

K980376

001070

510(K) SUMMARY
FOR THE
BAYER IMMUNO 1™ COMPLEXED PSA (cPSA) ASSAY

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: _____

1. GENERAL INFORMATION

Trade Name: Bayer Immuno 1™ Complexed PSA (cPSA) Assay

Classification Name: Tumor-Associated Antigen Immunological Test Systems

Gabriel J. Muraca, Jr.

Gabriel J. Muraca, Jr.
Manager, Regulatory Affairs
Bayer Corporation
Business Group Diagnostics

11/29/98
Date

15

001071

This premarket notification is to add the quantitative measurement of complexed prostate specific antigen (cPSA) in human serum to the intended use of the Bayer Immuno 1™ Immunoassay System. The performance of the Bayer Immuno 1™ Complexed PSA (cPSA) Assay has been established by comparison to a predicate device, the Bayer Immuno 1™ PSA Assay, in accordance with the “Guidance Document For Submission of Tumor Associated Antigen Premarket Notifications, 510(k), to the FDA.” Clinical evaluations of the Bayer Immuno 1™ Complexed PSA (cPSA) Assay at three US clinical trial sites demonstrated clinical safety and effectiveness and substantial equivalence to the predicate device.

2. INDICATIONS FOR USE

The Bayer Immuno 1™ Complexed PSA (cPSA) Assay is an *in vitro* diagnostic assay intended to quantitatively measure complexed prostate specific antigen (cPSA) in human serum on the Bayer Immuno 1™ System. Complexed prostate specific antigen (cPSA) values obtained should be used as an aid in the management (monitoring) of prostate cancer patients

3. DEVICE DESCRIPTION

The Bayer Immuno 1™ cPSA Assay utilizes the same immunoassay technology and the same R1 and R2 reagents as in the Bayer Immuno 1™ PSA Assay except for the addition of a third, unlabeled, monoclonal antibody to the R2 reagent. Reagent 1 (or R1) contains monoclonal PSA antibody conjugated to fluorescein while Reagent 2 (or R2) contains polyclonal PSA antibody conjugated to alkaline phosphatase and a third unlabeled antibody specific for free PSA. The R1 and R2 conjugates are reacted with patient sample, calibrator, or control and are incubated at 37°C on the system. Free PSA in the serum is bound by the unlabeled free PSA antibody while the remaining complexed PSA is bound by the PSA antibody conjugated to alkaline phosphatase. Immuno 1 Magnetic Particles coated with an anti-fluorescein antibody are then added and a second incubation occurs during which the antibody enzyme conjugate complex is bound. Washing of the particles is followed by addition of substrate (PNPP) reagent. The rate of conversion of substrate to a compound with absorbance at 405 and 450 nm is measured and the measured rate is proportional to the concentration of cPSA antigen in the sample. A cubic-through-zero curve fitting algorithm is used to generate standard curves.

The assay has a range of 0.02 to 100 ng/mL. The Bayer Setpoint™ Complexed PSA (cPSA) Calibrators consist of a set of six calibrator levels at 0, 2, 10, 25, 50, and 100 ng/mL. The Bayer Setpoint™ Complexed PSA (cPSA) Controls consist of a set of 3 control levels at approximately 3.5, 15, and 75 ng/mL.

001072

4. **SUMMARY OF STUDIES**

Nonclinical studies were performed at Bayer Corporation, Diagnostics Division, Tarrytown, New York to evaluate the purity of the calibrators, the purity and specificity of the reagents, and the efficacy of the reagent and calibrator preservatives. Data were also collected to evaluate specificity and interfering substances, cross-reactivity, heterophilic antibodies, linearity, hook effect/antigen excess, and parallelism. The clinical evaluation of Immuno 1 cPSA Assay as a quantitative measure of serum complexed PSA for use as an adjunctive test in the management of prostate cancer patients, was conducted at three US clinical trial sites. In addition, the Immuno 1 cPSA Assay was evaluated at the clinical sites for imprecision/reproducibility and analytical sensitivity.

4.1 **Characterization of the Antigen**

The calibrator antigen used in the Bayer Immuno 1 cPSA assay is purified PSA-ACT which is PSA isolated from human seminal fluid and complexed *in vitro* with alpha-1-antichymotrypsin (ACT). The antigen is manufactured by Scripps Laboratories (San Diego, CA) and is supplied to Bayer. Antigen preparations were characterized using SDS-polyacrylamide gels under reducing conditions and results were consistent with the molecular weight of the antigen reported in the literature. Isoelectric focusing of the PSA-ACT antigen resolved pIs that were consistent with published values.

