SIEMENS

REF RF627

Dimension® EXL™ integrated chemistry system
LOCI® Module

Flex® reagent cartridge — TNIH

See shaded sections: Updated information from 2018-03 version.

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LOCI High-Sensitivity Troponin I

Intended Use: The Dimension® EXL™ High-Sensitivity Troponin I (TNIH) assay is for *in vitro* diagnostic use in the quantitative measurement of cardiac troponin I in human plasma using the Dimension® EXL™ integrated chemistry system with LOCI® module. The assay can be used to aid in the diagnosis of acute myocardial infarction (AMI).

Summary: Troponin I (TnI) exists in three distinct isoforms: cardiac muscle, slow-twitch skeletal muscle, and fast-twitch skeletal muscle.[1] Each isoform is encoded by a distinct gene, each with a unique amino acid sequence, leading to a 40% dissimilarity among isoforms.[1–4]

Cardiac troponin I (cTnI) is an inhibitory protein of the troponin-tropomyosin complex. cTnI is the only TnI isotype present in the myocardium and is not expressed during any developmental stage in skeletal muscle.[2,5,6] cTnI has a molecular weight of 24,000 daltons.[7]

The cardiac form of TnI is further unique in that it has 31 additional amino acid residues on its N-terminal, not present in the skeletal forms, which allows for specific monoclonal antibody development.[7] The cardiac specificity of this isoform improves the accuracy of detection of cardiac muscle ischemia in patients with acute or chronic skeletal muscle injury and possible concomitant myocardial injury, and is the basis for its selection as a cardiac marker in the diagnosis of AMI.[1,3–5,7,8]

The Global MI Task Force's third version of the universal definition of myocardial infarction defined AMI as evidence of myocardial necrosis in a clinical setting consistent with acute myocardial ischemia.[9] Under these circumstances, the following criterion meets the diagnosis of AMI:

Detection of a rise and/or fall of cardiac biomarker values (preferably cardiac troponin) with at least one value above the 99th percentile upper reference limit (URL) and with at least one of the following conditions:

- Symptoms of ischemia.
- New or presumed new significant ST-segment-T wave (ST-T) changes or new left bundle branch block (LBB).
- Development of pathological Q waves in the electrocardiogram (EKG).
- Imaging evidence of new loss of viable myocardium, or new regional wall motion abnormality.
- Identification of an intracoronary thrombus by angiography or autopsy.

Troponin values must be used in the context of the patient clinical presentation. Serial sampling is recommended to detect the temporal rise and fall of troponin levels characteristic of AMI. The demonstration of a temporal rise and fall in troponin is needed to distinguish AMI from troponin elevations associated with non-AMI conditions,such as renal failure, arrhythmias, pulmonary embolism, chronic renal disease, myocarditis, and cardiotoxicity.[9-14]

The IFCC Task Force on Clinical Applications of Cardiac Bio-Markers defines a troponin assay as a high-sensitivity assay if it meets the following criteria.[12]

- Total imprecision (CV) at the 99th percentile value should be at or below 10%.
- Measurable concentrations should be attainable at concentrations above the limit of detection (LoD) in at least 50% of healthy subjects.

Principles of Procedure: The Dimension® EXL™ TNIH assay is a homogeneous, sandwich chemiluminescent immunoassay based on LOCI® technology. The LOCI® reagents include two synthetic bead reagents and two biotinylated anti-cardiac troponin I monoclonal antibody fragments. The first bead reagent (Sensibeads) is coated with streptavidin and contains photosensitizer dye. The second bead reagent (Chemibeads) is coated with a third anti-cardiac troponin I monoclonal antibody and contains chemiluminescent dye. Sample is incubated with Chemibeads and biotinylated antibodies to form bead-cardiac troponin I-biotinylated antibody sandwiches. Sensibeads are added and bind to the biotin to form bead-pair immunocomplexes. Illumination of the complex at 680 nm generates singlet oxygen from Sensibeads which diffuses into the Chemibeads, triggering a chemiluminescent reaction. The resulting signal is measured at 612 nm and is a direct function of the cardiac troponin I concentration in the sample.[15–17]

Reagents

Wells[a]	Form	Ingredient	Concentration[b,c]	Source
1–2	Liquid	Biotinylated Antibody[c] Biotinylated Antibody	5 µg/mL 2 µg/mL	Mouse monoclonal Sheep monoclonal
3–4	Liquid	Troponin I Chemibeads[c]	30 µg/mL	Sheep monoclonal
5–6	Liquid	Streptavidin Sensibead[c]	975 µg/mL	Recombinant *E. coli*
7–8	Liquid	Assay Buffer		

a. Wells are numbered consecutively from the wide end of the cartridge.
b. Nominal value per well in a cartridge.
c. Contains buffers, stabilizers and preservatives.

