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510(K) SUMMARY
FOR THE
BAYER IMMUNO 1™ HER-2/neu 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: K992228

1. GENERAL INFORMATION

Trade Name: Bayer Immuno 1™ HER-2/neu Assay

Classification Name: Tumor-Associated Antigen Immunological Test Systems

9-22-2000
Date

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This premarket notification is to add the Bayer Immuno 1™HER-2/neu Assay to the intended use of the Bayer Immuno 1™System. In this 510(k) application, the performance and clinical safety and effectiveness of the Bayer Immuno 1 HER-2/neu Assay for the management (monitoring) of metastatic breast cancer patients has been established by external clinical studies in the target population of longitudinal metastatic breast cancer patients and by comparison to accepted diagnostic procedures 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 HER-2/neu Assay at three US clinical trial sites demonstrated clinical safety and effectiveness. These studies validated clinical performance characteristics and the comparison to accepted diagnostic procedures.

2. INDICATIONS FOR USE

The Bayer Immuno 1™ HER-2/neu Assay is an *in vitro* diagnostic assay intended to quantitatively measure HER-2/neu protein in human serum on the Bayer Immuno 1™ System. HER-2/neu values obtained may be used in the follow-up and monitoring of patients with metastatic breast cancer. HER-2/neu values should be used in conjunction with information available from clinical and other diagnostic procedures in the management of breast cancer. The clinical utility of serum measurement of HER-2/neu as a prognostic indicator for early detection of recurrence and in the management of patients on immunotherapy regimens has not been fully established.

3. DEVICE DESCRIPTION

The Bayer Immuno 1™ HER-2/neu Assay utilizes a well-established immunoassay technology in which one monoclonal HER-2/neu antibody (NB-3) is conjugated to fluorescein (designated Reagent 1, or R1) and the Fab' fragment of another monoclonal HER-2/neu antibody (TA-1) is conjugated to alkaline phosphatase (Reagent 2, or R2). The R1 and R2 conjugates are reacted with patient sample, calibrator, or control and are incubated at 37°C on the system. Immuno 1 Magnetic Particles coated with an anti-fluorescein antibody (*mIMP*™ Reagent) are then added and a second incubation occurs during which the antibody complex is bound. The magnetic particles complexed with the

immunological sandwich are then washed to separate unbound molecules, and a colorimetric substrate is added. The rate of conversion of substrate to a compound with absorbance at 405 and 450 nm is measured is proportional to the concentration of HER-2/neu in the sample. A cubic-through-zero curve-fitting algorithm is used to generate standard curves.

The assay has a range of zero to 250 ng/mL. The Bayer SETpoint™ HER-2/neu Calibrators consist of a set of six calibrator levels at 0, 10, 25, 60, 125, and 250 ng/mL. The Bayer TESTpoint™ HER-2/neu Controls consist of a set of three control levels at approximately 15, 50 and 100 ng/mL.

4. SUMMARY OF STUDIES

Non-clinical studies were performed to validate the performance of the method according to the protocol entitled "Non-clinical Testing Protocol for the Evaluation of the of the Bayer Immuno 1™ HER-2/neu Assay." Protocols were performed at the Bayer Corporation laboratories in Tarrytown, NY and Elkhart, IN. These studies included evaluation of interfering substances, cross-reactivity, heterophilic antibodies, calibration linearity, sample linearity, parallelism (sample dilution), hook effect, reproducibility, and reagent lot-to-lot variation.

The clinical evaluation of Immuno 1 HER-2/neu Assay as an aid in the management of breast cancer patients with Stage IV metastatic disease, during the course of disease and therapy, was conducted at three US clinical trial sites.

4.1 Characterization of the Antigen.

The calibrator antigen used in the Bayer Immuno 1 HER-2/neu assay is derived from a recombinant 3T3 mouse cell line 3-30. HER-2/neu p105 antigen is harvested from the tissue culture media and concentrated 10-fold. Western blot analysis shows a single dominant band with a molecular weight of 105,000 Daltons consistent with the HER-2/neu extracellular domain.

4.2 Characterization of the Antibodies

The NB-3 monoclonal (part no. 7591MR) and TA-1 monoclonal anti-HER-2/neu (part no. 7590MR) are used in the preparation of the R1 and R2 reagents for the Bayer Immuno 1™ HER-2/neu Assay. The procedures for the preparation of the NB-3 R1 Reagent fluorescein and TA-1 R2 Reagent alkaline phosphatase conjugates are standard protocols similar to those used for conjugate preparation for other 510(k) Bayer Immuno 1 assays. Bayer Corporation (Business Group Diagnostics) in Elkhart is the approved supplier for the antibodies and antibody conjugates.

