

**510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY**

A. 510(k) Number: K081687

B. Purpose for Submission: Initial Premarket Notification

C. Measurand: Anti-HSV 2 IgG Antibodies

D. Type of Test: Qualitative, Chemiluminescent Immunoassay (CLIA)

E. Applicant: *Diasorin, Inc.*

F. Proprietary and Established Names: LIAISON[®] HSV-2 Type Specific IgG

G. Regulatory Information:

| Product Code | Classification | Regulation Section | Panel |
|---|----------------|--------------------|-------------------|
| MYF & JJX : Herpes Simplex Virus-2 (IgG Antibody) | Class II | 21CFR 866.3305 | Microbiology (83) |

H. Intended Use:

The LIAISON[®] HSV-2 Type Specific IgG assay is a chemiluminescent immunoassay (CLIA) technology to be used with the LIAISON[®] Analyzer for the qualitative determination of type specific IgG antibodies to Herpes simplex virus Type 2 (HSV-2) in human serum. The assay is indicated for testing sexually active adults or expectant mothers to aid in the presumptive diagnosis of HSV-2 infection.

The LIAISON[®] HSV-2 Type Specific IgG assay has not been established for use in the pediatrics population, for neonatal screening, or for testing immunocompromised or immunosuppressed patients. The assay is neither FDA cleared nor approved for testing blood or plasma donors.

Caution: U.S. Federal Law restricts this device to sale by or on the order of a physician.

3) Special conditions for use statement(s): For Prescription use only

4) Special instrument requirements: LIAISON[®] Analyzer with Chemiluminescence reader

I. Device Description: The LIAISON[®] HSV-2 type specific IgG assay is an *in vitro* diagnostic device consisting of reagents provided within a plastic container/kit called the Reagent Integral. The reagent integral kit contains magnetic particles, calibrators, specimen diluent, and conjugate for 100 tests. Controls are required to run the assay and

sold separately. The LIAISON[®] HSV-2 IgG immunoassay is performed on the LIAISON[®] Analyzer (Model 15970) that was cleared previously (K052499). The magnetic particles are beads coated with HSV-2 IgG2 recombinant antigen. During first incubation, the magnetic particles are incubated with serum to capture IgG antibodies to HSV-2. During the second incubation, HSV-2 IgG and antigen complex bound to the magnetic particles are mixed with the detector antibody conjugate. The detector antibody conjugate is mouse monoclonal to human IgG conjugated to an isoluminol derivative. The unbound material is removed with a wash cycle after each incubation. Subsequently, a flash chemiluminescence reaction is induced by adding the starter reagents. The light signal, and hence the amount of isoluminol-antibody conjugate, is measured by a photomultiplier as relative light units (RLU) that is indicative of IgG anti-HSV-2 present in the samples.

J. Substantial Equivalence Information:

a) Predicate device name (s):

The HerpeSelect[®] 1 and 2 immunoblot

b) Predicate Numbers (s):

K000238

Comparison with predicate:

| Similarities | | |
|---------------------|---|---|
| Item | LIAISON[®] HSV-2 Specific IgG Assay | FOCUS Diagnostic HSV 1 and 2 Immunoblot IgG |
| Intended Use | The LIAISON [®] HSV-2 Type Specific IgG assay is a chemiluminescent immunoassay (CLIA) technology to be used with the LIAISON [®] Analyzer for the qualitative determination of type specific IgG antibodies to Herpes simplex virus Type 2 (HSV-2) in human serum. The assay is indicated for testing sexually active adults or expectant mothers to aid in the presumptive diagnosis of HSV-2 infection | Focus Diagnostics' HerpeSelect [®] 1 and 2 Immunoblot IgG test is intended for qualitatively detecting the presence or absence of human IgG class antibodies to HSV-1 and HSV-2 in human sera. The test is indicated for testing sexually active adults or pregnant women for aiding in the presumptive diagnosis of HSV-1 and HSV-2 infection. The predictive value of a positive or negative result depends on the population's prevalence and the pretest likelihood of HSV-1 |

