SIEMENS

ADVIA Centaur® CP
Immunoassay System

CE 0197

BNP

Assay Summary

Sample Type	***EDTA Plasma***
Sample Volume	***100 µL***
Calibrator	***BNP***
Sensitivity and Assay Range	***2.0 – 5000 pg/mL (0.58 – 1445 pmol/L)***

Contents

REF	*Contents*	*Number of Tests*
02816634	5 ReadyPack® primary reagent packs containing ADVIA Centaur® BNP Lite Reagent and Solid Phase	500
	ADVIA Centaur and ADVIA Centaur CP BNP Master Curve card	
or		
02816138	1 ReadyPack primary reagent pack containing ADVIA Centaur BNP Lite Reagent and Solid Phase	
	ADVIA Centaur and ADVIA Centaur CP BNP Master Curve card	100

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Intended Use

For *in vitro* diagnostic use in the quantitative determination of B-type Natriuretic Peptide (BNP) in human plasma using the ADVIA Centaur CP System. This assay is indicated for the measurement of plasma BNP as an aid in the diagnosis and assessment of the severity of heart failure. In patients with acute coronary syndromes (ACS), this test, in conjunction with other known risk factors, can also be used to predict survival as well as to predict the likelihood of future heart failure. This assay is not intended for use on any other system.

Materials Required but Not Provided

REF	*Description*	*Contents*
02817266	BNP Calibrator	2 vials of low calibrator CAL L
		2 vials of high calibrator CAL H
01137199 (112351)	ADVIA Centaur Wash 1 WASH 1	2 x 1500 mL/pack
or		
03773025	ADVIA Centaur Wash 1 WASH 1	2 x 2500 mL/pack

Optional Reagents

REF	Description	Contents
11200097	ADVIA Centaur Multi-Diluent 15 M-DIL 15	2 ReadyPack ancillary reagent packs containing 25 mL/pack
02817045	BNP 1,2,3 quality control material	3 x 2 mL Level 1 CONTROL 1 3 x 2 mL Level 2 CONTROL 2 3 x 2 mL Level 3 CONTROL 3
02815905	BNP Master Curve Material	5 x 1 mL

Summary and Explanation of the Test

Heart failure is an important clinical syndrome which compromises left ventricular systolic or diastolic function or a combination of both. Heart failure occurs when the heart is unable to pump blood at a rate sufficient for metabolic requirements. Its most common causes are coronary artery disease, hypertension, valvular heart diseases and cardiomyopathies. Accurate and early diagnosis is important since effective therapeutic interventions (e.g., angiotensin converting enzyme inhibitors, beta-blockers) are available, which improve both morbidity and mortality. Based on clinical signs and symptoms, the severity of heart failure is classified into four classes of increasing disease progression according to the New York Heart Association classification (NYHA class I – IV).[1,2]

The natriuretic peptide system is a family of structurally similar but genetically distinct peptides, which include atrial natriuretic peptide (ANP) and B-type natriuretic peptide (BNP) of myocardial cell origin and C-type natriuretic peptide (CNP) of endothelial cell origin. These peptides are characterized by a common 17 amino acid ring structure with a disulfide bond between two cysteine residues.[3-5] The cardiac natriuretic peptides are the naturally occurring antagonists of the renin-angiotensin-aldosterone system and of the sympathetic nervous system. They promote natriuresis and diuresis, act as vasodilators, and exert antimitogenic effects on cardiovascular tissues.[6] ANP and BNP are secreted by the heart in response to hemodynamic stress. Increased levels of BNP are produced mainly in response to left ventricular wall stretch and volume overload. ANP and BNP are expressed predominantly in the atria and ventricles, respectively, and are important in regulation of blood pressure, electrolyte and volume homeostasis.[6-10]

The cardiac natriuretic peptide system is activated to its highest degree in ventricular dysfunction and has an important role in maintaining the compensated state of asymptomatic heart failure and delaying disease progression. BNP is synthesized within the cardiomyocyte as a preprohormone (preproBNP) of 134 amino acids, from which a prehormone (proBNP) of 108 amino acids and a signal peptide of 26 amino acids is derived. The proBNP precursor protein is then cleaved into a physiologically active 32 amino acid C-terminal peptide (BNP 77-108; BNP) and a 76 amino acid N-terminal prohormone fragment (NT-proBNP 1-76). Studies indicate that the proBNP protein precursor is cleaved either within or on the surface of cardiomyocytes, and that both NT-proBNP (1-76) and physiologically active C-terminal BNP molecule (77-108) are released into the bloodstream.[11-13] The ADVIA Centaur BNP assay measures only the physiologically active BNP molecule (77-108) and utilizes monoclonal antibodies specific to its C-terminal portion and ring structure.

