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MONOLISA™ Anti-HAV IgM EIA **510(k) SUMMARY** MAY - 3 2007

This summary of 510(k) safety and effectiveness information is being submitted in accordance with the requirements of SMDA 1990 and 21 CFR 807.92.

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CLASSIFICATION INFORMATION

CLASSIFICATION NAME: Hepatitis A Test (IgM Antibody)

COMMON NAME: IgM Antibody to Hepatitis A Virus

PRODUCT TRADE NAME: MONOLISA™ Anti-HAV IgM EIA

DEVICE CLASS : Class II LOL

CLASSIFICATION PANEL : Immunology and Microbiology Devices

REGULATION NUMBER : 21 CFR 866.3310

LEGALLY MARKETED EQUIVALENT (SE) DEVICE

DiaSorin ETI-HA-IGMK PLUS
PMA Number : P890014
Decision Date : 12/14/2005

DEVICE DESCRIPTION

The MONOLISA™ Anti-HAV IgM EIA is an enzyme immunoassay (IgM antibody capture format) for the detection of IgM antibodies to Hepatitis A Virus. In the assay procedure, patient specimens, a calibrator, and controls are incubated with anti-human IgM antibodies coated on the microwells. If IgM antibodies to HAV are present in a specimen or control, they bind to the antibody. Excess sample is removed by a wash step. The HAV Viral Antigen and the Conjugate (containing horseradish peroxidase – labeled mouse monoclonal antibody to HAV) are successively added to the microwells and allowed to incubate. The presence of IgM anti-HAV in the sample enables the HAV Viral Antigen and the Conjugate to bind to the solid phase. Excess Conjugate and HAV Viral Antigen are removed by a wash step, and a TMB Chromogen / Substrate solution is added to the microwells and allowed to incubate. If a sample contains anti-HAV IgM, the bound enzyme (HRP) causes the colorless TMB in the Chromogen solution to change to blue. The blue color turns yellow after the addition of a Stopping Solution. If a sample does not contain anti-HAV IgM, the Chromogen / Substrate solution in the well remains colorless during the substrate incubation, and after the addition of the Stopping Solution. The color intensity is measured spectrophotometrically. Absorbance value readings for patient specimens are compared to the cutoff value.

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KIT COMPONENTS

Component	Description
R1 Microwell Strip Plates	Two (2) x 12 strips of 8 wells coated with polyclonal anti-human IgM antibodies.
R2 Wash Solution Concentrate (30x)	One (1) 120 mL bottle, Tris buffer containing NaCl and Tween 20.
C0 Negative Control	One (1) 1 mL vial, containing human plasma, negative for IgM anti-HAV antibodies, total anti-HAV antibodies, HBs antigen, anti-HCV antibodies and anti-HIV-1/HIV-2 antibodies. Preservatives: Sodium azide (< 0.1%) and Proclin™ 300 (0.25%).
C1 Positive Control	One (1) 1 mL vial, containing human plasma, positive for IgM anti-HAV antibodies and negative for HBs antigen, anti-HCV antibodies and anti-HIV-1/HIV-2 antibodies, diluted in human plasma pool negative for anti-HAV antibodies. Preservatives : Sodium azide (< 0.1%) and Proclin™300 (0.25%).
C2 Calibrator	One (1) 1.6 mL vial, containing human plasma, positive for IgM anti-HAV antibodies and negative for HBs antigen, anti-HCV antibodies and anti anti-HIV-1/HIV-2 antibodies, diluted in colored synthetic base. Preservatives: Sodium azide (< 0.1%) and Proclin™ 300 (0.25%).
R6 Sample Diluent	Two (2) x 14 mL bottles, Tris buffer containing protein and sample indicator dye. Preservative: Proclin™ 300 (0.1%).
R7a HAV Viral Antigen	One (1) 13 mL bottle, Inactivated HAV virus in Tris buffer containing proteins and sample indicator dye. Preservative: Proclin™ 300 (0.1%).
R7b Conjugate	One (1) 13 mL bottle, Conjugate (peroxidase labeled mouse monoclonal antibody to HAV) in Tris buffer containing proteins, detergent, and sample indicator dye. Preservative: Proclin™ 300 (0.1%).
R8 Substrate Buffer	One (1) 120 mL bottle, containing Hydogen Peroxide, citric acid / sodium acetate buffer and Dimethylsulfoxide (DMSO).
R9 Chromogen (11x)	One (1) 12 mL bottle, Solution containing Tetramethylbenzidine (TMB).
R10 Stopping Solution	One (1) 120 mL bottle, 1 N H_2SO_4.

Plate sealers	Eight (8) clear plastic sealers.

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INTENDED USE

The MONOLISA™ Anti-HAV IgM EIA is an *in vitro* enzyme immunoassay kit intended for use in the qualitative detection of IgM antibodies to Hepatitis A virus (anti-HAV IgM) in human (adult and pediatric) serum or plasma (EDTA, Heparin, Citrate, ACD).

This assay is not intended for screening blood or solid or soft tissue donors.

INDICATIONS FOR USE

The MONOLISA™ Anti-HAV IgM EIA kit is indicated for testing specimens from individuals who have signs and symptoms consistent with acute Hepatitis. Assay results, in conjunction with other serological or clinical information, may be used for the laboratory diagnosis of individuals with acute or recent Hepatitis A.

Assay performance characteristics have not been established for immunocompromised or immunosuppressed patients, and core blood or neonatal specimens.

TECHNOLOGICAL CHARACTERISTICS

The following tables summarize similarities and differences between the MONOLISA™ Anti-HAV IgM EIA kit and the predicate device ETI-HA-IGMK PLUS.

