

K121533

510(k) Summary

JUN 15 2012

**ST AIA-PACK HOMOCYSTEINE**

- 1. **Date:** May 17, 2012
- 2. **Submitter:** Tosoh Bioscience, Inc  
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- 4. **Device Name:** ST AIA-PACK Homocysteine Classification:  
Class II  
LPS  
Clinical Chemistry  
21 CFR 862.1377  
  
**Device Name:** ST AIA-PACK Homocysteine Calibrator Set  
**Classification:** Class II  
JIT  
Clinical Chemistry  
21 CFR 862.1150  
  
**Device Name:** AIA-PACK Homocysteine Control Set  
**Classification:** Class I, Reserved  
JJX  
Clinical Chemistry  
21 CFR 862.1660
- 5. **Predicate Device:** k 003597  
Siemens  
IMMULITE 2000 Homocysteine Immunoassay

## 6. Intended Use

### Reagents:

ST AIA-PACK Homocysteine is designed for IN VITRO DIAGNOSTIC USE ONLY for the quantitative measurement of homocysteine in human serum, heparinized plasma or EDTA plasma using a TOSOH AIA System Analyzer. Homocysteine measurements are used in the diagnosis and treatment of hyperhomocysteinemia or homocysteinuria.

### Calibrators:

ST AIA-PACK Homocysteine Calibrator Set is intended for IN VITRO DIAGNOSTIC USE ONLY for the calibration of the ST AIA-PACK Homocysteine assay using a Tosoh AIA System Analyzer.

### Controls:

The AIA-PACK Homocysteine Control Set is intended for IN VITRO DIAGNOSTIC USE ONLY for performing quality control procedures with the ST AIA-PACK Homocysteine Assay.

## 7. Device Description

The ST AIA-PACK Homocysteine is a competitive enzyme immunoassay which, after sample pretreatment, is performed entirely in the ST AIA-PACK Homocysteine test cups.

Oxidized homocysteine is reduced by tris (2-carboxyethyl) phosphine (TCEP) to the free form and converted to S-adenosyl-L-homocysteine (SAH) by the SAH hydrolase and excess adenosine prior to the immunoassay. SAH present in the pretreated sample competes with immobilized SAH on magnetic beads for binding sites of the enzyme-labeled anti-SAH mouse monoclonal antibody. The magnetic beads are washed to remove unbound anti-SAH mouse monoclonal antibody and are then incubated with a fluorogenic substrate, 4-methylumbelliferyl phosphate (4MUP). The rate of fluorescence produced by the enzyme reaction indicates the amount of enzyme-labeled anti-SAH mouse monoclonal antibody. The amount of antibody that binds to the beads is inversely proportional to the homocysteine concentration in the test sample. A standard curve is constructed, and unknown sample concentrations are calculated using this curve.

## 8. Substantial Equivalence Information

1. Predicate Device Name:  
IMMULITE 2000 Homocysteine
2. k003597
3. Comparison with predicate

### Similarities

Parameter	ST AIA-PACK Homocysteine	IMMULITE 2000 Homocysteine
Intended use	ST AIA-PACK Homocysteine is designed for IN VITRO DIAGNOSTIC USE ONLY for the quantitative measurement of homocysteine in human EDTA plasma, heparinized plasma or serum on TOSOH AIA System Analyzers.	For in vitro diagnostic use with the IMMULITE 2000 Analyzer — for the quantitative determination of L-homocysteine in human plasma or serum. This device can assist in the diagnosis and treatment of patients suspected of having hyperhomocysteinemia or homocystinuria
Specimen type	EDTA plasma, heparinized plasma or serum	EDTA plasma, heparinized plasma or serum
Assay range	0.50 to 50.0 µmol/L	0.5 to 50 µmol/L
Sensitivity	0.50 µmol/L	0.50 µmol/L