Several studies indicate that BNP can be used for a wide range of clinical applications; including diagnosis, monitoring and prognosis.[3,4,11,12,14-16] The circulating levels of BNP increase with decreasing left ventricular function and increasing clinical severity of heart failure, according to the NYHA classification, which makes it an appropriate test for diagnosis and staging of heart failure.[17-27] Other studies have demonstrated that an increased level of circulating BNP correlates with higher incidence of cardiac events and mortality in patients with heart failure[28-31] and Acute Coronary Syndromes,[32-33] and supports utilization of BNP as a marker for patient prognosis. The Thrombolysis in Myocardial Infarction 23 (ENTIRE-TIMI 23) Sub-Study evaluated the prognostic performance of the ADVIA Centaur BNP method assessed at the time of initial presentation in a well-characterized cohort of patients enrolled in the Enoxaparin and tenecteplase (TNK-tPA) with or without GPIIb/IIIa Inhibitor as Reperfusion Strategy in ST Elevation Myocardial Infarction (STEMI).[34] Plasma BNP was measured retrospectively in 438 STEMI patients who had an episode of ischemic discomfort of at least 30 minutes duration within the prior 6 hours. This study found that BNP levels greater than 80 pg/mL at presentation were associated with a substantially higher risk of death within the 30-day follow-up period. There are also indications that BNP can be used to provide an index to modulate treatment of patients with heart failure.[16,17,35,36]

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.[37] 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.[38] The ADVIA Centaur BNP assay is not approved for nesiritide monitoring.

Assay Principle

The ADVIA Centaur BNP assay is a fully automated two-site sandwich immunoassay 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.

The system automatically performs the following steps:

1. Dispenses 100 µL of sample into a cuvette.
2. Dispenses 100 µL of Lite Reagent and incubates for 6.3 minutes at 37°C.
3. Dispenses 200 µL of Solid Phase and incubates for 3.0 minutes at 37°C.
4. Separates, aspirates, and washes the cuvettes with Wash 1.
5. Dispenses 300 µL each of Acid Reagent (R1) and Base Reagent (R2) to initiate the chemiluminescent reaction.
6. Reports results according to the selected option, as described in the system operating instructions or in the online help system.

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.

Specimen Collection and Handling

EDTA plasma is the recommended sample type for this assay. Plastic blood collection tubes are recommended for sample collection, as BNP is unstable in glass containers. Use of glass tubes and transfer pipettes affects accurate quantitation of BNP.[39,40]

- Collect blood samples in EDTA collection tubes and mix gently.
- The average percentage of BNP recovery in uncentrifuged whole blood after 24 hour storage at 2–8°C or room temperature was 96%. For optimal recovery of BNP values, it is suggested that samples be tested within 24 hours.
- After centrifugation, store separated plasma samples at 2–8°C until testing.
- The average percentage of BNP recovery in EDTA plasma after 24 hours storage at 2–8°C was 91%. It is recommended not to store EDTA-plasma at room temperature. For optimal recovery of BNP values, it is suggested that plasma samples be tested within 24 hours. If plasma samples are not tested within 24 hours, store samples in plastic tubes and freeze at or below -20°C in non-frost free freezers.
- Samples may undergo up to 4 freeze/thaw cycles without degradation. Samples are stable up to 9 months when stored frozen at or below -20°C.
- Mix samples thoroughly after thawing and store at 2–8°C until use. Samples should be tested within 8 hours after thawing.

The following recommendations for handling and storing blood samples are furnished by the Clinical and Laboratory Standards Institute (CLSI, formerly NCCLS):[41]

- Collect all blood samples observing universal precautions for venipuncture.
- Keep tubes stoppered and upright at all times.

Before placing samples on the system, ensure that samples have the following characteristics:

- Samples are free of fibrin or other particulate matter. Remove particulates by centrifugation at 1000 x g for 15 to 20 minutes.
- Samples are free of bubbles.

Specimen collection and handling requirements were determined using the ADVIA Centaur system.

Reagents

Store the reagents upright at 2–8°C.

Mix all primary reagent packs by hand before loading them onto the system. Visually inspect the bottom of the reagent pack to ensure that all particles are dispersed and resuspended. For detailed information about preparing the reagents for use, see the system operator's guide.

Reagent Pack	Reagent	Volume	Ingredients	Storage	Stability
ADVIA Centaur BNP ReadyPack primary reagent pack	Lite Reagent	10.5 mL/ reagent pack	monoclonal mouse anti-human BNP F(ab')$_2$ fragment antibody (~ 0.50 µg/mL) labeled with acridinium ester in buffer with bovine gamma globulin, mouse gamma globulin and preservatives	2–8°C	until the expiration date on the pack label. For onboard stability, refer to *Onboard Stability and Calibration Interval*.
	Solid Phase	21 mL/ reagent pack	monoclonal mouse anti-human BNP antibody (~6.0 µg/mL) in bovine gamma globulin, mouse gamma globulin and preservatives	2–8°C	until the expiration date on the pack label. For onboard stability, refer to *Onboard Stability and Calibration Interval*.
ADVIA Centaur M-DIL 15 ReadyPack ancillary reagent pack	Multi-Diluent 15	25 mL/reagent pack	equine serum with sodium azide (0.1%) and preservatives	2–8°C	Until the expiration date on the pack label or onboard–7 consecutive days after accessing the ancillary reagent pack.
ADVIA Centaur WASH 1*	Wash 1*	2 x 1500 mL/ vial	phosphate buffered saline with sodium azide (< 0.1%), surfactant	2–25°C	Until the expiration date on the vial or onboard–1 month.
ADVIA Centaur WASH 1	Wash 1*	2 x 2500 mL/ vial	phosphate buffered saline with sodium azide (< 0.1%), surfactant	2–25°C	Until the expiration date on the vial or onboard–1 month.

* Refer to *Materials Required but Not Provided.*

Warnings and Precautions

Safety data sheets (MSDS/SDS) available on siemens-healthineers.com.