| | | |
|----------------------------|--|--|
| | Specific IgG assay has not been established for use in the pediatrics population, for neonatal screening, or for testing immunocompromised or immunosuppressed patients. The assay is neither FDA cleared nor approved for testing blood or plasma donors. | and HSV-2 infection. The performance of this assay has not been established for use in a pediatric population, for neonatal screening, for testing of immunocompromised patients, for use by a point of care facility or for use with automated equipment. |
| Controls | 2 (Negative and Positive) | 2 (Negative and Positive) |
| Sample Matrix | Serum | Serum |
| Reagent Storage | 2-8°C, On-board or in Refrigerator | 2-8°C Refrigerator only |
| Differences | | |
| Item | LIAISON® HSV-2 Specific IgG Assay | FOCUS Diagnostic HSV 1 and 2 Immunoblot IgG |
| Type of Assay | Indirect Chemiluminescence Immunoassay | Immunoblot |
| Sample Handling/processing | Automated | Manual |
| Cutoff | Index Value 1.0 | Dark band on the Cutoff/Positive control strip |
| Calibrators | Two | Cutoff/Positive control |
| Detector | Mouse Monoclonal antibody to human IgG conjugated to an isoluminol derivative | Alkaline phosphate-conjugated goat antihuman IgG |
| Capture Reagent | Magnetic particles coated with HSV-2 IgG2 recombinant antigen | A blend of HSV-1 and HSV-2 native virus antigens, a recombinant gG1 and a recombinant gG2 antigen |
| Equivocal zone | Index Value of >0.90 and <1.1 | Positive anti-human serum, positive HSV common antigen, negative gG-1 and gG-2 |
| Unit of Measure | Index | Positive or Negative reading |
| Measurement System | Photomultiplier (flash chemiluminescence reader) | Visual manual reading |
| Total incubation | 35 minutes | 2 hours 20 minutes |

K. Standard/Guidance Document Referenced (if applicable):

1. Class II Special Controls Guidance Document: Herpes Simplex Virus Types 1 & 2 Serological Assays, April 3, 2007. <http://www.fda.gov/cdrh/ode/guidance/1305.pdf>

2. Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices, May 11, 2005. <http://www.fda.gov/cdrh/ode/guidance/337.pdf>

L. Test Principle: The method for qualitative determination of specific IgG to HSV-2 is an indirect chemiluminescence immunoassay (CLIA). HSV-2 gG2 recombinant antigen is used for coating magnetic particles (solid phase) and a mouse monoclonal antibody is linked to an isoluminol derivative (isoluminol-antibody conjugate). During the first incubation, HSV-2 antibodies present in calibrators, samples or controls bind to the solid phase. During the second incubation, the antibody conjugate reacts with HSV-2 IgG already bound to the solid phase. After each incubation, the unbound material is removed with a wash cycle. Subsequently, the starter reagents are added and a flash chemiluminescence reaction is thus induced. The light signal, and hence the amount of isoluminol-antibody conjugate, is measured by a photomultiplier as relative light units (RLU) and is indicative of HSV-2 IgG present in calibrators, samples or controls.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

a. *Precision/Reproducibility:* A reproducibility/precision study was conducted at two external and one internal. Each site used a different lot of the LIAISON[®] HSV-2 Type Specific IgG for the study. A coded panel comprised of 8 “engineered” serum samples was prepared by DiaSorin S.p.A. and provided to the sites. The coded panel samples were prepared by spiking positive samples into negative samples to achieve high negative, low positive and high positive results.

