P950021/S1

SUMMARY OF SAFETY AND EFFECTIVENESS

I. GENERAL INFORMATION

Device Generic Name:	PSA Immunoassay for the quantitative measurement of Prostate-Specific Antigen (PSA) in human serum.
Trade Name:	Bayer Immuno 1™ PSA System (hereinafter referred to as Bayer Immuno 1 Assay)
Applicant's Name And Address:	Bayer Corporation Business Group Diagnostics 511 Benedict Avenue Tarrytown, NY 10591
Premarket Approval (PMA) Number:	P950021/S1
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 was not the subject of an FDA Immunology Devices Advisory Panel meeting because the information in the PMA substantially duplicated information previously reviewed by this Panel.
Date of Notice of Approval of Application:	June 25, 1999

II. INDICATIONS FOR USE

The Bayer Immuno 1™ PSA System is an in vitro device intended for the quantitative measurement of prostate specific antigen (PSA) in human serum. This device is 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. This device is 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.[1] It is estimated that in 1998, 184,500 men will develop prostate cancer and approximately 39,200 men will die due to this malignancy[1]. The mortality rate for prostate cancer is nearly two-times higher for African-American men than white men[1]. 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%[1]. The survival rates for all stages combined have increased from 67% to 89% over the past 20 years[1]. 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.

As discussed by Brawer et al., a number of different diagnostic procedures are available for the detection of prostate cancer[2]. Today, the digital rectal examination (DRE) is still considered standard practice in the detection of prostate cancer. Transrectal ultrasound (TRUS) allows the oncologist to visualize suspicious prostatic lesions and is commonly used to direct the biopsy of potentially neoplastic tissue. Serum biomarkers, prostatic acid phosphatase (PAP) and prostate specific antigen (PSA) have been shown to be effective in the detection of prostate malignancy.

PSA has been identified by Wang et al. as a 33-34,000 dalton glycoprotein[3,4]. The cDNA sequence for PSA is now known and codes for a glycoprotein of 237 amino acids with homology to members of the kallikrein gene family, including pancreatic kallikrein and human kallikrein 1, hGK-1[5,6]. PSA contains from one to four N-linked oligosaccharide chains and functions to liquefy the coagulum formed following ejaculation.

A number of recent 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[7,8]. 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[2,9,10,11].

As a result of these and other reports, the American Cancer Society has recommended that both the prostate specific antigen (PSA) blood test and the digital rectal examination be offered annually, beginning at age 50, to men who have a life expectancy of at least 10 years and to younger men who are at high risk[1]. Patients should be given information regarding the potential risks and benefits of intervention[1].

III. DEVICE DESCRIPTION

The Bayer Immuno 1 PSA Assay is a sandwich immunoassay which employs a monoclonal PSA antibody conjugated to fluorescein (R1), a polyclonal PSA antibody conjugated to alkaline phosphatase (R2), and anti-fluorescein coated magnetic particles (mIMP™ Reagent) as the solid phase[12]. Sample, Reagent 1 and Reagent 2 are simultaneously incubated at 37°C in a reaction tray cuvette on the Immuno 1 analyzer. During the incubation period, the Reagent 1 antibody and Reagent 2 antibody both bind to different sites on the PSA molecule in the sample to form "sandwich complexes." The complex formed in the solution is then captured by the mIMP™ Reagent via a fluorescein-anti-fluorescein linkage. The solid phase is then held in the cuvettes by magnets on the instrument and washed to remove unbound PSA, excess reagent, and sample components. After the washing step, the solid phase is then incubated with a colorimetric enzyme substrate containing p-nitrophenyl phosphate. The substrate is hydrolyzed by alkaline phosphatase in the bound immune complex to produce color. Color formation is monitored via optical density measurements at 405 or 450 nanometers depending upon the rate of absorbance change. Formation of color is directly proportional to the concentration of PSA in the test specimen. The rate of reaction is determined using a linear least squares algorithm. The rate is compared to a standard curve to derive the PSA concentration in the sample. The PSA calibration curve encompasses a range of 0 to 100 ng/mL and is generated using a cubic fit through zero algorithm. Results are reported after 38.5 minutes. The assay requires 20 μL of serum.

