

## Summary of Safety and Effectiveness

### I. GENERAL INFORMATION

Device Generic Name: Immunoassay for the in vitro quantitative measurement of prostate specific antigen (PSA) in human serum.

Device Trade Names: Bayer ACS: 180™ and ADVIA Centaur™ PSA Assay

Applicant's Name and Address: Bayer Corporation  
Business Group Diagnostics  
511 Benedict Avenue  
Tarrytown, NY 10591

Premarket Approval Number: P950021/S2

Date of Panel Recommendation: None

Dates of Good Manufacturing Practice Inspection: None

Date of Notice of Approval to the applicant: DEC 22 2000

### II. INDICATIONS FOR USE

The purpose of this PMA supplement is to expand the intended use of the Bayer Diagnostics ACS: 180™ and ADVIA Centaur™ PSA Assays to read as follows:

The Bayer ACS: 180™ and ADVIA Centaur™ PSA Assays are in vitro devices intended for the quantitative measurement of prostate-specific antigen (PSA) in human serum. These devices are indicated for the measurement of serum PSA in conjunction with digital rectal exam (DRE) as an aid in the detection of prostate cancer in men aged 50 years and older. Prostate biopsy is required for the diagnosis of prostate cancer. These devices are further indicated as an aid in the management (monitoring) of prostate cancer patients.

#### Background

Carcinoma of the prostate is currently the most prevalent form of cancer in men and the second leading cause of male cancer death in the U.S.<sup>1</sup> It is estimated that in 1998, 184,500 men will develop prostate cancer and approximately 39,200 men will die due to this malignancy.<sup>1</sup> The mortality rate for prostate cancer is nearly two-times higher for African-American men than white men.<sup>1</sup> Fifty-eight percent of all prostate cancers are discovered at a local stage (confined to the prostate) and the 5-year relative survival rate for patients diagnosed at this early stage of disease is 100%.<sup>1</sup> The survival rates for all stages combined have increased from 67% to 89% over the past 20 years.<sup>1</sup> This increase in survival may be due to the increasing awareness of prostate cancer among practicing physicians, the general public, and development of effective diagnostic tools for detection of prostatic carcinoma.

A number of studies have suggested that measurement of serum PSA levels may be of value as an adjunct in the diagnosis of patients with prostate cancer. Because of the tissue specificity of PSA secretion, a concentration of serum PSA in excess of 10 ng/mL is frequently associated with prostatic carcinoma.<sup>2,3</sup> Serum PSA values may be useful as an adjunct in the diagnosis of prostate cancer, but only in the context of additional diagnostic information such as digital rectal exam (DRE), transurethral ultrasonography, and needle biopsy.<sup>4</sup>

This clinical evaluation was designed to demonstrate the Intended Use of the ACS: 180 PSA and ADVIA Centaur assay as an aid in the detection of prostate cancer in men aged 50 years or older in conjunction with DRE. Additionally, it is intended to demonstrate equivalent performance of the ACS: 180 vs. the Immuno-1 PSA assay. The ACS: 180 (and ADVIA Centaur PSA) assays are equimolar methods that measure serum concentrations of PSA accurately.

This submission supplements the PMA of the Bayer Immuno-1 PSA assay which is approved to measure serum concentrations of PSA in conjunction with DRE in the detection of prostate cancer patients (PMA No. P950021/S1). The ACS: 180 PSA and ADVIA Centaur methods have been cleared by the FDA for use to measure serum concentrations of PSA during the course of disease and therapy as an adjunctive test in the management of prostate cancer patients (FDA 510(k) No. K994221). Since the ACS: 180 PSA method uses identical antibodies and antigen as those of the Immuno 1 PSA method, a retrospective analysis was conducted to evaluate and demonstrate the clinical utility of the ACS: 180 PSA method as an aid in the detection of cancer and compare results to those obtained using the Immuno-1 PSA method.