Risk and Safety:

H317
P280, P272, P302 + P352, P333 + P313, P363, P501
Warning!
May cause an allergic skin reaction.

Wear protective gloves/protective clothing/eye protection/face protection. Contaminated work clothing should not be allowed out of the workplace. IF ON SKIN: Wash with plenty of soap and water. If skin irritation or rash occurs: Get medical advice/attention. Wash contaminated clothing before reuse. Dispose of contents and container in accordance with all local, regional, and national regulations.
Contains: 5-chloro-2-methyl-3(2h)-isothiazolone mixture with 2-methyl-3(2h)-isothiazolone

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

Precautions: Used HM reaction vessels contain human body fluids; handle with appropriate care to avoid skin contact or ingestion.

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

For *in vitro* diagnostic use.

For professional use.

Reagent Preparation: All reagents are liquid and ready to use.

Store at: 2–8°C

Expiration: Refer to carton for expiration date of individual unopened reagent cartridges. Sealed wells on the instrument are stable for 30 days.

Open Well Stability: 7 days for wells 1–8.

Specimen Collection and Handling: Recommended specimen: lithium heparin plasma. Observe universal precautions when collecting specimens. Handle all specimens as if they are capable of transmitting disease.[18]

Separated samples are stable for 8 hours at room temperature and for 24 hours when stored at 2–8°C. Samples can be frozen at or below -20°C for up to 40 days in a non-frost free freezer and at or below -70°C for up to 1 year. Do not store frozen samples in an automatic defrosting freezer (frost free freezer).

Freeze samples only once and mix thoroughly after thawing. Frozen samples must be centrifuged at 2200 x g for 10 minutes after thawing, before analysis. Samples containing precipitates must be centrifuged before performing the assay.

Samples and controls stabilized with sodium azide cannot be used.

Plasma samples can be collected using recommended procedures for collection of diagnostic blood specimens by venipuncture.[19]

Follow the instructions provided with your specimen collection device for use and processing.[20]

Plasma should be physically separated from cells as soon as possible with a maximum limit of two hours from the time of collection.[21]

Samples must be free of fibrin or other particulate matter. The presence of fibrin, red blood cells, or suspended particles may lead to inaccurate results.

Avoid transferring white blood cells or platelets from the layer located just above the red blood cells.

If a fixed angle rotor is used for centrifugation, care should be taken to avoid re-suspending cellular material (platelets) upon removal from the centrifuge.

The purpose of specimen storage information is to provide guidance to users; however, users may validate their own procedures for storing patient samples.

Procedure

Materials Provided

TNIH Flex reagent cartridge, Cat. No. RF627

Materials Required But Not Provided

LOCI TNIH CAL, Cat. No. RC627
HM reaction vessels, Cat. No. RXV1A
CTNI SDIL, Cat. No. KD692
Quality Control Materials

Test Steps

Sampling, reagent delivery, mixing, and processing are automatically performed by the Dimension® EXL™ integrated chemistry system. For details of this processing, refer to your Dimension® EXL™ Operator's Guide.

Test Conditions

Sample Volume (delivered to the HM reaction vessel)	10 µL
Chemibead Reagent Volume	20 µL
Biotinylated Antibody Reagent Volume	20 µL
Sensibead Volume	20 µL
Assay Buffer Volume	100 µL
Temperature	37°C
Reaction Time	10 minutes
Wavelength	Illumination (680 nm) Emission (612 nm)
Type of Measurement	Chemiluminescence

Calibration

Assay Range	4.0-25,000 pg/mL [ng/L][d]
Calibration Material	LOCI TNIH CAL Cat. No. RC627
Calibration Scheme	5 levels, Level 1 n=5, Levels 2-5 n=3
Units	pg/mL [ng/L] (pg/mL x 1) = [ng/L]
Typical Calibration Levels	Level 1 - 0 pg/mL [ng/L] Level 2 - 60 pg/mL [ng/L] Level 3 - 500 pg/mL [ng/L] Level 4 - 8000 pg/mL [ng/L] Level 5 - 27,000 pg/mL [ng/L]
Calibration Frequency	Every 21 days for any one lot
A new calibration is required	• For each new lot of Flex® reagent cartridges • After major maintenance or service, if indicated by quality control results • As indicated in laboratory quality control procedures • When required by government regulations

d. Système International d'Unités [SI Units] are in brackets.

Quality Control

Follow government regulations or accreditation requirements for quality control frequency. At least once each day of use, analyze two levels of a Quality Control (QC) material with known cardiac troponin I concentrations. Follow your laboratory internal QC procedures if the results obtained are outside acceptable limits.