Table 1: Similarities between kit components and materials

Similarities in Components / Materials	**MONOLISA™ Anti-HAV IgM EIA Catalog# 72495**	**ETI-HA-IGMK PLUS Catalog# P001925**
Conjugate	Peroxidase-labeled mouse monoclonal antibody to HAV.	Peroxidase-labeled mouse monoclonal antibody to HAV.
Positive Control	Human plasma, positive for IgM anti-HAV antibodies, diluted in human plasma negative for anti-HAV antibodies.	Human serum/plasma reactive for IgM anti-HAV, diluted with buffer.
Chromogen	Tetramethylbenzidine (TMB)	Tetramethylbenzidine (TMB)
Substrate	Hydrogen Peroxide	Hydrogen Peroxide
Washing Solution	Concentrated buffered solution with Tween 20.	Concentrated buffered solution with detergents.
Sample diluent	Buffered solution with proteins and sample indicator dye.	Buffered solution with proteins and an inert blue dye.

Table 2: Differences between kit components and materials

Differences in Components / Materials	MONOLISA™ Anti-HAV IgM EIA Catalog# 72495	ETI-HA-IGMK PLUS Catalog# P001925
Solid Phase	Microplate wells coated with polyclonal anti-human IgM antibodies.	Microplate wells coated with mouse monoclonal antibodies to human IgM.
Negative Control	Human plasma, negative for IgM anti-HAV antibodies and total anti-HAV antibodies.	Human serum/plasma non-reactive for IgM anti-HAV and reactive for IgG anti-HAV, diluted in buffer.
Calibrator	Human plasma, positive for IgM anti-HAV antibodies diluted in buffer.	Human serum/plasma non-reactive for IgM anti-HAV and reactive for IgG anti-HAV diluted with buffer.
Conjugate	Ready-to-use	To be diluted.
Stopping Solution	1N H_2SO_4.	0.4N H_2SO_4.
Required sample volume	20 µl	10 µl

Table 3: Similarities between kits with regard to function and use

Similarities in Function and Use	MONOLISA™ Anti-HAV IgM EIA Catalog# 72495	ETI-HA-IGMK PLUS Catalog# P001925
Test Method	EIA (antibody capture)	EIA (antibody capture)
Specimen Storage Requirements	Samples may be stored at 2-8°C for up to 24 hours.	Samples may be stored at 2-8°C for up to 24 hours.
Format	96-well microplate	96-well microplate
Intended Use	Assay for the qualitative detection of anti-HAV IgM antibodies in human serum or plasma.	Assay for the qualitative detection of anti-HAV IgM antibodies in human serum or plasma.
Wavelength	Dual wavelength reading at 450 nm and 615/630 nm.	Dual wavelength reading at 450 nm and 630 nm.
Interpretation of results	Obtained absorbance readings for patient specimens compared to cut-off value determined by the mean of the calibrator absorbance values.	Obtained absorbance readings for patient samples compared to cut-off value determined by the mean of the calibrator absorbance values.

Table 4: Differences between kits with regard to function and use

Differences in Function and Use	**MONOLISA™ Anti-HAV IgM EIA Catalog# 72495**	**ETI-HA-IGMK PLUS Catalog# P001925**
Spectrophotometric Verification of Sample and Reagent Pipeting	Possible (but optional)	NA
Cutoff calculation	Mean absorbance of calibrator values divided by 4	Mean absorbance of the calibrator values + 0.250

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EXPECTED VALUES

Healthy individuals

The expected results of the MONOLISA™ Anti-HAV IgM EIA assay were determined in presumably healthy individuals from the Mid-west US (St Louis, Missouri), the Western US (California and Washington) and from Europe (Parma, Italy).

In the Mid -west, the population was 55% female and 45% male, with ages that ranged from 1 to 96 years. 48% (134) were pediatric specimens.

The majority of the subjects were White/Caucasian (64%), and 32% were black or African American; for 4% data were not available.

In the Western USA, 73% were from California and 27% were from Washington. The population was 56% female and 44% male, with ages that ranged from 15 to 90 years.

In Europe, the population was 50% female and 50% male, with ages that ranged from 18 to 87 years.

The expected results for presumably healthy individuals living in the United States and in Europe are presented below (Tables 5, 6 and 7).

The percent of Anti-HAV IgM reactive results with MONOLISA™ Anti-HAV IgM EIA were 0.4% for both Mid-west and Western US and 0.7% in Europe.

Table 5: Expected Results for MONOLISA™ Anti-HAV IgM EIA in subjects from the Mid-West US (N= 280)

MONOLISA™ Anti-HAV IgM EIA								
Age Range	Gender	Reactive		Borderline		Nonreactive		Total
		N	%	N	%	N	%	
< 10	Female	0	N/A	0	N/A	35	100.0%	35
	Male	0	N/A	0	N/A	38	100.0%	38
10 -19	Female	0	N/A	0	N/A	38	100.0%	38
	Male	0	N/A	0	N/A	23	100.0%	23
20- 29	Female	0	N/A	0	N/A	5	100.0%	5
	Male	0	N/A	0	N/A	3	100.0%	3
30 -39	Female	0	N/A	0	N/A	10	100.0%	10
	Male	0	N/A	0	N/A	9	100.0%	9
40 -49	Female	0	N/A	0	N/A	13	100.0%	13
	Male	0	N/A	0	N/A	8	100.0%	8
50 -59	Female	1	5.6%	1	5.6%	16	88.9%	18
	Male	0	N/A	0	N/A	17	100.0%	17
60 -69	Female	0	N/A	0	N/A	14	100.0%	14
	Male	0	N/A	0	N/A	13	100.0%	13
70-79	Female	0	N/A	0	N/A	9	100.0%	9
	Male	0	N/A	0	N/A	6	100.0%	6
80-89	Female	0	N/A	0	N/A	13	100.0%	13
	Male	0	N/A	0	N/A	6	100.0%	6
>=90	Female	0	N/A	0	N/A	0	N/A	0
	Male	0	N/A	0	N/A	2	100.0%	2
Total		**1***	**0.4%**	**1****	**0.4%**	**278**	**99.3%**	**280**