The summary of safety and performance for this *in vitro* diagnostic medical device is available to the public in the European database on medical devices, EUDAMED, when this database is available and the information has been uploaded by the Notified Body. The web address of the EUDAMED public website is: https://ec.europa.eu/tools/eudamed.

CAUTION: This device contains material of animal origin and should be handled as a potential carrier and transmitter of disease.

NOTE: Sodium azide can react with copper and lead plumbing to form explosive metal azides. On disposal, flush reagents with a large volume of water to prevent the buildup of azides, if disposal into a drain is in compliance with federal, state, and local requirements.

Dispose of hazardous or biologically contaminated materials according to the practices of your institution. Discard all materials in a safe and acceptable manner and in compliance with prevailing regulatory requirements.

For Professional Use.

CAUTION: Federal (USA) law restricts this device to sale by or on the order of a licensed healthcare professional.

For *in vitro* diagnostic use.

Loading Reagents

Ensure that the system has sufficient primary and ancillary reagent packs. For detailed information about preparing the system, refer to the system operating instructions or to the online help system.

Mix all primary reagent packs by hand before loading them onto the system. Visually inspect the bottom of the reagent pack to ensure that all particles are dispersed and resuspended. For detailed information about preparing the reagents for use, see the system operator's guide.

Load the primary reagent packs in the primary reagent area. The arrows on the end label can be used as a placement guide. However left, center, and right placement of the primary reagent packs is not required because there is only one reagent probe on the ADVIA Centaur CP System. The system automatically mixes the primary reagent packs to maintain homogeneous suspension of the reagents. For detailed information about loading reagents, refer to the system operating instructions or to the online help system.

If dilution of a sample is required, load the ADVIA Centaur Multi-Diluent 15 in the ancillary reagent area.

Onboard Stability and Calibration Interval

Onboard Stability	*Calibration Interval*
41.6 days	28 days

Additionally, the ADVIA Centaur BNP assay requires a two-point calibration:

- When changing lot numbers of primary reagent packs.
- When replacing system components.
- When quality control results are repeatedly out of range.

NOTE:

- Discard the primary reagent packs at the end of the onboard stability interval.
- Do not use reagents beyond the expiration date.

Effect of Ambient Temperature on Results

CAUTION: The operating range for the ADVIA Centaur BNP assay is 20–25°C (68–77°F). Do not report results for the ADVIA Centaur BNP assay if your laboratory temperature is below 20°C (68°F) or above 25°C (77°F). The ADVIA Centaur BNP assay is susceptible to ambient temperature change, which has the potential to affect recoveries of patient samples and controls. The recoveries of patient samples and control materials may change by ±4.0% for each Celsius degree change in an ambient temperature range of 20–25°C (68–77°F).

Quality control results for this assay will reflect any temperature effects on assay results. To ensure optimal assay performance, each laboratory should determine how often quality control material is run based on the ambient temperature conditions for that laboratory.

Master Curve Calibration

The ADVIA Centaur BNP assay requires a Master Curve calibration when using a new lot number of Lite Reagent and Solid Phase. For each new lot number of Lite Reagent and Solid Phase, use the bar-code reader or keyboard to enter the Master Curve values on the system. The Master Curve card contains the Master Curve values. For detailed information about entering calibration values, refer to the system operating instructions or to the online help system.

Performing Quality Control

To monitor system performance and chart trends, as a minimum requirement, quality control samples should be assayed on each day that samples are analyzed. Quality control samples should also be assayed when performing a two-point calibration. Treat all quality control samples the same as patient samples.

For quality control of the ADVIA Centaur BNP assay, use the Siemens Healthcare Diagnostics BNP 1,2,3 QC material or an equivalent quality control material. Refer to the quality control product insert for the suggested Expected Values.

Additional quality control material can be used at the discretion of the laboratory. Use the quality control material in accordance with the quality control instructions for use.

In addition, perform quality control:

- Following a valid calibration
- With use of a new lot of reagent
- When troubleshooting test results that do not match clinical conditions or symptoms

Follow government regulations or accreditation requirements for quality control frequency. Individual laboratory quality control programs and procedures may require more frequent quality control testing.

Acceptable performance is achieved when the analyte values obtained are within the expected control interval for the system, as indicated by the manufacturer of the control material or within the interval determined by an internal laboratory quality control procedure.

Follow your laboratory's quality control procedures if the results obtained do not fall within the acceptable limits. For information about entering quality control definitions, refer to the system online help.

If the quality control results do not fall within the Expected Values or within the laboratory's established values, do not report results. Take the following actions:

- Verify that the materials are not expired.
- Verify that required maintenance was performed.
- Verify that the assay was performed according to the instructions for use.
- Rerun the assay with fresh quality control samples.
- If necessary, contact your local technical support provider or distributor for assistance.

Sample Volume

This assay requires 100 µL of sample for a single determination. This volume does not include the unusable volume in the sample container or the additional volume required when performing duplicates or other tests on the same sample. Refer to *Dilutions* for information about samples with values above the assay range. For detailed information about determining the minimum required volume, refer to the system operating instructions or to the online help system.

Assay Procedure

For detailed procedural information, refer to the system operating instructions or to the online help system.

Procedural Notes

Calculations

For detailed information about how the system calculates results, refer to the system operating instructions or to the online help system.

The system reports BNP results in pg/mL (common units) or pmol/L (SI units), depending on the units defined when setting up the assay. The conversion formula is 1 pg/mL = 0.289 pmol/L.