Results: The instrument calculates the concentration of cardiac troponin I in pg/mL [ng/L] using the calculation scheme described in your Dimension® EXL™ Operator's Guide.

Results of this test should always be interpreted in conjunction with the patient's medical history, clinical presentation and other findings.

Analytical Measurement Range (AMR): 4.0 – 25,000.0 pg/mL [ng/L]

This is the range of analyte values that can be measured directly from the specimen without any dilution or pretreatment that is not part of the usual analytical process and is equivalent to the assay range.

• Samples with results in excess of 25,000.0 pg/mL [ng/L] should be repeated on dilution.

Manual Dilution: Dilute with CTNI Sample Diluent (Cat. No. KD692) to obtain results within reportable range. Enter the dilution factor on the instrument, but no greater than 1:5. Reassay. Resulting readout is corrected for dilution. Refer to your Dimension® EXL™ Operator's Guide.

• Samples with results less than 4.0 pg/mL [ng/L] will be reported as "less than 4.0 pg/mL [ng/L]" by the instrument.

Limitations of Procedure

Patient samples may contain cardiac troponin-specific autoantibodies that could react in immunoassays to give falsely elevated or depressed results. A test result that is inconsistent with the clinical picture and patient history should be interpreted with caution.[22]

Samples from patients receiving preparations of mouse monoclonal antibodies for therapy or diagnosis may contain human anti-mouse antibodies (HAMA). Such samples may show either falsely elevated or falsely depressed values. This assay has been designed to minimize interference from heterophilic antibodies. Nevertheless, complete elimination of this interference from all patient specimens cannot be guaranteed. A test result that is inconsistent with the clinical picture and patient history should be interpreted with caution. [23–25]

Specimens that contain biotin at a concentration of 300 ng/mL demonstrate a less than 10% change in results. Biotin concentrations greater than this may lead to falsely depressed results for patient samples. Testing specimens from renal dysfunction patients taking biotin may lead to false negative results. Therefore, do not use this device in patients with renal impairment (eGFR<60), unless it is confirmed that the patient is not taking biotin. Patients taking more than 20 mg/day of biotin may have falsely negative results, and should not use this test. There have been reports of multiple sclerosis patients taking biotin doses exceeding 20 mg/day. Therefore, do not use this device in patients with Multiple Sclerosis, unless it is confirmed that the patient is not taking more than 20 mg/day of biotin.

Dextran 40 at 60 g/L increases the troponin result in plasma at 33.0 pg/mL [ng/L] and 1089.3 pg/mL [ng/L] by 16% and 4% respectively. Dextran 40 at 15 g/L and 45 g/L demonstrates less than 10% change in results when testing plasma samples at the concentrations stated above.

Protein Gamma Globulin at 6 g/dL causes anomalous results in plasma at approximately 40 pg/mL [ng/L] and 1000 pg/mL [ng/L] of troponin. Protein gamma globulin at 2.5 g/dL demonstrates less than 10% change in results when testing plasma samples at the concentrations stated above.

The instrument reporting system contains flags and comments to provide the user with information regarding instrument processing errors, instrument status information and potential errors in TNIH results. Refer to your Dimension® EXL™ Operator's Guide for the meaning of report flags and comments. Any report containing flags and/or comments should be addressed according to your laboratory's procedure manual and not reported.

Maximum Observed Repeatability

The expected maximum observed standard deviations for repeatability (within-run precision) using n=5 replicates at the following TNIH concentrations are:

Concentration	Acceptable SD Maximum
50.0 pg/mL [ng/L]	4.8 pg/mL [ng/L]
500.0 pg/mL [ng/L]	33.5 pg/mL [ng/L]

A system malfunction may exist if the maximum 5-test SD precision is exceeded.

Expected Results

n	Age (years)	99th Percentile pg/mL [ng/L]	90% CI[e] pg/mL [ng/L]
2020	22–91	60.4	43.2–81.3

[e] Confidence interval

Lithium heparin plasma specimens were collected from apparently healthy individuals with no known diseases of the cardiovascular system or other serious acute or chronic diseases or infections from the United States who ranged in age from 22–91 years of age. Each specimen was frozen, thawed and assayed once. The 99th percentile values were determined using the non-parametric statistical method described in CLSI Guidance EP28-A3c.[26]

The combined gender was used to determine the overall observed 99th percentile of 60.4 pg/mL [ng/L]. The potential range of results for the 99th percentile is 43.2–81.3 pg/mL [ng/L] for the Dimension® EXL™ family of systems, dependent upon instrument and reagent lot. Two female subjects had troponin values of approximately 400 pg/mL and 4700 pg/mL, and were considered to be outliers. These results were not included in the 99th percentile determination.