*1 subject was reactive with a result of 2.25 (S/CO)

** 1 subject gave an initial borderline result of 1.04 (S/CO).

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Table 6: Expected Results for MONOLISA™ Anti-HAV IgM EIA in subjects from the Western US (N= 245)

MONOLISA™ Anti-HAV IgM EIA								
Age Range	**Gender**	**Reactive**		**Borderline**		**Nonreactive**		**Total**
		N	**%**	**N**	**%**	**N**	**%**	
<19	Female	0	N/A	0	N/A	5	100.0%	5
	Male	0	N/A	0	N/A	5	100.0%	5
20- 29	Female	0	N/A	0	N/A	26	100.0%	26
	Male	0	N/A	0	N/A	24	100.0%	24
30 -39	Female	0	N/A	0	N/A	20	100.0%	20
	Male	0	N/A	0	N/A	18	100.0%	18
40 -49	Female	0	N/A	0	N/A	18	100.0%	18
	Male	0	N/A	0	N/A	22	100.0%	22
50 -59	Female	1	2.6%	0	N/A	38	97.4%	39
	Male	0	N/A	1	4.8%	20	95.2%	21
60 -69	Female	0	N/A	0	N/A	12	100.0%	12
	Male	0	N/A	0	N/A	12	100.0%	12
70-79	Female	0	N/A	0	N/A	9	100.0%	9
	Male	0	N/A	0	N/A	2	100.0%	2
80-89	Female	0	N/A	0	N/A	6	100.0%	6
	Male	0	N/A	0	N/A	4	100.0%	4
>=90	Female	0	N/A	0	N/A	1	100.0%	1
	Male	0	N/A	0	N/A	0	N/A	0
Unknown	Female	0	N/A	0	N/A	1	100.0%	1
Total		**1***	**0.4%**	**1****	**0.4%**	**243**	**99.2%**	**245**

*1 subject was reactive with a result of 1.34 (S/CO)
** 1 subject gave an initial borderline result of 0.96 (S/CO).

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Table 7: Expected Results for MONOLISA™ Anti-HAV IgM EIA in subjects from Italy, Europe (N= 285)

MONOLISA™ Anti-HAV IgM EIA								
Age Range	Gender	Reactive		Borderline		Nonreactive		Total
		N	%	N	%	N	%	
< 19	Female	0	N/A	0	N/A	1	100.0%	1
	Male	0	N/A	0	N/A	1	100.0%	1
20- 29	Female	0	N/A	0	N/A	3	100.0%	3
	Male	0	N/A	0	N/A	2	100.0%	2
30 -39	Female	0	N/A	0	N/A	7	100.0%	7
	Male	0	N/A	0	N/A	7	100.0%	7
40 -49	Female	0	N/A	0	N/A	21	100.0%	21
	Male	0	N/A	0	N/A	19	100.0%	19
50 -59	Female	0	N/A	0	N/A	22	100.0%	22
	Male	0	N/A	0	N/A	27	100.0%	27
60 -69	Female	1	2.5%	1	2.5%	41	95.0%	43
	Male	0	N/A	0	N/A	27	100.0%	27
70-79	Female	1	3.6%	0	N/A	31	96.4%	32
	Male	0	N/A	0	N/A	37	100%	37
80-89	Female	0	N/A	0	N/A	13	100%	13
	Male	0	N/A	0	N/A	23	100%	23
Total		**2***	**0.7%**	**1****	**0.4%**	**282**	**98.9%**	**285**

*2 subjects gave reactive results of 3.4 and 1.2 (S/CO)
** 1 subject gave an initial borderline result of 1.07 (S/CO)

Adult Subjects at High Risk for Viral Hepatitis:

Expected results of asymptomatic prospective high-risk subjects determined from a multi-center study in the US and in Europe are reported in the following tables.
A total of 230 US Subjects were at high risk for viral hepatitis including intravenous drug users (N= 55), homosexual males (N=15), sex workers (N=39), prison history (N= 92), high-risk sex partners (N=25), high-risk occupation/health care workers (N=4). Many had more than 1 high-risk behavior or risk factor. Subjects were from Los Angeles, CA, (86.5%), Santa Ana, CA (4.3%), or Miami, FL (9.1%). The group was Caucasian (7.4%), Black or African American (74.3%), Hispanic or Latino (15.2%), Asian (0.4%), Native Hawaiian or other Pacific Islander (0.4%), and American Indian or Alaska native (0.9%), with the remaining 1.3% represented by multiple ethnic groups.
The subjects were 81% male and 19% female, and ranged in age from 18 to 70 years (mean age of 45). The data are reported in Table 8.
The percent of Anti-HAV IgM reactive results with MONOLISA™ Anti-HAV IgM EIA in this high-risk asymptomatic population was 0%.

The European group (N= 62) was 87% male and 13% female and ranged in age from 21 to 75 years (mean age of 40). It consisted of intravenous drug users (30), subjects who had clotting factor disorders (7) and MSM patients (25). The data are reported in Table 9.
The percent of Anti-HAV IgM reactive results with MONOLISA™ Anti-HAV IgM EIA in this high-risk asymptomatic population was 0%.