Dilutions

The following information pertains to dilutions:

- Samples with levels of BNP greater than 5000 pg/mL (1445 pmol/L) must be diluted and retested to obtain accurate results.
- For automated dilutions, ensure that ADVIA Centaur Multi-Diluent 15 is loaded.
- For automatic dilutions, set the system parameters as follows:

  Dilution point: ≤ 5000 pg/mL (≤ 1445 pmol/L)

  Dilution factor: 2

For detailed information about automated dilutions, refer to the system operating instructions or to the online help system.

High-Dose Hook Effect

Human plasma spiked to BNP levels up to 100,000 pg/mL (28,900 pmol/L) do not demonstrate a paradoxical decrease in the RLUs (high-dose hook effect).

Limitations

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.

The results of the ADVIA Centaur BNP assay should always be assessed in conjunction with the patient's medical history, clinical evaluation and other diagnostic procedures.

Siemens BNP test results should not be used interchangeably with other manufacturers' BNP assays, nor should Siemens BNP test results be used interchangeably with NT-proBNP assay results.

Heterophilic antibodies in human serum can react with reagent immunoglobulins, interfering with *in vitro* immunoassays.[42] Patients routinely exposed to animals or to animal serum products can be prone to this interference and anomalous values may be observed. Additional information may be required for diagnosis.

Specimens that are or contain . . .	*Demonstrate ≤ 10% change in results up to . . .*
hemolyzed	100 mg/dL of hemoglobin
lipemic	800 mg/dL of triglycerides
	1000 mg/dL of cholesterol
uremic	200 mg/dL of urea
	2.5 mg/dL of creatinine
icteric	25 mg/dL of unconjugated bilirubin
	25 mg/dL of conjugated bilirubin
proteinemic	5.3 g/dL of human IgG
biotin	38 ng/mL

Analyte Concentration (pg/mL)	Biotin Test Level (ng/mL)							
	27	55	110	219	439	878	1755	3510
	% Bias							
50	-6%	-11%	-12%	-12%	-14%	-11%	-12%	-14%
450	-2%	-5%	-7%	-8%	-7%	-7%	-9%	-9%
1800	-2%	-4%	-4%	-6%	-6%	-6%	-5%	-8%

Specimens that contain biotin at a concentration of 38 ng/mL demonstrate a less than or equal to 10% change in results. Biotin concentrations greater than this may lead to falsely depressed results for patient samples.

The recommended adult daily dietary intake for biotin is 30 µg/day. Over the counter dietary supplements promoted for use in hair, skin and nail health may contain 5–100 mg of biotin, with recommendations to take multiple pills per day. Pharmacokinetic studies in healthy adults have shown that, in subjects ingesting 5 mg, 10 mg, and 20 mg of biotin, serum concentrations of biotin can reach up to 73 ng/mL, 141 ng/mL, and 355 ng/mL, respectively.[43] Subjects who take up to 300 mg of biotin per day may have plasma biotin levels as high as 1160 ng/mL.[44]

The following drugs were added to a human plasma-based sample at two times the maximum therapeutic dosage and evaluated for potential interference in the ADVIA Centaur BNP assay. The results demonstrated a ≤ 10% interference from each drug at the following concentrations.

Drug	Drug Concentration	Drug	Drug Concentration
Acetaminophen	12 µg/mL	Indomethacin	16 µg/mL
Acetylsalicylic acid	200 µg/mL	Isosorbide dinitrate	4 µg/mL
Allopurinol	240 µg/mL	Lisinopril	16 µg/mL
Amiodarone	20 µg/mL	Lovastatin	16 µg/mL
Ampicillin	200 µg/mL	L-thyroxine	46 pg/mL
Ascorbic Acid	24 µg/mL	Methyldopa	100 µg/mL
Amlodipine Besylate	4 µg/mL	Milrinone lactate	2.4 µg/mL
Atenolol	40 µg/mL	Nicotine	1.6 µg/mL
Atorvastatin	32 µg/mL	Nicotinic Acid	40 µg/mL
Caffeine	30 µg/mL	Nifedipine	36 µg/mL
Captopril	40 µg/mL	Nitrofurantoin	40 µg/mL
Chloramphenicol	50 µg/mL	Nitroglycerin	0.16 µg/mL
Clopidogrel Bisulfate	30 µg/mL	Oxazepam	12 µg/mL
Creatinine	110 µg/mL	Oxytetracycline	100 µg/mL
Cyclosporine	40 µg/mL	Phenobarbital	40 µg/mL
Diclofenac	60 µg/mL	Phenytoin	40 µg/mL
Digitoxin	60 ng/mL	Probenecid	200 µg/mL
Digoxin	4 ng/mL	Procainamide	20 µg/mL
Diltiazem	120 µg/mL	Propranolol	64 µg/mL
Dipyridamole	30 µg/mL	Quinidine	20 µg/mL
Dopamine HCl	116 pg/mL	Simvastatin	32 µg/mL
Enalapril Maleate	16 µg/mL	Spironolactone	40 µg/mL
Erythromycin	100 µg/mL	Sulfamethoxazole	320 µg/mL
Furosemide	16 µg/mL	Theophylline	40 µg/mL
Heparin	8 U/mL	Trimethoprim	64 µg/mL
Hydralazine	20 µg/mL	Verapamil	96 µg/mL
Hydrochlorothiazide	20 µg/mL	Warfarin	4 µg/mL

Interference testing was determined according to CLSI Document EP7-A2.[45]

Expected Results

The expected results for the ADVIA Centaur BNP assay were previously established.