4.2 **Immunoreactivity of the Antibodies**

The monoclonal and polyclonal anti-PSA antibodies used in the preparation of the R1 and R2 reagent for the Bayer Immuno 1™ Complexed PSA (cPSA) Assay are identical to those used in the Bayer Immuno 1™ PSA Assay. A third unlabeled monoclonal antibody was added to the R2 reagent of the cPSA Assay. The unlabeled monoclonal antibody was characterized in a series of experiments including isotype analysis, relative affinity analysis by ELISA, reducing and non-reducing SDS-PAGE and isoelectric focusing. These results demonstrated that the unlabeled monoclonal antibody bound to the PSA antigen quantitatively and specifically, and displayed biophysical properties expected of mouse monoclonal antibodies.

4.3 **Reagent Microbial Testing**

The formulation of cPSA Assay R1 reagent is identical to that of the Bayer Immuno 1 PSA Assay R1 reagent, therefore, no additional microbiological testing

001073

was required. Preservative challenge testing was performed on the R2 reagent due to the addition of a third unlabeled monoclonal antibody. Results indicated an acceptable preservative system according to US Pharmacopoeia guidelines.

4.4 Calibrator Microbial Testing

Immuno 1 cPSA calibrator preservative was challenged with known concentrations of five strains of microorganisms recommended by US Pharmacopoeia standards and performance of the calibrators was tested. Microbial performance challenge testing on cPSA calibrators demonstrated that inoculation of the calibrators with up to 10^6 of each of the microorganisms per mL of calibrator had no significant effects on calibrator performance.

4.5 Assay Performance

4.5.1 Specificity: Interference

The recovery of cPSA from patient samples was studied before and after spiking the serum samples with the potentially interfering. Each potential interferent was tested at a maximum concentration.

The Immuno 1 cPSA Assay was performed on serum samples or pools of serum to which was added various concentrations of either triglycerides, immunoglobulin, hemoglobin, heparin, bilirubin, or albumin. cPSA values were also measured in serum samples after spiking with either an individual chemotherapeutic drug, "Over the Counter" (OTC) drug, or vitamin. None of the potential endogenous or exogenous interferents demonstrated any significant interfering effects on cPSA recovery. The test specification was $\pm 10\%$ deviation and none of the substances demonstrated an interference outside of this range.

4.5.2 Cross-Reactivity

Possible cross-reactions in the Immuno 1 cPSA Assay were studied by comparing cPSA recoveries in patient samples with and without various spiked amounts of kallikrein, trypsin, and chymotrypsin. The maximum effect seen with each cross-reactant was not significant ($\leq 1\%$).

4.5.3 Heterophilic Antibodies

To investigate the effectiveness of the assay's reagent formulation in minimizing

heterophilic antibody interferences, a total of 206 patient samples with HAMA, RF titers, or autoimmune diseases were tested for possible interference in the cPSA assay. The observed cPSA recoveries indicated a lack of significant heterophilic interference in the assay and demonstrated the effectiveness of the reagent formulation in minimizing these interferences.

4.5.4 Linearity

To determine the linearity of this assay, four individual serum samples from prostate cancer patients were diluted (100%, 75%, 50%, 25%, and 0%) with a pool of female human sera. Recoveries of the intermediate dilutions were all between 95 and 103 percent of the expected values. These results demonstrate the linearity of cPSA recoveries over the entire calibration range.

4.5.5 Hook Effect (Antigen Excess)

Extremely high concentrations of cPSA seen in some malignant conditions may cause a "hook effect" in an assay. An excess of analyte saturates both label and capture antibody and causes the reported concentration to "hook" back into the assay range rather than be flagged as above range. cPSA antigen (PSA-ACT) was diluted in Level 1 Calibrator at concentrations of 50 ng/mL to 100,000 ng/mL. Results clearly demonstrated the lack of a hook effect in the Immuno 1 cPSA Assay at cPSA values $\leq 12,500$ ng/mL.

4.5.6 Parallelism (Dilution Studies)

As a further verification of assay linearity, and to qualify the Level 1 Calibrator as a sample diluent, four patient serum samples containing a high level of cPSA were diluted (100%, 75%, 50%, 25%, and 0%) with Level 1 Calibrator. Linear regression analysis for the determination of deviations from linearity for each of these clinical samples showed no deviation from linearity. The recovery of cPSA assay values ranged from 97.0 to 107.6%. These data demonstrate that Level 1 calibrator is an acceptable diluent for high samples, with accurate recovery of diluted values.

