K991459

MAY 14 1999

May 5, 1999

510 (k) SUMMARY

SUBMITTED BY:

Judith J. Smith
DiaSorin, Inc.
9175 Guilford Rd. Suite 100
Columbia, MD 21046

NAME OF DEVICES:

Trade Name: Copalis® EBV-M Antibody Assay

Common Names/Descriptions: Immunoassay for the Detection of IgM Antibodies to VCA antigen of *Epstein Barr Virus*

Classification Names: EBV Serology Test

PREDICATE DEVICES: Gull Laboratories EBV IgM IFA

DEVICE DESCRIPTION:

INTENDED USE: The Copalis® EBV-M Antibody Assay uses Coupled Particle Light Scattering technology in a microparticle agglutination-based assay for the qualitative detection of IgM antibodies to the EBV VCA antigen. The assay is designed for human serum using the Copalis I® Immunoassay System. The presence of VCA IgM antibodies is used as an aid in the diagnosis of EBV associated mononucleosis when used in conjunction with other EBV serologies in pediatric, adult, transplant donor and transplant recipient populations.

KIT DESCRIPTION: Coupled Particle Light Scattering (Copalis®) technology provides a rapid method for the measurement of antibodies to specific pathogens. The Copalis® EBV-M Antibody Assay is a microparticle agglutination test using the Copalis® light scattering technology. Polystyrene microparticles are coated with synthetic VCA antigen and are contained within a special covered reaction well in the test cup. The dried reagent is reconstituted with a reaction buffer on the instrument at the start of the assay. Patient sample is added to the reaction mixture and incubated for 10 minutes. The presence of IgM antibodies specific to the VCA antigen in the patient sample results in agglutination of the monomer microparticles to form aggregates. The reaction mixture is passed through a flow cell and the instrument uses light scattering technology to measure the monomer concentration. The decrease in the monomer population resulting from agglutination is related to the amount of antibody in the sample. The residual monomer concentration in each reaction mixture is compared to a cutoff values to determine sample reactivity and nonreactivity.

PERFORMANCE DATA:

Clinical Correlation: Fresh (12%) and frozen (88%) samples were analyzed at two clinical laboratories and at DiaSorin. Patients from the disease states defined below and representing the eastern, midwestern and western United States were tested.

The screening population is a group of samples from patients suspected of disease. The samples were chosen for each disease state population based upon comparison to expected patterns of serological testing results for the 4 EBV markers (EBV VCA IgG and IgM, EBNA, and EA), and for primary infection, heterophile test . For primary infection, the first level of inclusion/exclusion was based on IFA results for VCA IgM, VCA IgG and EBNA. Samples with positive results for the VCA antigen and negative results for the EBNA were included and further examined. The next level of inclusion/exclusion criteria was based upon the heterophile results. A positive result is expected for this test in acute EBV infection. Samples with positive VCA IgM, VCA IgG, and heterophile test and negative EBNA result were included in the primary infection population. If a negative result was obtained on the heterophile test, the results of the EA IFA test were examined. A positive EA IFA resulted in inclusion of the sample. A negative EA IFA result resulted in exclusion of the sample. A summary of the expected marker patterns for the EBV markers is summarized below.

Summary of Expected Patterns for EBV Antigen Reactivity

Antibody	Seronegative	Primary	Reactivated	Past
IgM anti-VCA	-	+	-	-
IgG anti-VCA	-	+	+	+
Anti EBNA	-	-	+	-/+
Anti-EA	-	+	+	+
Heterophile	-	+	N/A	N/A

The age of the primary disease population varied from 1 to 48 years of age (mean and median age: 22 years old). The age of the patients with reactivated disease varied from 3 to 68 (mean: 27, median 23). The age range of the seronegative group was 1 to 74 (mean: 14, median: 12). The Copalis EBV-M Antibody Assay was compared to expected marker patterns in the defined disease states and separated into adult and pediatric populations. The results of these studies are summarized below with the 95% confidence intervals (95% CI). Equivocal results by Copalis or IFA or non-specific staining by IFA were not included in the calculations.