These results were confirmed for the ADVIA Centaur BNP assay by analyzing 227 samples in the range of 4 to 4473 pg/mL (1.2 to 1293 pmol/L). Refer to *Method Comparison*.

BNP concentrations in the Reference Group are shown in the tables below. 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 determining 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 and future heart failure in patients with acute coronary syndromes is 80 pg/mL.

As with all *in vitro* diagnostic assays, each laboratory should determine its own reference range(s) for the diagnostic evaluation of patient results.[46]

Reference Group

To establish the expected results for the ADVIA Centaur BNP assay, 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. Published research indicates that BNP levels increase with age in the general population with the highest values seen in individuals greater than 75 years of age.[47] In this subgroup of patients, age needs to be taken into consideration for accurate interpretation of test results.

Reference Group – 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	14.4	8.6	10.4	13.8	22.1	43.7
95th 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

Reference Group – 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
95th 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

Reference Group – 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
95th 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
5th percentile, pg/mL	10.8	1.6	5.4	21.1	109
95th 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
5th percentile, pg/mL	10.7	3.9	4.4	23.2	71.5
95th 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

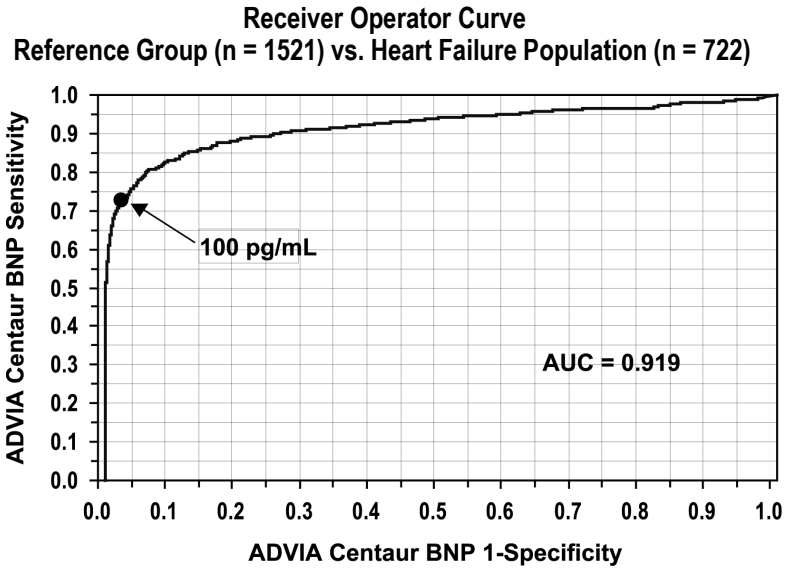
Heart Failure Population – Females

		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
5th percentile, pg/mL	11.0	0	9.5	15.9	115
95th 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

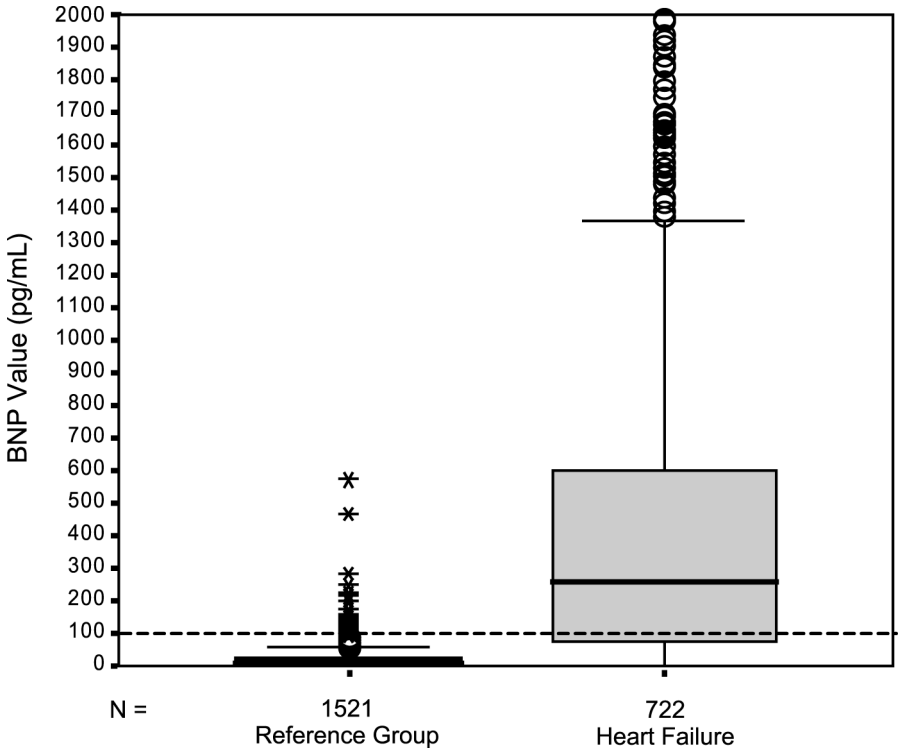
These results show that there is a relationship between the severity of the clinical signs and symptoms of heart failure and the median BNP concentrations of each NYHA functional class. The proportional increase in BNP concentration is greater than 2 fold as heart failure severity increases from Class I to II, II to III, and III to IV. Siemens BNP test results should not be used interchangeably with other manufacturers' BNP assays, nor should Siemens BNP test results be used interchangeably with NT-proBNP assay results.