### III. CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS

There are no known contraindications for the Bayer ACS: 180™ and ADVIA Centaur™ PSA Assays.

Refer to the product labeling for a list of warnings and precautions.

### IV. DEVICE DESCRIPTION

The Bayer ACS: 180™ and ADVIA Centaur™ PSA Assays are in vitro devices indicated for the quantitative measurement of serum PSA in conjunction with digital rectal exam (DRE) as an aid in the detection of prostate cancer in men aged 50 years and older. This device is further indicated as an aid in the management (monitoring) of prostate cancer patients. The Bayer ACS: 180™ and ADVIA Centaur™ PSA Assays have been designed to run on the Bayer ACS: HOW and ADVIA Centaur™ immunoassay systems, fully automated random access analyzers which perform both homogeneous and heterogeneous immunoassays.

The ACS: 180™ and ADVIA Centaur™ are automated chemiluminescence systems that measure the amount of light emitted during a reaction. The PSA assay utilizes a monoclonal antibody conjugated to fluorescein (Reagent 1, R1) and a second monoclonal antibody conjugated to acridinium ester (R2), that are incubated with patient specimen, calibrator, or control to form a R1-cPSA-R2 "sandwich". Monoclonal Immuno Magnetic Particle (mIMP) Reagent, coated with anti-fluorescein antibody, is added to magnetically capture the antibody-antigen complex. Acid and base are added to initiate the chemiluminescent reaction, and concentration is determined from relative light units (RLUs) in relation to a standard curve.

## V. ALTERNATIVE PRACTICES AND PROCEDURES

Alternative practices and procedures for aiding in the detection of prostate cancer include physical examination using digital rectal examination (DRE) and diagnostic imaging by transrectal ultrasound (TRUS). Confirmation of prostate cancer is determined by biopsy with histological examination of prostate tissue.

## VI. MARKETING HISTORY

The ACS: 180™ and ADVIA Centaur™ PSA Assays with the intended use as an aid in the management (monitoring) of prostate cancer patients have been marketed since March 2000 in Australia, Italy, Belgium, France, Germany, the United Kingdom and the Netherlands. The assay has been marketed in the U.S. as of April 2000.

There have been no recalls or withdrawals of the reagent or calibrators for any reason related to the safety and effectiveness of this device.

## VII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

There are no known potential adverse effects on the health of patients when these devices are used as indicated. Because elevated levels of PSA occur in benign prostatic diseases, it is imperative that the physician use PSA test results in conjunction with the patient's overall clinical assessment and other diagnostic tests such as DRE and TRUS. A low serum PSA test result does not necessarily indicate the absence of prostate cancer, and therefore, assessment of patient status should not be based exclusively on a serum PSA result. Conversely, elevated PSA levels are observed in patients with nonmalignant diseases of the prostate including benign prostatic hyperplasia (BPH). Therefore, PSA values should be used in conjunction with the information from a complete clinical evaluation including DRE or other diagnostic tests. Confirmation of prostate cancer can only be determined by prostatic biopsy.

## VIII. SUMMARY OF STUDIES

### A. Preclinical Studies

Because approval was requested only for an additional intended use and did not involve any changes in test procedures or reagents, no pre-clinical study data were required. Analytical performance data were presented in previously cleared K994221.

### B. Clinical Study

#### 1. Study Objectives

To evaluate the intended use of the Bayer ACS: 180™ or ADVIA Centaur™ PSA Assays in conjunction with digital rectal exam (DRE) as an aid in the detection of prostate cancer in men aged 50 years or older. For this evaluation the Positive Predictive Value (PPV) of PSA and DRE exam together, was determined.

The null hypothesis tested was the PPV of the combination of DRE and the serum PSA test is < 13%. PPV is defined as the percent of patients with prostate cancer when either serum PSA or DRE results are abnormal.

Abnormality is defined as serum PSA value > 4.0 ng/mL and/or DRE irregularities suggesting cancer as determined by the physician.