The 99th percentile values determined for lithium heparin (female, male, and combined) are shown in the following table. The 90% confidence intervals demonstrate that there is no statistical basis for using separate 99th percentile values based on gender and age.

Sample Type	Gender	n	99th Percentile[a] pg/mL [ng/L]	90% CI[b] pg/mL [ng/L]
Lithium Heparin	Female	1017	51.4	35.6–109.2
	Male	1003	76.2	42.3–117.0
	Combined	2020	60.4	43.2–81.3

[a] IFCC Task Force on Clinical Applications of Cardiac Bio-Markers recommends that troponin values be reported as whole numbers.[12]

[b] Confidence interval

The Dimension® EXL™ TNIH assay meets the IFCC Task Force on Clinical Applications of Cardiac Bio-Markers' definition of a high-sensitivity troponin assay.[12]

1. Total imprecision (CV) at the 99th percentile value should be at or below 10%.
   • The 10% CV (Within-Lab Imprecision) for the Dimension® EXL™ TNIH assay was measured to be 12.0 pg/mL [ng/L].
2. Measurable concentrations should be attainable at concentrations above the limit of detection (LoD) in at least 50% of healthy subjects.
   • Greater than 50% of the healthy patient population used to determine the 99th percentile produced a value above the LoD.

Clinical Performance

A prospective study was performed to assess diagnostic accuracy for 2495 subjects. Specimens were collected at 29 emergency departments across the United States, from subjects presenting with symptoms consistent with acute coronary syndrome (ACS).

All subject diagnoses were adjudicated by panels of certified cardiologists and emergency physicians according to the Third Universal Definition Of Myocardial Infarction consensus guideline[9] endorsed by the European Society of Cardiology (ESC), the American College of Cardiology Foundation (ACCF), the American Heart Association (AHA), and the World Heart Federation (WHF). The observed AMI prevalence in this study was 13.0%.

The results were analyzed using the serial sampling time points collected during the emergency department visit. A positive is defined as a sample exceeding the 99th percentile cutoff at the particular time point. The results are presented using serial timed intervals analyzed according to the time of presentation to the emergency department. The pooled gender results based on time of presentation to the emergency department, calculated using the overall 99th percentile of 60.4 pg/mL, are summarized in Table 1. Gender-specific data are presented in Tables 2 and 3.

Elevated TnI Values in Patients Without AMI

There are conditions other than AMI that are known to cause myocardial injury and elevated TnI values.[9-14, 27-34]

The Dimension® EXL™ TNIH clinical trial enrolled all patients presenting to the emergency department with symptoms consistent with ACS. Some of these patients had an acute or chronic condition other than AMI.

In the clinical trial, 11% of patients without an AMI diagnosis had at least one Dimension® EXL™ TNIH test result above the 99th percentile (>60.4 pg/mL [ng/L]) on one or more serial draws. 88% of these patients were found to have one or more of the following conditions:

Cardiac conditions: Angina, Atrial fibrillation, Cardiomyopathy, Coronary artery disease, Heart failure, Hypertensive urgency, Pericarditis, Recent cardiac intervention, Severe valvular heart disease, Tachycardia

Non-cardiac conditions: Chronic lung disease, Cardiac contusion related to a traumatic injury, Renal failure, Pneumonia, Pulmonary embolism, Shock, Systemic sclerosis

Table 1: Pooled gender results based on time from presentation to the emergency department.

	Sensitivity			Specificity			Positive Predictive Value			Negative Predictive Value		
Time Since Presentation (hours)	n	%	95% CI	n	%	95% CI	n	%	95% CI	n	%	95% CI
Lithium Heparin Plasma												
0–<1.5	138	78.3	70.7–84.3	978	92.9	91.2–94.4	177	61.0	53.7–67.9	939	96.8	95.5-97.8
≥1.5– <2.5	240	88.8	84.1–92.2	1658	91.6	90.1–92.8	353	60.3	55.2–65.3	1545	98.3	97.5-98.8
≥2.5– <3.5	199	89.9	85.0–93.4	1379	90.6	89.0–92.1	308	58.1	52.5–63.5	1270	98.4	97.6-99.0
≥3.5– <4.5	144	92.4	86.8–95.7	1094	91.2	89.4–92.8	229	58.1	51.6–64.3	1009	98.9	98.1-99.4
≥4.5– <6	67	95.5	87.6–98.5	463	89.2	86.0–91.7	114	56.1	47.0–64.9	416	99.3	97.9-99.8
≥6– <9	191	92.7	88.1–95.6	917	88.0	85.7–90.0	287	61.7	55.9–67.1	821	98.3	97.2-99.0
≥9– <24	215	93.0	88.8–95.7	849	86.2	83.7–88.4	317	63.1	57.7–68.2	747	98.0	96.7-98.8
≥24	63	95.2	86.9–98.4	256	86.3	81.6–90.0	95	63.2	53.1–72.2	224	98.7	96.1-99.5

Results for females based on time of presentation to the emergency department, calculated using the female-specific 99th percentile of 51.4 pg/mL, are summarized in table 2.

