
510(k) SUMMARY

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.

The assigned 510(k) number is: K072939

JUN - 9 2008

Submitter Information

Address: Fujirebio Diagnostics, Inc.
201 Great Valley Parkway
Malvern, PA 19355

Contact person: Diana L. Dickson
(610) 240-3917
FAX (610) 240-3803
dicksond@fdi.com

Summary preparation date: May 13, 2008

Name of Device

Trade/Proprietary Name: HE4 EIA Kit
Common/Usual Name: HE4 EIA Test Kit
Regulation Number: 21 CFR 866.6010
Regulatory Class: Class II
Product Code: To be determined

Predicate Device

ABBOTT ARCHITECT CA 125 II Assay (K042731)

Device Description

The HE4 EIA is a solid-phase, non-competitive immunoassay based upon the direct sandwich technique based on two mouse monoclonal antibodies, 2H5 and 3D8, directed against two epitopes in the C-WFDC domain of HE4. Calibrators, controls and patient samples are incubated together with biotinylated Anti-HE4 monoclonal antibody (MAb) 2H5 in streptavidin coated microstrips. HE4 present in calibrators or samples is adsorbed to the streptavidin coated microstrips by the biotinylated Anti-HE4 MAb during the incubation. The strips are then washed and incubated with HRP labeled Anti-HE4 MAb 3D8. After washing, buffered Substrate/Chromogen reagent (hydrogen peroxide and 3, 3', 5, 5' tetra-methyl-benzidine) is added to each well and the enzyme reaction is allowed to proceed. During the enzyme reaction a blue color will develop if antigen is present. The intensity of the color is proportionate to the

amount of HE4 present in the samples. The color intensity is determined in a microplate spectrophotometer at 620 nm (or optionally at 405 nm after addition of Stop Solution).

Calibration curves are constructed for each assay by plotting absorbance value versus the concentration for each calibrator. The HE4 concentrations of patient samples are then read from the calibration curve.

Reportable Range

The reportable range for the HE4 EIA Kit is 15 – 900 pM

Intended Use

The HE4 EIA is an enzyme immunometric assay for the quantitative determination of HE4 in human serum. The assay is to be used as an aid in monitoring recurrence or progressive disease in patients with epithelial ovarian cancer. Serial testing for patient HE4 assay values should be used in conjunction with other clinical methods used for monitoring ovarian cancer.

Statement of Substantial Equivalence

The HE4 EIA is an enzyme immunometric assay for the quantitative determination of HE4 in human serum. The assay is to be used as an aid in monitoring recurrence or progressive disease in patients with epithelial ovarian cancer. Serial testing for patient HE4 assay values should be used in conjunction with other clinical methods used for monitoring ovarian cancer.

As there is no FDA cleared or approved device for the HE4 EIA Kit, substantial equivalence for the HE4 EIA test kit was determined by comparing the clinical performance to the ARCHITECT CA 125 II assay as an aid in monitoring patients with epithelial ovarian cancer.

The regulatory submission will be prepared pursuant to Title 21CFR § 866.6010(b) which states Tumor Markers must comply with the following special controls;

1. Guidance document entitled “Guidance Document for the Submission of Tumor Associated Antigen Premarket Notifications (510(k)s) to FDA”.
2. Voluntary assay performance standards issued by the National Committee on Clinical Laboratory Standards (NCCLS).

A comparison of the features of the HE4 EIA Kit and the ARCHITECT CA 125 II assay are as follows:

| Similarities | | |
|-----------------------------------|---|---|
| | HE4 EIA Kit (Proposed Device) | ARCHITECT CA 125 II (Predicate Device) K042731 |
| Device Type | <i>In vitro</i> diagnostic | <i>In vitro</i> diagnostic |
| Classification | Class II | Class II |
| Regulation Number | 21 CFR 866.6010 | 21 CFR 866.6010 |
| Product Usage | Clinical and Hospital laboratories | Clinical and Hospital laboratories |
| Intended Use | Aid in monitoring patients with epithelial ovarian cancer | Aid in monitoring patients with epithelial ovarian cancer |
| Specimen Collection Method | Routine Phlebotomy Techniques | Routine Phlebotomy Techniques |
| Interpretation of Results | Standard Curve | Standard Curve |