4.5.7 Reproducibility

Intra- and inter-assay reproducibility were evaluated at three clinical trial sites for three levels of Bayer SETpoint Complexed PSA (cPSA) Controls and a human serum pool with complexed PSA concentration < 1.0 ng/mL. Imprecision data pooled across Immuno 1 cPSA reagent lots and systems/sites showed maximal

total coefficients of variation (%CV) of 2.4% over the range of the assay method. This is well within acceptable limits for an assay of this type.

Immuno 1 Complexed PSA (cPSA) Imprecision Pooled Across Three Clinical Sites and Three Immuno 1 cPSA Reagent Lots						
Product	Mean ng/mL	Total N	Within-Run		Total	
			SD ng/mL	CV %	SD ng/mL	CV %
Serum Pool	0.67	360	0.01	1.31	0.02	2.3
Control Level 1	3.35	358	0.06	1.9	0.08	2.3
Control Level 2	14.88	359	0.24	1.6	0.30	2.0
Control Level 3	74.34	360	1.38	1.9	1.76	2.4

4.5.8 Sensitivity (Detection Limit)

Sensitivity of the Immuno 1 Complexed PSA (cPSA) Assay was evaluated at three clinical trial sites by determining the Minimum Detectable Concentration (MDC). An MDC of 0.016 ng/mL was observed when assaying 717 replicates of the Immuno 1 cPSA zero calibrator using two Immuno 1 cPSA calibrator lots and three Immuno 1 cPSA reagent lots.

Immuno 1 Complexed PSA (cPSA) analytical sensitivity, determined from data collected at three clinical trial sites using three Immuno 1 cPSA reagent lots and two Immuno 1 cPSA calibrator lots is excellent, and qualifies this assay as an ultrasensitive complexed PSA method.

4.6 CLINICAL STUDIES

4.6.1 Introduction

To assess the safety and effectiveness of the Bayer Immuno 1™ Complexed PSA (cPSA) Assay, clinical studies were performed at three investigational sites. All patients were studied retrospectively. Assay values were determined for surplus serum samples which had been collected and stored (-70° C) in specimen banks prior to the study.

001076

4.6.2 Serial Monitoring - Management Value of the Immuno 1 Complexed PSA (cPSA) Assay Results for Prostate Cancer Patients

The Immuno 1 Complexed PSA (cPSA) Assay was used to determine complexed PSA values in sequential serum specimens collected from 155 patients with malignant prostate disease. Approximately four to nine specimens were collected from patients entered into the study for sampling periods that ranged from 3 months to 7 years. The specimens were assayed for complexed PSA concentration with the Immuno 1 cPSA Assay and for total PSA concentration with the Immuno 1 PSA Assay which has FDA Pre-Market Approval (PMA) for the management of prostate cancer patients. A medical history was also collected for each patient.

The use of the Immuno 1 Complexed PSA (cPSA) Assay as an aid in the management of prostate cancer patients during the course of disease and therapy was demonstrated in this study. Serial complexed PSA testing using the Immuno 1 cPSA Assay demonstrated agreement between serum complexed PSA concentrations and the patients' clinical status for 150 out of 155 (97%) of the longitudinally monitored prostate cancer patients. Increasing concentrations of complexed PSA were found in patients prior to and during the onset of progressive or recurrent disease. Complexed PSA concentrations significantly decreased following successful surgery and/or administration of radiation therapy, chemotherapy or hormonal therapy.

The Immuno 1 Complexed PSA (cPSA) Assay and the Immuno 1 PSA Assay for which there is an approved PMA for the management of prostate cancer patients, showed identical patterns of increases and decreases for the serially monitored patients. The management value of both assays are equivalent.

These data support the clinical utility of the Immuno 1 Complexed PSA (cPSA) Assay as an adjunctive test for use in the management of prostate cancer patients during the course of disease and therapy.

4.6.3 Distribution of Complexed PSA Concentrations; Sensitivity and Specificity of the Immuno 1 cPSA Assay

The Immuno 1 cPSA Assay was used to determine the distribution of complexed PSA concentrations in healthy females, healthy males, patients with active prostate cancer, male patients with benign urogenital diseases,

male patients with various non-urogenital non-malignant diseases, and male patients with various malignant diseases of non-prostate origin.

The distribution of complexed PSA concentrations determined by the Immuno 1 cPSA Assay is equivalent to the distribution of total PSA concentrations determined by the Immuno 1 PSA Assay for which there is an approved PMA and is similar to the distribution of total PSA values reported in the literature for the same population groups.

As with all tests, each laboratory should establish its own reference range. Since Complexed PSA is a proportion of total PSA, the upper limit of normal can be expected to be different than that for the total PSA.

