K991660

JUN 4

May 25, 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® Multiplex EBV Antibody Assay

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

Classification Names: EBV Serology Test

PREDICATE DEVICES:

Gull Laboratories EBV IgG IFA
Gull Laboratories EBV-NA IFA
Gull Laboratories EBV-EA IFA

DEVICE DESCRIPTION:

INTENDED USE: The Copalis® Multiplex EBV Antibody Assay uses Coupled Particle Light Scattering technology in a microparticle agglutination-based assay for the qualitative or semi-quantitative detection of antibodies to EBV VCA (total antibodies), EBNA (IgG), and EA (IgG and IgM) antigens. The assay is designed for human serum using the Copalis® I Immunoassay System. The presence of VCA, EBNA and EA 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. The disease state distinction is made based on the antibody pattern of reactivity. When evaluating properly paired sera, the results of these assays are used to demonstrate seroconversion or significant change in antibody titer as evidence of recent infection. Both specimens should be tested simultaneously.

KIT DESCRIPTION: Coupled Particle Light Scattering (Copalis®) technology provides a rapid method for the measurement of antibodies to specific pathogens. The Copalis® Multiplex EBV Antibody Assay is a microparticle agglutination test using the Copalis® light scattering technology. Polystyrene microparticles of 3 sizes are coated with VCA synthetic peptide, EBNA recombinant antigen or EA recombinant 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 antibodies specific to EBV antigens 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 value to determine sample reactivity and nonreactivity.

PERFORMANCE DATA:

Clinical Correlation: Fifty fresh (12%) and 373 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 components of the Copalis Multiplex EBV Antibody Assay were 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 - Adult

Expected Pattern[4]	+	-	+
Copalis®/IFA	**VCA**	**EBNA[a]**	**EA vs Heterophile/IFA[b]**
Relative Sensitivity (95% CI)	61/61 = 100.0% (94.1 – 100%)	N/A	56/59 = 94.9% (85.8 – 98.9%)
Relative Specificity (95% CI)	N/A	56/59 = 94.9% (85.8 – 98.9%)	N/A
Agreement with IFA	61/61 = 100.0%	56/59 = 94.9%	56/59 = 94.9%
Prevalence Copalis®	61/61 = 100.0%	3/61 = 4.9%	56/59 = 94.9%
Prevalence IFA	61/61 = 100.0%	0/59 = 0%	13/54 = 24.1%
Prevalence Heterophile	N/A	N/A	56/61 = 91.8%
Prevalence HtphI/IFA	N/A	N/A	61/61 = 100%

[a] 2 Copalis negative/IFA equivocal [b] 2 Copalis equivocal/IFA positive

Primary Disease State Population - Pediatric

Expected Pattern[4]	+	-	+
Copalis®/IFA	**VCA**	**EBNA**	**EA vs Heterophile/IFA**
Relative Sensitivity (95% CI)	12/12 = 100% (73.5 – 100.0%)	N/A	12/12 = 100.0% (73.5 – 100.0%)
Relative Specificity (95% CI)	N/A	6/12 = 50.0% (21.1 – 78.9%)	N/A
Agreement with IFA	12/12 = 100.0%	6/6 = 50.0%	12/12 = 100.0%
Prevalence Copalis®	12/12 = 100.0%	6/12 = 50.0%	12/12 = 100.0%
Prevalence IFA	12/12 = 100.0%	0/12 = 0%	8/11[c] = 32.3%
Prevalence Heterophile	N/A	N/A	8/12 = 66.6%
Prevalence Htphl/IFA	N/A	N/A	12/12 = 100%

[c] 1 Copalis + /IFA equivocal

Reactivated Disease State Population

Expected Pattern	+	+	+
Copalis®/IFA	**VCA**	**EBNA[d]**	**EA[e]**
Relative Sensitivity (95% CI)	43/43 = 100.0% (91.8 – 100%)	35/39 = 89.7% (75.8 – 97.1%)	39/39 = 100.0% (91.0 – 100%)
Relative Specificity	N/A	N/A	N/A
Agreement	43/43 = 100.0%	35/39 = 89.7%	39/39 = 100.0%
Prevalence Copalis®	43/43 = 100.0%	39/43 = 90.7%	42/42 = 100%
Prevalence IFA	43/43 = 100.0%	39/39 = 100%	40/40 = 100%

[d] 4 Copalis positive/IFA equivocal [e] 1 Copalis equivocal/IFA positive; 3 Copalis positive/IFA equivocal