## 2. Study design

### **Clinical Utility for Detection of Prostate Cancer**

The study population included 300 retrospective serum specimens with biopsy results. The Clinical Protocol demonstrated that a Positive Predictive Value equal to 20% for the Bayer ACS: 180 PSA Assay or digital rectal exam, when used in conjunction, can be determined with 95% confidence if results were available for at least 249 biopsies. Since the positive predictive value can be estimated with 95% confidence, the sample size of this study was justified.

Retrospective serum samples were tested internally at Bayer Corporation in Tarrytown, New York. All specimens were collected under Institutional Review Board (IRB) approval with appropriate informed consent.

Retrospective samples, which met the inclusion/exclusion criteria, were selected sequentially for entry into the study. DRE results were obtained not more than one month after or at least one week and not more than one month before specimen draw. Samples were drawn no more than one month before DRE, or at a time point greater than or equal to one week, but not less than one week after DRE. All diagnoses of prostate cancer were made by histological analysis of TRUS guided biopsy tissue and clinical stage and grade of disease was provided. The minimum specimen requirement was 2.0 mL and serum storage at -80°C for no greater than 2 years.

Each specimen was assayed by the ACS: 180™ PSA Assay and the Immuno 1 PSA assay to evaluate the intended use of the ACS: 180™ PSA Assay in conjunction with DRE as an aid in the detection of prostate cancer. For this evaluation, the positive predictive value (PPV) of the ACS: 180™ PSA test and DRE exam, together, and the ACS: 180™ PSA test, as a stand alone procedure was evaluated.

### **Clinical Study Results**

#### **Clinical Utility for Detection of prostate cancer**

TRUS guided biopsies were performed for all 291 male subjects who were tested by DRE and serum PSA using the Bayer ACS: 180 PSA assay. Of the 291 biopsied men, 76 men or 26.1 % were found to have prostate cancer.

The positive predictive value (PPV) of the Bayer ACS: 180 PSA assay, at a cutoff of 4 ng/mL was 28.4%. The PPV of PSA and DRE as a parallel test was 28.9%, as compared to 28.5% for Immuno-1 PSA assay. In a parallel test a person is positive if he has 1) an abnormal DRE, 2) a PSA above 4.0 ng/mL or 3) both. The null hypothesis (PPV of the combined tests is < 13%) was, therefore, rejected. These results indicate that the Bayer ACS: 180 PSA assay was suitable for the detection of prostate cancer.

Of the 76 biopsies with malignant diagnosis, clinical staging indicated that 96.05% (73/76) of these patients had organ confined early stage disease (Stage T1 or T2). The majority of these patients were, therefore diagnosed in an early stage of disease, with treatable and potentially curable cancer.

## Method Comparison

A total of 300 patient samples were used for the method comparison study. PSA results obtained from subjects entered in Part A of the study were evaluated. Specimens were tested with the Immuno-1 PSA assay for purposes of comparison to the ACS: 180 PSA assay.

The method comparison studies indicate that the Bayer ACS: 180™ PSA assay results correlate well with those obtained using Bayer Immuno-1 PSA Assay, which is FDA approved for use as an aid for the detection of prostate cancer (P950021/S1). The regression analysis using ordinary least squares regression analysis indicates that the methods correlate well at PSA ranges of a) 0-5 ng/mL, b) 0-10 ng/mL and c) full ranges. The overall regression analysis of 300 samples yielded  $ACS:180 = 0.92 \times (\text{Immuno } 1) + 0.16$  with  $r = 0.985$ .

A second comparison study was also performed using 661 samples tested on the ACS:180 and the ADVIA Centaur assays. The assay architectures and formulations are identical for both assays and since it is the intention to produce reagents for the two platforms in the same batch it was decided that a comparison study would be sufficient to document comparability. The results of the method comparison study indicated:

$$ACS: \text{Centaur} = 0.99 \text{ ACS:180} + 0.09$$

The correlation coefficient  $r$  was 0.99, and  $r^2 = 0.980$ .

