

**510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
DEVICE ONLY TEMPLATE**

A. 510(k) Number:

k040425

B. Purpose for Submission:

Labeling changes, Indications for Use modified to include: assessment of severity of heart failure and, in conjunction with other known risk factors, to predict survival in patients after myocardial infarction.

C. Analyte:

B-type natriuretic peptide test system (BNP)

D. Type of Test:

Quantitative

E. Applicant:

Bayer HealthCare LLC

F. Proprietary and Established Names:

Bayer Diagnostics ADVIA® Centaur® BNP Assay, Bayer Diagnostics ACS:180® BNP Assay

G. Regulatory Information:

1. Regulation section:
21 CFR 862.1117 B-type natriuretic peptide test system
2. Classification:
Class II
3. Product Code:
NBC
4. Panel:
75 Chemistry

H. Intended Use:

1. Intended use(s):
For in vitro diagnostic use in the quantitative determination of B-type natriuretic peptide (BNP) in human plasma using the ADVIA Centaur® System. This assay is indicated for the measurement of plasma BNP as an aid in the diagnosis and assessment of severity of heart failure. This test, in conjunction with other known risk factors, can also be used to predict survival in patients after myocardial infarction. This assay is not intended for use on any other system.

For in vitro diagnostic use in the quantitative determination of B-type natriuretic peptide (BNP) in human plasma using the ACS:180® System. This assay is indicated for the measurement of plasma BNP as an aid in the diagnosis and assessment of severity of heart failure. This test, in conjunction with other known risk factors, can also be used to predict survival in patients after myocardial infarction. This assay is not intended for use on any other system.

2. Indication(s) for use:
See Intended Use above
3. Special condition for use statement(s):
Prescription use
4. Special instrument Requirements:
Bayer Diagnostics ADVIA® Centaur®, Bayer Diagnostics ACS:180®

I. Device Description:

5 ReadyPack® primary reagent packs containing ADVIA Centaur® BNP Lite Reagent (monoclonal mouse anti-human BNP fragment antibody labeled with acridium ester in buffer with bovine gamma globulin, mouse gamma globulin and preservatives) and Solid Phase (monoclonal mouse anti-human BNP antibody in bovine gamma globulin, mouse gamma globulin and preservatives), ADVIA Centaur® Master Curve card for 500 tests or 1 ReadyPack® primary reagent pack containing ADVIA Centaur® BNP Lite Reagent and Solid Phase, ADVIA Centaur® Master Curve card for 100 tests

Or

6 vials of ACS:180® BNP Lite Reagent, 6 vials of ACS:180® Solid Phase, ACS:180® BNP Master Curve Card or 1 vial of ACS:180® BNP Lite Reagent, 1 vial of ACS:180® Solid Phase, ACS:180® BNP Master Curve Card

J. Substantial Equivalence Information:

1. Predicate device name(s):
Bayer Diagnostics ADVIA® Centaur® BNP Assay
2. Predicate K number(s):
k031038
3. Comparison with predicate:

Similarities		
Item	Device	Predicate
Assay principle	Chemiluminescence immunoassay	Same
Traceability	Synthetic human BNP in buffer based matrix	Same
Sample type	EDTA plasma	Same

Differences		
Item	Device	Predicate
Indications for Use	For in vitro diagnostic use in the quantitative determination of B-type natriuretic peptide (BNP) in human plasma using the ADVIA Centaur® and ACS:180® Systems. This assay is indicated for the measurement of plasma BNP as an aid in the diagnosis and assessment of severity of heart failure. This test, in conjunction with other known risk factors, can also be used to predict survival in patients after myocardial infarction. This assay is not intended for use on any other system.	For in vitro diagnostic use in the quantitative determination of B-type natriuretic peptide (BNP) in human plasma using the ADVIA® Centaur® System. This assay is indicated for the measurement of plasma BNP as an aid in the diagnosis of heart failure. This assay is not intended for use on any other system
Assay cut-off	Age and gender matched descriptive statistics provided. Decision threshold of 100 pg/mL recommended for diagnosis of heart failure. Decision threshold of 80 pg/mL recommended for prediction of survival after myocardial infarction.	Age and gender matched descriptive statistics provided. Decision threshold of 100 pg/mL recommended.

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

NCCLS EP5, NCCLS EP7-P

L. Test Principle:

The ADVIA Centaur and ACS:180 BNP assays are fully automated two-site sandwich immunoassays using direct chemiluminescent technology, which uses constant amounts of two monoclonal antibodies. The first antibody, in the Lite Reagent, is an acridinium ester labeled monoclonal mouse anti-human BNP F(ab')₂ fragment specific to the ring structure of BNP. The second antibody, in the Solid Phase, is a biotinylated monoclonal mouse anti-human antibody specific to the C-terminal portion of BNP, which is coupled to streptavidin magnetic particles. A direct relationship exists between the amount of BNP present in the patient sample and the amount of relative light units (RLUs) detected by the system.

