

MAR - 6 1998

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**SUMMARY OF SAFETY AND EFFECTIVENESS - ACS: 180 BR**

This summary of safety and effectiveness information is being submitted in accordance with the requirements of The Safe Medical Devices Act of 1990 (SMDA 1990) and 21 CFR Part 807.92.

Date of Summary Preparation: January 16, 1998

Company Name: Chiron Diagnostics Corporation  
333 Coney Street  
East Walpole, MA 02032

Company Contact: Nancy Hornbaker  
Regulatory Affairs  
Chiron Diagnostics  
Chiron Corporation  
4560 Horton Street  
Emeryville, CA 94608

Telephone Number: 510.923.2758  
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Device Name: ACS:180 BR  
Automated Chemiluminescence System

Common or Usual Name: Automated Tumor Associated Antigen

Classification: Class II device

Predicate Device: Biomira TRUQUANT® BR™ RIA  
PMA P950011; 510(k) K965141

**Intended Use and Indications for Use:**

Chiron Diagnostics ACS:180 BR is an *in vitro* diagnostic test for the quantitative serial determination of cancer antigen CA 27.29 in human serum using the Chiron Diagnostics ACS 180: Automated Chemiluminescence Systems. The test is intended for use as an aid in monitoring patients previously treated for Stage II or Stage III breast cancer. Serial testing for CA 27.29 in the serum of patients who are clinically free of disease should be used in conjunction with other clinical methods used for the early detection of cancer recurrence. The test is also intended for use as an aid in the management of breast cancer patients with metastatic disease by monitoring the progression or regression of disease in response to treatment.

**Description of the Device:**

The Chiron Diagnostics ACS:180 BR assay is a fully automated, competitive, chemiluminescent assay. One reagent, designated Lite Reagent, is composed of a mouse monoclonal antibody specific for CA 27.29, labeled with acridinium ester. The antibody used in the assay, MAb B27.29, binds to a peptide epitope in the tandem repeat region of the MUC-1 gene product. The Solid Phase is composed of purified breast cancer antigen (CA 27.29) which is covalently coupled to paramagnetic particles (PMP). The patient serum sample is incubated with both reagents simultaneously for 7.5 minutes.

The ACS: 180 system automatically performs the following steps:

- dispenses sample into a cuvette
- dispenses Lite Reagent and Solid Phase and incubates for 7.5 minutes
- separates, aspirates and washes the cuvettes
- dispenses reagents which initiate the chemiluminescent reaction
- reports results

An inverse relationship exists between the concentration of CA 27.29 in a sample and the relative light units (RLU) detected by the system.

**Specific Performance Characteristics:**

**Analytical Sensitivity**

|                        |           |
|------------------------|-----------|
| Analytical Sensitivity | <3.5 U/mL |
|------------------------|-----------|

**Assay Upper Limit of Normal**

A total of 314 healthy volunteer donors were tested at three laboratories to determine the normal range of the assay and to determine the upper limit of normal (ULN). Following good laboratory practice, each laboratory should determine its own normal range and ULN.

|                             |           |
|-----------------------------|-----------|
| Upper Limit of Normal (ULN) | 38.6 U/mL |
|-----------------------------|-----------|

**Assay Specificity**

The specificity of the assay was determined by testing serum samples from patients with active malignancies other than breast and serum from patients with other diseases and conditions. Results from the clinical study are presented below.

Patients with non breast malignancies frequently have raised levels of the CA 27.29 antigen as indicated by their specificities. CA 27.29 is normally expressed by most epithelial tissues and over-expressed by many epithelial cancers. It is not a breast specific antigen.

**Specificity of the ACS180:BR in Patients with Malignancies other than Breast**

| <b>Malignancy</b> | <b>N</b> | <b>Specificity</b> |
|-------------------|----------|--------------------|
| Colon             | 43       | 74.4%              |
| Liver             | 20       | 45.0%              |
| Lung              | 47       | 57.5%              |
| Ovary             | 50       | 44.0%              |
| Pancreas          | 45       | 53.3%              |
| Prostate          | 34       | 82.4%              |
| Stomach           | 29       | 93.1%              |
| Uterus            | 30       | 86.7%              |

Specificity of the ACS:180 BR in Patients with Other Diseases And Conditions

| Condition                | N  | Specificity |
|--------------------------|----|-------------|
| Benign Breast Disease    |    |             |
| Breast Adenoma           | 61 | 95.08%      |
| Fibrocystic Breasts      | 68 | 98.53%      |
| Cirrhosis                | 25 | 76.00%      |
| Endometriosis            | 24 | 91.67%      |
| Lactating Woman          | 37 | 89.19%      |
| Mild Chronic Hepatitis   | 28 | 85.71%      |
| Ovarian Cyst             | 50 | 94.00%      |
| Pregnancy                | 49 | 97.96%      |
| Renal Impairment         | 20 | 85.00%      |
| Severe Chronic Hepatitis | 20 | 95.00%      |

**Potentially Interfering Substances**

There are no known cross-reactants for CA 27.29 as measured by the ACS:180 BR assay.