## IX. CONCLUSIONS DRAWN FROM THE STUDIES

Results from method comparison indicate that the Bayer ACS: 180™ PSA assays are substantially equivalent to the Bayer Immuno-1 PSA assay, for which there is an approved PMA for the detection of prostate cancer in conjunction with DRE in men aged 50 years and older. Therefore, the Bayer ACS: 180™ and ADVIA Centaur™ PSA methods are suitable tests for the detection of prostate cancer in men 50 years of age or older and when used in conjunction with DRE.

The ACS: 180 PSA results indicate a positive predictive value of 28.4 %, for detection of prostate cancer. However, DRE can result in the detection of cancers that are not detected by PSA. Therefore, the two methods should be used in conjunction to enhance the detection of prostate cancer.

The combined use of PSA and DRE demonstrated that cancers detected were largely early stage (Stage A and B), organ confined, and of low grade histologically and therefore have the potential to be treated and cured. The results from the clinical and the method comparison studies indicate that the Bayer ACS: 180™ PSA Assay results are acceptable and equivalent to results obtained using the Bayer Immuno-1 PSA Assay, a test for which there is an approved PMA for use as an aid in the detection of prostate cancer in men aged 50 years and older. The Bayer ACS: 180™ PSA Assay is, therefore, safe and effective for quantifying serum PSA for use as an aid in the detection of prostatic carcinoma.

### Risks and Benefits

There are no known adverse effects on the health of patients whose serum PSA concentrations are measured when this device is used as indicated. The device is not indicated as a sole diagnostic tool to confirm the presence or absence of malignant prostate disease. Patients with confirmed

prostate cancer may have serum levels within the normal range. Conversely, elevated PSA levels are observed in patients with non-malignant diseases of the prostate including benign prostatic hypertrophy (BPH). Therefore, PSA values should be used in conjunction with complete clinical evaluation and other medical procedures including DRE and TRUS-guided needle biopsy.

Manipulations of the prostate including DRE, needle biopsy and transurethral resection can cause transient increases in serum PSA levels. Therefore, care should be taken to draw serum samples before performing these procedures, and retesting of PSA following these procedures should be delayed for at least two weeks to allow serum PSA to drop to original levels.

There is the risk that a false positive serum PSA result may expose the patient to additional medical procedures such as TRUS guided and needle biopsy.

The benefits associated with the use of the device are that in conjunction with DRE, more men are identified who should be further evaluated for prostate cancer. This results in the detection of more organ-confined cancers that are treatable and potentially curable.

Based on the results of the foregoing studies, the Bayer ACS: 180™ PSA assay is a safe and effective method for quantifying serum PSA for use as an aid in the detection of prostatic carcinoma in men aged 50 years and older when used in conjunction with DRE.

#### **X. Panel Recommendation**

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

#### **XI. CDRH Decision on Application**

FDA issued an approval order on DEC 22 2000.

A GMP inspection was not warranted, as the changes in this supplement were limited to an expansion of the indications for use.

#### **XII. REFERENCES**

1. Cancer Facts & Figures - 1998. The American Cancer Society. Atlanta, GA. 1998. pgs. 14-15,20-24.
2. Partin AW, Carter HB, Chan DW, et al. Prostate specific antigen in the staging of localized prostate cancer: influence of tumor differentiation, tumor volume, and benign hyperplasia. J Urol. 1990;143:747-752.
3. Lange PH, Ercole CJ, Lightner DJ, Fraley EE, Vessella R. The value of serum prostate specific antigen determinations before and after radical prostatectomy. J Urol. 1989;141:873-879.
4. Oesterling JE. Prostate specific antigen: a critical assessment of the most useful tumor marker for adenocarcinoma of the prostate. J Urol. 1991; 145:907-923.