4.3 Assay Performance

4.3.1 Specificity: Interference

The recovery of HER-2/neu from patient samples was studied before and after spiking the serum samples with the potentially interfering substance. Each potential interferent was tested at a maximum concentration.

The Immuno 1 HER-2/neu Assay was performed on serum samples or pools of serum to which were added various concentrations of triglycerides, hemoglobin, immunoglobulin, bilirubin, albumin or cholesterol. HER-2/neu values were also measured in serum samples after spiking with either an individual chemotherapeutic drug, "Over the Counter" (OTC) drug, vitamin or HERCEPTIN® (Trastuzumab), trademark of Genetech BioOncology, South San Francisco, CA. None of the potential endogenous or exogenous interferents demonstrated any significant interfering effects on HER-2/neu recovery.

4.3.2 Cross-Reactivity

Possible cross-reactions in the Immuno 1 HER-2/neu assay were studied by comparing HER-2/neu recoveries in patient samples with Human Epidermal Growth Factor. The maximum effect seen with this cross-reactant was not significant (≤1%).

4.3.3 Heterophilic Antibodies

To investigate the effectiveness of the assay's reagent formulation in minimizing heterophilic antibody interferences, patient samples with HAMA, RF titers, or autoimmune diseases were tested for possible interference in the HER-2/neu assay. The observed HER-2/neu recoveries indicated a lack of significant heterophilic interference in the assay and demonstrated the effectiveness of the reagent formulation in minimizing these interferences.

4.3.4 Linearity

To determine the linearity of this assay, five individual serum samples from breast cancer patients were diluted (100%, 75%, 50%, 25%, and 0%) with a pool of human sera. Recoveries of the intermediate dilutions were all between 95 and 102 percent of the expected values. These results demonstrate the linearity of HER-2/neu recoveries over the entire calibration range.

4.3.5 Hook Effect (Antigen Excess)

Extremely high concentrations of HER-2/neu 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. HER-2/neu antigen was diluted in Level 1 Calibrator at concentrations of 300 ng/mL to 10,000 ng/mL. Results clearly demonstrated the lack of a hook effect in the Immuno 1 HER-2/neu Assay at Her-2/neu values $\leq$10,000 ng/mL.

4.3.6 Parallelism (Dilution Studies)

As a further verification of assay linearity, and to qualify the Level 1 Calibrator as a sample diluent, five patient serum samples containing a high level of HER-2/neu 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 HER-2/neu assay values ranged from 90% to 103%. These data demonstrate that Level 1 calibrator is an acceptable diluent for high samples, with accurate

recovery of diluted values. This study was repeated using the same samples to qualify Immuno 1 Sample Diluent B as a sample diluent. The recovery of HER-2/neu assay values ranged from 100% to 110%. These data demonstrate that Immuno 1 Sample Diluent B is also an acceptable diluent for high samples, with accurate recovery of diluted values.

4.3.7 Reproducibility

Intra- and inter-assay reproducibility were evaluated at three clinical trial sites for Bayer SETpoint Complexed Her-2/neu Calibrators, Controls and a human serum pool with HER-2/neu concentration approximately 15 ng/mL. Imprecision data pooled across Immuno 1 HER-2/neu 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.

	Number of Runs	Number of Replicates	Mean	Within Run		Total	
			ng/mL	STD DEV	%CV	STD DEV	%CV
Serum Pool	80	400	15.6	0.27	1.7	0.28	1.8
Calibrator 2	80	640	10.0	0.24	2.4	0.24	2.4
Calibrator 3	80	640	24.9	0.51	2.0	0.52	2.1
Calibrator 4	80	640	59.3	1.09	1.8	1.12	1.9
Calibrator 5	80	640	123.2	2.33	1.9	2.38	1.9
Calibrator 6	80	490	245.2	4.16	1.7	4.26	1.7
Control L3	80	400	108.6	1.77	1.6	1.79	1.7

4.3.8 Sensitivity (Detection Limit)

Sensitivity of the Immuno 1 HER-2/neu Assay was evaluated at three clinical trial sites by determining the Minimum Detectable Concentration (MDC). An MDC of 0.11 ng/mL was observed when assaying 480 replicates of the Immuno 1 HER-2/neu zero calibrator using two Immuno 1 HER-2/neu calibrator lots and three Immuno 1 HER-2/neu reagent lots.