The potential interference of chemotherapeutic agents, therapeutic drugs, and tumor marker antigens was tested by adding these substances to five serum pools containing CA 27.29 ranging from 20.0 to 445.8 U/mL. The level of CA 27.29 in each of these pools was then determined using the ACS:180 BR assay and normalized to the level without the respective drugs or antigens.

| Substance                 | Mean % Recovery | Substance                  | Mean % Recovery |
|---------------------------|-----------------|----------------------------|-----------------|
| Acetaminophen (10X)       | 96.3            | Granisetron HCl (10X)      | 99.9            |
| Cimetidine (40X)          | 100.9           | Lorazepam (10X)            | 98.0            |
| Ciprofloxacin (10X)       | 100.1           | Megestrol acetate (5X)     | 105.2           |
| Codeine (10X)             | 96.9            | Methotrexate (10X)         | 105.8           |
| Cyclophosphamide (1X)     | 96.2            | Morphine (10X)             | 95.6            |
| Dexamethasone (10X)       | 100.2           | Ondansetron (10X)          | 93.3            |
| Diphenhydramine HCl (10X) | 101.8           | Paclitaxel (2X)            | 101.7           |
| Doxorubicin (10X)         | 95.9            | Prochlorperazine (10X)     | 96.4            |
| Etoposide (2X)            | 99.5            | Tamoxifen (10X)            | 96.6            |
| 5-Fluorouracil (10X)      | 104.2           | Vinorelbine tartrate (10X) | 104.9           |

| Antigen                           | Mean % Recovery |
|-----------------------------------|-----------------|
| Carcinoembryonic antigen<br>(CEA) | 103.8           |
| Ovarian Cancer antigen<br>(CA125) | 105.9           |
| GI Cancer antigen<br>(CA 19.9)    | 103.6           |

### Correlation with Predicate Device

The performance of the ACS:180 BR assay was compared with that of the predicate device in a study of 203 specimens. These specimens had CA 27.29 levels that spanned the range from 7 to 994 U/mL. The results of the linear regression analysis indicated that the two methods were correlated. The correlation coefficient ( $r$ ) was 0.96; the slope was 1.05 and y-intercept was 6 U/mL.

The CA 27.29 results from a subset of this population, 103 women with histologically confirmed breast cancer, were also highly correlated ( $r = 0.96$ ). In this analysis, the slope was 1.04 and the y-intercept was 8 U/mL.

### Clinical Performance of the ACS:180 BR

#### Aid in Monitoring Patients Previously Treated for Stage II or Stage III Breast Cancer

One clinical study of the ACS:180 BR comprised 942 specimen from 162 patients who were enrolled in a multicenter-prospective study. These patients were previously treated for Stage II or Stage III breast cancer and had no evidence of disease (NED) at the time of study entry (at least one year post-surgery). Patients were monitored over the length of the study (2.4 - 24 months) by determining the CA 27.29 levels in serial blood specimens drawn at each visit with their clinician. All patients included in the ACS:180 BR clinical study were lymph node positive at time of surgery and had at least three serial bleeds after study enrollment. Two laboratories tested all specimens using the ACS:180 BR assay and the predicate device.

Sensitivity, specificity, and predictive values (PPV and NPV) of the ACS:180 BR as an aid in monitoring the recurrence of breast cancer were calculated against disease recurrence as defined by clinical outcome<sup>1</sup>. Of the 162 patients included in the

<sup>1</sup> Breast cancer recurrence was established using clinical symptoms, and/or general or specific imaging techniques; e.g., x-ray, mammogram, magnetic resonance imaging, computerized tomography, ultrasound, bone or liver scan.

study, 25 showed clinical evidence of disease recurrence. The utility of the ACS:180 BR assay as an aid for the detection of breast cancer recurrence was analyzed under two scenarios:

1. Using any single ACS:180 BR result greater than the ULN (38.6 U/mL) prior to disease recurrence
2. Using two consecutive ACS:180 BR results greater than the ULN (38.6 U/mL) prior to disease recurrence.