Using the lower female-specific 99th percentile instead of the overall 99th percentile of 60.4 pg/mL (ng/L) may result in a higher proportion of positive test results for females that are non-MI. Taking into consideration the lower bound of the 95% confidence interval, in the worst-case scenario (drawn at ≥4.5–<6 hours after presentation), up to 71% of positive test results for females may be non-MI.

Table 2: Results for females based on time from presentation to the emergency department.

	Sensitivity			Specificity			Positive Predictive Value			Negative Predictive Value		
Time Since Presentation (hours)	n	%	95% CI	n	%	95% CI	n	%	95% CI	n	%	95% CI
Lithium Heparin Plasma												
0– <1.5	42	83.3	69.4–91.7	407	94.6	92.0–96.4	57	61.4	48.4–72.9	392	98.2	96.4–99.1
≥1.5– <2.5	78	91.0	82.6–95.6	728	91.9	89.7–93.7	130	54.6	46.0–62.9	676	99.0	97.9–99.5
≥2.5– <3.5	73	94.5	86.7–97.8	624	92.0	89.6–93.9	119	58.0	49.0–66.5	578	99.3	98.2–99.7
≥3.5– <4.5	51	94.1	84.1–98.0	492	90.9	88.0–93.1	93	51.6	41.6–61.5	450	99.3	98.1–99.8
≥4.5– <6	25	96.0	80.5–99.3	242	85.5	80.6–89.4	59	40.7	29.1–53.4	208	99.5	97.3–99.9
≥6– <9	68	94.1	85.8–97.7	380	87.9	84.2–90.8	110	58.2	48.8–67.0	338	98.8	97.0–99.5
≥9– <24	72	93.1	84.8–97.0	348	88.5	84.7–91.4	107	62.6	53.2–71.2	313	98.4	96.3–99.3
≥24	26	100.0	87.1–100.0	111	82.0	73.8–88.0	46	56.5	42.2–69.8	91	100.0	95.9–100.0

Results for males based on time of presentation to the emergency department, calculated using the male-specific 99th percentile of 76.2 pg/mL, are summarized in table 3.

Using the higher male-specific 99th percentile instead of the overall 99th percentile of 60.4 pg/mL (ng/L) may result in a higher proportion of negative test results for males that are MI. For males that are MI, data analyzed using the male-specific cutoff versus the overall cutoff increased the false-negative rate by up to 3.3%.

Table 3: Results for males based on time from presentation to the emergency department.

	Sensitivity			Specificity			Positive Predictive Value			Negative Predictive Value		
Time Since Presentation (hours)	n	%	95% CI	n	%	95% CI	n	%	95% CI	n	%	95% CI
Lithium Heparin Plasma												
0– <1.5	96	74.0	64.4–81.7	571	92.3	89.8–94.2	115	61.7	52.6–70.1	552	95.5	93.4–96.9
≥1.5– <2.5	162	85.2	78.9–89.8	930	92.5	90.6–94.0	208	66.3	59.7–72.4	884	97.3	96.0–98.2
≥2.5– <3.5	126	84.9	77.6–90.1	755	91.0	88.7–92.8	175	61.1	53.8–68.1	706	97.3	95.8–98.3
≥3.5– <4.5	93	86.0	77.5–91.6	602	92.7	90.3–94.5	124	64.5	55.8–72.4	571	97.7	96.1–98.7
≥4.5– <6	42	88.1	75.0–94.8	221	91.4	87.0–94.4	56	66.1	53.0–77.1	207	97.6	94.5–99.0
≥6– <9	123	88.6	81.8–93.1	537	90.9	88.1–93.0	158	69.0	61.4–75.7	502	97.2	95.4–98.3
≥9– <24	143	90.9	85.1–94.6	501	87.2	84.0–89.9	194	67.0	60.1–73.2	450	97.1	95.1–98.3
≥24	37	89.2	75.3–95.7	145	91.0	85.3–94.7	46	71.7	57.5–82.7	136	97.1	92.7–98.9

Specific Performance Characteristics

The following data represent typical performance for the Dimension® EXL™ System.