EBV Screening Population - Adult

Copalis®/IFA	VCA	EBNA	EA[f]
Relative Sensitivity (95% CI)	26/27 = 96.8% (83.3 – 99.9%)	23/25 = 92.0% (74.0 – 99.0%)	15/18 = 83.3% (58.6 – 96.4%)
Relative Specificity (95% CI)	2/2 = 100.0% (15.8 – 100.0%)	3/4 = 75.0% (19.4 – 99.4%)	7/9= 77.8% (40.0 – 97.2%)
Agreement with IFA	28/29 = 96.6%	26/29 = 89.7	22/27 = 81.5%
Prevalence Copalis®	26/29 = 89.7%	24/29 = 82.9%	17/29 = 58.6%
Prevalence IFA	27/29 = 93.1%	25/29 = 86.2%	18/29 = 62.1%

[f] 1 Copalis equivocal/IFA positive; 1 Copalis equivocal/IFA negative

EBV Screening Population - Pediatric

Copalis®/IFA	VCA	EBNA	EA
Relative Sensitivity (95% CI)	5/6 = 83.3% (35.9 – 99.6%)	6/6 = 100.0% (54.1 – 100.0%)	4/6 = 66.7% (22.3 – 95.7%)
Relative Specificity (95% CI)	6/7 = 85.7% (42.1 – 99.6%)	7/7 = 100.0% (59.0 – 100.0%)	6/7 = 85.7% (42.1 – 99.6%)
Agreement with IFA	11/13 = 84.6%	13/13 = 100.0%	10/13 = 76.9%
Prevalence Copalis®	6/13 = 46.2%	6/13 = 46.2%	5/13 = 38.5%
Prevalence IFA	6/13 = 46.2%	6/13 = 46.2%	6/13 = 46.2%

Seronegative Population - Adult

Expected Pattern	-	-	-
Copalis®/IFA	**VCA**	**EBNA**	**EA[g]**
Relative Sensitivity (95% CI)	N/A	N/A	N/A
Relative Specificity (95% CI)	5/8 = 62.5% (24.5 – 91.5%)	8/8 = 100.0% (63.1 – 100.0%)	7/7 = 100% (59.0 – 100.0%)
Agreement	5/8 = 62.5%	8/8 = 100.0%	7/7 = 100.0%
Prevalence Copalis®	3/8 = 37.5%	0/8 = 0%	0/7 = 0%
Prevalence IFA	0/8 = 0%	0/8 = 0%	0/7 = 0%

[g] 1 Copalis negative/IFA non-specific staining

Seronegative Population - Pediatric

Expected Pattern	-	-	-
Copalis®/IFA	**VCA[h]**	**EBNA**	**EA[i]**
Relative Sensitivity (95% CI)	N/A	N/A	N/A
Relative Specificity (95% CI)	29/34 = 85.3% (68.9 – 95.0%)	40/42 = 95.2% (83.8 – 99.4%)	34/39 = 87.2% (72.6 – 95.7%)
Agreement	29/34 = 85.3%	40/42 = 95.2%	34/39 = 87.2%
Prevalence Copalis®	5/36 = 13.9%	2/42 = 4.8%	5/39 = 12.8%
Prevalence IFA	0/40 = 0%	0/42 = 0%	0/42 = 0%

[h] 6 Copalis equivocal/IFA negative; 2 Copalis negative/IFA equivocal
[i] 3 Copalis equivocal/IFA negative

Apparently Healthy Population

Copalis®/IFA	VCA[j]	EBNA	EA[k]
Relative Sensitivity (95% CI)	94/98 = 95.9% (89.9 – 98.9%)	95/102 = 93.1% (86.4 – 97.2%)	26/65 = 40.0% (28.0 – 52.9%)
Relative Specificity (95% CI)	N/A	N/A	25/31 = 80.6% (62.5 – 92.6%)
Agreement with IFA	94/98 = 95.9%	95/102 = 93.1%	51/96 = 53.1%
Prevalence Copalis®	94/98 = 95.9%	95/102 = 93.1%	33/98 = 33.7%
Prevalence IFA	102/102 = 100%	102/102 = 100%	69/100 = 69%

[j] 4 Copalis equivocal/IFA positive
[k] 4 Copalis equivocal/IFA positive; 1 Copalis positive/IFA equivocal; 1 Copalis negative/IFA equivocal

Transplant Recipients

Copalis®/IFA	VCA	EBNA[l]	EA[m]
Relative Sensitivity (95% CI)	48/48 = 100% (92.6 – 100%)	35/40 = 87.5% (73.2 – 95.8%)	44/44 = 100% (92.0 – 100%)
Relative Specificity (95% CI)	N/A	3/3 = 100.0% (29.2 – 100%)	N/A
Agreement with IFA	48/48 = 100.0%	38/43 = 88.4%	45/44 = 100%
Prevalence Copalis®	48/48 = 100%	40/48 = 83.3%	47/48 = 97.9%
Prevalence IFA	48/48 = 100%	40/48 = 83.3%	45/48 = 93.8

[l] 5 Copalis positive/IFA equivocal
[m] 1 Copalis equivocal/IFA positive; 3 Copalis positive/IFA nss

