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

A. 510(k) Number:

k080578

B. Purpose for Submission:

Change in antibodies from polyclonal to monoclonal

C. Measurand:

N-terminal pro-brain natriuretic peptide

D. Type of Test:

Quantitative, chemiluminescent

E. Applicant:

Siemens Healthcare Diagnostics, Inc.

F. Proprietary and Established Names:

Dimension Vista® N-terminal Pro-Brain Natriuretic Peptide (PBNP) Flex® Reagent Cartridge (K6423A)

Dimension Vista® N-terminal Pro-Brain Natriuretic Peptide (PBNP) Calibrator (KC676A)

G. Regulatory Information:

1. Regulation section:

   21 CFR 862.1117, B-type natriuretic peptide

   21 CFR 862.1150, Calibrator secondary

2. Classification:

   Class II

3. Product code:

NBC; JIT

4. Panel:

75, Chemistry

H. Intended Use:

1. Intended use(s):

   See indications for use below.

2. Indication(s) for use:

   The PBNP method is an in vitro diagnostic assay for the quantitative measurement of N-terminal pro-brain natriuretic peptide (NT-proBNP) in human serum and plasma on the Dimension Vista® System. 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.

   The PBNP CAL is an *in vitro* diagnostic product for the calibration of the N-Terminal Pro-Brain Natriuretic Peptide (PBNP) method for the Dimension Vista® System

3. Special conditions for use statement(s):

   Prescription use

4. Special instrument requirements:

   Dimension Vista® System

I. Device Description:
The Dimension Vista® PBNP Flex® reagent cartridge is a prepackaged *in-vitro* diagnostic test method that is specifically designed to be used on the Dimension Vista® System. The reagent cartridge contains twelve wells. The wells contain the following reagents:

Well	Reagent
1 - 2	Biotinylated sheep monoclonal antibody
3 - 4	NT-PBNP Chemibeads, sheep monoclonal antibody
7 - 8	Streptavidin Sensibeads, recombinant *E. coli*
9 - 12	Assay Buffer

Wells 5 - 6 are empty. Wells are numbered consecutively from the wide end of the cartridge.

Calibrator

The PBNP Calibrator is a frozen liquid product containing synthetic human N-terminal pro-brain natriuretic peptide in bovine albumin matrix with stabilizers and preservative. The kit consists of ten vials, two vials per level (A, B, C, D, and E), 1.0 mL per vial.

J. Substantial Equivalence Information:

1. Predicate device name(s):

   Dimension Vista® N-terminal Pro-Brain Natriuretic Peptide (PBNP) Flex® Reagent Cartridge (K6423)

   Dimension Vista® N-terminal Pro-Brain Natriuretic Peptide (PBNP) Calibrator (KC676)

2. Predicate K number(s):

   k061795

3. Comparison with predicate:

PBNP Flex® Reagent Cartridge Similarities		
Item	Device	Predicate
Intended Use	The PBNP method is an in vitro diagnostic assay for the quantitative measurement of N-terminal pro-brain natriuretic peptide (NT-proBNP) in human serum and plasma on the Dimension Vista® System. 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.	Same
Technology	Chemiluminescent	Same
Measuring range	5 – 35,000 pg/mL	Same
Cutoff	125 pg/mL for patients <75 years 450 pg/mL for patients ≥ 75 years	Same

PBNP Flex® Reagent Cartridge Differences		
Item	Device	Predicate
Antibody	Monoclonal sheep antibody	Polyclonal sheep antibody

PBNP Calibrator Similarities		
Item	Device	Predicate
Matrix	Bovine albumin	Same
Form	Liquid frozen	Same

PBNP Calibrator Differences		
Item	Device	Predicate
Volume	Ten vials, two vials per level	Twelve vials, two vials per level
Levels	Five levels	Six levels

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

CLSI EP7-A: Interference Testing in Clinical Chemistry; Approved Guideline

CLSI EP 9-A2: Method Comparison and Bias Estimation Using Patient Samples; Approved Guideline

CLSI EP5-A2: Evaluation of Precision Performance of Quantitative Measurement Methods; Approved Guideline-Second Edition

CLSI C28-A2: How to Define and Determine Reference Intervals in the Clinical Laboratory; Approved Guideline - Second Edition

CLSI EP17-A: Protocols for Determination of Limits of Detection and Limits of Quantitation

CLSI EP6-A: Evaluation of the Linearity of Quantitative Measurement Procedures

Class II Special Control Guidance Document for B-Type Natriuretic Peptide Premarket Notifications; Final Guidance for Industry and FDA Reviewers