| Differences | | |
|-------------------------------|---|---|
| | HE4 EIA Kit (Proposed Device) | ARCHITECT CA 125 II (Predicate Device) K042731 |
| Product Code | To be determined | LTK |
| Type of Specimen | Human Serum Only | Human serum or plasma (EDTA, Lithium Heparin, Sodium Heparin) |
| Antigen Detected | HE4 | CA 125 |
| Capture Antibody | 2H5 mouse monoclonal | OC 125 mouse monoclonal |
| Detection Antibody | 3D8 mouse monoclonal | M11 mouse monoclonal |
| Calibrators | 6 Levels (0 – 900 pM) Supplied with Kit | 6 Levels (0 – 1000 U/mL) Supplied as separate Kit |
| Controls | 2 Levels (50 and 400 pM) Supplied with Kit | 3 Levels (40, 300 and 650 U/mL) Supplied as separate Kit |
| Principle of Operation | Manual Enzymatic Immunoassay (EIA) | Automated Chemiluminescent Microparticle Immunoassay (CMIA) |

Performance Characteristics

Precision:

A study was performed with the HE4 EIA Kit modeled after the NCCLS (CLSI) guideline EP5-A2. A panel of four serum samples was assayed, using two lots of reagents, in replicates of two, at two separate times per day for 20 days. The HE4 EIA Kit precision is $\leq 15\%$ total CV.

Linearity:

A dilution linearity study was conducted for the HE4 EIA Kit modeled after the NCCLS (CLSI) guideline EP6-A. Serum samples with elevated HE4 values were diluted with HE4 Calibrator A (zero). The HE4 concentration was determined for each dilution and the percent (%) recovery was calculated.

The HE4 EIA Kit was determined to have a mean recovery within 15% of the expected result for diluted samples.

Functional Sensitivity:

The functional sensitivity of the HE4 EIA Kit is ≤ 25 pM. The functional sensitivity is expressed as the concentration of an analyte at which the CV is 20%. The NCCLS guideline EP5-A2 was used to design the experiments for determination of functional sensitivity. A study was conducted where a five member sensitivity panel was tested in replicates of 4 in 2 runs on twenty separate days with two lots of reagents. The functional sensitivity determined for the HE4 EIA was found to be < 5 pM.

Detection Limit:

The limit of detection of the HE4 EIA Kit is ≤ 15 pM. The limit of detection (LoD) corresponds to the upper limit of the 95% confidence interval and represents the lowest concentration of HE4 antigen that can be distinguished from zero. The NCCLS guideline EP17-A was used to design the LoD experiments. A study was conducted where HE4 Calibrator A (zero) and 4 samples from healthy subjects diluted to 5 pM with Sample Diluent was tested in replicates of 24 per run in 4 runs on two separate days. The LoD was calculated as follows:

$$\text{LoD (pM)} = 5.0 \text{ pM} \times (1.65 \times \text{SD}_0 + 1.65 \times \text{SD}_5) / (\text{OD}_5 - \text{OD}_0)$$

The Limit of Detection of the HE4 EIA Kit was calculated to be < 2.5 pM.

Interference:

The HE4 EIA Kit mean assay specificity is $100 \pm 15\%$. Recovery studies were performed to compare sera containing the following compounds at the indicated concentrations with control sera. The NCCLS guideline EP7-A was used to design the interference experiments. The following substances and concentrations were tested and found not to interfere with the test.

| Endogenous serum interferences | Test Concentration |
|---------------------------------------|---------------------------|
| Triglycerides | 30 mg/mL |
| Billirubin | 0.2 mg/mL |
| Hemoglobin | 10 mg/mL |
| Total Protein | 120 mg/mL |

| Chemotherapeutic drug interferences | Test Concentration |
|--|---------------------------|
| Carboplatin | 500 µg/mL |
| Cisplatin | 165 µg/mL |
| Clotrimazole | 0.3 µg/mL |
| Cyclophosphamide | 500 µg/mL |
| Dexamethasone | 10 µg/mL |
| Doxorubicin | 1.16 µg/mL |
| Leucovorin | 2.68 µg/mL |
| Melphalan | 2.8 µg/mL |
| Methotrexate | 45 µg/mL |
| Paclitaxel | 3.5 ng/mL |

Potentially interfering clinical conditions

The HE4 EIA Kit mean assay specificity is 100 ± 15%. The HE4 EIA Kit was evaluated using specimens with HAMA and Rheumatoid Factor (RF) to further assess the assay specificity. Five specimens positive for HAMA and five specimens positive for RF were evaluated for % recovery with HE4 EIA antigen spiked into each specimen at approximately 50 and 450 pM.