The coded panel was tested at all three sites, using four replicates per run in two runs per day with different operators performing each run during five operating days. The mean, standard deviation, and coefficient of variation (%CV) of the results were computed for each of the tested specimens for each of the sites and across sites. The Inter/Intra-operator and Inter/Intra-site reproducibility results are summarized in the following table.

| Sample ID | N | Mean Index | Within run %CV | Between run %CV | Total (by site) %CV | Between site %CV | Overall SD | Overall %CV |
|-----------|-----|------------|----------------|-----------------|---------------------|------------------|------------|-------------|
| NC | 120 | 0.04 | 51.4 | 54.7 | 66.4 | 78.3 | 0.03 | 83.2 |
| PC | 120 | 2.25 | 4.1 | 5.7 | 6.7 | 12.0 | 0.29 | 13.1 |
| HSV2A | 120 | 0.91 | 4.9 | 8.9 | 9.7 | 12.2 | 0.14 | 15.0 |
| HSV2B | 120 | 1.19 | 4.5 | 7.4 | 8.2 | 2.8 | 0.10 | 8.7 |
| HSV2C | 120 | 2.06 | 5.1 | 7.9 | 9.2 | 5.0 | 0.22 | 10.8 |
| HSV2D | 120 | 0.77 | 5.0 | 9.5 | 10.4 | 6.8 | 0.10 | 13.6 |
| HSV2E | 120 | 0.88 | 5.1 | 8.8 | 10.1 | 4.0 | 0.09 | 10.7 |
| HSV2F | 120 | 1.38 | 4.2 | 8.5 | 9.3 | 4.3 | 0.14 | 10.5 |
| HSV2G | 120 | 1.37 | 3.8 | 7.5 | 7.8 | 5.8 | 0.13 | 9.8 |
| HSV2H | 120 | 15.7 | 8.1 | 8.0 | 10.7 | 3.7 | 1.75 | 11.2 |

- b. *Linearity/assay reportable range:* NA
- c. *Traceability, Stability, Expected values (controls, calibrators, or methods):* NA
- d. *Detection limit:* This device is for the HSV-2 antibody detection and was not tested for the limit of detection. There is no standard available for measuring the HSV antibody units in the serum.
- e. *Analytical specificity:*

1. **Cross Reactivity:** Cross reactivity studies for the HSV-2 Type Specific IgG assay were designed to evaluate potential interference directed against closely related members of the Herpes virus family (EBV, CMV, VZV) and other conditions that may mimic an HSV -2 infection.

| Organism/Condition | N | Comparator HSV-2 Assay | LIAISON [®] HSV-2 Positive | LIAISON [®] HSV-2 Negative | LIAISON [®] HSV-2 Equivocal |
|------------------------------------|-----|------------------------|-------------------------------------|-------------------------------------|--------------------------------------|
| Epstein Barr Virus (IgG) | 114 | Negative | 0 | 114 | 0 |
| Cytomegalovirus (IgG) | 35 | Negative | 0 | 35 | 0 |
| Cytomegalovirus (IgM) | 6 | Negative | 0 | 6 | 0 |
| Toxoplasmosis (IgG) | 27 | Negative | 0 | 27 | 0 |
| Rubella (IgG) | 87 | Negative | 0 | 87 | 0 |
| Varicella-Zoster (IgG) | 114 | Negative | 0 | 114 | 0 |
| HSV-1 IgG | 383 | Negative | 4 | 377 | 2 |
| HAMA Samples | 6 | Negative | 0 | 6 | 0 |
| <i>Chlamydia trachomatis</i> | 8 | Negative | 0 | 8 | 0 |
| Human Papilloma Virus | 6 | Negative | 1 | 5 | 0 |
| <i>Treponema pallidum</i> | 13 | Negative | 2 | 10 | 1 |
| <i>Gardnerella vaginalis</i> | 4 | Negative | 0 | 4 | 0 |
| <i>Candida albicans</i> | 7 | Negative | 0 | 7 | 0 |
| <i>Neisseria Gonorrhoea</i> | 3 | Negative | 1 | 2 | 0 |
| Rheumatoid Factor (RF) | 15 | Negative | 0 | 15 | 0 |
| Anti-Nuclear Antibody (ANA) | 12 | Negative | 0 | 12 | 0 |
| Total | 840 | | 8 | 829 | 3 |