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Table 8: Expected results for MONOLISA™ Anti-HAV IgM EIA in the US High risk Group for Viral Hepatitis A (N=230)

MONOLISA™ Anti-HAV IgM EIA								
Age Range	Gender	Reactive		Borderline		Nonreactive		Total
		N	%	N	%	N	%	
< 19	Female	0	N/A	0	N/A	1	100.0%	1
	Male	0	N/A	0	N/A	1	100.0%	1
20- 29	Female	0	N/A	0	N/A	3	100.0%	3
	Male	0	N/A	0	N/A	2	100.0%	2
30 -39	Female	0	N/A	0	N/A	7	100.0%	7
	Male	0	N/A	0	N/A	36	100.0%	36
40 -49	Female	0	N/A	0	N/A	24	100.0%	24
	Male	0	N/A	1	1.2 %	84	98.8%	85
50 -59	Female	0	N/A	0	N/A	7	100.0%	7
	Male	0	N/A	0	N/A	51	100.0%	51
60 -69	Female	0	N/A	0	N/A	1	100.0%	1
	Male	0	N/A	0	N/A	10	100.0%	10
70-79	Female	0	N/A	0	N/A	0	N/A	0
	Male	0	N/A	0	N/A	2	100.0%	2
Total		**0**	**N/A**	**1**	**0.4%**	**229**	**99.6%**	**230**

Table 9: Expected results for MONOLISA™ Anti-HAV IgM EIA in the European High risk group for Viral Hepatitis A (N=62)

MONOLISA™ Anti-HAV IgM EIA								
Age Range	Gender	Reactive		Borderline		Non reactive		Total
		N	%	N	%	N	%	
< 19	Female	0	N/A	0	N/A	0	N/A	0
	Male	0	N/A	0	N/A	0	N/A	0
20- 29	Female	0	N/A	0	N/A	5	100.0%	5
	Male	0	N/A	0	N/A	11	100.0%	11
30 -39	Female	0	N/A	0	N/A	2	100.0%	2
	Male	0	N/A	0	N/A	14	100.0%	14
40 -49	Female	0	N/A	0	N/A	1	100.0%	1
	Male	0	N/A	0	N/A	14	100.0%	14
50 -59	Female	0	N/A	0	N/A	0	N/A	0
	Male	0	N/A	0	N/A	11	100.0%	11
60 -69	Female	0	N/A	0	N/A	0	N/A	0
	Male	0	N/A	0	N/A	2	100.0%	2
70-79	Female	0	N/A	0	N/A	0	N/A	0
	Male	0	N/A	0	N/A	2	100.0%	2
>80	Female	0	N/A	0	N/A	0	N/A	0
	Male	0	N/A	0	N/A	0	N/A	0
Total		**0**	**N/A**	**0**	**N/A**	**62**	**100.0%**	**62**

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PERFORMANCE CHARACTERISTICS

Clinical Performance

A multi-center prospective and retrospective study was conducted to evaluate the clinical performance of the MONOLISA™ Anti-HAV IgM EIA assay among individuals with signs or symptoms and those at high risk for Hepatitis infection. Specimens were collected in 3 different geographical areas: 404 specimens were collected in the US and 929 were collected in Europe (France and Italy).

The US population consisted of 174 subjects with signs and symptoms of Hepatitis. In this group, 60% were male and 40% were female, and they ranged in age from 17 to 72 years (mean age of 38). The group was Caucasian (13.2%), Black or African American (4.6%), Hispanic or Latino (2.9%), and Asian (41.9%), with the remaining 1.1% represented by multiple ethnic groups. The ethnicity of 36.8% was unknown. Among these subjects, 23 (13.2%) were pediatric samples.

The 230 subjects from the high-risk group for Hepatitis A include intravenous drug users (N= 55), homosexual males (N=15), sex workers (N=39), prison history (N= 92), high-risk sex partners (N=25), high-risk occupation/health care workers (N=4). Many had more than 1 high-risk behavior or risk factor. The group was Caucasian (7.4%), Black or African American (74.3%), Hispanic or Latino (15.2%), Asian (0.4%), Native Hawaiian or other Pacific Islander (0.4%), and American Indian or Alaska native (0.9%), with the remaining 1.3% represented by multiple ethnic groups. In this group, 81% were male and 19% were female, and they ranged in age from 18 to 70 years (mean age of 45). Among these 230 subjects, 2 (0.9%) were pediatric samples.

The European population consisted of 253 specimens collected from patients with signs and symptoms of Hepatitis. In this group, 51% were male and 49% were female and they ranged in age from 1 to 105 years (mean age of 53).
Sixty-two (62) specimens were collected from a population at high risk for hepatitis composed of intravenous drug users (30), subjects who had clotting factor disorders (7) and MSM patients (25). The group was 87% male and 13% female and ranged in age from 21 to 75 years (mean age of 40).
There were 345 specimens from an asymptomatic hospitalized population and 34 were from healthcare workers (for HAV pre-vaccination screening).
One hundred and fifty one (151) patients had recovered HAV infection.
Among these 845 european samples, 36 (4.3%) were from pediatric subjects.

Percent Agreement
The results obtained with MONOLISA™ Anti-HAV IgM EIA were compared with the results obtained using the comparative assay.
The positive and negative percent agreements and the 95% exact confidence between MONOLISA™ Anti-HAV IgM EIA and the comparative assay were calculated.