## Differences

Parameter	ST AIA-PACK Homocysteine	IMMULITE 2000 Homocysteine
Interference	Hb, Biliirubin, Lipemia, Protein, Ascorbic Acid, Trisodium Citrate, EDTA, Heparinized Sodium, RH factor tested with no interference	Bilirubin, Hb and Lipemia tested with no interference
Reference Range	6.6 – 17.8 µmol/L	5 -12 µmol/L
Assay Technology	Immunofluorescence	Chemiluminescent
Limit of detection	0.334 µmol/L	0.5 µmol/L
Incubation Time	10 minute cycle	60 Minute Cycle
Calibration	Calibrators at 0,2,4,8,15 and 55 µmol/L	Calibration Adjusters range of 2 to 50 µmol/L
Calibration Frequency	90 Days	28 Days

### 9. Standard/Guidance Document Reference

- User Evaluation of Precision Performance of Clinical Chemistry Devices: Approved Guideline (CLSI EP5-A2)
- Evaluation of the Linearity of Quantitative Measurement Procedures: a Statistical Approach: Approved Guideline (CLSI EP6-A2)
- How to Define and Determine Reference Intervals in the Clinical Laboratory; Approved Guideline (C28-A2)
- Protocols for Determination of Limits of Detection and Limits of Quantitation; Approved Guideline (CLSI EP17-A).
- Method Comparison and Bias Estimation Using Patient Samples; Approved Guideline-Second Edition (CLSI EP9-A2)
- Estimation of Total Analytical Error for Clinical Laboratory Methods (CLSI EP21-A)

### 10. Test Principle

The ST AIA-PACK Homocysteine is a competitive enzyme immunoassay which, after sample pretreatment, is performed entirely in the ST AIA-PACK Homocysteine test cups.

Oxidized homocysteine is reduced by tris (2-carboxyethyl) phosphine (TCEP) to the free form and converted to S-adenosyl-L-homocysteine (SAH) by the SAH hydrolase and excess adenosine prior to the immunoassay. SAH present in the pretreated sample competes with immobilized SAH on magnetic beads for binding sites of the enzyme-labeled anti-SAH mouse monoclonal antibody. The magnetic beads are washed to remove unbound anti-SAH mouse monoclonal antibody and are then incubated with a fluorogenic substrate, 4-methylumbelliferyl phosphate (4MUP). The rate of fluorescence produced by the enzyme reaction indicates the amount of enzyme-labeled anti-SAH mouse monoclonal antibody. The amount of antibody that binds to the beads is inversely proportional to the homocysteine concentration in the test sample. A standard curve is constructed, and unknown sample concentrations are calculated using this curve.

**WARNING:** Specimens from patients who are on drug therapy involving S-adenosyl-methionine may show falsely elevated levels of homocysteine. Specimens from patients taking methotrexate, carbamazepine, phenytoin, nitrous oxide or 6-azauridine triacetate may have elevated levels of homocysteine due to their effect on the metabolic pathway.

## 11. Performance Characteristics

### 1. Analytical Performance:

#### a. *Precision/Reproducibility*

The precision for ST AIA-PACK Homocysteine was determined based on guidance from CLSI Protocol EP5-A2.

Within run precision was determined using nine pooled samples (3 each of EDTA plasma, heparinized plasma and serum) in a total of 20 runs. Within each run, one set of duplicates per sample was assayed. The mean of each duplicate was used to obtain the pooled standard deviation (SD), which was then used to calculate the coefficient of variation (CV).

Intra-assay (within run) Precision

<b>Sample</b>	<b>Mean (<math>\mu\text{mol/L}</math>)</b>	<b>Standard Deviation (<math>\mu\text{mol/L}</math>)</b>	<b>Coefficient of Variation (%)</b>
EDTA Plasma A3	7.4	0.2	3.3
EDTA Plasma B3	17.4	0.7	3.9
EDTA Plasma C3	44.0	1.4	3.1
HEP Plasma A3	7.0	0.2	3.2
HEP Plasma B3	14.4	0.5	3.4
HEP Plasma C3	32.2	1.1	3.5
Serum A3	5.6	0.2	4.3
Serum B3	14.3	0.5	3.6
Serum C3	40.9	1.3	3.2

The total precision was determined by the duplicate assay of nine pooled samples (3 each of EDTA plasma, heparinized plasma and serum) in 20 separate runs. The means of each run were used to calculate the pooled standard deviation (SD) and coefficient of variation (CV).