2. **Interference:** The device performance was evaluated with the presence of interferents. The assay performance was not affected by hemolysis (at 138.5 mg/dL Hemoglobin), lipemia (at 3000 mg/dL triglycerides), icterus (at 20 mg/dL of bilirubin), cholesterol (at 500 mg/dL) and serum Albumin at (10,000 mg/dL).

f. *Assay cut-off:* NA

2. Comparison studies:

a. *Method comparison with reference method:*

The HerpeSelect[®] 1 and 2 immunoblot

b. *Matrix comparison:* NA

3. Clinical studies:

a. *Clinical Sensitivity:* NA

b. *Clinical specificity:* NA

Performance Characteristics

Summary of Clinical Studies

DiaSorin tested 951 samples collected in the Northeastern United States and compared the LIAISON[®] HSV-2 Type Specific IgG assay to an FDA cleared Immunoblot. The samples were classified as “At risk” samples (n=401) from sexually active adults (at risk for a Sexually Transmitted Disease (STD)), Expectant Mothers (n=430) and “Low Prevalence” samples (n=120) from patients seen at the clinic for anything other than an STD. The studies were conducted at two (2) independent external laboratories.

The sample populations were divided between the sites. Site 1 tested a total of 460 samples (201 At risk, 199 Expectant Mothers and 60 Low prevalence. Site 2 tested a total of 491 samples (200 at risk, 231 Expectant Mothers and 60 Low prevalence). Site 3 tested a total of 951 samples (401 At risk, 430 Expectant Mothers and 120 Low prevalence). Equivocal samples were repeat tested as per the Instructions for use. Any repeat equivocal samples on the predicate device were sent to a Reference Laboratory in the Pacific Northwest for Western Blot testing.

Sexually Active Adults (401)

Four hundred one (401) samples were obtained from Sexually Active Adults who were seen at STD clinics in the Northeastern U.S. were tested with the LIAISON[®] HSV-2 Type Specific IgG assay and the HSV-2 predicate method Immunoblot.

| LIAISON [®] HSV-2 Type Specific IgG | Predicate Device | | | Total |
|--|------------------|-----------|----------|-------|
| | Positive | Equivocal | Negative | |
| Positive | 104 | 1 | 5 | 110 |
| Equivocal | 0 | 0 | 0 | 0 |
| Negative | 1 | 1 | 289 | 291 |
| Total | 105 | 2* | 294 | 401 |

| | Percent | 95% Confidence Intervals |
|-------------|-----------------|--------------------------|
| Sensitivity | 98.1% (104/106) | 95.6 - 99.9% |
| Specificity | 98.0% (289/295) | 96.0 – 99.1% |

Expectant Mother Population (430)

Four hundred thirty (430) samples collected from expectant mothers in the Northeastern U.S. were tested with the LIAISON[®] HSV-2 Type Specific IgG assay and the HSV-2 predicate method Immunoblot.

| LIAISON [®] HSV-2 Type Specific IgG | Predicate Device | | | Total |
|--|------------------|-----------|----------|-------|
| | Positive | Equivocal | Negative | |
| Positive | 91 | 0 | 8 | 99 |
| Equivocal | 1 | 0 | 1 | 2 |
| Negative | 4 | 0 | 325 | 329 |
| Total | 96 | 0 | 334 | 430 |

| | Percent | 95% Confidence Intervals |
|-------------|-----------------|--------------------------|
| Sensitivity | 94.8% (91/96) | 89.4 – 97.9% |
| Specificity | 97.3% (325/334) | 95.3 – 98.6% |

Low Prevalence Population (120)

One hundred twenty (120) “Low Prevalence” samples were obtained from patients who were seen at clinics (not for STD) in the Northeastern U.S. were tested with the LIAISON[®] HSV-2 Type Specific IgG assay and the HSV-2 predicate method Immunoblot.