To determine the percent agreement on borderline results the following criteria were used:

- Specimens that were borderline with the comparative assay and reactive with MONOLISA™ Anti-HAV IgM EIA were considered as false positives for MONOLISA™ Anti-HAV IgM EIA assay
- Specimens that were borderline with the comparative assay and non reactive with MONOLISA™ Anti-HAV IgM EIA were considered as false negatives for MONOLISA™ Anti-HAV IgM EIA

The results obtained with the US specimens and with the European specimens are presented in the following tables:

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Table 10: MONOLISA™ Anti-HAV IgM EIA versus the comparative assay results in the US population (N=404)

Subject category	Comparative assay: Positive			Comparative assay : Borderline			Comparative assay: Negative			Total
	MONOLISA™ Anti-HAV IgM EIA			MONOLISA™ Anti-HAV IgM EIA			MONOLISA™ Anti-HAV IgM EIA			
	R	BRD	NR	R	BRD	NR	R	BRD	NR	
Subjects with signs and symptoms	1	0	0	0	0	0	2	0	171	174
Subjects with high risk for Hepatitis	0	0	0	0	0	0	0	1	229	230
Total	**1**	**0**	**0**	**0**	**0**	**0**	**2[b]**	**1[a b]**	**400**	**404**

R: Reactive, NR: Nonreactive, BRD : Borderline
[a]: the borderline sample with MONOLISA was considered as "false positive"
[b]: these samples were found HAV IgG reactive.

	Positive percent agreement	95% Exact Confidence interval	Negative percent agreement	95% Exact Confidence interval
Total	100% (1/1)	NA	99.3% (400/403)	97.8– 99.9%

Table 11: MONOLISA™ Anti-HAV IgM EIA versus the comparative assay results in the European population (N= 845)

Subject category	Comparative assay: Positive			Comparative assay: Borderline			Comparative assay: Negative			Total
	MONOLISA™ Anti-HAV IgM EIA			MONOLISA™ Anti-HAV IgM EIA			MONOLISA™ Anti-HAV IgM EIA			
	R	BRD	NR	R	BRD	NR	R	BRD	NR	
General hospitalized population	1	0	0	0	0	0	1	1[b]	342	345
Sign / Symptoms of Hepatitis	0	0	0	0	0	0	3	0	250	253
Subjects with high risk for Hepatitis	0	0	0	0	0	0	0	0	62	62
Healthcare workers	0	0	0	0	0	0	0	0	34	34
Infected/ recovered HAV	0	0	0	2[a]	0	0	1	0	148	151

Total	**1**	**0**	**0**	**2[c]**	**0**	**0**	**5[c]**	**1[c]**	**836**	**845**

	Positive percent agreement	95% Exact Confidence interval	Negative percent agreement	95% Exact Confidence interval
Total	100% (1/1)	N/A	99.0% (836/844)	98.1-99.6

R: Reactive, NR: Nonreactive, BRD : Borderline
[a] the 2 borderline samples with the comparative assay were considered "false positive" with MONOLISA
[b]: the borderline sample with MONOLISA was considered as "false positive"
[c]: these samples were found HAV IgG Reactive

Acute HAV Infection:

Among the retrospective samples, 84 were from subjects with a medical history and laboratory results indicative of acute Hepatitis A. The subjects included 56% male, 37% female; the gender was not available for 7%. The mean age was 21, and subjects ranged from 1 to 55 years. Among them 39 were pediatric subjects.
The results are presented in the following table:

Table 12 : Comparison of Results for MONOLISA™ Anti-HAV IgM EIA versus the comparative assay on Acute HAV infection in the adult and pediatric European Population (N= 84) :

	Comparative assay: Positive			Comparative assay: Borderline			Comparative assay : Negative			
	MONOLISA™ Anti-HAV IgM EIA			MONOLISA™ Anti-HAV IgM EIA			MONOLISA™ Anti-HAV IgM EIA			total
	R	BRD	NR	R	BRD	NR	R	BRD	NR	
Adults	45	0	0	0	0	0	0	0	0	45
Pediatrics	39	0	0	0	0	0	0	0	0	39
Total	**84**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**84**

R: Reactive, NR: Nonreactive, BRD : Borderline

The positive agreement was 100% (84/84) with a 95% exact confidence interval of 96.5% to 100%.

Performance of MONOLISA™ Anti-HAV EIA in Pediatric subjects:

Sixty-one (61) pediatric samples were tested during the US and European clinical studies in addition to the 39 samples from acute HAV infection.
Among the US population, 23 had signs and symptoms of hepatitis and 2 were from the high risk group. In the European population, 3 belonged to the general hospitalized population, 23 had signs and symptoms of hepatitis, 2 were from the high risk group, 3 were healthcare workers, 5 had recovered from Hepatitis A infection. The results from these pediatric samples are summarized in the following table.

Table 13 : Comparison of Results for MONOLISA™ Anti-HAV IgM EIA versus the comparative assay in the Pediatric European and US Population (N= 61)

Subject category	Comparative assay: Positive			Comparative assay: Borderline			Comparative assay : Negative			Total
	MONOLISA™ Anti-HAV IgM EIA			MONOLISA™ Anti-HAV IgM EIA			MONOLISA™ Anti-HAV IgM EIA			
	R	BRD	NR	R	BRD	NR	R	BRD	NR	
European pediatrics	0	0	0	0	0	0	1	0	35	36
US pediatrics	0	0	0	0	0	0	1	0	24	25
Total	**0**	**0**	**0**	**0**	**0**	**0**	**2[a]**	**0**	**59**	**61**

R: Reactive, NR: Nonreactive, BRD : Borderline
[a]: these samples were found HAV IgG Reactive

	Positive percent agreement	95% Exact Confidence interval	Negative percent agreement	95% Exact Confidence interval
Total	**0**	**N/A**	**96.7% (59/61)**	**88.6 – 99.6**