Monitoring of Disease status in Patients Diagnosed with Ovarian Cancer

The effectiveness of the HE4 EIA as an aid in monitoring of disease status in ovarian cancer patients was determined by assessing changes in HE4 levels in serial serum samples from 80 patients compared to changes in disease status. A study involving a total of 354 pairs of observations was undertaken with an average number of 4.4 observations per patient. A positive change in HE4 was defined as an increase in the value that was at least 25% greater than the previous value of the test. This level of change takes into account the variability of the assay and the biological variability. Sixty percent (60%) or 76/126 of the patient samples with a positive change correlated with the disease progression while seventy-five percent (75%) or 171/228 of the patient serial samples with no significant change in HE4 value correlated with no progression. The total concordance was seventy percent (70% or 247/354). The following table presents the data in a 2 x 2 format.

| Change in Disease State per Sequential Pair | | | |
|--|--------------------|-----------------------|--------------|
| Increase in HE-4 concentration | Progression | No Progression | Total |
| >25% | 76 | 57 | 133 |
| ≤25% | 50 | 171 | 221 |
| Total | 126 | 228 | 354 |



The following table shows the resulting sensitivities and specificities of the HE4 EIA compared to the disease status at various changes in HE4 EIA concentrations.

Sensitivity is represented as a concordance of the HE4 EIA to progression of disease.

Specificity is represented as a concordance of the HE4 EIA to no progression of disease.

| Percent Change in HE4 Concentration (%) | Sensitivity (%) | Specificity (%) |
|--|----------------------------------|----------------------------------|
| 10 | 71 | 62 |
| 25 | 60 | 75 |
| 50 | 43 | 88 |
| 75 | 38 | 92 |
| 100 | 31 | 95 |



Fujirebio Diagnostics, Inc.
c/o Ms. Diana L. Dickson
Manager Regulatory Affairs
201 Great Valley Parkway
Malvern, PA 19355-1308

JUN - 9 2008

Food and Drug Administration
2098 Gaither Road
Rockville MD 20850

Re: k072939

Trade/Device Name: HE4 EIA
Regulation Number: 21 CFR 866.6010
Regulation Name: Tumor-associated antigen immunological test system
Regulatory Class: Class II
Product Code: OIU
Dated: May 29, 2008
Received: May 30, 2008

Dear Ms Dickson:

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.

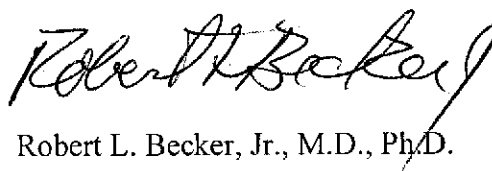
If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to such additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 898. In addition, FDA may publish 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 Part 801); 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.

Page 2 –

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 (240) 276-0450. 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 240-276-3474. For questions regarding the reporting of device adverse events (Medical Device Reporting (MDR)), please contact the Division of Surveillance Systems at 240-276-3464. 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 (240) 276-3150 or at its Internet address <http://www.fda.gov/cdrh/industry/support/index.html>.

Sincerely yours,

A handwritten signature in black ink, appearing to read "Robert L. Becker, Jr.", written in a cursive style.

Robert L. Becker, Jr., M.D., Ph.D.

Director

Division of Immunology and Hematology Devices

Office of In Vitro Diagnostic Device Evaluation and Safety

Center for Devices and Radiological Health

Enclosure

Indications for Use

510(k) Number (if known): K072939

Device Name: HE4 EIA

Indications For Use:

The HE4 EIA is an enzyme immunometric assay for the quantitative determination of HE4 in human serum. The assay is to be used as an aid in monitoring recurrence or progressive disease in patients with epithelial ovarian cancer. Serial testing for patient HE4 assay values should be used in conjunction with other clinical methods used for monitoring ovarian cancer.

Prescription Use ✓
(Part 21 CFR 801 Subpart D)

AND/OR

Over-The-Counter Use _____
(21 CFR 801 Subpart C)

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

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

Mona M Chan

Division Sign-Off

**Office of In Vitro Diagnostic
Device Evaluation and Safety**

Page 1 of 1

510(k) K072939