IV. ALTERNATIVE PRACTICES AND PROCEDURES

Alternative practices and procedures for aiding in the detection of prostate cancer include, use of other approved PSA tests, 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.

V. MARKETING HISTORY

The Bayer Immuno 1 PSA Assay with the intended use as an aid in the management (monitoring) of prostate cancer patients has been marketed since May 1994 in Canada, South Africa, Japan, Taiwan and the following European countries: Belgium, Denmark, Finland, France, Germany, Italy, Norway, Spain, Sweden, Switzerland, The Netherlands and the United Kingdom; and since February 1996 in the U.S.

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

VI. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

The Bayer Immuno 1 PSA Assay is intended for in vitro diagnostic use only. There are no known potential adverse effects on the health of patients when this device is 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 level of serum PSA test results 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.

PRECAUTIONS AND WARNINGS

This 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[7,8,13]. Conversely, elevated PSA levels are observed in patients with non-malignant diseases of the prostate including benign prostatic hyperplasia (BPH)[8]. 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.

Manipulations of the prostate including DRE, needle biopsy, and transurethral resection can cause transient and often large increases in serum PSA levels[14]. Therefore, care should be taken to draw PSA samples before performing these procedures and retesting should be delayed at least two weeks to allow serum PSA to return to original levels[15].

The concentration of PSA in a given specimen determined with assays from different manufacturers can vary due to differences in assay methodology and reagent specificity. The results reported by the laboratory to the physician must include the identity of the PSA assay used. Values obtained with different PSA assays cannot be used interchangeably.

VII. 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 because analytical test performance was established in the original PMA.

B. CLINICAL STUDY

A multi-site clinical trial was conducted to evaluate the safety and effectiveness of the device, in conjunction with DRE to aid in the detection of prostate cancer in men aged 50 years or older. The study was performed at five sites in the United States.

1. STUDY OBJECTIVES

a.) To evaluate the intended use of the Bayer Immuno 1 PSA Assay 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 the Bayer Immuno 1 PSA test and DRE exam, together, and as stand alone procedures was determined. The added value of each test was determined from the percent of additional cancers that each test detects over the other.

The null hypothesis tested is the PPV of the combination of (DRE) and the serum PSA test is less than 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 greater than 4.0 ng/mL and/or DRE irregularities suggesting cancer as determined by the physician.

b.) To describe the relationship between the Bayer Immuno 1 PSA Assay results with those of other legally marketed PSA assays using comparative studies and regression analysis.

2. STUDY DESIGN

2.1 Part A: Clinical Utility for Detection of Prostate Cancer

Male subjects of various racial and ethnic backgrounds aged 50 years and older without evidence of acute prostatitis, urinary tract disease, or personal history of prostate cancer were enrolled both prospectively and retrospectively at five clinical study sites. All enrolled men had a DRE and determinations of serum PSA using the Bayer Immuno 1 PSA Assay. If the Bayer Immuno 1 PSA test result was greater than 4.0 ng/mL or DRE was considered abnormal by the attending physician, TRUS-guided biopsy was recommended by the physician. If the patient consented to undergo biopsy, diagnosis of prostate cancer was made by histological analysis of TRUS-guided biopsy tissue, and the clinical stage and grade of disease were provided. The TNM clinical staging system describing the anatomic extent of disease was employed by the evaluation sites[16]. Histological grading of tumors was determined using the Gleason grading system[16].

2.2 Part B: Method Comparison

A total of 750 patient samples were enrolled into the method comparison study. Specimens from 250 subjects chosen at random from subjects entered into Part A of the study were evaluated at each of three investigational sites. Specimens included both retrospective and prospective specimens. Specimens were tested with other PSA methods for purposes of comparison to the Bayer Immuno 1 PSA result. The mean, minimum and maximum difference between Bayer Immuno 1 PSA and comparison PSA results for patient samples in the ranges of 0 to 5 ng/mL, 0 to 10 ng/mL, and 0 to the highest PSA value obtained, was determined. Patient values derived using both the Bayer Immuno 1 PSA Assay and the other PSA assay were modeled via linear regression statistics using the Bayer Immuno 1 PSA results as the dependent variable. In addition, the Passing-Bablock regression technique was applied which is robust to the presence of outliers. This method is the preferred method of analysis due to large effects that sporadic outliers have on ordinary least squares regression analysis. Analysis was performed for 250 specimens from each of the investigational sites as well as a combined analysis. Comparison of results and regressions was performed over the ranges: 0 to 5 ng/mL, 0 to 10 ng/mL and 0 to the highest PSA value obtained.