<b>Sample</b>	<b>Mean (<math>\mu\text{mol/L}</math>)</b>	<b>Standard Deviation (<math>\mu\text{mol/L}</math>)</b>	<b>Coefficient of Variation (%)</b>
EDTA Plasma A3	7.4	0.3	4.1
EDTA Plasma B3	17.4	0.8	4.5
EDTA Plasma C3	44.0	1.6	3.6
HEP Plasma A3	7.0	0.3	4.4
HEP Plasma B3	14.4	0.6	4.0
HEP Plasma C3	32.2	1.6	4.9
Serum A3	5.6	0.3	5.0
Serum B3	14.3	0.7	4.7
Serum C3	40.9	1.8	4.4

*b. Linearity/assay reportable range*

The linearity for the ST AIA-PACK Homocysteine was determined, based on guidance from CLSI Protocol EP6-A. The linearity was measured on the AIA-2000 instrument and has been demonstrated to be linear from 0.5 to 50.0  $\mu\text{mol/L}$ .

*c. Traceability,*

The ST AIA-PACK Homocysteine Calibrator Set contains assigned concentrations of S-adenosyl -L-homocysteine. The assigned value is determined on a lot-by-lot basis and is designed to provide an assay calibration range of 0.5 to 50.0  $\mu\text{mol/L}$  of homocysteine. The calibrators in this set are referred to NIST (National Institute of Standards & Technology) Standard Reference Material 1955.

The Tosoh AIA-PACK Control Set contains two controls of buffered bovine serum albumin with each control containing approximately 12  $\mu\text{mol/L}$  and 25  $\mu\text{mol/L}$  of homocysteine with sodium azide as a preservative.

*d. Stability*

The shelf life of the ST AIA-PACK Homocysteine test cups, ST AIA-PACK Homocysteine Calibrator Set, ST AIA-PACK Homocysteine Sample Diluting Solution, ST AIA-PACK Homocysteine Pretreatment Set and the AIA PACK Homocysteine Control Set is 12 months from the date of manufacture when stored at 2-8° C.

The in-use stability of the ST AIA-PACK Homocysteine test cups, is 40 hours at a room temperature of 18-25°C. When stored at 2-8°C, the test cups can be used for up to 30 days.

The in-use stability of the ST AIA-PACK Homocysteine Calibrator Set is 1 day when stored at 2 - 8° C.

The in-use stability of the ST AIA-PACK Homocysteine Sample Diluting Solution is 9 days provided: 1) it is used for automatic dilutions, 2) it is at 18-25° C for only 8 hours per day, and 3) the vials are closed and kept refrigerated immediately after use. In-use stability is 90 days provided: 1) it is used for manual dilutions ONLY, and 2) the vials are closed and refrigerated immediately after use.

The in-use stability of the ST AIA-PACK Homocysteine Pretreatment Reagent is stable at 18-25° C for 20 hours. The in-use stability is stable at 2-8° C for 1 day provided: 1) it is used for manual pretreatment ONLY, and 2) the bottles are closed and refrigerated immediately after use.

The in-use stability of the AIA-PACK Homocysteine CONTROL is 14 days at 2-8° C. If stored at 18-25 degree C the in-use stability is 1 day.

*e. Detection limit:*

Limit of detection: The limit of detection of the ST AIA-PACK Homocysteine was determined based on CLSI guideline EP17-A. A blank sample was measured in 60 replicates. Six low level samples were measured in 10 replicates each. As a result, the limit of detection was estimated to be 0.334 µmol/L.

The reportable range for the assay is 0.5 to 50.0 µmol/L.