Precision[a]

Material	Mean pg/mL [ng/L]	Repeatability SD[b] pg/mL [ng/L]	Repeatability %CV[c]	Within-Lab SD pg/mL [ng/L]	Within-Lab %CV
Plasma 1	48.0	1.11	2.3	2.87	6.0
Plasma 2	71.8	1.45	2.0	2.09	2.9
Plasma 3	155.7	2.75	1.8	4.62	3.0
QC	7411.7	145.59	2.0	246.56	3.3

a. CLSI EP05-A3[35] was used. During each day of testing, two separate runs with two test samples for each test material were analyzed for 20 days for a total of 80 replicates.
b. Standard Deviation.
c. Coefficient of Variation.

Hemolysis, Icterus, Lipemia (HIL) Interference

The TNIH assay was evaluated for interference according to CLSI EP07-A2.[36] Bias is the difference in the results between the control sample (without the interferent) and the test sample (contains the interferent) expressed in percent. Lithium heparin test sample ranges were 40± 20 pg/mL [ng/L] and 1350 ± 650 pg/mL [ng/L]. Bias exceeding 10% is considered interference.

Substance Tested	Substance concentration	Bias (%)*
Hemoglobin hemolysate (monomer)	400 mg/dL [0.25 mmol/L]	≤ 10
Bilirubin (conjugated)	30 mg/dL [356 µmol/L]	≤ 10
Bilirubin (conjugated)	40 mg/dL [475 µmol/L]	-11
Bilirubin (unconjugated)	40 mg/dL [684 µmol/L]	≤ 10
Lipemia (Intralipid®)	3000 mg/dL [33.9 mmol/L]	≤ 10

Intralipid® is a registered trademark of Fresenius Kabi AD, Bad Homburg, Germany.
*Analyte results should not be corrected based on this bias.

Biotin Interference

The TNIH assay was evaluated for interference according to CLSI EP07-A2.[36] Bias is the difference in the results between the control sample (without the interferent) and the test sample (contains the interferent) expressed in percent. Lithium heparin plasma test sample ranges were: 40 ± 20 pg/mL [ng/L] and 1350 ± 650 pg/mL [ng/L]. Bias exceeding 10% is considered interference.

		Lithium Heparin Plasma	
Interfering Substance	Substance Concentration	TNIH (pg/mL)	Bias, %
Biotin	300 ng/mL	30.6	-3
		992.2	-5
	360 ng/mL	36.7	-10
		1175.5	-10
	480 ng/mL	36.7	-15
		1175.5	-11
	840 ng/mL	36.7	-67
		1175.5	-35
	1200 ng/mL	36.7	-79
		1175.5	-84

See limitations section for information regarding patients with either renal impairment or multiple sclerosis. Some studies have shown that serum concentrations of biotin can reach 355 ng/mL within the first hour after biotin ingestion for apparently healthy subjects consuming supplements of 20 mg biotin per day[37] and plasma concentrations of biotin can reach up to 1160 ng/mL for apparently healthy subjects after a single dose of 300 mg biotin.[38]

Non-Interfering Substances

The following substances have no significant effect (less than or equal to 10%) in the TNIH assay when added to lithium heparin plasma pools with troponin levels of 40±20 pg/mL [ng/L] and 1350±650 pg/mL [ng/L] at the low/therapeutic and high/toxic concentrations indicated.