M. Performance Characteristics (if/when applicable):1. Analytical performance:a. *Precision/Reproducibility:*

ADVIA Centaur: Six samples were assayed 4 times in 20 runs on 2 systems (n = 160 for each sample), over a period of 20 days. Two separate studies were performed, each with a separate lot of reagents. Within run precision % CV ranged from 4.3 % at 29.4 pg/mL to 2.1% at 1736 pg/mL, with total precision of 4.7 % and 2.9 %, respectively.

ACS:180: Six samples were assayed 3 times in 20 runs on 2 systems(n = 120 for each sample) over a period of 20 days. Within run precision % CV ranged from 7.9 % at 51.5 pg/mL to 2.5% at 1783 pg/mL, with total precision of 9.9 % and 3.8 %, respectively.

b. *Linearity/assay reportable range:*

Reportable range: ADVIA Centaur <2 to 5000 pg/mL, ACS 180 < 7.5 to 5000 pg/mL. Patient samples with high BNP levels were mixed in various proportions with patient samples containing low levels of BNP. When compared to the expected value, the measured (recovered) values of BNP averaged 103% with a range of 93 to 113% for the ADVIA Centaur and averaged 98% with a range of 96 to 102% for the ACS:180.

c. *Traceability (controls, calibrators, or method):*

The ADVIA Centaur and ACS:180 BNP assays are traceable to an internal standard manufactured using synthetic human BNP (amino acid 77-108). Assigned calibrator doses and ranges for quality control material are traceable to this standardization.

d. *Detection limit:*

The functional sensitivity is defined as the lowest BNP concentration determined at a coefficient of variation of 20%. The functional sensitivity was determined to be 2.5 pg/mL for the ADVIA Centaur and 11.0 pg/mL for the ACS:180. The minimum detectable concentration (MDC) of the assay is < 2pg/mL for the ADVIA Centaur and < 7.5 pg/mL for the ACS:180. The MDC is defined as the concentration of BNP that corresponds to the relative light units (RLU's) that are 2 SD > the mean RLU's of 20 replicate determinations of the BNP zero standard. This response is an estimate of the MDC with 95% confidence.

e. *Analytical specificity:*

<i>Specimens that are . . .</i>	<i>Demonstrate ≤5% change in results up to . . .</i>
hemolyzed	1000 mg/dL of hemoglobin
lipemic	800 mg/dL of triglycerides
	1000 mg/dL of cholesterol
uremic	200 mg/dL of urea

Specimens that are . . . Demonstrate \leq 5% change in results up to . . .

	2.5 mg/dL of creatinine
icteric	25 mg/dL of unconjugated bilirubin

Specimens that are . . . Demonstrate \leq 7% change in results up to . . .

icteric	25 mg/dL of conjugated bilirubin
proteinemic	5.3 g/dL of human IgG

A total of 55 commonly used pharmaceutical drugs were added to human plasma-based samples at two times the maximum therapeutic dosage and evaluated for potential interference. The results demonstrated \leq 10% interference from each drug.

The drug Neseritide is a synthetic form of BNP-32 which is thought to be virtually identical to the endogenous active hormone BNP.

The Bayer BNP assays measure Neseritide as BNP. The following statement in the labeling addresses the use of the test with patients receiving Neseritide:

It has been reported that patients with acute decompensated heart failure who are candidates for nesiritide (recombinant BNP) infusion should have a baseline BNP measurement taken prior to initiation of therapy. Measurements taken during infusion are reflective of the dose of nesiritide. Because of the short half-life of BNP (20 minutes), measurements taken 2 hours after the cessation of treatment again reflect the level of endogenous BNP. It has also been reported that following infusion, endogenous BNP levels return to baseline by 1-2 hours and continue to drop at 6 hours to about 80% of preinfusion levels, suggesting a resetting of the neuro-hormonal axis and improvement in ventricular wall tension as a result of treatment. The ADVIA Centaur and ACS:180 BNP assays are not approved for nesiritide monitoring.

f. *Assay cut-off:*

See clinical cut-off below

2. Comparison studies:

a. *Method comparison with predicate device:*

The method comparison was previously established for the ADVIA Centaur in k031038. For 949 samples in the range of 0 to 1290 pg/mL, the relationship between the ADVIA Centaur BNP assay and a predicate device is described by the Passing & Bablok regression equation:

ADVIA Centaur BNP = 0.74 (Predicate Device) – 0.60 pg/mL
Correlation coefficient (r) = 0.90

For 730 samples in the range of < 7.5 to 4135 pg/mL, the relationship between the ACS:180 BNP assay and the ADVIA Centaur BNP assay is described by the Passing & Bablok regression equation:

ACS:180 BNP = 1.03 (ADVIA Centaur BNP) – 0.10 pg/mL
Correlation coefficient (r) = 1.00

b. Matrix comparison:

This test has been evaluated with plasma using EDTA as the anticoagulant. Serum, sodium citrate, lithium heparin and sodium fluoride sample tubes have also been tested and are not recommended. This information was provided in k031038.