*f. Interference/Analytical specificity:*

Interference

Interference is defined, for the purposes of this study, with recovery outside of 100 +/- 10% of the known concentration of the specimen after the following substances are added to human specimens. Three studies were conducted using EDTA plasma, heparinized plasma and serum

- Hemoglobin (up to 1445 mg/dL),
- free bilirubin (up to 18 mg/dL) and conjugated bilirubin (up to 18 mg/dL) do not interfere with the assay.
- Lipemia, as indicated by triglyceride concentration (up to 1667 mg/dL), does not interfere with the assay.

- Added protein (up to 50 mg/ml), as indicated by human g-globulin concentrations, for a total protein concentration of approximately 120 mg/ml, does not interfere with the assay.
- Ascorbic acid (up to 20 mg/dL) does not interfere with the assay
- EDTA-2K (up to 5.0 mg/mL) does not interfere with the assay.
- Heparin (up to 100 U/mL) does not interfere with the assay.

Specificity

The following substances were tested for cross-reactivity. The cross-reactivity (%) is the percent of the compound which will be identified as Homocysteine. If these compounds are present in the specimen at the same concentration as Homocysteine, the final result will be increased by these percentages.

Compound	Concentration (µmol/L)	Cross-reactivity (%)
Adenosine	5.10	0.045
S-Adenosyl-L-methionine	04.74	1.26
L-Cystathionine	0.486	0.159
L-Cysteine	103	0.003
L-Glutathione	99.6	0.005
L-Methionine	0.399	0.059
DL-Homocysteine thiolactone	0.257	6.99

- g. *Assay cut off*  
Not applicable

2. Comparison Studies:

a. *Method comparison*

The methods comparison study was developed with the reference to the CLSI protocol entitled: Method Comparison and Bias Estimation Using Patient Samples; Approved Guideline (EP9-A2).

A total of 138 unaltered EDTA plasma specimens were assayed in singleton utilizing the ST AIA-PACK Homocysteine assay on the AIA-2000 analyzer and the alternate method. The regression analysis for the correlation between the alternate method (x) and the ST AIA-PACK Homocysteine is as follows:



	Deming	Regular
Slope:	1.079	1.061
Intercept:	0.193	0.499
Standard Error Estimate:	2.268	2.257
Corr Coef( R):	0.984	
Points (Plotted/Total):	138/138	
Result Ranges:	2.8 to 48.3 $\mu\text{mol/L}$	

b. *Matrix comparison*

The correlation between EDTA plasma (x) and heparinized plasma (y) on the ST AIA-PACK Homocysteine was carried out using 98 unaltered specimens.

	Deming		Regular	
Slope:	1.007	(0.979 to 1.035)	0.998	(0.970 to 1.025)
Intercept:	-0.235	(-0.591 to 0.121)	-0.124	(-0.480 to 0.231)
Standard Error Estimate:	0.682		0.680	
Corr Coef( R):	0.991			
Result Ranges	EDTA	6.25-38-3 $\mu\text{mol/L}$	Heparin	6.15 - 37.5 $\mu\text{mol/L}$

The correlation between EDTA plasma (x) and serum (y) on the ST AIA-PACK Homocysteine was carried out using 98 unaltered specimens.

	Deming		Regular	
Slope:	1.007	(0.979 to 1.035)	0.998	(0.970 to 1.025)
Intercept:	-0.235	(-0.591 to 0.121)	-0.124	(-0.480 to 0.231)
Standard Error Estimate:	0.682		0.680	
Corr Coef( R):	0.991			
Result Ranges	EDTA	6.25-38-3 $\mu\text{mol/L}$	Heparin	6.15 - 37.5 $\mu\text{mol/L}$

3. Clinical Studies:

Not applicable

4. Clinical cut-off:

Not applicable

5. Expected values/Reference range:

The interval given here was determined in unaltered EDTA plasma samples from 130 apparently healthy individuals.

A reference range study was conducted based on guidance from Clinical and Laboratory Standards Institute (CLSI) Protocol C28-A2.

Number of Samples (n)      130  
Reference Interval            6.6 - 17.8  $\mu\text{mol/L}$

The central 95% of the reference range was used to determine the reference interval.