Interpretation of the Results

The Receiver Operator Curve (ROC) compares clinical sensitivity and specificity at various decision thresholds. The ROC analysis for the ADVIA Centaur BNP assay is presented in the following figure. The AUC for the ADVIA Centaur BNP assay is 0.919 with a 95% confidence interval of 0.904 to 0.934.



A box and whiskers plot for the clinical study population is also presented below, with a horizontal dashed line representing the suggested decision threshold of 100 pg/mL.



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% (37/63)	49.2% (31/63)	69.9% (86/123)	83.7% (87/104)	88.6% (93/105)
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% (129/129)	100% (140/140)	99.5% (222/223)	96.8% (182/188)	94.6% (53/56)
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% (10/22)	56.3% (18/32)	60.4% (29/48)	68.9% (31/45)	87.2% (102/117)
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% (187/188)	99.3% (150/151)	97.8% (176/180)	97.2% (172/177)	79.8% (71/89)
95% Confidence Interval	97.1 – 100	96.4 – 100	94.4 – 99.4	93.5 – 99.0	69.9 – 87.6

Prognostic Utility in Patients with Acute Coronary Syndromes

Two independent retrospective studies have demonstrated the prognostic utility of BNP in patients with ACS. In the first study, BNP was assayed on 438 patients with myocardial infarction 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.[48] 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 pg/mL) compared to survivors (n = 423, 15 pg/mL; 25th–75th, 8.8–32 pg/mL, 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.[34]

Another study was performed on 2,525 patients with acute coronary syndromes. Patients with a BNP level of more than 80 pg/mL were significantly more likely to die, have a new recurrent infarction, or have new or progressive heart failure than those with a level of 80 pg/mL or less. After adjustment for other independent predictors of the long-term risk of death, a BNP level of more than 80 pg/mL remained significantly associated with an increased 10-month mortality rate (P = 0.04). [32]

Method Comparison

For 227 samples in the range of 4 to 4473 pg/mL (1.2 to 1293 pmol/L), the relationship between the ADVIA Centaur BNP assay on the ADVIA Centaur CP system and the ADVIA Centaur BNP assay is described by the Passing & Bablok regression equation:

ADVIA Centaur CP BNP = 1.01 (ADVIA Centaur BNP) – 6.22 pg/mL

Correlation coefficient (r) = 1.00

For 225 samples in the range of 2.7 to 4566 pg/mL (0 to 1320 pmol/L), the relationship between the ADVIA Centaur BNP assay on the ADVIA Centaur CP system and the ACS:180® BNP is described by the Passing & Bablok regression equation:

ADVIA Centaur CP BNP = 1.00 (ACS:180 BNP) + 1.96 pg/mL

Correlation coefficient (r) = 1.00

Analytical Comparison and Clinical Agreement

A paired comparison was performed at 2 clinical trial sites to assess the relationship of the ADVIA Centaur BNP assay to the predicate device. A total of 167 patients with heart failure (HF; clinical diagnoses of Class I – IV) and 20 individuals without heart failure (non-HF) were compared for both analytical and clinical agreement at a decision threshold of 100 pg/mL.

Analytical Comparison – ADVIA Centaur vs. Predicate Device

		Predicate Device		
		≥ 100 pg/mL	***< 100 pg/mL***	***Total***
ADVIA Centaur	***≥ 100 pg/mL***	145	4	149
	< 100 pg/mL	6	32	38
	Total	151	36	187

	Estimate	***95% Confidence Interval***
% Analytical Agreement	94.7% (177/187)	90.4% to 97.4%

Clinical Agreement – ADVIA Centaur BNP

		Clinical Status		
		HF	***Non-HF***	***Total***
ADVIA Centaur	***≥ 100 pg/mL***	146	3	149
	< 100 pg/mL	21	17	38
	Total	167	20	187

	Estimate	***95% Confidence Interval***
% Clinical Agreement	87.2% (163/187)	81.5% to 91.6%
% Sensitivity	87.4% (146/167)	81.4% to 92.0%
% Specificity	85.0% (17/20)	62.1% to 96.8%

Clinical Agreement – Predicate Device

		Clinical Status		
		HF	***Non-HF***	***Total***
Predicate Device	***≥ 100 pg/mL***	146	5	151
	< 100 pg/mL	21	15	36
	Total	167	20	187

	Estimate	***95% Confidence Interval***
% Clinical Agreement	86.1% (161/187)	80.3% to 90.7%
% Sensitivity	87.4% (146/167)	81.4% to 92.0%
% Specificity	75.0% (15/20)	50.9% to 91.3%

Age-Matched Analysis

An age-matched analysis of the clinical data was performed with the following common age distribution in the groups of individuals with and without heart failure.

Individuals less than 45 years old comprise 9% of the total number of observations, individuals 45 to 54 years old comprise 11% of the total, individuals 55 to 64 years old comprise 22% of the total, individuals 65 to 74 years old comprise 26% of the total, and individuals 75 years and older comprise 32% of the total. This age distribution reflects the prevalence of heart failure within the age groups, according to data published by the American Heart Association in the *2000 Heart and Stroke Statistical Update*, and also reflects the age structure of the United States population, according to data published by the National Center for Health Statistics in *Health, United States, 2000*. The resulting area under the ROC curve is 0.906 with a 95% confidence interval of 0.886 to 0.927. The AUC is not significantly different from the AUC described previously (0.919).