	Low or Therapeutic Concentration		High or Toxic Concentration	
Potential Interferent	Conventional Units	SI Units	Conventional Units	SI Units
Abciximab	0.4 mg/dL	NA	4.0 mg/dL	NA
Acetaminophen	2.0 mg/dL	133 µmol/L	20.0 mg/dL	1324 µmol/L
Acetylsalicylic Acid	26.1 mg/dL	1.45 mmol/L	65.2 mg/dL	3.62 mmol/L
Allopurinol	1.3 mg/dL	91.9 µmol/L	4.0 mg/dL	294 µmol/L
Amiodarone	0.2 mg/dL	2.6 µmol/L	0.6 mg/dL	8.92 µmol/L
Ampicilin	1.1 mg/dL	29.1 µmol/L	5.6 mg/dL	152 µmol/L
Ascorbic Acid	1.2 mg/dL	68.5 µmol/L	6.0 mg/dL	342 µmol/L
Atenolol	0.1 mg/dL	0.04 µmol/L	1.0 mg/dL	37.6 µmol/L
Biotin	10 ng/dL	1.6 µmol/L	300 ng/dL	1.2 µmol/L
Caffeine	1.3 mg/dL	64.4 µmol/L	6.0 mg/dL	308 µmol/L
Captropril	0.1 mg/dL	4.6 µmol/L	0.5 mg/dL	23 µmol/L
Cefoxitin	12.63 mg/dL	281 µmol/L	69.5 mg/dL	1546 µmol/L
Cholesterol	NA[j]	NA[j]	300 mg/dL	7.8 mmol/L
Cinnarizine	0.0285 mg/dL	0.8 µmol/L	2.5 mg/dL	67.8 µmol/L
Clopidogrel	0.32 mg/dL	9.9 µmol/L	7.5 mg/dL	233 µmol/L
Cocaine	0.05 mg/dL	1.6 µmol/L	1.0 mg/dL	33 µmol/L
Dextran 40	15 g/L	375 µmol/L	45 g/L	1125 µmol/L
Digitoxin	17 ng/mL	22.2 nmol/L	60 ng/mL	78.4 nmol/L
Digoxin	1.4 ng/mL	1.8 nmol/L	6.1 ng/mL	7.8 nmol/L
Diltiazem	0.025 mg/dL	0.55 µmol/L	0.68 mg/dL	15 µmol/L
Disopyramide	0.45 mg/dL	10.4 µmol/L	1.3 mg/dL	29.5 µmol/L
Dopamine	0.04 mg/dL	1.96 µmol/L	0.11 mg/dL	5.87 µmol/L
Doxycycline	1.1 mg/dL	22.5 µmol/L	3.2 mg/dL	67.5 µmol/L
Erythromycin	1.1 mg/dL	15 µmol/L	6.0 mg/dL	81.6 µmol/L
Furosemide	2.0 mg/dL	60.4 µmol/L	6.0 mg/dL	181 µmol/L
Ibuprofen	4.0 mg/dL	194.3 µmol/L	50 mg/dL	2425 µmol/L
Isosorbide Dinitrate	50.1 ng/mL	212 nmol/L	150.2 ng/mL	636 nmol/L
Lisinopril	0.01 mg/dL	0.25 µmol/L	0.03 mg/dL	0.74 µmol/L
Low MW Heparin	0.85 U/mL	NA	2.0 U/mL	NA
Lovastatin	17.2 ng/mL	42.4 nmol/L	80 ng/mL	197.8 nmol/L
Methotrexate	50 mg/dL	1.1 mmol/L	91 mg/dL	2 mmol/L
Methyldopa	0.48 mg/dL	20.1 µmol/L	1.69 mg/dL	70.9 µmol/L
Methylprednisolone	1.65 mg/dL	44 µmol/L	4.0 mg/dL	106.8 µmol/L
Mexiletine	0.15 mg/dL	7 µmol/L	0.48 mg/dL	22.3 µmol/L
Nicotine	0.004 mg/dL	0.2 µmol/L	0.10 mg/dL	6.2 µmol/L
Nifedipine	0.013 mg/dL	361.3 nmol/L	0.04 mg/dL	1156.1 nmol/L
Nitrofurantoin	0.20 mg/dL	8.4 µmol/L	0.40 mg/dL	16.8 µmol/L
Nitroglycerine	7.5 ng/mL	33 nmol/L	160 ng/mL	704.5 nmol/L
Phenobarbital	2.5 mg/dL	107.8 µmol/L	10.0 mg/dL	431.5 µmol/L
Phenytoin	1.36 mg/dL	49.6 µmol/L	5.43 mg/dL	198 µmol/L
Primidone	1.1 mg/dL	48.2 µmol/L	4.0 mg/dL	183.5 µmol/L
Propranolol	0.06 mg/dL	1.93 µmol/L	0.23 mg/dL	7.71 µmol/L
Protein, Albumin	NA[j]	NA[j]	6 g/dL	60 g/L
Protein, Gamma Globulin	2.5 g/dL	NA	NA	NA
Protein, Total	NA[j]	NA[j]	12 g/dL	NA
Quinidine	0.38 mg/dL	11.7 µmol/L	1.2 mg/dL	37 µmol/L
Rheumatoid Factor	750 IU/mL	NA	1500 IU/mL	NA
Simvastatin	0.004 ug/mL	0.01 µmol/L	32 ug/mL	76.5 µmol/L
Theophylline	1.25 mg/dL	69.4 µmol/L	4.0 mg/dL	222.2 µmol/L
Tissue plasminogen activator (TPA)	0.52 µg/mL	NA	2.3 µg/mL	NA
Thyroxine	0.023 mg/dL	0.3 µmol/L	0.06 mg/dL	0.8 µmol/L
Triglyceride	500 mg/dL	NA	1000 mg/dL	NA
Trimethoprim	1.25 mg/dL	43.1 µmol/L	4.0 mg/dL	138.3 µmol/L
Verapamil	0.035 mg/dL	0.8 µmol/L	0.22 mg/dL	4.4 µmol/L
Warfarin	0.20 mg/dL	6.6 µmol/L	1.0 mg/dL	32.5 µmol/L

j. Low level testing is not relevant for this endogenous substance.