| LIAISON [®] HSV-2 Type Specific IgG | Predicate Device | | | Total |
|--|------------------|-----------|----------|-------|
| | Positive | Equivocal | Negative | |
| Positive | 20 | 0 | 0 | 20 |
| Equivocal | 0 | 0 | 0 | 0 |
| Negative | 0 | 0 | 100 | 100 |
| Total | 20 | 0 | 100 | 120 |

| | Percent | 95% Confidence Intervals |
|-------------|------------------|--------------------------|
| Sensitivity | 100.0% (20/20) | 86.1 – 100.0% |
| Specificity | 100.0% (100/100) | 97.0 – 100.0% |

Agreement with a CDC Panel

A serum panel was obtained from the Centers for Disease Control and Prevention and tested by the LIAISON[®] HSV-2 Type Specific IgG assay. The panel consisted of 52% positive and 48% negative samples. The LIAISON[®] HSV-2 Type Specific IgG assay demonstrated 100% total agreement with the CDC positive results (52/52) and negative results (48/48).

4. Clinical cut-off: NA
5. Expected values/Reference range:

The prevalence may vary depending upon geographical location, age, gender, type of test employed, specimen collection and handling procedures as well as clinical history of the patient. The observed and the hypothetical predictive values for the sexually active adults and expectant mothers populations are shown below. The positive predictive value (PPV) will decrease proportionally to the prevalence of HSV-2 infection as reflected in the table. The calculations are based on LIAISON[®] HSV-2 sensitivity and specificity of 98.1% and 98.0%, respectively, in a sexually active adult population and 94.8% and 97.3%, respectively, in an expectant mothers population and both 100% in a low prevalence population.

Observed Prevalence with Sexually Active Adults, Expectant Mothers and Low Prevalence populations

| Population | Sero-Status | Observed Prevalence | |
|--------------------------------|----------------|---------------------|-----------------|
| | | LIAISON | Predicate |
| Sexually Active Adults* | HSV-2 Negative | 72.7% (290/399) | 73.7%(294/399) |
| | HSV-2 Positive | 27.3% (109/399) | 26.3%(105/399) |
| Expectant Mothers** | HSV-2 Negative | 76.9% (329/428) | 77.8%(333/428) |
| | HSV-2 Positive | 23.1% (99/428) | 22.2% (95/428) |
| Low Prevalence | HSV-2 Negative | 83.3% (100/120) | 83.3% (100/120) |
| | HSV-2 Positive | 16.7% (20/120) | 16.7% (20/120) |

*Excludes 2 Indeterminate results for Predicate device

**Excludes 2 Equivocal results for LIAISON device

HSV-2 Prevalence vs. Hypothetical Predictive Values

| Prevalence | Sexually Active Adults | | Expectant Mothers | | Low Prevalence Adults | |
|------------|------------------------|-------|-------------------|-------|-----------------------|------|
| | PPV | NPV | PPV | NPV | PPV | NPV |
| 80% | 99.5% | 92.8% | 99.3% | 82.4% | 100% | 100% |
| 70% | 99.1% | 95.7% | 98.8% | 88.9% | 100% | 100% |
| 60% | 98.7% | 97.2% | 98.1% | 92.6% | 100% | 100% |
| 50% | 98.0% | 98.1% | 97.2% | 94.9% | 100% | 100% |
| 40% | 97.0% | 98.7% | 95.9% | 96.6% | 100% | 100% |
| 30% | 95.5% | 99.2% | 93.8% | 97.8% | 100% | 100% |
| 20% | 92.5% | 99.5% | 89.8% | 98.7% | 100% | 100% |
| 10% | 84.5% | 99.8% | 79.6% | 99.4% | 100% | 100% |

N. Proposed Labeling:

The labeling is sufficient and it satisfies the requirements of 21 CFR Part 809.10.

O. Conclusion: The submitted information in this premarket notification is complete and supports a substantial equivalence decision.