Including the combined US and European Sites, the positive percent agreement of the MONOLISA™ Anti-HAV IgM EIA with the comparative assay was **100% (86/86)**, with a 95% exact confidence interval of **96.6% to 100%**. The negative percent agreement of the MONOLISA™ Anti-HAV IgM EIA with the comparative assay was **99.1% (1233/1244)** with a 95% exact confidence interval of **98.4% to 99.6%.**

Seroconversion Panels

Eight commercially available HAV seroconversion panels were tested using MONOLISA™ Anti-HAV IgM EIA and the comparative assay to determine the sensitivity of the assay. The results are summarized in the following table:

Table 14: MONOLISA™Anti-HAV IgM EIA Seroconversion panels Results

Panel ID	MONOLISA™ Anti-HAV IgM EIA	Anti-HAV IgM Comparative Assay	
	Post bleed day of first reactive result	Post bleed day of first reactive result	Difference in Days to Reactive result
07467A	0	0	0
60160K	0	0	0
60162K	0	0	0
HAV01	0	0	0
RP-004	6	6	0
RP-013	8	8	0
PHT901	12	12	0
PHT902	16	16	0

Panel ID	MONOLISA™ Anti-HAV IgM EIA	Anti-HAV IgM Comparative Assay	
	Post bleed day of last reactive result*	Post bleed day of last reactive result*	Difference in Days from last Reactive result
HAV01	91[a]	77	+14

a: last bleed of the panel

For all seroconversion panels, both MONOLISA™ Anti-HAV IgM EIA and the comparative assay detected HAV IgM antibodies at the same first bleed. MONOLISA™ Anti-HAV IgM EIA appears to detect IgM for a longer period than the comparator assay for qualitative determination of IgM antibody to Hepatitis A.

Among seroconversion panels beginning with samples negative for anti-HAV antibodies and having subsequent samples to 5-6 months, one (PHT-902) becomes borderline after 5 months and one (PHT-901) gives a negative result after more than 20 months. Another seroconversion panel (RP-013) with samples collected through 6 months has a declining ratio but still remains positive.
The other panels contain members collected through 2 to 3 months.

Cross Reactivity Study

The potential for cross reactivity to other disease states, or viruses was evaluated for the MONOLISA™ Anti-HAV IgM EIA Assay. In addition, samples containing rheumatoid factors, auto-antibodies, anti-mouse antibodies were tested.

In total, 255 specimens (including both serum and plasma) from 16 groups of potential cross reactivity were tested. FDA approved methods were used to confirm the disease state of each specimen. All the samples were found negative on another commercially Anti-HAV IgM assay.

The results are summarized in the following table:

Table 15: Potential cross reactivity study

Clinical condition	Number tested	MONOLISA™ Anti-HAV IgM EIA nonreactive
Hepatitis C (HCV)	15	15
Hepatitis B (HBV) HBs Ag	15	15
Hepatitis B (HBV) anti HBc	15	15
Human Immunodeficiency Virus (HIV)	15	15
Epstein Barr Virus (EBV) IgG	15	15
Epstein Barr Virus (EBV) IgM	15	15
Cytomegalovirus (CMV) IgG	15	15
Cytomegalovirus (CMV) IgM	15	15
Rubella IgG	15	15
Toxoplasmosis IgG	15	15
Toxoplasmosis IgM	15	15
Mumps IgG	15	15
Varicella Zoster Virus(VZV) IgG	15	15
Varicella Zoster Virus(VZV) IgM	15	15
Anti Nuclear Antibody (ANA)	15	15
Human Anti Mouse Antibody (HAMA)	15	15
Rheumatoid Arthritis	15	15
Total Samples tested	**255**	**255**

All the 255 specimens were found nonreactive with HAV IgM with MONOLISA™ Anti-HAV IgM and with the predicate assay.

BIO-RAD

Precision Study

Within – Laboratory Precision Study

A 21-member panel was tested: serum samples with the 6 corresponding plasma samples (EDTA K2, EDTA K3, Sodium Citrate, Sodium Heparin, Lithium heparin, ACD) at 3 different levels (1 negative, 1 negative near the cutoff, 1 low positive near the cutoff) were tested on 1 lot, in duplicate, in 2 different runs per day (am and pm), by the same operator for a period of 20 days. The data were analyzed following the CLSI guidance EP5A2. The mean ratio, the Standard Deviation (SD) and percent coefficient of variation (%CV) were calculated for each panel member.

The data summary is shown in the following table:

Table 16: MONOLISA™ Anti-HAV IgM EIA Precision Results by Panel Member Signal to Cutoff (S/CO)

