

C. Measurand:

N-terminal pro-brain natriuretic peptide

D. Type of Test:

Quantitative

E. Applicant:

Dade Behring, Inc.

F. Proprietary and Established Names:

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

G. Regulatory Information:

1. Regulation section:

   21 CFR 862.1117, B-type natriuretic peptide

2. Classification:

   Class II

3. Product code:

   NBC

4. Panel:

    75, Chemistry

H. Intended Use:

1. Intended use(s):

    The PBNP assay used on the Dimension® clinical chemistry system with the heterogeneous immunoassay module is an *in vitro* diagnostic assay for the quantitative determination of N-terminal pro-brain natriuretic peptide (NT-proBNP) in human serum or plasma. In individuals suspected of having congestive heart failure (CHF), measurements of NT-proBNP are used as an aid in the diagnosis and assessment of severity. The test is further indicated for the risk stratification of patients with acute coronary syndrome and heart failure.

2. Indication(s) for use:

    See Intended use (above).

3. Special conditions for use statement(s):

    Prescription use

4. Special instrument requirements:

    Dade Behring Dimension RxL Max™, RxL, and Xpand®

I. Device Description:

The Dade Behring Dimension® 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.

J. Substantial Equivalence Information:

1. Predicate device name(s):

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

2. Predicate k number(s):

    k042347

3. Comparison with predicate:

Similarities and differences		
Item	Dimension® NT-proBNP (PBNP) Flex® reagent cartridge method (modified device)	Dimension® NT-proBNP (PBNP) Flex® reagent cartridge method
Intended Use	For the *in vitro* quantitative determination of N-terminal pro-brain natriuretic peptide in human serum and plasma as an aid in the diagnosis and assessment of severity of individuals suspected of having congestive heart failure. The test is further indicated for the risk stratification of patients with acute coronary syndrome and heart failure.	For the *in vitro* quantitative determination of N-terminal pro-brain natriuretic peptide in human plasma as an aid in the diagnosis and assessment of severity of individuals suspected of having congestive heart failure. The test is further indicated for the risk stratification of patients with acute coronary syndrome and heart failure.
Assay Type	Immunoassay (chemiluminescent)	Same
Reportable range	10-30,000 pg/mL	Same
Antibody	Monoclonal sheep antibody	Polyclonal sheep antibody
Cut-off	125 pg/mL for patients <75 years 450 pg/mL for patients ≥ 75 years	Same
Analytical sensitivity	≤ 10 pg/mL	Same
Functional sensitivity	≤ 30 pg/mL	Same
Interferences/specificity	No significant interference from: bilirubin, conj. and unconj.up to 60 mg/dL, hemoglobin up to 1000 mg/dL, lipemia up to 3000 mg/dL, rheumatoid factors up to 500 IU/mL.	No significant interference from: bilirubin, conj.up to 60 mg/dL, unconj. up to 20 mg/dL, hemoglobin up to 1000 mg/dL, lipemia up to 3000 mg/dL, rheumatoid factors up to 500 IU/mL
Specificity	The pharmaceutical Natrecor shows no significant cross reactivity at 0 and 125 pg/mL NT-proBNP; 16 other substances also show not significant cross reactivity	Same
Sample volume	50 µL	Same

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

CLSI EP5-A2: Evaluation of Precision Performance of Quantitative Measurement Methods, CLSI EP7-A: Interference Testing in Clinical Chemistry, FDA guidance document: Class II Special Controls Guidance Document for B-Type Natriuretic Peptide Premarket Notifications: Final Guidance for Industry and FDA Reviewers (11/30/2000).

L. Test Principle:

The PBNP method is a one-step enzyme immunoassay based on the "sandwich" principle. Sample is incubated with chromium dioxide particles coated with monoclonal antibodies which recognize an epitope located in the N-terminal part of proBNP, and a conjugate reagent [alkaline phosphatase (ALP)] labeled monoclonal 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 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 NT-proBNP present in the patient sample.

M. Performance Characteristics (if/when applicable):

1. <u>Analytical performance:</u>

   a. *Precision/Reproducibility:*
      A precision study was conducted in accordance with CLSI EP5-A2 guideline. During each day of testing, two separate run, with two test samples for each test material were analyzed for 20 days. The precision results are shown below:

Sample	Mean (pg/mL)	Within-Run Precision		Within-lab precision	
		SD (pg/mL)	% CV	SD (pg/mL)	% CV
Human serum pool 1	136	6.0	4.4	7.7	5.6
Human plasma pool 1	123	5.3	4.3	6.8	5.6
Human plasma pool 2	462	18.1	3.9	23.3	5.1
Human plasma pool 3	1071	40.6	3.8	52.9	4.9
Human plasma pool 4	5359	203.2	3.8	287.9	5.4

   b. *Linearity/assay reportable range:*

      The reportable range of the assay is from 10-30,000 pg/mL. A high PBNP plasma pool (PBNP = 31,883 pg/mL) was diluted with a low PBNP pool (PBNP = 12 pg/mL) to produce 6 levels of PBNP. High range linearity was evaluated by comparing observed vs. expected values obtained with the PBNP