Performance Characteristics

Specificity

The assay shows high specificity for BNP. Cross-reactivity was determined by spiking each of the following compounds into a plasma sample with known BNP concentration.

$$\% \text{ cross-reactivity} = \frac{(\text{concentration of spiked sample} - \text{concentration of unspiked sample})}{(\text{concentration of compound added})} \times 100$$

Compound	Concentration Added	% Cross-reactivity
Alpha-ANP (1-28)	1000 pg/mL	ND*
NT-proBNP (1-21)	1000 pg/mL	ND
NT-proBNP (1-46)	1000 pg/mL	ND
NT-proBNP (1-76)	1000 pg/mL	ND
NT-proBNP (22-46)	1000 pg/mL	ND
NT-proBNP (47-76)	1000 pg/mL	ND
CNP (7-28)	1000 pg/mL	ND
DNP	1000 pg/mL	ND
VNP	1000 pg/mL	ND
Adrenomedullin	1000 pg/mL	ND
Aldosterone	1000 ng/mL	ND
Angiotensin I	600 pg/mL	ND
Angiotensin II	600 pg/mL	ND
Angiotensin III	1000 pg/mL	ND
Arg-Vasopressin	1000 pg/mL	ND
Renin	50 ng/mL	ND
Urodilatin	1000 pg/mL	ND

* ND = Not Detectable

Interference testing was previously determined for the ADVIA Centaur BNP assay.

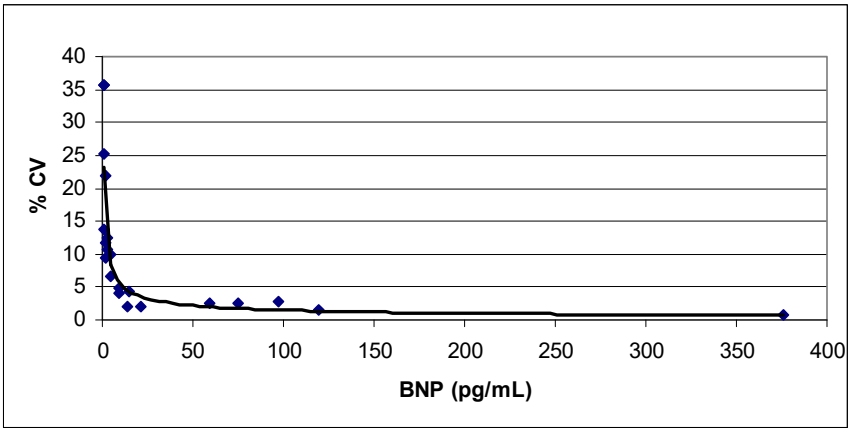
Analytical Sensitivity and Assay Range

The ADVIA Centaur BNP assay measures BNP concentrations on the ADVIA Centaur CP system up to 5000 pg/mL (1445 pmol/L) with a minimum detectable concentration (analytical sensitivity) of < 2.0 pg/mL (0.58 pmol/L). Analytical sensitivity is defined as the concentration of BNP that corresponds to the RLUs that are two standard deviations more than the mean RLUs of 20 replicate determinations of the BNP zero standard. This response is an estimate of the minimum detectable concentration with 95% confidence.

Functional Sensitivity

The functional sensitivity is defined as the lowest BNP concentration determined at a coefficient of variation of 20%. The ADVIA Centaur BNP assay functional sensitivity was determined to be 2.5 pg/mL (0.72 pmol/L) on the ADVIA Centaur CP system. The Total % CV profile in the assay range of 0–500 pg/mL is shown in the following figure:

Total CV Profile for ADVIA Centaur BNP Assay



Dilution Recovery

Three human plasma samples were diluted on-board the system with Multi-Diluent 15. The recoveries are shown below.

Sample	Dilution	Observed (pg/mL)	Expected (pg/mL)	Observed (pmol/L)	Expected (pmol/L)	Recovery (%)
1	1:2	4629	5090	1338	1471	91
2	1:2	5413	5844	1564	1689	93
3	1:2	6162	6411	1781	1853	96
Mean						93

Linearity

Patient samples with high BNP concentrations were mixed in various proportions with patient samples containing low levels of BNP ranging from 52.3 to 218.1 pg/mL (15.1 to 63.0 pmol/L). The samples with high BNP concentrations varied from 516.4 to 3085.8 pg/mL (149.2 to 891.8 pmol/L). When compared to the expected value, the measured (recovered) values of BNP averaged 94.4% with a range of 90.6 to 97.4%.