Primary Disease State Population

Expected Pattern	Heterophile +;VCA IgM +; VCA IgG +; EBNA –; EA +	
	Pediatric	Adult
Copalis®/IFA Result*	EBV VCA IgM	EBV VCA IgM
Sensitivity (95% CI)	12/12 = 100% (73.5 – 100.0%)	59/59* = 100.0% (93.9 – 100.0%)
Specificity	NA	NA
Agreement	12/12 = 100%	59/59 = 100.0%
Prevalence Copalis®	12/12 = 100%	59/61 = 96.7%
Prevalence IFA	12/12 = 100%	61/61 = 100.0%

*(2 Copalis equivocal/IFA positive)

Reactivated Disease State Population

Expected Pattern	VCA IgM –[a]; VCA IgG +; EBNA +; EA +
Copalis®/IFA Result[b]	EBV VCA IgM
Sensitivity	NA
Specificity (95% CI)	29/39 = 74.4% (57.8 – 87.0%)
Agreement	29/39 = 74.4%
Prevalence Copalis®	10/39 = 25.6%
Prevalence IFA[c]	0/39 = 0%

[a] Literature reports show that IgM can be present in reactivated disease[7]
[b] 2 Copalis equivocal/IFA negative, 1 Copalis equivocal/IFA non-specific staining (nss); 1 Copalis negative/IFA nss
[c] Prevalence of IFA before exclusion was 4/50 = 8%

EBV Screening Population

Expected Pattern	VCA IgM -/+ (Primary, Reactiviated, Seronegative, or Past	
	Pediatric	Adult
Copalis®/IFA* Result	EBV VCA IgM	EBV VCA IgM
Sensitivity (95% CI)	N/A	N/A
Specificity (95% CI)	13/13 = 100.0% (75.. – 100.0%)	25/28* = 89.3% (71.8 – 97.7)
Agreement	13/13 = 100.0%	25/28 = 89.3%
Prevalence Copalis®	0/14 = 0.0%	3/29 = 10.3%
Prevalence IFA	0/14 = 0.0%	0/29 = 0.0%

*(1 Copalis equivocal/IFA negative)

SeroNegative Population

Expected Pattern	VCA IgM -; VCA IgG -; EBNA -; EA -	
	Pediatric	Adult
Copalis®/IFA* Result	EBV VCA IgM	EBV VCA IgM
Sensitivity (95% CI)	NA	NA
Specificity (95% CI)	40/42 = 95.2% (83.8 – 99.4%)	8/8 = 100% (63.1 – 100.0%)
Agreement	40/42 = 95.2%	8/8 = 100.0%
Prevalence Copalis®	2/42 = 4.8%	0/8 = 0%
Prevalence IFA	0/42 = 0%	0/8 = 0%

*(no equivocal results)

Apparently Healthy Adult Population

Expected Pattern	-
Copalis®/IFA* Result	EBV VCA IgM
Sensitivity	NA
Specificity (95% CI)	91/97 = 93.8% (82.0 – 97.8%)
Agreement	91/97 = 93.8%
Prevalence Copalis®	6/97 = 6.2%
Prevalence IFA	0/97 = 0%

*(5 Copalis equivocal/IFA negative)

Transplant Recipients (Reactivated)

Copalis®/IFA* Result	
Sensitivity	NA
Specificity (95% CI)	30/41 = 73.2% (57.1 – 85.8%)
Agreement	3/42 = 71.4%
Prevalence Copalis®	10/42 = 23.8%
Prevalence IFA	4/46 = 8.7%

*(3 Copalis equivocal/IFA positive; 3 Copalis equivocal/IFA negative; 1 Copalis negative/IFA nss; 1 Copalis equivocal/IFA nss)

Transplant Donors

Copalis®/IFA* Result	
Sensitivity	NA
Specificity (95% CI)	46/50 = 92.0% (80.8 – 97.8%)
Agreement	56/50 = 92.0%
Prevalence Copalis®	4/46 = 8.7%
Prevalence IFA	0/53 = 0%

*(4 Copalis equivocal/IFA negative)

The Copalis® EBV-M Antibody Assay identified all patients with primary disease. It gave equivalent or better prevalence results than IFA in defined disease states when compared to the literature. Review of the data from serial samples (next section) shows that the Copalis® assay closely matches the expected pattern for the markers in primary infection (acute and convalescent). In the reactivated disease state population, the IFA result was negative in 10 samples in which the Copalis® assay results were positive. Although most tables of marker patterns in defined diseases state that the IgM should be negative in reactivated disease, literature reports show that IgM can be present in reactivated disease. Thus, the presence of IgM in this state is not unexpected.

