# Summary of Safety and Effectiveness

I. General Information

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| Generic Name: | Chemiluminometric assay for the quantitative determination of prostate specific antigen (PSA) |
| Trade Name: | ACS:180 PSA2 |
| Applicant's Name and Address: | Chiron Diagnostics<br>Chiron Corporation<br>4560 Horton Street<br>Emeryville, CA 94608 |
| Premarket Approval Supplemental Application: | P920030/S2 |
| Date of Panel Recommendation: | |

Pursuant to section 515(c) (2) of the Act as amended by the Safe Medical Devices Act of 1990, this PMA supplement was not the subject of an FDA immunology Devices Advisory Panel meeting because the information in the PMA supplement substantially duplicates information previously reviewed by this panel.

Date of Notice of Approval of Application:

DEC - 8 1998

II. Indications for Use

The Chiron Diagnostics ACS:180 PSA2 assay was previously indicated for the quantitative, serial determination of prostate-specific antigen (PSA) in human serum to aid in the management of patients with prostate cancer. The original ACS:180 PSA assay was approved on September 2, 1994 (P920030) and the ACS:180 PSA2 assay was approved on December 13, 1995 (P920030/S1). Further information may be obtained in writing from Dockets Management Branch (HFA-305), Food and Drug Administration, 12420 Parklawn Drive, Room 1-23, Rockville, MD 10857, Docket number 94M-0349.

The ACS:180 PSA2 assay is indicated for the quantitative measurement of prostate-specific antigen (PSA) in human serum as: 1) an aid in the management of patients with prostate cancer and 2) as an aid in the detection of prostate cancer when used in conjunction with digital rectal examination (DRE) in men aged 50 years or older. Prostatic biopsy is required for the diagnosis of cancer.

III. Background

The most common type of cancer in men in the U.S. and the second most common cancer in men worldwide is cancer of the prostate.[1,2] It is the second leading cause of cancer deaths in American and European men[1,3], and the lifetime probability for U.S. men of developing prostatic cancer is approximately 1 in 5.[4] Rates of prostate cancer increase with advancing age[5]; thus, as life-expectancy continues to rise, the number of new cases and deaths due to prostate cancer also continues to rise. Targets for decreasing prostate cancer mortality are to decrease incidence; improve therapy; and provide early detection, when treatment is more effective. Prior to the initiation of prostate specific antigen (PSA) screening, two thirds of cancers had spread beyond the prostate when first identified.[6] Thus, the development of improved methods of early detection is critical to successful intervention. When PSA determinations were made in serial specimens from men who did and did not develop prostate cancer, the results showed a linear increase in PSA levels with increasing age. However, in men who developed prostate cancer, PSA levels started to rise exponentially approximately 7 years prior to a clinical diagnosis by digital rectal examination (DRE) of local/regional tumors and 9 years prior to a clinical diagnosis of advanced/metastatic tumors.[7] PSA levels in these men rose to ≥4.0 ng/mL, 2.6 to 11.2 years, before the clinical diagnosis, and thus suggested that PSA screening should detect cancers at an earlier stage than DRE alone. Several recent studies have confirmed that the use of PSA testing, in combination with DRE, aids in the detection of prostate cancer before it spreads beyond the prostate gland.[8-10] Studies have also shown that serum PSA levels are more predictive of prostate cancer than DRE.[11-13] Based on

these studies, both the American Cancer Society and the American Urological Association have recommended the use of PSA in conjunction with DRE for detection of prostate cancer in men aged 50 or older.[14,15] Prostate cancer screening programs have been developed in other parts of the world to aid in the early detection of organ-confined disease.[16-18] PSA is a single-chain glycoprotein normally found in the cytoplasm of the epithelial cells lining the acini and ducts of the prostate gland.[19] PSA is a neutral serine protease of 240 amino acids involved in the lysis of seminal coagulum.[20,21] PSA is detected in the serum of males with normal, benign hyperplastic, and malignant prostate tissue. PSA is not detected (or detected at very low levels) in the serum of males without prostate tissue (because of radical prostatectomy or cystoprostatectomy) or in the serum of most females[22]. The fact that PSA is unique to prostate tissue makes it a suitable marker for monitoring men with cancer of the prostate. PSA is also useful for determining possible recurrence after therapy when used in conjunction with other diagnostic indices.[23,24] PSA levels increase in men with cancer of the prostate, and after radical prostatectomy PSA levels routinely fall to the undetectable range.[23] If prostatic tissue remains after surgery or metastasis has occurred, PSA appears to be useful in detecting residual disease and early recurrence of tumor.[25,26] Therefore, serial PSA levels can help determine the success of prostatectomy, and the need for further treatment, such as radiation, endocrine or chemotherapy, and in the monitoring of the effectiveness of therapy.[23,24,27,28]

IV. Contraindications

There are no known contraindications for the ACS:180 PSA2 assay.