3. STUDY RESULTS

3.1 Part A: Clinical Utility for Detection of prostate cancer

A total of 2,848 enrolled male subjects were tested by DRE and serum PSA using the Bayer Immuno 1 PSA Assay. A total of 675 men were found to have an abnormal DRE or PSA result greater than 4 ng/mL. TRUS guided biopsies were performed for 313 subjects (299 whose PSA was greater than 4.0 ng/mL or DRE was suspicious for prostate cancer and 14 whose results were normal on either diagnostic test). Of the 313 biopsied men, 108 men (34.5%) were found to have prostate cancer. The results can be summarized as follows:

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	Number of subjects (%)	Number of Biopsies	Number of cancers	% positive biopsies (95% CI)
All	2848 (100%)	313	108	35 (29.3 – 39.9)
PSA > 4	495 (17.4)%	259	95	37 (30.9 – 42.7)
DRE +	290 (10.2%)	108	51	47 (37.8 – 56.6)
PSA ≤ 4; DRE -	2173 (76.3%)	14	2	14
PSA > 4; DRE -	385 (13.5%)	191	55	29 (22.5 – 35.4)
PSA ≤ 4; DRE +	180 (6.3%)	40	11	28 (13.7 – 41.3)
PSA > 4; DRE +	110	68	40	59 (47.1 – 70.5)

The positive predictive value (PPV) of the Bayer Immuno 1 PSA Assay, at a cutoff of 4 ng/mL, was 36.8% ± 3.0%. The PPV of the (DRE) exam was 47% ± 4.8% and was not significantly different from the PPV of PSA. The PPV of PSA and DRE as a parallel test was 35% ± 2.8% and was not significantly different from the PPV of PSA. In a parallel test, a person is positive if they either have an abnormal DRE or have a PSA above 4 ng/mL. The PPV for PSA and DRE as a combined test was 58.8% ± 6.0%. The PPV for PSA and DRE as a combined test was significantly different from the PPV of PSA but not different from the PPV for DRE. In a combined test, a person is positive if they have both an abnormal DRE and a PSA above 4 ng/mL. The clinical sensitivity of PSA was 88% ± 3% and a clinical specificity of 20% ± 2.8%.

In the current study, the parallel combination of PSA and DRE at a cutoff of 4 ng/mL detected 50.9% more cases of prostate cancer than DRE alone. If PSA is considered as a stand alone test using a cutoff of 4 ng/mL, the Bayer Immuno 1 PSA Assay would identify 40.7% more cancer cases than DRE alone. When DRE was positive and PSA was less than or equal to 4.0 ng/mL, DRE detected 10% (11/108) of cancers that PSA determinations did not.

Taken together, these data indicate that the Bayer Immuno 1 PSA Assay contributes to the detection of prostate cancer as compared to DRE alone. PSA elevations greater than 4.0 ng/mL may warrant additional testing even if the DRE is negative. However, the converse is also true; a subject with suspicious DRE and a normal PSA may also require additional testing since DRE detected cancers that PSA determinations did not.

Of the 108 biopsies with a malignant diagnosis, 102 Gleason scores were available. 85% (87/102) of these men had a Gleason score less than or equal to 7 with a median Gleason score of 6. One biopsy had a Gleason score of 10 and one had a score of 4. Of the 108 biopsies with malignant diagnosis, clinical staging was available for 98 subjects. Clinical staging indicated that 87% (85/98) of these patients had organ confined early stage disease (stage T1 or T2). Thirteen men were classified as having either extraprostatic organ invasion, lymph node invasion, or distant metastasis. The majority of these patients, therefore, were diagnosed in early stage disease, with treatable and potentially curable cancers.