method. A linear regression analysis was then performed on the data to yield the following: slope = 1.0017, r =0.9989, intercept = 68.02 pg/mL. Percent recoveries for the 6 levels ranged from 97 to 102 %. An additional study was performed to assess low level linearity. A sample with a value of 1177 pg/mL was diluted with a sample with a value of 21 pg/mL to produce 5 levels of PBNP. A linear regression was performed on the data to yield the following: slope = 1.014, r = 0.999, intercept = -14 pg/mL. The Y-intercept is not statistically significant at a 95% confidence interval (CI) (p = 0.39, 95% CI – 60 to 31). The Passing-Bablock linear regression equation was 1.01, r = 0.9988, intercept = -12.9 pg/mL with 95 % CI -104 to +28). Percent recovery ranged from 92 -102%. An additional low level linearity study was performed using a serum sample with NT-proBNP = 1,081 pg/mL diluted with a level one calibrator with a value of 0 pg/mL to produce 7 levels of PBNP. Passing-Bablock linear regression provided a slope of 1.04 and an intercept of 0.60 pg/mL with 95% CI-9 to +8. Percent recovery ranged from 94 to 106 %.

Hook effect was evaluated using samples containing NT-proBNP concentrations ranging from 0 to 750,000 pg/mL. The studies indicated that there was no hook-effect up to 750,000 pg/mL. A claim of 300,000 pg/mL is used. The Dimension® system will report an error code to the user when the signal generated by a high sample exceeds a pre-defined limit.

c. *Traceability, Stability, Expected values (controls, calibrators, or methods):*

The assay is referenced to Roche purified synthetic NT-proBNP. The assigned values for the Dimension® PBNP Calibrator are referenced to a master pool containing synthetic human N-terminal pro-brain natriuretic peptide in a human serum matrix.

d. *Detection limit:*

The limit of the blank for the PBNP assay was determined to be 6.6 pg/mL. A claim of ≤ 10 pg/mL is made. This was determined by assaying 20 consecutive replicates of the analyte free (0 level) calibrator. The value was then calculated by determining the standard deviation (SD) of the 20 replicates, multiplying by 2, and adding it to the absolute value of the mean. Functional sensitivity is defined as the analyte concentration corresponding to a 20% inter-assay coefficient of variation (CV). This was determined by performing a 20 day precision experiment using samples prepared from normal human serum at appropriate concentrations. Two replicates of each sample were analyzed twice per day for 20 days. Within lab CV was computed by ANOVA and plotted versus the mean concentration. The functional sensitivity was determined to be 17.5 pg/mL. A claim of ≤ 30 pg/mL is made.

e. *Analytical specificity:*

No significant interference was found for bilirubin (conjugated) up to 60 mg/dL, bilirubin (unconjugated) up to 60 mg/dL, hemoglobin up to 1000 mg/dL, triglycerides up to 3000 mg/dL, and rheumatoid factor up to 500 IU/mL. The pharmaceutical Natrecor® shows no significant cross reactivity at 0 and 125 pg/mL NT-proBNP. An extensive list of other compounds was evaluated for interference and was found to have no significant interference or cross reactivity. A list of these compounds is presented in the labeling.

f. *Assay cut-off:*

See expected values below.

2. <u>Comparison studies:</u>

a. *Method comparison with predicate device:*

A method comparison study was conducted using split patient samples between the Dimension NT-proBNP assay (modified) and the Dimension NT-proBNP assay (predicate) with sample values ranging from 22 – 28,982 pg/mL using the Dimension RxL chemistry system. 122 heparinized plasma samples were used and yielded the following correlation regression:

Comparative Method	Slope	Intercept (pg/mL)	Correlation Coefficient	n
Dimension NT-proBNP assay (predicate)	1.02	- 5	0.99	122

Concordance testing was completed at a university setting. Concordance was determined by comparing the results of the modified Dimension NT-proBNP method with patient samples from both a reference study population and a disease study population. The reference study examined 29 samples from a < 75years of age population and 18 samples from a ≥ 75 years of age population. The disease study group examined 25 samples from each of the New York Heart Association (NYHA) classes (I – IV). The cut-offs of 125 pg/mL for patients < 75 years of age, and 450 pg/mL for patients ≥ years of age were used in the concordance determination. Concordance for the reference group < 75 years old and ≥ 75 years old were both 100%. Concordance for the disease group was 96% for Class I, 100% for Class.II, 96% for Class III, and 100% for Class IV. Average for the reference and disease groups combined was 98.6%.

b. *Matrix comparison:*

A comparison of 63 matched serum and lithium heparin plasma samples ranging from 36 to 26,327 pg/mL on the Dimension® system produced a slope of 1.02, an intercept of 1.7 pg/mL and a correlation coefficient of 0.991 using Passing-Bablock linear regression statistics. Comparison of 59 matched serum and sodium heparin plasma samples ranging from 11 to 25,734 pg/mLon the Dimension® RxL chemistry system produced a slope of 0.97, an intercept of – 2.2 pg/mL and a correlation coefficient 0f 0.993 using Passing-Bablock linear regression statistics.

3. <u>Clinical studies</u>:

a. *Clinical Sensitivity:*

Refer to decision summary for k042347

b. *Clinical specificity:*

Refer to decision summary for k042347

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

4. <u>Clinical cut-off</u>**:**

Refer to decision summary for k042347

5. <u>Expected values/Reference range</u>:

NT-proBNP concentrations in the reference group are shown in the following tables. The recommended medical decision thresholds, by age group which were established for k042347 are as follows:

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

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

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.