Panel Member	N	Mean	Within run[1]		Between Run[2]		Between Day[3]		Total[4]	
		S/CO	SD	CV (%)	SD	CV (%)	SD	CV (%)	SD	CV (%)
Negative Control C0	40	0.08	NA	NA	0.01	11.0%	0.00	0.8%	0.01	11.0%
Positive Control C1	40	2.03	NA	NA	0.08	4.2%	0.05	2.5%	0.10	4.8%
serum 1	80	0.05	0.00	5.5%	0.01	14.1%	0.00	7.7%	0.01	17.0%
EDTA K2 1	80	0.05	0.00	6.3%	0.01	13.4%	0.00	6.4%	0.01	16.1%
EDTA K3 1	80	0.05	0.00	6.3%	0.01	15.2%	0.00	4.6%	0.01	17.1%
Sodium Citrate 1	80	0.05	0.00	6.7%	0.01	14.0%	0.00	0.0%	0.01	15.5%
Sodium Heparin 1	80	0.05	0.00	6.7%	0.01	12.6%	0.00	5.6%	0.01	15.4%
Lithium Heparin 1	80	0.05	0.00	6.7%	0.01	14.5%	0.00	7.6%	0.01	17.7%
ACD A	80	0.05	0.00	6.3%	0.01	14.0%	0.00	0.4%	0.01	15.3%
Serum 2	80	0.55	0.02	3.7%	0.02	4.0%	0.02	3.6%	0.04	6.5%
EDTA K2 2	80	0.66	0.02	3.5%	0.03	4.9%	0.03	5.3%	0.05	8.0%
EDTA K3 2	80	0.65	0.02	3.3%	0.04	6.1%	0.03	4.7%	0.05	8.3%
Sodium Citrate 2	80	0.65	0.03	5.0%	0.03	5.0%	0.02	3.8%	0.05	8.0%
Sodium Heparin 2	80	0.57	0.01	2.5%	0.02	3.7%	0.03	4.8%	0.04	6.6%
Lithium Heparin 2	80	0.57	0.02	2.7%	0.04	6.1%	0.02	4.0%	0.05	7.8%
ACD 2	80	0.68	0.03	5.2%	0.04	6.3%	0.03	4.4%	0.06	9.2%
Serum 3	80	1.33	0.03	2.1%	0.06	4.8%	0.06	5.2%	0.09	7.4%
EDTA K2 3	80	1.44	0.03	2.5%	0.06	4.8%	0.06	4.7%	0.09	7.2%
EDTA K3 3	80	1.35	0.07	6.2%	0.07	5.4%	0.05	4.5%	0.11	9.4%
Sodium Citrate 3	80	1.44	0.04	3.1%	0.05	4.2%	0.06	5.2%	0.09	7.4%
Sodium Heparin 3	80	1.36	0.02	2.1%	0.06	5.1%	0.06	4.7%	0.09	7.2%
Lithium Heparin 3	80	1.35	0.05	4.1%	0.07	5.8%	0.05	4.3%	0.10	8.3%
ACD 3	80	1.47	0.04	3.5%	0.10	8.4%	0.06	5.1%	0.13	10.5%

NA : Not Applicable

[1] Within Run: variability of the assay performance from replicate to replicate

[2]Between Run: variability of the assay performance from Run to Run

[3]Between Day: variability of the assay performance from Day to Day

[4]Total :total variability of the assay performance includes within run, between run and between day.

Reproducibility Study:

A 6 member panel consisting of diluted plasma specimens (negative and different levels of positive) was tested in triplicate, once a day for 3 days on 3 lots* of MONOLISA™ Anti-HAV IgM EIA at 3 separate clinical trial sites.
Each panel was coded with a different number on each day tested in order to blind the operator to the expected value of the sample.
** :3 different lots were used at the Bio-Rad site and 2 lots were used on each of the external sites.*
The data from all reagent lots and sites were combined to obtain standard deviation (SD) and percent coefficient of variation (CV) for within run, between day, between lot, between site and total variance.
The data were analyzed according to the principles described in the Clinical Laboratory Standards Institute guidance EP5-A2, revised November 2004 and ISO/TR 22971:2005. The PROC GLM procedure in SAS® was used to estimate the variance components of the model. The model was y = site + lot (site) + day (lot site) + error.
The summaries are shown in the following tables:

Table 17: MONOLISA™ Anti-HAV IgM EIA Reproducibility Results by Panel Member Signal to Cutoff (S/CO)

Test site	Panel Member	N	Mean S/CO	Within Run[1]		Between Day[2]		Between Lot[3]		Total[4]	
				SD	%CV	SD	%CV	SD	%CV	SD	%CV
Site #1	P1	18	0.05	0.03	74.6	0[5]	0	0[5]	0	0.03	74.6
	P2	18	0.69	0.03	4.7	0.06	8.1	0[5]	0	0.06	9.4
	P3	18	1.10	0.04	3.6	0.07	6.7	0[5]	0	0.08	7.6
	P4	18	1.69	0.05	2.7	0.13	7.6	0[5]	0	0.14	8.1
	P5	18	3.26	0.07	2.2	0.03	1.1	0[5]	0	0.08	2.4
	P6	18	4.19	0.19	4.6	0.00	0.0	0.05	1.1	0.20	4.7
Site#2	P1	18	0.06	0.00	6.4	0.01	12.2	0.00	6.7	0.01	15.4
	P2	18	0.82	0.02	2.8	0.06	7.0	0[5]	0	0.06	7.5
	P3	18	1.27	0.05	3.8	0.08	6.6	0.11	8.6	0.15	11.5
	P4	18	2.01	0.12	5.7	0.14	7.0	0[5]	0	0.18	9.1
	P5	18	3.8	0.15	4.0	0.20	5.2	0[5]	0	0.25	6.6
	P6	18	4.8	0.14	2.8	0.38	7.9	0[5]	0	0.40	8.3
Site #3	P1	27	0.04	0.00	6.7	0.01	13.0	0.00	11.7	0.01	18.7
	P2	27	0.71	0.02	3.3	0.03	4.0	0.04	6.1	0.06	8.0
	P3	27	1.12	0.05	4.3	0.02	2.1	0.09	7.7	0.10	9.1
	P4	27	1.77	0.06	3.4	0.08	4.3	0.10	5.8	0.14	8.0
	P5	27	3.26	0.09	2.8	0.10	3.1	0.13	4.0	0.19	5.8
	P6	27	3.93	0.10	2.6	0.10	2.5	0.20	5.1	0.25	6.3

[1] Within Run: variability of the assay performance from replicate to replicate
[2]Between Day: variability of the assay performance from Day to Day
[3]Between Lot: variability of the assay performance from Lot to Lot
[4]Total: total variability of the assay performance includes within run, between day and between lot.
[5] Negative variances were rounded to zero, per statistical convention.