L. Test Principle:
The PBNP method is a one-step sandwich chemiluminescent immunoassay based on LOCI® technology. LOCI® reagents include two synthetic bead reagents and a biotinylated monoclonal antibody fragment which recognize an epitope located in the N-terminal part of proBNP. The first bead reagent (Sensibeads) is coated with streptavidin and contains photosensitive dye. The second bead reagent (Chemibeads) is coated with a second antibody specific for a second independent epitope on NT-proBNP and contains chemiluminescent dye. Sample is incubated with Chemibeads and biotinylated antibody to form a particle/NT-proBNP/biotinylated antibody sandwich. Sensibeads then are added and bind to the biotin to form a bead-aggregated immunocomplex. Illumination of the complex by light at 680 nm generates singlet

oxygen from Sensibeads, which diffuses to the Chemibeads and triggers a chemiluminescent reaction. The resulting chemiluminescent signal is measured at 612 nm and is directly proportional to the concentration of NT-proBNP in the sample.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

   a. *Precision/Reproducibility:*

   Testing was conducted in accordance with CLSI EP5-A2. During each day of testing, two separate runs, with two test samples, for each test material, were analyzed for 20 days. The results are summarized in the table below:

Material	Mean pg/mL	Repeatability SD	Repeatability %CV	Within Lab SD	Within Lab %CV
Serum Pool 1	120	1.72	1.4	2.06	1.7
Serum Pool 2	438	4.75	1.1	4.75	1.1
Serum Pool 3	880	9.05	1.0	12.24	1.4
Serum Pool 4	5075	69.06	1.4	91.97	1.8
Internal QC	32633	763.39	2.3	1140.27	3.5

   b. *Linearity/assay reportable range:*

   CLSI EP6-A Evaluation of the Linearity of Quantitative Measurement Procedures was followed. De-identified high and low concentration serum samples were mixed to cover 5 equally spaced expected levels across the assay range. A sample with a value of 41,812 pg/mL was diluted for the full range linearity study and a sample with a value of 1266 pg/mL was diluted for the low range linearity study. The samples were diluted with low level patient plasma pools. The studies support the analytical measuring range for the assay of 5 – 35,000 pg/mL. The following table summarizes the results of the studies:

	Sample A Full range	Sample B Low range
Starting concentration (pg/mL)	41812	1266
Regression Statistics		
Slope	1.004	1.003
Intercept	-55.8	-3.5
Correlation	0.9999	0.999
% Recovery		
Average	99.9	99.5
Range	98 – 101	98 - 100

Hook effect was evaluated using a high concentration PBNP sample. The sample was diluted at 1:10, 1:20, 1:40 and 1:80. The neat and diluted samples were tested. The data demonstrated that the Dimension Vista® PBNP method showed no hook effect up to 400,000 pg/mL.

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

The design and function of the Dimension Vista® PBNP-Calibrator is equivalent to that of the previously cleared Dimension Vista® PBNP-Calibrator (k061795).

The artificial matrix for the calibrator is BSA based spiked with synthetic NT-proBNP peptide. The master pool is a multi-level, liquid BSA-based artificial matrix spiked with synthetic NT-proBNP peptide stored at -70°C.

Constituent	Traceability
PBNP	Master Pool containing synthetic human N-terminal pro-brain natriuretic peptide (consensus values)

Values are assigned to each lot of calibrator from the master pool using the Dimension Vista® PBNP method. Values are assigned to the master pool from the patient sample anchor pool, which has been assigned on the Elecsys PBNP assay.

The stability claims for this product are as follows:

Unopened product (Frozen) – 12 months

Unopened product (Thawed) – 30 days at 2 – 8 degrees Celsius

Opened product – Punctured vials are stable for seven days, when stored on board the Dimension Vista® System. Once cap is removed, the product is stable for 30 days when stored securely capped at 2 – 8 degrees Celsius.

d. *Detection limit:*

The estimation of the Limit of Blank (LoB) was performed by running twenty replicas of the PBNP Calibrator, level A, calculating the mean and adding 2 standard deviations to the mean. CLSI EP17-A, Protocols for Determination of Limits of Detection and Limits of Quantitation, was followed. The Limit of Blank was estimated to be 0.2 pg/mL.

To determine the Limit of Detection (LoD), five samples of PBNP Calibrator Level A and five low patient samples were tested on four different days, using two different instruments and two different reagent lots. A total N=60 blank samples and N=60 low-level samples were tested. One trained operator performed the testing. The calculation of the Limit of Detection was performed by the following formula:

LoD = LoB + (cp)x(sd)

LoD = 0.2 pg/mL + (1.646) x (0.4) = 0.8 pg/mL

The nonparametric approach described in EP17-A was followed to determine the Limit of Detection with proportions of false positives (α) less than 5% and false negatives (β) less than 5%; based on 60 determinations, with 5 blank and 5 low level samples. The LoD was estimated to be 0.8 pg/mL. The analytical measuring range for the assay is from 5 – 35,000 pg/mL.