Sample (ratio high/low)	Observed (pg/mL)	Expected (pg/mL)	Observed (pmol/L)	Expected (pmol/L)	% Recovery
1					
Neat	3085.8		891.8		
(3:1)	2305.8	2368.9	666.4	684.6	97.3
(1:1)	1590.3	1651.9	459.6	477.4	96.3
(1:3)	847.3	935.0	244.9	270.2	90.6
Neat	218.1		63.0		
	Mean				94.7
2					
Neat	516.4		149.2		
(3:1)	408.7	419.8	118.1	121.3	97.4
(1:1)	305.0	323.2	88.1	93.4	94.4
(1:3)	208.6	226.5	60.3	65.5	92.1
Neat	129.9		37.5		
	Mean				94.6
3					
Neat	818.5		236.5		
(3:1)	605.3	643.4	174.9	185.9	94.1
(1:1)	437.1	468.3	126.3	135.3	93.3

Sample (ratio high/low)	*Observed (pg/mL)*	*Expected (pg/mL)*	*Observed (pmol/L)*	*Expected (pmol/L)*	*% Recovery*
(1:3)	277.2	293.2	80.1	84.7	94.6
Neat	118.1		34.1		
	Mean				94.0
4					
(3:1)	679.5		196.4		
(1:1)	503.0	522.7	145.4	151.1	96.2
(1:3)	340.3	365.9	98.3	105.7	93.0
	192.5	209.1	55.6	60.4	92.1
	52.3		15.1		
5	Mean				93.8
Neat					
(3:1)	625.8		180.9		
(1:1)	462.8	488.0	133.7	141.0	94.8
(1:3)	332.6	350.1	96.1	101.2	95.0
Neat	202.3	212.2	58.5	61.3	95.3
	74.4		21.5		
	Mean				95.1
Mean					**94.4**

Precision

Precision was evaluated according to the CLSI protocol EP5-A2.[49] According to this protocol, the assay was tested daily, for 5 to 20 days, using multiple reagent lots, on multiple systems across multiple sites. The system was calibrated immediately prior to the first test of day one. Assay results were calculated using the two-point calibration. The following results were obtained:

Mean (pg/mL)	*Mean (pmol/L)*	*Within-run CV(%)*	*Between run CV(%)*	*Total CV(%)*
43	12.5	2.7	3.3	4.2
455	131.5	2.2	3.3	3.9
1771	511.7	1.9	2.9	3.5

Based on internal testing on the ADVIA Centaur CP system, the overall reproducibility is estimated to be ≤ 9% CV for samples tested and includes multiple reagent lots, instruments, days, and replicates. Performance of the assay at individual laboratories may vary.

Standardization

The ADVIA Centaur BNP assay on the ADVIA Centaur CP system is 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.

The ADVIA Centaur BNP value assignment was adjusted based on a decision threshold that provides both high assay specificity (> 95%) and also is above the upper confidence interval of the 95th percentile of the reference population without heart failure. At 100 pg/mL, based on the outcome of clinical trials, this decision threshold exceeds both criteria with a clinical specificity of 97.4%. In clinically confirmed heart failure, 72.6% of the patients had elevations greater than 100 pg/mL.

Technical Assistance

According to EU regulation 2017/746, any serious incident that has occurred in relation to the device shall be reported to the manufacturer and the competent authority of the EU Member State in which the user and/or patient is established.

For customer support, contact your local technical support provider or distributor.

siemens-healthineers.com

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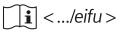
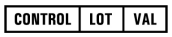
Definition of Symbols

The following symbols may appear on the product labeling:

Symbol	Symbol Title	Source	Symbol	Symbol Title	Source
	Manufacturer	5.1.1[a]		Authorized representative in the European Community	5.1.2[a]
	Use-by date	5.1.4[a]		Authorized representative in Switzerland	Proprietary
	Catalog number	5.1.6[a]		Batch code	5.1.5[a]
	Consult Instructions for Use	5.4.3[a]		Contains sufficient for <n> tests	5.5.5[a]
	Internet URL address to access the electronic instructions for use	Proprietary		Version of Instructions for Use	Proprietary
	*In vitro* diagnostic medical device	5.5.1[a]		Revision	Proprietary
	Prescription device (US only)	FDA[c]		Unique Device Identifier	5.7.10[b]
	CE Marking with Notified Body	EU IVDR[d]		CE Marking	EU IVDR[d]
	Temperature limit	5.3.7[a]		Keep away from sunlight	5.3.2[a]

Symbol	Symbol Title	Source	Symbol	Symbol Title	Source
	Upper limit of temperature	5.3.6[a]		Lower limit of temperature	5.3.5[a]
	Do not re-use	5.4.2[a]		Do not freeze	Proprietary
	Recycle	1135[e]		This way up	0623[e]
	Biological risks	5.4.1[a]		Caution	5.4.4[a]
	Common Units	Proprietary		Document face up[f]	1952[e]
YYYY-MM-DD	Date format (year-month-day)	N/A		International System of Units	Proprietary
	Target	Proprietary	**YYYY-MM**	Date format (year-month)	N/A
				Interval	Proprietary
	Handheld barcode scanner	Proprietary		Variable hexadecimal number that ensures the Master Curve and Calibrator definition values entered are valid.	Proprietary
	Lot details	Proprietary		Master Curve definition	Proprietary
	Calibrator lot value	Proprietary		Quality control lot value	Proprietary

a International Standard Organization (ISO). ISO 15223-1 Medical Devices- Symbols to be used with medical device labels, labelling and information to be supplied.

b ISO 15223-1:2020-04

c Federal Register. Vol. 81, No 115. Wednesday, June 15, 2016. Rules and Regulations: 38911.

d IVDR REGULATION (EU) 2017/746

e International Standard Organization (ISO). ISO 7000 Graphical symbols for use on equipment.

f Indicates Assay-eNote

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