Table 18: MONOLISA™ Anti-HAV IgM EIA Reproducibility summary by Panel Member Signal to Cutoff (S/CO).

Panel Member	N	Mean S/CO	Within Run[1]		Between Day[2]		Between Lot[3]		Between Site[5]		Total[4]	
			SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV
P1	63	0.05	0.02	37.8	0.00	0.0	0.00	8.1	0.01	19.6	0.02	43.3
P2	63	0.74	0.03	3.6	0.05	6.4	0.02	2.6	0.06	8.0	0.08	11.1
P3	63	1.16	0.05	3.9	0.06	5.3	0.08	6.8	0.07	5.8	0.13	11.1
P4	63	1.82	0.08	4.2	0.11	6.3	0.05	3.0	0.15	8.1	0.21	11.5
P5	63	3.41	0.11	3.0	0.13	3.7	0.09	2.5	0.29	8.5	0.35	10.1
P6	63	4.25	0.14	3.3	0.21	5.0	0.14	3.2	0.43	10.1	0.52	12.2

[1] Within Run: variability of the assay performance from replicate to replicate
[2]Between Day: variability of the assay performance from Day to Day
[3]Between Lot: variability of the assay performance from Lot to Lot
[5]Between site: variability of the assay performance from Site to Site
[4]Total :total variability of the assay performance includes within run, between day between lot and between Site.

Reproducibility study on Negative and Positive Controls:

The negative and positive controls were tested in triplicate, once a day by 3 different operators for 3 days. The data were analyzed according to the principles described in the Clinical Laboratory Standards Institute guidance EP5-A2, revised November 2004 and ISO/TR 22971:2005.

Table 19 : MONOLISA™ Anti-HAV IgM EIA Control Reproducibility summary by Operator by Signal to Cutoff (S/CO).

Samples	N	Mean	Within Run[1]		Between Day[2]		Between Operator [3]		Total[4]	
			SD	%CV	SD	%CV	SD	%CV	SD	%CV
Negative Control	27	0.06	0.02	24.2	0.02	23.3	0[5]	0	0.02	N/A
Positive Control	27	1.91	0.08	4.1	0.02	0.9	0[5]	0	0.08	4.17

1 Within Run: variability of the assay performance from replicate to replicate
2 Between Day: variability of the assay performance from Day to Day
3 Between Operator: variability of the assay performance from Operator to Operator
4Total: total variability of the assay performance includes within run, between day and between Operator.
5: Negative variances were rounded to zero, per statistical convention.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
2098 Gaither Road
Rockville MD 20850

MAY - 3 2007

Manuela Kaul
RA-Manager
Bio-Rad France
3, Boulevard Raymond Poincaré
92430 Marnes-la-Coquette, France

Re: k063319
Trade/Device Name: MONOLISA™ Anti-HAV IgM EIA
Regulation Number: 21 CFR 866.3310
Regulation Name: Hepatitis A Virus (HAV) Serological Reagents
Regulatory Class: Class II
Product Code: LOL
Dated: March 21, 2007
Received: April 3, 2007

Dear Ms. Kaul:

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.

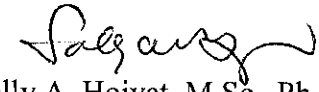
If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to such additional controls. Existing major regulations affecting your device can be found in Title 21, Code of Federal Regulations (CFR), Parts 800 to 895. In addition, FDA may publish 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); and good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820).

This letter will allow you to begin marketing your device as described in your Section 510(k) premarket notification. The FDA finding of substantial equivalence of your device to a legally marketed predicate device results in a classification for your device and thus, permits your device to proceed to the market.

If you desire specific information about the application of labeling requirements to your device, or questions on the promotion and advertising of your device, please contact the Office of In Vitro Diagnostic Device Evaluation and Safety at (301) 594-3084. Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21CFR Part 807.97). Other general information on your responsibilities under the Act may be obtained from the Division of Small Manufacturers, International and Consumer Assistance at its toll-free number (800) 638-2041 or (301) 443-6597 or at its Internet address http://www.fda.gov/cdrh/dsma/dsmamain.html.

Sincerely yours,



Sally A. Hojvat, M.Sc., Ph.D.
Director
Division of Microbiology Devices
Office of *In Vitro* Diagnostic Devices
Evaluation and Safety
Center for Devices and
Radiological Health

Enclosure

INDICATIONS FOR USE STATEMENT

510(k) Number : K 063319

Device Name: MONOLISA™ Anti-HAV IgM EIA

Indications for Use:

The MONOLISA™ Anti-HAV IgM EIA is an *in vitro* enzyme immunoassay kit intended for use in the qualitative detection of IgM antibodies to Hepatitis A virus (anti-HAV IgM) in human (adult and pediatric) serum or plasma (EDTA, Heparin, Citrate, ACD). This assay is indicated for testing specimens from individuals who have signs and symptoms consistent with acute Hepatitis. Assay results, in conjunction with other serological or clinical information, may be used for the laboratory diagnosis of individuals with acute or recent Hepatitis A.

Assay performance characteristics have not been established for immunocompromised or immunosuppressed patients, and cord blood or neonatal specimens

WARNING :This assay is not intended for screening blood or solid or soft tissue donors.

Prescription Use: ___X___ AND/OR Over-The-Counter Use: _____
(Per 21 CFR 801.109) (Optional Format 1-2-96)

(PLEASE DO NOT WRITE BELOW THIS LINE – CONTINUE ON ANOTHER PAGE IF NEEDED)

Concurrence of CDRH, Office of Device Evaluation (ODE)

Division Sign-Off

Office of In Vitro Diagnostic
Device Evaluation and Safety

510(k) K063319