V. Warnings and Precautions

Warnings and precautions for use of the device are stated in the attached product labeling (Attachment A).

VI. Device Description

The ACS:180 PSA2 is an *in vitro* diagnostic device to measure PSA in human serum. The assay is a two-site solid phase sandwich immunoassay which uses chemiluminometric technology and is performed on a fully-automated, random-access analyzer. In the assay, anti-PSA antibody labeled with a chemiluminescent tracer (acridinium ester, or AE) and a second anti-PSA antibody covalently coupled to paramagnetic particles bind to PSA in the sample to form a sandwich. The amount of PSA in the sample is directly related to the photons (expressed in relative light units, or RLU) detected by the analyzer. The sample's PSA concentration is calculated from a calibration curve.

The analyzer performs the assay procedure as follows:[4]

1. Adds sample to sample cuvette.

2. Adds ACS PSA2 Lite Reagent (AE labeled anti-PSA, or tracer) and Solid Phase (anti-PSA covalently coupled to paramagnetic particles) to the sample cuvette.

3. Incubates the cuvette.

4. Magnetically separates, washes and aspirates fluid from the cuvettes to separate anti-bound PSA from unbound tracer.

5. Activates the chemiluminescent reaction by addition of hydrogen peroxide followed by addition of sodium hydroxide.

6. Processes the RLU signal and converts it to a test result (ng PSA per mL).

7. Reschedules, dilutes and retests the sample if the first result is above the assay's dilution set point.

The analyzer stores a calibration curve using the PSA concentrations and corresponding RLU values defined by the PSA2 Master Curve card. The Master Curve information defines the shape of the calibration curve for each lot of ACS:180 PSA reagents. Periodically (at least once every 28 days) a two-point calibration is performed by assaying a low and a high calibrator; the analyzer uses these calibrator values to adjust the stored curve. The PSA concentrations of controls and specimens are determined from the calibration curve.

## VII. Alternate Practices and Procedures

Alternate practices and/or procedures for the detection of prostate cancer include digital rectal examination, ultrasonography and biopsy.

Alternate practices and procedures for the management of patients with prostate cancer include serial determinations of enzymes such as prostatic acid phosphatase, alkaline phosphatase, total acid phosphatase, or total alkaline phosphatase; imaging, including bone scans, whole body scans, lymphangiography. X-ray or ultrasonography; biopsy; digital rectal examination.

VIII. Marketing History

The ACS:180 PSA and/or PSA2 assay has been marketed outside the US since 1991 and has been marketed in the US since 1994 for the management of patients with prostate cancer. In 1997, one lot of ACS:180 PSA and three lots of ACS:180 PSA2 were withdrawn from the market. The affected countries were: Argentina, Australia, Austria, Belgium, Brazil, Canada, Chile, Czechoslovakia, Finland, France, Germany, Greece, Hong Kong, Italy, Japan, Korea, Malaysia, Mexico, Netherlands, New Zealand, Poland, Portugal, Puerto Rico, Singapore, Spain, Switzerland, Taiwan, Turkey, United Kingdom and USA.

IX. Potential Adverse Effects of the Device on Health

Since elevated PSA levels can occur in the absence of prostate cancer and low levels of PSA do not necessarily indicate the absence of prostate cancer, clinical decisions should not be based solely on PSA results. The following adverse events may occur:

1. A falsely low PSA result could lead to a medical decision that deprives a patient of potential beneficial treatment.

2. A falsely elevated PSA result could lead to a medical decision that causes a patient to undergo unnecessary treatment.

X. Summary of Studies

A. Non-Clinical Studies

Because approval was requested for an additional intended use and did not involve any changes in the reagents or test procedures, limited data were necessary to characterize the assay for the new Intended Use.

A Precision Study was performed at the three Testing Sites. The data generated were consistent with the data generated in the original clinical trial.

A Freeze Thaw Study was performed using 15 specimens > 4.0 ng/mL and 16 specimens ≤ 4.0 ng/mL. Specimens were tested fresh and after one, two, and three freeze thaw cycles. No statistically significant differences could be seen between ACS:180 PSA2 values for specimens tested fresh or after as many as three freeze thaw cycles. The results confirmed that specimens that have undergone up to three freeze thaw cycles can be tested in the ACS:180 PSA2 assay.

B. Clinical Study

Specimens were collected at six Collection Sites from men who participated in Prostate Screening Programs in 1993 - 1997.

The clinical study was retrospective in design. The primary objective of the clinical study was to demonstrate that the ACS:180 PSA2 assay can be used for the measurement of serum PSA in conjunction with DRE as an aid in the detection of prostate cancer in men aged 50 yeas or older. Prostatic biopsy is required for diagnosis of cancer.