3. Clinical studies:

a. Clinical sensitivity:

The clinical sensitivity and specificity of the ADVIA Centaur BNP assay using a decision threshold of 100 pg/mL for various age groups within each gender are presented in the following tables:

Clinical Sensitivity and Specificity vs. Age and Gender

Males					
	Age Group				
	<45 years	45-54 years	55-64 years	65-74 years	75 + years
% Sensitivity	58.7	49.2	69.9	83.7	88.6
95% Confidence Interval	40.4 - 71.0	36.4 - 62.1	61.0 - 77.9	75.1 - 90.2	80.9 - 93.9
% Specificity	100	100	99.5	96.8	94.6
95% Confidence Interval	97.2 - 100	97.4 - 100	97.6 - 100	93.2 - 98.8	85.1 - 98.9

Females					
	Age Group				
	<45 years	45-54 years	55-64 years	65-74 years	75 + years
% Sensitivity	45.5	56.3	60.4	68.9	87.2
95% Confidence Interval	24.4 - 67.8	37.7 - 73.7	45.3 - 74.2	53.4 - 81.8	79.7 - 92.6
% Specificity	99.5	99.3	97.8	97.2	79.8
95% Confidence Interval	97.1 - 100	96.4 - 100	94.4 - 99.4	93.5 - 99.0	69.9 - 87.6

b. Clinical specificity:

see above

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

4. Clinical cut-off:

The decision threshold for diagnosing heart failure was determined based on the BNP level at the 95th percentile of the Reference Group. The most appropriate decision threshold for diagnosing heart failure apparent from these distributions is 100 pg/mL. This BNP value translates into a general specificity of the test of greater than 97 %.

The decision threshold for predicting survival in patients with myocardial infarction is 80 pg/mL. Retrospective analysis of BNP was performed on 438 patients with AMI from the ENTIRE-TIMI 23 (Thrombolysis in Myocardial Infarction) study, a multi-national trial conducted between February 2000 and

September 2001. The study design has been published previously. Patients were eligible for inclusion if they had an episode of ischemic discomfort of at least 30 minutes duration within the prior 6 hours, and exhibited positive ECG changes. The baseline BNP concentration was significantly higher in patients who died within 30 days (n = 15, 89 pg/mL, 25th – 75th: 40-192) compared to survivors (n = 423, 15 pg/mL, 25th – 75th: 8.8 – 32, p<0.0001). BNP levels greater than 80 pg/mL were associated with a substantially higher risk of death through 30 days of follow-up (17.4% vs. 1.8%, p<0.0001). The odds ratio for death within 30 days for patients with BNP levels greater than 80 pg/mL was 11.5. The odds ratio for death within 30 days for patients with BNP levels greater than 80 pg/mL, adjusted for age, history of hypertension, and prior angina, was 8.3 with a 95% confidence interval of 2.7 to 25.8. Patients with elevated BNP levels also had an increased risk of composite end points for death and heart failure combined (23.9% vs. 5.1%, p<0.0001). The odds ratio for death within 30 days for patients with BNP levels greater than 80 pg/mL was 5.8. The odds ratio for death or CHF within 30 days for patients with BNP levels greater than 80 pg/mL, adjusted for age, history of CHF, history of hypertension, and prior angina, was 3.6 with a 95% confidence interval of 1.5 to 8.8. Elevated levels of BNP at initial presentation are associated with an increased risk of mortality in patients with myocardial infarction.

5. Expected values/Reference range:

The expected results for the ADVIA Centaur BNP assay were previously established (k031038). These results were confirmed for the ACS:180 by analyzing 730 samples (see method comparison). The circulating BNP concentration was determined from 1521 individuals without heart failure (785 women and 736 men). This population included apparently healthy individuals and individuals with hypertension, diabetes, renal insufficiency, and chronic obstructive pulmonary disease. The descriptive statistics for BNP concentrations in the population without heart failure are shown in the following tables. These values are representative of the results obtained from clinical studies. Clinical studies indicate that BNP levels increase with age in the general population with the highest values seen in individuals greater than 75 years of age. In this subgroup of patients, age needs to be taken into consideration for accurate interpretation of test results.