Assay results above the ULN must have occurred prior at or before the clinical diagnosis of recurrence in order to be considered predictive of disease recurrence.

| Assay Parameter           | One value > ULN  | Two Consecutive Values > ULN |
|---------------------------|------------------|------------------------------|
| Sensitivity               | 60%<br>(39, 79)* | 48%<br>(28, 69)              |
| Specificity               | 93%<br>(87, 96)  | 98%<br>(94, 100)             |
| Positive Predictive Value | 60%<br>(39, 79)  | 80%<br>(52, 96)              |
| Negative Predictive Value | 93%<br>(87, 96)  | 91%<br>(85, 95)              |

\* Numbers in parentheses represent the 95% confidence intervals.

By comparison, the sensitivity of the predicate device, using one value > ULN, ranged from 58% to 62% at the two sites, specificity ranged from 53% to 97%, PPV ranged from 23% to 73%, and NPV ranged from 84% to 94%. Using two consecutive values > ULN, the sensitivity of the predicate device at the two sites ranged from 38% to 42%, specificity ranged from 86% to 100%, PPV ranged from 42% to 100%, and NPV ranged from 86% to 92%.

#### Correlation with Predicate Device

The sensitivity, specificity and predictive values determined in this study were substantially equivalent to those of the predicate device.

Aid in Management of Breast Cancer Patients with Metastatic Disease

This clinical study was a multicenter prospective study of 97 breast cancer patients with metastatic disease. All patients received treatment during the study. Patients were enrolled at six sites and all ACS:180 Br testing was performed at three laboratories. The clinical sensitivity and specificity of the ACS:180 Br assay in relation to changing disease status in metastatic breast cancer patients were determined using a 20% increase in assay levels as an indication of progressing disease. The positive predictive value was calculated against disease progression. Calculations were based on the 79 patients who had assay levels above the ULN. Patients were considered to have completed the trial at the time of diagnosis of progressing or regressing disease. Patients with stable disease were followed from two to seven months. The following table summarizes the study results:

| Measure   | Estimate         |
|---|------------------|
| Sensitivity to Change in Disease Status               | 73%<br>(58, 85)* |
| Specificity to Change in Disease Status               | 71%<br>(53, 85)  |
| Positive Predictive Value to Change in Disease Status | 77%<br>(61, 88)  |
| Negative Predictive Value to Change in Disease Status | 67%<br>(49, 81)  |

\*Numbers in parentheses represent the 95% confidence interval.

Results from this study demonstrated that changes in CA 27.29 levels, as measured by the ACS:180 Br assay, can be a predictor of disease status and response to therapy in patients with metastatic breast cancer.



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

MAR - 6 1998

Food and Drug Administration  
2098 Gaither Road  
Rockville MD 20850

Ms. Nancy Hornbaker  
Regulatory Affairs  
Chiron Diagnostics Corporation  
4560 Horton Street  
Emeryville, California 94608

Re: K980190  
Trade Name: ACS:180 BR (CA 27.29) Automated Chemiluminescence  
System  
Regulatory Class: II  
Product Code: MOI  
Dated: January 16, 1998  
Received: January 20, 1998

Dear Ms. Hornbaker:

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 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 requirement, 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.

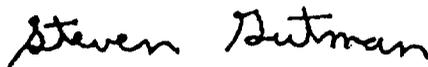
Page 2

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

Enclosure

510(k) Number (if known): K 980190

Device Name: ACS:180

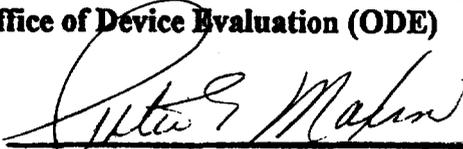
**Indications For Use:**

**ADDENDUM**

The Chiron Diagnostics ACS:180 BR is an in vitro diagnostic test for the quantitative serial determination of cancer antigen CA 27.29 in human serum using the Chiron Diagnostics ACS:180® Automated Chemiluminescence Systems. The test is intended for use as an aid in monitoring patients previously treated for Stage II or Stage III breast cancer. Serial testing for CA 27.29 in the serum of patients who are clinically free of disease should be used in conjunction with other clinical methods used for the early detection of cancer recurrence. The test is also intended for use as an aid in the management of breast cancer patients with metastatic disease by monitoring the progression or regression of disease in response to treatment.

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Concurrence of CDRH, Office of Device Evaluation (ODE)

  
\_\_\_\_\_  
(Division Sign-Off)  
Division of Clinical Laboratory Devices  
510(k) Number K980190

Prescription Use   
(Per 21 CFR 801.109)

OR

Over-The-Counter Use

(Optional Format 1-2-96)