4.4 CLINICAL STUDIES

The clinical utility of the Bayer Immuno I HER-2/neu assay in monitoring patients with metastatic breast cancer was evaluated using retrospective serum samples from three clinical sites in the United States. Serum HER-2/neu values were measured in 60 patients with metastatic breast cancer over a 6-12 month period. These results were then separated into groups that either showed HER-2/neu values that paralleled the clinical course of disease, or HER-2/neu values that did not parallel the clinical course as follows: For all patients whose pretreatment serum HER-2/neu values exceeded 15 ng/mL, all serial measurements were analyzed visit-to-visit and serial changes in serum HER-2/neu were correlated with changes in clinical status. For each pair of serial measurements, an increase of equal or greater than 15% was considered to indicate progression, and a change of less than 15% increase was considered to indicate a lack of progression. Results presented in Table 1 show the overall correspondence of the serial HER-2/neu changes and changes in clinical status.

Table 1: Correspondence of Serial HER-2/neu Changes and Clinical Status

	Change In Clinical Status		
Change In HER-2/Neu	**Progression**	**Lack Of Progression**	**Total**
≥ 15% increased	66	33	99
< 15% increase	44	109	154
Total	111	142	253

Distribution of HER-2/neu Concentrations; Sensitivity and Specificity

The Immuno 1 HER-2/neu Assay was used to estimate the clinical (cross-sectional) sensitivity in patients with breast cancer and characterize the frequency distribution of Immuno 1 HER-2/neu assay values in a population of breast cancer patients by stage of disease.

Specificity of the Immuno 1 HER-2/neu Assay was determined in patients with benign breast diseases, other non-malignant diseases, and in normal healthy individuals.

The Upper Limit of 15 ng/ml is comparable to the Upper Limit seen with manual kits used for research purposes, and is also equivalent to the 15 ng/ml Upper Limit found by Bayer in a previous study.

Conclusions from the Clinical Studies

The results of this retrospective clinical trial demonstrate that the Bayer Immuno 1™ HER-2/neu assay is reproducible, and is safe and effective for the management and follow-up of patients with metastatic breast cancer.

HER-2/neu is the first cellular oncogene, which has been shown useful in this clinical setting. Data collected from this study show that changes in serum HER-2/neu concentrations over time in metastatic breast cancer patients reflect changes in clinical status such as progression of disease.

The reproducibility of the Immuno 1 HER-2/neu assay is outstanding with total CVs of less than 3%. The detection limit of 0.1 ng/mL is acceptable for the intended use of this assay. This demonstrates that this assay should provide reliable and reproducible results when tested by different laboratories using different manufactured lots of reagents at different times.

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 Clinical 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 HER-2/neu assays.

Method Performance

Immuno 1 HER-2/neu results are highly reproducible with a maximum inter-assay %CV pooled over reagent lots and clinical sites of 2.4% over the range of the assay. Other performance characteristics including analytical sensitivity and specificity, cross-reactivity, linearity, antigen excess hook effect meet the accepted specifications set for an assay of this type.

Safety and Effectiveness

These clinical studies confirm the safety and effectiveness of the Immuno 1 HER-2/neu Assay as an aid in the follow-up and management of metastatic breast cancer patients. The correspondence between Immuno 1 HER-2/neu concentrations and the patients' clinical course of disease demonstrate that the Immuno 1 HER-2/neu Assay may be used in conjunction with other clinical indicators to confirm disease progression in metastatic breast cancer patients.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
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SEP 2 9 2000

Mr. Fredrick Clerie
Director Regulatory Affairs
Bayer Corporation
Business Group Diagnostics
511 Benedict Avenue
Tarrytown, New York 10591

Re: K992228
Trade Name: Bayer Immuno 1™ HER-2/neu Assay
Regulatory Class: II
Product Code: NCW
Dated: July 6, 2000
Received: July 10, 2000

Dear Mr. Clerie:

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 legally marketed predicate 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 requirements, 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.

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" (21CFR 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 (301) 443-6597 or at its internet address "http://www.fda.gov/cdrh/dsma/dsmamain.html".

Sincerely yours,

Steven Gutman

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): K992228

Device Name: Bayer Immuno 1™ HER-2/neu Assay

Indications For Use:

The Bayer Immuno 1™ Her-2/neu Assay is an *in vitro*, diagnostic device intended for use in the quantitative determination of HER-2/neu in human serum. HER-2/neu values obtained may be used in the follow-up and monitoring of patients with metastatic breast cancer. HER-2/neu values should be used in conjunction with information available from clinical and other diagnostic procedures in the management of breast cancer. The clinical utility of the serum measurement of HER-2/neu as a prognostic indicator for early recurrence and in the management of patients on immunotherapy regimens has not been fully established.

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

Concurrence of CDRH, Office of Device Evaluation (ODE)

Peter D. Maxim

(Division Sign-Off)
Division of Clinical Laboratory Devices
510(k) Number K992228

Prescription Use ✓ OR Over-the-counter Use____
(Per 21 CFR 801.109)

(Optional Format 1-2-96)