4.6.4 Conclusions from the Clinical Studies

These clinical studies demonstrated that Immuno 1 Complexed PSA (cPSA) Assay measurement of complexed PSA in serial serum specimens over a disease course can aid the physician in the management of prostate cancer patients. Clinical equivalence to the Immuno 1 PSA Assay for which there is an approved PMA was demonstrated by excellent trending agreement for serially monitored patients. The frequency distribution of Immuno 1 cPSA concentrations were similar to the distribution of Immuno 1 PSA assay values in the same population groups.

Immuno 1 Complexed PSA (cPSA) results are highly reproducible with maximum inter-assay %CV pooled over reagent lots and clinical sites of 2.4% over the range of the assay. The detection limit of 0.02 is acceptable for an ultrasensitive complexed PSA assay.

5. CONCLUSIONS DRAWN FROM ALL THE STUDIES

Valid Scientific Evidence

The conclusions drawn from these studies are based upon valid scientific evidence. Data were gathered following a well-designed protocol, in a research laboratory operating under the principles of Good Laboratory Practices. Clinical data were gathered during well controlled investigations conducted by qualified experts. Patient case histories were well documented. The results of this study are comparable to literature reports of experiences with commercial total PSA assays.

Method Performance

Immuno 1 Complexed PSA (cPSA) performance including reproducibility, analytical sensitivity and specificity, cross-reactivity, linearity, antigen excess hook effect, and parallelism meet the accepted specifications set for an assay of this type.

Safety and Effectiveness

The clinical studies confirm the safety and effectiveness of the Immuno 1 cPSA Assay as an aid in the management of prostate cancer patients. The correlations between Immuno 1 cPSA concentrations and the patients' clinical course of disease demonstrate that the Immuno 1 cPSA Assay may be used in conjunction with other clinical indicators to confirm the success of primary therapy and to signal possible recurrence of malignant disease.

Substantial Equivalence

The results of the comparison between Immuno 1 cPSA and Immuno 1 PSA, for which there is an approved PMA, demonstrate that the two kits are equivalent with respect to safety and effectiveness. There is excellent trending agreement between the Immuno 1 cPSA and Immuno 1 PSA concentration results for serially monitored patients. For prostate cancer patients, the distribution of Immuno 1 Complexed PSA (cPSA) values are consistent with stage of disease and treatment status. The frequency distribution of the serum complexed PSA concentrations found in apparently healthy individuals as well as patients with various benign urogenital and non-urogenital diseases, and various non-prostatic malignant diseases, when assayed with Immuno 1 cPSA, correspond to the serum PSA concentrations reported in the literature. Therefore, based upon the clinical concordance established in these studies, the Bayer Immuno 1™ Complexed PSA (cPSA) Assay and the Bayer Immuno 1™ PSA Assay are equivalent with respect to method performance, clinical utility, and device safety and effectiveness.



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

APR 23 1998

Food and Drug Administration
2098 Gaither Road
Rockville MD 20850

Mr. Gabriel J. Muraca, Jr.
Manager, Regulatory Affairs
Bayer Corporation
Business Group Diagnostics
511 Benedict Avenue
Tarrytown, New York 10591-5097

Re: K980376
Trade Name: Bayer Immuno 1™ System Complexed PSA (cPSA) Assay
Regulatory Class: II
Product Code: LTJ
Dated: January 29, 1998
Received: January 30, 1998

Dear Mr. Muraca:

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.

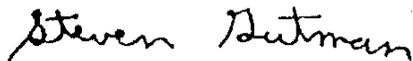
Page 2

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

001103

Page 1 of 1

510(k) Number (if known): _____

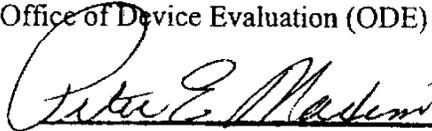
Device Name: Bayer Immuno 1™ cPSA Assay

Indications For Use:

The Bayer Immuno 1™ cPSA Assay is an *in vitro* diagnostic assay intended to quantitatively measure complexed prostate specific antigen (cPSA) in human serum on the Bayer Immuno 1™ System. Complexed prostate specific antigen (cPSA) values obtained should be used as an aid in the management (monitoring) of prostate cancer patients.

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

Concurrence of CDRH, Office of Device Evaluation (ODE)



(Division Sign-Off)
Division of Clinical Laboratory Devices
510(k) Number 1C 980376

Prescription Use
(Per 21 CFR 801.109)

OR

Over-the-counter Use

(Optional Format 1-2-96)