Transplant Donors

Copalis®/IFA	VCA[n]	EBNA	EA[o]
Relative Sensitivity (95% CI)	50/50 = 100.0% (92.9 – 100%)	50/53 = 94.3% (84.3 – 98.8%)	20/43 = 46.5% (31.2 – 62.3%)
Relative Specificity (95% CI)	N//A	N/A	4/4 = 100.0% (39.8 – 100.0%)
Agreement with IFA	50/50 = 100.0%	50/50 = 94.3%	24/47 = 51.1%
Prevalence Copalis®	50/53 = 94.3%	50/50 = 94.3%	21/53 = 39.6%
Prevalence IFA	53/53 = 100.0%	53/53 = 100.0%	47/51 = 92.9%

[n] 3 Copalis positive/IFA equivocal
[o] 4 Copalis equivocal/IFA positive; 1 Copalis positive/ IFA nss; 1 Copalis negative/IFA nss

When viewed as a panel of results, the Copalis® Multiplex EBV Antibody Assay gives equivalent performance to IFA. Prevalence by Copalis® Multiplex EBV Antibody Assay components in the defined disease states more closely matches expected prevalences[4] than IFA. This is especially noticeable with EA IFA which shows poor correlation to disease state or heterophile result. The EA IFA prevalence in the primary infection population was lower than expected and in the apparently healthy population was higher than expected. The same pattern was seen in the recipient/donor population study. The poor agreement between the EA component of the Copalis® assay and EA IFA is also due to the EA IFA results that do not correlate to clinical state. Copalis® Multiplex EBV EA component detects EA(D) whereas EA IFA detects both EA(D) and EA(R). This could account for the large number of apparently false positive EA IFA results since EA(D) is present only in primary infection and EA(R) is present long after recovery. Regarding EBNA comparison, it has been reported that recombinant EBNA assays are more sensitive to EBNA IgG 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, Combined Sites – VCA

Sample	Mean CI	Within Run %CV	Total %CV
Neg Control	0.78	--	3.9%
Low Pos Control	2.17	--	12.3%
High Pos Control	11.23	--	21.8%
RP 1	0.81	1.9%	6.4%
RP 2	0.81	2.0%	6.1%
RP 3	13.78	7.3%	15.5%
RP 4	34.89	18.5%	18.7%
RP 5	5.39	8.6%	12.5%
RP 6	1.05	2.8%	7.3%
RP 7	1.35	7.6%	13.3%

Reproducibility Results, Combined – EBNA

Sample	Mean CI	Within Run %CV	Total %CV
Neg Control	0.82	--	2.8%
Low Pos Control	1.80	--	7.3%
High Pos Control	8.95	--	14.5%
RP 1	0.84	3.1%	4.9%
RP 2	0.85	2.6%	4.2%
RP 3	0.92	2.6%	6.9%
RP 4	31.36	13.9%	13.0%
RP 5	2.10	8.2%	10.2%
RP 6	60.20	13.8%	18.0%
RP 7	2.65	9.7%	12.8%

Reproducibility Results, Combined –EA

Sample	Mean CI	Within Run %CV	Total %CV
Neg Control	0.84	--	5.4%
Low Pos Control	1.83	--	8.7%
High Pos Control	7.37	--	19.5%
RP 1	0.86	1.9%	6.1%
RP 2	0.87	0.8%	5.9%
RP 3	16.68	9.1%	23.4%
RP 4	2.18	8.6%	22.3%
RP 5	5.50	9.0%	16.3%
RP 6	0.99	4.0%	12.4%
RP 7	0.96	4.7%	10.4%

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

JUN 4 1999

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

Re: K991660
Trade Name: Copalis® Multiplex EBV Antibody Assay
Regulatory Class: I
Product Code: LSE
Dated: May 27, 1999
Received: May 28, 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): not known

Device Name: Copalis® Multiplex EBV Antibody Assay

Indications For Use: The Copalis® Multiplex EBV Antibody Assay uses Coupled Particle Light Scattering technology in a microparticle agglutination-based assay for the qualitative or semi-quantitative detection of antibodies to EBV VCA (total antibodies), EBNA (IgG), and EA (IgG and IgM) antigens. The assay is designed for human serum using the Copalis® I Immunoassay System. The presence of VCA, EBNA and EA 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. The disease state distinction is made based on the antibody pattern of reactivity. When evaluating properly paired sera, the results of these assays are used to demonstrate seroconversion or significant change in antibody titer as evidence of recent infection. Both specimens should be tested simultaneously.

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Concurrence of CDRH, Office of Device Evaluation (ODE)

Woody Dubois

(Division Sign-Off)
Division of Clinical Laboratory Devices
510(k) Number K991660

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

(Optional Format 1-2-96)