Hook Effect

The Dimension® EXL™ TNIH assay shows no hook effect up to 1,000,000 pg/mL [ng/L].

Specificity

The TNIH assay shows high specificity for cTnI. The following compounds were added at the concentrations indicated to lithium heparin samples with cTnI concentrations of less than 4.0 pg/mL [ng/L] and 20–60 pg/mL [ng/L]. TNIH assay results from the spiked samples were compared with those of unspiked control samples. Percent cross-reactivity is calculated as:

$$\% \text{ Cross-reactivity} = \frac{[\text{measured analyte}] - [\text{control analyte}]}{[\text{cross-reactant}]} \times 100$$

Cross-reactant	Amount ng/mL [µg/L]	Cross-reactivity (%)
Cardiac Troponin T	1000	0.003
Skeletal Troponin I	1000	0.001
Tropomyosin	1000	ND*
Actin	1000	ND*
Troponin C	1000	ND*
Myosin Light Chain	1000	ND*
Myoglobin	1000	ND*
CK-MB	1000	ND*

*ND= Not detectable

Limit of Detection and Limit of Blank

The limit of blank (LoB) and limit of detection (LoD) were determined as described in CLSI Document EP17-A2.[39]

The limit of blank (LoB) is defined as the highest measurement result that is likely to be observed for a blank sample. The Dimension® EXL™ TNIH assay has an LoB of 1.1 pg/mL [ng/L].

The limit of detection (LoD) is defined as the lowest concentration of cTnI that can be detected with 95% probability. The observed LoD ranged from 1.0–1.8 pg/mL [ng/L] across three reagent lots. The Dimension® EXL™ TNIH assay has an LoD of 2.7 pg/mL [ng/L].

Limit of Quantitation

The limit of quantitation (LoQ) was determined as described in CLSI Document EP17-A2.[39]

The LoQ is defined as the lowest concentration of cTnI that can be detected at a total CV of 20%. The Dimension® EXL™ TNIH assay has an LoQ of 4.0 pg/mL [ng/L].

Linearity

The Dimension® EXL™ TNIH assay is linear from 4.0–25,000 pg/mL [ng/L].

Linearity was evaluated according to CLSI Document EP06-A.[40] Native lithium heparin plasma samples were used to create a dilution series by mixing high and low level samples. The resulting sample mixtures were tested with the Dimension® EXL™ TNIH assay.

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Symbols Key
Symbolschlüssel
Explication des Symboles
Interpretazione simboli
Clave de los Símbolos

	Do not reuse / Nicht zur Wiederverwendung / Ne pas réutiliser / Non riutilizzare / No reutilizar
	Use By / Verwendbar bis / Utiliser jusque / Utilizzare entro / Fecha de caducidad
LOT	Batch Code / Chargenbezeichnung / Code du lot / Codice del lotto / Código de lote
REF	Catalogue Number / Bestellnummer / Référence du catalogue / Numero di catalogo / Número de catálogo
	Caution, consult accompanying documents / Achtung, Begleitdokumente beachten / Attention voir notice d'instructions / Attenzione, vedere le istruzioni per l'uso / Atención, ver instrucciones de uso
	Manufacturer / Hersteller / Fabricant / Fabbricante / Fabricante
	Contains sufficient for <n> tests / Inhalt ausreichend für <n> Tests / Contenu suffisant pour "n" tests / Contenuto sufficiente per "n" saggi / Contenido suficiente para <n> ensayos
	Temperature Limitation / Temperaturbegrenzung / Limites de température / Limiti di temperatura / Límite de temperatura
	Consult Instructions for Use / Gebrauchsanweisung beachten / Consulter les instructions d'utilisation / Consultare le istruzioni per l'uso / Consulte las instrucciones de uso
NON STERILE	Non-sterile / Nicht steril / Non stérile / Non sterile / No estéril
CONTENTS	Contents / Inhalt / Contenu / Contenuto / Contenido
	Reconstitution Volume / Rekonstitutionsvolumen / Volume de reconstitution / Volume di ricostituzione / Volumen de reconstitución
LEVEL	Level / Konzentration / Niveau / Livello / Nivel
RxOnly	Prescription Device (US Only) / Verschreibungspflichtiges Medizinprodukt (nur USA) / Dispositif soumis à prescription (États-Unis uniquement) / Dispositivo su prescrizione (solo USA) / Dispositivo de prescripción médica (solo EE. UU.)

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