Serial Sample Studies

Seven serial sample panels were evaluated by Copalis® EBV-M Antibody Assay and by IFA. The panels were also tested for EBV VCA, EBNA and EA antibodies. The samples ranged from 2 to 960 days following onset of illness. The Copalis® assay was equivalent to IFA in the detection of marker patterns. In 3 of 7 patients, the Copalis® EBV-M assay detected the presence of IgM for more days than detected by IFA. In one sample, the Copalis® EBV-M assay and IFA detected IgM for the same number of days. The assay CI's show changes in IgM antibody titers more clearly than IFA. When reviewing all 4 markers together, in 6/7 patients the Copalis® assay pattern was more consistent with disease than IFA.

Reproducibility: Reproducibility studies were performed at the 3 sites using one lot of tests. Assay reproducibility was determined by testing 6 samples that spanned the range of the assay components CTRs. Samples were tested in duplicate once a day for 5 days. The results are summarized below.

REPRODUCIBILITY RESULTS FOR COPALIS® EBV-M ANTIBODY ASSAY - COMBINED SITES

Sample	Mean mg/dL	Within Run %CV	%CV
Neg Control	0.90	--	1.3%
Pos Control	2.25	--	10.7%
RP 1	1.87	7.8%	12.6%
RP 2	0.89	2.0%	1.7%
RP 3	5.06	8.4%	19.3%
RP 4	0.90	0.9%	1.4%
RP 5	5.53	19.4%	26.7%
RP 6	1.35	7.6%	13.2%
N for RP	30	30	30

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

MAY 14 1999

DiaSorin
c/o Carole Stamp
TUV Product Service Inc.
1775 Old Highway 8 NW
Suite 104
New Brighton, MN 55112

Re: K991459
Trade Name: Copalis® EBV-M Assay
Regulatory Class: I
Product Code: LJN
Dated: May 7, 1999
Received: May 10, 1999

Dear Ms. Stamp:

We have reviewed your Section 510(k) notification of intent to market the device referenced above and we 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). 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 (Premarket Approval), it may be subject to such additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 895. A substantially equivalent determination assumes compliance with the Current Good Manufacturing Practice requirements, as set forth in the Quality System Regulation (QS) for Medical Devices: General regulation (21 CFR Part 820) and that, through periodic QS inspections, the Food and Drug Administration (FDA) will verify such assumptions. Failure to comply with the GMP regulation may result in regulatory action. In addition, FDA may publish further announcements concerning your device in the Federal Register. Please note: this response to your premarket notification submission does not affect any obligation you might have under sections 531 through 542 of the Act for devices under the Electronic Product Radiation Control provisions, or other Federal laws or regulations.

Under the Clinical Laboratory Improvement Amendments of 1988 (CLIA-88), this device may require a CLIA complexity categorization. To determine if it does, you should contact the Centers for Disease Control and Prevention (CDC) at (770)488-7655.

This letter will allow you to begin marketing your device as described in your 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 advice for your device on our labeling regulation (21 CFR Part 801 and additionally 809.10 for in vitro diagnostic devices), please contact the Office of Compliance at (301) 594-4588. Additionally, for questions on the promotion and advertising of your device, please contact the Office of Compliance at (301) 594-4639. Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21 CFR 807.97). Other general information on your responsibilities under the Act may be obtained from the Division of Small Manufacturers Assistance at its toll free number (800) 638-2041 or at (301) 443-6597 or at its internet address "http://www.fda.gov/cdrh/dsmamain.html"

Sincerely yours,

Steven Gutman

Steven I. Gutman, M.D., M.B.A.
Director
Division of Clinical Laboratory Devices
Office of Device Evaluation
Center for Devices and Radiological Health

Enclosure

INDICATIONS FOR USE

510(k) Number (if known): K991459

Device Name: Copalis® EBV-M Assay

Indications For Use: The Copalis® EBV-M Assay uses Coupled Particle Light Scattering technology in a microparticle agglutination-based assay for the qualitative detection of IgM antibodies to the EBV VCA antigen. The assay is designed for human serum using the Copalis® I Immunoassay System. The presence of VCA IgM antibodies is used as an aid in the diagnosis of EBV associated mononucleosis when used in conjunction with other EBV serologies in pediatric, adult, transplant donor and transplant recipient populations.

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Concurrence of CDRH, Office of Device Evaluation (ODE)

Woody Dufour

(Division Sign-Off)
Division of Clinical Laboratory Devices
510(k) Number K991459

Prescription Use X OR Over-The-Counter Use _____
(Per 21 CFR 801.109)

(Optional Format 1-2-96)