3.2 Part B: Method Comparison

The results of the method comparison studies indicate that the Bayer Immuno 1 PSA Assay results correlate with those obtained using the other legally marketed methods for use as an aid for the detection of prostate cancer. The regression analysis using ordinary least squares regression analysis and Passing-Bablok regression analysis indicate that the methods correlate at PSA ranges of a) 0-5 ng/mL, b) 0-10 ng/mL, and c) full ranges. The combined ordinary least squares regression analysis for 750 paired PSA results over all specimens tested at the three evaluation sites yielded Immuno 1= 0.98x + 0.08. The combined Passing-Bablok regression analysis for 750 paired PSA results, over all specimens tested at three evaluation sites yielded Immuno 1 = 1.03x - 0.09.

3.3 Part C: Analysis Using Incremental Values[21]

Using this analysis, the PSA (when used alone) detected 95 cancers in the 2848 patients studied (a diagnostic yield of 3.3%) at a cost of 259 biopsies. Assuming the cancers are true positives (no biopsy sampling errors) and that the negative biopsy readings by the pathologist are true negatives (even if the biopsy represents a false negative biopsy sampling error), the FP/TP ratio is 2.7. For the combined use of PSA positive and DRE positive results, the total cancers found were 40 (a 1.4% diagnostic yield) at a cost of 68 biopsies with a FP/TP ratio of 1.7.

VIII. CONCLUSIONS DRAWN FROM THE STUDIES

Results of the clinical studies using determinations of serum PSA support the safety and effectiveness of the Bayer Immuno 1 PSA Assay as an aid in the detection of prostate cancer in men aged 50 years and older. The Bayer Immuno 1 PSA results indicate a positive predictive value for PSA only of 36.8%, which agrees well with literature reports[11,17,18]. The use of serum PSA determinations when used with DRE indicate that the Bayer Immuno 1 PSA Assay will detect 50.9% more cancers than DRE testing alone. However, DRE resulted in the detection of cancers (10%) that were not detected by PSA. The use of the Bayer Immuno 1 PSA Assay at a cutoff of 4 ng/mL should, therefore, be considered as an appropriate tool for detection of this disease. When used with DRE, the Bayer Immuno 1 PSA Assay contributes to the detection of prostate cancer as compared to the use of DRE alone. These findings agree well with literature reports[11,17,18,19,20,21].

The detected cancers were mostly early stage (stage T1 and T2), organ confined, and of low grade histologically (Gleason scores ≤ 7). These findings agree well with other large scale studies reported in the literature[11,17,19,20,21] which also found that tumors detected by serum PSA and DRE were predominantly localized, organ confined cancers with Gleason scores of less than 7 indicating early stage, potentially curable cancer. These studies demonstrate the clinical utility of the Bayer Immuno 1 PSA Assay in conjunction with DRE for detection of prostate cancer.

The results from the method comparison studies indicate that the Bayer Immuno 1 PSA Assay results are equivalent to results obtained using other legally marketed PSA assays.

The Bayer Immuno 1 PSA Assay is therefore safe and effective 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 conjunstion with DRE.

Risks and Benefits

The device is not indicated as a sole diagnostic tool to confirm the presence or absence of malignant prostate disease. Elevated PSA levels are observed in patients with non-malignant diseases of the prostate, including benign prostatic hypertrophy (BPH)[8], and frequently have negative biopsy results. In the current study, 191 of 313 biopsied subjects had elevated PSA determinations and a rectal examination not suspicious for cancer. Of the 191 men, 55 men were found with cancer (50.9% of cancers detected in this study) and 136 men were found without cancer (66.3% of benign diseases detected in this study) but underwent an unneeded biopsy. Conversely, patients with confirmed prostate cancer may have serum levels within the normal range (14% of subjects in this study)[7,8,13]. 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 and often large increases in serum PSA levels[14]. 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[15].

There is the risk that a false positive serum PSA result may expose the patient to additional medical procedures such as TRUS-guided 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 Immuno 1 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.

IX. PANEL RECOMMENDATION

Pursuant to Section 515(c)(2) of the act as amended by the Safe Medical Devices Act if 1990, this PMA was not the subject of an FDA Immunology Devices Advisory Panel meeting because the information in the PMA substantially duplicated information previously reviewed by this Panel.

X. CDRH ACTION ON THE APPLICATION

CDRH issued an approval for the application on June 25, 1999.

XI. APPROVAL SPECIFICATION

Directions for Use: See Attached Labeling

Conditions for Approval: CDRH Approval of the PMA is subject to final compliance with the conditions described in the Approval Order

XII. REFERENCES

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