Limit of quantitation was evaluated by determining the total imprecision of natural NT-proBNP serum samples. Total imprecision was measured by a two replicate per day, twenty day ANOVA study. The intra-assay imprecision profile for the Dimension Vista® PBNP method corresponds to a coefficient of variation (CV) of 20% at an NT-proBNP level of ≤30 pg/mL.

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, and triglycerides up to 3000 mg/dL. An extensive list of other compounds was evaluated for interference when added to samples with NT-proBNP concentrations of 135 and 2000 pg/mL and was found to have no significant interference (<10%). A list of these compounds is presented in the labeling.

The following substances have no significant cross-reactivity (less than 1%) at the concentrations indicated when added to samples containing 0 and approximately 125 pg/mL NT-proBNP:

Substance	Concentration
ANP_{28}	3.1 µg/mL
NT-proANP$_{1-30}$ (preproANP $_{26-55}$)	3.5 µg/mL
NT-proANP$_{31-67}$ (preproANP $_{56-92}$)	1.0 ng/mL
NT-proANP$_{79-98}$ (preproANP $_{104-123}$)	1.0 ng/mL
BNP_{32} (Natrecor®)	3.5 µg/mL
CNP_{32}	2.2 µg/mL
DNP	1.0 ng/mL
VNP	1.0 ng/mL
Adrenomedullin	1.0 ng/mL
Aldosterone	1.0 ng/mL
Angiotensin I	1.0 ng/mL
Angiotensin II	0.6 ng/mL
Angiotensin III	0.6 ng/mL
Endothelin	0.6 ng/mL
Renin	1.0 ng/mL
Urodilatin	20 pg/mL
Arg-Vasopressin	50 ng/mL

f. *Assay cut-off:*

See expected values below.

2. Comparison studies:

a. *Method comparison with predicate device:*

CLSI EP9-A2, Method Comparison and Bias Estimation Using Patient Samples, was followed to perform the method comparison study. The predicate was the Dimension Vista® PBNP Flex® reagent cartridge polyclonal assay (k061795). One hundred and sixty samples, single measurement per sample, were used for the study. The range of values in the

correlation study was 12 - 29,519 pg/mL.

Comparative Method	Slope	Intercept (pg/mL)	Correlation Coefficient	N
Dimension Vista® P-BNP (Polyclonal) k061795	1.02	-3.2	0.996	160

Concordance testing between Dimension Vista® PBNP polyclonal assay (k061795) and Dimension Vista® PBNP monoclonal assay was completed on reference group and disease group samples. The reference group studies were performed in house and examined 51 samples from a < 75 years of age population and 41 samples from a ≥ 75 years of age population. The disease group studies were performed in a university setting and in house using the same clinical samples and examined 21 samples from a <75 years of age population and 79 samples from a ≥ 75 years of age population, with 25 samples in each New York Heart Association (NYHA) class I – IV category.

NYHA Classification	≥ 75 Years Old	< 75 Years Old
Class I	4	21
Class II	5	20
Class III	7	18
Class IV	5	20

Cut-offs of 125 pg/mL for patients less than 75 years old and 450 pg/mL for patients 75 years and older were used. Concordance was 100% for Class I, 96% for Class II, 100% for Class III, and 100% for Class IV. The data demonstrated 99% overall concordance between the predicate device (polyclonal) and the Dimension Vista® PBNP (monoclonal) assay.

b. *Matrix comparison:*

Comparison studies for serum and plasma equivalency were performed. The method used to fit the regression lines was Passing-Bablok statistics. The comparison test results on the Dimension Vista® System for lithium heparin, sodium heparin and EDTA plasma samples versus serum samples is provided as follows:

X - Axis	Serum	Serum	Serum
Y - Axis	EDTA	Li Heparin	Na Heparin
Range	16 - 35,000 pg/mL	5 - 25,000 pg/mL	12 - 35,000 pg/mL
N	59	53	57

Slope	0.9976	1.009	0.9985
Intercept	0.5339	-1.975	4.7895
Correlation	0.9997	0.9984	0.9987

3. Clinical studies:

   a. *Clinical Sensitivity:*

      Refer to decision summary for k061795

   b. *Clinical specificity:*

      Refer to decision summary for k061795

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

4. Clinical cut-off:

   Refer to decision summary for k061795

5. Expected values/Reference range:

   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 k061795 are:

   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.