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
10903 New Hampshire Avenue  
Silver Spring, MD 20993

Tosoh Bioscience, Inc  
c/o Judith K. Ogden  
6000 Shoreline Court  
Suite 101  
South San Francisco, CA 94080

JUN 15 2012

Re: k121533  
Trade Name: ST AIA-PACK Homocysteine,  
ST AIA-PACK Homocysteine Calibrator Set  
AIA-PACK Homocysteine Control Set  
Regulation Number: 21 CFR §862.1377  
Regulation Name: Urinary homocysteine (non-quantitative) test system  
Regulatory Class: Class II  
Product Codes: LPS, JIT, JJX  
Dated: May 22, 2012  
Received: May 25, 2012

Dear Ms. Ogden:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration.

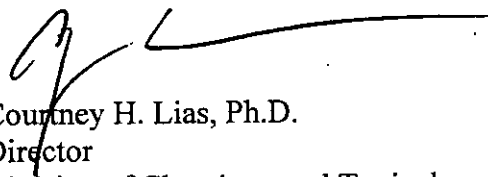
If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to such additional controls. Existing major regulations affecting your device can be found in Title 21, Code of Federal Regulations (CFR), Parts 800 to 895. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Parts 801 and 809); medical device reporting (reporting of medical device-related adverse events) (21 CFR 803); and good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820).

If you desire specific advice for your device on our labeling regulation (21 CFR Part 801), please contact the Office of In Vitro Diagnostic Device Evaluation and Safety at (301) 796-5450. Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21 CFR Part 807.97). For questions regarding postmarket surveillance, please contact CDRH's Office of Surveillance and Biometric's (OSB's) Division of Postmarket Surveillance at (301) 796-5760. For questions regarding the reporting of adverse events under the MDR regulation (21 CFR Part 803), please go to <http://www.fda.gov/MedicalDevices/Safety/ReportaProblem/default.htm> for the CDRH's Office of Surveillance and Biometrics/Division of Postmarket Surveillance...

You may obtain other general information on your responsibilities under the Act from the Division of Small Manufacturers, International and Consumer Assistance at its toll-free number (800) 638-2041 or (301) 796-5680 or at its Internet address <http://www.fda.gov/MedicalDevices/ResourcesforYou/Industry/default.htm>

Sincerely yours,



Courtney H. Lias, Ph.D.  
Director  
Division of Chemistry and Toxicology Devices  
Office of *In Vitro* Diagnostic Device  
Evaluation and Safety  
Center for Devices and Radiological Health

Enclosure

# Indications for Use Form

510(k) Number (if known): k121533

Device Name: ST AIA-PACK Homocysteine; ST AIA-PACK Homocysteine Calibrator Set; AIA-PACK Homocysteine Control Set

## Indications for Use:

### Reagents:

ST AIA-PACK Homocysteine is designed for IN VITRO DIAGNOSTIC USE ONLY for the quantitative measurement of homocysteine in human serum, heparinized plasma or EDTA plasma using a Tosoh AIA System Analyzer. Homocysteine measurements are used in the diagnosis and treatment of hyperhomocysteinemia or homocysteinuria.

### Calibrators:

ST AIA-PACK Homocysteine Calibrator Set is intended for IN VITRO DIAGNOSTIC USE ONLY for the calibration of the ST AIA-PACK Homocysteine assay using a Tosoh AIA System Analyzer.

### Controls:

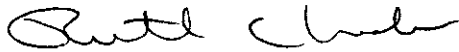
The AIA-PACK Homocysteine Control Set is intended for IN VITRO DIAGNOSTIC USE ONLY for performing quality control procedures with the ST AIA-PACK Homocysteine Assay.

Prescription Use   X   AND/OR Over-The-Counter Use \_\_\_\_\_  
(Part 21 CFR 801 Subpart D) (21 CFR 801 Subpart C)

(PLEASE DO NOT WRITE BELOW THIS LINE-CONTINUE ON ANOTHER PAGE OF NEEDED)

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Concurrence of CDRH, Office of In Vitro Diagnostic Devices (OIVD)



Division Sign-Off  
Office of In Vitro Diagnostic Device  
Evaluation and Safety

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