All	Age Group					
	All	<45 years	45-54 years	55-64 years	65-74 years	75 + years
Mean, pg/mL	23.2	11.9	15.6	19.5	28.3	60.3
SD, pg/mL	32.5	12.9	15.9	22.6	25.4	73.0
Median, pg/mL	14.5	8.6	10.4	13.8	22.1	43.7
95 th Percentile, pg/mL	70.8	33.3	46.7	53.2	72.3	176
% < 100 pg/mL	97.4	99.7	99.7	98.8	97.0	85.5
Minimum, pg/mL	<2	<2	<2	<2	<2	<2
Maximum, pg/mL	576	128	119	286	164	576
N	1521	317	291	403	365	145

Males	Age Group					
	All	<45 years	45-54 years	55-64 years	65-74 years	75 + years
Mean, pg/mL	17.9	9.1	11.2	14.5	25.8	41.9
SD, pg/mL	22.9	9.4	11.8	13.9	25.1	48.8
Median, pg/mL	11.3	5.9	7.6	11.9	17.8	26.1
95 th Percentile, pg/mL	54.3	29.4	32.8	38.8	67.6	121
% < 100 pg/mL	98.6	100	100	99.5	96.8	94.6
Minimum, pg/mL	<2	<2	<2	<2	<2	<2
Maximum, pg/mL	250	56.6	88.9	132	151	250
N	736	129	140	223	188	56

Females	Age Group					
	All	<45 years	45-54 years	55-64 years	65-74 years	75 + years
Mean, pg/mL	28.1	13.8	19.8	25.6	31.0	71.9
SD, pg/mL	38.8	14.6	18.0	29.0	25.5	82.9
Median, pg/mL	18.5	10.4	14.8	19.4	25.7	54.3
95 th Percentile, pg/mL	86.1	35.9	56.7	75.5	72.9	167
% < 100 pg/mL	96.3	99.5	99.3	97.8	97.1	79.8
Minimum, pg/mL	<2	<2	<2	<2	<2	<2
Maximum, pg/mL	576	128	119	286	164	576
N	785	188	151	180	177	89

Patients with Heart Failure

To establish the expected results for the ADVIA Centaur BNP assay in individuals with heart failure, plasma samples were obtained from 722 patients diagnosed with heart failure (264 women and 458 men). The descriptive statistics for BNP concentrations in patients with heart failure are presented in the following tables. These values are representative of the results obtained from clinical studies. In addition, laboratories should be aware of their respective institution's current practice for the evaluation of heart failure.

	Heart Failure Population – All		NYHA Functional Class			
	All	NYHA I	NYHA II	NYHA III	NYHA IV	
Mean, pg/mL	505	178	270	525	1134	
SD, pg/mL	711	347	402	576	1141	
Median, pg/mL	262	64.3	130	355	843	
5 th percentile, pg/mL	10.8	1.6	5.4	21.1	109	
95 th percentile, pg/mL	1873	772	999	1696	3157	
% ≥ 100 pg/mL	72.6	43.1	58.7	82.0	95.8	
Minimum, pg/mL	<2	<2	<2	<2	4.0	
Maximum, pg/mL	6989	2310	3107	4052	6989	
N	722	72	242	289	119	

	Heart Failure Population – Males		NYHA Functional Class		
	All	NYHA I	NYHA II	NYHA III	NYHA IV
Mean, pg/mL	518	121	308	542	1214
SD, pg/mL	726	135	475	588	1200
Median, pg/mL	245	77.7	135	339	950
5 th percentile, pg/mL	10.7	3.9	4.4	23.2	71.5
95 th percentile, pg/mL	1946	400	1280	1852	3157
% ≥ 100 pg/mL	72.9	44.7	61.3	81.4	93.9
Minimum, pg/mL	<2	<2	<2	<2	33.7
Maximum, pg/mL	6989	552	3107	3503	6989
N	458	47	150	194	66

	Heart Failure Population - Females		NYHA Functional Class		
	All	NYHA I	NYHA II	NYHA III	NYHA IV
Mean, pg/mL	482	285	207	492	1034
SD, pg/mL	687	551	228	556	1068
Median, pg/mL	291	62.5	117	355	779
5 th percentile, pg/mL	11.0	0	9.5	15.9	115
95 th percentile, pg/mL	1575	1447	552	1518	2970
% > 100 pg/mL	72.0	40.0	54.3	83.2	98.1
Minimum, pg/mL	<2	<2	<2	4.8	4.0
Maximum, pg/mL	5845	2310	1231	4052	5845
N	264	25	92	94	53

These results show that there is a relationship between the severity of the clinical signs and symptoms of heart failure and the median BNP concentrations of each NYHA functional class.

N. Conclusion:

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