Inclusion criteria for the study were as follows: age 50 years and older, no personal history of prostate cancer and a DRE exam performed at the time of screening. Exclusion criteria were: age younger than 50 years, a history of prostate cancer, and no DRE performed at the time of screening.

A total of 7039 men, aged 50 or older with no history of prostate cancer, comprised the screening population. All subjects provided a personal history, had a blood sample drawn for PSA determination, followed by a digital rectal examination (DRE). A DRE was considered abnormal if the examiner recorded the result as being suspicious for the presence of cancer.

The mean age of the screening population was 62, with a range of 50 to 96 years. The ethnic origin of the subjects was as follows: 85% Caucasian (36% from the U.S., 49% from Chile), 13% African-American, 1% Asian, 1% Hispanic, 1% Other or Unknown.

Four of the Collection Sites provided the entire screening cohort for testing by the ACS:180 PSA2 assay, while two sites provided specimens from subjects with an abnormal DRE and/or a screening PSA value of > 4.0 ng/mL. The clinical trial results are based on the testing of 3,607 subjects.

1. ACS:180 PSA2 and DRE Results

Of the 3607 study population, 1040 subjects (29%) had abnormal results on either or both ACS:180 PSA2 assay or DRE: 613 (17%) had ACS:180 PSA2 levels > 4.0 ng/mL, and 568 (16%) had abnormal results on DRE. The 2567 subjects (71%) with normal DRE and ACS:180 PSA2 values ≤ 4.0 ng/mL exited the study.

Only 141 men (4%) had abnormal results by both methods, compared to 472 (13%) with ACS:180 PSA2 levels > 4.0 ng/mL and normal DRE, and 427 (12%) with abnormal DRE findings and ACS:180 PSA2 levels ≤ 4.0 ng/mL. The percent of men with

abnormal findings increased with increasing age: 11% of men aged 50-60 had abnormal results, compared to 21% of men aged 60-70, and 30% of men older than 70.

2. Subjects with Biopsy

Of the 1040 subjects with abnormal results on DRE and/or ACS:180 PSA2 assay results > 4.0 ng/mL, 506 (49%) underwent biopsy. Of the subjects biopsied, 380 had an ACS:180 PSA2 level > 4.0 ng/mL and 219 had an abnormal DRE. Of the 506 men with biopsy results, 147 (29%) had prostate cancer.

3. Positive Predictive Values

The positive predictive value was 33% for an ACS:180 PSA2 value > 4.0 ng/mL and 32% for a suspicious DRE. When the ACS:180 PSA2 level was > 4.0 ng/mL and the DRE was normal, the positive predictive value was 26%. When the DRE was abnormal but the ACS:180 PSA2 level was ≤ 4.0 ng/mL, the positive predictive value was 16%. When the ACS:180 PSA2 level was > 4.0 ng/mL and the DRE was abnormal, the positive predictive value was 55%.

ACS:180 PSA2 assay results > 4.0 ng/mL in conjunction with an abnormal DRE provided the greatest predictive value for the detection of prostate cancer. However, PSA2 detected a greater number of the total cancers (127 of the 147 cancers, 86%) than did DRE (71 of the 147 cancers, 48%).

XI. Conclusions drawn from the Studies

The primary objective of this multiple site, retrospective clinical study was to demonstrate that the ACS:180 PSA2 assay can be used for the measurement of serum PSA in conjunction with DRE as an aid in the detection of prostate cancer in men aged 50 yeas or older. The data generated in this clinical trial supports the clinical utility of the ACS:180 PSA2 assay for this intended use.

Serum PSA concentrations, regardless of the value, should not be interpreted as diagnostic for the presence or absence of prostate cancer. PSA testing should always be performed in conjunction with DRE, as the combination of an ACS:180 PSA2 value > 4.0 ng/mL and/or an abnormal DRE predicted the greatest number of cancers. Prostatic biopsy is required for a definitive diagnosis of prostate cancer.

XII. Panel Recommendation

Pursuant to section 515 (c)(2) of the Act as amended by the Safe Medical Devices Act of 1990, this PMA supplement was not referred to the Immunology Devices Panel, an FDA advisory panel, for review and recommendation because the information in the PMA supplement substantially duplicates information previously reviewed by this panel.

XIII. CDRH Action on the Application

CDRH issued an approval order for the applicant's PMA for the ACS180 PSA2 on DEC - 8 1998.

XIV. Approval Specifications

Directions for use: See labeling.

Conditions of Approval: CDRH approval of this PMA supplement is subject to full compliance with the conditions described in the approval order.

## References for the Summary of Safety and Effectiveness


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